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(54) Title: NANOMATERIALS COMPRISING ESTER-LINKED ACETALS

(57) Abstract: The present disclosure describes compositions, preparations, nanoparticles (such as lipid nanoparticles), and/or nanomaterials and methods of their use.

NANOMATERIALS COMPRISING ESTER-LINKED ACETALS

Cross Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Application Nos. 63/128,680, filed December 21, 2020, 63/223,971, filed July 20, 2021, and 63/287,390, filed December 8, 2021, each of which is herein incorporated by reference in its entirety.

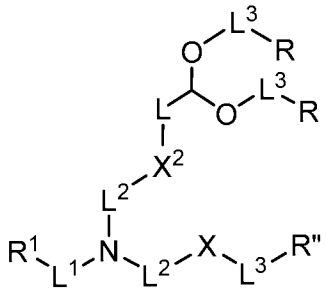
Background

[0002] Delivery of drug delivery systems poses challenges in fields of chemistry, biology, and medicine. For example, drug delivery systems are hindered due to poor understanding of how molecular properties of a system control delivery to tissues and confer drug efficacy.

Summary

[0003] The present invention recognizes a need for compositions, preparations, nanoparticles, and/or nanomaterials and methods of their use. Among other things, the present disclosure recognizes that structural features of compositions, preparations, nanoparticles, and/or nanomaterials impact functional responses *in vivo*, *in vitro*, and *ex vivo*. For example, the present disclosure describes, among other things, that selection and combination of one or more components described herein influence functional activity of lipid nanoparticles. In some embodiments, for example, functional activity can refer to desired tropisms, stabilization, and/or drug delivery efficacy. In some embodiments, among other things, the present disclosure describes that different ratios of one of more components influence one or more functional activities of compositions, preparations, nanoparticles, and/or nanomaterials described herein.

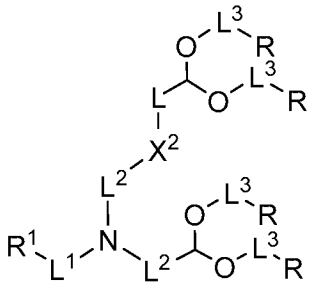
[0004] Moreover, among other things, the present disclosure recognizes that chemical structures of lipids confer improved properties compared to reference lipid structures. For example, in some embodiments, the present disclosure describes compounds of Formula A':



A'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of L, L^1, L^2, L^3, X, X^2, R, R", and R^1 is as defined herein.

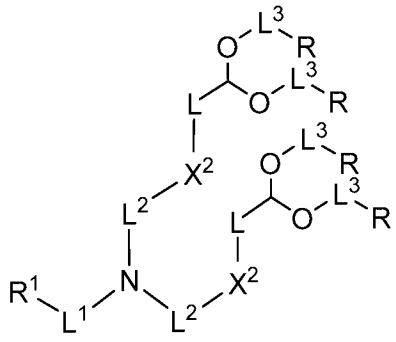
[0005] In some embodiments, the present disclosure describes compounds of Formula II":



II"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of L, L^1, L^2, L^3, X^2, R, and R^1 is as defined herein.

[0006] In some embodiments, the present disclosure describes compounds of Formula III':



III'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of L, L^1, L^2, L^3, X^2, R, and R^1 is as defined herein.

[0007] Among other things, as described herein, the present disclosure demonstrates surprising attributes of ionizable lipids (e.g., unexpected tropism, stabilization, and delivery efficacy of

cargos such as therapeutic or prophylactic agents) comprising an ester-linked acetal feature, and compositions, preparations, nanoparticles, and/or nanomaterials (e.g., LNPs and/or LNP-containing compositions, preparations, nanoparticles, and/or nanomaterials) thereof, and methods of their use. In particular embodiments, the present disclosure demonstrates particularly surprising attributes of ionizable lipids (e.g., unexpected tropism, stabilization, and delivery efficacy of cargos such as therapeutic or prophylactic agents) comprising at least two ester-linked acetal features, and compositions, preparations, nanoparticles, and/or nanomaterials (e.g., LNPs and/or LNP-containing compositions, preparations, nanoparticles, and/or nanomaterials), and methods of their use. In some embodiments, provided lipids include two symmetrical (e.g., identical) ester-linked acetal features; in some embodiments provided lipids include two or more different ester-linked acetal features.

[0008] Among other things, the present disclosure recognizes that lipid nanoparticle (LNP) compositions comprising one or more ionizable lipids. For example, the present disclosure provides that LNP compositions and/or preparations comprising one or more of the disclosed ionizable lipids conferred unexpected tropisms.

[0009] In some embodiments, provided compositions, preparations, nanoparticles, and/or nanomaterials are for use in methods of treatment, delivery, producing polypeptides, or delaying/arresting progression of a disease or disorder.

[0010] In some embodiments, provided compositions, preparations, nanoparticles, and/or nanomaterials are for use in methods of manufacturing.

[0011] In some embodiments, provided compositions, preparations, nanoparticles, and/or nanomaterials are for use in methods of characterization.

[0012] Elements of embodiments involving one aspect of the invention (e.g., methods) can be applied in embodiments involving other aspects of the invention, and vice versa.

Brief Description of the Drawing

[0013] FIG. 1 depicts an exemplary mRNA screening system of LNP preparations, in accordance with an embodiment of the present disclosure.

[0014] FIG. 2 depicts an exemplary siRNA screening system of LNP preparations, in accordance with an embodiment of the present disclosure.

[0015] FIG. 3 depicts a bar graph that shows overall potency of three exemplary LNP screens (Screen 33, Screen 35, Screen 36) across various cell types (splenic B cells, splenic T cells, bone marrow B cells, bone marrow T cells, liver endothelial cells, hepatocytes, liver Kuppfer cells (liver macrophages)).

[0016] FIG. 4 depicts a bar graph that shows potent delivery of exemplary LNP preparations (Exemplary Lipid 7, Exemplary Lipid 5, Exemplary Lipid 6, Exemplary Lipid 1, each having been characterized as an LNP preparation comprising an ester-linked acetal feature, and MC3 control) with potent delivery to various cell-types such as splenic B cells and T cells.

[0017] FIG. 5 depicts a bar graph that shows potent delivery of exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 2, Exemplary Lipid 3, Exemplary Lipid 4, and saline control) with potent delivery to various cell-types such as bone marrow B cells, bone marrow memory B cells, bone marrow T cells, bone marrow monocytes, spleen monocytes, spleen T cells, spleen B cells, and spleen memory B cells.

[0018] FIG. 6 depicts a bar graph that shows functional delivery of mRNA payloads encoding hEPO in vivo using exemplary LNP preparations (Exemplary Lipid 7, Exemplary Lipid 5, Exemplary Lipid 1) in mice. Amount of hEPO in plasma (ng/mL) was measured at 6 hours post-injection of exemplary LNP preparations in mice.

[0019] FIG. 7 depicts a bar graph showing tolerability of two exemplary LNP preparations (Exemplary Lipid 5, Exemplary Lipid 1) delivering hEPO in rats at 24 hour post-injection. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels (U/L) were measured at 24 hours post-injection.

[0020] FIG. 8 depicts a bar graph showing tolerability of two exemplary LNP preparations (Exemplary Lipid 5, Exemplary Lipid 1) delivering hEPO in rats. Monocyte Chemoattractant Protein-1 (MCP-1) (ng/mL) was measured at 6 hours post injection.

[0021] FIG. 9 depicts a bar graph showing efficacy of two exemplary LNP preparations (Exemplary Lipid 5, Exemplary Lipid 1) delivering hEPO in a rat model. hEPO was measured in plasma (ng/mL) across various time points (0, 2, 4, 6, 24, 48, and 72 hours).

[0022] FIG. 10 depicts a bar graph that shows functional delivery of mRNA payloads encoding a reporter in vivo using six exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) in C57BL6 mice across a variety of HSC cell types (Lin-, Sca-1+, LSK cells, LT-HSCs (CD34-Flk2-), and

LT-HSCs (CD150+CD48-)), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle).

[0023] FIG. 11 depicts a bar graph that shows functional delivery of mRNA payloads encoding a reporter in vivo using six exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) in C57BL6 mice across a variety of bone marrow (BM) cell types (Live, T cells, B cells, CD11b, Macrophages, NK cells, CD11c), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle).

[0024] FIG. 12 depicts a bar graph that shows functional delivery of mRNA payloads encoding reporter in vivo using six exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to C57BL6 mice across a variety of spleen cell types (T cells, B cells, CD11b, Macrophages, NK cells, CD11c), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle).

[0025] FIG. 13 depicts a bar graph that shows functional delivery of mRNA payloads encoding a reporter in vivo using six exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to C57BL6 mice across a variety of liver cell types (CD31, Hepatocytes, CD45, CD11b, Kupffer cells, NK cells, T cells, B cells), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle).

[0026] FIG. 14 depicts heat maps showing median fluorescence of a variety of LNP preparations containing different ionizable lipids normalized to the median fluorescence of an LNP preparation containing Exemplary Lipid 1 across a variety of cell types (bone marrow dendritic cells, splenic B cells, and splenic dendritic cells). Bottom left schematic shows experimental layout of each heat map for a variety of LNP preparations using exemplary lipids described in accordance with embodiments of the present disclosure. "X" in the bottom left schematic indicates a variety of different exemplary lipids that were tested in a variety of experiments accordance with the embodiments of the present disclosure.

[0027] FIG. 15 depicts two heat maps showing normalized average % reporter expression (left) or normalized average median fluorescence (right) of a variety of LNP preparations containing different ionizable lipids. Average % reporter and median average fluorescence values were

normalized to average % reporter expression or median average fluorescence (right), respectively, of an LNP preparation containing Exemplary Lipid 1 delivered to T cells (bone marrow cells). Stars indicate LNP formulations that resulted in greater average % reporter expression compared to average % reporter expression using an LNP preparation containing Exemplary Lipid 1. The design layout of exemplary LNP preparations tested a variety of experiments is depicted in the bottom left schematic of FIG. 14.

[0028] FIG. 16 depicts two heat maps showing normalized average % reporter expression (left) or median average fluorescence (right) of a variety of LNP preparations containing different ionizable lipids. Average % reporter and median average fluorescence values were normalized to % reporter expression (left) or median fluorescence (right), respectively, of an LNP preparation containing Exemplary Lipid 1 delivered to LSK (Lin-Sca-1+c-Kit+) cells. Stars indicate LNP formulations that resulted in greater average % reporter expression compared to average % reporter expression using an LNP preparation containing Exemplary Lipid 1. The design layout of exemplary LNP preparations tested a variety of experiments is depicted in the bottom left schematic of FIG. 14.

[0029] FIG. 17 depicts plots showing reporter expression of Exemplary Lipid 1 compared to Exemplary Lipid 11 in HSPCs and mouse LT-HSCs.

[0030] FIG. 18 shows bar graphs that each depict delivery of mRNA using exemplary LNP preparations described herein to bone marrow cells (left) and blood cells (right) in humanized (NSG-CD34+) mice.

[0031] FIG. 19 shows bar graphs that each depict delivery of mRNA using exemplary LNP preparations described herein to blood cells (left), bone marrow (live cells) (middle), and bone marrow (LSK cells) in two mouse strains (Balb/C, C57BL6J mice).

[0032] FIG. 20 shows a bar graph of relative luminescence intensity after intramuscular administration of a variety of LNP preparations containing Trilink Fluc mRNA. Images of luminescence intensity also are shown in FIG. 20.

[0033] FIGS. 21-23 show bar graphs depicting base editing in bone marrow cells, spleen cells, and liver cells using a variety of LNP preparations containing different exemplary lipids described herein.

[0034] FIG. 24 depicts a bar graph that shows dose-dependent delivery of an exemplary LNP preparation comprising Exemplary Lipid 1 to mouse HSPCs.

[0035] FIG. 25A and FIG. 25B depict bar graphs that show durability of delivery of an exemplary LNP preparation comprising Exemplary Lipid 1 to mouse HSPCs. FIG. 25C and FIG. 25D depict bar graphs that show reconstitution of immune and hematopoietic lineages by transfected HSPCs.

[0036] FIG. 26A and FIG. 26B depict bar graphs that show delivery of an exemplary LNP preparation comprising Exemplary Lipid 1 to human CD34+ HSPCs *in vitro*.

[0037] FIG. 27 depicts a bar graph that shows delivery of an exemplary LNP preparation comprising Exemplary Lipid 1 to non-human primate (NHP) HSPCs.

Definitions

[0038] ***About:*** As used herein, the term "about" or "approximately," when used herein in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by "about" or "approximately" in that context. For example, in some embodiments, the term "about" may encompass a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or in either direction (greater than or less than) of the reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0039] ***Administration:*** As used herein, the term "administration" typically refers to the administration of a composition to a subject or system. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, etc. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, etc), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (e. g. intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time. In some embodiments, a

pharmaceutical composition comprising lipid nanoparticles can be formulated for administration by parenteral (intramuscular, intraperitoneal, intravenous (IV) or subcutaneous injection), transdermal (either passively or using iontophoresis or electroporation), or transmucosal (nasal, vaginal, rectal, or sublingual) routes of administration or using bioerodible inserts and can be formulated in dosage forms appropriate for each route of administration.

[0040] ***Aliphatic:*** The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "carbocyclic", "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 carbon atoms. In some embodiments, aliphatic groups contain 1-4 carbon atoms. In some embodiments, aliphatic groups contain 1-3 carbon atoms, and in some embodiments, aliphatic groups contain 1-2 carbon atoms. In some embodiments, "carbocyclic" (or "cycloaliphatic" or "carbocycle" or "cycloalkyl") refers to an optionally substituted monocyclic C_3-C_8 hydrocarbon, or an optionally substituted C_6-C_{12} bicyclic hydrocarbon, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0041] ***Alkenyl***: As used herein, the term "alkenyl" refers to an alkyl group, as defined herein, having one or more double bonds. In some embodiments, the term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched hydrocarbon chain having at least one double bond and having (unless otherwise specified) 2-20, 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-20}, C_{2-18}, C_{2-16}, C_{2-14}, C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Exemplary alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, and heptenyl.

[0042] ***Alkenylene:*** The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or

more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0043] ***Alkyl:*** As used herein, the term "alkyl" is given its ordinary meaning in the art and may include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some embodiments, alkyl has 1-100 carbon atoms. In certain embodiments, a straight chain or branched chain alkyl has about 1-20 carbon atoms in its backbone (e.g., C_1-C_{20} for straight chain, C_2-C_{20} for branched chain), and alternatively, about 1-10. In some embodiments, a cycloalkyl ring has from about 3-10 carbon atoms in their ring structure where such rings are monocyclic or bicyclic, and alternatively about 5, 6 or 7 carbons in the ring structure. In some embodiments, an alkyl group may be a lower alkyl group, wherein a lower alkyl group comprises 1-4 carbon atoms (e.g., C_1-C_4 for straight chain lower alkyls).

[0044] ***Alkylenyl:*** The term “alkylenyl” or “alkylene” refers to a bivalent alkyl group (i.e., a bivalent saturated hydrocarbon chain) that is a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted. Any of the above mentioned monovalent alkyl groups may be an alkylenyl by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an “alkylenyl” is a polymethylene group, i.e., $–(CH_2)_n–$, wherein n is a positive integer, preferably from 1 to 10, from 1 to 9, from 1 to 8, from 1 to 7, from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 5, or from 4 to 8. A substituted alkylenyl is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0045] ***Alkynyl***: As used herein, the term “alkynyl” refers to an alkyl group, as defined herein, having one or more triple bonds. In some embodiments, the term “alkynyl”, used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having (unless otherwise specified) 2-20, 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms (e.g., C_{2-20}, C_{2-18}, C_{2-16}, C_{2-14}, C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, C_{2-4}, or C_{2-3}). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and heptynyl.

[0046] ***Amino acid:*** in its broadest sense, as used herein, refers to any compound and/or substance that can be incorporated into a polypeptide chain, e.g., through formation of one or more peptide bonds. In some embodiments, an amino acid has the general structure $H_2N–C(H)(R)–COOH$. In

some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a non-natural amino acid; in some embodiments, an amino acid is a D-amino acid; in some embodiments, an amino acid is an L-amino acid. "Standard amino acid" refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. "Nonstandard amino acid" refers to any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or obtained from a natural source. In some embodiments, an amino acid, including a carboxy- and/or amino-terminal amino acid in a polypeptide, can contain a structural modification as compared with the general structure above. For example, in some embodiments, an amino acid may be modified by methylation, amidation, acetylation, pegylation, glycosylation, phosphorylation, and/or substitution (e.g., of the amino group, the carboxylic acid group, one or more protons, and/or the hydroxyl group) as compared with the general structure. In some embodiments, such modification may, for example, alter the circulating half-life of a polypeptide containing the modified amino acid as compared with one containing an otherwise identical unmodified amino acid. In some embodiments, such modification does not significantly alter a relevant activity of a polypeptide containing the modified amino acid, as compared with one containing an otherwise identical unmodified amino acid. As will be clear from context, in some embodiments, the term "amino acid" may be used to refer to a free amino acid; in some embodiments it may be used to refer to an amino acid residue of a polypeptide.

[0047] ***Animal:*** as used herein refers to any member of the animal kingdom. In some embodiments, "*animal*" refers to humans, of either sex and at any stage of development. In some embodiments, "*animal*" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, insects, and/or worms. In some embodiments, an animal may be a transgenic animal, genetically engineered animal, and/or a clone.

[0048] ***Aptamer:*** As used herein, the term "aptamer" refers to a macromolecule composed of nucleic acid (e.g., RNA, DNA) that binds tightly to a specific molecular target (e.g., an umbrella topology glycan). A particular aptamer may be described by a linear nucleotide sequence and is typically about 15-60 nucleotides in length. Without wishing to be bound by any theory, it is contemplated that the chain of nucleotides in an aptamer form intramolecular interactions that fold

the molecule into a complex three-dimensional shape, and this three-dimensional shape allows the aptamer to bind tightly to the surface of its target molecule. Given the extraordinary diversity of molecular shapes that exist within the universe of all possible nucleotide sequences, aptamers may be obtained for a wide array of molecular targets, including proteins and small molecules. In addition to high specificity, aptamers typically have very high affinities for their targets (e.g., affinities in the picomolar to low nanomolar range for proteins). In many embodiments, aptamers are chemically stable and can be boiled or frozen without loss of activity. Because they are synthetic molecules, aptamers are amenable to a variety of modifications, which can optimize their function for particular applications. For example, aptamers can be modified to dramatically reduce their sensitivity to degradation by enzymes in the blood for use in *in vivo* applications. In addition, aptamers can be modified to alter their biodistribution or plasma residence time.

[0049] ***Aryl:*** The term "aryl" refers to monocyclic and bicyclic ring systems having a total of six to fourteen ring members (e.g., C_{6-14}), wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In some embodiments, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Unless otherwise specified, "aryl" groups are hydrocarbons.

[0050] ***Associated:*** Two events or entities are "associated" with one another, as that term is used herein, if the presence, level, degree, type and/or form of one is correlated with that of the other. For example, a particular entity (e.g., polypeptide, genetic signature, metabolite, microbe, etc) is considered to be associated with a particular disease, disorder, or condition, if its presence, level and/or form correlates with incidence of and/or susceptibility to the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, two or more entities are physically "associated" with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another. In some embodiments, two or more entities that are physically associated with one another are covalently linked to one another; in some embodiments, two or more entities that are physically associated with one another are not covalently linked to one another but are non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and combinations thereof.

[0051] ***Biocompatible:*** The term "biocompatible", as used herein, refers to materials that do not cause significant harm to living tissue when placed in contact with such tissue, e.g., *in vivo*. In

certain embodiments, materials are "biocompatible" if they are not toxic to cells. In certain embodiments, materials are "biocompatible" if their addition to cells *in vitro* results in less than or equal to 20% cell death, and/or their administration *in vivo* does not induce significant inflammation or other such adverse effects.

[0052] ***Biodegradable***: As used herein, the term "biodegradable" refers to materials that, when introduced into cells, are broken down (e.g., by cellular machinery, such as by enzymatic degradation, by hydrolysis, and/or by combinations thereof) into components that cells can either reuse or dispose of without significant toxic effects on the cells. In certain embodiments, components generated by breakdown of a biodegradable material are biocompatible and therefore do not induce significant inflammation and/or other adverse effects *in vivo*. In some embodiments, biodegradable polymer materials break down into their component monomers. In some embodiments, breakdown of biodegradable materials (including, for example, biodegradable polymer materials) involves hydrolysis of ester bonds. Alternatively or additionally, in some embodiments, breakdown of biodegradable materials (including, for example, biodegradable polymer materials) involves cleavage of urethane linkages. Exemplary biodegradable polymers include, for example, polymers of hydroxy acids such as lactic acid and glycolic acid, including but not limited to poly(hydroxyl acids), poly(lactic acid)(PLA), poly(glycolic acid)(PGA), poly(lactic-co-glycolic acid)(PLGA), and copolymers with PEG, polyanhydrides, poly(ortho)esters, polyesters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxyalkanoates, poly(lactide-co-caprolactone), blends and copolymers thereof. Many naturally occurring polymers are also biodegradable, including, for example, proteins such as albumin, collagen, gelatin and prolamines, for example, zein, and polysaccharides such as alginate, cellulose derivatives and polyhydroxyalkanoates, for example, polyhydroxybutyrate blends and copolymers thereof. Those of ordinary skill in the art will appreciate or be able to determine when such polymers are biocompatible and/or biodegradable derivatives thereof (e.g., related to a parent polymer by substantially identical structure that differs only in substitution or addition of particular chemical groups as is known in the art).

[0053] ***Biologically active:*** as used herein, refers to an observable biological effect or result achieved by an agent or entity of interest. For example, in some embodiments, a specific binding interaction is a biological activity. In some embodiments, modulation (e.g., induction, enhancement, or inhibition) of a biological pathway or event is a biological activity. In some

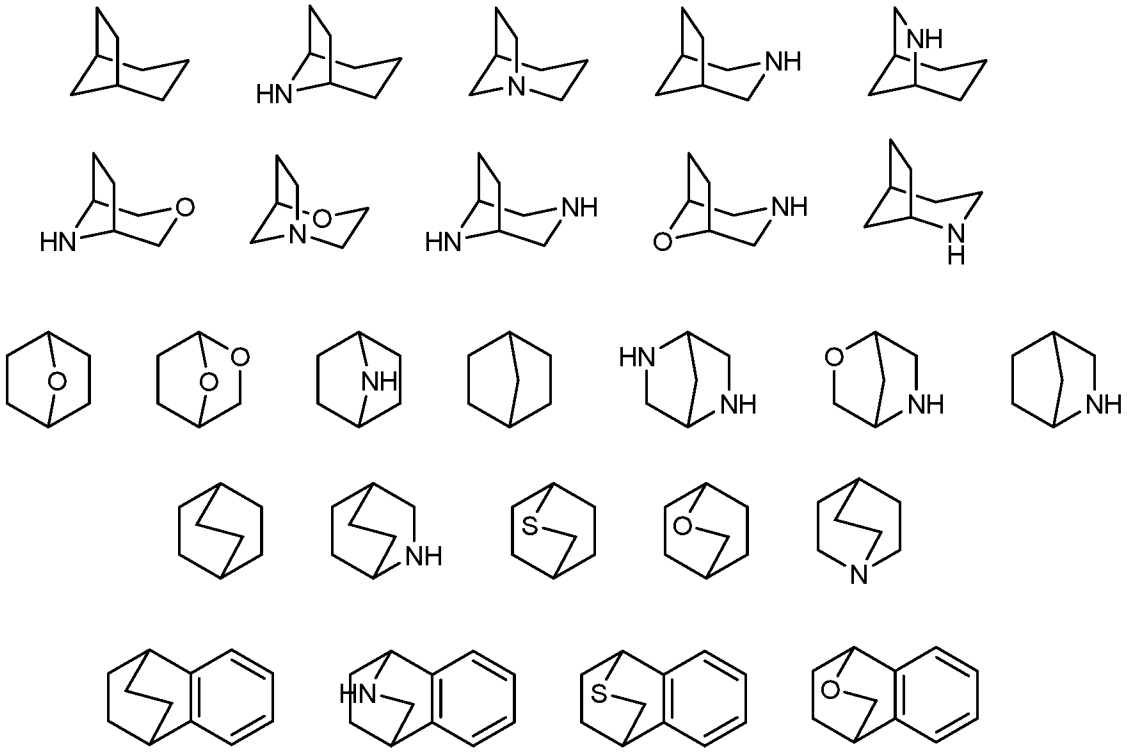
embodiments, presence or extent of a biological activity is assessed through detection of a direct or indirect product produced by a biological pathway or event of interest.

[0054] ***Biological sample***: As used herein, the term "biological sample" typically refers to a sample obtained or derived from a biological source (e.g., a tissue or organism or cell culture) of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or broncheoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, *etc*. In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy), surgery, collection of body fluid (*e.g.*, blood, lymph, feces *etc.*), *etc.* In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, *etc.*

[0055] ***Bivalent:*** As used herein, the term "bivalent" refers to a chemical moiety with two points of attachment. For example, a "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0056] ***Bridged bicyclic***: As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one

bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include but are not limited to:



[0057] ***Cancer***: The terms "cancer", “malignancy”, "neoplasm", "tumor", and "carcinoma", are used herein to refer to cells that exhibit relatively abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In some embodiments, a tumor may be or comprise cells that are precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. The present disclosure specifically identifies certain cancers to which its teachings may be particularly relevant. In some embodiments, a relevant cancer may be characterized by a solid tumor. In some

embodiments, a relevant cancer may be characterized by a hematologic tumor. In general, examples of different types of cancers known in the art include, for example, hematopoietic cancers including leukemias, lymphomas (Hodgkin's and non-Hodgkin's), myelomas and myeloproliferative disorders; sarcomas, melanomas, adenomas, carcinomas of solid tissue, squamous cell carcinomas of the mouth, throat, larynx, and lung, liver cancer, genitourinary cancers such as prostate, cervical, bladder, uterine, and endometrial cancer and renal cell carcinomas, bone cancer, pancreatic cancer, skin cancer, cutaneous or intraocular melanoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, head and neck cancers, breast cancer, gastro-intestinal cancers and nervous system cancers, benign lesions such as papillomas, and the like.

[0058] ***Carrier:*** as used herein, refers to a diluent, adjuvant, excipient, or vehicle with which a composition is administered. In some exemplary embodiments, carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like. In some embodiments, carriers are or include one or more solid components.

[0059] ***Carbocyclyl:*** The terms "carbocyclyl," "carbocycle," and "carbocyclic ring" as used herein, refer to saturated or partially unsaturated cyclic aliphatic monocyclic, bicyclic, or polycyclic ring systems, as described herein, having from 3 to 14 members, wherein the aliphatic ring system is optionally substituted as described herein. Carbocyclic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, adamantyl, and cyclooctadienyl. In some embodiments, "carbocyclyl" (or "cycloaliphatic") refers to an optionally substituted monocyclic C_3-C_8 hydrocarbon, or an optionally substituted C_6-C_{12} bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. The term "cycloalkyl" refers to an optionally substituted saturated ring system of about 3 to about 10 ring carbon atoms. In some embodiments, cycloalkyl groups have 3–6 carbons. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon

atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0060] ***Comparable***: As used herein, the term "comparable" refers to two or more agents, entities, situations, sets of conditions, etc., that may not be identical to one another but that are sufficiently similar to permit comparison therebetween so that one skilled in the art will appreciate that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, etc. to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

[0061] ***Composition:*** Those skilled in the art will appreciate that the term "composition" may be used to refer to a discrete physical entity that comprises one or more specified components. In general, unless otherwise specified, a composition may be of any form – e.g., gas, gel, liquid, solid, etc.

[0062] ***Comprising:*** A composition or method described herein as "comprising" one or more named elements or steps is open-ended, meaning that the named elements or steps are essential, but other elements or steps may be added within the scope of the composition or method. To avoid prolixity, it is also understood that any composition or method described as "comprising" (or which "comprises") one or more named elements or steps also describes the corresponding, more limited composition or method "consisting essentially of" (or which "consists essentially of") the same named elements or steps, meaning that the composition or method includes the named essential elements or steps and may also include additional elements or steps that do not materially affect the basic and novel characteristic(s) of the composition or method. It is also understood that any composition or method described herein as "comprising" or "consisting essentially of" one or more named elements or steps also describes the corresponding, more limited, and closed-ended

composition or method "consisting of" (or "consists of") the named elements or steps to the exclusion of any other unnamed element or step. In any composition or method disclosed herein, known or disclosed equivalents of any named essential element or step may be substituted for that element or step.

[0063] ***"Improve," "increase", "inhibit"*** or ***"reduce":*** As used herein, the terms "improve", "increase", "inhibit', "reduce", or grammatical equivalents thereof, indicate values that are relative to a baseline or other reference measurement. In some embodiments, an appropriate reference measurement may be or comprise a measurement in a particular system (e.g., in a single individual) under otherwise comparable conditions absent presence of (e.g., prior to and/or after) a particular agent or treatment, or in presence of an appropriate comparable reference agent. In some embodiments, an appropriate reference measurement may be or comprise a measurement in comparable system known or expected to respond in a particular way, in presence of the relevant agent or treatment.

[0064] ***Determine:*** Many methodologies described herein include a step of "determining". Those of ordinary skill in the art, reading the present specification, will appreciate that such "determining" can utilize or be accomplished through use of any of a variety of techniques available to those skilled in the art, including for example specific techniques explicitly referred to herein. In some embodiments, determining involves manipulation of a physical sample. In some embodiments, determining involves consideration and/or manipulation of data or information, for example utilizing a computer or other processing unit adapted to perform a relevant analysis. In some embodiments, determining involves receiving relevant information and/or materials from a source. In some embodiments, determining involves comparing one or more features of a sample or entity to a comparable reference.

[0065] ***Encapsulated:*** The term "encapsulated" is used herein to refer to substances that are completely surrounded by another material.

[0066] ***Excipient:*** as used herein, refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example to provide or contribute to a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0067] ***Expression:*** As used herein, the term "expression" of a nucleic acid sequence refers to the generation of any gene product from the nucleic acid sequence. In some embodiments, a gene product can be a transcript. In some embodiments, a gene product can be a polypeptide. In some embodiments, expression of a nucleic acid sequence involves one or more of the following: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5' cap formation, and/or 3' end formation); (3) translation of an RNA into a polypeptide or protein; and/or (4) post-translational modification of a polypeptide or protein.

[0068] ***Haloaliphatic***: The term "haloaliphatic" refers to an aliphatic group substituted by one or more halogen atoms (e.g., one, two, three, four, five, six, or seven halo, such as fluoro, iodo, bromo, or chloro). In some embodiments, haloaliphatic groups contain 1-7 halogen atoms. In some embodiments, haloaliphatic groups contain 1-5 halogen atoms. In some embodiments, haloaliphatic groups contain 1-3 halogen atoms.

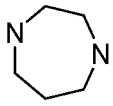
[0069] ***Haloalkyl***: The term "haloalkyl" refers to an alkyl group substituted by one or more halogen atoms (e.g., one, two, three, four, five, six, or seven halo, such as fluoro, iodo, bromo, or chloro). In some embodiments, haloalkyl groups contain 1-7 halogen atoms. In some embodiments, haloalkyl groups contain 1-5 halogen atoms. In some embodiments, haloalkyl groups contain 1-3 halogen atoms.

[0070] ***Heteroalkylenyl***: The term "heteroalkylenyl" or "heteroalkylene", as used herein, denotes an optionally substituted straight–chain (*i.e.,* unbranched), or branched bivalent alkyl group (i.e., bivalent saturated hydrocarbon chain) having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" is described below. In some embodiments, heteroalkylenyl groups contain 2–10 carbon atoms wherein 1–3 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, heteroalkylenyl groups contain 2–8 carbon atoms wherein 1–3 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, heteroalkylenyl groups contain 4-8 carbon atoms, wherein 1–3 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, heteroalkylenyl groups contain 2-5 carbon atoms, wherein 1–2 carbon atoms are optionally and independently replaced with heteroatoms selected from oxygen, nitrogen, and sulfur. In yet other embodiments, heteroalkylenyl groups contain 1–3 carbon atoms,

wherein 1 carbon atom is optionally and independently replaced with a heteroatom selected from oxygen, nitrogen, and sulfur. Suitable heteroalkylenyl groups include, but are not limited to $-CH_2O-$, $-(CH_2)_2O-$, $-CH_2OCH_2-$, $-O(CH_2)_2-$, $-(CH_2)_3O-$, $-(CH_2)_2OCH_2-$, $-CH_2O(CH_2)_2-$, $-O(CH_2)_3-$, $-(CH_2)_4O-$, $-(CH_2)_3OCH_2-$, $-CH_2O(CH_2)_3-$, $-(CH_2)_2O(CH_2)_2-$, $-O(CH_2)_4-$. Unless otherwise specified, C_x heteroalkylenyl refers to heteroalkylenyl having *x* number of carbon atoms prior to replacement with heteroatoms.

[0071] ***Heteroaryl:*** The terms "heteroaryl" and "heteroar–", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to monocyclic or bicyclic ring groups having 5 to 10 ring atoms (e.g., 5- to 6-membered monocyclic heteroaryl or 9- to 10-membered bicyclic heteroaryl); having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Exemplary heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridonyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyridinyl, thienopyrimidinyl, triazolopyridinyl, and benzoisoxazolyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring (i.e., a bicyclic heteroaryl ring having 1 to 3 heteroatoms). Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, pyrido[2,3–b]–1,4–oxazin–3(4H)–one, and benzoisoxazolyl. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted.

[0072] ***Heteroatom:*** The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0073] ***Heterocycle:*** The terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably herein, and refer to a stable 3- to 8-membered monocyclic, a 7- to 12-membered bicyclic, or a 10- to 16-membered polycyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, such as one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, azetidinyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, tetrahydropyranyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, thiamorpholinyl, and  . A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. A bicyclic heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings. Exemplary bicyclic heterocyclic groups include indolinyl, isoindolinyl, benzodioxolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydrobenzofuranyl, and tetrahydroquinolinyl. A bicyclic heterocyclic ring can also be a spirocyclic ring system (e.g., 7- to 11-membered spirocyclic fused heterocyclic ring having, in addition to carbon atoms, one or more heteroatoms as defined above (e.g., one, two, three or four heteroatoms)). A bicyclic heterocyclic ring can also be a bridged ring system (e.g., 7- to 11-membered bridged heterocyclic ring having one, two, or three bridging atoms.

[0074] ***Inhibitory agent:*** As used herein, the term "inhibitory agent" refers to an entity, condition, or event whose presence, level, or degree correlates with decreased level or activity of a target). In some embodiments, an inhibitory agent may be act directly (in which case it exerts its influence directly upon its target, for example by binding to the target); in some embodiments, an inhibitory agent may act indirectly (in which case it exerts its influence by interacting with and/or otherwise

altering a regulator of the target, so that level and/or activity of the target is reduced). In some embodiments, an inhibitory agent is one whose presence or level correlates with a target level or activity that is reduced relative to a particular reference level or activity (e.g., that observed under appropriate reference conditions, such as presence of a known inhibitory agent, or absence of the inhibitory agent in question, etc).

[0075] ***In vitro*:** The term "*in vitro*" as used herein refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, etc., rather than within a multi-cellular organism.

[0076] ***Isolated:*** as used herein, refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) designed, produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% of the other components with which they were initially associated. In some embodiments, isolated agents are about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "*pure*" if it is substantially free of other components. In some embodiments, as will be understood by those skilled in the art, a substance may still be considered "*isolated*" or even "*pure*", after having been combined with certain other components such as, for example, one or more carriers or excipients (e.g., buffer, solvent, water, etc.); in such embodiments, percent isolation or purity of the substance is calculated without including such carriers or excipients. To give but one example, in some embodiments, a biological polymer such as a polypeptide or polynucleotide that occurs in nature is considered to be "*isolated*" when, a) by virtue of its origin or source of derivation is not associated with some or all of the components that accompany it in its native state in nature; b) it is substantially free of other polypeptides or nucleic acids of the same species from the species that produces it in nature; c) is expressed by or is otherwise in association with components from a cell or other expression system that is not of the species that produces it in nature. Thus, for instance, in some embodiments, a polypeptide that is chemically synthesized or is synthesized in a cellular system different from that which produces it in nature is considered to be an "*isolated*" polypeptide.

Alternatively or additionally, in some embodiments, a polypeptide that has been subjected to one or more purification techniques may be considered to be an "*isolated*" polypeptide to the extent that it has been separated from other components a) with which it is associated in nature; and/or b) with which it was associated when initially produced.

[0077] ***In vivo:*** as used herein refers to events that occur within a multi-cellular organism, such as a human and a non-human animal. In the context of cell-based systems, the term may be used to refer to events that occur within a living cell (as opposed to, for example, *in vitro* systems).

[0078] ***Linker:*** as used herein, is used to refer to that portion of a multi-element agent that connects different elements to one another. For example, those of ordinary skill in the art appreciate that a polypeptide whose structure includes two or more functional or organizational domains often includes a stretch of amino acids between such domains that links them to one another. In some embodiments, a polypeptide comprising a linker element "L'" has an overall structure of the general form S1-L'-S2, wherein S1 and S2 may be the same or different and represent two domains associated with one another by the linker. In some embodiments, a polyptide linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length. In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, but rather provides flexibility to the polypeptide. A variety of different linker elements that can appropriately be used when engineering polypeptides (e.g., fusion polypeptides) known in the art (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2: 1 121-1123).

[0079] ***Nanoparticle:*** As used herein, the term "nanoparticle" refers to a particle having a diameter of less than 1000 nanometers (nm). In some embodiments, a nanoparticle has a diameter of less than 300 nm, as defined by the National Science Foundation. In some embodiments, a nanoparticle has a diameter of less than 100 nm as defined by the National Institutes of Health. In some embodiments, nanoparticles are micelles in that they comprise an enclosed compartment, separated from the bulk solution by a micellar membrane, typically comprised of amphiphilic entities which surround and enclose a space or compartment (*e.g.*, to define a lumen). In some embodiments, a micellar membrane is comprised of at least one polymer, such as for example a biocompatible and/or biodegradable polymer. In some embodiments, lipid nanoparticles described herein can have an average hydrodynamic diameter from about 30 to about 170 nm. In some

embodiments, lipid nanoparticles described herein can have an average hydrodynamic diameter that is about 30 nm, 35 nm,40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, 150 nm, 155 nm, 160 nm, 165 nm, 170 nm, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, lipid nanoparticles described herein have an average hydrodynamic diameter from between 50 nm to 100 nm.

[0080] ***Nanoparticle composition:*** As used herein, the term "nanoparticle composition" refers to a composition that contains at least one nanoparticle and at least one additional agent or ingredient. In some embodiments, a nanoparticle composition contains a substantially uniform collection of nanoparticles as described herein.

[0081] ***Nucleic acid***: As used herein, in its broadest sense, refers to any compound and/or substance that is or can be incorporated into an oligonucleotide chain. In some embodiments, a nucleic acid is a compound and/or substance that is or can be incorporated into an oligonucleotide chain via a phosphodiester linkage. As will be clear from context, in some embodiments, "*nucleic acid*" refers to an individual nucleic acid residue (e.g., a nucleotide and/or nucleoside); in some embodiments, "*nucleic acid*" refers to an oligonucleotide chain comprising individual nucleic acid residues. In some embodiments, a "*nucleic acid*" is or comprises RNA; in some embodiments, a "*nucleic acid*" is or comprises DNA. In some embodiments, a nucleic acid is, comprises, or consists of one or more natural nucleic acid residues. In some embodiments, a nucleic acid is, comprises, or consists of one or more nucleic acid analogs. In some embodiments, a nucleic acid analog differs from a nucleic acid in that it does not utilize a phosphodiester backbone. For example, in some embodiments, a nucleic acid is, comprises, or consists of one or more "*peptide nucleic acids*", which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. Alternatively or additionally, in some embodiments, a nucleic acid has one or more phosphorothioate and/or 5'-N-phosphoramidite linkages rather than phosphodiester bonds. In some embodiments, a nucleic acid is, comprises, or consists of one or more natural nucleosides (e.g., adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxy guanosine, and deoxycytidine). In some embodiments, a nucleic acid is, comprises, or consists of one or more nucleoside analogs (e.g., 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3 - methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-

aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5 -propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, O(6)-methylguanine, 2-thiocytidine, methylated bases, intercalated bases, and combinations thereof). In some embodiments, a nucleic acid comprises one or more modified sugars (e.g., 2'-fluororibose, ribose, 2'-deoxyribose, arabinose, and hexose) as compared with those in natural nucleic acids. In some embodiments, a nucleic acid has a nucleotide sequence that encodes a functional gene product such as an RNA or protein. In some embodiments, a nucleic acid includes one or more introns. In some embodiments, nucleic acids are prepared by one or more of isolation from a natural source, enzymatic synthesis by polymerization based on a complementary template (*in vivo* or *in vitro*), reproduction in a recombinant cell or system, and chemical synthesis. In some embodiments, a nucleic acid is at least 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 1 10, 120, 130, 140, 150, 160, 170, 180, 190, 20, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 or more residues long. In some embodiments, a nucleic acid is partly or wholly single stranded; in some embodiments, a nucleic acid is partly or wholly double stranded. In some embodiments a nucleic acid has a nucleotide sequence comprising at least one element that encodes, or is the complement of a sequence that encodes, a polypeptide. In some embodiments, a nucleic acid has enzymatic activity.

[0082] ***Operably linked***: as used herein, refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control element "*operably linked*" to a functional element is associated in such a way that expression and/or activity of the functional element is achieved under conditions compatible with the control element. In some embodiments, "*operably linked*" control elements are contiguous (e.g., covalently linked) with the coding elements of interest; in some embodiments, control elements act in *trans* to or otherwise at a from the functional element of interest.

[0083] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic

Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0084] ***Parenteral:*** The phrases "parenteral administration" and "administered parenterally" as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0085] ***Patient:*** As used herein, the term "patient" refers to any organism to which a provided composition is or may be administered, *e.g.*, for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient displays one or more symptoms of a disorder or condition. In some embodiments, a patient has been diagnosed with one or more disorders or conditions. In some embodiments, the disorder or condition is or includes cancer, or presence of one or more tumors. In some embodiments, the patient is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

[0086] ***Pharmaceutical composition:*** As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a

pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0087] ***Pharmaceutically acceptable:*** As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0088] ***Pharmaceutically acceptable carrier:*** As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0089] ***Pharmaceutically acceptable salt:*** The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, *i.e.*, salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts,

which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

[0090] ***Prevent* or *prevention:*** as used herein when used in connection with the occurrence of a disease, disorder, and/or condition, refers to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0091] ***Protein:*** As used herein, the term "protein" refers to a polypeptide (*i.e.*, a string of at least two amino acids linked to one another by peptide bonds). Proteins may include moieties other than amino acids (*e.g.*, may be glycoproteins, proteoglycans, etc.) and/or may be otherwise processed or modified. Those of ordinary skill in the art will appreciate that a "protein" can be a complete polypeptide chain as produced by a cell (with or without a signal sequence), or can be a characteristic portion thereof. Those of ordinary skill will appreciate that a protein can sometimes include more than one polypeptide chain, for example linked by one or more disulfide bonds or associated by other means. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful

modifications include, *e.g.*, terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0092] ***Polypeptide***: The term "polypeptide", as used herein, generally has its art-recognized meaning of a polymer of at least three amino acids. Those of ordinary skill in the art will appreciate that the term "polypeptide" is intended to be sufficiently general as to encompass not only polypeptides having a complete sequence recited herein, but also to encompass polypeptides that represent functional fragments (i.e., fragments retaining at least one activity) of such complete polypeptides. Moreover, those of ordinary skill in the art understand that protein sequences generally tolerate some substitution without destroying activity. Thus, any polypeptide that retains activity and shares at least about 30-40% overall sequence identity, often greater than about 50%, 60%, 70%, or 80%, and further usually including at least one region of much higher identity, often greater than 90% or even 95%, 96%, 97%, 98%, or 99% in one or more highly conserved regions, usually encompassing at least 3-4 and often up to 20 or more amino acids, with another polypeptide of the same class, is encompassed within the relevant term "polypeptide" as used herein. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful modifications include, *e.g.*, terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0093] ***Prevention***: The term "prevention", as used herein, refers to a delay of onset, and/or reduction in frequency and/or severity of one or more symptoms of a particular disease, disorder or condition. In some embodiments, prevention is assessed on a population basis such that an agent is considered to "prevent" a particular disease, disorder or condition if a statistically

significant decrease in the development, frequency, and/or intensity of one or more symptoms of the disease, disorder or condition is observed in a population susceptible to the disease, disorder, or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0094] ***Protecting Group*:** The phrase "protecting group," as used herein, refers to temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. A "Si protecting group" is a protecting group comprising a Si atom, such as Si-trialkyl (e.g., trimethylsilyl, tributylsilyl, t-butyldimethylsilyl), Si-triaryl, Si-alkyl-diphenyl (e.g., t-butyldiphenylsilyl), or Si-aryl-dialkyl (e.g., Si-phenyldialkyl). Generally, a Si protecting group is attached to an oxygen atom. The field of protecting group chemistry has been reviewed (Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed.; Wiley: New York, 1991). Such protecting groups (and associated protected moieties) are described in detail below.

[0095] Protected hydroxyl groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Examples of suitably protected hydroxyl groups further include, but are not limited to, esters, carbonates, sulfonates, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of suitable esters include formates, acetates, proprionates, pentanoates, crotonates, and benzoates. Specific examples of suitable esters include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetate), crotonate, 4-methoxy-crotonate, benzoate, p-benzylbenzoate, 2,4,6-trimethylbenzoate. Examples of suitable carbonates include 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl carbonate. Examples of suitable silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl ether, and other trialkylsilyl ethers. Examples of suitable alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, and allyl ether, or derivatives thereof. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-

(trimethylsilyl)ethoxymethyl, and tetrahydropyran-2-yl ether. Examples of suitable arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, 2- and 4-picolyl ethers.

[0096] Protected amines are well known in the art and include those described in detail in Greene (1999). Suitable mono-protected amines further include, but are not limited to, aralkylamines, carbamates, allyl amines, amides, and the like. Examples of suitable mono-protected amino moieties include t-butyloxycarbonylamino (–NHBOC), ethyloxycarbonylamino, methyloxycarbonylamino, trichloroethyloxycarbonylamino, allyloxycarbonylamino (–NHAlloc), benzyloxocarbonylamino (–NHCBZ), allylamino, benzylamino (–NHBn), fluorenylmethylcarbonyl (–NHFmoc), formamido, acetamido, chloroacetamido, dichloroacetamido, trichloroacetamido, phenylacetamido, trifluoroacetamido, benzamido, t-butyldiphenylsilyl, and the like. Suitable di-protected amines include amines that are substituted with two substituents independently selected from those described above as mono-protected amines, and further include cyclic imides, such as phthalimide, maleimide, succinimide, and the like. Suitable di-protected amines also include pyrroles and the like, 2,2,5,5-tetramethyl-[1,2,5]azadisilolidine and the like, and azide.

[0097] Protected aldehydes are well known in the art and include those described in detail in Greene (1999). Suitable protected aldehydes further include, but are not limited to, acyclic acetals, cyclic acetals, hydrazones, imines, and the like. Examples of such groups include dimethyl acetal, diethyl acetal, diisopropyl acetal, dibenzyl acetal, bis(2-nitrobenzyl) acetal, 1,3-dioxanes, 1,3-dioxolanes, semicarbazones, and derivatives thereof.

[0098] Protected carboxylic acids are well known in the art and include those described in detail in Greene (1999). Suitable protected carboxylic acids further include, but are not limited to, optionally substituted C_{1-6} aliphatic esters, optionally substituted aryl esters, silyl esters, activated esters, amides, hydrazides, and the like. Examples of such ester groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, benzyl, and phenyl ester, wherein each group is optionally substituted. Additional suitable protected carboxylic acids include oxazolines and ortho esters.

[0099] Protected thiols are well known in the art and include those described in detail in Greene (1999). Suitable protected thiols further include, but are not limited to, disulfides, thioethers, silyl thioethers, thioesters, thiocarbonates, and thiocarbamates, and the like. Examples of such groups

include, but are not limited to, alkyl thioethers, benzyl and substituted benzyl thioethers, triphenylmethyl thioethers, and trichloroethoxycarbonyl thioester, to name but a few.

[0100] ***Protein***: The term "protein" as used herein refers to one or more polypeptides that function as a discrete unit. If a single polypeptide is the discrete functioning unit and does not require permanent or temporary physical association with other polypeptides in order to form the discrete functioning unit, the terms "polypeptide" and "protein" may be used interchangeably. If the discrete functional unit is comprised of more than one polypeptide that physically associate with one another, the term "protein" may be used to refer to the multiple polypeptides that are physically associated and function together as the discrete unit. In some embodiments, proteins may include moieties other than amino acids (*e.g.*, may be glycoproteins, proteoglycans, etc.) and/or may be otherwise processed or modified. Those of ordinary skill in the art will appreciate that in some embodiments the term "protein" may refer to a complete polypeptide chain as produced by a cell (e.g., with or without a signal sequence), and/or to a form that is active within a cell (e.g., a truncated or complexed form). In some embodiments where a protein is comprised of multiple polypeptide chains, such chains may be covalently associated with one another, for example by one or more disulfide bonds, or may be associated by other means.

[0101] ***Pure***: As used herein, an agent or entity is "pure" if it is substantially free of other components. For example, a preparation that contains more than about 90% of a particular agent or entity is typically considered to be a pure preparation. In some embodiments, an agent or entity is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% pure.

[0102] ***Reference:*** As used herein describes a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence or value of interest is compared with a reference or control agent, animal, individual, population, sample, sequence or value. In some embodiments, a reference or control is tested and/or determined substantially simultaneously with the testing or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Typically, as would be understood by those skilled in the art, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. Those skilled in the art will appreciate when sufficient similarities are present to justify reliance on and/or comparison to a particular possible reference or control.

[0103] ***Sample:*** As used herein, the term "sample" typically refers to an aliquot of material obtained or derived from a source of interest, as described herein. In some embodiments, a source of interest is a biological or environmental source. In some embodiments, a source of interest may be or comprise a cell or an organism, such as a microbe, a plant, or an animal (e.g., a human). In some embodiments, a source of interest is or comprises biological tissue or fluid. In some embodiments, a biological tissue or fluid may be or comprise amniotic fluid, aqueous humor, ascites, bile, bone marrow, blood, breast milk, cerebrospinal fluid, cerumen, chyle, chime, ejaculate, endolymph, exudate, feces, gastric acid, gastric juice, lymph, mucus, pericardial fluid, perilymph, peritoneal fluid, pleural fluid, pus, rheum, saliva, sebum, semen, serum, smegma, sputum, synovial fluid, sweat, tears, urine, vaginal secreations, vitreous humour, vomit, and/or combinations or component(s) thereof. In some embodiments, a biological fluid may be or comprise an intracellular fluid, an extracellular fluid, an intravascular fluid (blood plasma), an interstitial fluid, a lymphatic fluid, and/or a transcellular fluid. In some embodiments, a biological fluid may be or comprise a plant exudate. In some embodiments, a biological tissue or sample may be obtained, for example, by aspirate, biopsy (e.g., fine needle or tissue biopsy), swab (e.g., oral, nasal, skin, or vaginal swab), scraping, surgery, washing or lavage (e.g., brocheoalvealar, ductal, nasal, ocular, oral, uterine, vaginal, or other washing or lavage). In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, a sample is a "primary sample" obtained directly from a source of interest by any appropriate means. In some embodiments, as will be clear from context, the term "sample" refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a "processed sample" may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to one or more techniques such as amplification or reverse transcription of nucleic acid, isolation and/or purification of certain components, *etc.*

[0104] ***Stable nanoparticle composition:*** The term "stable," when applied to compositions herein, means that the compositions maintain one or more aspects of their physical structure (*e.g.*, size range and/or distribution of particles) over a period of time. In some embodiments, a stable nanoparticle composition is one for which the average particle size, the maximum particle size, the range of particle sizes, and/or the distribution of particle sizes (*i.e.*, the percentage of particles

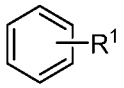
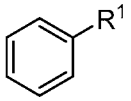
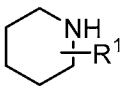
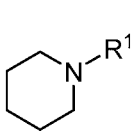
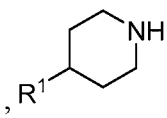
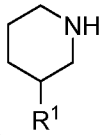
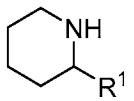
above a designated size and/or outside a designated range of sizes) is maintained for a period of time under specified conditions. In some embodiments, a stable provided composition is one for which a biologically relevant activity is maintained for a period of time. In some embodiments, the period of time is at least about one hour; in some embodiments the period of time is about 5 hours, about 10 hours, about one (1) day, about one (1) week, about two (2) weeks, about one (1) month, about two (2) months, about three (3) months, about four (4) months, about five (5) months, about six (6) months, about eight (8) months, about ten (10) months, about twelve (12) months, about twenty-four (24) months, about thirty-six (36) months, or longer. In some embodiments, the period of time is within the range of about one (1) day to about twenty-four (24) months, about two (2) weeks to about twelve (12) months, about two (2) months to about five (5) months, etc. For example, if a population of nanoparticles is subjected to prolonged storage, temperature changes, and/or pH changes, and a majority of the nanoparticles in the composition maintain a diameter within a stated range, the nanoparticle composition is stable. In some embodiments, a stable composition is stable at ambient conditions. In some embodiments, a stable composition is stable under biologic conditions (i.e. 37 ºC in phosphate buffered saline).

[0105] ***Sterolyl:*** The term "sterolyl," as used herein, refers to a 17-membered fused polycyclic ring moiety that is either saturated or partially unsaturated and substituted with at least one hydroxyl group, and has a single point of attachment to the rest of the molecule at any substitutable carbon or oxygen atom. In some embodiments, a sterolyl group is a cholesterolyl group, or a variant or derivative thereof. In some embodiments, a cholesterolyl group is modified. In some embodiments, a cholesterolyl group is an oxidized cholesterolyl group (*e.g.,* oxidized on the beta-ring structure or on the hydrocarbon tail structure). In some embodiments, a cholesterolyl group is an esterified cholesterolyl group. In some embodiments, a sterolyl group is a phytosterolyl group. Exemplary sterolyl groups include but are not limited to 25-hydroxycholesterolyl (25-OH), 20α-hydroxycholesterolyl (20α-OH), 27-hydroxycholesterolyl, 6-keto-5α-hydroxycholesterolyl, 7-ketocholesterolyl, 7β-hydroxycholesterolyl, 7α-hydroxycholesterolyl, 7β-25-dihydroxycholesterolyl, beta-sitosterolyl, stigmasterolyl, brassicasterolyl, and campesterolyl.

[0106] ***Subject:*** As used herein, the term "subject" refers an organism, typically a mammal (e.g., a human, in some embodiments including prenatal human forms). In some embodiments, a subject is suffering from a relevant disease, disorder or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or

more symptoms or characteristics of a disease, disorder or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0107] ***Substantially:*** As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0108] ***Substituted or optionally substituted***: As described herein, compounds of this disclosure may contain optionally substituted and/or substituted moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. "Substituted" applies to one or more hydrogens that are either explicit or implicit from the structure (e.g.,  refers to at least  ; and  refers to at least  ,  ,  , or ). Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein. Groups described as being "substituted" preferably have between 1 and 4 substituents,

more preferably 1 or 2 substituents. Groups described as being "optionally substituted" may be unsubstituted or be "substituted" as described above.

[0109] Suitable monovalent substituents include halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$–, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-SiR^\circ_3$; $-OSiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0110] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, –CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}C(O)NH_2$, $-(CH_2)_{0-2}C(O)NHR^\bullet$, $-(CH_2)_{0-2}C(O)NR^\bullet_2$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more

halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0111] Suitable divalent substituents include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0112] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, –O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0113] In some embodiments, suitable substituents on a substitutable nitrogen include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0114] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, –O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or –

NO_2, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0115] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0116] ***Susceptible to***: An individual who is "susceptible to" a disease, disorder, or condition is at risk for developing the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition does not display any symptoms of the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition has not been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition is an individual who has been exposed to conditions associated with development of the disease, disorder, or condition. In some embodiments, a risk of developing a disease, disorder, and/or condition is a population-based risk (e.g., family members of individuals suffering from the disease, disorder, or condition).

[0117] ***Systemic:*** The phrases "systemic administration," "administered systemically," "peripheral administration," and "administered peripherally" as used herein have their art-understood meaning referring to administration of a compound or composition such that it enters the recipient's system.

[0118] ***Tautomeric forms:*** The phrase "tautomeric forms," as used herein, is used to describe different isomeric forms of organic compounds that are capable of facile interconversion. Tautomers may be characterized by the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. In some embodiments, tautomers may result from prototropic tautomerism (*i.e.*, the relocation of a proton). In some embodiments, tautomers may result from valence tautomerism (*i.e.*, the rapid reorganization of bonding electrons). All such tautomeric forms are intended to be included within the scope of the present disclosure. In some embodiments, tautomeric forms of a compound exist in mobile equilibrium with each other, so that attempts to prepare the separate substances results in the formation of a mixture. In some embodiments, tautomeric forms of a compound are separable and isolatable compounds. In some embodiments of the disclosure, chemical compositions may be provided that are or include pure preparations of a single tautomeric form of a compound. In some embodiments, chemical compositions may be provided as mixtures of two or more tautomeric forms of a compound. In certain embodiments, such mixtures contain equal amounts of different tautomeric forms; in certain embodiments, such mixtures contain different amounts of at least two different tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain all tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain less than all tautomeric forms of a compound. In some embodiments of the disclosure, chemical compositions may contain one or more tautomeric forms of a compound in amounts that vary over time as a result of interconversion. In some embodiments of the disclosure, the tautomerism is keto-enol tautomerism. One of skill in the chemical arts would recognize that a keto-enol tautomer can be "trapped" (*i.e.*, chemically modified such that it remains in the "enol" form) using any suitable reagent known in the chemical arts in to provide an enol derivative that may subsequently be isolated using one or more suitable techniques known in the art. Unless otherwise indicated, the present disclosure encompasses all tautomeric forms of relevant compounds, whether in pure form or in admixture with one another.

[0119] ***Therapeutic agent:*** As used herein, the phrase "therapeutic agent" refers to an agent that, when administered to a subject, has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect. In some embodiments, a therapeutic agent is any substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition.

[0120] ***Therapeutically effective amount:*** As used herein, the term "therapeutically effective amount" means an amount of a substance (*e.g.*, a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, inhibit, alleviate, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, *etc.* For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount. The precise dosage will vary according to a variety of factors such as subject-dependent variables (e.g., age, immune system health, etc.), the disease, and the treatment being effected.

[0121] ***"Tissue" and/or "organ":*** As used herein, the term, "tissue" and/or "organ" refers to viable cellular materials in an aggregate form, e.g., small portions of an organ, as well as dispersed cells, e.g., cells dispersed, isolated and/or grown from muscle, heart muscle, liver or kidney, including bone marrow cells and progeny cells, blood born stem cells and progeny, and the various other blood elements, unless otherwise specified. In some embodiments, the tissue and/or organ refers to kidney, heart liver, stomach, spleen, pancreas, lung, brain, eye, intestines, bladder, skin or dermal tissue, blood vessel, veins, arteries, heart valves, sperm, and oocyte(s). As used herein, the term "organ" encompasses both solid organs, e.g., kidney, heart, liver, lung, as well as functional parts of organs, e.g., segments of skin, sections of artery, veins, transplantable lobes of a liver, kidney, lung, and the like.

[0122] ***Treatment***: As used herein, the term "treatment" (also "treat" or "treating") refers to administration of a therapy that partially or completely alleviates, ameliorates, relives, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or

condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition. Thus, in some embodiments, treatment may be prophylactic; in some embodiments, treatment may be therapeutic.

Detailed Description of Certain Embodiments

[0123] The present disclosure describes that selection and combination of one or more of the components of the described compositions, preparations, nanoparticles, and/or nanomaterials impact functional activity of lipid nanoparticles such as desired tropisms, stabilization, and drug delivery efficacy. Among other things, the present invention provides compositions, preparations, nanoparticles, and/or nanomaterials for delivery of therapeutic and/or prophylactic agents to target cells and/or tissue. For example, the present disclosure describes lipid compounds for use in compositions, preparations, nanoparticles, and/or nanomaterials. In some embodiments, compositions, preparations, and/or nanomaterials comprise LNPs carrying cargo to designated target cells, tissue, and/or organs.

I. Lipid nanoparticles (LNPs)

[0124] The present invention provides for compositions, preparations, and/or nanomaterials that comprise lipid nanoparticles. In some embodiments, lipid nanoparticles comprise one or more components. In some embodiments, lipid nanoparticles comprise one or more components such as compounds, ionizable lipids, sterols, conjugate-linker lipids, and phospholipids. Among other things, the present disclosure describes that selection and combination of one or more of the components as described herein impacts characteristics of lipid nanoparticles such as diameter, pKa, stabilization, and ionizability.

[0125] Among other things, the present disclosure describes that selection and combination of one or more of the components as described herein impacts functional activity of lipid nanoparticles such as tropism, stabilization, and drug delivery efficacy. For example, the present disclosure

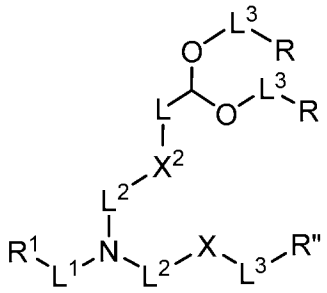
describes that a combination of components may better suit delivery of siRNA. As another example, the present disclosure describes that a combination of components may better suit delivery of mRNA. As another example, the present disclosure describes that a combination of components may better suit delivery of DNA.

[0126] In some embodiments, lipid nanoparticles comprise one or more compounds as described herein. In some embodiments, lipid nanoparticles comprise one or more ionizable lipids as described herein. In some embodiments, lipid nanoparticles comprise one or more sterols as described herein. In some embodiments, lipid nanoparticles comprise one or more conjugate-linker lipids as described herein. In some embodiments, lipid nanoparticles comprise one or more phospholipids as described herein.

A. Compounds

[0127] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more compounds as described herein.

[0128] In some embodiments, the present disclosure provides a compound of Formula A':



A'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

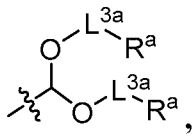
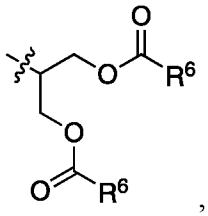
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

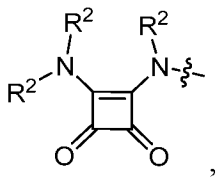
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each of R and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl

each of L^3 and L^{3a} is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen,

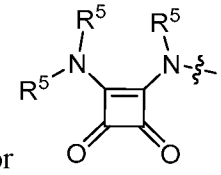
oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

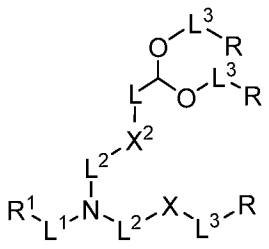
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0129] In some embodiments, the present disclosure provides a compound of Formula A:



A

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

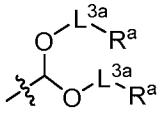
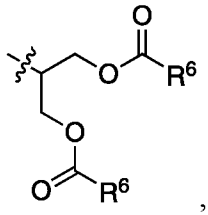
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

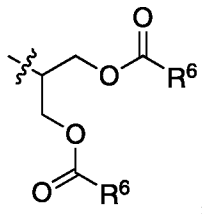
each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

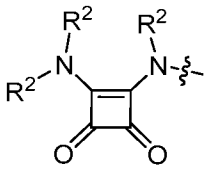
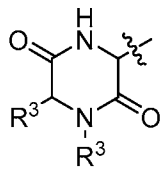
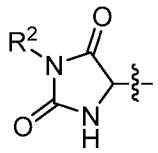
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each L^{3a} is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$,

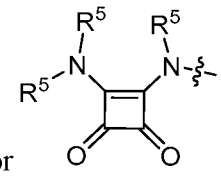
$-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

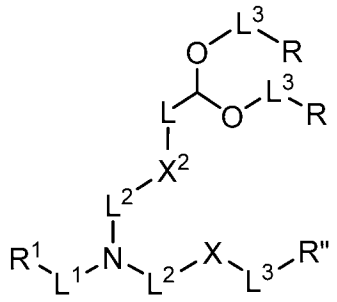
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0130] In some embodiments, the present disclosure provides a compound of Formula I":



I"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

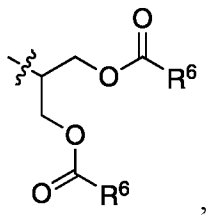
each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

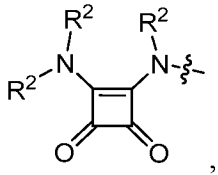
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

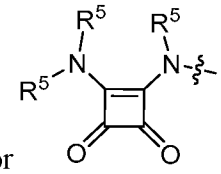
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

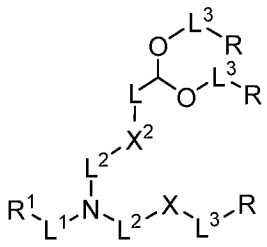
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0131] In some embodiments, the present disclosure provides a compound of Formula I':



I'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

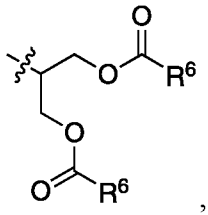
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

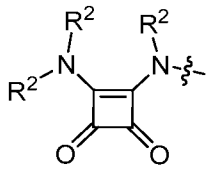
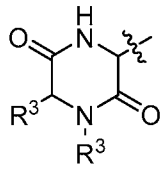
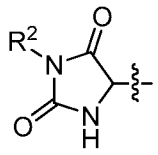
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

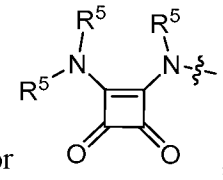
R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

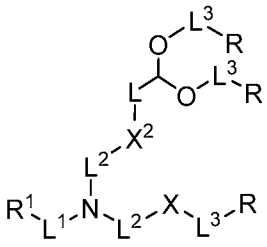
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0132] In some embodiments, the present disclosure provides a compound of Formula I:



I

or its N-oxide, or a salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

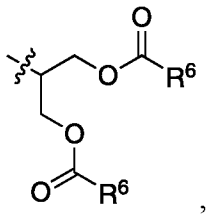
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

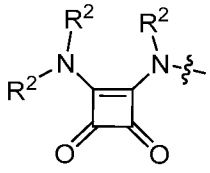
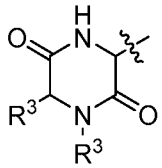
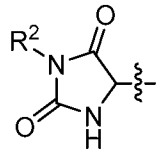
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, a 3- to 7-membered cycloaliphatic ring, a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  ,  , or ;

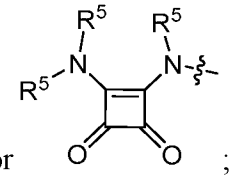
each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, a 3- to 7-membered cycloaliphatic ring, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$,



$-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or ;

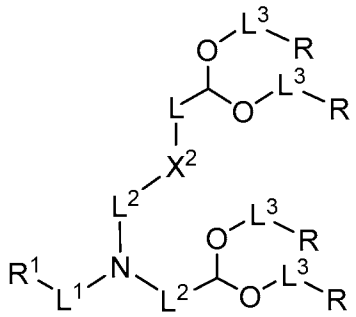
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0133] In some embodiments, the present disclosure provides a compound of Formula II":



II"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

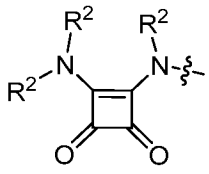
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$;

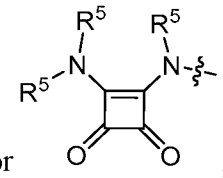
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

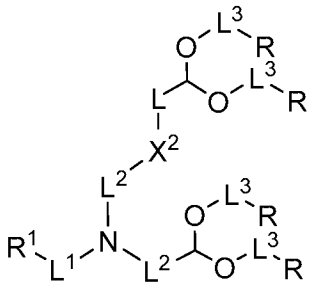
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0134] In some embodiments, the present disclosure provides a compound of Formula II':



II'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

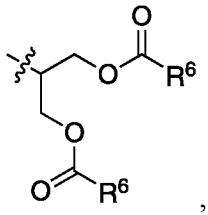
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

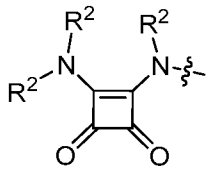
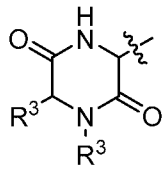
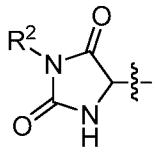
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

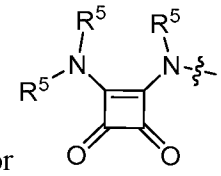
R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

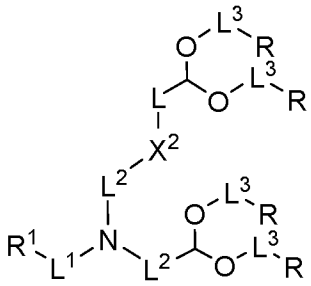
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0135] In some embodiments, the present disclosure provides a compound of Formula II:



II

or its N-oxide, or a salt thereof, wherein

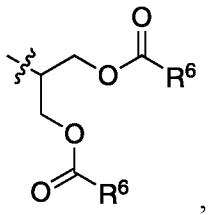
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

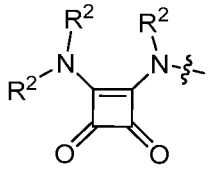
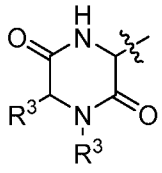
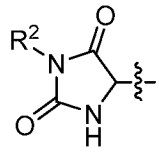
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

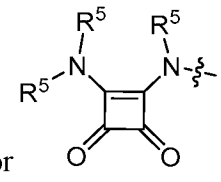
each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, a 3- to 7-membered cycloaliphatic ring, a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  ,  ; each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, a 3- to 7-membered cycloaliphatic ring, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

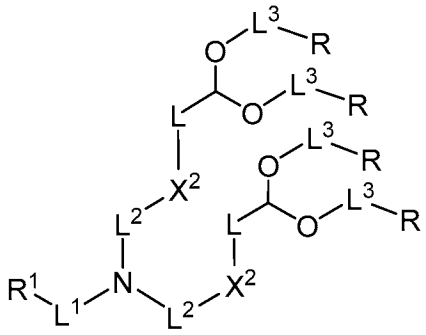
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0136] In some embodiments, the present disclosure provides a compound of Formula III':



III'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

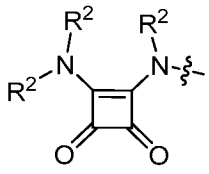
each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

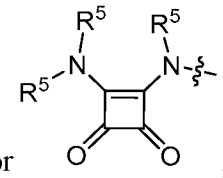
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

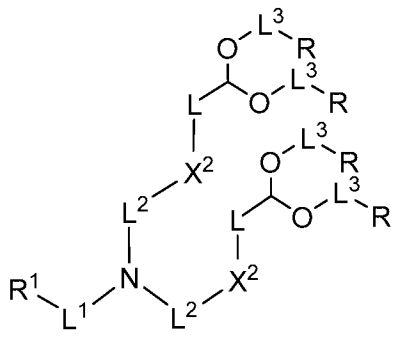
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

[0137] In some embodiments, the present disclosure provides a compound of Formula III:



III

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

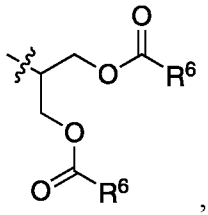
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

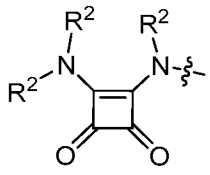
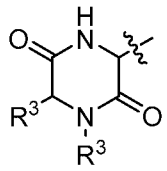
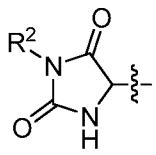
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

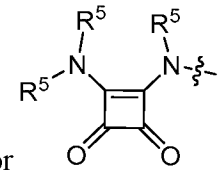
R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

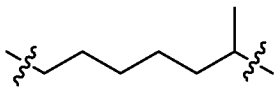
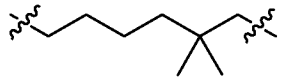
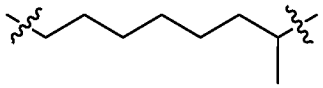
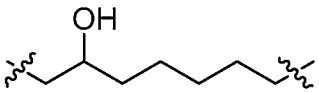
[0138] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl. In some embodiments, L^1 is absent, C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, L^1 is absent, C_{1-4} alkylenyl, or C_{2-4} heteroalkylenyl. In some embodiments, L^1 is absent. In some embodiments, L^1 is C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl. In some embodiments, L^1 is C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, L^1 is C_{1-5} alkylenyl. In some embodiments, L^1 is C_{2-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, L^1 is C_{2-5} alkylenyl. In some embodiments, L^1 is C_{2-5} heteroalkylenyl. In some embodiments, L^1 is C_{1-4} alkylenyl, or C_{2-4} heteroalkylenyl. In some embodiments, L^1 is C_{1-4} alkylenyl. In some embodiments, L^1 is C_{2-4} heteroalkylenyl. In some embodiments, L^1 is C_1 alkylenyl. In some embodiments, L^1 is C_2 alkylenyl. In some embodiments, L^1 is C_3 alkylenyl. In some embodiments, L^1 is C_4 alkylenyl. In some embodiments, L^1 is C_5 alkylenyl. In some embodiments, L^1 is C_6 alkylenyl. In some embodiments, L^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$

, or -$CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2-, -CH_2CH_2-, or -$CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2CH_2- or -$CH_2CH_2CH_2$-. In some embodiments, L^1 is -CH_2-. In some embodiments, L^1 is -CH_2CH_2-. In some embodiments, L^1 is -$CH_2CH_2CH_2$-. In some embodiments, L^1 is -$CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is -$CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, L^1 is C_2 heteroalkylenyl. In some embodiments, L^1 is C_3 heteroalkylenyl. In some embodiments, L^1 is C_4 heteroalkylenyl. In some embodiments, L^1 is C_5 heteroalkylenyl. In some embodiments, L^1 is C_6 heteroalkylenyl. In some embodiments, L^1 is C_2 heteroalkylenyl comprising 1 heteroatom. In some embodiments, L^1 is C_3 heteroalkylenyl comprising 1 heteroatom. In some embodiments, L^1 is C_4 heteroalkylenyl comprising 1 heteroatom. In some embodiments, L^1 is C_5 heteroalkylenyl comprising 1-2 heteroatoms. In some embodiments, L^1 is C_6 heteroalkylenyl comprising 1-2 heteroatoms. In some embodiments, L^1 is C_2 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, L^1 is C_3 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, L^1 is C_4 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, L^1 is -$CH_2OCH_2CH_2$-. In some embodiments, L^1 is C_5 heteroalkylenyl comprising 1-2 oxygen atoms. In some embodiments, L^1 is C_6 heteroalkylenyl comprising 1-2 oxygen atoms.

[0139] As described above, in some embodiments of any of Formulae A', I", II", and III', each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-12} alkylenyl, or optionally substituted C_{3-12} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-10} alkylenyl, or optionally substituted C_{3-10} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-9} alkylenyl, or optionally substituted C_{3-9} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-10} alkylenyl, or optionally substituted C_{5-10} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-9} alkylenyl, or optionally substituted C_{5-9} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{6-8} alkylenyl, or optionally substituted C_{6-8} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-8} alkylenyl, or optionally

substituted C_{5-8} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-7} alkylenyl, or optionally substituted C_{5-7} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{4-8} alkylenyl, or optionally substituted C_{4-8} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-15} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{3-15} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-12} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{3-12} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-10} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{3-10} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{2-9} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{3-9} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-10} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-10} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-9} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-9} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{6-8} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{6-8} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-8} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-8} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-7} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{5-7} heteroalkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{4-8} alkylenyl. In some embodiments, each L^2 is independently optionally substituted C_{4-8} heteroalkylenyl.

[0140] In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with –R° or –OR°. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with –R°. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with –OR°. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one or two –R°s. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one –R°. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with two –R°s. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one –OR°. In some

embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one or two C_{1-6} aliphatics. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one C_{1-6} aliphatic. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with two C_{1-6} aliphatics. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one or two methyls. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one methyl. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with two methyls. In some embodiments, each L^2 is independently C_{6-8} alkylenyl substituted with one –OH. In some embodiments, each L^2 is independently  ,  , or  . In some embodiments, one L^2 is C_{6-8} alkylenyl substituted with one –OR°, and the other L^2 is C_{6-8} alkylenyl. In some embodiments, one L^2 is C_{6-8} alkylenyl substituted with one –OH, and the other L^2 is C_{6-8} alkylenyl. In some embodiments, one L^2 is C_7 alkylenyl substituted with one –OR°, and the other L^2 is C_6 alkylenyl. In some embodiments, one L^2 is C_7 alkylenyl substituted with one –OH, and the other L^2 is C_6 alkylenyl. In some embodiments, one L^2 is  , and the other L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2$-.

[0141] In some embodiments of any of Formulae A', I", II", and III', each L^2 is independently C_{2-15} alkylenyl, or C_{3-15} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-12} alkylenyl, or C_{3-12} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-15} alkylenyl. In some embodiments, each L^2 is independently C_{3-15} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-12} alkylenyl. In some embodiments, each L^2 is independently C_{3-12} heteroalkylenyl.

[0142] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-9} alkylenyl, or C_{3-9} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-10} alkylenyl, or C_{5-10} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-9} alkylenyl, or C_{5-9} heteroalkylenyl. In some embodiments, each L^2 is independently C_{6-8} alkylenyl, or C_{6-8} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-8} alkylenyl, or C_{5-8} heteroalkylenyl. In some embodiments, each L^2 is

independently C_{4-8} alkylenyl, or C_{4-8} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-10} alkylenyl. In some embodiments, each L^2 is independently C_{3-10} heteroalkylenyl. In some embodiments, each L^2 is independently C_{2-9} alkylenyl. In some embodiments, each L^2 is independently C_{3-9} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-10} alkylenyl. In some embodiments, each L^2 is independently C_{5-10} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-9} alkylenyl. In some embodiments, each L^2 is independently C_{5-9} heteroalkylenyl. In some embodiments, each L^2 is independently C_{6-8} alkylenyl. In some embodiments, each L^2 is independently C_{6-8} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-8} alkylenyl. In some embodiments, each L^2 is independently C_{5-8} heteroalkylenyl. In some embodiments, each L^2 is independently C_{4-8} alkylenyl. In some embodiments, each L^2 is independently C_{4-8} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-7} alkylenyl, or C_{5-7} heteroalkylenyl. In some embodiments, each L^2 is independently C_{5-7} alkylenyl. In some embodiments, each L^2 is independently C_{5-7} heteroalkylenyl.

[0143] In some embodiments, each L^2 is independently C_2 alkylenyl. In some embodiments, each L^2 is independently C_3 alkylenyl. In some embodiments, each L^2 is independently C_4 alkylenyl. In some embodiments, each L^2 is independently C_5 alkylenyl. In some embodiments, each L^2 is independently C_6 alkylenyl. In some embodiments, each L^2 is independently C_7 alkylenyl. In some embodiments, each L^2 is independently C_8 alkylenyl. In some embodiments, each L^2 is independently C_9 alkylenyl. In some embodiments, each L^2 is independently C_{10} alkylenyl. In some embodiments, each L^2 is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -

$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is independently -$CH_2CH_2CH_2CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^2 is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, the two L^2 groups are the same. In some embodiments, the two L^2 groups are the same and are selected from the group consisting of -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, the two L^2 groups are the same and are selected from the group consisting of -$CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, the two L^2 groups are the same and are selected from the group consisting of -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, the two L^2 groups are the same and are selected from the group consisting of -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, the two L^2 groups are the same and are selected from the group consisting of -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, and -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments,

the two L^2 groups are the same and are selected from the group consisting of $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, the two L^2 groups are different. In some embodiments, one L^2 is $-CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, one L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, and the other L^2 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$.

[0144] In some embodiments, each L^2 is independently C_4 heteroalkylenyl. In some embodiments, each L^2 is independently C_5 heteroalkylenyl. In some embodiments, each L^2 is independently C_6 heteroalkylenyl. In some embodiments, each L^2 is independently C_7 heteroalkylenyl. In some embodiments, each L^2 is independently C_8 heteroalkylenyl. In some embodiments, each L^2 is independently C_4 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^2 is independently C_5 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^2 is independently C_6 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L^2 is independently C_7 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L^2 is independently C_8 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L^2 is independently C_4 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^2 is independently C_5 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^2 is independently C_6 heteroalkylenyl comprising 1 or 2 oxygen atoms. In some embodiments, each L^2 is independently C_7 heteroalkylenyl comprising 1 or 2 oxygen

atoms. In some embodiments, each L^2 is independently C_8 heteroalkylenyl comprising 1 or 2 oxygen atoms.

[0145] As described above, in some embodiments of any of Formulae A', A, I", I', I, II', II', II, III', and III, each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl. In some embodiments, each L is independently C_{1-8} alkylenyl, or C_{2-8} heteroalkylenyl. In some embodiments, each L is independently C_{1-10} alkylenyl. In some embodiments, each L is independently C_{2-10} heteroalkylenyl. In some embodiments, each L is independently C_{1-8} alkylenyl. In some embodiments, each L is independently C_{2-8} heteroalkylenyl. In some embodiments, each L is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, each L is independently C_{1-5} alkylenyl. In some embodiments, each L is independently C_{2-5} heteroalkylenyl. In some embodiments, each L is independently C_{1-4} alkylenyl, or C_{2-4} heteroalkylenyl. In some embodiments, each L is independently C_{1-4} alkylenyl. In some embodiments, each L is independently C_{2-4} heteroalkylenyl. In some embodiments, each L is independently C_1 alkylenyl. In some embodiments, each L is independently C_2 alkylenyl. In some embodiments, each L is independently C_3 alkylenyl. In some embodiments, each L is independently C_4 alkylenyl. In some embodiments, each L is independently C_5 alkylenyl. In some embodiments, each L is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L is independently -CH_2CH_2- or -$CH_2CH_2CH_2$-. In some embodiments, each L is -CH_2-. In some embodiments, each L is -CH_2CH_2-. In some embodiments, each L is -$CH_2CH_2CH_2$-. In some embodiments, each L is -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L is -$CH_2CH_2CH_2$-. In some embodiments, each L is -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, one L is -CH_2CH_2-, and the other L is -$CH_2CH_2CH_2$-. In some embodiments, one L is -CH_2CH_2-, and the other L is -$CH_2CH_2CH_2CH_2$-. In some embodiments, one L is -$CH_2CH_2CH_2$-, and the other L is -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L is independently C_2 heteroalkylenyl. In some embodiments, each L is independently C_3 heteroalkylenyl. In some embodiments, each L is independently C_4 heteroalkylenyl. In some embodiments, each L is independently C_5 heteroalkylenyl. In some embodiments, each L is independently C_2 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L is independently C_3 heteroalkylenyl comprising 1 heteroatom. In some

embodiments, each L is independently C_4 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L is independently C_2 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L is independently C_3 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L is independently C_4 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L is independently C_5 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L is independently C_5 heteroalkylenyl comprising 2 oxygen atoms.

[0146] In some embodiments, each L is independently C_{6-10} alkylenyl, or C_{6-10} heteroalkylenyl. In some embodiments, each L is independently C_{6-10} alkylenyl. In some embodiments, each L is independently C_{6-10} heteroalkylenyl. In some embodiments, each L is independently C_6 alkylenyl. In some embodiments, each L is independently C_7 alkylenyl. In some embodiments, each L is independently C_8 alkylenyl. In some embodiments, each L is independently C_9 alkylenyl. In some embodiments, each L is independently C_{10} alkylenyl. In some embodiments, each L is independently $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L is $-CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2-. In some embodiments, each L is independently C_6 heteroalkylenyl. In some embodiments, each L is independently C_7 heteroalkylenyl. In some embodiments, each L is independently C_8 heteroalkylenyl. In some embodiments, each L is independently C_9 heteroalkylenyl. In some embodiments, each L is independently C_{10} heteroalkylenyl. In some embodiments, each L is independently C_6 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L is independently C_7 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L is independently C_8 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L is independently C_9 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L is independently C_{10} heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L is independently C_6 heteroalkylenyl comprising 1 or 2 oxygen atoms. In some embodiments, each L is independently C_7 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L is independently C_8 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L is independently C_9 heteroalkylenyl

comprising 1-3 oxygen atoms. In some embodiments, each L is independently C_{10} heteroalkylenyl comprising 1-3 oxygen atoms.

[0147] As described above, in some embodiments of any of Formulae A', I", II", and III', each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-8} alkylenyl, or optionally substituted C_{2-8} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-10} alkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-8} alkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{2-8} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-5} alkylenyl, or optionally substituted C_{2-5} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-5} alkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{2-5} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-4} alkylenyl, or optionally substituted C_{2-4} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{1-4} alkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{2-4} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{6-10} alkylenyl, or optionally substituted C_{6-10} heteroalkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{6-10} alkylenyl. In some embodiments, each L^3 is independently optionally substituted C_{6-10} heteroalkylenyl.

[0148] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is absent. In some embodiments, each L^3 is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-8} alkylenyl, or C_{2-8} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-10} alkylenyl. In some embodiments, each L^3 is independently C_{2-10} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-8} alkylenyl. In some embodiments, each L^3 is independently C_{2-8} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-5} alkylenyl. In some embodiments, each L^3 is

independently C_{2-5} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-4} alkylenyl, or C_{2-4} heteroalkylenyl. In some embodiments, each L^3 is independently C_{1-4} alkylenyl. In some embodiments, each L^3 is independently C_{2-4} heteroalkylenyl. In some embodiments, each L^3 is independently C_1 alkylenyl. In some embodiments, each L^3 is independently C_2 alkylenyl. In some embodiments, each L^3 is independently C_3 alkylenyl. In some embodiments, each L^3 is independently C_4 alkylenyl. In some embodiments, each L^3 is independently C_5 alkylenyl. In some embodiments, each L^3 is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently C_2 heteroalkylenyl. In some embodiments, each L^3 is independently C_3 heteroalkylenyl. In some embodiments, each L^3 is independently C_4 heteroalkylenyl. In some embodiments, each L^3 is independently C_2 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^3 is independently C_3 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^3 is independently C_4 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^3 is independently C_2 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^3 is independently C_3 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^3 is independently C_4 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^3 is independently C_5 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^3 is independently C_5 heteroalkylenyl comprising 2 oxygen atoms.

[0149] In some embodiments, each L^3 is independently C_{6-10} alkylenyl, or C_{6-10} heteroalkylenyl. In some embodiments, each L^3 is independently C_{6-10} alkylenyl. In some embodiments, each L^3 is independently C_{6-10} heteroalkylenyl. In some embodiments, each L^3 is independently C_6 alkylenyl. In some embodiments, each L^3 is independently C_7 alkylenyl. In some embodiments, each L^3 is independently C_8 alkylenyl. In some embodiments, each L^3 is independently C_9 alkylenyl. In some embodiments, each L^3 is independently C_{10} alkylenyl. In some embodiments, each L^3 is independently is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$,

$-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is independently is $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^3 is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2-. In some embodiments, each L^3 is independently C_6 heteroalkylenyl. In some embodiments, each L^3 is independently C_7 heteroalkylenyl. In some embodiments, each L^3 is independently C_8 heteroalkylenyl. In some embodiments, each L^3 is independently C_9 heteroalkylenyl. In some embodiments, each L^3 is independently C_{10} heteroalkylenyl. In some embodiments, each L^3 is independently C_6 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L^3 is independently C_7 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^3 is independently C_8 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^3 is independently C_9 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^3 is independently C_{10} heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^3 is independently C_6 heteroalkylenyl comprising 1 or 2 oxygen atoms. In some embodiments, each L^3 is independently C_7 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^3 is independently C_8 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^3 is independently C_9 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^3 is independently C_{10} heteroalkylenyl comprising 1-3 oxygen atoms.

[0150] As described above, in some embodiments of Formulae A', each L^{3a} is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-8} alkylenyl, or optionally substituted C_{2-8} heteroalkylenyl. In some embodiments,

each L^{3a} is independently optionally substituted C_{1-10} alkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-8} alkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{2-8} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-5} alkylenyl, or optionally substituted C_{2-5} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-5} alkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{2-5} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-4} alkylenyl, or optionally substituted C_{2-4} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{1-4} alkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{2-4} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{6-10} alkylenyl, or optionally substituted C_{6-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{6-10} alkylenyl. In some embodiments, each L^{3a} is independently optionally substituted C_{6-10} heteroalkylenyl.

[0151] in some embodiments of Formula A' or A, each L^{3a} is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is absent. In some embodiments, each L^{3a} is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-8} alkylenyl, or C_{2-8} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-10} alkylenyl. In some embodiments, each L^{3a} is independently C_{2-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-8} alkylenyl. In some embodiments, each L^{3a} is independently C_{2-8} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-5} alkylenyl. In some embodiments, each L^{3a} is independently C_{2-5} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-4} alkylenyl, or C_{2-4} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{1-4} alkylenyl. In some embodiments, each L^{3a} is independently C_{2-4} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_1 alkylenyl. In some embodiments, each L^{3a} is independently C_2 alkylenyl. In some embodiments, each L^{3a} is independently C_3 alkylenyl. In some embodiments, each L^{3a} is independently C_4 alkylenyl. In some embodiments, each L^{3a} is independently C_5 alkylenyl. In some embodiments, each L^{3a} is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^{3a} is independently

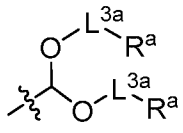
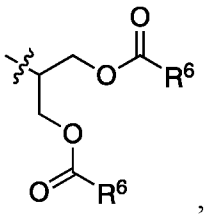
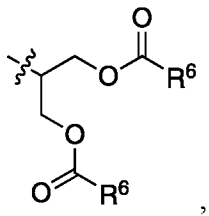
-CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently -CH_2CH_2- or -$CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is -CH_2-. In some embodiments, each L^{3a} is -CH_2CH_2-. In some embodiments, each L^{3a} is -$CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is -$CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is -$CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently C_2 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_3 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_4 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_2 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^{3a} is independently C_3 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^{3a} is independently C_4 heteroalkylenyl comprising 1 heteroatom. In some embodiments, each L^{3a} is independently C_2 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^{3a} is independently C_3 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^{3a} is independently C_4 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^{3a} is independently C_5 heteroalkylenyl comprising 1 oxygen atom. In some embodiments, each L^{3a} is independently C_5 heteroalkylenyl comprising 2 oxygen atoms.

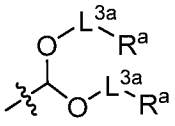
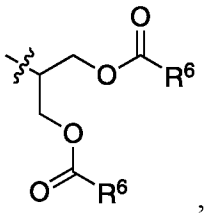
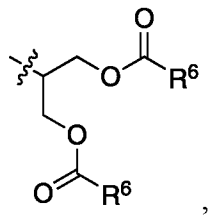
[0152] In some embodiments, each L^{3a} is independently C_{6-10} alkylenyl, or C_{6-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{6-10} alkylenyl. In some embodiments, each L^{3a} is independently C_{6-10} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_6 alkylenyl. In some embodiments, each L^{3a} is independently C_7 alkylenyl. In some embodiments, each L^{3a} is independently C_8 alkylenyl. In some embodiments, each L^{3a} is independently C_9 alkylenyl. In some embodiments, each L^{3a} is independently C_{10} alkylenyl. In some embodiments, each L^{3a} is independently is -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently is -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is independently is -$CH_2CH_2CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$- or -$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-. In some embodiments, each L^{3a} is

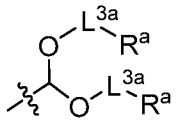
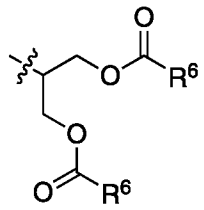
$-CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^{3a} is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^{3a} is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^{3a} is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$. In some embodiments, each L^{3a} is $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2 CH_2CH_2-$. In some embodiments, each L^{3a} is independently C_6 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_7 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_8 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_9 heteroalkylenyl. In some embodiments, each L^{3a} is independently C_{10} heteroalkylenyl. In some embodiments, each L^{3a} is independently C_6 heteroalkylenyl comprising 1 or 2 heteroatoms. In some embodiments, each L^{3a} is independently C_7 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^{3a} is independently C_8 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^{3a} is independently C_9 heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^{3a} is independently C_{10} heteroalkylenyl comprising 1-3 heteroatoms. In some embodiments, each L^{3a} is independently C_6 heteroalkylenyl comprising 1 or 2 oxygen atoms. In some embodiments, each L^{3a} is independently C_7 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^{3a} is independently C_8 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^{3a} is independently C_9 heteroalkylenyl comprising 1-3 oxygen atoms. In some embodiments, each L^{3a} is independently C_{10} heteroalkylenyl comprising 1-3 oxygen atoms.

[0153] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", I', II, III', and III, each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-. In some embodiments, each X^2 is independently -OC(O)-. In some embodiments, each X^2 is independently -C(O)O-. In some embodiments, each X^2 is independently -OC(O)O-.

[0154] As described above, in some embodiments of any of Formulae A', A, I", I', and I, X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-. In some embodiments, X is absent. In some embodiments, X is -OC(O)-, -C(O)O-, or -OC(O)O-. In some embodiments, X is -OC(O)-. In some embodiments, X is -C(O)O-. In some embodiments, X is -OC(O)O-.

[0155] As described above, in some embodiments of Formula A', R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl. In some embodiments of Formula I", R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

[0156] In some embodiments, R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl. In some embodiments, R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl.

[0157] In some embodiments, R" is hydrogen. In some embodiments, R" is  . In some embodiments, R" is  .

[0158] In some embodiments, R" is optionally substituted C_{6-20} aliphatic. In some embodiments, R" is optionally substituted C_{6-12} aliphatic. In some embodiments, R" is optionally substituted C_{8-11} aliphatic. In some embodiments, R" is optionally substituted C_{9-10} aliphatic. In some embodiments, R" is optionally substituted C_6 aliphatic. In some embodiments, R" is optionally substituted C_7 aliphatic. In some embodiments, R" is optionally substituted C_8 aliphatic. In some embodiments, R" is optionally substituted C_9 aliphatic. In some embodiments, R" is optionally substituted C_{10} aliphatic. In some embodiments, R" is optionally substituted C_{11} aliphatic. In some embodiments, R" is optionally substituted C_{12} aliphatic. In some embodiments, R" is optionally substituted C_{13-20} aliphatic. In some embodiments, R" is optionally substituted C_{15-20} aliphatic. In some embodiments, R" is optionally substituted C_{13} aliphatic. In some embodiments, R" is optionally substituted C_{14} aliphatic. In some embodiments, R" is optionally substituted C_{15} aliphatic. In some embodiments, R" is optionally substituted C_{16} aliphatic. In some embodiments, R" is optionally substituted C_{17} aliphatic. In some embodiments, R" is optionally substituted C_{18} aliphatic. In some embodiments, R" is optionally substituted C_{19} aliphatic. In some embodiments, R" is optionally substituted C_{20} aliphatic.

[0159] In some embodiments, R" is optionally substituted straight-chain C_{6-20} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{6-12} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{8-11} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{9-10} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_6 aliphatic. In some embodiments, R" is optionally substituted straight-chain C_7 aliphatic. In some embodiments, R" is optionally substituted straight-chain C_8 aliphatic. In some embodiments, R" is optionally substituted straight-chain C_9 aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{10} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{11} aliphatic. In some embodiments, R" is optionally substituted

straight-chain C_{12} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{13-20} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{15-20} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{13} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{14} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{15} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{16} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{17} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{18} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{19} aliphatic. In some embodiments, R" is optionally substituted straight-chain C_{20} aliphatic.

[0160] In some embodiments, R" is optionally substituted branched C_{6-20} aliphatic. In some embodiments, R" is optionally substituted branched C_{6-12} aliphatic. In some embodiments, R" is optionally substituted branched C_{8-11} aliphatic. In some embodiments, R" is optionally substituted branched C_{9-10} aliphatic. In some embodiments, R" is optionally substituted branched C_6 aliphatic. In some embodiments, R" is optionally substituted branched C_7 aliphatic. In some embodiments, R" is optionally substituted branched C_8 aliphatic. In some embodiments, R" is optionally substituted branched C_9 aliphatic. In some embodiments, R" is optionally substituted branched C_{10} aliphatic. In some embodiments, R" is optionally substituted branched C_{11} aliphatic. In some embodiments, R" is optionally substituted branched C_{12} aliphatic. In some embodiments, R" is optionally substituted branched C_{13-20} aliphatic. In some embodiments, R" is optionally substituted branched C_{15-20} aliphatic. In some embodiments, R" is optionally substituted branched C_{13} aliphatic. In some embodiments, R" is optionally substituted branched C_{14} aliphatic. In some embodiments, R" is optionally substituted branched C_{15} aliphatic. In some embodiments, R" is optionally substituted branched C_{16} aliphatic. In some embodiments, R" is optionally substituted branched C_{17} aliphatic. In some embodiments, R" is optionally substituted branched C_{18} aliphatic. In some embodiments, R" is optionally substituted branched C_{19} aliphatic. In some embodiments, R" is optionally substituted branched C_{20} aliphatic.

[0161] In some embodiments, R" is C_{6-20} aliphatic. In some embodiments, R" is C_{6-12} aliphatic. In some embodiments, R" is C_{8-11} aliphatic. In some embodiments, R" is C_{9-10} aliphatic. In some embodiments, R" is C_6 aliphatic. In some embodiments, R" is C_7 aliphatic. In some embodiments, R" is C_8 aliphatic. In some embodiments, R" is C_9 aliphatic. In some embodiments, R" is C_{10} aliphatic. In some embodiments, R" is C_{11} aliphatic. In some embodiments, R" is C_{12} aliphatic.

In some embodiments, R" is C_{13-20} aliphatic. In some embodiments, R" is C_{15-20} aliphatic. In some embodiments, R" is C_{13} aliphatic. In some embodiments, R" is C_{14} aliphatic. In some embodiments, R" is C_{15} aliphatic. In some embodiments, R" is C_{16} aliphatic. In some embodiments, R" is C_{17} aliphatic. In some embodiments, R" is C_{18} aliphatic. In some embodiments, R" is C_{19} aliphatic. In some embodiments, R" is C_{20} aliphatic.

[0162] In some embodiments, R" is straight-chain C_{6-20} aliphatic. In some embodiments, R" is straight-chain C_{6-12} aliphatic. In some embodiments, R" is straight-chain C_{8-11} aliphatic. In some embodiments, R" is straight-chain C_{9-10} aliphatic. In some embodiments, R" is straight-chain C_6 aliphatic. In some embodiments, R" is straight-chain C_7 aliphatic. In some embodiments, R" is straight-chain C_8 aliphatic. In some embodiments, R" is straight-chain C_9 aliphatic. In some embodiments, R" is straight-chain C_{10} aliphatic. In some embodiments, R" is straight-chain C_{11} aliphatic. In some embodiments, R" is straight-chain C_{12} aliphatic. In some embodiments, R" is straight-chain C_{13-20} aliphatic. In some embodiments, R" is straight-chain C_{15-20} aliphatic. In some embodiments, R" is straight-chain C_{13} aliphatic. In some embodiments, R" is straight-chain C_{14} aliphatic. In some embodiments, R" is straight-chain C_{15} aliphatic. In some embodiments, R" is straight-chain C_{16} aliphatic. In some embodiments, R" is straight-chain C_{17} aliphatic. In some embodiments, R" is straight-chain C_{18} aliphatic. In some embodiments, R" is straight-chain C_{19} aliphatic. In some embodiments, R" is straight-chain C_{20} aliphatic.

[0163] In some embodiments, R" is branched C_{6-20} aliphatic. In some embodiments, R" is branched C_{6-12} aliphatic. In some embodiments, R" is branched C_{8-11} aliphatic. In some embodiments, R" is branched C_{9-10} aliphatic. In some embodiments, R" is branched C_6 aliphatic. In some embodiments, R" is branched C_7 aliphatic. In some embodiments, R" is branched C_8 aliphatic. In some embodiments, R" is branched C_9 aliphatic. In some embodiments, R" is branched C_{10} aliphatic. In some embodiments, R" is branched C_{11} aliphatic. In some embodiments, R" is branched C_{12} aliphatic. In some embodiments, R" is branched C_{13-20} aliphatic. In some embodiments, R" is branched C_{15-20} aliphatic. In some embodiments, R" is branched C_{13} aliphatic. In some embodiments, R" is branched C_{14} aliphatic. In some embodiments, R" is branched C_{15} aliphatic. In some embodiments, R" is branched C_{16} aliphatic. In some embodiments, R" is branched C_{17} aliphatic. In some embodiments, R" is branched C_{18} aliphatic. In some embodiments, R" is branched C_{19} aliphatic. In some embodiments, R" is branched C_{20} aliphatic.

[0164] In some embodiments, R" is optionally substituted C_{6-20} alkyl. In some embodiments, R" is optionally substituted C_{6-12} alkyl. In some embodiments, R" is optionally substituted C_{8-11} alkyl. In some embodiments, R" is optionally substituted C_{9-10} alkyl. In some embodiments, R" is optionally substituted C_6 alkyl. In some embodiments, R" is optionally substituted C_7 alkyl. In some embodiments, R" is optionally substituted C_8 alkyl. In some embodiments, R" is optionally substituted C_9 alkyl. In some embodiments, R" is optionally substituted C_{10} alkyl. In some embodiments, R" is optionally substituted C_{11} alkyl. In some embodiments, R" is optionally substituted C_{12} alkyl. In some embodiments, R" is optionally substituted C_{13-20} alkyl. In some embodiments, R" is optionally substituted C_{15-20} alkyl. In some embodiments, R" is optionally substituted C_{13} alkyl. In some embodiments, R" is optionally substituted C_{14} alkyl. In some embodiments, R" is optionally substituted C_{15} alkyl. In some embodiments, R" is optionally substituted C_{16} alkyl. In some embodiments, R" is optionally substituted C_{17} alkyl. In some embodiments, R" is optionally substituted C_{18} alkyl. In some embodiments, R" is optionally substituted C_{19} alkyl. In some embodiments, R" is optionally substituted C_{20} alkyl.

[0165] In some embodiments, R" is C_{6-20} alkyl. In some embodiments, R" is C_{6-12} alkyl. In some embodiments, R" is C_{8-11} alkyl. In some embodiments, R" is C_{9-10} alkyl. In some embodiments, R" is C_6 alkyl. In some embodiments, R" is C_7 alkyl. In some embodiments, R" is C_8 alkyl. In some embodiments, R" is C_9 alkyl. In some embodiments, R" is C_{10} alkyl. In some embodiments, R" is C_{11} alkyl. In some embodiments, R" is C_{12} alkyl. In some embodiments, R" is C_{13-20} alkyl. In some embodiments, R" is C_{15-20} alkyl. In some embodiments, R" is C_{13} alkyl. In some embodiments, R" is C_{14} alkyl. In some embodiments, R" is C_{15} alkyl. In some embodiments, R" is C_{16} alkyl. In some embodiments, R" is C_{17} alkyl. In some embodiments, R" is C_{18} alkyl. In some embodiments, R" is C_{19} alkyl. In some embodiments, R" is C_{20} alkyl.

[0166] In some embodiments, R" is straight-chain C_{6-20} alkyl. In some embodiments, R" is straight-chain C_{6-12} alkyl. In some embodiments, R" is straight-chain C_{8-11} alkyl. In some embodiments, R" is straight-chain C_{9-10} alkyl. In some embodiments, R" is straight-chain C_6 alkyl. In some embodiments, R" is straight-chain C_7 alkyl. In some embodiments, R" is straight-chain C_8 alkyl. In some embodiments, R" is straight-chain C_9 alkyl. In some embodiments, R" is straight-chain C_{10} alkyl. In some embodiments, R" is straight-chain C_{11} alkyl. In some embodiments, R" is straight-chain C_{12} alkyl. In some embodiments, R" is straight-chain C_{13-20} alkyl. In some embodiments, R" is straight-chain C_{15-20} alkyl. In some embodiments, R" is

straight-chain C_{13} alkyl. In some embodiments, R" is straight-chain C_{14} alkyl. In some embodiments, R" is straight-chain C_{15} alkyl. In some embodiments, R" is straight-chain C_{16} alkyl. In some embodiments, R" is straight-chain C_{17} alkyl. In some embodiments, R" is straight-chain C_{18} alkyl. In some embodiments, R" is straight-chain C_{19} alkyl. In some embodiments, R" is straight-chain C_{20} alkyl.

[0167] In some embodiments, R" is branched C_{6-20} alkyl. In some embodiments, R" is branched C_{6-12} alkyl. In some embodiments, R" is branched C_{8-11} alkyl. In some embodiments, R" is branched C_{9-10} alkyl. In some embodiments, R" is branched C_6 alkyl. In some embodiments, R" is branched C_7 alkyl. In some embodiments, R" is branched C_8 alkyl. In some embodiments, R" is branched C_9 alkyl. In some embodiments, R" is branched C_{10} alkyl. In some embodiments, R" is branched C_{11} alkyl. In some embodiments, R" is branched C_{12} alkyl. In some embodiments, R" is branched C_{13-20} alkyl. In some embodiments, R" is branched C_{15-20} alkyl. In some embodiments, R" is branched C_{13} alkyl. In some embodiments, R" is branched C_{14} alkyl. In some embodiments, R" is branched C_{15} alkyl. In some embodiments, R" is branched C_{16} alkyl. In some embodiments, R" is branched C_{17} alkyl. In some embodiments, R" is branched C_{18} alkyl. In some embodiments, R" is branched C_{19} alkyl. In some embodiments, R" is branched C_{20} alkyl.

[0168] In some embodiments, R" is optionally substituted C_{6-20} alkenyl. In some embodiments, R" is optionally substituted C_{6-12} alkenyl. In some embodiments, R" is optionally substituted C_{8-11} alkenyl. In some embodiments, R" is optionally substituted C_{9-10} alkenyl. In some embodiments, R" is optionally substituted C_6 alkenyl. In some embodiments, R" is optionally substituted C_7 alkenyl. In some embodiments, R" is optionally substituted C_8 alkenyl. In some embodiments, R" is optionally substituted C_9 alkenyl. In some embodiments, R" is optionally substituted C_{10} alkenyl. In some embodiments, R" is optionally substituted C_{11} alkenyl. In some embodiments, R" is optionally substituted C_{12} alkenyl. In some embodiments, R" is optionally substituted C_{13-20} alkenyl. In some embodiments, R" is optionally substituted C_{15-20} alkenyl. In some embodiments, R" is optionally substituted C_{13} alkenyl. In some embodiments, R" is optionally substituted C_{14} alkenyl. In some embodiments, R" is optionally substituted C_{15} alkenyl. In some embodiments, R" is optionally substituted C_{16} alkenyl. In some embodiments, R" is optionally substituted C_{17} alkenyl. In some embodiments, R" is optionally substituted C_{18} alkenyl. In some embodiments, R" is optionally substituted C_{19} alkenyl. In some embodiments, R" is optionally substituted C_{20} alkenyl.

[0169] In some embodiments, R" is C_{6-20} alkenyl. In some embodiments, R" is C_{6-12} alkenyl. In some embodiments, R" is C_{8-11} alkenyl. In some embodiments, R" is C_{9-10} alkenyl. In some embodiments, R" is C_6 alkenyl. In some embodiments, R" is C_7 alkenyl. In some embodiments, R" is C_8 alkenyl. In some embodiments, R" is C_9 alkenyl. In some embodiments, R" is C_{10} alkenyl. In some embodiments, R" is C_{11} alkenyl. In some embodiments, R" is C_{12} alkenyl. In some embodiments, R" is C_{13-20} alkenyl. In some embodiments, R" is C_{15-20} alkenyl. In some embodiments, R" is C_{13} alkenyl. In some embodiments, R" is C_{14} alkenyl. In some embodiments, R" is C_{15} alkenyl. In some embodiments, R" is C_{16} alkenyl. In some embodiments, R" is C_{17} alkenyl. In some embodiments, R" is C_{18} alkenyl. In some embodiments, R" is C_{19} alkenyl. In some embodiments, R" is C_{20} alkenyl.

[0170] In some embodiments, R" is straight-chain C_{6-20} alkenyl. In some embodiments, R" is straight-chain C_{6-12} alkenyl. In some embodiments, R" is straight-chain C_{8-11} alkenyl. In some embodiments, R" is straight-chain C_{9-10} alkenyl. In some embodiments, R" is straight-chain C_6 alkenyl. In some embodiments, R" is straight-chain C_7 alkenyl. In some embodiments, R" is straight-chain C_8 alkenyl. In some embodiments, R" is straight-chain C_9 alkenyl. In some embodiments, R" is straight-chain C_{10} alkenyl. In some embodiments, R" is straight-chain C_{11} alkenyl. In some embodiments, R" is straight-chain C_{12} alkenyl. In some embodiments, R" is straight-chain C_{13-20} alkenyl. In some embodiments, R" is straight-chain C_{15-20} alkenyl. In some embodiments, R" is straight-chain C_{13} alkenyl. In some embodiments, R" is straight-chain C_{14} alkenyl. In some embodiments, R" is straight-chain C_{15} alkenyl. In some embodiments, R" is straight-chain C_{16} alkenyl. In some embodiments, R" is straight-chain C_{17} alkenyl. In some embodiments, R" is straight-chain C_{18} alkenyl. In some embodiments, R" is straight-chain C_{19} alkenyl. In some embodiments, R" is straight-chain C_{20} alkenyl.

[0171] In some embodiments, R" is branched C_{6-20} alkenyl. In some embodiments, R" is branched C_{6-12} alkenyl. In some embodiments, R" is branched C_{8-11} alkenyl. In some embodiments, R" is branched C_{9-10} alkenyl. In some embodiments, R" is branched C_6 alkenyl. In some embodiments, R" is branched C_7 alkenyl. In some embodiments, R" is branched C_8 alkenyl. In some embodiments, R" is branched C_9 alkenyl. In some embodiments, R" is branched C_{10} alkenyl. In some embodiments, R" is branched C_{11} alkenyl. In some embodiments, R" is branched C_{12} alkenyl. In some embodiments, R" is branched C_{13-20} alkenyl. In some embodiments, R" is branched C_{15-20} alkenyl. In some embodiments, R" is branched C_{13} alkenyl. In some

embodiments, R" is branched C_{14} alkenyl. In some embodiments, R" is branched C_{15} alkenyl. In some embodiments, R" is branched C_{16} alkenyl. In some embodiments, R" is branched C_{17} alkenyl. In some embodiments, R" is branched C_{18} alkenyl. In some embodiments, R" is branched C_{19} alkenyl. In some embodiments, R" is branched C_{20} alkenyl.

[0172] In some embodiments, R" is optionally substituted C_{6-20} alkynyl. In some embodiments, R" is optionally substituted C_{6-12} alkynyl. . In some embodiments, R" is optionally substituted C_{8-11} alkynyl. In some embodiments, R" is optionally substituted C_{9-10} alkynyl. In some embodiments, R" is optionally substituted C_6 alkynyl. In some embodiments, R" is optionally substituted C_7 alkynyl. In some embodiments, R" is optionally substituted C_8 alkynyl. In some embodiments, R" is optionally substituted C_9 alkynyl. In some embodiments, R" is optionally substituted C_{10} alkynyl. In some embodiments, R" is optionally substituted C_{11} alkynyl. In some embodiments, R" is optionally substituted C_{12} alkynyl. In some embodiments, R" is optionally substituted C_{13-20} alkynyl. In some embodiments, R" is optionally substituted C_{15-20} alkynyl. In some embodiments, R" is optionally substituted C_{13} alkynyl. In some embodiments, R" is optionally substituted C_{14} alkynyl. In some embodiments, R" is optionally substituted C_{15} alkynyl. In some embodiments, R" is optionally substituted C_{16} alkynyl. In some embodiments, R" is optionally substituted C_{17} alkynyl. In some embodiments, R" is optionally substituted C_{18} alkynyl. In some embodiments, R" is optionally substituted C_{19} alkynyl. In some embodiments, R" is optionally substituted C_{20} alkynyl.

[0173] In some embodiments, R" is C_{6-20} alkynyl. In some embodiments, R" is C_{6-12} alkynyl. In some embodiments, R" is C_{8-11} alkynyl. In some embodiments, R" is C_{9-10} alkynyl. In some embodiments, R" is C_6 alkynyl. In some embodiments, R" is C_7 alkynyl. In some embodiments, R" is C_8 alkynyl. In some embodiments, R" is C_9 alkynyl. In some embodiments, R" is C_{10} alkynyl. In some embodiments, R" is C_{11} alkynyl. In some embodiments, R" is C_{12} alkynyl. In some embodiments, R" is C_{13-20} alkynyl. In some embodiments, R" is C_{15-20} alkynyl. In some embodiments, R" is C_{13} alkynyl. In some embodiments, R" is C_{14} alkynyl. In some embodiments, R" is C_{15} alkynyl. In some embodiments, R" is C_{16} alkynyl. In some embodiments, R" is C_{17} alkynyl. In some embodiments, R" is C_{18} alkynyl. In some embodiments, R" is C_{19} alkynyl. In some embodiments, R" is C_{20} alkynyl.

[0174] In some embodiments, R" is straight-chain C_{6-20} alkynyl. In some embodiments, R" is straight-chain C_{6-12} alkynyl. In some embodiments, R" is straight-chain C_{8-11} alkynyl. In some

embodiments, R" is straight-chain C_{9-10} alkynyl. In some embodiments, R" is straight-chain C_6 alkynyl. In some embodiments, R" is straight-chain C_7 alkynyl. In some embodiments, R" is straight-chain C_8 alkynyl. In some embodiments, R" is straight-chain C_9 alkynyl. In some embodiments, R" is straight-chain C_{10} alkynyl. In some embodiments, R" is straight-chain C_{11} alkynyl. In some embodiments, R" is straight-chain C_{12} alkynyl. In some embodiments, R" is straight-chain C_{13-20} alkynyl. In some embodiments, R" is straight-chain C_{15-20} alkynyl. In some embodiments, R" is straight-chain C_{13} alkynyl. In some embodiments, R" is straight-chain C_{14} alkynyl. In some embodiments, R" is straight-chain C_{15} alkynyl. In some embodiments, R" is straight-chain C_{16} alkynyl. In some embodiments, R" is straight-chain C_{17} alkynyl. In some embodiments, R" is straight-chain C_{18} alkynyl. In some embodiments, R" is straight-chain C_{19} alkynyl. In some embodiments, R" is straight-chain C_{20} alkynyl.

[0175] In some embodiments, R" is C_{6-20} haloaliphatic. In some embodiments, R" is C_{6-12} haloaliphatic. In some embodiments, R" is C_{6-10} haloaliphatic. In some embodiments, R" is C_6 haloaliphatic. In some embodiments, R" is C_7 haloaliphatic. In some embodiments, R" is C_8 haloaliphatic. In some embodiments, R" is C_9 haloaliphatic. In some embodiments, R" is C_{10} haloaliphatic. In some embodiments, R" is C_{15-20} haloaliphatic. In some embodiments, R" is C_{15} haloaliphatic. In some embodiments, R" is C_{16} haloaliphatic. In some embodiments, R" is C_{17} haloaliphatic. In some embodiments, R" is C_{18} haloaliphatic. In some embodiments, R" is C_{19} haloaliphatic. In some embodiments, R" is C_{20} haloaliphatic.

[0176] In some embodiments, R" is straight-chain C_{6-20} haloaliphatic. In some embodiments, R" is straight-chain C_{6-12} haloaliphatic. In some embodiments, R" is straight-chain C_{6-10} haloaliphatic. In some embodiments, R" is straight-chain C_6 haloaliphatic. In some embodiments, R" is straight-chain C_7 haloaliphatic. In some embodiments, R" is straight-chain C_8 haloaliphatic. In some embodiments, R" is straight-chain C_9 haloaliphatic. In some embodiments, R" is straight-chain C_{10} haloaliphatic. In some embodiments, R" is straight-chain C_{15-20} haloaliphatic. In some embodiments, R" is straight-chain C_{15} haloaliphatic. In some embodiments, R" is straight-chain C_{16} haloaliphatic. In some embodiments, R" is straight-chain C_{17} haloaliphatic. In some embodiments, R" is straight-chain C_{18} haloaliphatic. In some embodiments, R" is straight-chain C_{19} haloaliphatic. In some embodiments, R" is straight-chain C_{20} haloaliphatic.

[0177] In some embodiments, R" is C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is

C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0178] In some embodiments, R" is C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{19} haloalkyl comprising

1-3 fluorine atoms. In some embodiments, R" is C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0179] In some embodiments, R" is straight-chain C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{10} haloalkyl comprising 1-3 fluorine atoms.

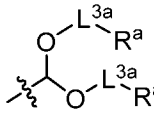
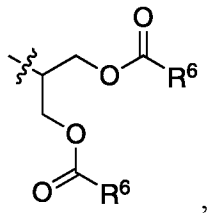
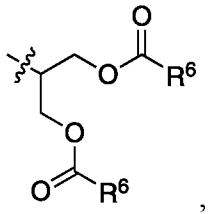
[0180] In some embodiments, R" is straight-chain C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{15} haloalkyl comprising 1-7 fluorine atoms. In some

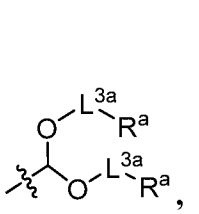
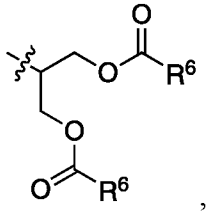
embodiments, R" is straight-chain C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, R" is straight-chain C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, R" is straight-chain C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R" is straight-chain C_{20} haloalkyl comprising 1-3 fluorine atoms.

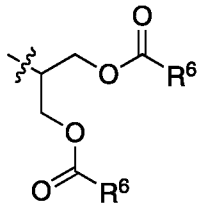
[0181] In some embodiments, R" is optionally substituted 3- to 12-membered cycloaliphatic. In some embodiments, R" is optionally substituted 3- to 7-membered cycloaliphatic. In some embodiments, R" is optionally substituted 4- to 7-membered cycloaliphatic. In some embodiments, R" is optionally substituted 5- to 7-membered cycloaliphatic. In some embodiments, R" is optionally substituted 6- to 7-membered cycloaliphatic. In some embodiments, R" is optionally substituted cyclopentyl. In some embodiments, R" is optionally substituted cyclohexyl. In some embodiments, R" is cyclohexyl substituted with R°. In some embodiments, R" is cyclohexyl substituted with a 5- or 6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which is further substituted with $-(CH_2)_{0-2}R^{\bullet}$. In some embodiments, R" is cyclohexyl substituted with cyclohexyl, which is further substituted with C_{1-6} aliphatic. In some embodiments, R" is optionally substituted cycloheptyl.

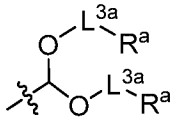
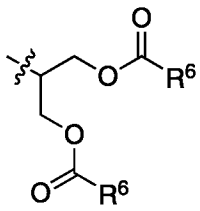
[0182] In some embodiments, R" is optionally substituted 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some

embodiments, R" is optionally substituted 1-adamantyl. In some embodiments, R" is optionally substituted 2-adamantyl. In some embodiments, R" is optionally substituted sterolyl. In some embodiments, R" is optionally substituted cholesterolyl. In some embodiments, R" is optionally substituted phenyl. In some embodiments, R" is phenyl substituted with R°. In some embodiments, R" is phenyl substituted with C_{1-6} aliphatic.

[0183] As described above, in some embodiments of any of Formulae A', I", II", and III', each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl. In some embodiments of Formula A, each R is independently hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl. In some embodiments of any of Formulae I', I, II', II, and III, each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

[0184] In some embodiments, each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl. In some embodiments, each R is independently hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 7-membered cycloaliphatic, 1-

adamantyl, and phenyl. In some embodiments, each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 7-membered cycloaliphatic, 1-adamantyl, and phenyl.

[0185] In some embodiments, each R is hydrogen. In some embodiments, each R is independently  . In some embodiments, each R is independently  .

[0186] In some embodiments, each R is independently optionally substituted C_{6-20} aliphatic. In some embodiments, each R is independently optionally substituted C_{6-12} aliphatic. In some embodiments, each R is independently optionally substituted C_{8-11} aliphatic. In some embodiments, each R is independently optionally substituted C_{9-10} aliphatic. In some embodiments, each R is independently optionally substituted C_6 aliphatic. In some embodiments, each R is independently optionally substituted C_7 aliphatic. In some embodiments, each R is independently optionally substituted C_8 aliphatic. In some embodiments, each R is independently optionally substituted C_9 aliphatic. In some embodiments, each R is independently optionally substituted C_{10} aliphatic. In some embodiments, each R is independently optionally substituted C_{11} aliphatic. In some embodiments, each R is independently optionally substituted C_{12} aliphatic. In some embodiments, each R is independently optionally substituted C_{13-20} aliphatic. In some embodiments, each R is independently optionally substituted C_{15-20} aliphatic. In some embodiments, each R is independently optionally substituted C_{13} aliphatic. In some embodiments, each R is independently optionally substituted C_{14} aliphatic. In some embodiments, each R is independently optionally substituted C_{15} aliphatic. In some embodiments, each R is independently optionally substituted C_{16} aliphatic. In some embodiments, each R is independently optionally substituted C_{17} aliphatic. In some embodiments, each R is independently optionally substituted C_{18} aliphatic. In some embodiments, each R is independently optionally substituted C_{19} aliphatic. In some embodiments, each R is independently optionally substituted C_{20} aliphatic.

[0187] In some embodiments, each R is independently optionally substituted straight-chain C_{6-20} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{6-12} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{8-11} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{9-10} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_6 aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_7 aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_8 aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_9 aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{10} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{11} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{12} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{13-20} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{15-20} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{13} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{14} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{15} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{16} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{17} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{18} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{19} aliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{20} aliphatic.

[0188] In some embodiments, each R is independently optionally substituted branched C_{6-20} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{6-12} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{8-11} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{9-10} aliphatic. In some embodiments, each R is independently optionally substituted branched C_6 aliphatic. In some embodiments, each R is independently optionally substituted branched C_7 aliphatic. In some embodiments, each R is independently optionally substituted branched C_8 aliphatic. In some embodiments, each R is independently optionally substituted branched C_9 aliphatic. In some embodiments, each R is independently optionally substituted branched C_{10}

aliphatic. In some embodiments, each R is independently optionally substituted branched C_{11} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{12} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{13-20} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{15-20} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{13} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{14} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{15} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{16} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{17} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{18} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{19} aliphatic. In some embodiments, each R is independently optionally substituted branched C_{20} aliphatic.

[0189] In some embodiments, each R is independently C_{6-20} aliphatic. In some embodiments, each R is independently C_{6-12} aliphatic. In some embodiments, each R is independently C_{8-11} aliphatic. In some embodiments, each R is independently C_{9-10} aliphatic. In some embodiments, each R is independently C_6 aliphatic. In some embodiments, each R is independently C_7 aliphatic. In some embodiments, each R is independently C_8 aliphatic. In some embodiments, each R is independently C_9 aliphatic. In some embodiments, each R is independently C_{10} aliphatic. In some embodiments, each R is independently C_{11} aliphatic. In some embodiments, each R is independently C_{12} aliphatic. In some embodiments, each R is independently C_{13-20} aliphatic. In some embodiments, each R is independently C_{15-20} aliphatic. In some embodiments, each R is independently C_{13} aliphatic. In some embodiments, each R is independently C_{14} aliphatic. In some embodiments, each R is independently C_{15} aliphatic. In some embodiments, each R is independently C_{16} aliphatic. In some embodiments, each R is independently C_{17} aliphatic. In some embodiments, each R is independently C_{18} aliphatic. In some embodiments, each R is independently C_{19} aliphatic. In some embodiments, each R is independently C_{20} aliphatic.

[0190] In some embodiments, each R is independently straight-chain C_{6-20} aliphatic. In some embodiments, each R is independently straight-chain C_{6-12} aliphatic. In some embodiments, each R is independently straight-chain C_{8-11} aliphatic. In some embodiments, each R is independently straight-chain C_{9-10} aliphatic. In some embodiments, each R is independently straight-chain C_6

aliphatic. In some embodiments, each R is independently straight-chain C_7 aliphatic. In some embodiments, each R is independently straight-chain C_8 aliphatic. In some embodiments, each R is independently straight-chain C_9 aliphatic. In some embodiments, each R is independently straight-chain C_{10} aliphatic. In some embodiments, each R is independently straight-chain C_{11} aliphatic. In some embodiments, each R is independently straight-chain C_{12} aliphatic. In some embodiments, each R is independently straight-chain C_{13-20} aliphatic. In some embodiments, each R is independently straight-chain C_{15-20} aliphatic. In some embodiments, each R is independently straight-chain C_{13} aliphatic. In some embodiments, each R is independently straight-chain C_{14} aliphatic. In some embodiments, each R is independently straight-chain C_{15} aliphatic. In some embodiments, each R is independently straight-chain C_{16} aliphatic. In some embodiments, each R is independently straight-chain C_{17} aliphatic. In some embodiments, each R is independently straight-chain C_{18} aliphatic. In some embodiments, each R is independently straight-chain C_{19} aliphatic. In some embodiments, each R is independently straight-chain C_{20} aliphatic.

[0191] In some embodiments, each R is independently branched C_{6-20} aliphatic. In some embodiments, each R is independently branched C_{6-12} aliphatic. In some embodiments, each R is independently branched C_{8-11} aliphatic. In some embodiments, each R is independently branched C_{9-10} aliphatic. In some embodiments, each R is independently branched C_6 aliphatic. In some embodiments, each R is independently branched C_7 aliphatic. In some embodiments, each R is independently branched C_8 aliphatic. In some embodiments, each R is independently branched C_9 aliphatic. In some embodiments, each R is independently branched C_{10} aliphatic. In some embodiments, each R is independently branched C_{11} aliphatic. In some embodiments, each R is independently branched C_{12} aliphatic. In some embodiments, each R is independently branched C_{13-20} aliphatic. In some embodiments, each R is independently branched C_{15-20} aliphatic. In some embodiments, each R is independently branched C_{13} aliphatic. In some embodiments, each R is independently branched C_{14} aliphatic. In some embodiments, each R is independently branched C_{15} aliphatic. In some embodiments, each R is independently branched C_{16} aliphatic. In some embodiments, each R is independently branched C_{17} aliphatic. In some embodiments, each R is independently branched C_{18} aliphatic. In some embodiments, each R is independently branched C_{19} aliphatic. In some embodiments, each R is independently branched C_{20} aliphatic.

[0192] In some embodiments, each R is independently optionally substituted C_{6-20} alkyl. In some embodiments, each R is independently optionally substituted C_{6-12} alkyl. In some embodiments,

each R is independently optionally substituted C_{8-11} alkyl. In some embodiments, each R is independently optionally substituted C_{9-10} alkyl. In some embodiments, each R is independently optionally substituted C_6 alkyl. In some embodiments, each R is independently optionally substituted C_7 alkyl. In some embodiments, each R is independently optionally substituted C_8 alkyl. In some embodiments, each R is independently optionally substituted C_9 alkyl. In some embodiments, each R is independently optionally substituted C_{10} alkyl. In some embodiments, each R is independently optionally substituted C_{11} alkyl. In some embodiments, each R is independently optionally substituted C_{12} alkyl. In some embodiments, each R is independently optionally substituted C_{13-20} alkyl. In some embodiments, each R is independently optionally substituted C_{15-20} alkyl. In some embodiments, each R is independently optionally substituted C_{13} alkyl. In some embodiments, each R is independently optionally substituted C_{14} alkyl. In some embodiments, each R is independently optionally substituted C_{15} alkyl. In some embodiments, each R is independently optionally substituted C_{16} alkyl. In some embodiments, each R is independently optionally substituted C_{17} alkyl. In some embodiments, each R is independently optionally substituted C_{18} alkyl. In some embodiments, each R is independently optionally substituted C_{19} alkyl. In some embodiments, each R is independently optionally substituted C_{20} alkyl.

[0193] In some embodiments, each R is independently C_{6-20} alkyl. In some embodiments, each R is independently C_{6-12} alkyl. In some embodiments, each R is independently C_{8-11} alkyl. In some embodiments, each R is independently C_{9-10} alkyl. In some embodiments, each R is independently C_6 alkyl. In some embodiments, each R is independently C_7 alkyl. In some embodiments, each R is independently C_8 alkyl. In some embodiments, each R is independently C_9 alkyl. In some embodiments, each R is independently C_{10} alkyl. In some embodiments, each R is independently C_{11} alkyl. In some embodiments, each R is independently C_{12} alkyl. In some embodiments, each R is independently C_{13-20} alkyl. In some embodiments, each R is independently C_{15-20} alkyl. In some embodiments, each R is independently C_{13} alkyl. In some embodiments, each R is independently C_{14} alkyl. In some embodiments, each R is independently C_{15} alkyl. In some embodiments, each R is independently C_{16} alkyl. In some embodiments, each R is independently C_{17} alkyl. In some embodiments, each R is independently C_{18} alkyl. In some embodiments, each R is independently C_{19} alkyl. In some embodiments, each R is independently C_{20} alkyl.

[0194] In some embodiments, each R is independently straight-chain C_{6-20} alkyl. In some embodiments, each R is independently straight-chain C_{6-12} alkyl. In some embodiments, each R is independently straight-chain C_{8-11} alkyl. In some embodiments, each R is independently straight-chain C_{9-10} alkyl. In some embodiments, each R is independently straight-chain C_6 alkyl. In some embodiments, each R is independently straight-chain C_7 alkyl. In some embodiments, each R is independently straight-chain C_8 alkyl. In some embodiments, each R is independently straight-chain C_9 alkyl. In some embodiments, each R is independently straight-chain C_{10} alkyl. In some embodiments, each R is independently straight-chain C_{11} alkyl. In some embodiments, each R is independently straight-chain C_{12} alkyl. In some embodiments, each R is independently straight-chain C_{13-20} alkyl. In some embodiments, each R is independently straight-chain C_{15-20} alkyl. In some embodiments, each R is independently straight-chain C_{13} alkyl. In some embodiments, each R is independently straight-chain C_{14} alkyl. In some embodiments, each R is independently straight-chain C_{15} alkyl. In some embodiments, each R is independently straight-chain C_{16} alkyl. In some embodiments, each R is independently straight-chain C_{17} alkyl. In some embodiments, each R is independently straight-chain C_{18} alkyl. In some embodiments, each R is independently straight-chain C_{19} alkyl. In some embodiments, each R is independently straight-chain C_{20} alkyl.

[0195] In some embodiments, each R is independently branched C_{6-20} alkyl. In some embodiments, each R is independently branched C_{6-12} alkyl. In some embodiments, each R is independently branched C_{8-11} alkyl. In some embodiments, each R is independently branched C_{9-10} alkyl. In some embodiments, each R is independently branched C_6 alkyl. In some embodiments, each R is independently branched C_7 alkyl. In some embodiments, each R is independently branched C_8 alkyl. In some embodiments, each R is independently branched C_9 alkyl. In some embodiments, each R is independently branched C_{10} alkyl. In some embodiments, each R is independently branched C_{11} alkyl. In some embodiments, each R is independently branched C_{12} alkyl. In some embodiments, each R is independently branched C_{13-20} alkyl. In some embodiments, each R is independently branched C_{15-20} alkyl. In some embodiments, each R is independently branched C_{13} alkyl. In some embodiments, each R is independently branched C_{14} alkyl. In some embodiments, each R is independently branched C_{15} alkyl. In some embodiments, each R is independently branched C_{16} alkyl. In some embodiments, each R is independently branched C_{17} alkyl. In some embodiments, each R is independently branched C_{18} alkyl. In some

embodiments, each R is independently branched C_{19} alkyl. In some embodiments, each R is independently branched C_{20} alkyl.

[0196] In some embodiments, each R is independently optionally substituted C_{6-20} alkenyl. In some embodiments, each R is independently optionally substituted C_{6-12} alkenyl. In some embodiments, each R is independently optionally substituted C_{8-11} alkenyl. In some embodiments, each R is independently optionally substituted C_{9-10} alkenyl. In some embodiments, each R is independently optionally substituted C_6 alkenyl. In some embodiments, each R is independently optionally substituted C_7 alkenyl. In some embodiments, each R is independently optionally substituted C_8 alkenyl. In some embodiments, each R is independently optionally substituted C_9 alkenyl. In some embodiments, each R is independently optionally substituted C_{10} alkenyl. In some embodiments, each R is independently optionally substituted C_{11} alkenyl. In some embodiments, each R is independently optionally substituted C_{12} alkenyl. In some embodiments, each R is independently optionally substituted C_{13-20} alkenyl. In some embodiments, each R is independently optionally substituted C_{15-20} alkenyl. In some embodiments, each R is independently optionally substituted C_{13} alkenyl. In some embodiments, each R is independently optionally substituted C_{14} alkenyl. In some embodiments, each R is independently optionally substituted C_{15} alkenyl. In some embodiments, each R is independently optionally substituted C_{16} alkenyl. In some embodiments, each R is independently optionally substituted C_{17} alkenyl. In some embodiments, each R is independently optionally substituted C_{18} alkenyl. In some embodiments, each R is independently optionally substituted C_{19} alkenyl. In some embodiments, each R is independently optionally substituted C_{20} alkenyl.

[0197] In some embodiments, each R is independently C_{6-20} alkenyl. In some embodiments, each R is independently C_{6-12} alkenyl. In some embodiments, each R is independently C_{8-11} alkenyl. In some embodiments, each R is independently C_{9-10} alkenyl. In some embodiments, each R is independently C_6 alkenyl. In some embodiments, each R is independently C_7 alkenyl. In some embodiments, each R is independently C_8 alkenyl. In some embodiments, each R is independently C_9 alkenyl. In some embodiments, each R is independently C_{10} alkenyl. In some embodiments, each R is independently C_{11} alkenyl. In some embodiments, each R is independently C_{12} alkenyl. In some embodiments, each R is independently C_{13-20} alkenyl. In some embodiments, each R is independently C_{15-20} alkenyl. In some embodiments, each R is independently C_{13} alkenyl. In some embodiments, each R is independently C_{14} alkenyl. In some embodiments, each R is

independently C_{15} alkenyl. In some embodiments, each R is independently C_{16} alkenyl. In some embodiments, each R is independently C_{17} alkenyl. In some embodiments, each R is independently C_{18} alkenyl. In some embodiments, each R is independently C_{19} alkenyl. In some embodiments, each R is independently C_{20} alkenyl.

[0198] In some embodiments, each R is independently straight-chain C_{6-20} alkenyl. In some embodiments, each R is independently straight-chain C_{6-12} alkenyl. In some embodiments, each R is independently straight-chain C_{8-11} alkenyl. In some embodiments, each R is independently straight-chain C_{9-10} alkenyl. In some embodiments, each R is independently straight-chain C_6 alkenyl. In some embodiments, each R is independently straight-chain C_7 alkenyl. In some embodiments, each R is independently straight-chain C_8 alkenyl. In some embodiments, each R is independently straight-chain C_9 alkenyl. In some embodiments, each R is independently straight-chain C_{10} alkenyl. In some embodiments, each R is independently straight-chain C_{11} alkenyl. In some embodiments, each R is independently straight-chain C_{12} alkenyl. In some embodiments, each R is independently straight-chain C_{13-20} alkenyl. In some embodiments, each R is independently straight-chain C_{15-20} alkenyl. In some embodiments, each R is independently straight-chain C_{13} alkenyl. In some embodiments, each R is independently straight-chain C_{14} alkenyl. In some embodiments, each R is independently straight-chain C_{15} alkenyl. In some embodiments, each R is independently straight-chain C_{16} alkenyl. In some embodiments, each R is independently straight-chain C_{17} alkenyl. In some embodiments, each R is independently straight-chain C_{18} alkenyl. In some embodiments, each R is independently straight-chain C_{19} alkenyl. In some embodiments, each R is independently straight-chain C_{20} alkenyl.

[0199] In some embodiments, each R is independently branched C_{6-20} alkenyl. In some embodiments, each R is independently branched C_{6-12} alkenyl. In some embodiments, each R is independently branched C_{8-11} alkenyl. In some embodiments, each R is independently branched C_{9-10} alkenyl. In some embodiments, each R is independently branched C_6 alkenyl. In some embodiments, each R is independently branched C_7 alkenyl. In some embodiments, each R is independently branched C_8 alkenyl. In some embodiments, each R is independently branched C_9 alkenyl. In some embodiments, each R is independently branched C_{10} alkenyl. In some embodiments, each R is independently branched C_{11} alkenyl. In some embodiments, each R is independently branched C_{12} alkenyl. In some embodiments, each R is independently branched C_{13-20} alkenyl. In some embodiments, each R is independently branched C_{15-20} alkenyl. In some

embodiments, each R is independently branched C_{13} alkenyl. In some embodiments, each R is independently branched C_{14} alkenyl. In some embodiments, each R is independently branched C_{15} alkenyl. In some embodiments, each R is independently branched C_{16} alkenyl. In some embodiments, each R is independently branched C_{17} alkenyl. In some embodiments, each R is independently branched C_{18} alkenyl. In some embodiments, each R is independently branched C_{19} alkenyl. In some embodiments, each R is independently branched C_{20} alkenyl.

[0200] In some embodiments, each R is independently optionally substituted C_{6-20} alkynyl. In some embodiments, each R is independently optionally substituted C_{6-12} alkynyl. In some embodiments, each R is independently optionally substituted C_{8-11} alkynyl. In some embodiments, each R is independently optionally substituted C_{9-10} alkynyl. In some embodiments, each R is independently optionally substituted C_6 alkynyl. In some embodiments, each R is independently optionally substituted C_7 alkynyl. In some embodiments, each R is independently optionally substituted C_8 alkynyl. In some embodiments, each R is independently optionally substituted C_9 alkynyl. In some embodiments, each R is independently optionally substituted C_{10} alkynyl. In some embodiments, each R is independently optionally substituted C_{11} alkynyl. In some embodiments, each R is independently optionally substituted C_{12} alkynyl. In some embodiments, each R is independently optionally substituted C_{13-20} alkynyl. In some embodiments, each R is independently optionally substituted C_{15-20} alkynyl. In some embodiments, each R is independently optionally substituted C_{13} alkynyl. In some embodiments, each R is independently optionally substituted C_{14} alkynyl. In some embodiments, each R is independently optionally substituted C_{15} alkynyl. In some embodiments, each R is independently optionally substituted C_{16} alkynyl. In some embodiments, each R is independently optionally substituted C_{17} alkynyl. In some embodiments, each R is independently optionally substituted C_{18} alkynyl. In some embodiments, each R is independently optionally substituted C_{19} alkynyl. In some embodiments, each R is independently optionally substituted C_{20} alkynyl.

[0201] In some embodiments, each R is independently C_{6-20} alkynyl. In some embodiments, each R is independently C_{6-12} alkynyl. In some embodiments, each R is independently C_{8-11} alkynyl. In some embodiments, each R is independently C_{9-10} alkynyl. In some embodiments, each R is independently C_6 alkynyl. In some embodiments, each R is independently C_7 alkynyl. In some embodiments, each R is independently C_8 alkynyl. In some embodiments, each R is independently C_9 alkynyl. In some embodiments, each R is independently C_{10} alkynyl. In some embodiments,

each R is independently C_{11} alkynyl. In some embodiments, each R is independently C_{12} alkynyl. In some embodiments, each R is independently C_{13-20} alkynyl. In some embodiments, each R is independently C_{15-20} alkynyl. In some embodiments, each R is independently C_{13} alkynyl. In some embodiments, each R is independently C_{14} alkynyl. In some embodiments, each R is independently C_{15} alkynyl. In some embodiments, each R is independently C_{16} alkynyl. In some embodiments, each R is independently C_{17} alkynyl. In some embodiments, each R is independently C_{18} alkynyl. In some embodiments, each R is independently C_{19} alkynyl. In some embodiments, each R is independently C_{20} alkynyl.

[0202] In some embodiments, each R is independently straight-chain C_{6-20} alkynyl. In some embodiments, each R is independently straight-chain C_{6-12} alkynyl. In some embodiments, each R is independently straight-chain C_{8-11} alkynyl. In some embodiments, each R is independently straight-chain C_{9-10} alkynyl. In some embodiments, each R is independently straight-chain C_6 alkynyl. In some embodiments, each R is independently straight-chain C_7 alkynyl. In some embodiments, each R is independently straight-chain C_8 alkynyl. In some embodiments, each R is independently straight-chain C_9 alkynyl. In some embodiments, each R is independently straight-chain C_{10} alkynyl. In some embodiments, each R is independently straight-chain C_{11} alkynyl. In some embodiments, each R is independently straight-chain C_{12} alkynyl. In some embodiments, each R is independently straight-chain C_{13-20} alkynyl. In some embodiments, each R is independently straight-chain C_{15-20} alkynyl. In some embodiments, each R is independently straight-chain C_{13} alkynyl. In some embodiments, each R is independently straight-chain C_{14} alkynyl. In some embodiments, each R is independently straight-chain C_{15} alkynyl. In some embodiments, each R is independently straight-chain C_{16} alkynyl. In some embodiments, each R is independently straight-chain C_{17} alkynyl. In some embodiments, each R is independently straight-chain C_{18} alkynyl. In some embodiments, each R is independently straight-chain C_{19} alkynyl. In some embodiments, each R is independently straight-chain C_{20} alkynyl.

[0203] In some embodiments, each R is independently optionally substituted C_{6-20} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{6-12} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{6-10} haloaliphatic. In some embodiments, each R is independently optionally substituted C_6 haloaliphatic. In some embodiments, each R is independently optionally substituted C_7 haloaliphatic. In some embodiments, each R is independently optionally substituted C_8 haloaliphatic. In some

embodiments, each R is independently optionally substituted C_9 haloaliphatic. In some embodiments, each R is independently optionally substituted C_{10} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{15-20} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{15} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{16} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{17} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{18} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{19} haloaliphatic. In some embodiments, each R is independently optionally substituted C_{20} haloaliphatic.

[0204] In some embodiments, each R is independently optionally substituted straight-chain C_{6-20} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{6-12} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{6-10} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_6 haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_7 haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_8 haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_9 haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{10} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{15-20} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{15} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{16} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{17} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{18} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{19} haloaliphatic. In some embodiments, each R is independently optionally substituted straight-chain C_{20} haloaliphatic.

[0205] In some embodiments, each R is independently optionally substituted branched C_{6-20} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{6-12} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{6-10} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_6 haloaliphatic. In some embodiments, each R is independently

optionally substituted branched C_7 haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_8 haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_9 haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{10} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{15-20} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{15} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{16} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{17} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{18} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{19} haloaliphatic. In some embodiments, each R is independently optionally substituted branched C_{20} haloaliphatic.

[0206] In some embodiments, each R is independently C_{6-20} haloaliphatic. In some embodiments, each R is independently C_{6-12} haloaliphatic. In some embodiments, each R is independently C_{6-10} haloaliphatic. In some embodiments, each R is independently C_6 haloaliphatic. In some embodiments, each R is independently C_7 haloaliphatic. In some embodiments, each R is independently C_8 haloaliphatic. In some embodiments, each R is independently C_9 haloaliphatic. In some embodiments, each R is independently C_{10} haloaliphatic. In some embodiments, each R is independently C_{15-20} haloaliphatic. In some embodiments, each R is independently C_{15} haloaliphatic. In some embodiments, each R is independently C_{16} haloaliphatic. In some embodiments, each R is independently C_{17} haloaliphatic. In some embodiments, each R is independently C_{18} haloaliphatic. In some embodiments, each R is independently C_{19} haloaliphatic. In some embodiments, each R is independently C_{20} haloaliphatic.

[0207] In some embodiments, each R is independently straight-chain C_{6-20} haloaliphatic. In some embodiments, each R is independently straight-chain C_{6-12} haloaliphatic. In some embodiments, each R is independently straight-chain C_{6-10} haloaliphatic. In some embodiments, each R is independently straight-chain C_6 haloaliphatic. In some embodiments, each R is independently straight-chain C_7 haloaliphatic. In some embodiments, each R is independently straight-chain C_8 haloaliphatic. In some embodiments, each R is independently straight-chain C_9 haloaliphatic. In some embodiments, each R is independently straight-chain C_{10} haloaliphatic. In some embodiments, each R is independently straight-chain C_{15-20} haloaliphatic. In some embodiments, each R is independently straight-chain C_{15} haloaliphatic. In some embodiments, each R is

independently straight-chain C_{16} haloaliphatic. In some embodiments, each R is independently straight-chain C_{17} haloaliphatic. In some embodiments, each R is independently straight-chain C_{18} haloaliphatic. In some embodiments, each R is independently straight-chain C_{19} haloaliphatic. In some embodiments, each R is independently straight-chain C_{20} haloaliphatic.

[0208] In some embodiments, each R is independently optionally substituted C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R is independently optionally substituted C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally

substituted C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0209] In some embodiments, each R is independently optionally substituted C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently optionally substituted C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0210] In some embodiments, each R is independently C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0211] In some embodiments, each R is independently C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{15} haloalkyl comprising 1-3 fluorine

atoms. In some embodiments, each R is independently C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0212] In some embodiments, each R is independently straight-chain C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_7 haloalkyl comprising 1-7 fluorine atoms.

In some embodiments, each R is independently straight-chain C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0213] In some embodiments, each R is independently straight-chain C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{19} haloalkyl comprising 1-7

fluorine atoms. In some embodiments, each R is independently straight-chain C_{1-9} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{1-9} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R is independently straight-chain C_{2-0} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R is independently straight-chain C_{2-0} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R is independently straight-chain C_{2-0} haloalkyl comprising 1-3 fluorine atoms.

[0214] In some embodiments, each R is independently optionally substituted 3- to 12-membered cycloaliphatic. In some embodiments, each R is independently optionally substituted 3- to 7-membered cycloaliphatic. In some embodiments, each R is independently optionally substituted 4- to 7-membered cycloaliphatic. In some embodiments, each R is independently optionally substituted 5- to 7-membered cycloaliphatic. In some embodiments, each R is independently optionally substituted 6- to 7-membered cycloaliphatic. In some embodiments, each R is independently optionally substituted cyclopentyl. In some embodiments, each R is independently optionally substituted cyclohexyl. In some embodiments, each R is independently cyclohexyl substituted with R°. In some embodiments, each R is independently cyclohexyl substituted with a 5- or 6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which is further substituted with $-(CH_2)_{0-2}R^{\bullet}$. In some embodiments, each R is independently cyclohexyl substituted with cyclohexyl, which is further substituted with C_{1-6} aliphatic. In some embodiments, each R is independently optionally substituted cycloheptyl.

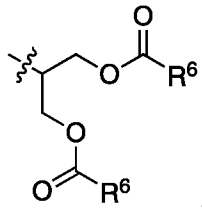
[0215] In some embodiments, each R is independently optionally substituted 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, each R is independently optionally substituted 1-adamantyl. In some embodiments, each R is independently optionally substituted 2-adamantyl. In some embodiments, each R is independently optionally substituted sterolyl. In some embodiments, each R is independently optionally substituted cholesterolyl. In some embodiments, each R is independently optionally substituted phenyl. In some embodiments, each R is independently phenyl substituted with R°. In some embodiments, each R is independently phenyl substituted with C_{1-6} aliphatic.

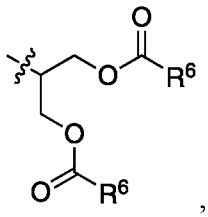
[0216] In some embodiments of any of Formulae A', A, I", I', and I, two Rs are optionally substituted C_{6-20} alkyl, and the third R is optionally substituted C_{6-20} alkenyl. In some

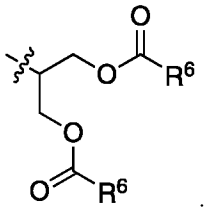
embodiments, two Rs are optionally substituted C_{6-20} alkenyl, and the third R is optionally substituted C_{6-20} alkynyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkyl, and the third R is optionally substituted C_{6-20} alkynyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkenyl, and the third R is optionally substituted C_{6-20} alkyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkynyl, and the third R is optionally substituted C_{6-20} alkyl. In some embodiments, two Rs are optionally substituted C_{6-20} aliphatic, and the third R is optionally substituted C_{6-20} haloaliphatic. In some embodiments, two Rs are optionally substituted C_{6-20} haloaliphatic, and the third R is optionally substituted C_{6-20} aliphatic. In some embodiments, two Rs are optionally substituted C_{6-20} alkyl, and the third R is optionally substituted C_{6-20} haloalkyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkenyl, and the third R is optionally substituted C_{6-20} haloalkyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkynyl, and the third R is optionally substituted C_{6-20} haloalkyl. In some embodiments, two Rs are optionally substituted C_{6-20} haloalkyl, and the third R is optionally substituted C_{6-20} alkyl. In some embodiments, two Rs are optionally substituted C_{6-20} haloalkyl, and the third R is optionally substituted C_{6-20} alkenyl. In some embodiments, two Rs are optionally substituted C_{6-20} haloalkyl, and the third R is optionally substituted C_{6-20} alkynyl.

[0217] In some embodiments of any of Formulae II", II', II, III', and III, two Rs are optionally substituted C_{6-20} alkyl, and the other two Rs are optionally substituted C_{6-20} alkenyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkenyl, and the other two Rs are optionally substituted C_{6-20} alkynyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkyl, and the other two Rs are optionally substituted C_{6-20} alkynyl. In some embodiments, two Rs are optionally substituted C_{6-20} aliphatic, and the other two Rs are optionally substituted C_{6-20} haloaliphatic. In some embodiments, two Rs are optionally substituted C_{6-20} alkyl, and the other two Rs are optionally substituted C_{6-20} haloalkyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkenyl, and the other two Rs are optionally substituted C_{6-20} haloalkyl. In some embodiments, two Rs are optionally substituted C_{6-20} alkynyl, and the other two Rs are optionally substituted C_{6-20} haloalkyl.

[0218] As described above, in some embodiments of Formula A', each R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl. In some

embodiments of Formula A, each R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

[0219] In some embodiments, each R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl. In some embodiments, each R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 7-membered cycloaliphatic, 1-adamantyl, and phenyl.

[0220] In some embodiments, each R^a is hydrogen. In some embodiments, each R^a is independently  .

[0221] In some embodiments, each R^a is independently optionally substituted C_{6-20} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{6-12} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{8-11} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{9-10} aliphatic. In some embodiments, each R^a is independently optionally substituted C_6 aliphatic. In some embodiments, each R^a is independently optionally substituted C_7 aliphatic. In some embodiments, each R^a is independently optionally substituted C_8 aliphatic. In some embodiments, each R^a is independently optionally substituted C_9 aliphatic. In some embodiments, each R^a is independently optionally substituted C_{10} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{11} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{12} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{13-20} aliphatic. In some

embodiments, each R^a is independently optionally substituted C_{15-20} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{13} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{14} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{15} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{16} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{17} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{18} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{19} aliphatic. In some embodiments, each R^a is independently optionally substituted C_{20} aliphatic.

[0222] In some embodiments, each R^a is independently optionally substituted straight-chain C_{6-20} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{6-12} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{8-11} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{9-10} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_6 aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_7 aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_8 aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_9 aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{10} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{11} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{12} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{13-20} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{15-20} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{13} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{14} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{15} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{16} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{17} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{18} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{19} aliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{20} aliphatic.

[0223] In some embodiments, each R^a is independently optionally substituted branched C_{6-20} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{6-12} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{8-11} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{9-10} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_6 aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_7 aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_8 aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_9 aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{10} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{11} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{12} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{13-20} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{15-20} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{13} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{14} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{15} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{16} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{17} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{18} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{19} aliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{20} aliphatic.

[0224] In some embodiments, each R^a is independently C_{6-20} aliphatic. In some embodiments, each R^a is independently C_{6-12} aliphatic. In some embodiments, each R^a is independently C_{8-11} aliphatic. In some embodiments, each R^a is independently C_{9-10} aliphatic. In some embodiments, each R^a is independently C_6 aliphatic. In some embodiments, each R^a is independently C_7 aliphatic. In some embodiments, each R^a is independently C_8 aliphatic. In some embodiments, each R^a is independently C_9 aliphatic. In some embodiments, each R^a is independently C_{10} aliphatic. In some embodiments, each R^a is independently C_{11} aliphatic. In some embodiments, each R^a is independently C_{12} aliphatic. In some embodiments, each R^a is independently C_{13-20} aliphatic. In some embodiments, each R^a is independently C_{15-20} aliphatic. In some embodiments,

each R^a is independently C_{13} aliphatic. In some embodiments, each R^a is independently C_{14} aliphatic. In some embodiments, each R^a is independently C_{15} aliphatic. In some embodiments, each R^a is independently C_{16} aliphatic. In some embodiments, each R^a is independently C_{17} aliphatic. In some embodiments, each R^a is independently C_{18} aliphatic. In some embodiments, each R^a is independently C_{19} aliphatic. In some embodiments, each R^a is independently C_{20} aliphatic.

[0225] In some embodiments, each R^a is independently straight-chain C_{6-20} aliphatic. In some embodiments, each R^a is independently straight-chain C_{6-12} aliphatic. In some embodiments, each R^a is independently straight-chain C_{8-11} aliphatic. In some embodiments, each R^a is independently straight-chain C_{9-10} aliphatic. In some embodiments, each R^a is independently straight-chain C_6 aliphatic. In some embodiments, each R^a is independently straight-chain C_7 aliphatic. In some embodiments, each R^a is independently straight-chain C_8 aliphatic. In some embodiments, each R^a is independently straight-chain C_9 aliphatic. In some embodiments, each R^a is independently straight-chain C_{10} aliphatic. In some embodiments, each R^a is independently straight-chain C_{11} aliphatic. In some embodiments, each R^a is independently straight-chain C_{12} aliphatic. In some embodiments, each R^a is independently straight-chain C_{13-20} aliphatic. In some embodiments, each R^a is independently straight-chain C_{15-20} aliphatic. In some embodiments, each R^a is independently straight-chain C_{13} aliphatic. In some embodiments, each R^a is independently straight-chain C_{14} aliphatic. In some embodiments, each R^a is independently straight-chain C_{15} aliphatic. In some embodiments, each R^a is independently straight-chain C_{16} aliphatic. In some embodiments, each R^a is independently straight-chain C_{17} aliphatic. In some embodiments, each R^a is independently straight-chain C_{18} aliphatic. In some embodiments, each R^a is independently straight-chain C_{19} aliphatic. In some embodiments, each R^a is independently straight-chain C_{20} aliphatic.

[0226] In some embodiments, each R^a is independently branched C_{6-20} aliphatic. In some embodiments, each R^a is independently branched C_{6-12} aliphatic. In some embodiments, each R^a is independently branched C_{8-11} aliphatic. In some embodiments, each R^a is independently branched C_{9-10} aliphatic. In some embodiments, each R^a is independently branched C_6 aliphatic. In some embodiments, each R^a is independently branched C_7 aliphatic. In some embodiments, each R^a is independently branched C_8 aliphatic. In some embodiments, each R^a is independently branched C_9 aliphatic. In some embodiments, each R^a is independently branched C_{10} aliphatic. In some embodiments, each R^a is independently branched C_{11} aliphatic. In some embodiments, each

R^a is independently branched C_{12} aliphatic. In some embodiments, each R^a is independently branched C_{13-20} aliphatic. In some embodiments, each R^a is independently branched C_{15-20} aliphatic. In some embodiments, each R^a is independently branched C_{13} aliphatic. In some embodiments, each R^a is independently branched C_{14} aliphatic. In some embodiments, each R^a is independently branched C_{15} aliphatic. In some embodiments, each R^a is independently branched C_{16} aliphatic. In some embodiments, each R^a is independently branched C_{17} aliphatic. In some embodiments, each R^a is independently branched C_{18} aliphatic. In some embodiments, each R^a is independently branched C_{19} aliphatic. In some embodiments, each R^a is independently branched C_{20} aliphatic.

[0227] In some embodiments, each R^a is independently optionally substituted C_{6-20} alkyl. In some embodiments, each R^a is independently optionally substituted C_{6-12} alkyl. In some embodiments, each R^a is independently optionally substituted C_{8-11} alkyl. In some embodiments, each R^a is independently optionally substituted C_{9-10} alkyl. In some embodiments, each R^a is independently optionally substituted C_6 alkyl. In some embodiments, each R^a is independently optionally substituted C_7 alkyl. In some embodiments, each R^a is independently optionally substituted C_8 alkyl. In some embodiments, each R^a is independently optionally substituted C_9 alkyl. In some embodiments, each R^a is independently optionally substituted C_{10} alkyl. In some embodiments, each R^a is independently optionally substituted C_{11} alkyl. In some embodiments, each R^a is independently optionally substituted C_{12} alkyl. In some embodiments, each R^a is independently optionally substituted C_{13-20} alkyl. In some embodiments, each R^a is independently optionally substituted C_{15-20} alkyl. In some embodiments, each R^a is independently optionally substituted C_{13} alkyl. In some embodiments, each R^a is independently optionally substituted C_{14} alkyl. In some embodiments, each R^a is independently optionally substituted C_{15} alkyl. In some embodiments, each R^a is independently optionally substituted C_{16} alkyl. In some embodiments, each R^a is independently optionally substituted C_{17} alkyl. In some embodiments, each R^a is independently optionally substituted C_{18} alkyl. In some embodiments, each R^a is independently optionally substituted C_{19} alkyl. In some embodiments, each R^a is independently optionally substituted C_{20} alkyl.

[0228] In some embodiments, each R^a is independently C_{6-20} alkyl. In some embodiments, each R^a is independently C_{6-12} alkyl. In some embodiments, each R^a is independently C_{8-11} alkyl. In some embodiments, each R^a is independently C_{9-10} alkyl. In some embodiments, each R^a is

independently C_6 alkyl. In some embodiments, each R^a is independently C_7 alkyl. In some embodiments, each R^a is independently C_8 alkyl. In some embodiments, each R^a is independently C_9 alkyl. In some embodiments, each R^a is independently C_{10} alkyl. In some embodiments, each R^a is independently C_{11} alkyl. In some embodiments, each R^a is independently C_{12} alkyl. In some embodiments, each R^a is independently C_{13-20} alkyl. In some embodiments, each R^a is independently C_{15-20} alkyl. In some embodiments, each R^a is independently C_{13} alkyl. In some embodiments, each R^a is independently C_{14} alkyl. In some embodiments, each R^a is independently C_{15} alkyl. In some embodiments, each R^a is independently C_{16} alkyl. In some embodiments, each R^a is independently C_{17} alkyl. In some embodiments, each R^a is independently C_{18} alkyl. In some embodiments, each R^a is independently C_{19} alkyl. In some embodiments, each R^a is independently C_{20} alkyl.

[0229] In some embodiments, each R^a is independently straight-chain C_{6-20} alkyl. In some embodiments, each R^a is independently straight-chain C_{6-12} alkyl. In some embodiments, each R^a is independently straight-chain C_{8-11} alkyl. In some embodiments, each R^a is independently straight-chain C_{9-10} alkyl. In some embodiments, each R^a is independently straight-chain C_6 alkyl. In some embodiments, each R^a is independently straight-chain C_7 alkyl. In some embodiments, each R^a is independently straight-chain C_8 alkyl. In some embodiments, each R^a is independently straight-chain C_9 alkyl. In some embodiments, each R^a is independently straight-chain C_{10} alkyl. In some embodiments, each R^a is independently straight-chain C_{11} alkyl. In some embodiments, each R^a is independently straight-chain C_{12} alkyl. In some embodiments, each R^a is independently straight-chain C_{13-20} alkyl. In some embodiments, each R^a is independently straight-chain C_{15-20} alkyl. In some embodiments, each R^a is independently straight-chain C_{13} alkyl. In some embodiments, each R^a is independently straight-chain C_{14} alkyl. In some embodiments, each R^a is independently straight-chain C_{15} alkyl. In some embodiments, each R^a is independently straight-chain C_{16} alkyl. In some embodiments, each R^a is independently straight-chain C_{17} alkyl. In some embodiments, each R^a is independently straight-chain C_{18} alkyl. In some embodiments, each R^a is independently straight-chain C_{19} alkyl. In some embodiments, each R^a is independently straight-chain C_{20} alkyl.

[0230] In some embodiments, each R^a is independently branched C_{6-20} alkyl. In some embodiments, each R^a is independently branched C_{6-12} alkyl. In some embodiments, each R^a is independently branched C_{8-11} alkyl. In some embodiments, each R^a is independently branched C_{9-}

$_{10}$ alkyl. In some embodiments, each R^a is independently branched C_6 alkyl. In some embodiments, each R^a is independently branched C_7 alkyl. In some embodiments, each R^a is independently branched C_8 alkyl. In some embodiments, each R^a is independently branched C_9 alkyl. In some embodiments, each R^a is independently branched C_{10} alkyl. In some embodiments, each R^a is independently branched C_{11} alkyl. In some embodiments, each R^a is independently branched C_{12} alkyl. In some embodiments, each R^a is independently branched C_{13-20} alkyl. In some embodiments, each R^a is independently branched C_{15-20} alkyl. In some embodiments, each R^a is independently branched C_{13} alkyl. In some embodiments, each R^a is independently branched C_{14} alkyl. In some embodiments, each R^a is independently branched C_{15} alkyl. In some embodiments, each R^a is independently branched C_{16} alkyl. In some embodiments, each R^a is independently branched C_{17} alkyl. In some embodiments, each R^a is independently branched C_{18} alkyl. In some embodiments, each R^a is independently branched C_{19} alkyl. In some embodiments, each R^a is independently branched C_{20} alkyl.

[0231] In some embodiments, each R^a is independently optionally substituted C_{6-20} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{6-12} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{8-11} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{9-10} alkenyl. In some embodiments, each R^a is independently optionally substituted C_6 alkenyl. In some embodiments, each R^a is independently optionally substituted C_7 alkenyl. In some embodiments, each R^a is independently optionally substituted C_8 alkenyl. In some embodiments, each R^a is independently optionally substituted C_9 alkenyl. In some embodiments, each R^a is independently optionally substituted C_{10} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{11} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{12} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{13-20} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{15-20} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{13} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{14} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{15} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{16} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{17} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{18}

alkenyl. In some embodiments, each R^a is independently optionally substituted C_{19} alkenyl. In some embodiments, each R^a is independently optionally substituted C_{20} alkenyl.

[0232] In some embodiments, each R^a is independently C_{6-20} alkenyl. In some embodiments, each R^a is independently C_{6-12} alkenyl. In some embodiments, each R^a is independently C_{8-11} alkenyl. In some embodiments, each R^a is independently C_{9-10} alkenyl. In some embodiments, each R^a is independently C_6 alkenyl. In some embodiments, each R^a is independently C_7 alkenyl. In some embodiments, each R^a is independently C_8 alkenyl. In some embodiments, each R^a is independently C_9 alkenyl. In some embodiments, each R^a is independently C_{10} alkenyl. In some embodiments, each R^a is independently C_{11} alkenyl. In some embodiments, each R^a is independently C_{12} alkenyl. In some embodiments, each R^a is independently C_{13-20} alkenyl. In some embodiments, each R^a is independently C_{15-20} alkenyl. In some embodiments, each R^a is independently C_{13} alkenyl. In some embodiments, each R^a is independently C_{14} alkenyl. In some embodiments, each R^a is independently C_{15} alkenyl. In some embodiments, each R^a is independently C_{16} alkenyl. In some embodiments, each R^a is independently C_{17} alkenyl. In some embodiments, each R^a is independently C_{18} alkenyl. In some embodiments, each R^a is independently C_{19} alkenyl. In some embodiments, each R^a is independently C_{20} alkenyl.

[0233] In some embodiments, each R^a is independently straight-chain C_{6-20} alkenyl. In some embodiments, each R^a is independently straight-chain C_{6-12} alkenyl. In some embodiments, each R^a is independently straight-chain C_{8-11} alkenyl. In some embodiments, each R^a is independently straight-chain C_{9-10} alkenyl. In some embodiments, each R^a is independently straight-chain C_6 alkenyl. In some embodiments, each R^a is independently straight-chain C_7 alkenyl. In some embodiments, each R^a is independently straight-chain C_8 alkenyl. In some embodiments, each R^a is independently straight-chain C_9 alkenyl. In some embodiments, each R^a is independently straight-chain C_{10} alkenyl. In some embodiments, each R^a is independently straight-chain C_{11} alkenyl. In some embodiments, each R^a is independently straight-chain C_{12} alkenyl. In some embodiments, each R^a is independently straight-chain C_{13-20} alkenyl. In some embodiments, each R^a is independently straight-chain C_{15-20} alkenyl. In some embodiments, each R^a is independently straight-chain C_{13} alkenyl. In some embodiments, each R^a is independently straight-chain C_{14} alkenyl. In some embodiments, each R^a is independently straight-chain C_{15} alkenyl. In some embodiments, each R^a is independently straight-chain C_{16} alkenyl. In some embodiments, each R^a is independently straight-chain C_{17} alkenyl. In some embodiments, each R^a is independently

straight-chain C_{18} alkenyl. In some embodiments, each R^a is independently straight-chain C_{19} alkenyl. In some embodiments, each R^a is independently straight-chain C_{20} alkenyl.

[0234] In some embodiments, each R^a is independently branched C_{6-20} alkenyl. In some embodiments, each R^a is independently branched C_{6-12} alkenyl. In some embodiments, each R^a is independently branched C_{8-11} alkenyl. In some embodiments, each R^a is independently branched C_{9-10} alkenyl. In some embodiments, each R^a is independently branched C_6 alkenyl. In some embodiments, each R^a is independently branched C_7 alkenyl. In some embodiments, each R^a is independently branched C_8 alkenyl. In some embodiments, each R^a is independently branched C_9 alkenyl. In some embodiments, each R^a is independently branched C_{10} alkenyl. In some embodiments, each R^a is independently branched C_{11} alkenyl. In some embodiments, each R^a is independently branched C_{12} alkenyl. In some embodiments, each R^a is independently branched C_{13-20} alkenyl. In some embodiments, each R^a is independently branched C_{15-20} alkenyl. In some embodiments, each R^a is independently branched C_{13} alkenyl. In some embodiments, each R^a is independently branched C_{14} alkenyl. In some embodiments, each R^a is independently branched C_{15} alkenyl. In some embodiments, each R^a is independently branched C_{16} alkenyl. In some embodiments, each R^a is independently branched C_{17} alkenyl. In some embodiments, each R^a is independently branched C_{18} alkenyl. In some embodiments, each R^a is independently branched C_{19} alkenyl. In some embodiments, each R^a is independently branched C_{20} alkenyl.

[0235] In some embodiments, each R^a is independently optionally substituted C_{6-20} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{6-12} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{8-11} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{9-10} alkynyl. In some embodiments, each R^a is independently optionally substituted C_6 alkynyl. In some embodiments, each R^a is independently optionally substituted C_7 alkynyl. In some embodiments, each R^a is independently optionally substituted C_8 alkynyl. In some embodiments, each R^a is independently optionally substituted C_9 alkynyl. In some embodiments, each R^a is independently optionally substituted C_{10} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{11} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{12} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{13-20} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{15-20} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{13} alkynyl. In some embodiments,

each R^a is independently optionally substituted C_{14} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{15} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{16} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{17} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{18} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{19} alkynyl. In some embodiments, each R^a is independently optionally substituted C_{20} alkynyl.

[0236] In some embodiments, each R^a is independently C_{6-20} alkynyl. In some embodiments, each R^a is independently C_{6-12} alkynyl. In some embodiments, each R^a is independently C_{8-11} alkynyl. In some embodiments, each R^a is independently C_{9-10} alkynyl. In some embodiments, each R^a is independently C_6 alkynyl. In some embodiments, each R^a is independently C_7 alkynyl. In some embodiments, each R^a is independently C_8 alkynyl. In some embodiments, each R^a is independently C_9 alkynyl. In some embodiments, each R^a is independently C_{10} alkynyl. In some embodiments, each R^a is independently C_{11} alkynyl. In some embodiments, each R^a is independently C_{12} alkynyl. In some embodiments, each R^a is independently C_{13-20} alkynyl. In some embodiments, each R^a is independently C_{15-20} alkynyl. In some embodiments, each R^a is independently C_{13} alkynyl. In some embodiments, each R^a is independently C_{14} alkynyl. In some embodiments, each R^a is independently C_{15} alkynyl. In some embodiments, each R^a is independently C_{16} alkynyl. In some embodiments, each R^a is independently C_{17} alkynyl. In some embodiments, each R^a is independently C_{18} alkynyl. In some embodiments, each R^a is independently C_{19} alkynyl. In some embodiments, each R^a is independently C_{20} alkynyl.

[0237] In some embodiments, each R^a is independently straight-chain C_{6-20} alkynyl. In some embodiments, each R^a is independently straight-chain C_{6-12} alkynyl. In some embodiments, each R^a is independently straight-chain C_{8-11} alkynyl. In some embodiments, each R^a is independently straight-chain C_{9-10} alkynyl. In some embodiments, each R^a is independently straight-chain C_6 alkynyl. In some embodiments, each R^a is independently straight-chain C_7 alkynyl. In some embodiments, each R^a is independently straight-chain C_8 alkynyl. In some embodiments, each R^a is independently straight-chain C_9 alkynyl. In some embodiments, each R^a is independently straight-chain C_{10} alkynyl. In some embodiments, each R^a is independently straight-chain C_{11} alkynyl. In some embodiments, each R^a is independently straight-chain C_{12} alkynyl. In some embodiments, each R^a is independently straight-chain C_{13-20} alkynyl. In some embodiments, each R^a is independently straight-chain C_{15-20} alkynyl. In some embodiments, each R^a is independently

straight-chain C_{13} alkynyl. In some embodiments, each R^a is independently straight-chain C_{14} alkynyl. In some embodiments, each R^a is independently straight-chain C_{15} alkynyl. In some embodiments, each R^a is independently straight-chain C_{16} alkynyl. In some embodiments, each R^a is independently straight-chain C_{17} alkynyl. In some embodiments, each R^a is independently straight-chain C_{18} alkynyl. In some embodiments, each R^a is independently straight-chain C_{19} alkynyl. In some embodiments, each R^a is independently straight-chain C_{20} alkynyl.

[0238] In some embodiments, each R^a is independently optionally substituted C_{6-20} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{6-12} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{6-10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_6 haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_7 haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_8 haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_9 haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{15-20} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{15} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{16} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{17} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{18} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{19} haloaliphatic. In some embodiments, each R^a is independently optionally substituted C_{20} haloaliphatic.

[0239] In some embodiments, each R^a is independently optionally substituted straight-chain C_{6-20} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{6-12} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{6-10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_6 haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_7 haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_8 haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_9 haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{15-20} haloaliphatic.

In some embodiments, each R^a is independently optionally substituted straight-chain C_{15} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{16} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{17} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{18} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{19} haloaliphatic. In some embodiments, each R^a is independently optionally substituted straight-chain C_{20} haloaliphatic.

[0240] In some embodiments, each R^a is independently optionally substituted branched C_{6-20} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{6-12} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{6-10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_6 haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_7 haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_8 haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_9 haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{10} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{15-20} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{15} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{16} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{17} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{18} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{19} haloaliphatic. In some embodiments, each R^a is independently optionally substituted branched C_{20} haloaliphatic.

[0241] In some embodiments, each R^a is independently C_{6-20} haloaliphatic. In some embodiments, each R^a is independently C_{6-12} haloaliphatic. In some embodiments, each R^a is independently C_{6-10} haloaliphatic. In some embodiments, each R^a is independently C_6 haloaliphatic. In some embodiments, each R^a is independently C_7 haloaliphatic. In some embodiments, each R^a is independently C_8 haloaliphatic. In some embodiments, each R^a is independently C_9 haloaliphatic. In some embodiments, each R^a is independently C_{10} haloaliphatic. In some embodiments, each R^a is independently C_{15-20} haloaliphatic. In some embodiments, each R^a is independently C_{15} haloaliphatic. In some embodiments, each R^a is independently C_{16} haloaliphatic. In some

embodiments, each R^a is independently C_{17} haloaliphatic. In some embodiments, each R^a is independently C_{18} haloaliphatic. In some embodiments, each R^a is independently C_{19} haloaliphatic. In some embodiments, each R^a is independently C_{20} haloaliphatic.

[0242] In some embodiments, each R^a is independently straight-chain C_{6-20} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{6-12} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{6-10} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_6 haloaliphatic. In some embodiments, each R^a is independently straight-chain C_7 haloaliphatic. In some embodiments, each R^a is independently straight-chain C_8 haloaliphatic. In some embodiments, each R^a is independently straight-chain C_9 haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{10} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{15-20} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{15} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{16} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{17} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{18} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{19} haloaliphatic. In some embodiments, each R^a is independently straight-chain C_{20} haloaliphatic.

[0243] In some embodiments, each R^a is independently optionally substituted C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, R^a is independently optionally substituted C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_6 haloalkyl comprising 1-3 fluorine

atoms. In some embodiments, each R^a is independently optionally substituted C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0244] In some embodiments, each R^a is independently optionally substituted C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{17} haloalkyl comprising 1-3

fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently optionally substituted C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0245] In some embodiments, each R^a is independently C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{6-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_9 haloalkyl comprising 1-7 fluorine

atoms. In some embodiments, each R^a is independently C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{10} haloalkyl comprising 1-3 fluorine atoms.

[0246] In some embodiments, each R^a is independently C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0247] In some embodiments, each R^a is independently straight-chain C_{6-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-}

$_{20}$ haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-12} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-12} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-12} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{6-10} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_6 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_6 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_6 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_7 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_7 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_7 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_8 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_8 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_8 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_9 haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_9 haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_9 haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{10} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{10} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{10} haloalkyl comprising 1-3 fluorine atoms.

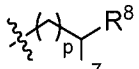
[0248] In some embodiments, each R^a is independently straight-chain C_{15-20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{15-20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{15-20} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{15} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{15} haloalkyl comprising 1-5 fluorine atoms. In some embodiments,

each R^a is independently straight-chain C_{15} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{16} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{16} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{16} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{17} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{17} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{17} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{18} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{18} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{18} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{19} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{19} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{19} haloalkyl comprising 1-3 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{20} haloalkyl comprising 1-7 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{20} haloalkyl comprising 1-5 fluorine atoms. In some embodiments, each R^a is independently straight-chain C_{20} haloalkyl comprising 1-3 fluorine atoms.

[0249] In some embodiments, each R^a is independently optionally substituted 3- to 12-membered cycloaliphatic. In some embodiments, each R^a is independently optionally substituted 3- to 7-membered cycloaliphatic. In some embodiments, each R^a is independently optionally substituted 4- to 7-membered cycloaliphatic. In some embodiments, each R^a is independently optionally substituted 5- to 7-membered cycloaliphatic. In some embodiments, each R^a is independently optionally substituted 6- to 7-membered cycloaliphatic. In some embodiments, each R^a is optionally substituted cyclopentyl. In some embodiments, each R^a is optionally substituted cyclohexyl. In some embodiments, each R^a is independently cyclohexyl substituted with R°. In some embodiments, each R^a is independently cyclohexyl substituted with a 5- or 6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which is further substituted with $-(CH_2)_{0-2}R^{\bullet}$. In some embodiments,

each R^a is independently cyclohexyl substituted with cyclohexyl, which is further substituted with C_{1-6} aliphatic. In some embodiments, each R^a is optionally substituted cycloheptyl.

[0250] In some embodiments, each R^a is optionally substituted 1-adamantyl. In some embodiments, each R^a is optionally substituted 2-adamantyl. In some embodiments, each R^a is independently optionally substituted sterolyl. In some embodiments, each R^a is independently optionally substituted cholesterolyl. In some embodiments, each R^a is optionally substituted phenyl. In some embodiments, each R^a is independently phenyl substituted with R°. In some embodiments, each R^a is independently phenyl substituted with C_{1-6} aliphatic.

[0251] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III' and III, each of $-L^3-R"$, $-L^3-R$, and $-L^{3a}-R^a$ is independently  .

[0252] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, R^7 is optionally substituted C_{4-10} aliphatic or C_{4-10} haloaliphatic. In some embodiments, R^7 is optionally substituted C_{4-10} aliphatic. In some embodiments, R^7 is optionally substituted C_{4-8} aliphatic. In some embodiments, R^7 is optionally substituted C_{4-6} aliphatic. In some embodiments, R^7 is optionally substituted C_4 aliphatic. In some embodiments, R^7 is optionally substituted C_5 aliphatic. In some embodiments, R^7 is optionally substituted C_6 aliphatic. In some embodiments, R^7 is optionally substituted C_7 aliphatic. In some embodiments, R^7 is optionally substituted C_8 aliphatic. In some embodiments, R^7 is optionally substituted C_9 aliphatic. In some embodiments, R^7 is optionally substituted C_{10} aliphatic.

[0253] In some embodiments, R^7 is optionally substituted C_{4-10} haloaliphatic. In some embodiments, R^7 is optionally substituted C_{4-8} haloaliphatic. In some embodiments, R^7 is optionally substituted C_{4-6} haloaliphatic. In some embodiments, R^7 is optionally substituted C_4 haloaliphatic. In some embodiments, R^7 is optionally substituted C_5 haloaliphatic. In some embodiments, R^7 is optionally substituted C_6 haloaliphatic. In some embodiments, R^7 is optionally substituted C_7 haloaliphatic. In some embodiments, R^7 is optionally substituted C_8 haloaliphatic. In some embodiments, R^7 is optionally substituted C_9 haloaliphatic. In some embodiments, R^7 is optionally substituted C_{10} haloaliphatic.

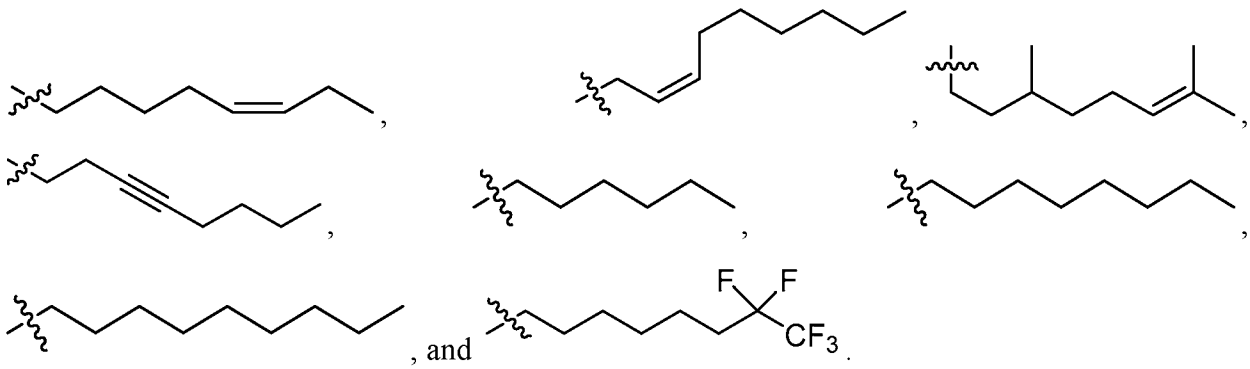
[0254] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, R^8 is optionally substituted C_{2-8} aliphatic or C_{2-8} haloaliphatic. In some embodiments, R^8 is optionally substituted C_{2-8} aliphatic. In some embodiments, R^8 is optionally substituted C_{2-6} aliphatic. In

some embodiments, R^8 is optionally substituted C_{2-4} aliphatic. In some embodiments, R^8 is optionally substituted C_2 aliphatic. In some embodiments, R^8 is optionally substituted C_3 aliphatic. In some embodiments, R^8 is optionally substituted C_4 aliphatic. In some embodiments, R^8 is optionally substituted C_5 aliphatic. In some embodiments, R^8 is optionally substituted C_6 aliphatic. In some embodiments, R^8 is optionally substituted C_7 aliphatic. In some embodiments, R^8 is optionally substituted C_8 aliphatic.

[0255] In some embodiments, R^8 is optionally substituted C_{2-8} haloaliphatic. In some embodiments, R^8 is optionally substituted C_{2-6} haloaliphatic. In some embodiments, R^8 is optionally substituted C_{2-4} haloaliphatic. In some embodiments, R^8 is optionally substituted C_2 haloaliphatic. In some embodiments, R^8 is optionally substituted C_3 haloaliphatic. In some embodiments, R^8 is optionally substituted C_4 haloaliphatic. In some embodiments, R^8 is optionally substituted C_5 haloaliphatic. In some embodiments, R^8 is optionally substituted C_6 haloaliphatic. In some embodiments, R^8 is optionally substituted C_7 haloaliphatic. In some embodiments, R^8 is optionally substituted C_8 haloaliphatic.

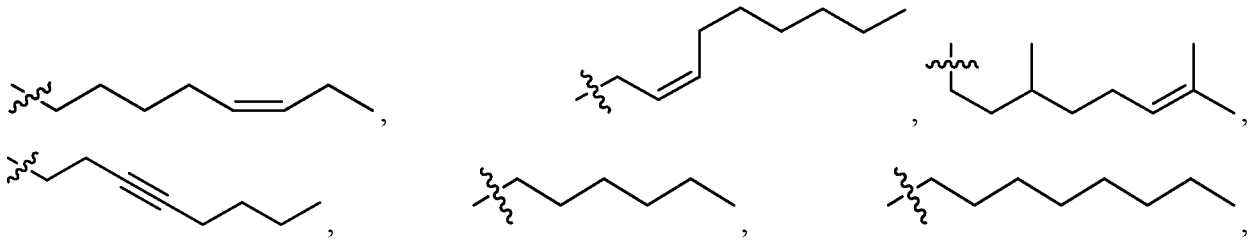
[0256] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1.

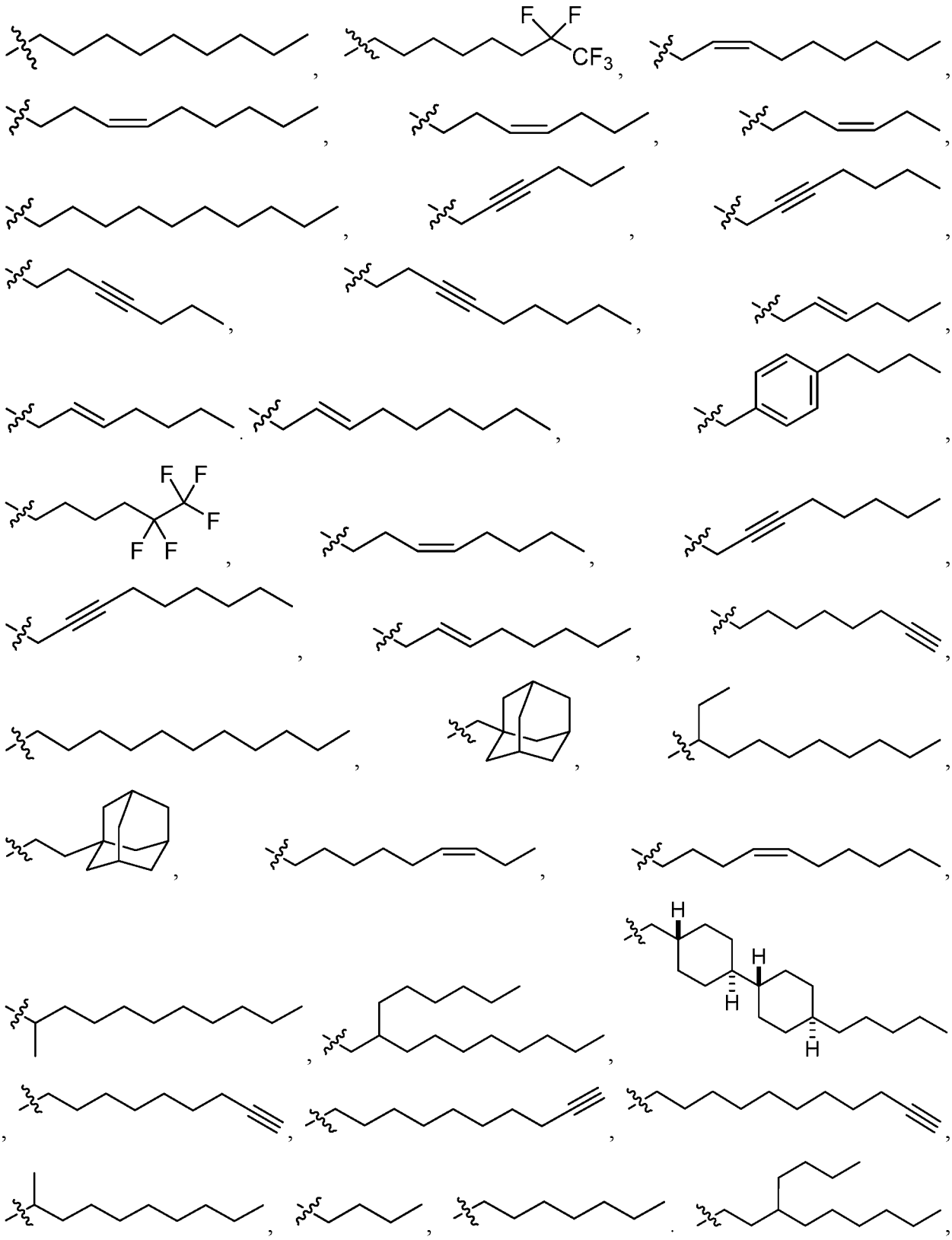
[0257] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III' and III, each of $-L^3-R$", $-L^3-R$, and $-L^{3a}-R^a$ is independently selected from the group consisting of



, and .

[0258] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III' and III, each of $--L^3-R$", L^3-R, and $-L^{3a}-R^a$ is independently selected from the group consisting of

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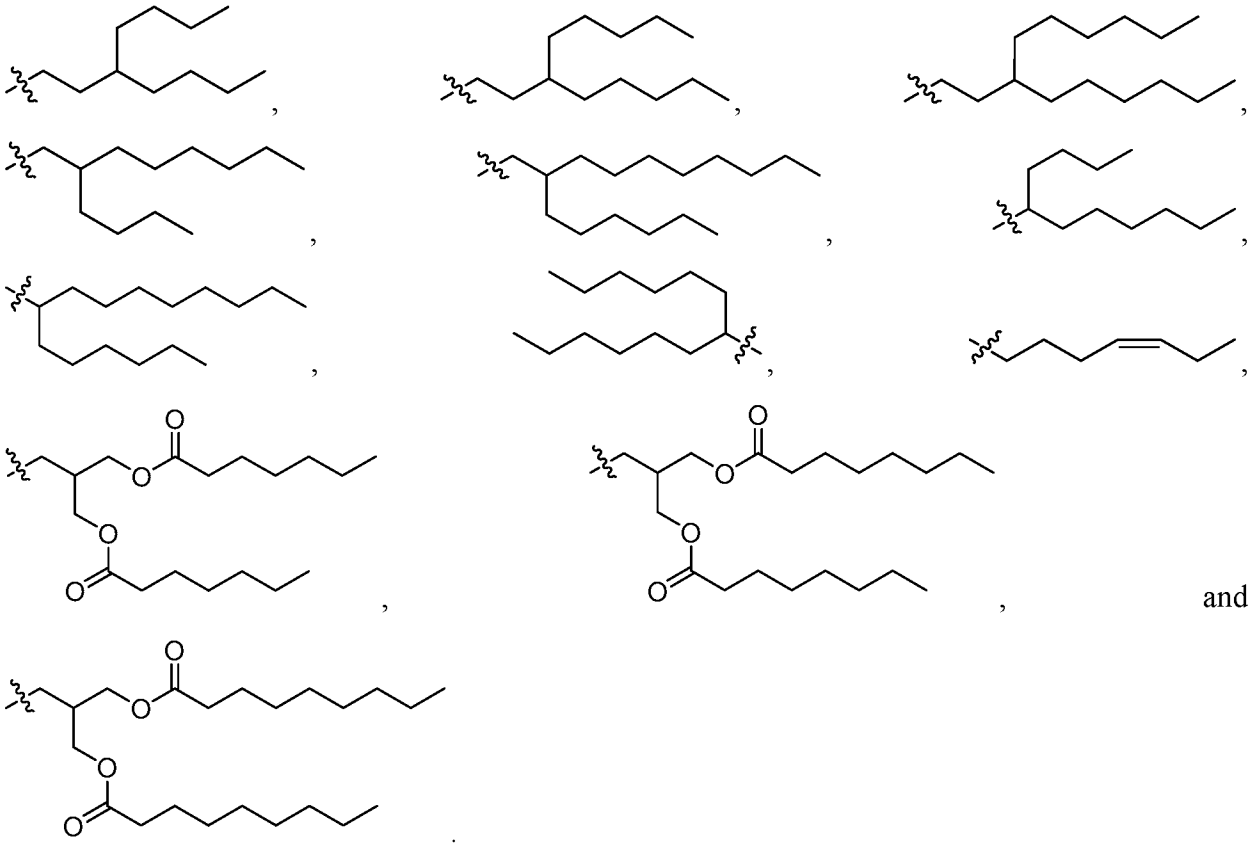
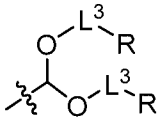
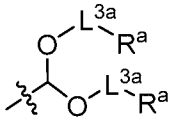
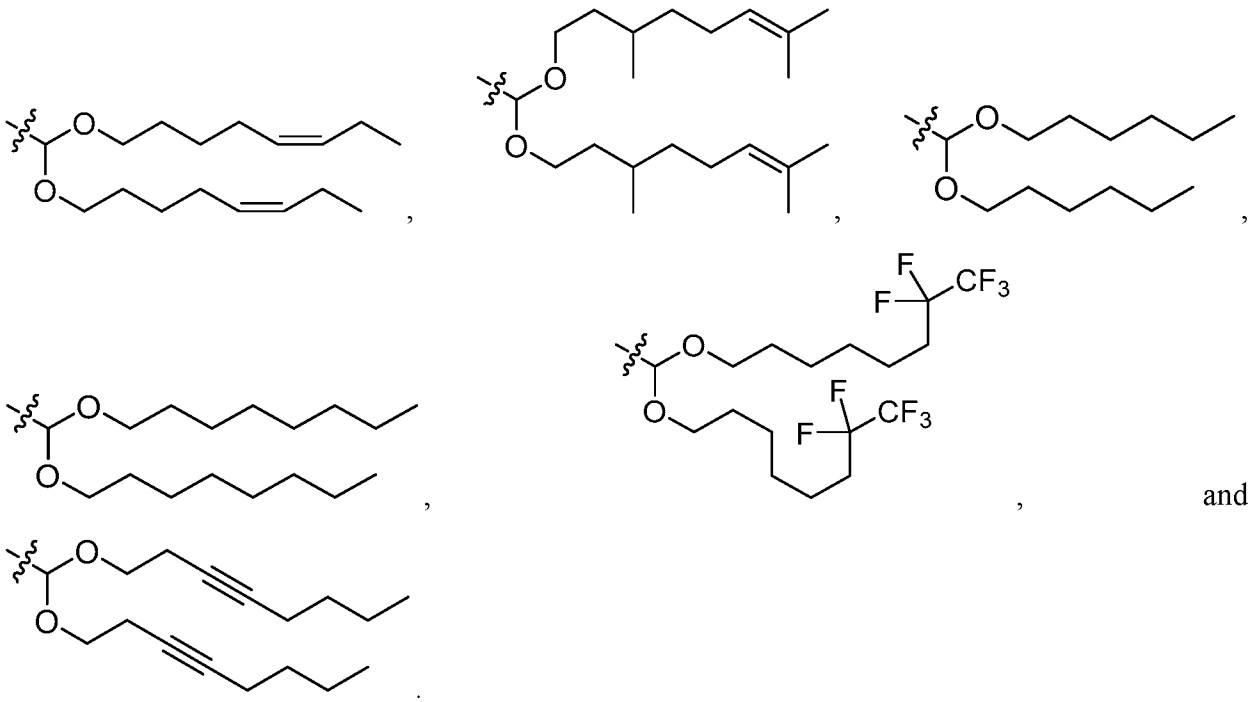


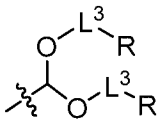
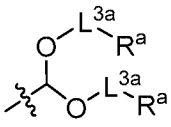
and

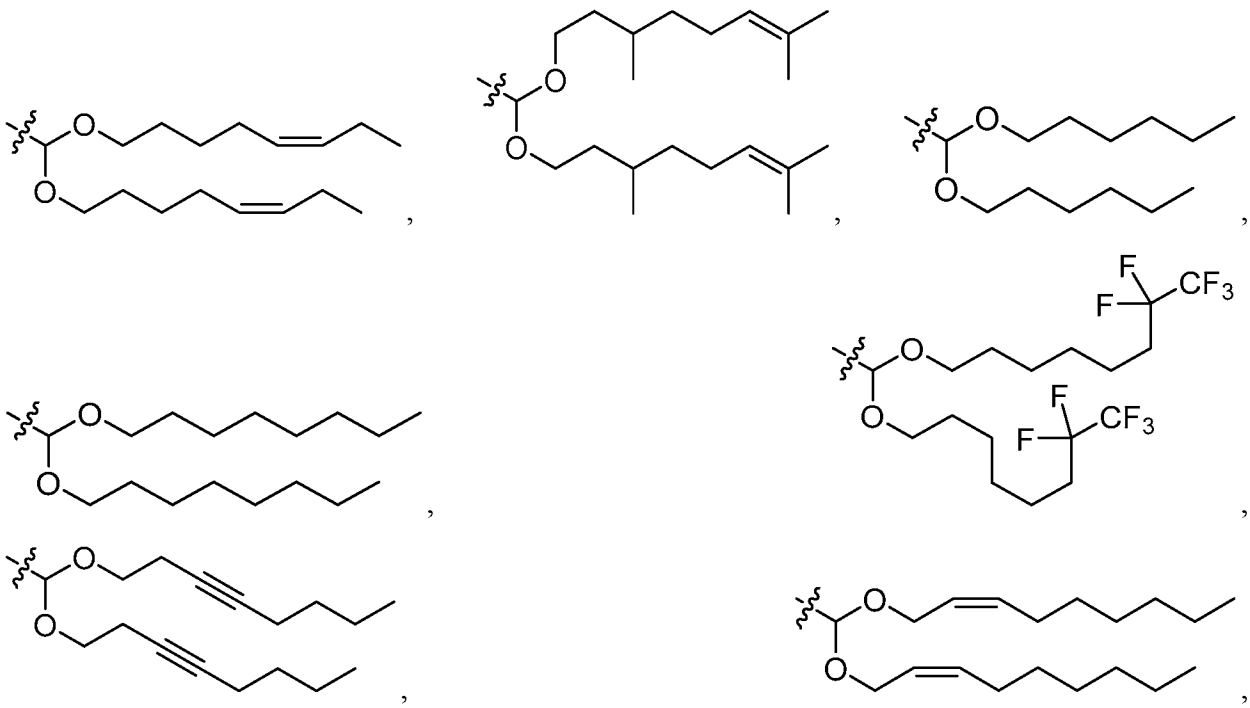
[0259] In some embodiments of any of Formulae A, I', I, II", II', II, III', and III, all of $-L^3-R$ moieties are the same. In some embodiments of any of Formulae A, I', and I, two of $-L^3-R$ moieties are the same, both of which are different from the third $-L^3-R$ moiety. In some embodiments of any of Formulae II", II', II, III', and III, two of $-L^3-R$ moieties are the same, both of which are different from the other two $-L^3-R$ moieties.

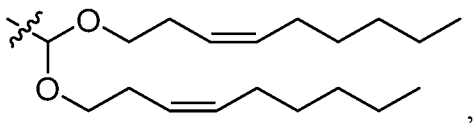
[0260] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each of

 and  is independently selected from the group consisting of



[0261] In some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each of  and  is independently selected from the group consisting of

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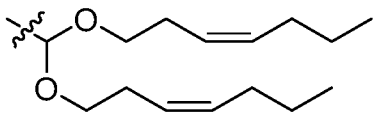
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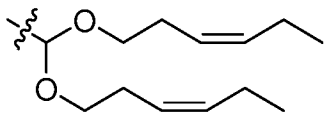
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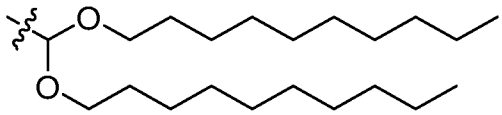
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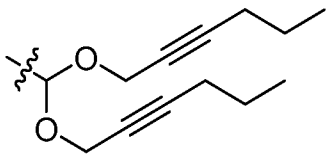
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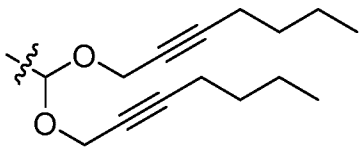
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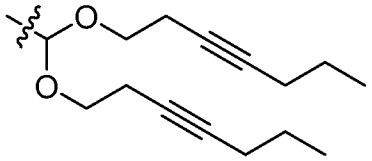
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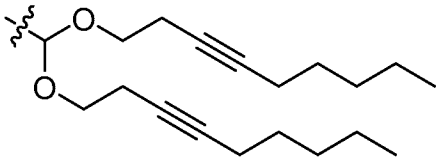
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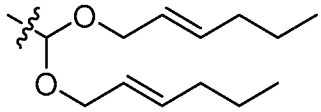
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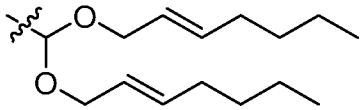
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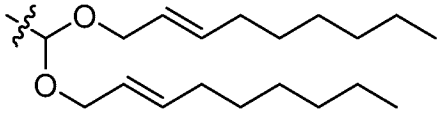
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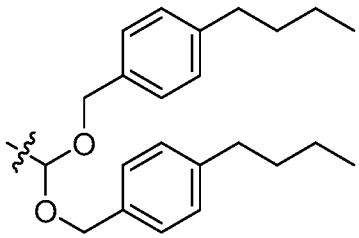
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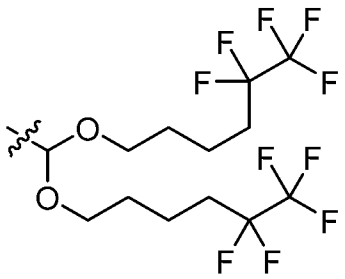
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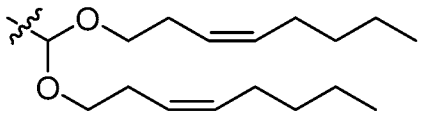
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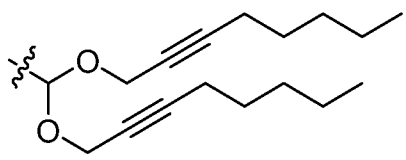
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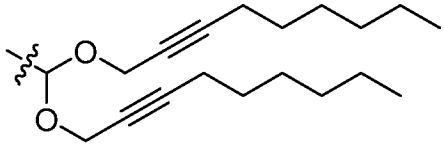
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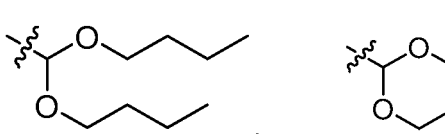
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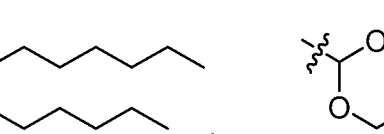
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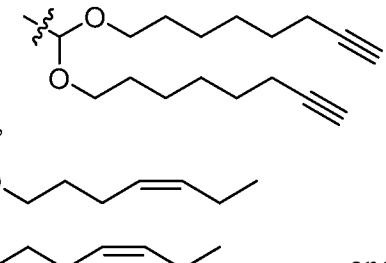
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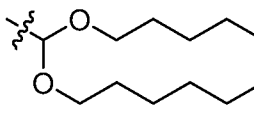
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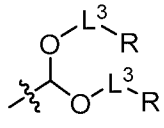
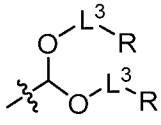
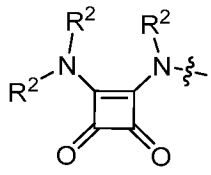
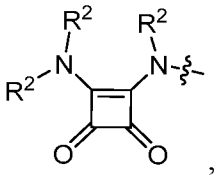
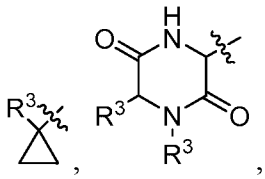
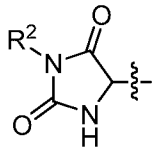
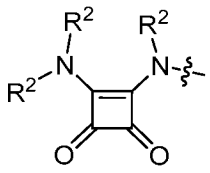
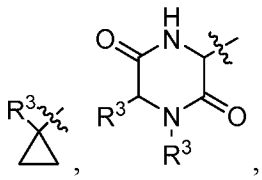
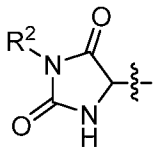
[0262] In some embodiments of any of Formulae II", II', II, III', and III, the two  moieties are the same. In some embodiments, the two  moieties are different.

[0263] As described above, in some embodiments of any of Formulae A', I", II", and III', R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups.

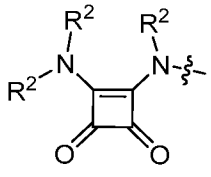
[0264] In some embodiments of any of Formulae A, I', II', and III, R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and

sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$,  , or  .

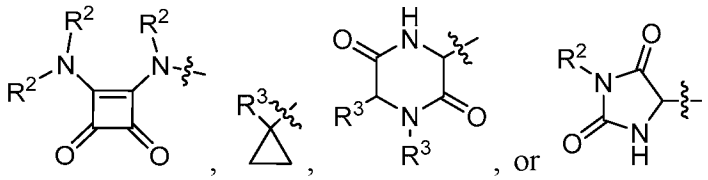
[0265] In some embodiments of any of Formulae I and II, R^1 is hydrogen, a 3- to 7-membered cycloaliphatic ring, a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$,  , or  .

[0266] In some embodiments, R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$,

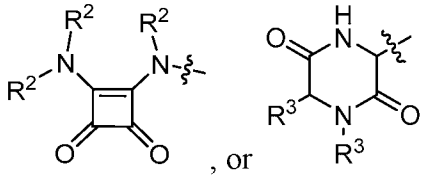
$-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$.



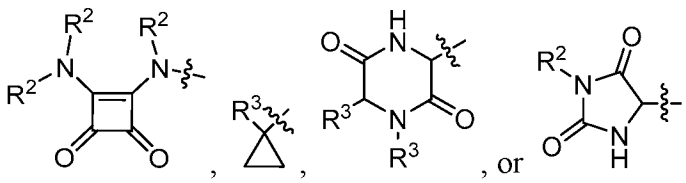
[0267] In some embodiments, R^1 is , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups.



[0268] In some embodiments, R^1 is , , , or . In some embodiments, R^1 is , or .



[0269] In some embodiments, R^1 is hydrogen, optionally substituted phenyl, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, $-P(O)(OR^2)_2$,



, , , or .

[0270] In some embodiments, R^1 is hydrogen.

[0271] In some embodiments, R^1 is optionally substituted phenyl. In some embodiments, R^1 is phenyl substituted with one or more -OR°, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more –OH, -OR•, –C(O)NH$_2$, –C(O)NHR•, or –C(O)NR•$_2$. In some embodiments, R^1 is phenyl substituted with -C(O)N(R°)$_2$, wherein one R° is further substituted with –C(O)NH$_2$. In some embodiments, R^1 is phenyl substituted with C_{1-4} alkyl.

[0272] In some embodiments, R^1 is optionally substituted 3- to 7-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 4- to 7-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 5- to 6-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 3-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 4-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 5-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 6-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted 7-membered cycloaliphatic. In some embodiments, R^1 is optionally substituted cyclopentyl. In some embodiments, R^1 is optionally substituted cyclohexyl. In some embodiments, R^1 is optionally substituted cycloheptyl.

[0273] In some embodiments, R^1 is optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 4- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5- to 6-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 5- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, =O, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, R^1 is optionally substituted 3-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 4-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5-membered heterocyclyl comprising 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 5-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, =O, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, R^1 is optionally substituted 5-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 5-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, =O, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, R^1 is optionally substituted 6-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, =O, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, R^1 is optionally substituted 6-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 6-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, =O, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, R^1 is optionally substituted 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 7-membered heterocyclyl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 7-membered heterocyclyl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is an optionally substituted group selected from morpholinyl, pyrrolidinyl, thiomorpholinyl, piperidinyl, piperazinyl, and imidazolidinyl. In some embodiments, R^1 is optionally substituted morpholinyl. In some embodiments, R^1 is optionally substituted pyrrolidinyl. In some embodiments, R^1 is optionally substituted thiomorpholinyl. In some embodiments, R^1 is an optionally substituted piperidinyl. In some embodiments, R^1 is optionally substituted piperazinyl. In some embodiments, R^1 is optionally substituted imidazolidinyl.

[0274] In some embodiments, R^1 is optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

In some embodiments, R^1 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 5-membered monocyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 6-membered monocyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 6-membered monocyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 6-membered monocyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted pyridinyl or triazolyl. In some embodiments, R^1 is optionally substituted pyridinyl. In some embodiments, R^1 is optionally substituted triazolyl.

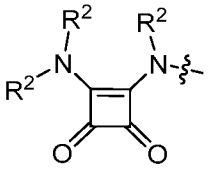
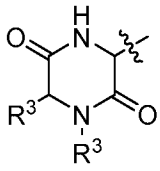
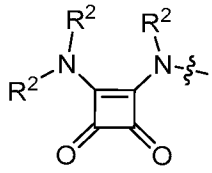
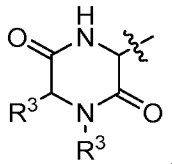
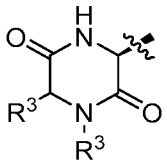
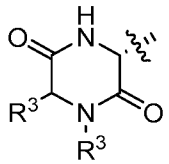
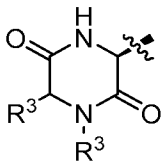
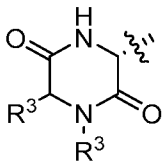
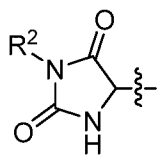
[0275] In some embodiments, R^1 is optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 8-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 8-membered bicyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 8-membered bicyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 8-membered bicyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with one or more $-OR^\circ$, $-C(O)N(R^\circ)_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or $-OR^\bullet$. In some embodiments, R^1 is optionally substituted 9-membered bicyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 9-membered

bicyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 9-membered bicyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 10-membered bicyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 10-membered bicyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted 10-membered bicyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^1 is optionally substituted indazolyl.

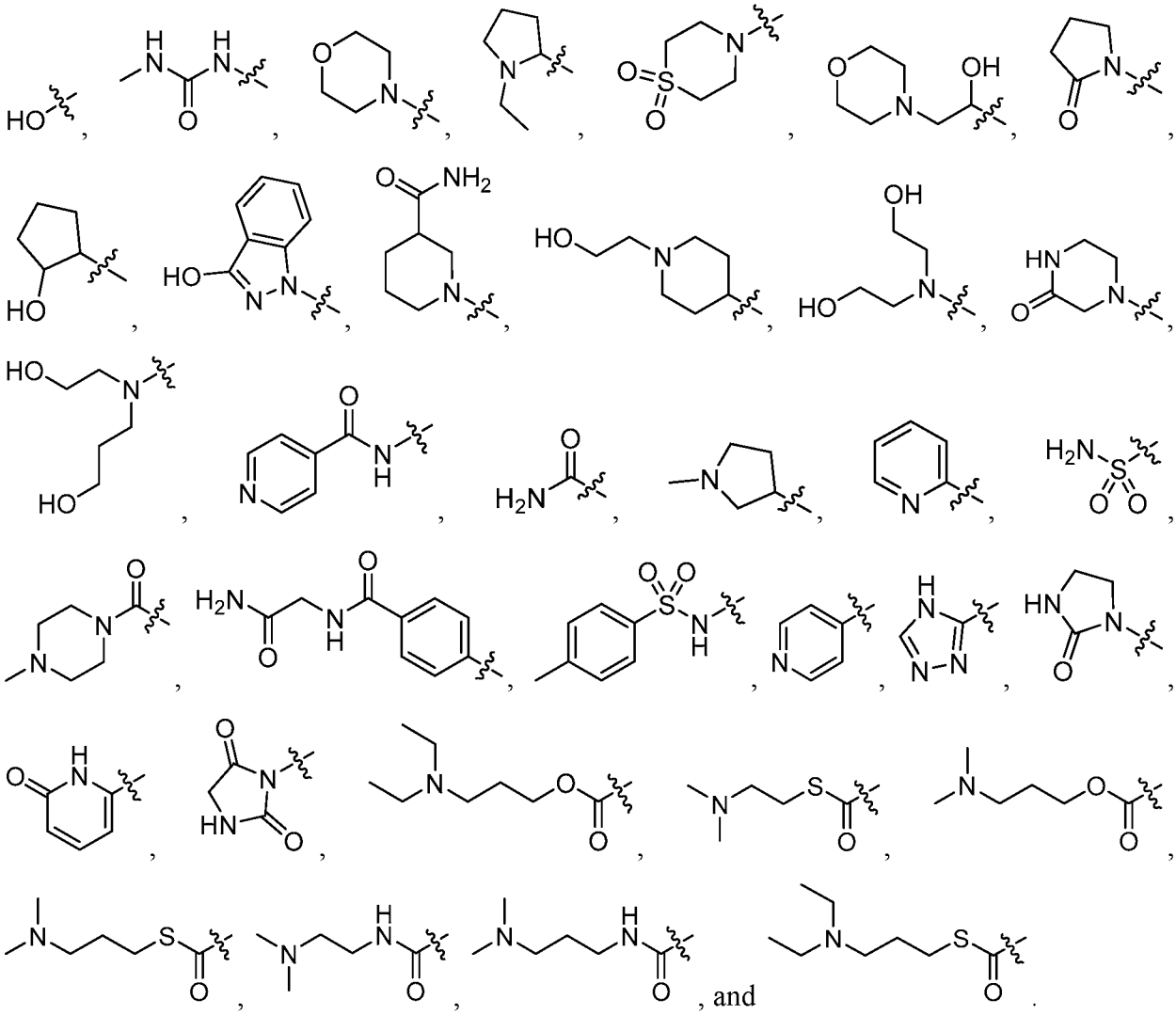
[0276] In some embodiments, R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$.

[0277] In some embodiments, R^1 is hydrogen, optionally substituted phenyl, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, $-P(O)(OR^2)_2$, or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups.

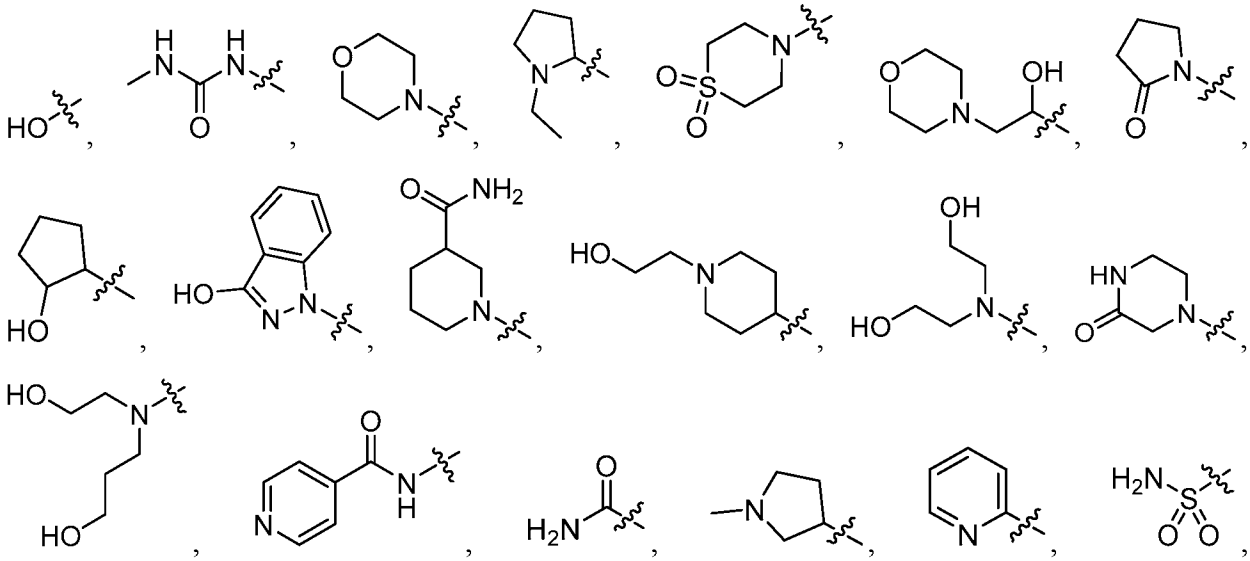
[0278] In some embodiments, R^1 is $-OR^2$, $-OC(O)OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, or $-CR^2(OR^2)R^3$. In some embodiments, R^1 is $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$,

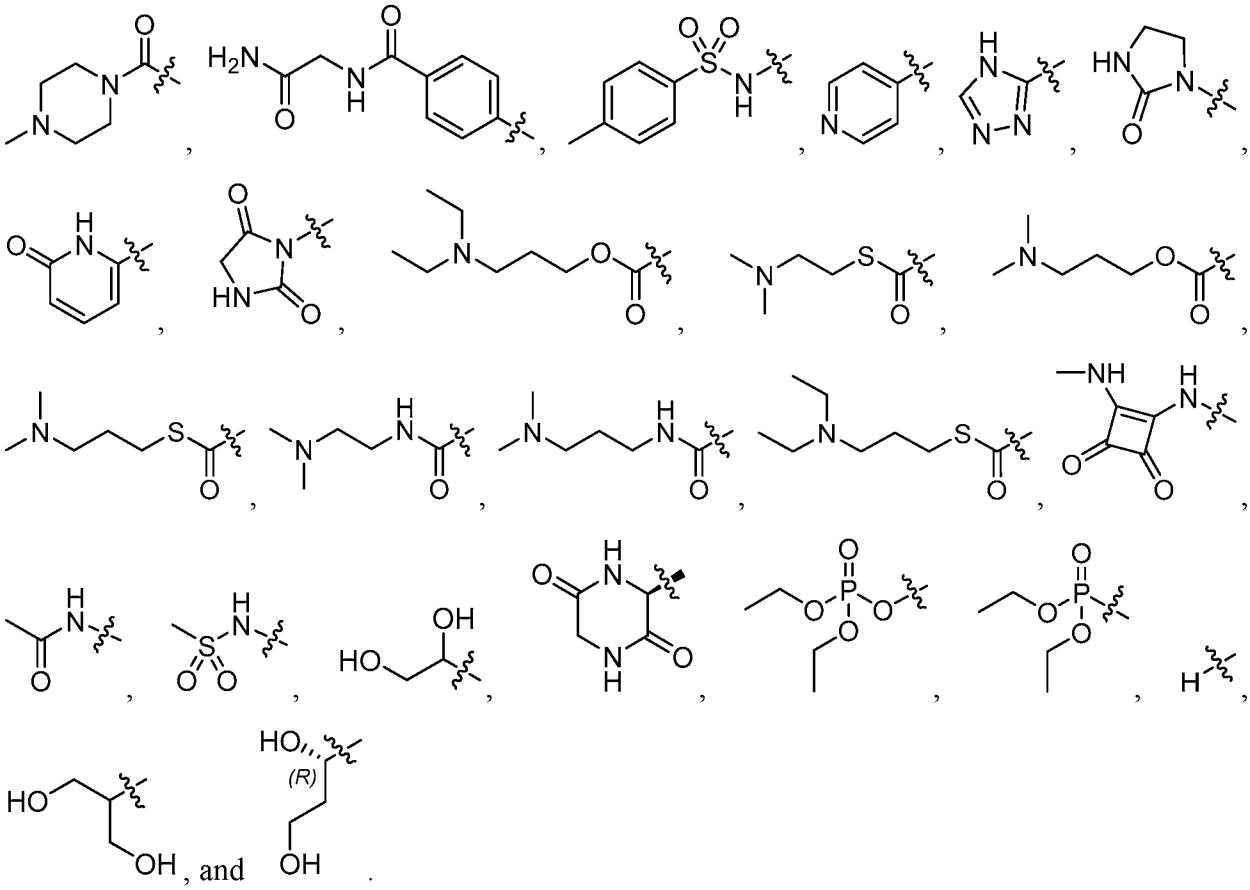
-C(O)N(R^2)$_2$, -S(O)$_2$N(R^2)$_2$, -NR^2C(O)R^2, or -CR^2(OR^2)R^3. In some embodiments, R^1 is -CR^2(OR^2)R^3, ,  or  . In some embodiments, R^1 is -OR^2. In some embodiments, R^1 is -OC(O)OR^2. In some embodiments, R^1 is -C(O)OR^2. In some embodiments, R^1 is -C(O)SR^2. In some embodiments, R^1 is -N(R^2)$_2$. In some embodiments, R^1 is -C(O)N(R^2)$_2$. In some embodiments, R^1 is -S(O)$_2$N(R^2)$_2$. In some embodiments, R^1 is -NR^2C(O)R^2. In some embodiments, R^1 is -NR^2S(O)$_2$$R^2$. In some embodiments, R^1 is -NR^2C(O)N(R^2)$_2$. In some embodiments, R^1 is -NR^2C(S)N(R^2)$_2$. In some embodiments, R^1 is -NR^2C(NR^2)N(R^2)$_2$. In some embodiments, R^1 is  . In some embodiments, R^1 is -CR^2(R^3)$_2$. In some embodiments, R^1 is -CR^2(OR^2)R^3. In some embodiments, R^1 is -OP(O)(OR^2)$_2$. In some embodiments, R^1 is -P(O)(OR^2)$_2$. In some embodiments, R^1 is . In some embodiments, R^1 is  . In some embodiments, R^1 is  or  . In some embodiments, R^1 is  . In some embodiments, R^1 is  . In some embodiments, R^1 is  .

[0279] In some embodiments, R^1 is selected from the group consisting of



[0280] In some embodiments, R^1 is selected from the group consisting of





[0281] As described above, in some embodiments of any of Formulae A', I", II", and III', each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0282] in some embodiments of any of Formulae A, I', II', and III, each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two occurrences of R^2, taken together with the atom(s) to

which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0283] In some embodiments of any of Formulae I and II, each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, a 3- to 7-membered cycloaliphatic ring, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0284] In some embodiments, each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0285] In some embodiments, each R^2 is independently hydrogen, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, and 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, each R^2 is independently hydrogen, oxo, $-(CH_2)_n-R^4$, or an optionally substituted group selected from phenyl, and 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0286] In some embodiments, each R^2 is independently hydrogen, $-(CH_2)_n-R^4$, or optionally substituted C_{1-6} aliphatic. In some embodiments, each R^2 is independently hydrogen, or $-(CH_2)_n-R^4$.

[0287] In some embodiments, each R^2 is hydrogen. In some embodiments, each R^2 is oxo. In some embodiments, each R^2 is -CN.

[0288] In some embodiments, each R^2 is independently $-(CH_2)_n-R^4$. In some embodiments, each R^2 is independently $-(CH_2)-R^4$, $-(CH_2)_2-R^4$, or $-(CH_2)_3-R^4$. In some embodiments, each R^2 is independently $-(CH_2)_2-R^4$ or $-(CH_2)_3-R^4$. In some embodiments, each R^2 is independently $-(CH_2)-R^4$. In some embodiments, each R^2 is independently $-(CH_2)_2-R^4$. In some embodiments, each R^2 is independently $-(CH_2)_3-R^4$. In some embodiments, each R^2 is independently $-(CH_2)_4-R^4$.

[0289] In some embodiments, each R^2 is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R^2 is independently optionally substituted C_{1-4} aliphatic. In some embodiments, each R^2 is independently optionally substituted C_1 aliphatic. In some embodiments, each R^2 is independently optionally substituted C_2 aliphatic. In some embodiments, each R^2 is independently optionally substituted C_3 aliphatic. In some embodiments, each R^2 is independently optionally substituted C_4 aliphatic. In some embodiments, each R^2 is independently optionally substituted C_5 aliphatic. In some embodiments, each R^2 is independently optionally substituted C_6 aliphatic. In some embodiments, each R^2 is methyl. In some embodiments, each R^2 is ethyl.

[0290] In some embodiments, each R^2 is optionally substituted phenyl. In some embodiments, R^2 is phenyl substituted with one or more $-OR^\circ$, $-C(O)N(R^\circ)_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or $-OR^\bullet$. In some embodiments, R^2 is phenyl substituted with C_{1-4} alkyl.

[0291] In some embodiments, R^2 is optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 5-membered monocyclic heteroaryl comprising 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 5-membered monocyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 6-membered monocyclic heteroaryl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 6-membered monocyclic heteroaryl comprising 1-2

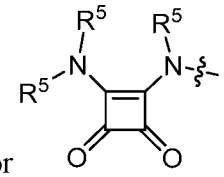
heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted 6-membered monocyclic heteroaryl comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, R^2 is optionally substituted pyridinyl.

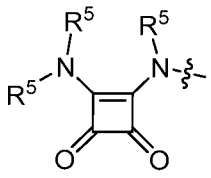
[0292] In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4-membered heterocyclyl comprising 0 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 5-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur substituted with one or more -OR°, -C(O)N(R°)$_2$, or C_{1-4} alkyl optionally substituted with one or more -OH or -OR•. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted piperazinyl.

[0293] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each R^3 is independently -$(CH_2)_n$-R^4; or two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0294] In some embodiments, each R^3 is independently R^4. In some embodiments, each R^3 is independently $-(CH_2)-R^4$. In some embodiments, each R^3 is independently $-(CH_2)_2-R^4$. In some embodiments, each R^3 is independently $-(CH_2)_3-R^4$. In some embodiments, each R^3 is independently $-(CH_2)_4-R^4$.

[0295] In some embodiments, two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

[0296] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  . In some embodiments, each R^4 is independently $-OR^5$ or $-N(R^5)_2$.

[0297] In some embodiments, each R^4 is hydrogen. In some embodiments, each R^4 is independently $-OR^5$. In some embodiments, each R^4 is independently $-N(R^5)_2$. In some embodiments, each R^4 is independently $-C(O)N(R^5)_2$. In some embodiments, each R^4 is independently $-NR^5C(O)R^5$. In some embodiments, each R^4 is independently $-NR^5C(S)N(R^5)_2$. In some embodiments, each R^4 is independently  .

[0298] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from

nitrogen, oxygen, and sulfur. In some embodiments, each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic.

[0299] In some embodiments, each R^5 is hydrogen.

[0300] In some embodiments, each R^5 is independently optionally substituted C_{1-6} aliphatic. In some embodiments, each R^5 is independently optionally substituted C_{1-4} aliphatic. In some embodiments, each R^5 is independently optionally substituted C_1 aliphatic. In some embodiments, each R^5 is independently optionally substituted C_2 aliphatic. In some embodiments, each R^5 is independently optionally substituted C_3 aliphatic. In some embodiments, each R^5 is independently optionally substituted C_4 aliphatic. In some embodiments, each R^5 is independently optionally substituted C_5 aliphatic. In some embodiments, each R^5 is independently optionally substituted C_6 aliphatic. In some embodiments, each R^5 is methyl. In some embodiments, each R^5 is ethyl.

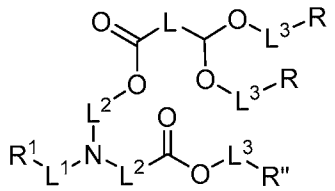
[0301] In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4-membered heterocyclyl comprising 0 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 5-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur. In some embodiments, two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted morpholinyl.

[0302] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each R^6 is independently C_{4-12} aliphatic. In some embodiments, each R^6 is independently C_{4-8} aliphatic. In some embodiments, each R^6 is independently C_{6-12} aliphatic. In some embodiments, each R^6 is independently C_{6-8} aliphatic. In some embodiments, each R^6 is independently C_4 aliphatic. In some embodiments, each R^6 is independently C_5 aliphatic. In some

embodiments, each R^6 is independently C_6 aliphatic. In some embodiments, each R^6 is independently C_7 aliphatic. In some embodiments, each R^6 is independently C_8 aliphatic. In some embodiments, each R^6 is independently C_9 aliphatic. In some embodiments, each R^6 is independently C_{10} aliphatic. In some embodiments, each R^6 is independently C_{11} aliphatic. In some embodiments, each R^6 is independently C_{12} aliphatic.

[0303] As described above, in some embodiments of any of Formulae A', A, I", I', I, II", II', II, III', and III, each n is independently 0 to 4. In some embodiments, each n is independently 1 to 4. In some embodiments, each n is independently 1 to 3. In some embodiments, each n is independently 2 or 3. In some embodiments, each n is 0. In some embodiments, each n is 1. In some embodiments, each n is 2. In some embodiments, each n is 3. In some embodiments, each n is 4.

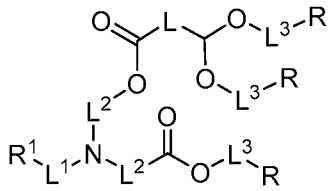
[0304] In some embodiments, the present disclosure provides a compound of Formula I"-a:



I"-a

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

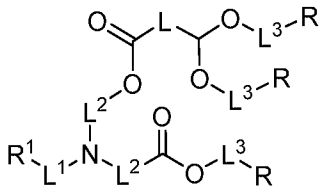
[0305] In some embodiments, the present disclosure provides a compound of Formula I'-a:



I'-a

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A and I', and described in classes and subclasses above and herein, both singly and in combination.

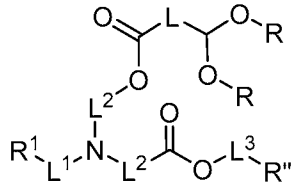
[0306] In some embodiments, the present disclosure provides a compound of Formula I-a:



I-a

or its N-oxide, or a salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for Formula I and described in classes and subclasses above and herein, both singly and in combination.

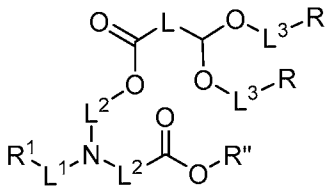
[0307] In some embodiments, the present disclosure provides a compound of Formula I"-a-*i*:



I"-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

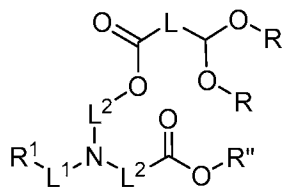
[0308] In some embodiments, the present disclosure provides a compound of Formula I"-a-*ii*:



I"-a-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

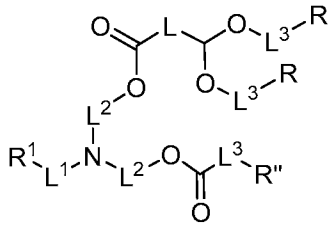
[0309] In some embodiments, the present disclosure provides a compound of Formula I"-a-*iii*:



I"-a-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, and L^2 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

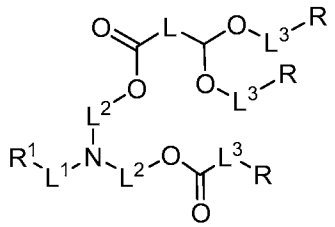
[0310] In some embodiments, the present disclosure provides a compound of Formula I"-b:



I"-b

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

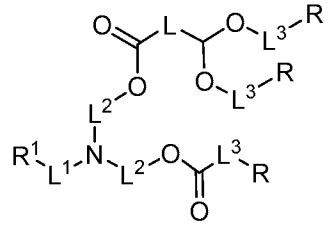
[0311] In some embodiments, the present disclosure provides a compound of Formula I'-b:



I'-b

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A and I', and described in classes and subclasses above and herein, both singly and in combination.

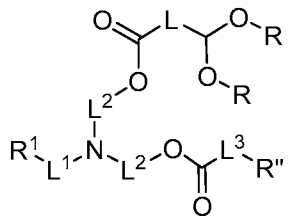
[0312] In some embodiments, the present disclosure provides a compound of Formula I-b:



I-b

or its N-oxide, or a salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for Formula I and described in classes and subclasses above and herein, both singly and in combination.

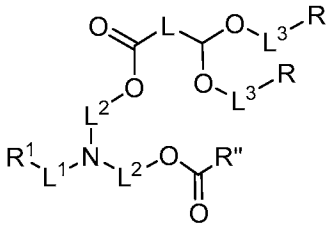
[0313] In some embodiments, the present disclosure provides a compound of Formula I"-b-*i*:



I"-b-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

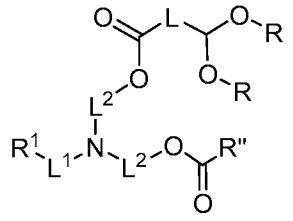
[0314] In some embodiments, the present disclosure provides a compound of Formula I"-b-*ii*:



I"-b-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

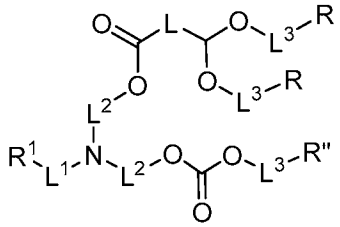
[0315] In some embodiments, the present disclosure provides a compound of Formula I"-b-*iii*:



I"-b-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, and L^2 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

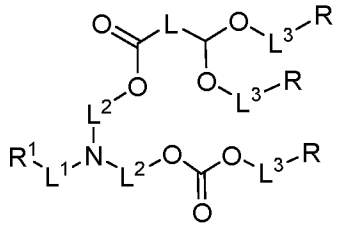
[0316] In some embodiments, the present disclosure provides a compound of Formula I"-c:



I"-c

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

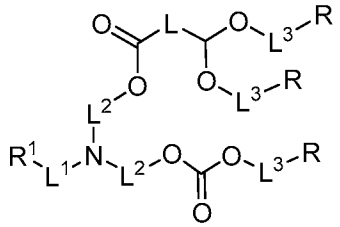
[0317] In some embodiments, the present disclosure provides a compound of Formula I'-c:



I'-c

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, L^3 is as defined above for any of Formulae A and I' and described in classes and subclasses above and herein, both singly and in combination.

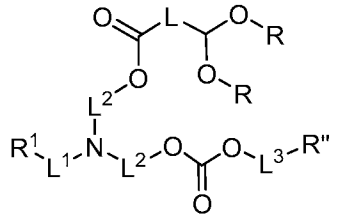
[0318] In some embodiments, the present disclosure provides a compound of Formula I-c:



I-c

or its N-oxide, or a salt thereof, wherein each of R, R^1, L, L^1, L^2, L^3 is as defined above for Formula I and described in classes and subclasses above and herein, both singly and in combination.

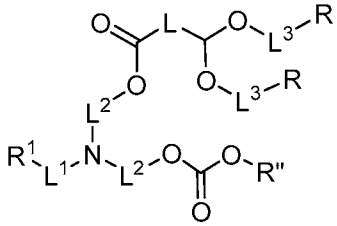
[0319] In some embodiments, the present disclosure provides a compound of Formula I"-c-*i*:



I"-c-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

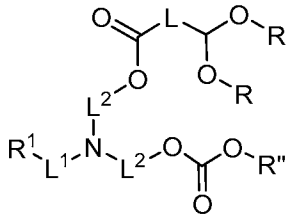
[0320] In some embodiments, the present disclosure provides a compound of Formula I"-c-*ii*:



I"-c-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

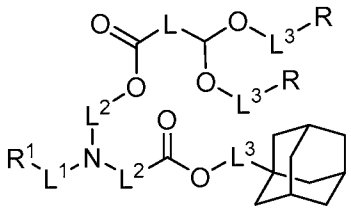
[0321] In some embodiments, the present disclosure provides a compound of Formula I"-c-*iii*:



I"-c-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R", R^1, L, L^1, and L^2 is as defined above for any of Formulae A' and I", and described in classes and subclasses above and herein, both singly and in combination.

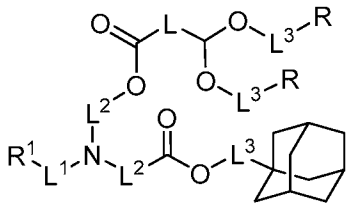
[0322] In some embodiments, the present disclosure provides a compound of Formula I'-d:



I'-d

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, L^3 is as defined above for any of Formulae A', A, I", and I' and described in classes and subclasses above and herein, both singly and in combination.

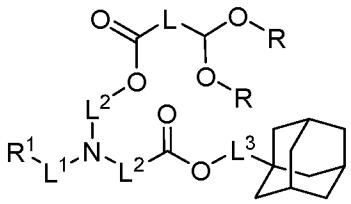
[0323] In some embodiments, the present disclosure provides a compound of Formula I-d:



I-d

or its N-oxide, or a salt thereof, wherein each of R, R^1, L, L^1, L^2, L^3 is as defined above for Formula I and described in classes and subclasses above and herein, both singly and in combination.

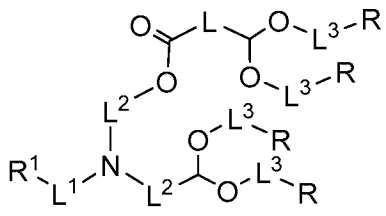
[0324] In some embodiments, the present disclosure provides a compound of Formula I'-d-*i*:



I'-d-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A', A, I", I' and I, and described in classes and subclasses above and herein, both singly and in combination.

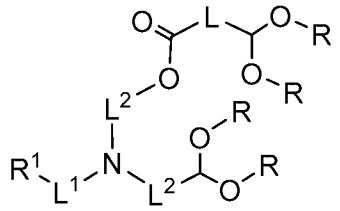
[0325] In some embodiments, the present disclosure provides a compound of Formula II-a:



II-a

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, and L^3 is as defined above for any of Formulae A', A, II", II' and II, and described in classes and subclasses above and herein, both singly and in combination.

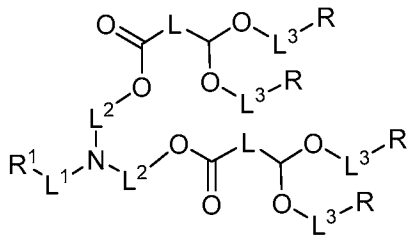
[0326] In some embodiments, the present disclosure provides a compound of Formula II-a-*i*:



II-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, and L^2 is as defined above for any of Formulae A', A, II", II' and II, and described in classes and subclasses above and herein, both singly and in combination.

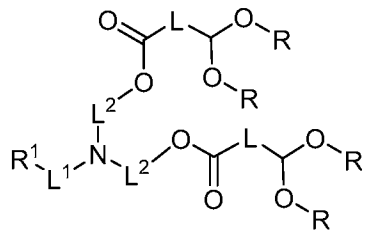
[0327] In some embodiments, the present disclosure provides a compound of Formula III-a:



III-a

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, L^2, L^3 is as defined above for any of Formulae A', A, III', and III, and described in classes and subclasses above and herein, both singly and in combination.

[0328] In some embodiments, the present disclosure provides a compound of Formula III-a-*i*:



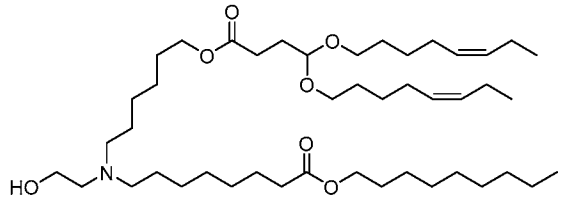
III-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, L, L^1, and L^2 is as defined above for any of Formulae A', A, III', and III, and described in classes and subclasses above and herein, both singly and in combination.

[0329] It will be appreciated that "[compound/formula] or its N-oxide, or a pharmaceutically acceptable salt thereof", as used herein, refers to pharmaceutically acceptable salts of i) the respective compound or formula or ii) N-oxides of such compound or formula.

[0330] In some embodiments, the present disclosure provides a compound selected from Table 1.

Table 1.



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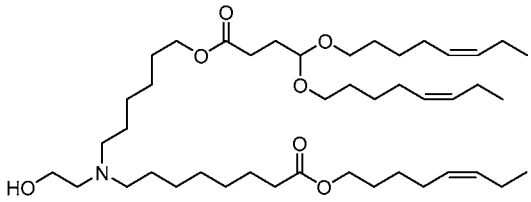

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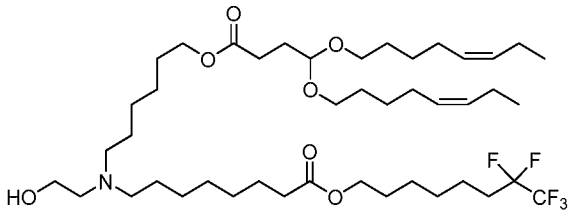

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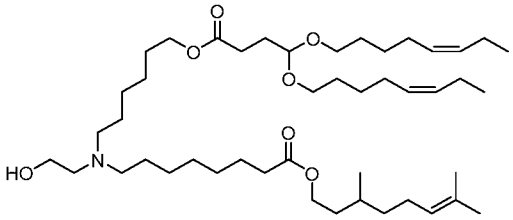

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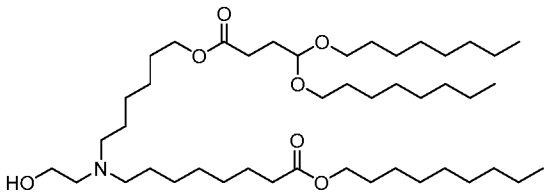

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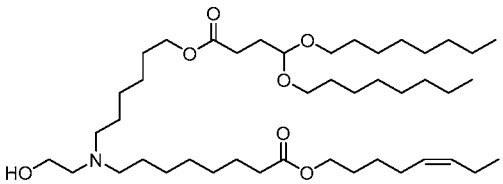

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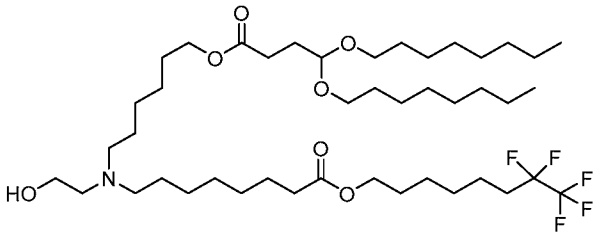

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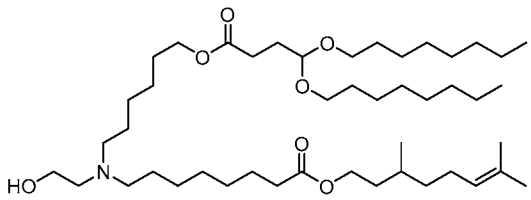

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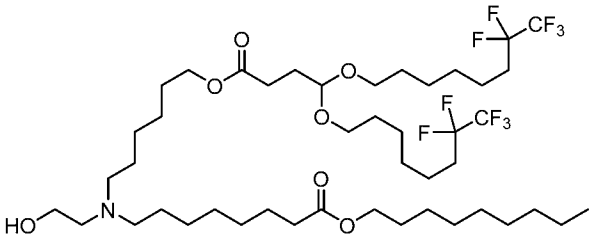

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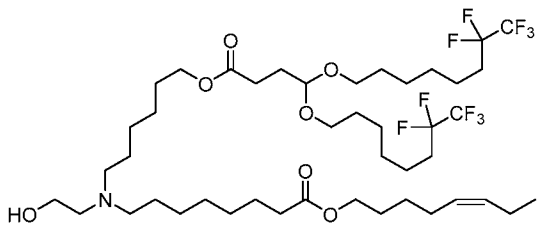

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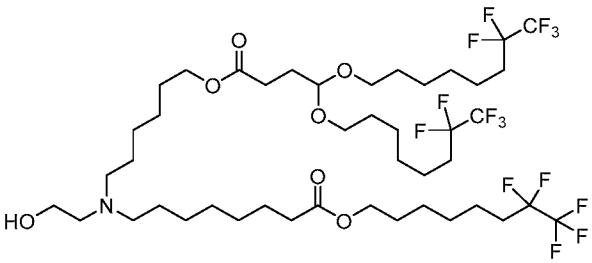

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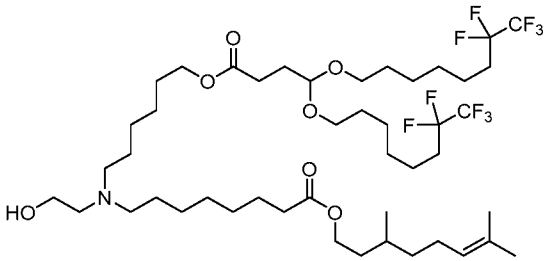

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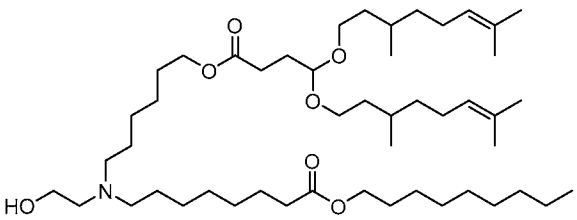

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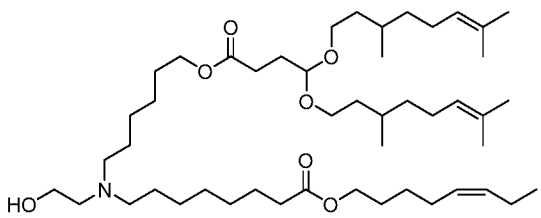

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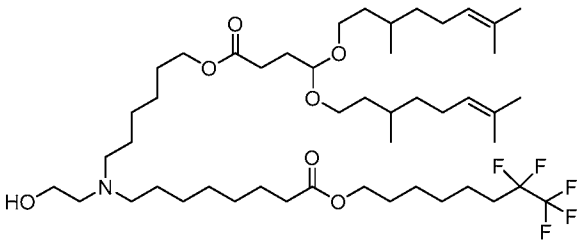

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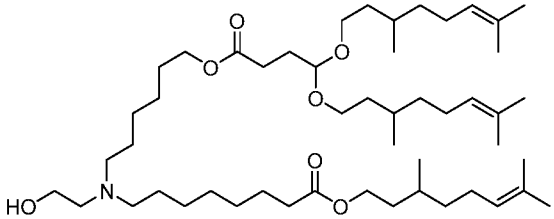

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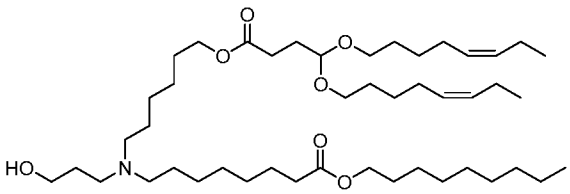

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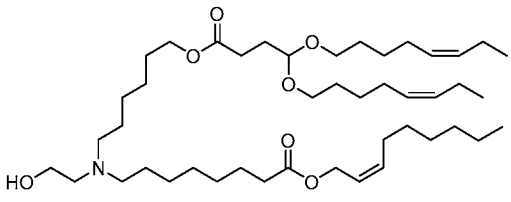

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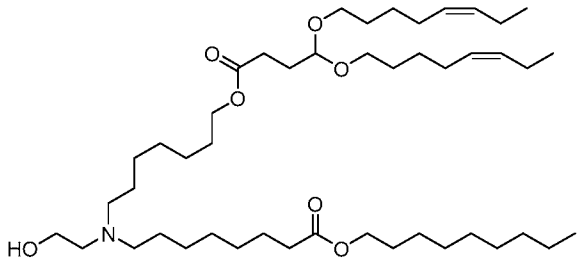

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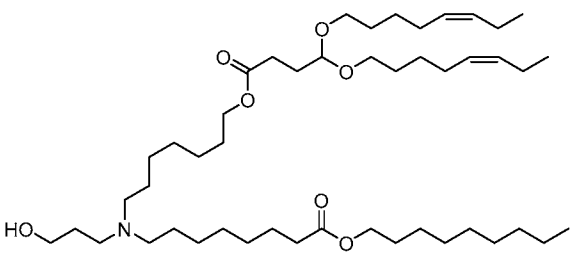

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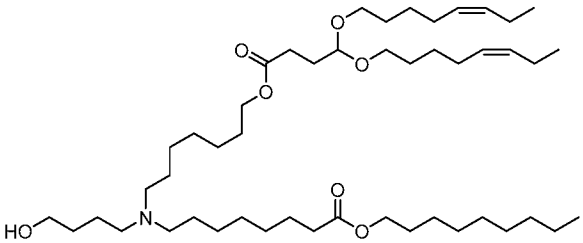

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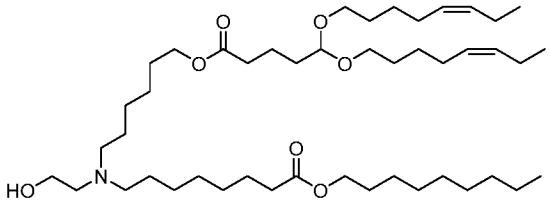

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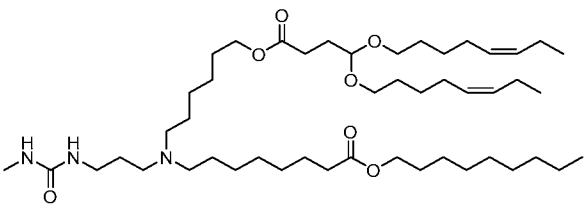

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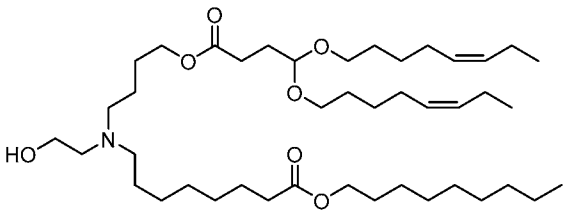

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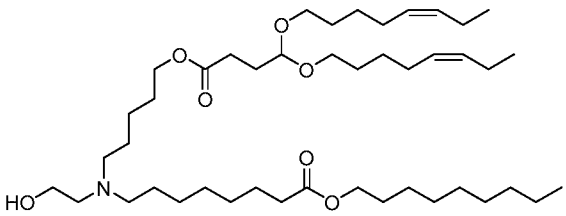

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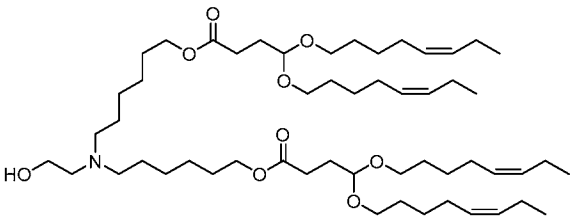

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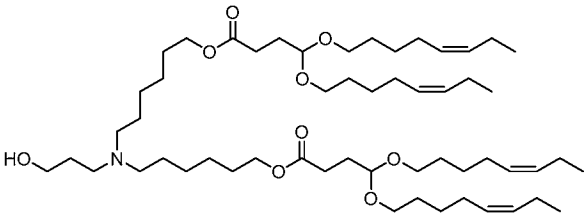

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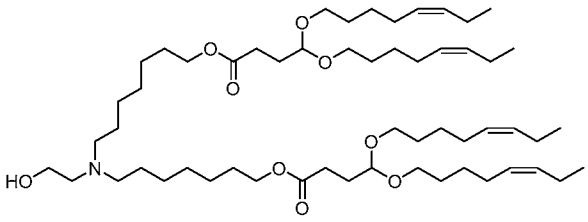

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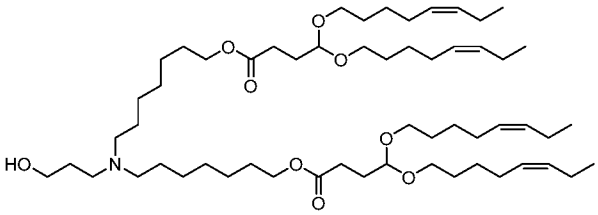

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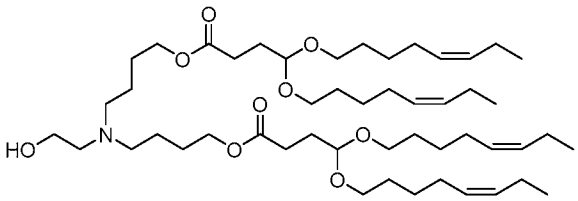

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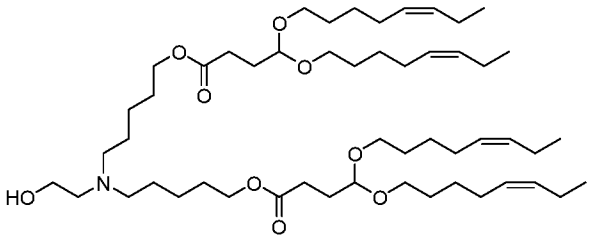

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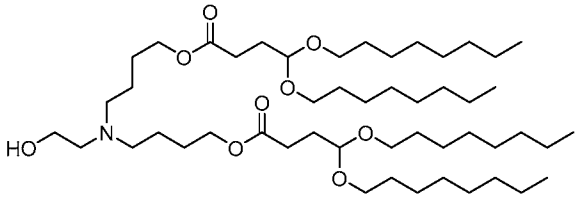

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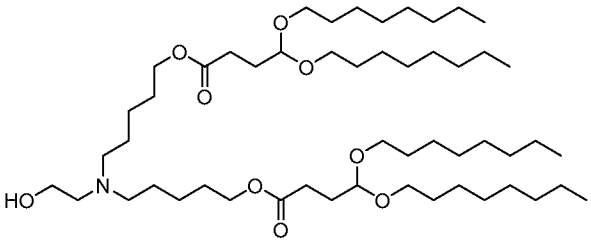

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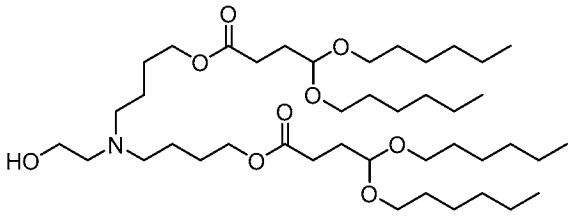

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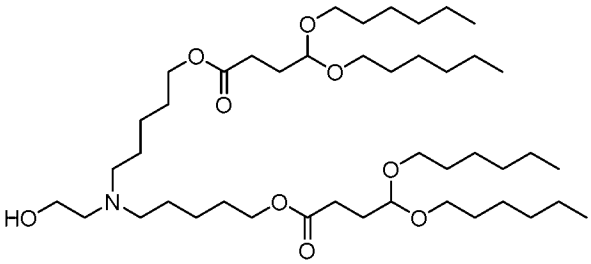

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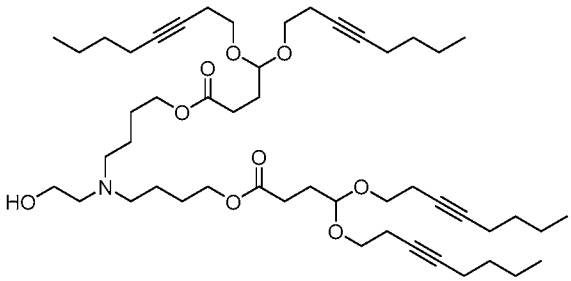

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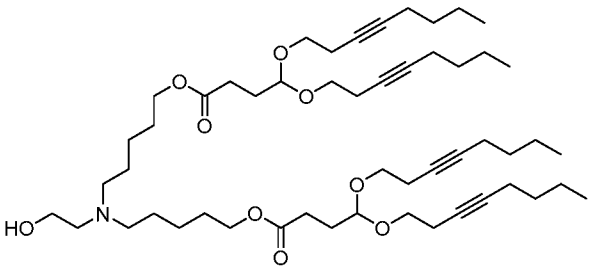

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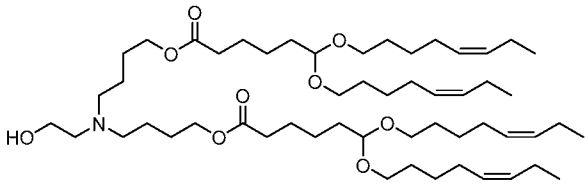

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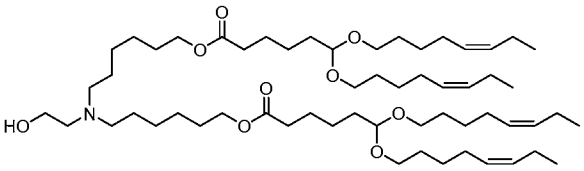

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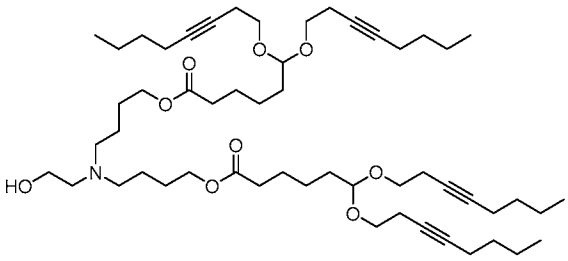

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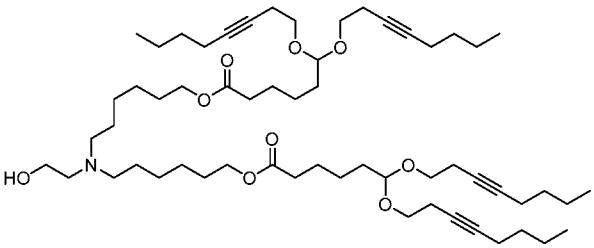

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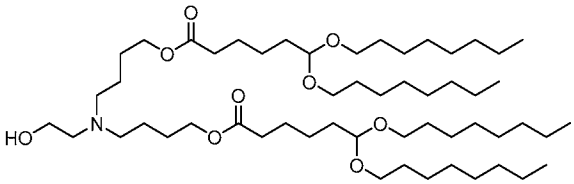

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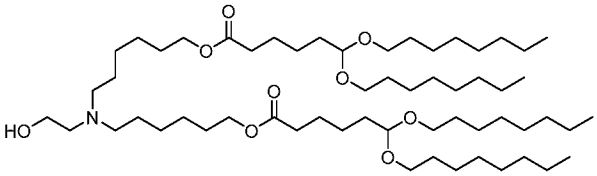

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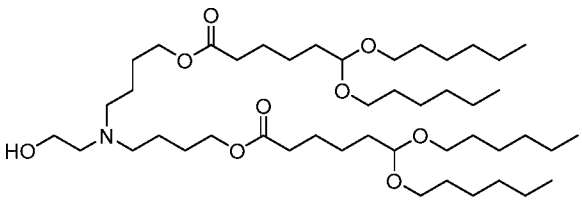

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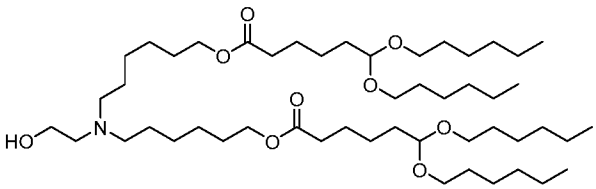

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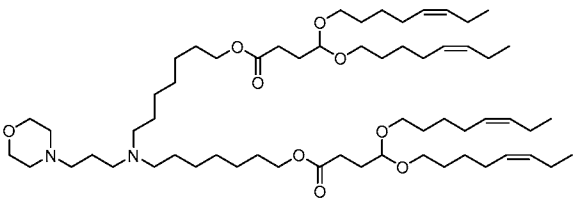

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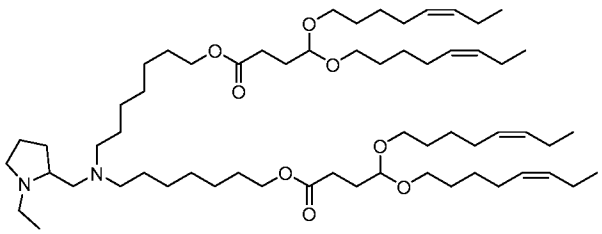

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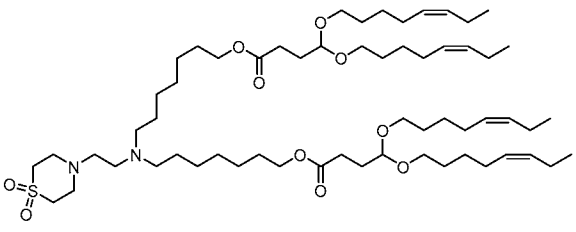

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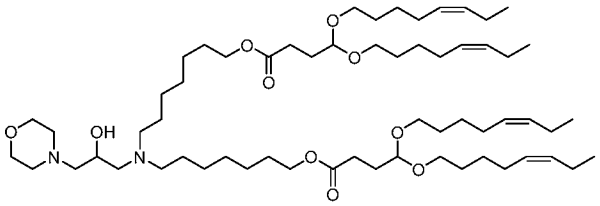

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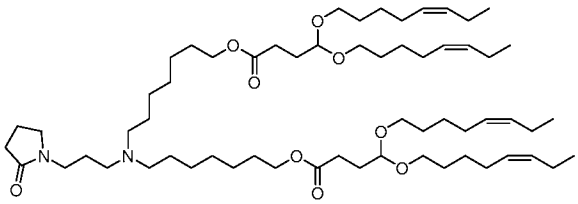

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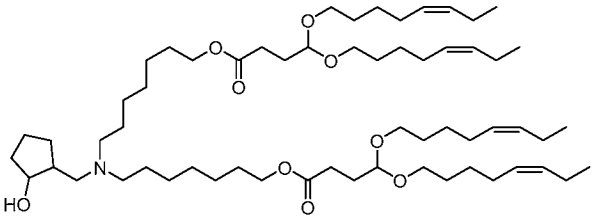

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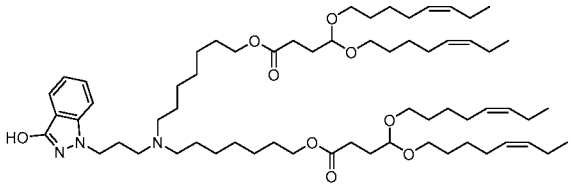

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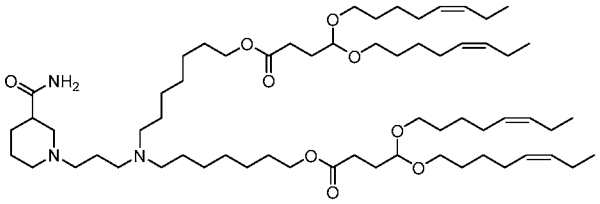

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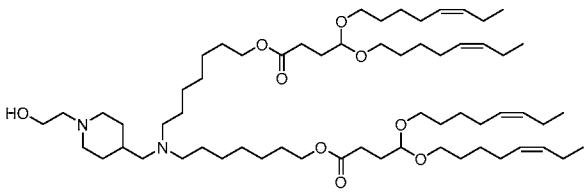

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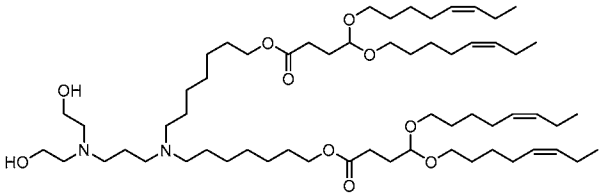

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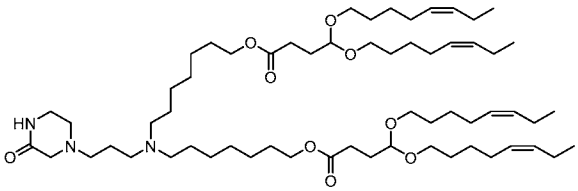

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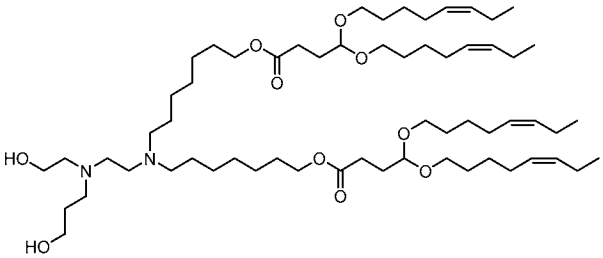

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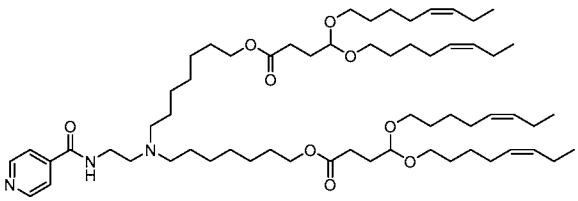

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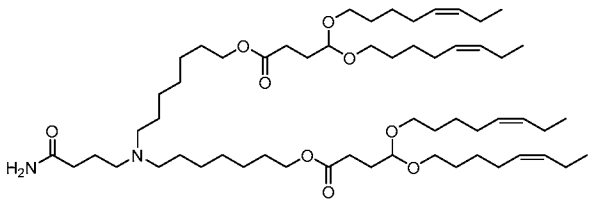

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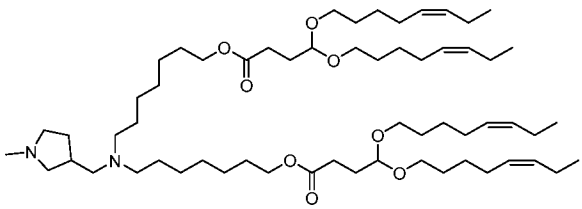

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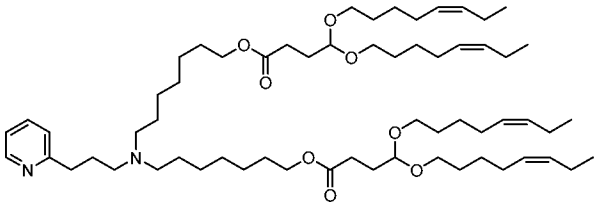

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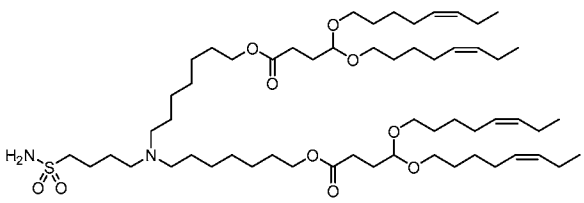

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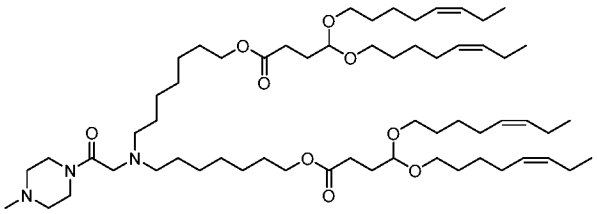

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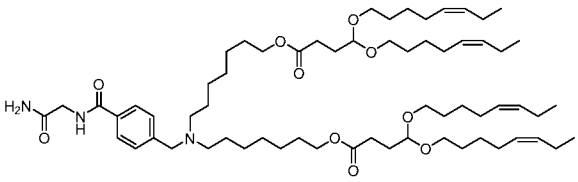

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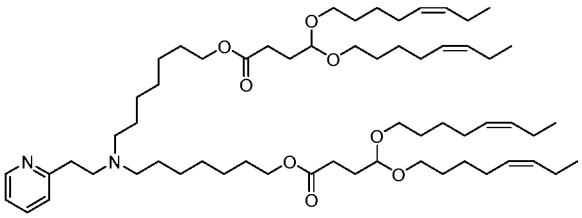

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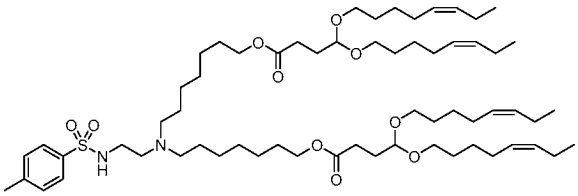

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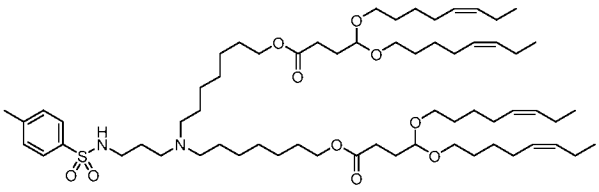

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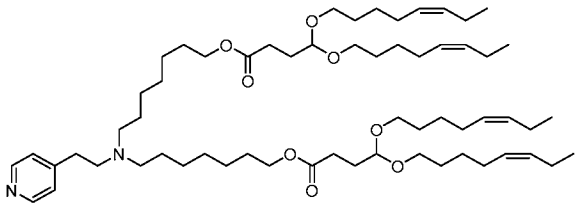

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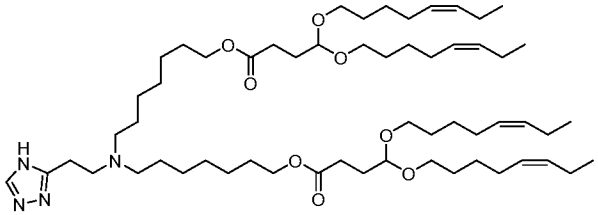

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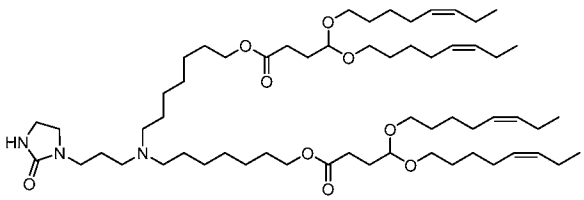

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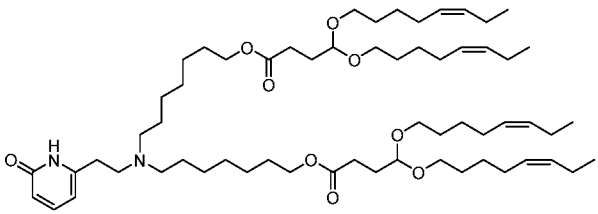

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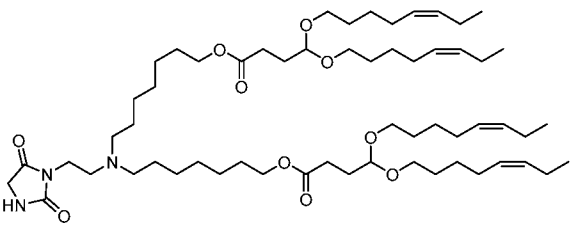

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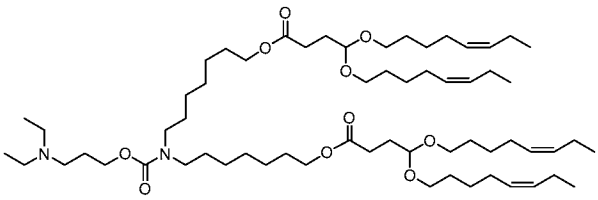

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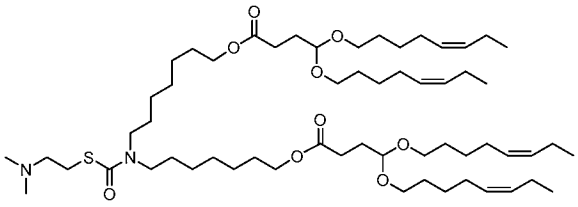

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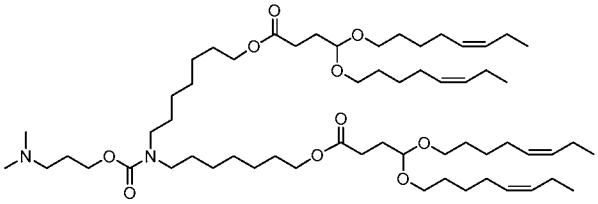

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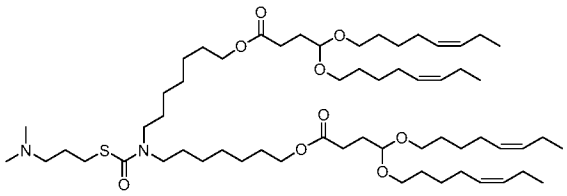

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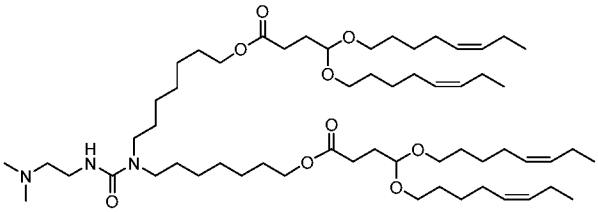

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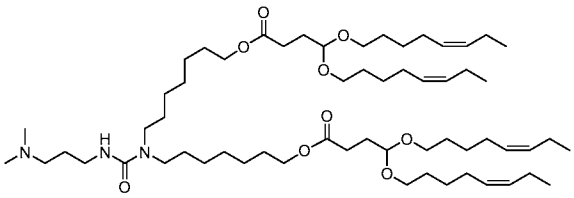

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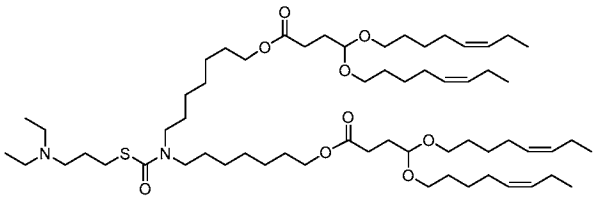

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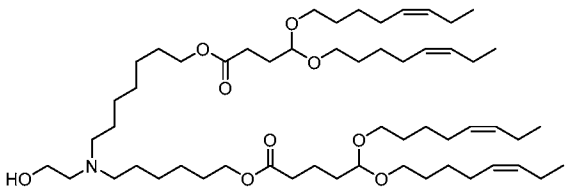

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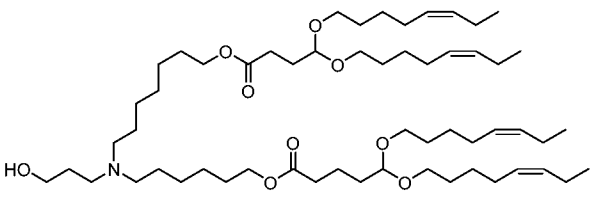

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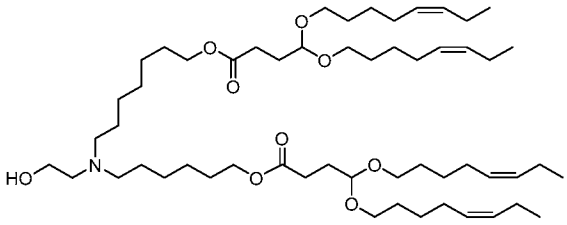

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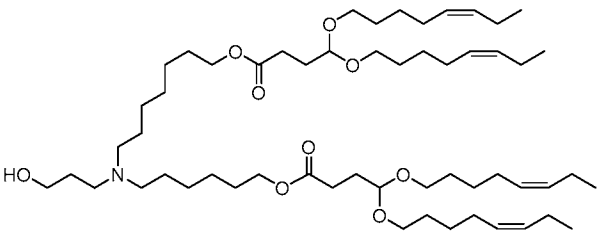

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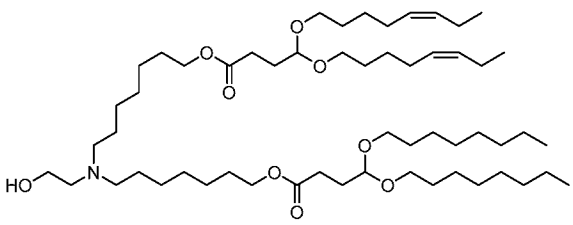

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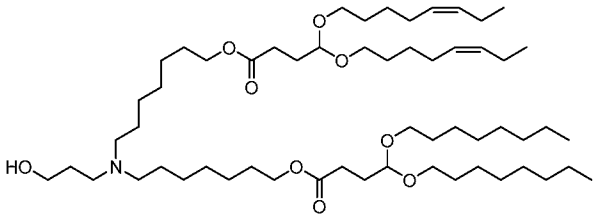

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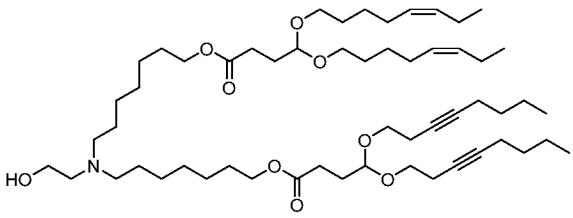

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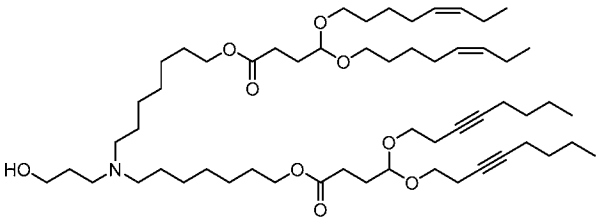

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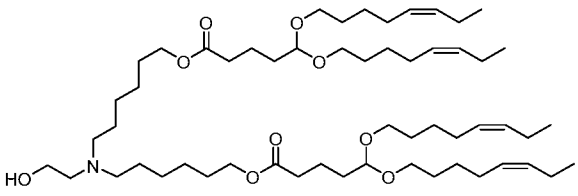

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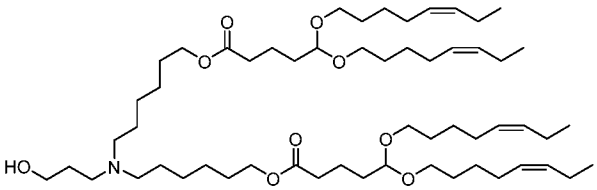

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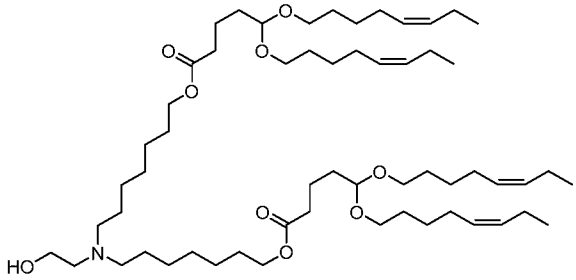

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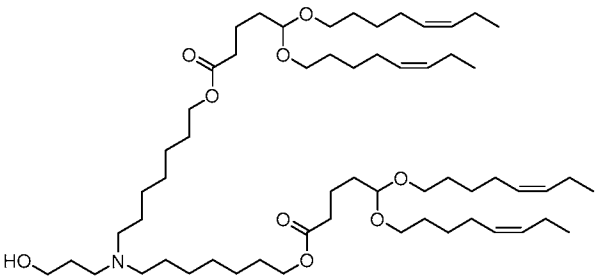

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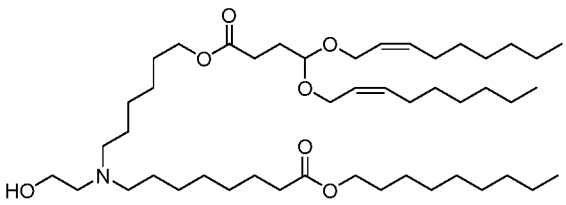

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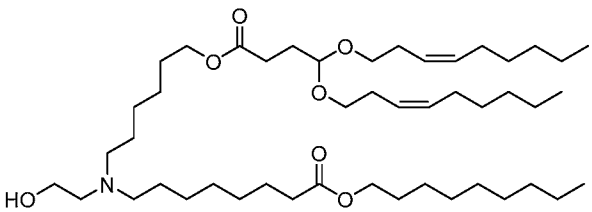

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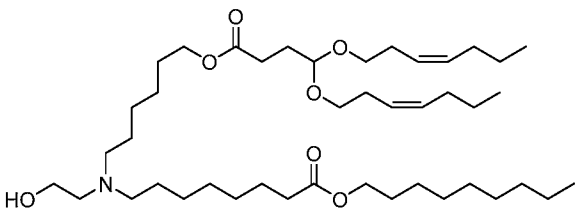

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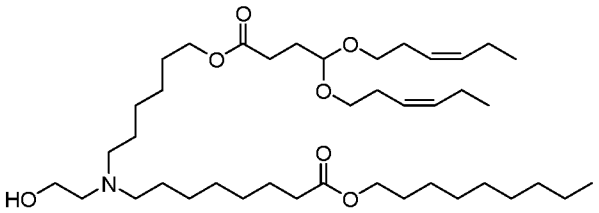

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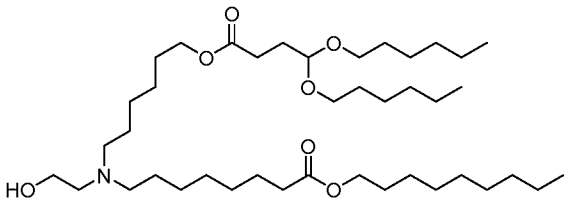

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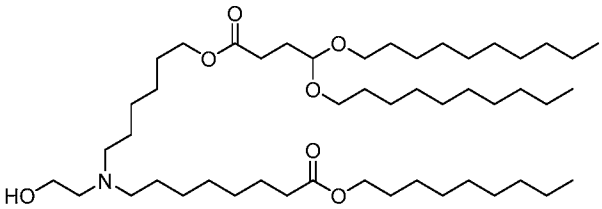

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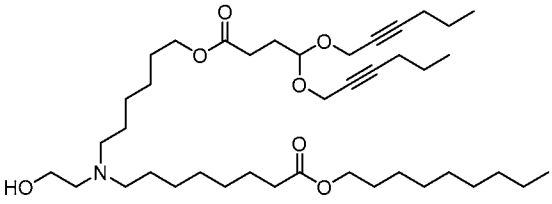

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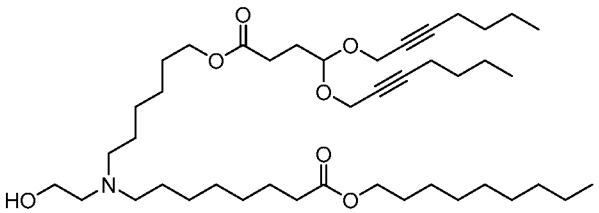

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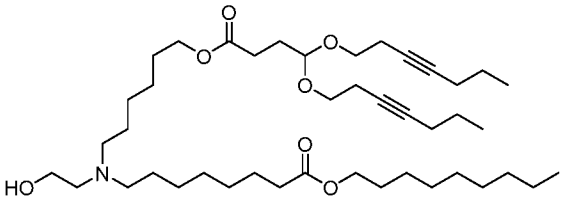

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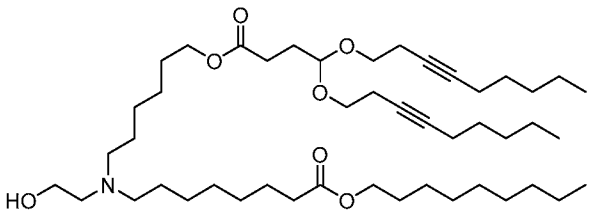

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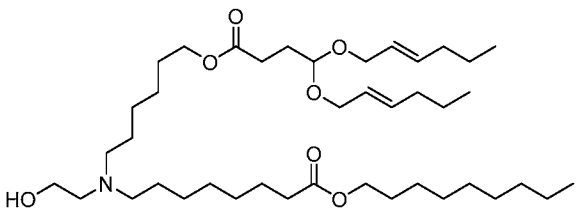

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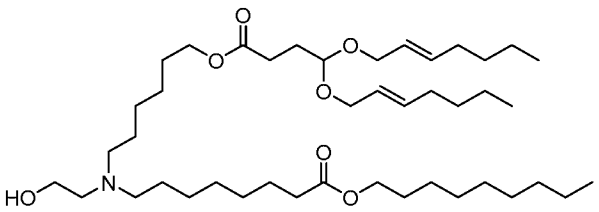

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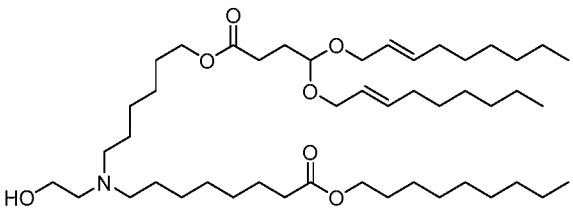

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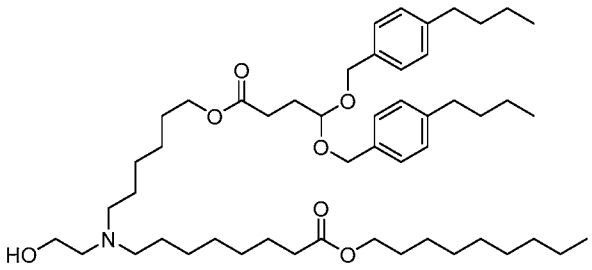

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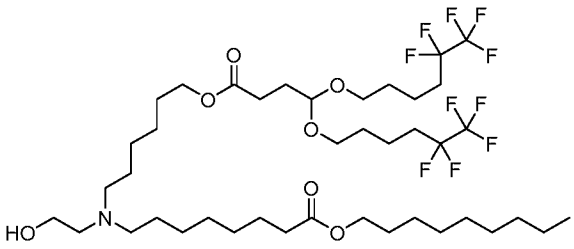

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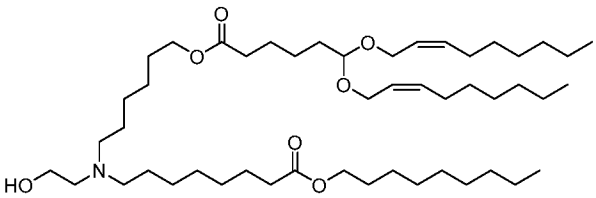

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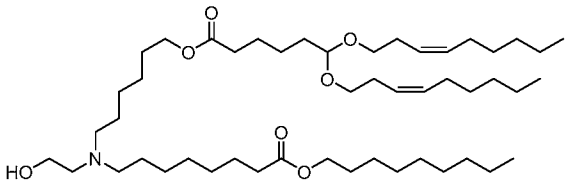

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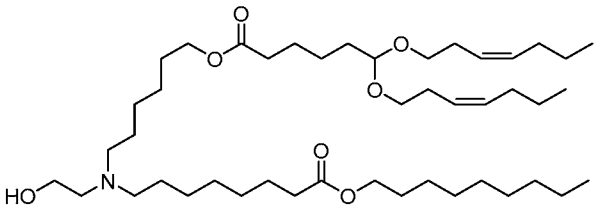

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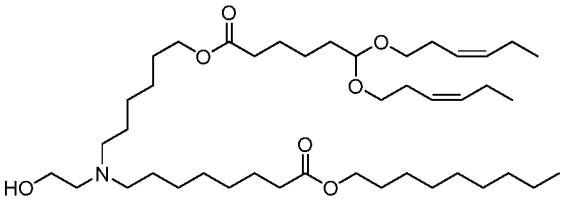

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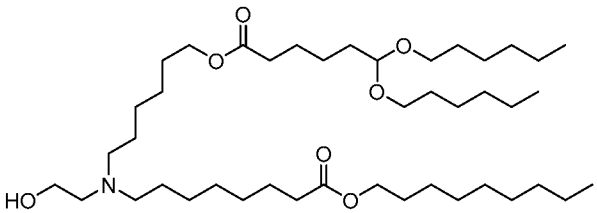

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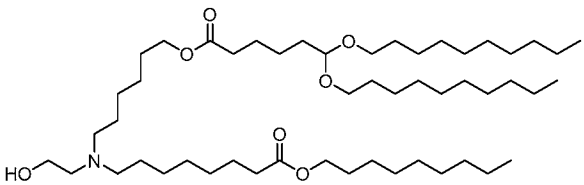

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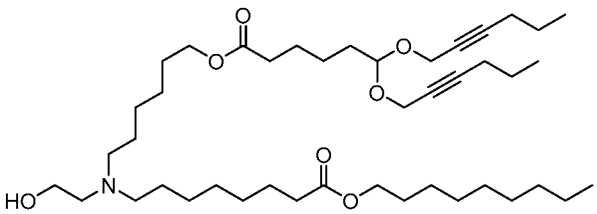

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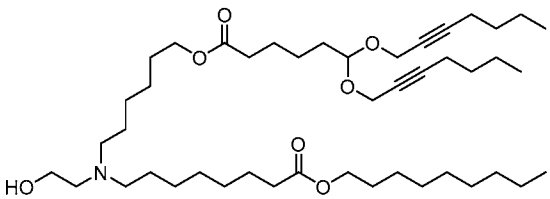

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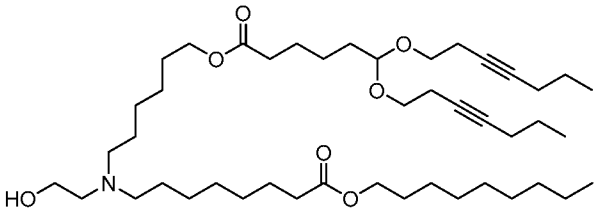

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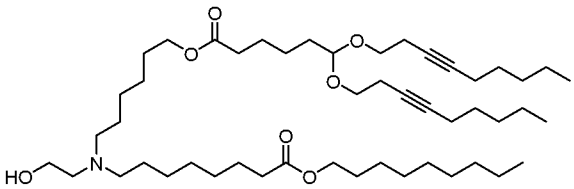

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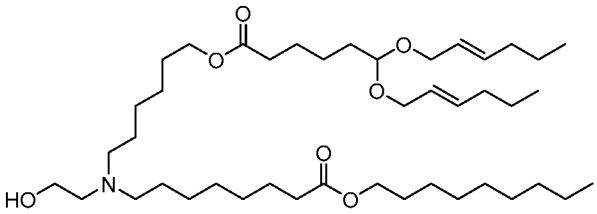

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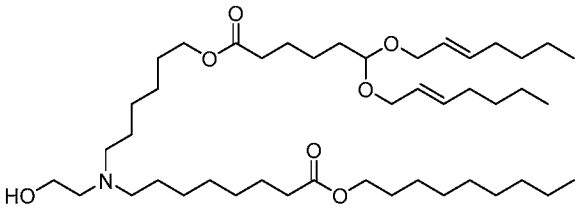

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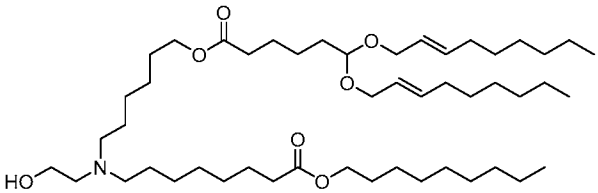

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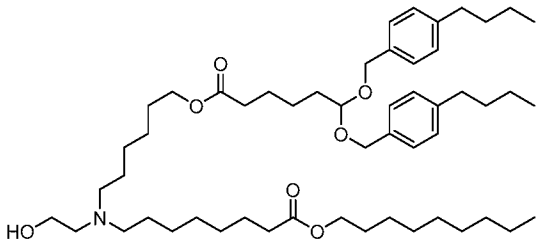

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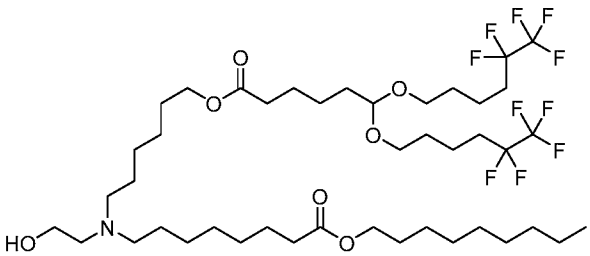

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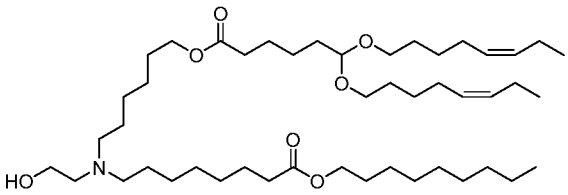

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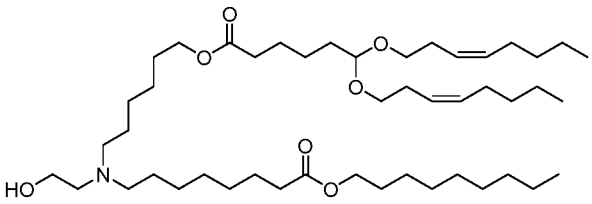

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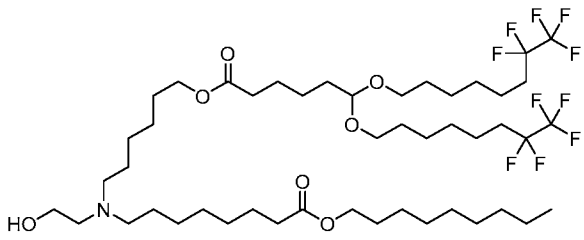

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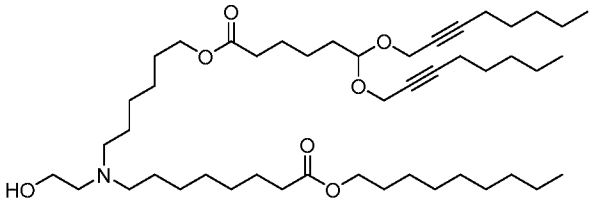

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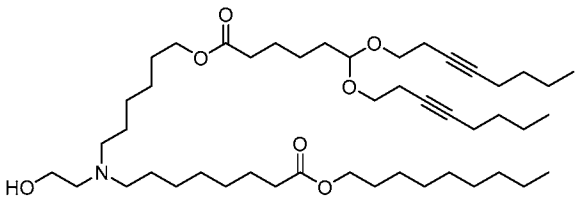

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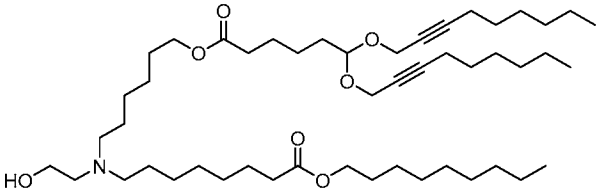

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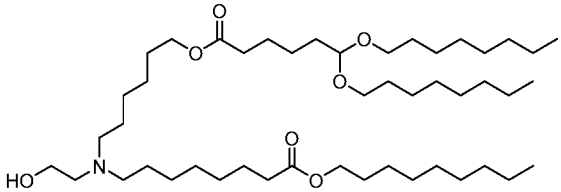

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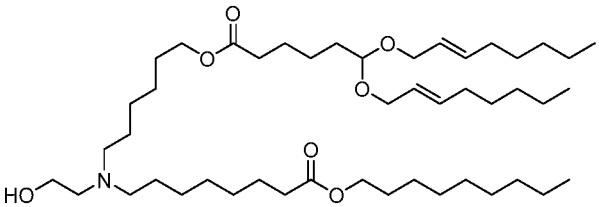

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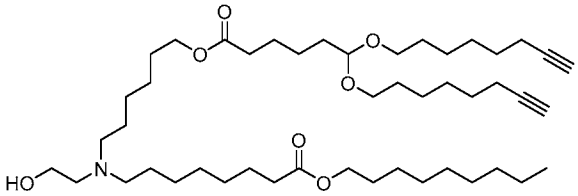

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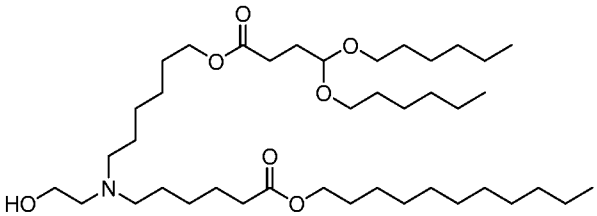

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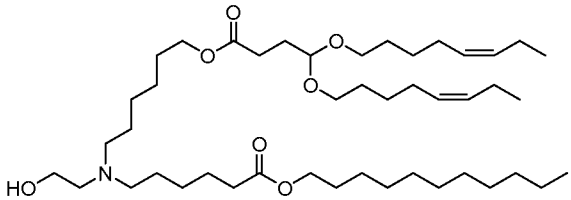

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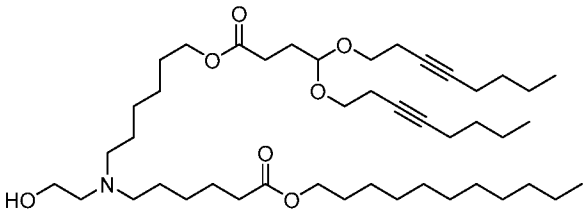

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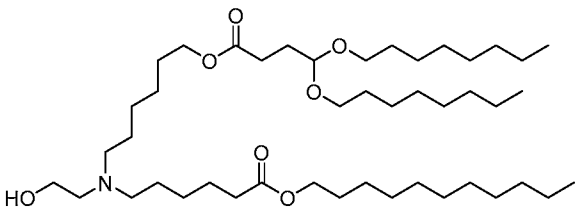

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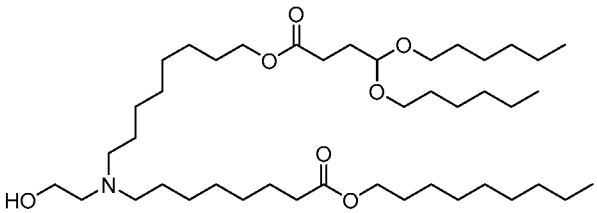

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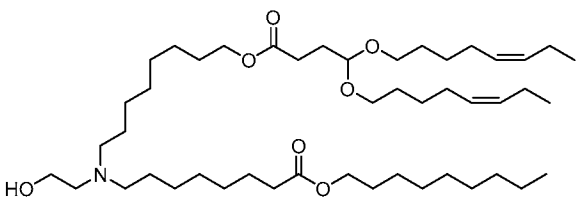

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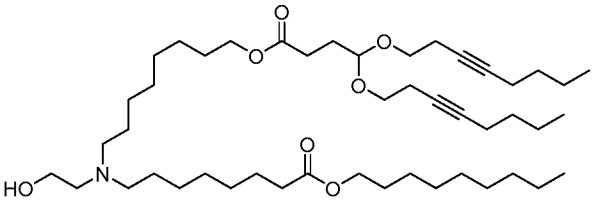

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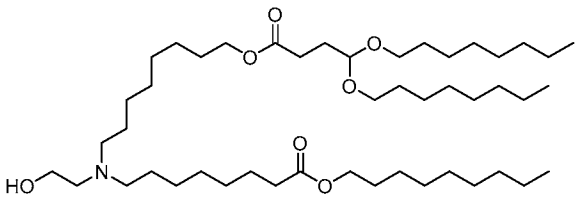

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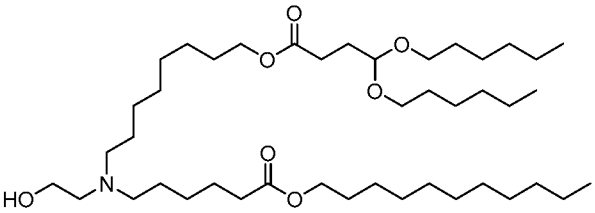

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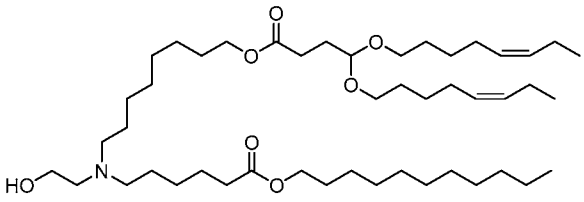

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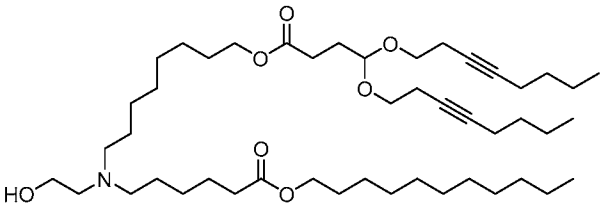

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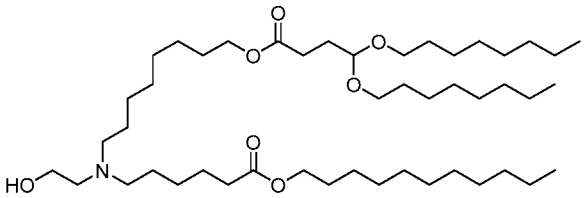

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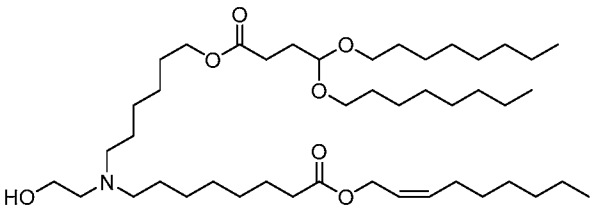

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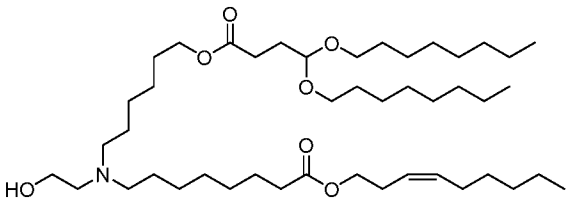

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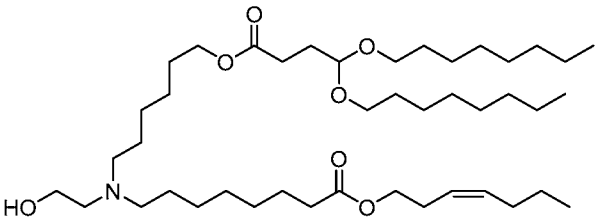

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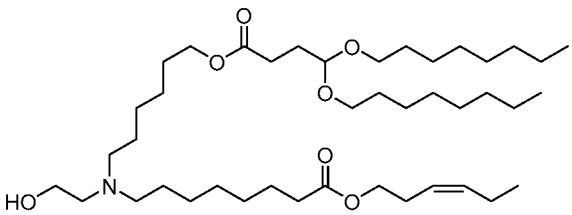

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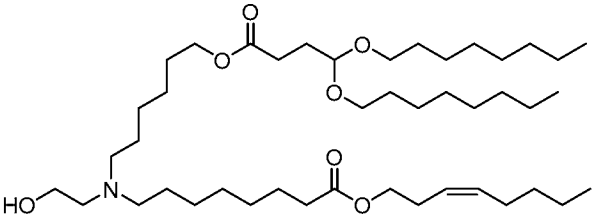

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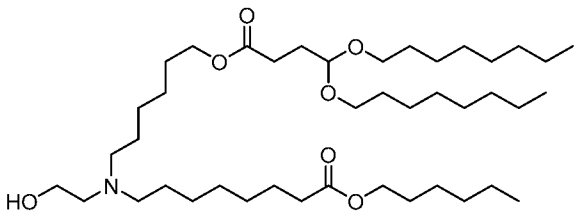

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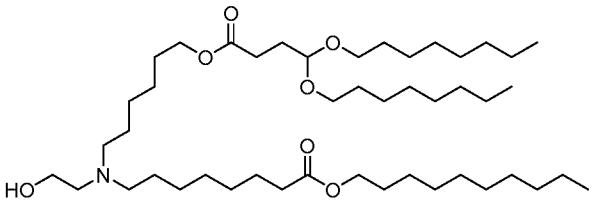

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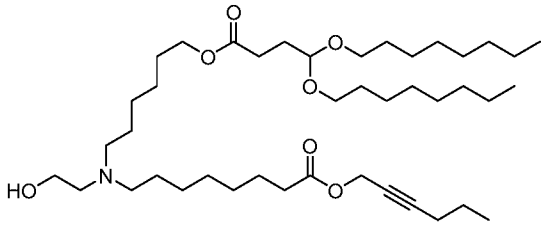

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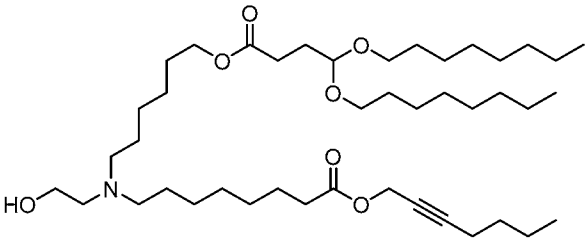

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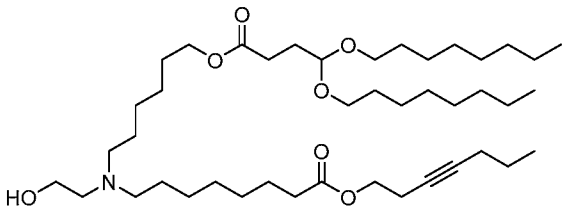

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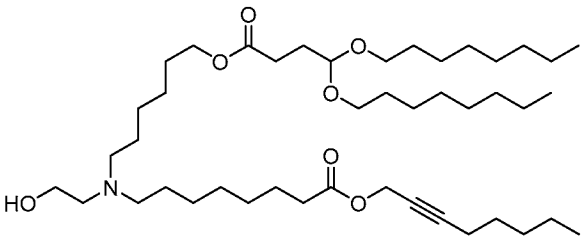

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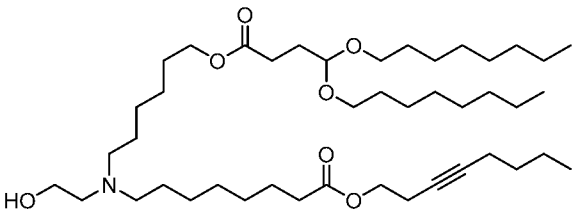

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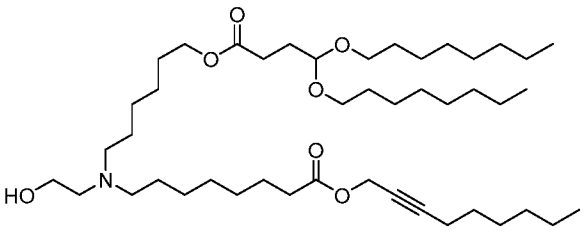

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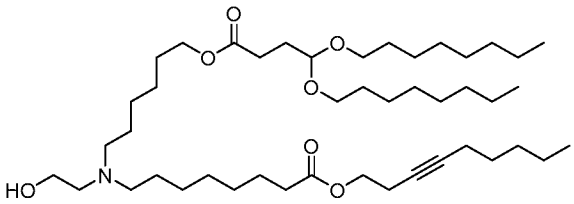

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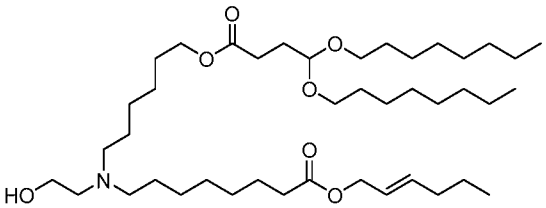

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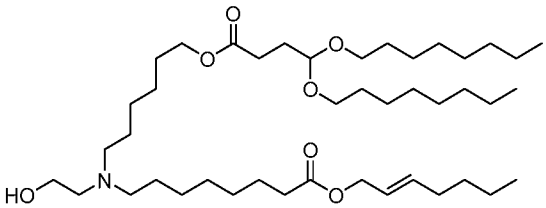

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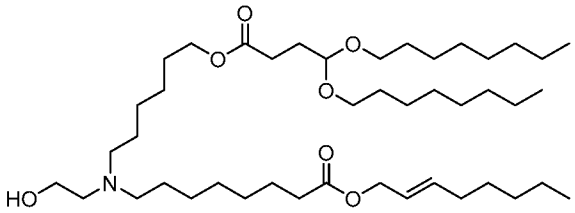

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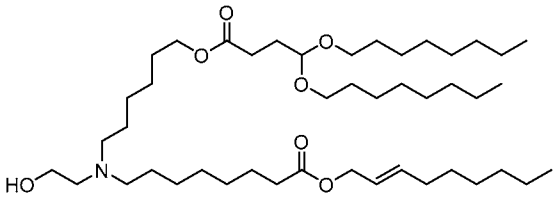

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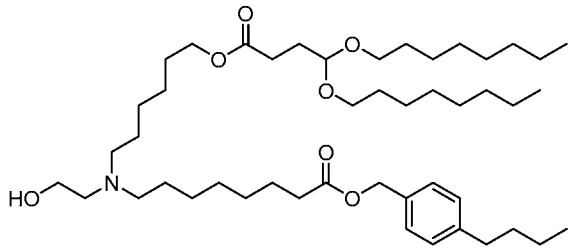

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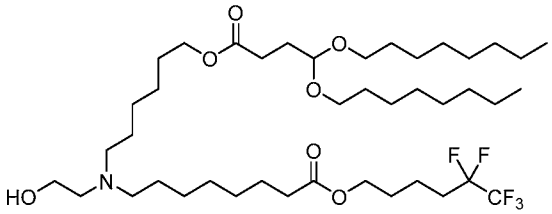

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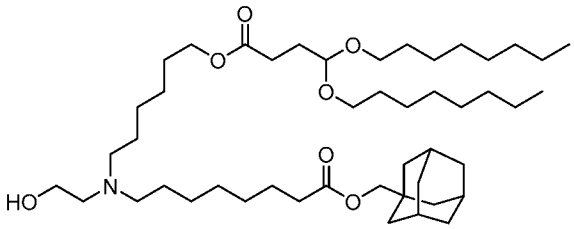

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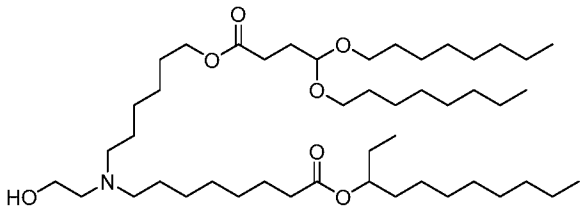

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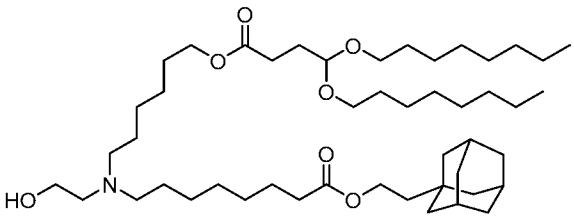

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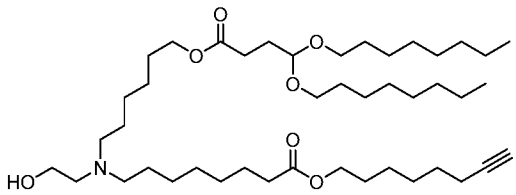

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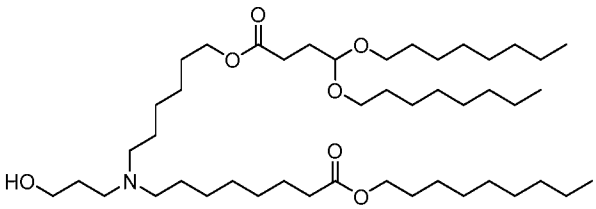

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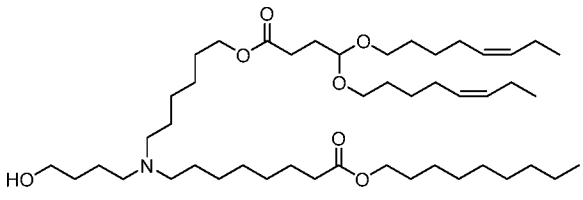

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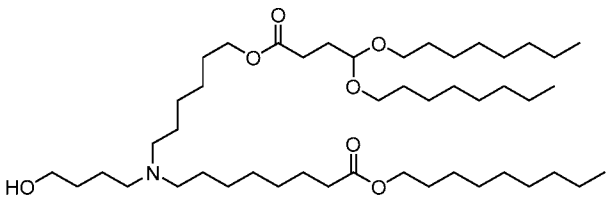

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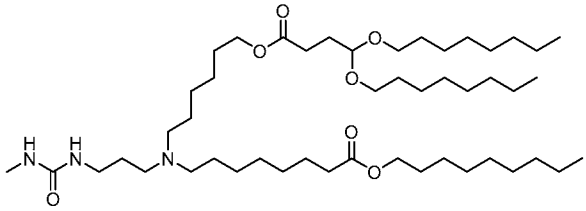

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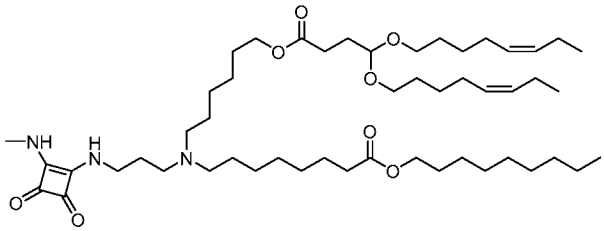

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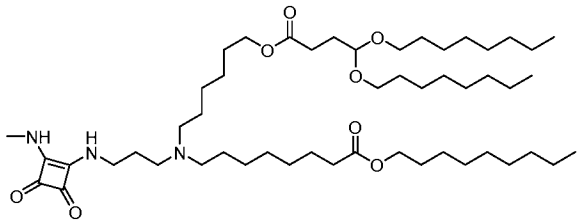

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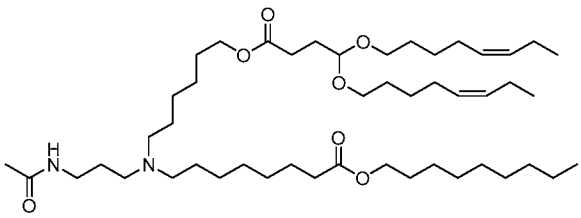

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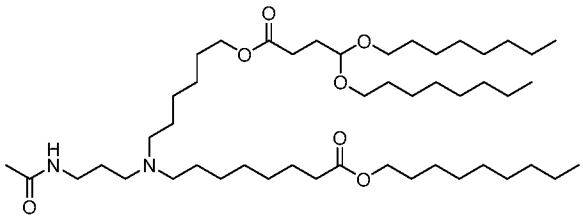

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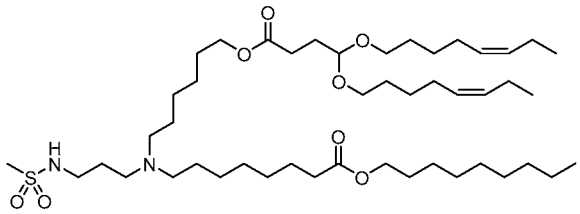

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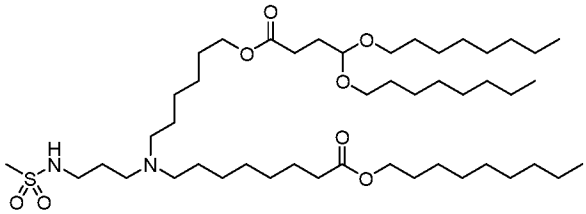

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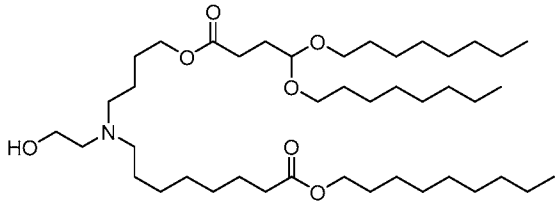

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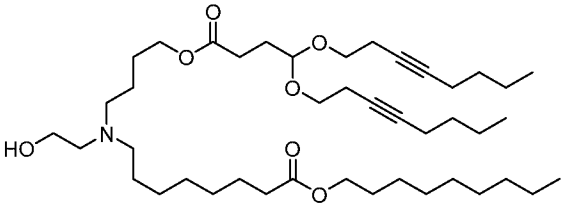

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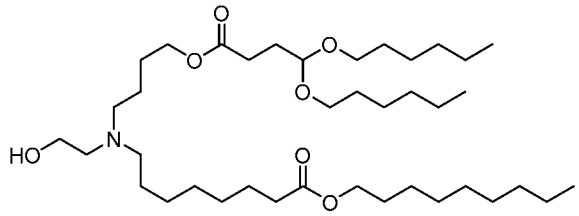

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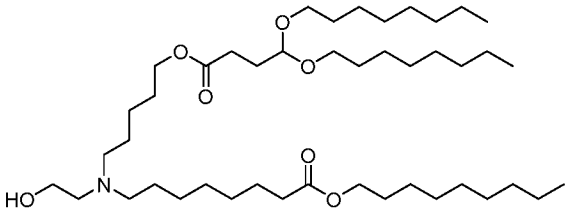

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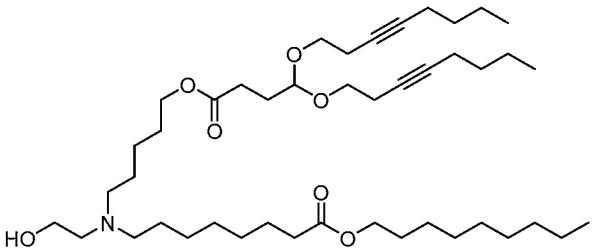

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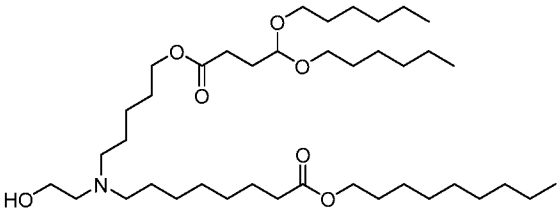

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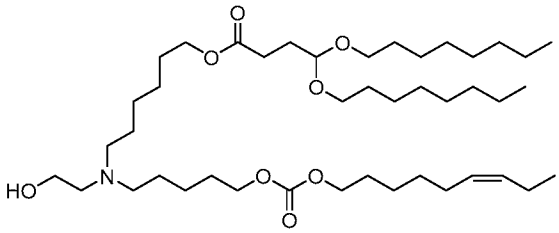

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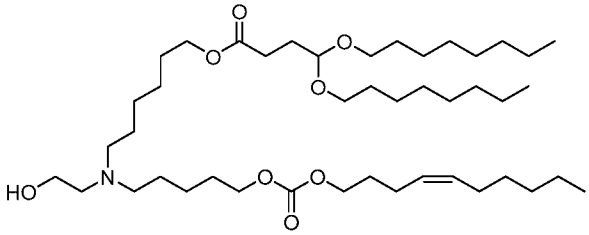

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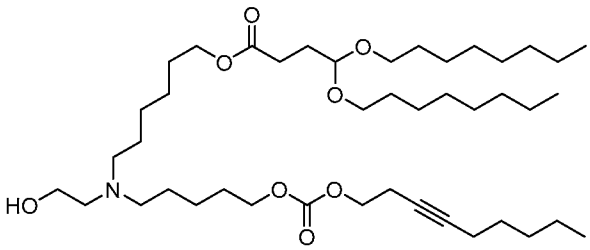

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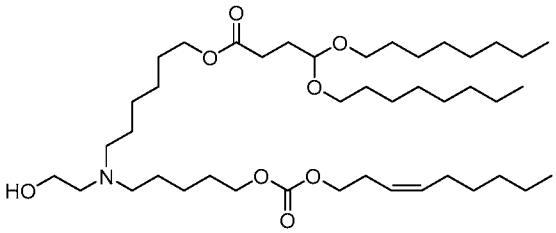

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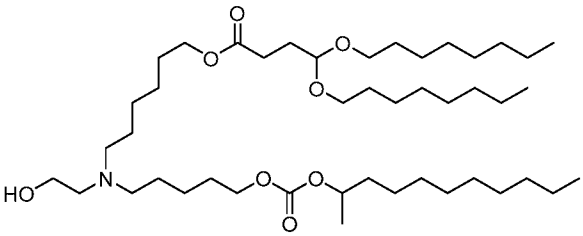

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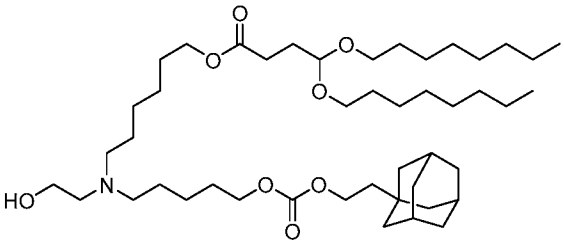

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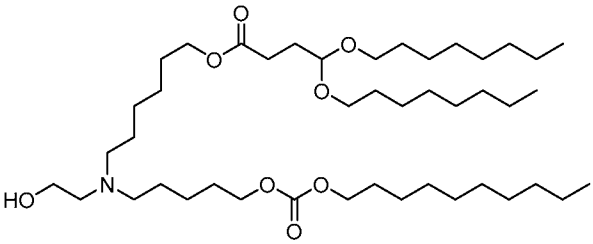

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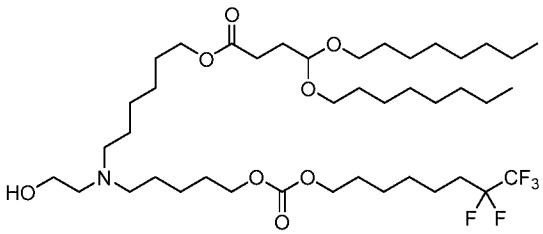

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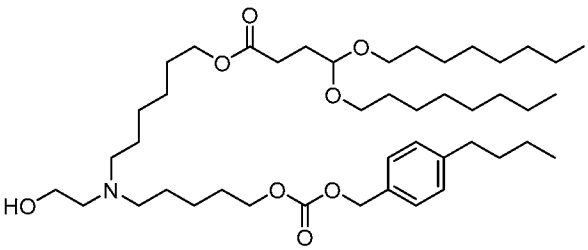

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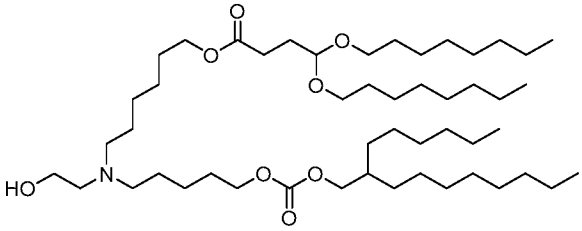

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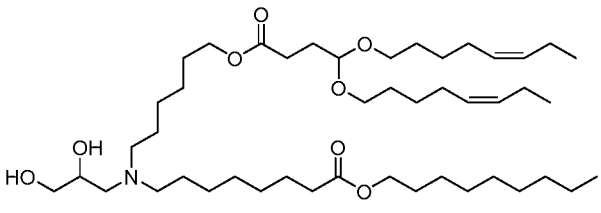

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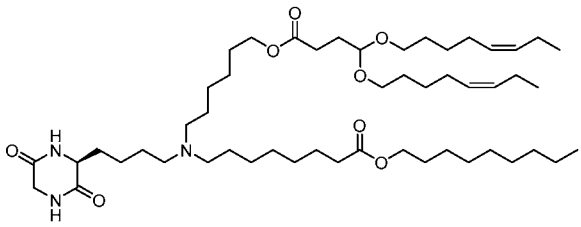

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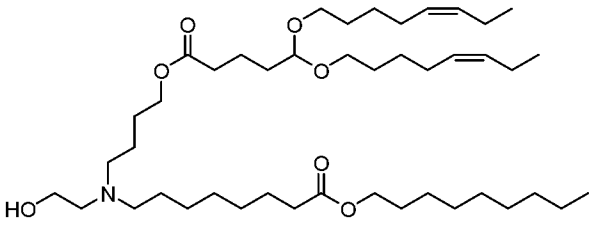

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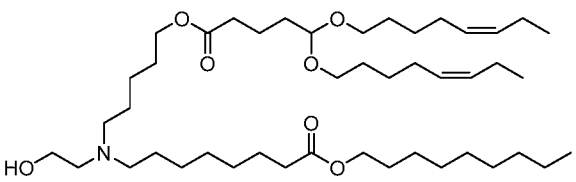

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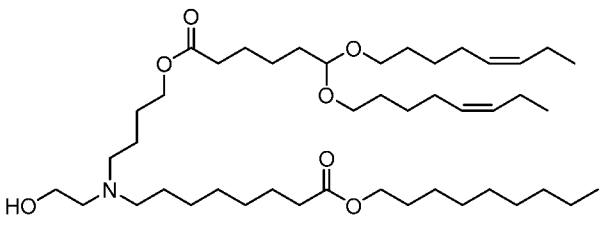

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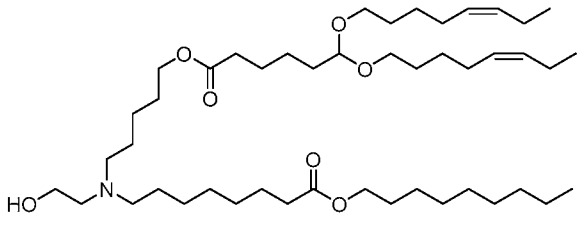

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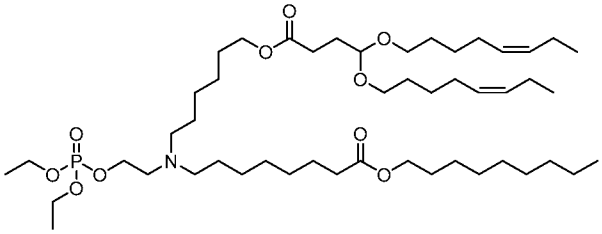

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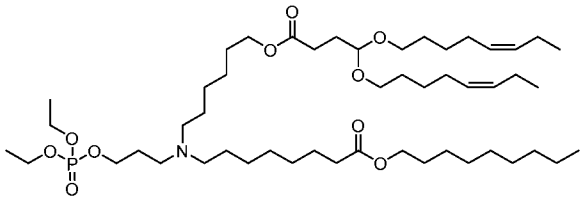

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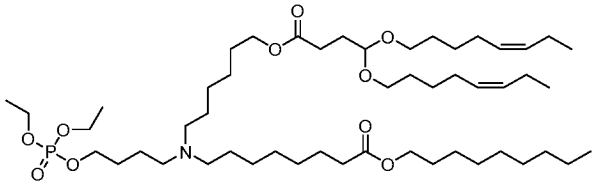

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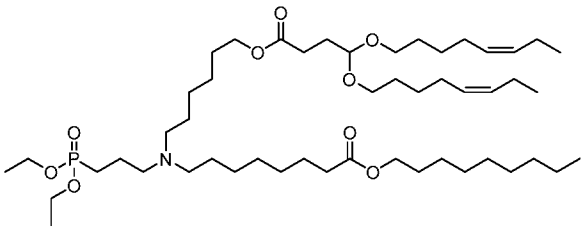

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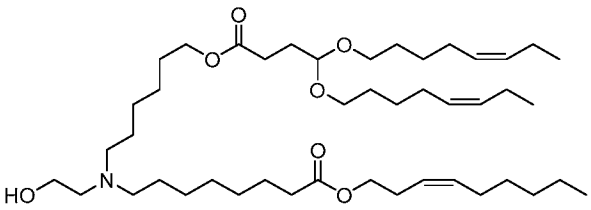

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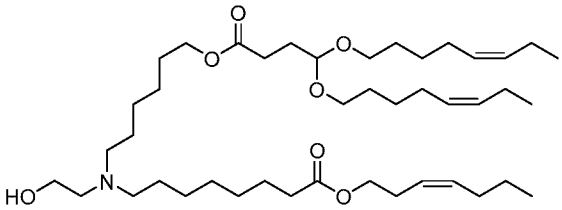

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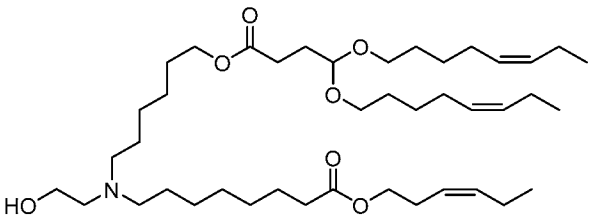

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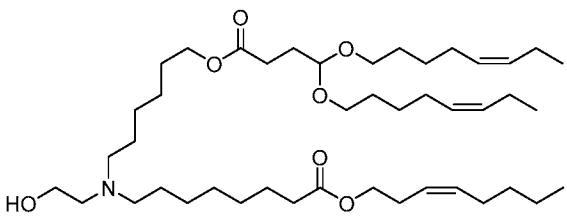

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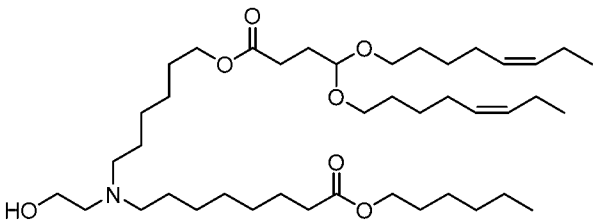

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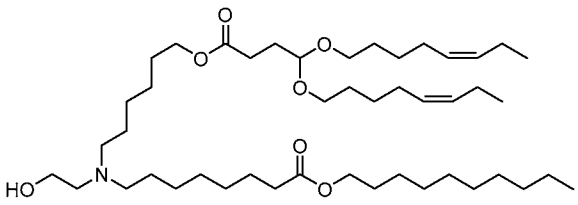

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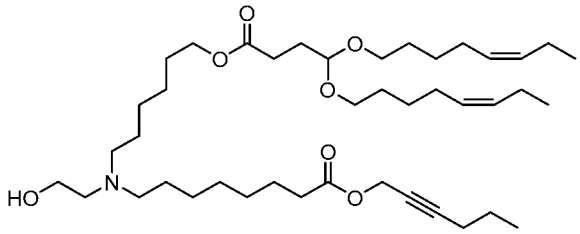

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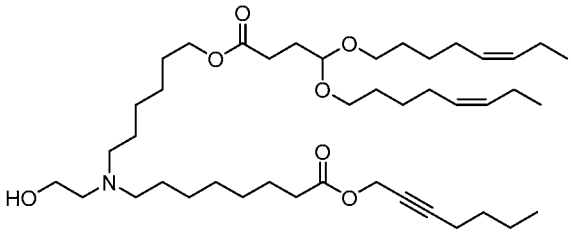

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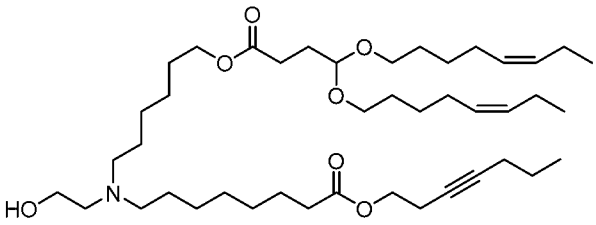

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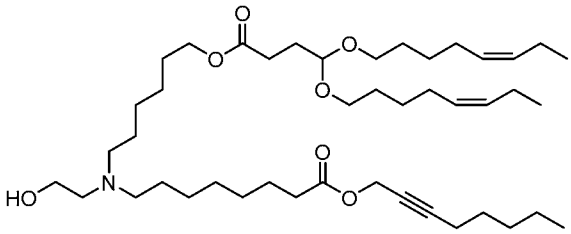

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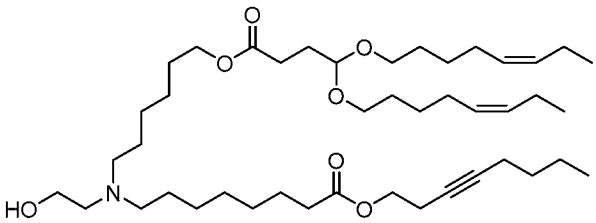

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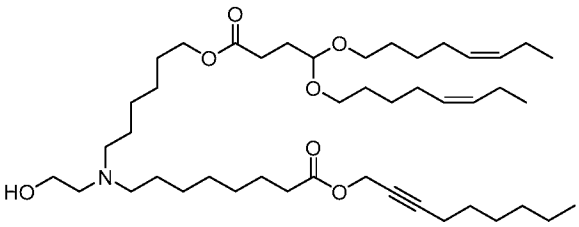

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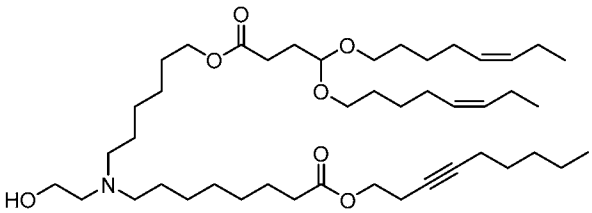

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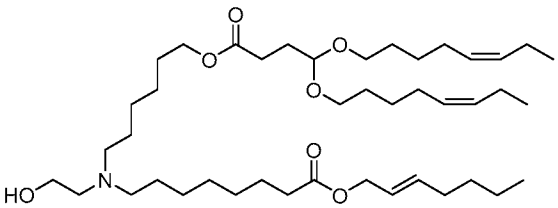

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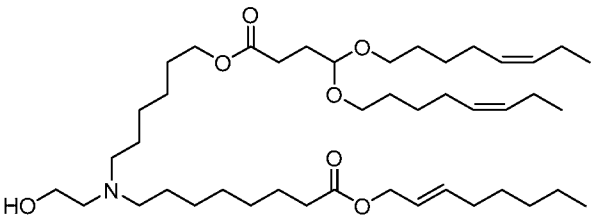

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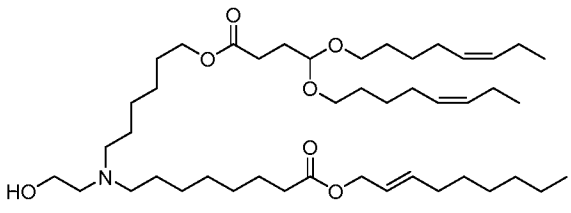

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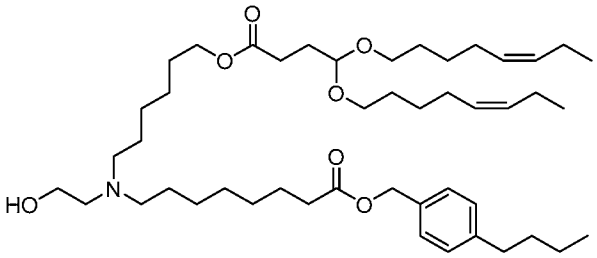

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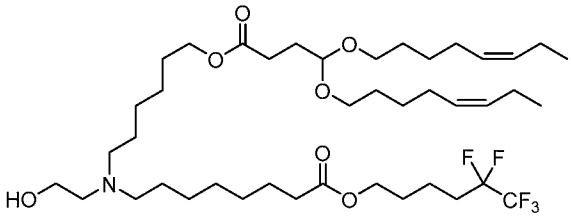

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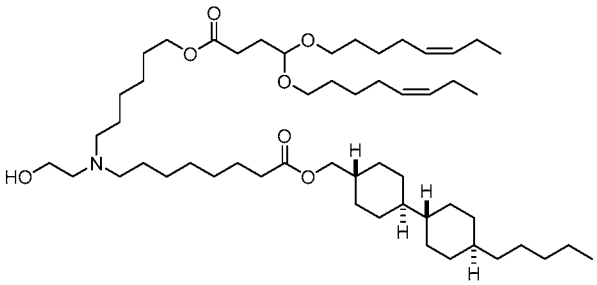

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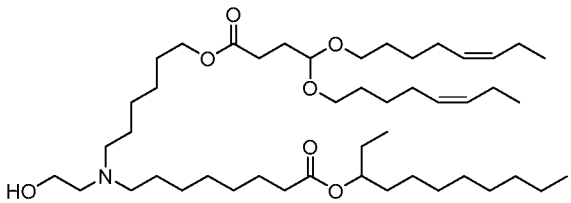

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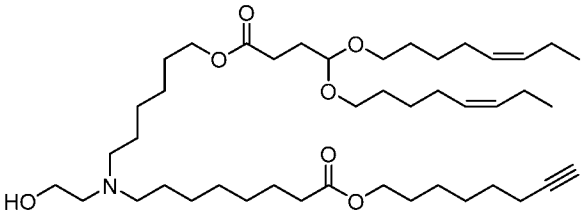

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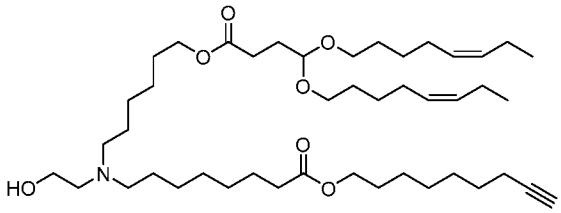

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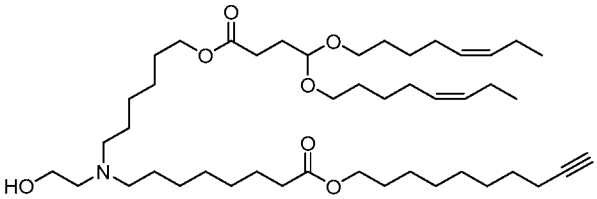

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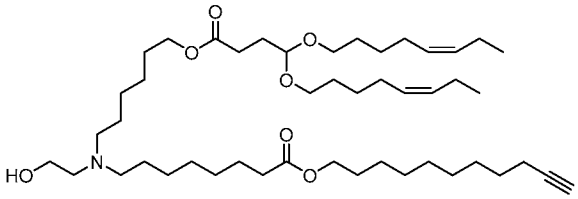

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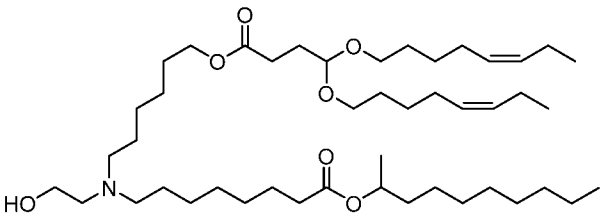

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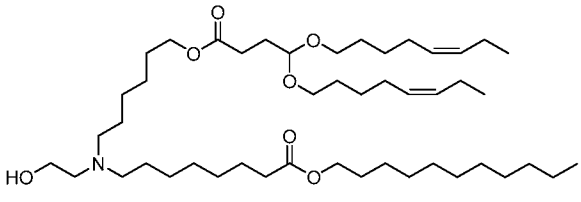

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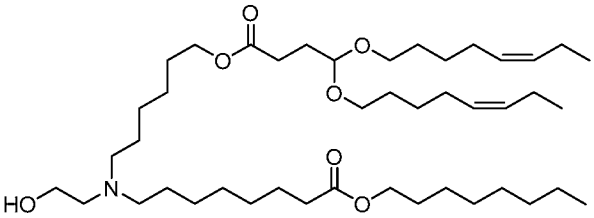

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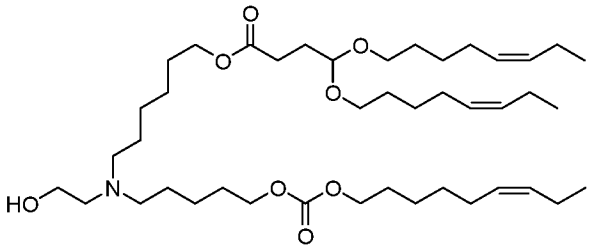

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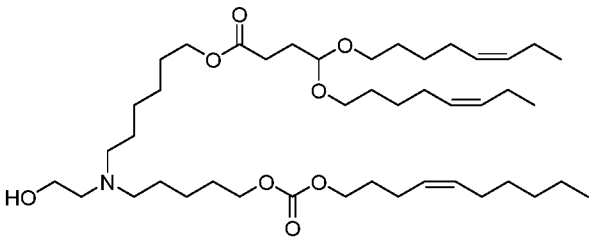

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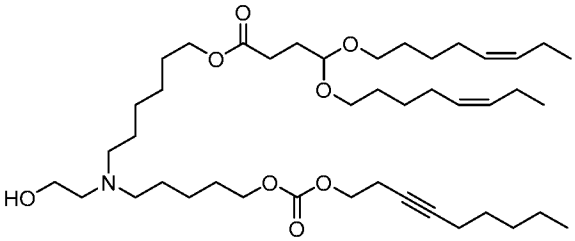

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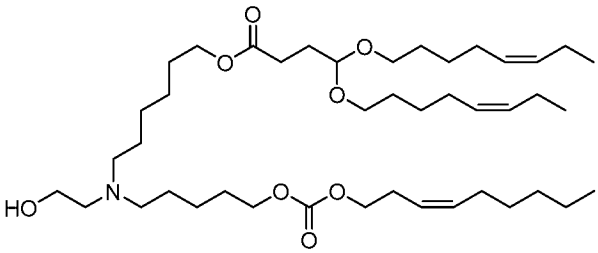

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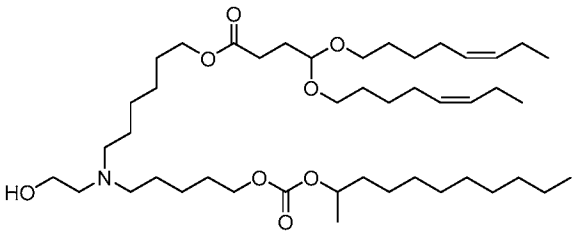

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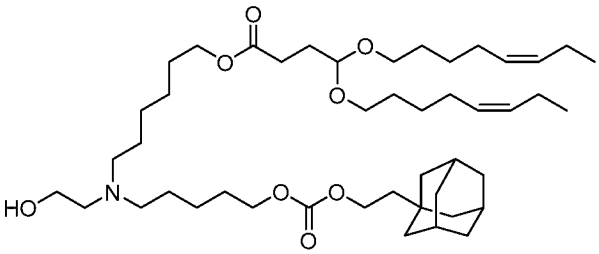

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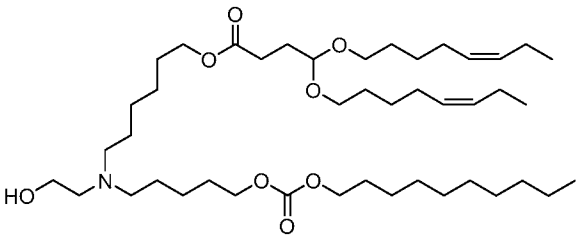

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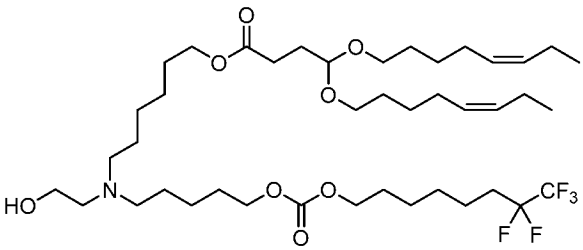

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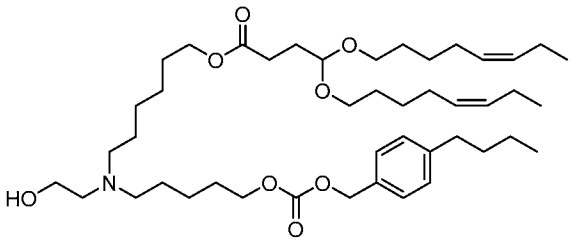

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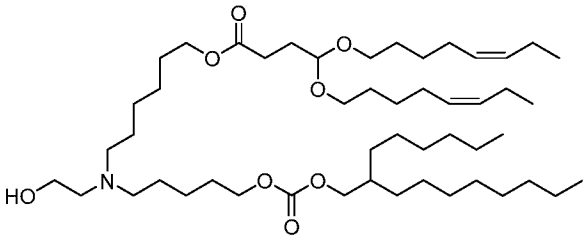

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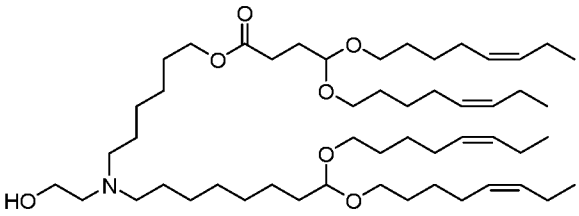

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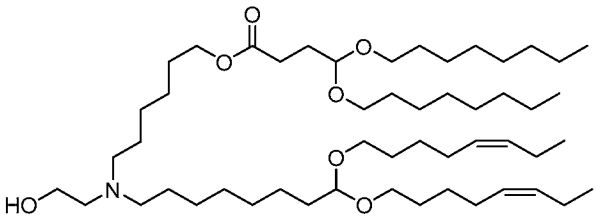

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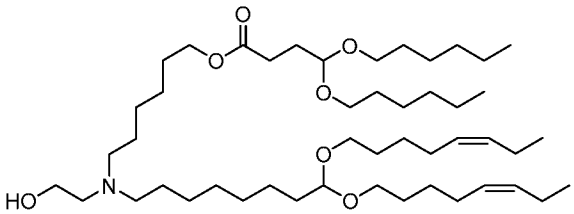

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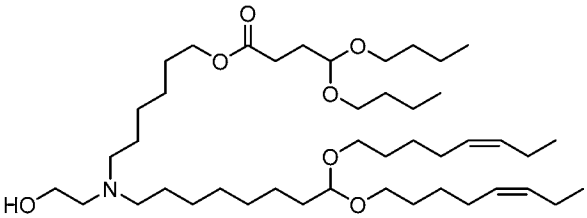

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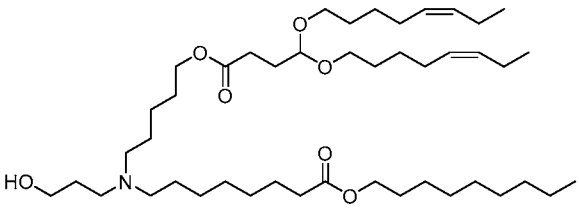

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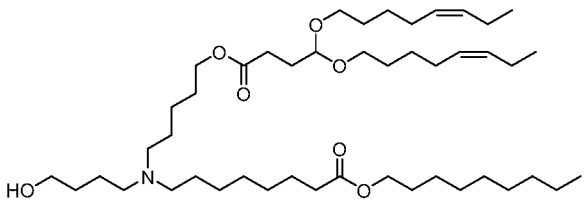

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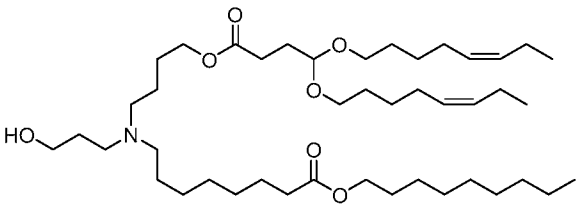

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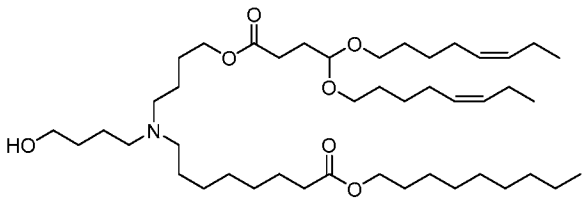

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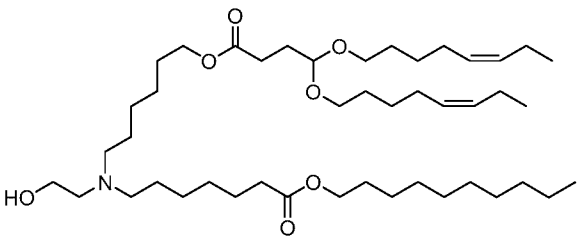

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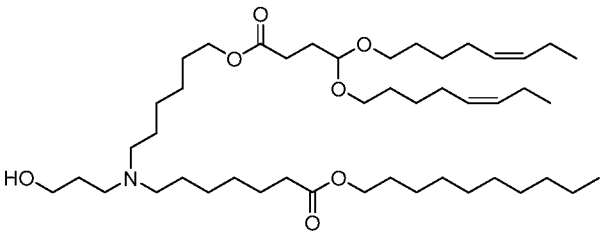

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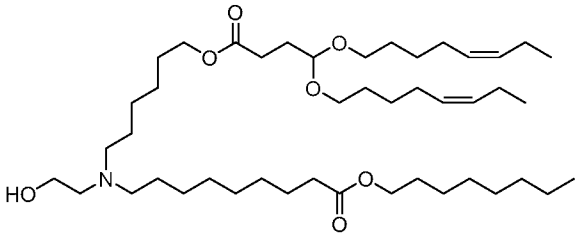

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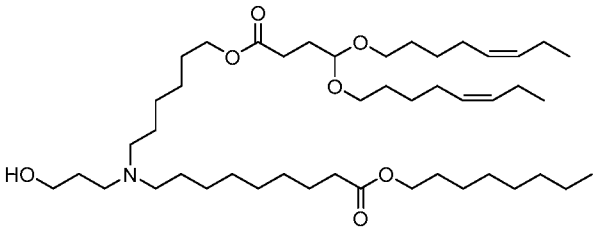

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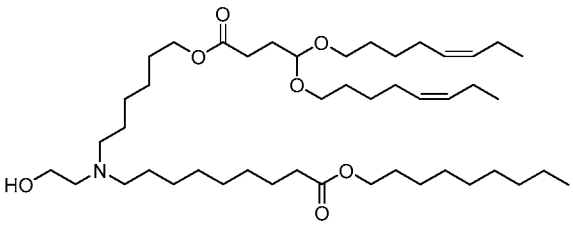

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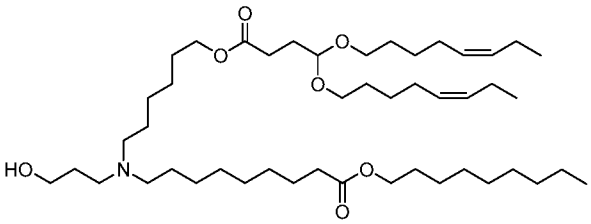

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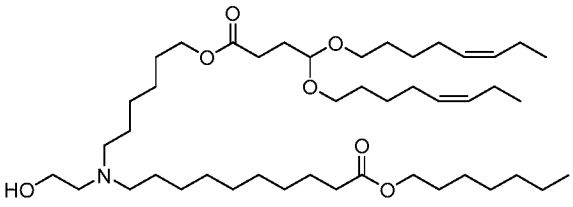

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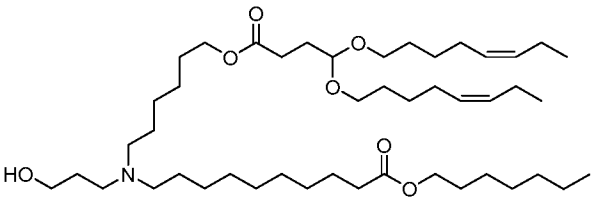

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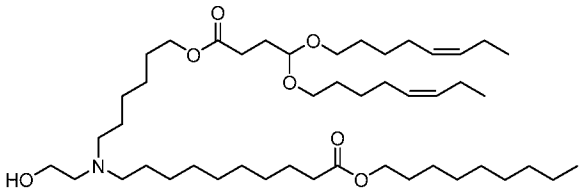

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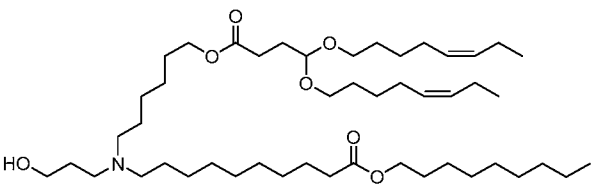

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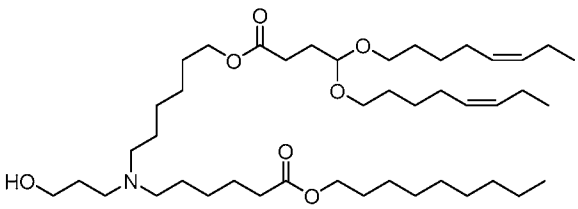

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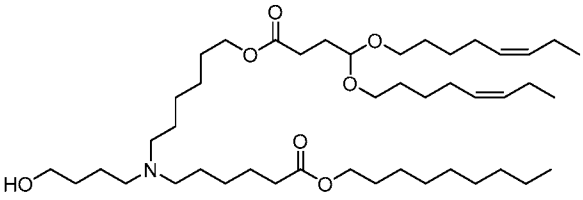

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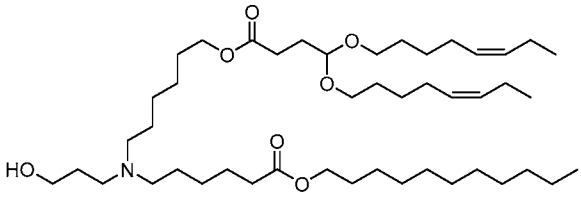

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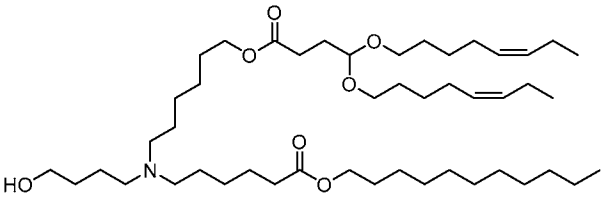

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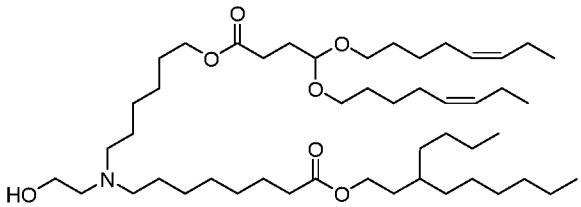

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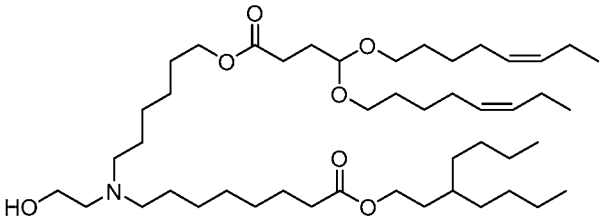

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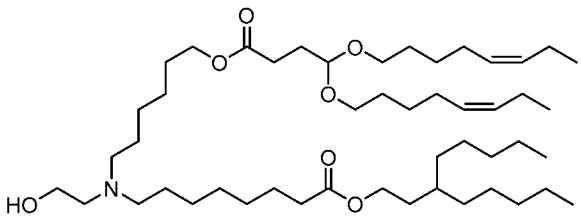

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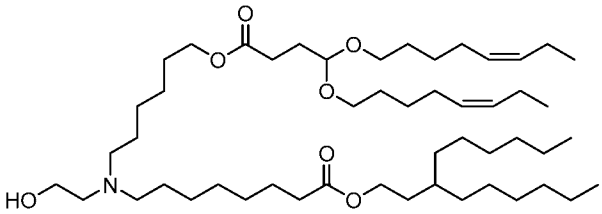

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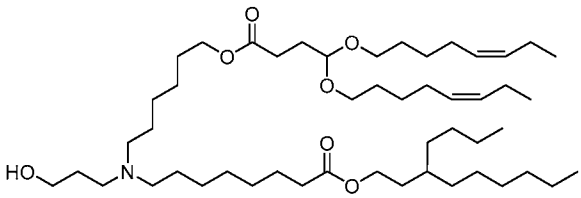

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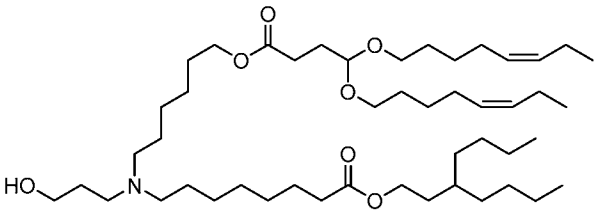

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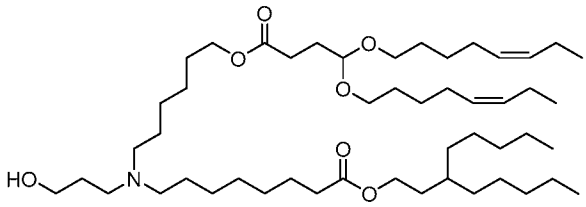

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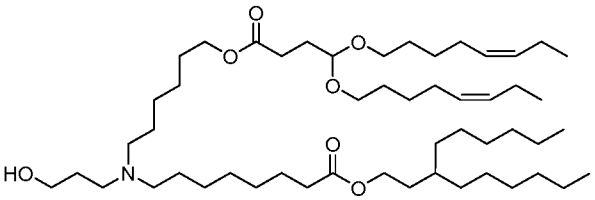

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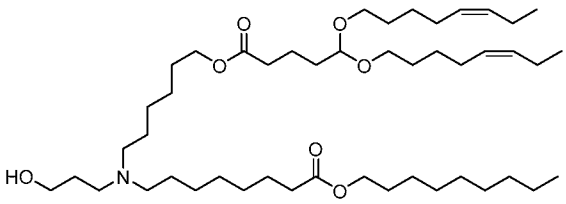

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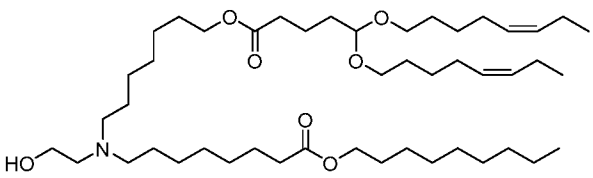

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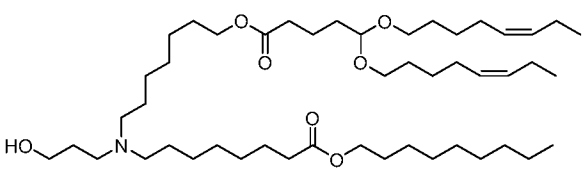

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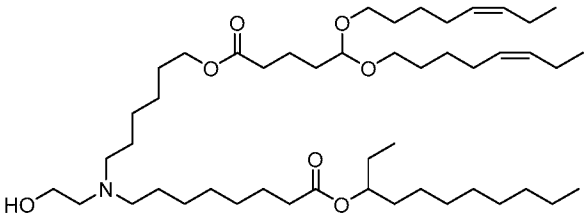

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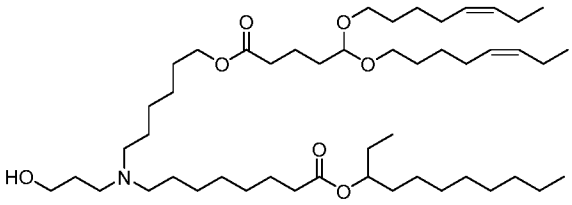

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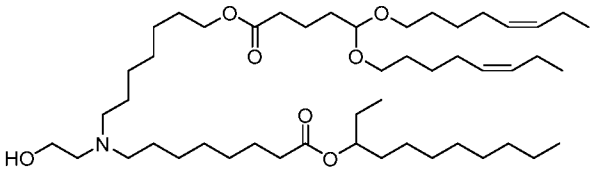

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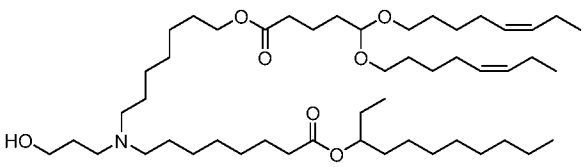

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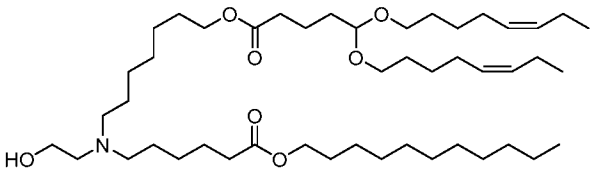

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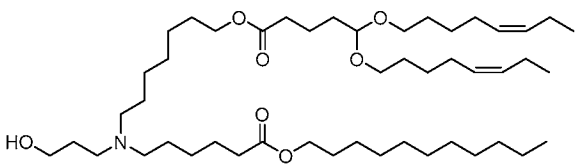

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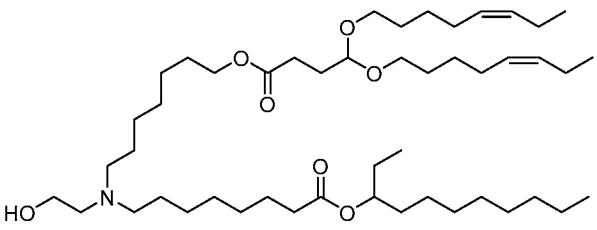

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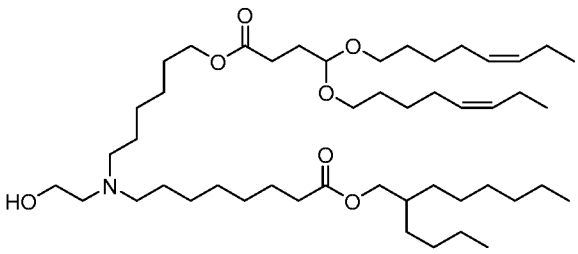

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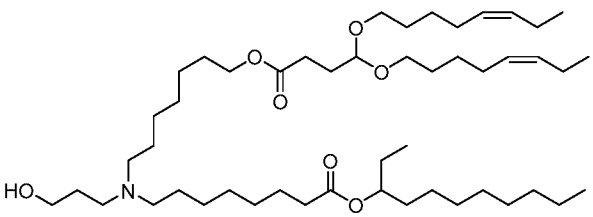

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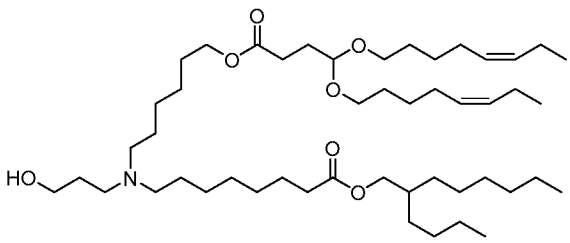

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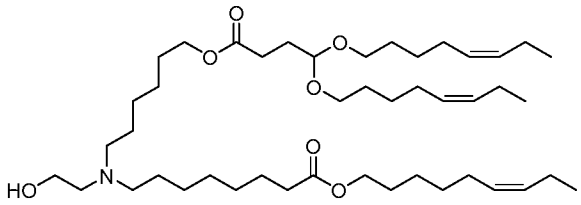

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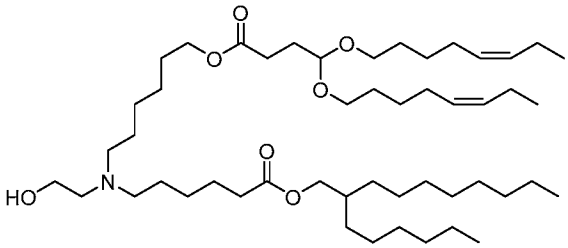

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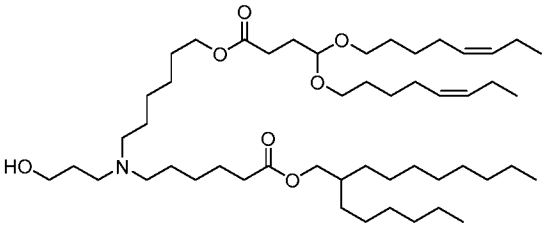

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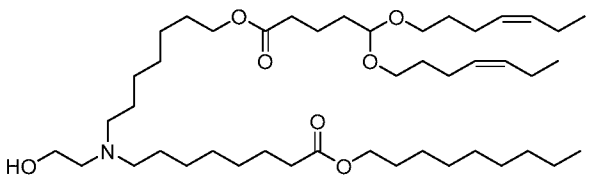

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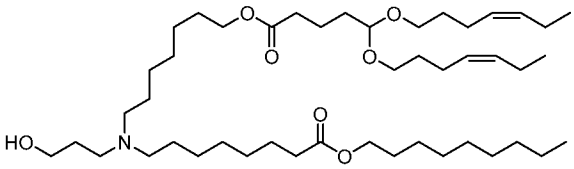

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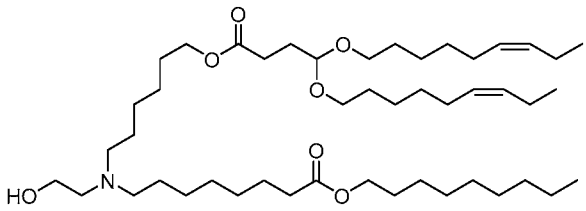

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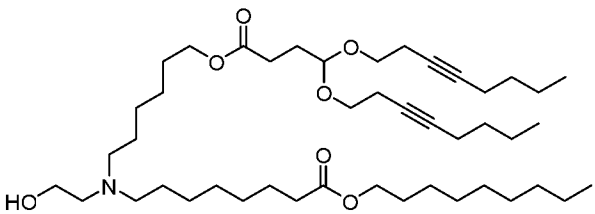

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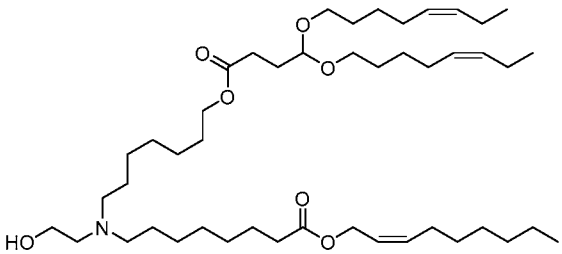

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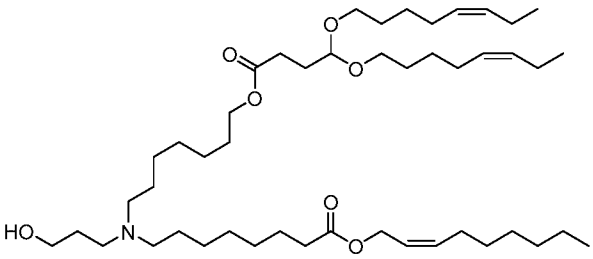

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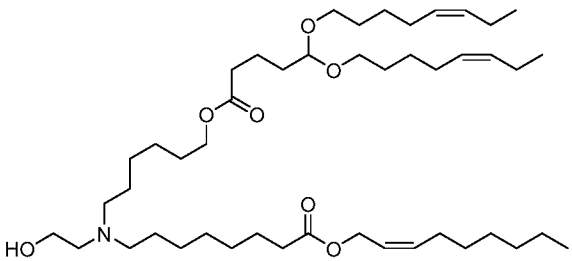

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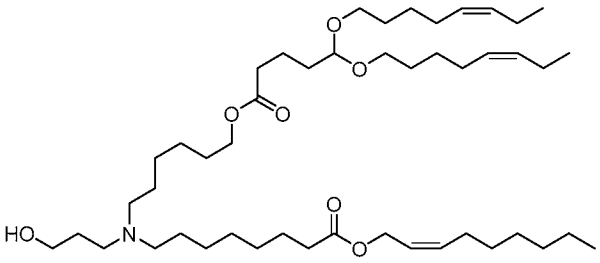

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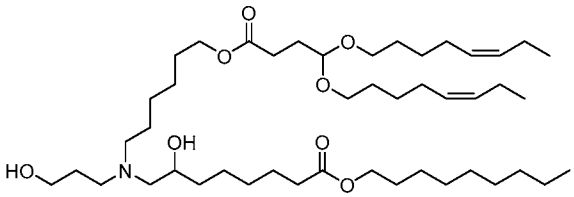

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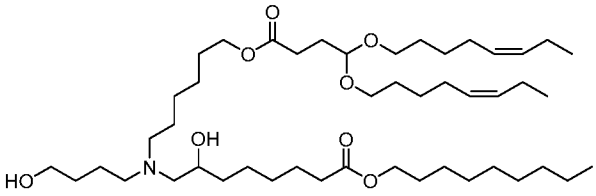

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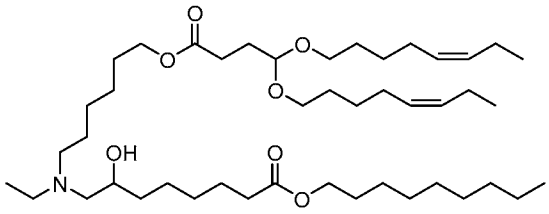

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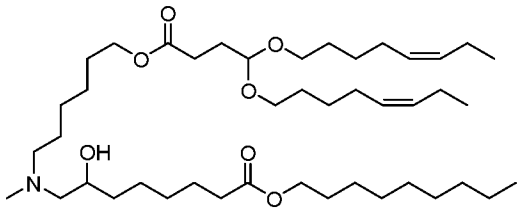

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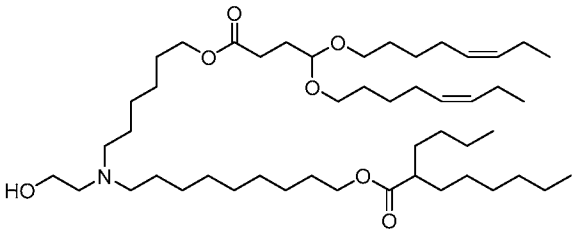

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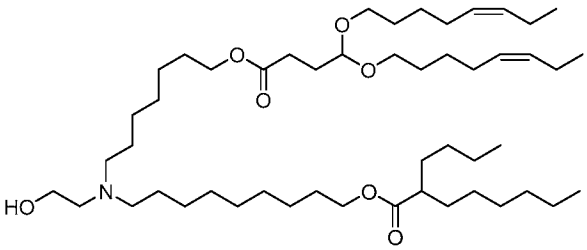

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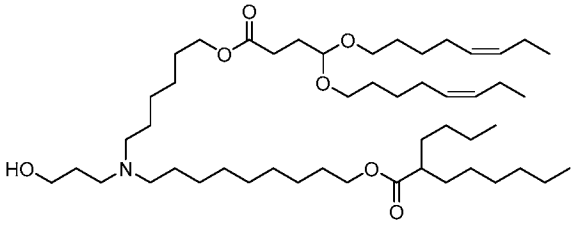

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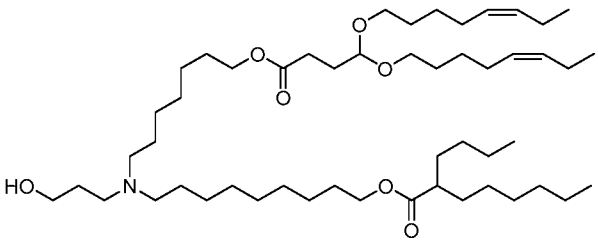

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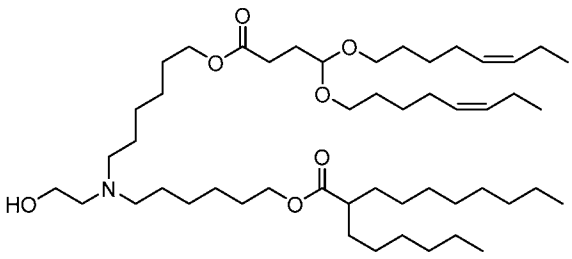

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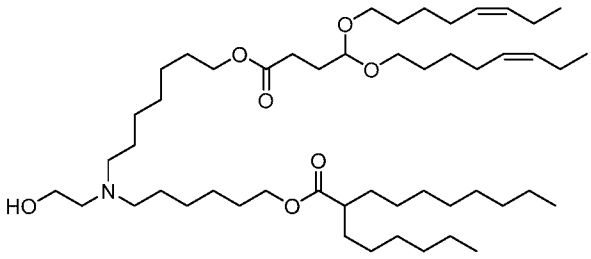

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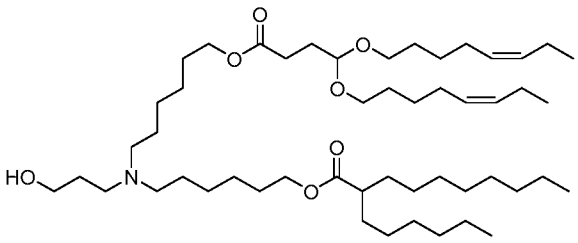

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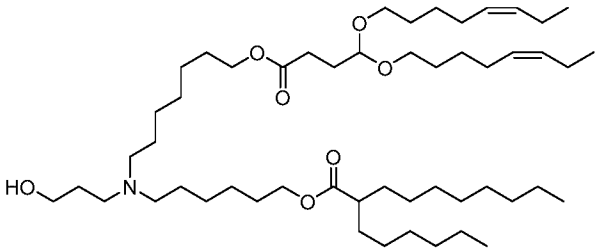

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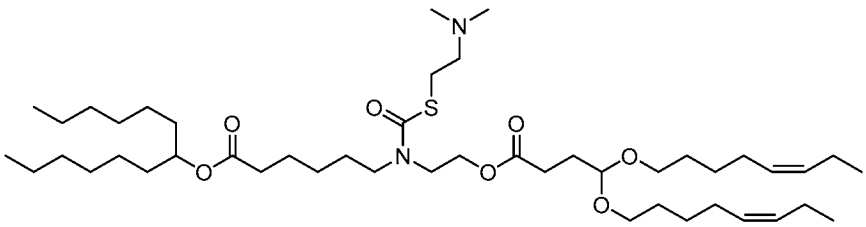

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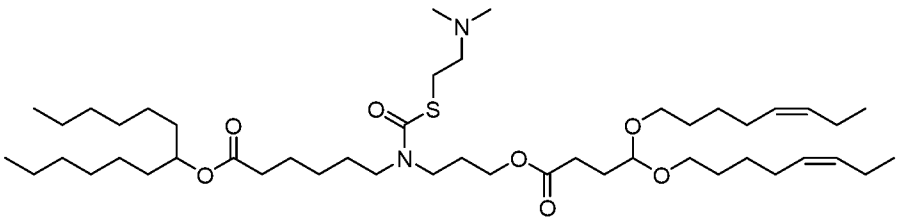

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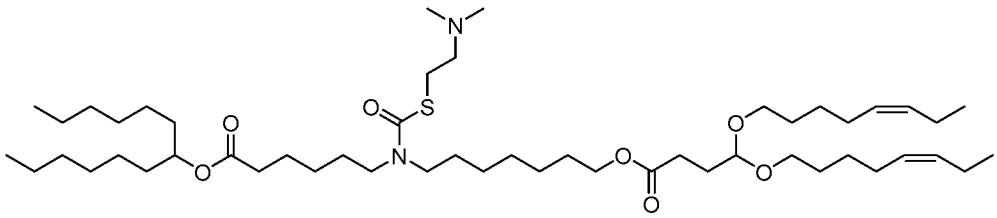

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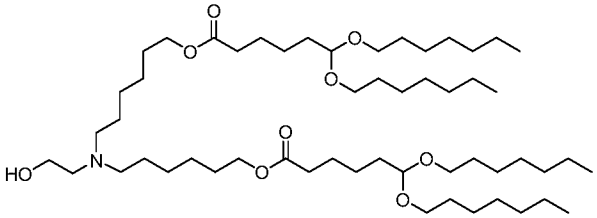

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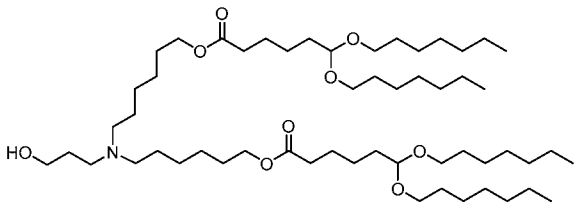

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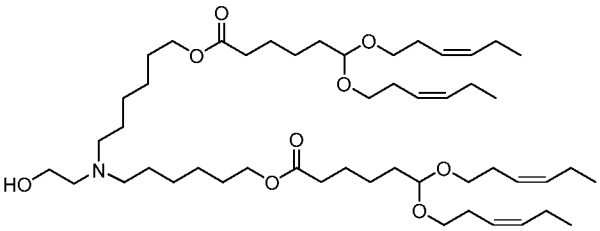

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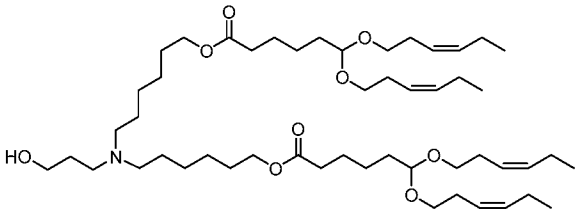

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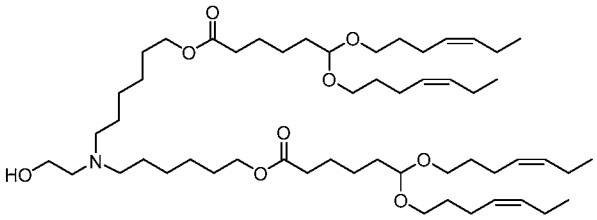

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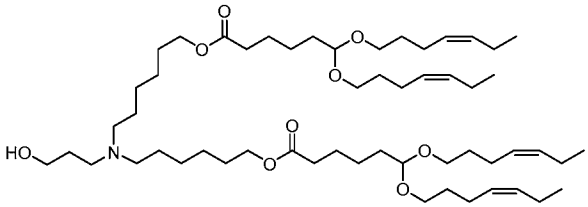

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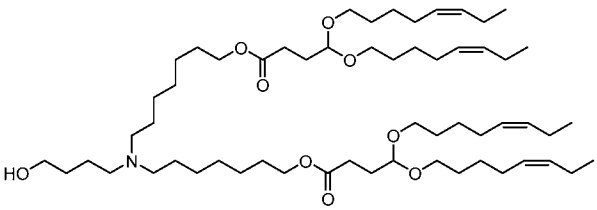

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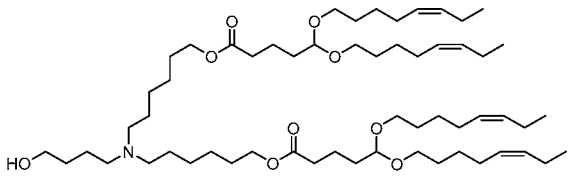

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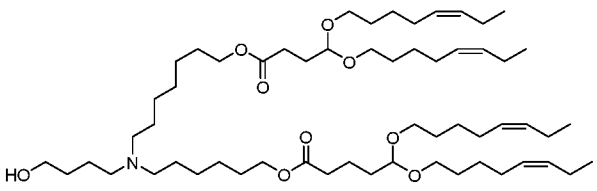

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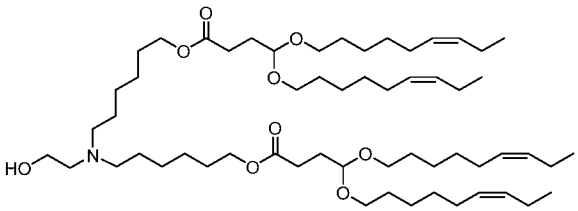

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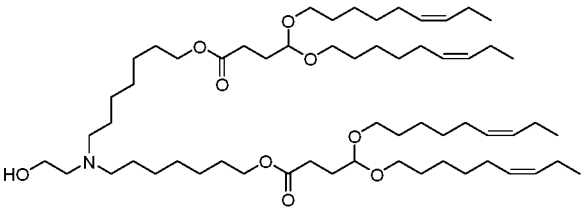

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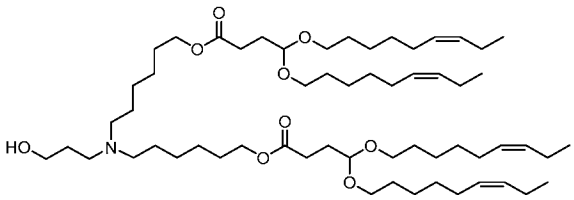

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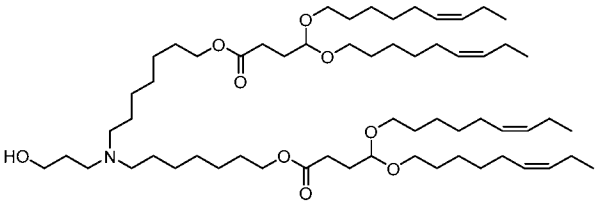

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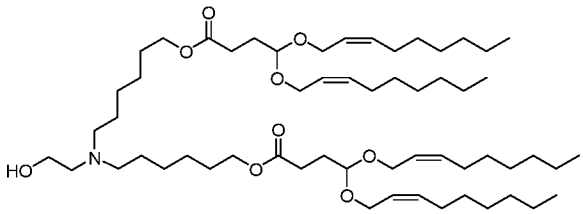

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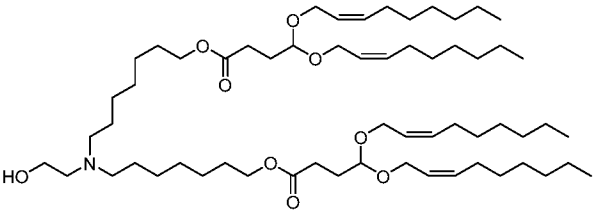

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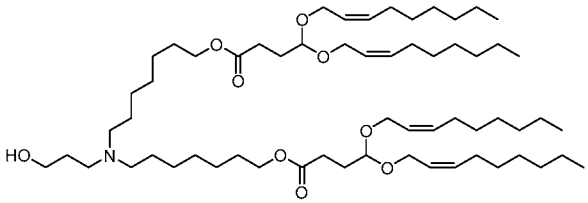

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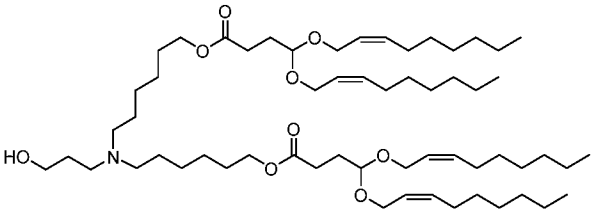

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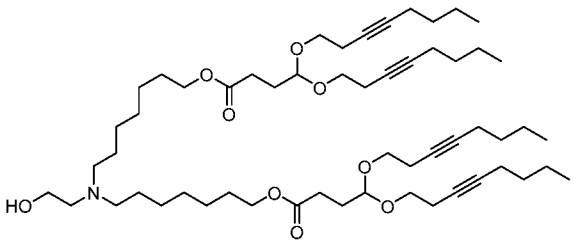

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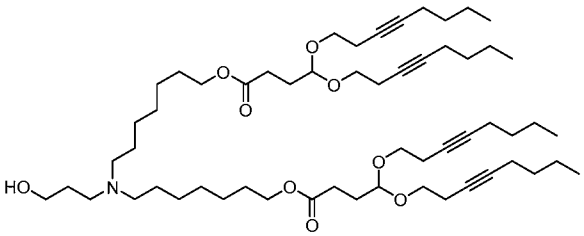

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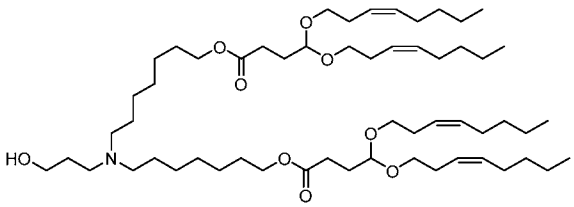

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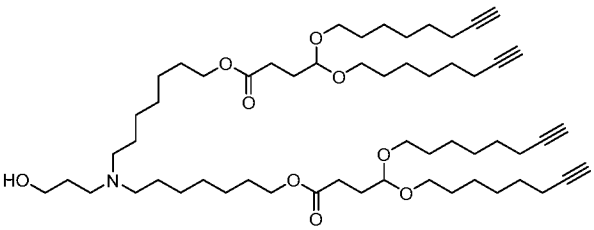

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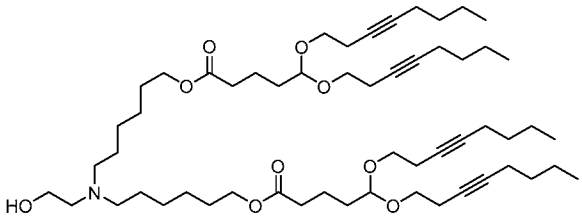

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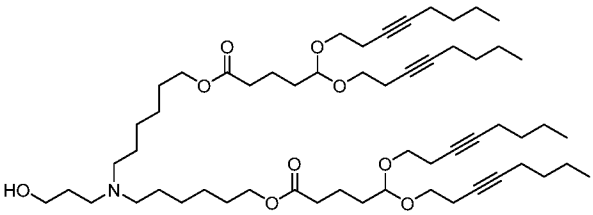

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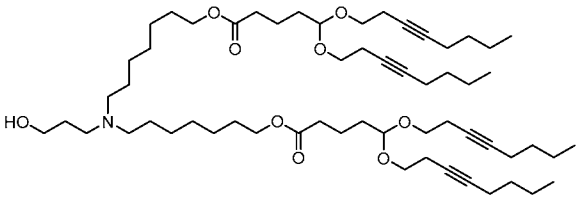

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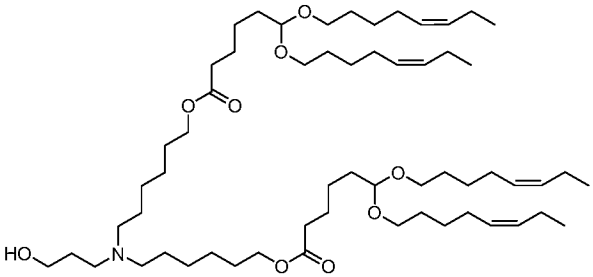

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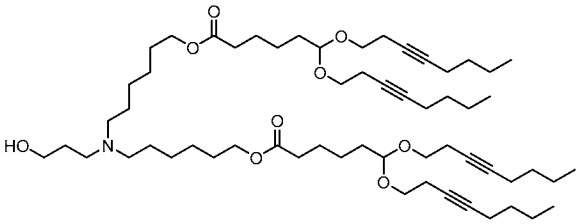

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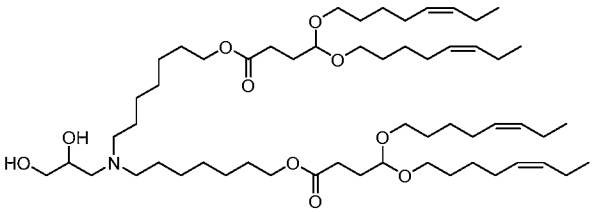

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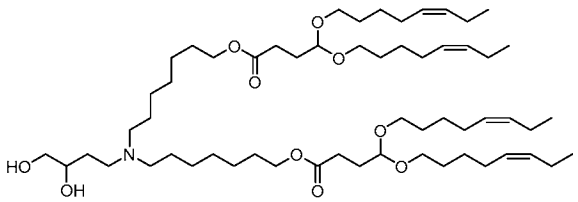

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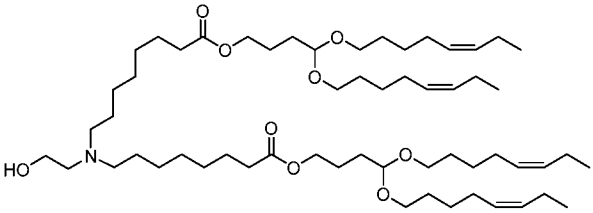

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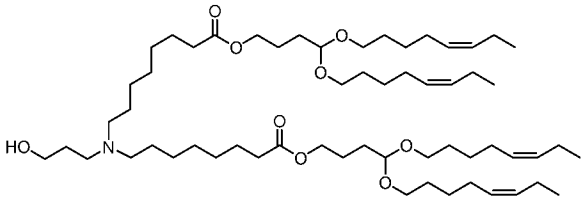

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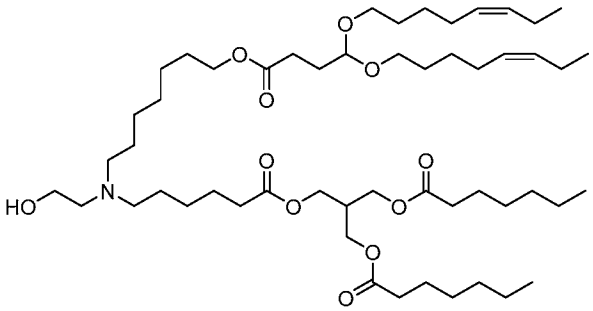

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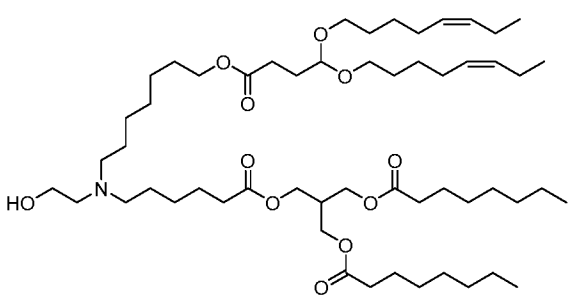

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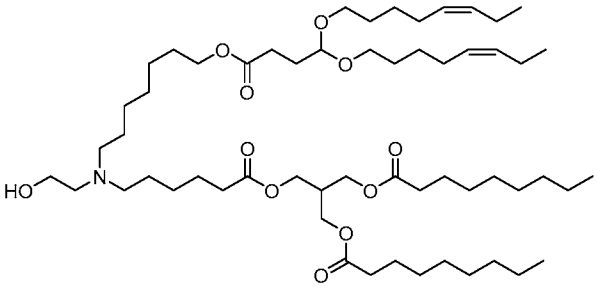

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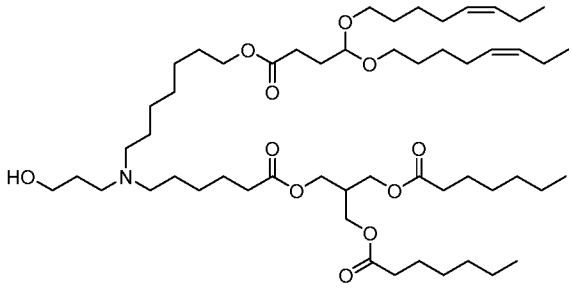

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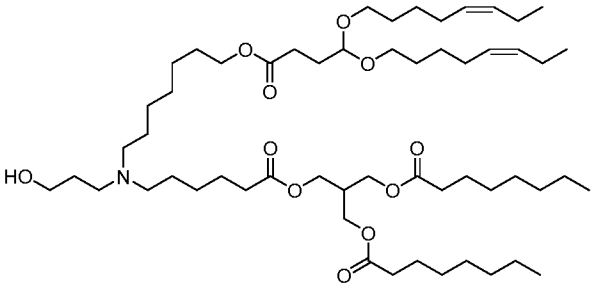

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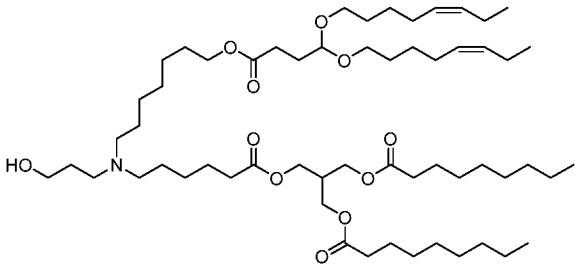

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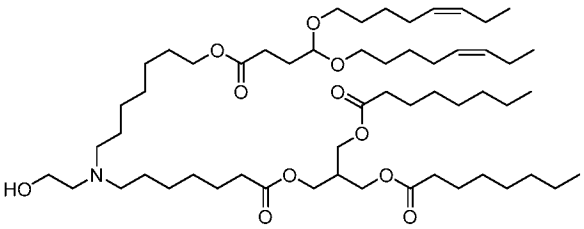

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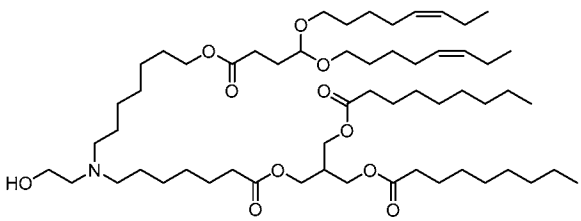

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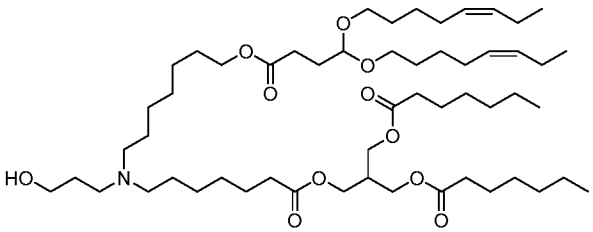

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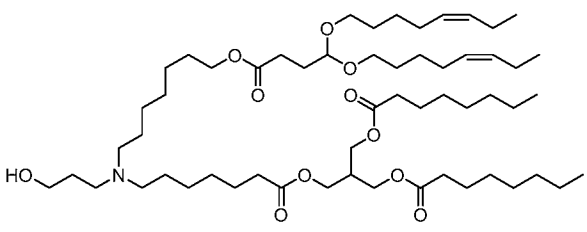

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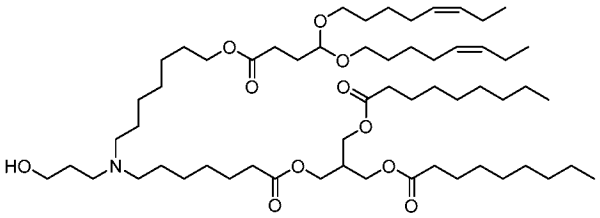

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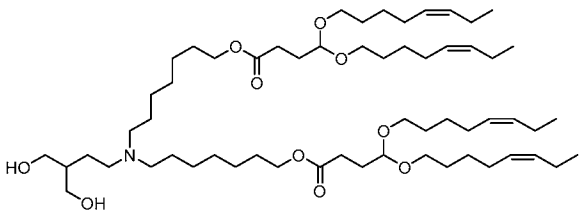

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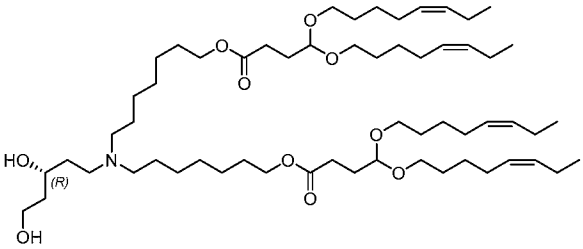

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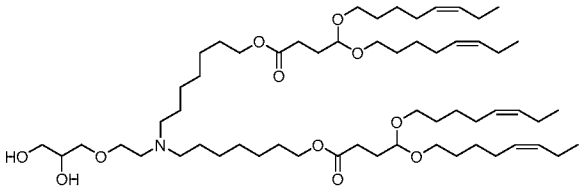

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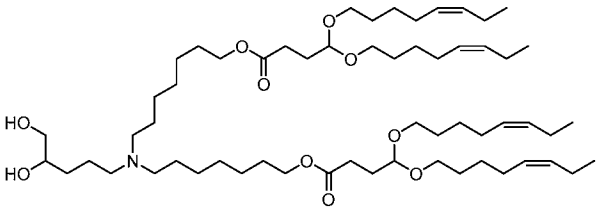

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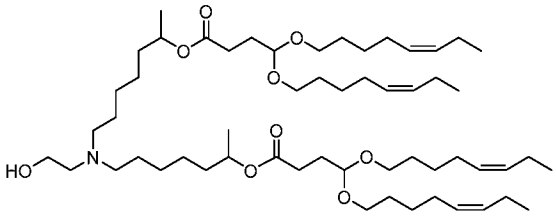

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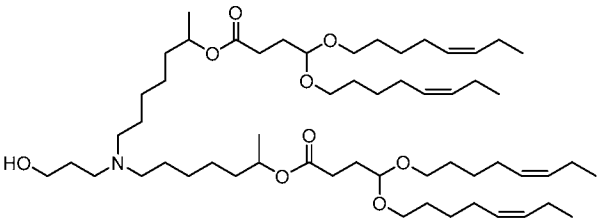

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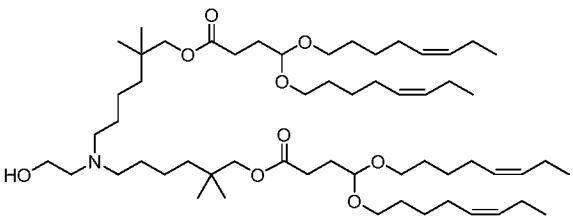

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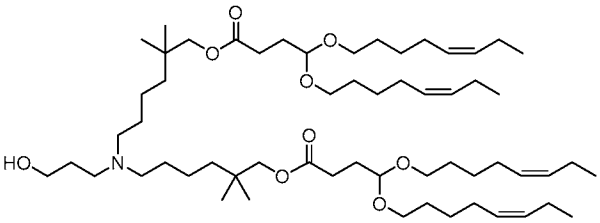

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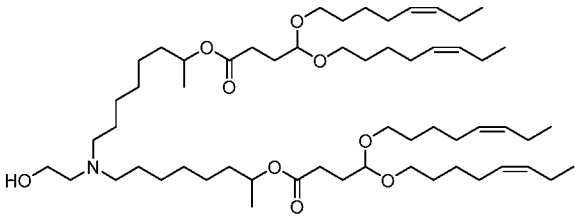

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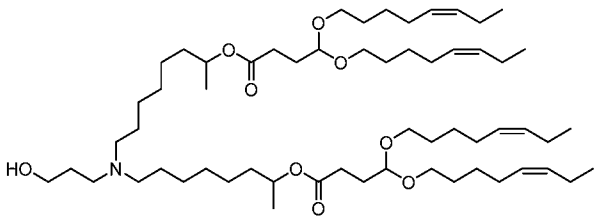


8-106

or a pharmaceutically acceptable salt thereof.

[0331] It will be understood that, unless otherwise specified or prohibited by the foregoing definition of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*, embodiments of variables L, L^1, L^2, L^3, L^{3a}, X, X^2, R", R, R^a, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, n, and p as defined above and described in classes and subclasses herein, apply to compounds of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*, both singly and in combination.

[0332] In some embodiments, provided compounds are provided and/or utilized in a salt form (e.g., a pharmaceutically acceptable salt form). Reference to a compound provided herein is understood to include reference to salts thereof, unless otherwise indicated.

[0333] It will be appreciated that throughout the present disclosure, unless otherwise indicated, reference to a compound of Formula A' is intended to also include A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*, and compound species of such formulae disclosed herein.

[0334] In some embodiments of any of Formulae I, I-a, I-b, I-c, I-d, and II, "a salt thereof" is a pharmaceutically acceptable salt thereof.

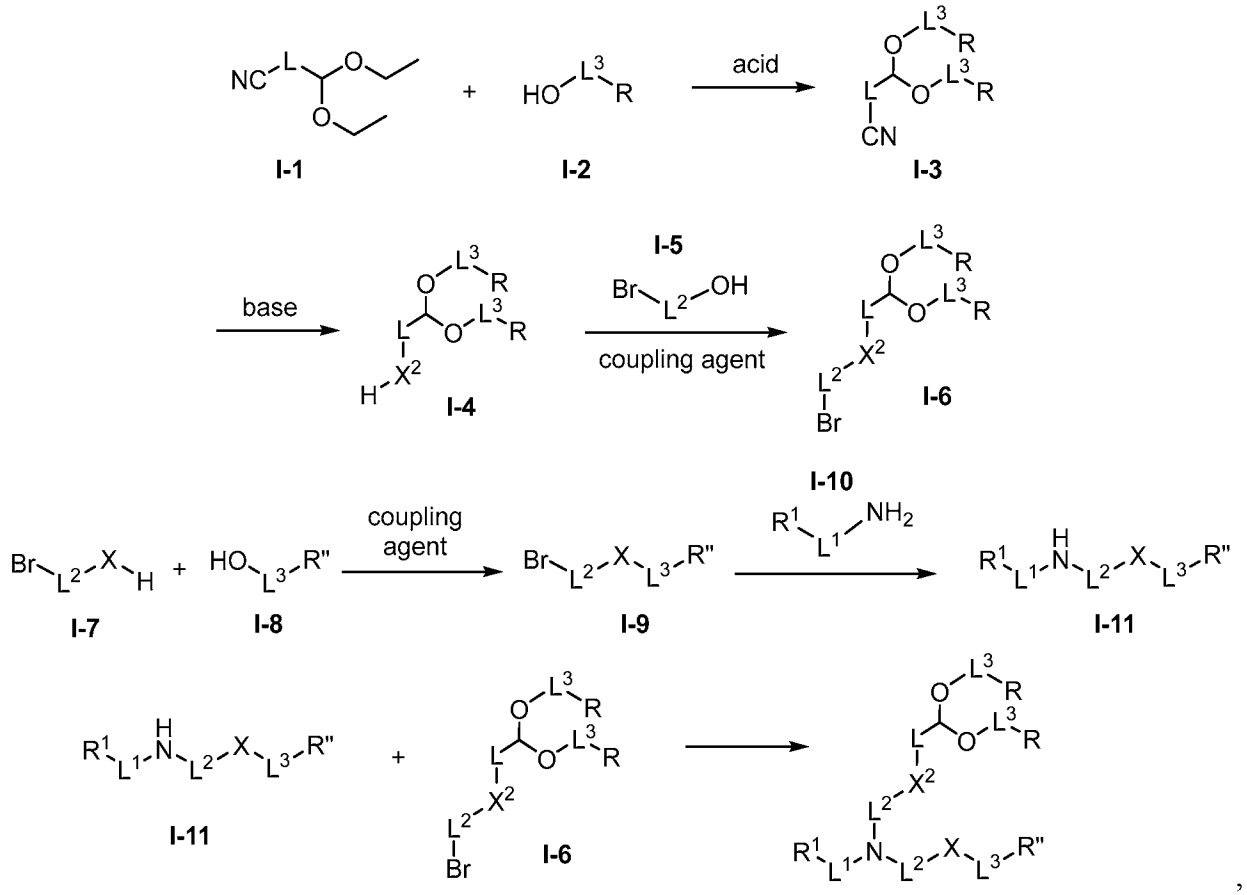
[0335] In some embodiments, the present disclosure encompasses the recognition that provided compounds display certain desirable characteristics, e.g., as compared to reference compounds or other known compounds. For example, in some embodiments, provided compounds exhibit more potent delivery to various cell types in one or more experiments described herein, and/or have one or more other characteristics that make them more suitable for delivery of cargos such as therapeutic or prophylactic agents than other known compounds. Without wishing to be bound by any particular theory, the present disclosure encompasses the recognition that provided compounds

characterized as including at least one ester-linked acetal feature display certain more desirable characteristics (e.g., more potent delivery to various cell types in one or more experiments described herein) than corresponding compounds lacking the same ester-linked acetal feature.

B. Preparing Provided Compounds

[0336] Provided compounds may generally be made by the processes described in the ensuing schemes and examples.

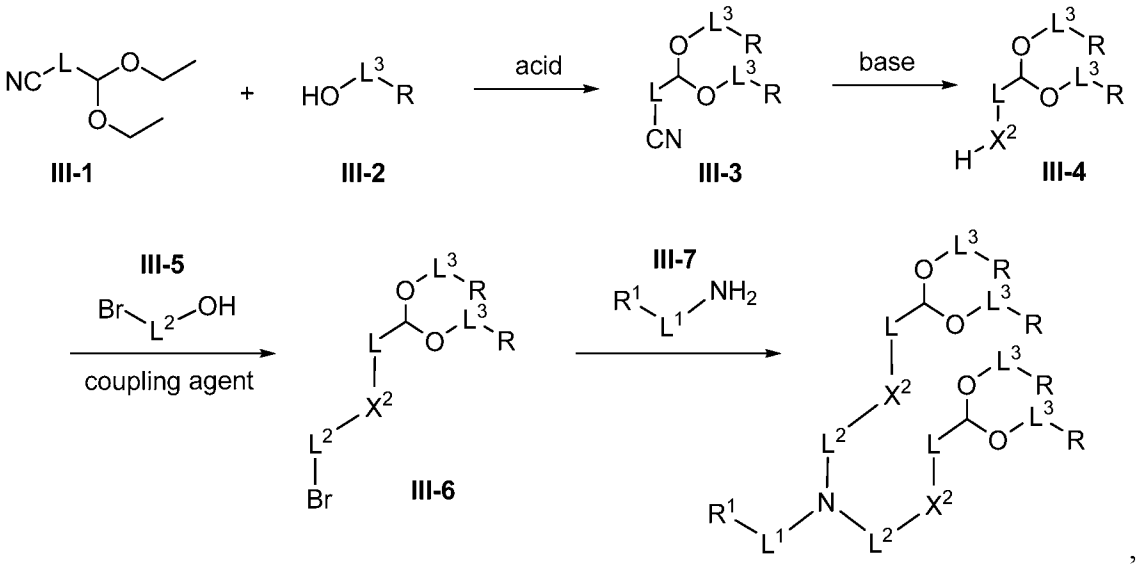
[0337] In some embodiments, provided compounds (e.g., compounds of Formula I") are prepared according to the following Scheme:



wherein each of L, L^1, L^2, L^3, X, X^2, R, R", and R^1 is as defined above for Formula I", and described in classes and subclasses herein, both singly and in combination. Accordingly, in some embodiments, intermediate I-3 is prepared by a process comprising contacting compounds of Formulae I-1 and I-2 in the presence of an acid reagent (e.g., PPTS). In some embodiments, intermediate I-4 is prepared by a process comprising contacting intermediate I-3 with a base reagent (e.g., KOH). In some embodiments, intermediate I-6 is prepared by a process comprising

contacting intermediate I-4 and compounds of Formula I-5 in the presence of a coupling reagent (e.g., EDC). In some embodiments, intermediate I-9 is prepared by a process comprising contacting compounds of Formulae I-7 and I-8 in the presence of a coupling reagent (e.g., EDC). In some embodiments, intermediate I-11 is prepared by a process comprising contacting intermediate I-9 with compounds of Formula I-10 under suitable conditions. In some embodiments, compounds of Formula I" are prepared by a process comprising contacting intermediates I-11 and I-6 under suitable conditions.

[0338] In some embodiments, provided compounds (e.g., compounds of any of Formulae III' and III) are prepared according to the following Scheme:



wherein each of L, L^1, L^2, L^3, X^2, R, and R^1 is as defined above for any of Formulae III' and III, and described in classes and subclasses herein, both singly and in combination. Accordingly, in some embodiments, intermediate III-3 is prepared by a process comprising contacting compounds of Formulae III-1 and III-2 in the presence of an acid reagent (e.g., PPTS). In some embodiments, intermediate III-4 is prepared by a process comprising contacting intermediate III-3 with a base reagent (e.g., KOH). In some embodiments, intermediate III-6 is prepared by a process comprising contacting compounds of Formulae III-4 and III-5 in the presence of a coupling reagent (e.g., EDC). In some embodiments, compounds of any of Formulae III' and III are prepared by a process comprising contacting intermediate III-6 with compounds of Formula III-7 under suitable conditions.

C. Ionizable lipids

[0339] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more ionizable lipids as described herein.

[0340] Among other things, it was surprisingly found that different ratios of ionizable lipids influence one or more functional activities such as desired tropisms, stabilization, and drug delivery efficacy of compositions, preparations, nanoparticles, and/or nanomaterials described herein. For example, the present disclosure demonstrates a surprising finding that amounts of ionizable lipids different to those amounts described in the art (e.g., see U.S. Patent No. 8,058,069 B2, or see, e.g., U.S. Patent No. 9,364,435, the contents of both which are hereby incorporated by reference in their entireties herein) are important to and/or influence one or more functional activities of compositions, preparations, nanoparticles, and/or nanomaterials described herein. For example, in some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials having an ionizable lipid that is at about 50 mol percent or less, based on total moles of components of the lipid nanoparticle, was found to be useful and/or critical to functional activity of lipid nanoparticles such as desired tropisms, stabilization, and drug delivery efficacy as described herein.

[0341] In some embodiments, an ionizable lipid may include an amine-containing group on the head group. In some embodiments, an ionizable lipid is or comprises a compound described herein (e.g., a compound of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*). In some embodiments, an ionizable lipid is present in a lipid nanoparticle (LNP) preparation from about 30 mole percent to about 70 mole percent, based on total moles of components of the lipid nanoparticle. In some embodiments, an ionizable lipid is present from about 33 mol percent to about 60 mole percent, based on total moles of components of the lipid nanoparticle. In some embodiments, an ionizable lipid is present from about 34 mol percent to about 55 mole percent, based on total moles of components of the lipid nanoparticle. In some embodiments, an ionizable lipid is present from about 33 mol percent to about 51 mole percent, based on total moles of components of the lipid nanoparticle. In some embodiments, an ionizable lipid is present at about 34.7 mole percent, based on total moles of components of the lipid nanoparticle. In some embodiments, an ionizable lipid is present at about 50 mole percent, based on total moles of components of the lipid nanoparticle.

[0342] Among other things, in some embodiments, a lipid nanoparticle composition comprises an ionizable lipid. In some embodiments, a lipid nanoparticle preparation comprises an ionizable lipid; a phospholipid; a conjugate-linker lipid; and a cholesterol. In some embodiments, an ionizable lipid is or comprises a structure according to a compound described herein (e.g., a compound of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*). In some embodiments, an ionizable lipid is present in a LNP preparation from about 30 mole percent to about 70 mole percent, based on total moles of components of the lipid nanoparticle.

D. Sterols

[0343] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more sterols as described herein.

[0344] In some embodiments, a sterol is a cholesterol, or a variant or derivative thereof. In some embodiments, a cholesterol is modified. In some embodiments, a cholesterol is an oxidized cholesterol. In some embodiments, a cholesterol is esterified cholesterol. Unmodified cholesterol can be acted upon by enzymes to form variants that are side-chain or ring oxidized. In some embodiments, a cholesterol can be oxidized on the beta-ring structure or on the hydrocarbon tail structure. In some embodiments, a sterol is a phytosterol. Exemplary sterols that are considered for use in the disclosed lipid nanoparticles include but are not limited to 25-hydroxycholesterol (25-OH), 20α-hydroxycholesterol (20α-OH), 27-hydroxycholesterol, 6-keto-5α-hydroxycholesterol, 7-ketocholesterol, 7β-hydroxycholesterol, 7α-hydroxycholesterol, 7β-25-dihydroxycholesterol, beta-sitosterol, stigmasterol, brassicasterol, campesterol, or combinations thereof**.** In some embodiments, a side-chain oxidized cholesterol can enhance cargo delivery relative to other cholesterol variants. In some embodiments, a cholesterol is an unmodified cholesterol.

[0345] In some embodiments, a LNP composition comprises from about 20 mol percent to about 50 mol percent sterol. In some embodiments, a LNP composition comprises about 38 mol percent sterol. In some embodiments, a LNP composition comprises about 38.5 mol percent sterol. In some embodiments, a LNP composition comprises about 33.8 mol percent cholesterol.

E. Conjugate-linker lipids

[0346] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more conjugate-linker lipids as described herein.

[0347] In some embodiments, a conjugate-linker lipid is or comprises a polyethylene glycol (PEG)-lipid or PEG-modified lipid. In some embodiments, PEG or PEG-modified lipids may be alternately referred to as PEGylated lipids or PEG-lipids. Inclusion of a PEGylating lipid can be used to enhance lipid nanoparticle colloidal stability *in vitro* and circulation time *in vivo*. In some embodiments, the PEGylation is reversible in that the PEG moiety is gradually released in blood circulation. Exemplary PEG-lipids include but are not limited to PEG conjugated to saturated or unsaturated alkyl chains having a length of C6-C20. PEG-modified phosphatidylethanolamines, PEG-modified phosphatidic acids, PEG-modified ceramides (PEG-CER), PEG-modified dialkylamines, PEG-modified diacylglycerols (PEG-DAG), PEG-modified dialkylglycerols, and mixtures thereof. For example, in some embodiments, a PEG lipid may be PEG-c-DOMG, PEG-DMG, PEG-DLPE, PEG-DMPE, PEG-DPPE, PEG-DSG or a PEG-DSPE lipid.

[0348] In some embodiments, a conjugate-linker lipid comprises a polyethylene glycol lipid. In some embodiments, the conjugate-linker lipid comprises DiMystyrlGlycerol (DMG), 1,2-Dipalmitoyl-rac-glycerol, methoxypolyethylene Glycol (DPG-PEG), or 1,2-Distearoyl-rac-glycero-3-methylpolyoxyethylene (DSG – PEG). In some embodiments, a conjugate-linker lipid has an average molecular mass from about 500 Da to about 5000 Da. In some embodiments, a conjugate-linker lipid has an average molecular mass of about 2000 Da. In some embodiments, a LNP composition comprises from about 0 mol percent to about 5 mol percent conjugate-linker lipid. In some embodiments, a LNP composition comprises about 1.5 mol percent conjugate-linker lipid. In some embodiments, a LNP composition comprises about 3 mol percent conjugate-linker lipid.

F. Phospholipids

[0349] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more phospholipids as described herein. In some embodiments, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that comprise one or more (poly)unsaturated lipids.

[0350] In some embodiments, one or more phospholipids may assemble into one or more lipid bilayers. In some embodiments, one or more phospholipids may include a phospholipid moiety. In some embodiments, one or more phospholipids may include one or more fatty acid moieties. In some embodiments, one or more phospholipids may include a phospholipid moiety and one or more fatty acid moieties. In some embodiments, a phospholipid moiety includes but is not limited to phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidyl serine, phosphatidic acid, 2-lysophosphatidyl choline, and sphingomyelin. In some embodiments, a fatty acid moiety includes but is not limited to lauric acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, alphalinolenic acid, erucic acid, phytanic acid, arachidic acid, arachidonic acid, eicosapentaenoic acid, behenic acid, docosapentaenoic acid, and docosahexaenoic acid. Non-natural species including natural species with modifications and substitutions including branching, oxidation, cyclization, and alkynes are also contemplated. For example, a phospholipid may be functionalized with or cross-linked to one or more alkynes *(e.g.,* an alkenyl group in which one or more double bonds is replaced with a triple bond). Under appropriate reaction conditions, an alkyne group may undergo a copper-catalyzed cycloaddition upon exposure to an azide. Such reactions may be useful in functionalizing a lipid bilayer of a nanoparticle composition to facilitate membrane permeation or cellular recognition or in conjugating a nanoparticle composition to a useful component such as a targeting or imaging moiety *(e.g.,* a dye).

[0351] Exemplary phospholipids include but are not limited to 1,2-distearoyl-*sn*glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-*sn*-glycerophosphocholine (DMPC), 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-diundecanoyl-*sn*-glycerophosphocholine (DUPC), l-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC), 1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC), 1-oleoyl-2-cholesterylhemisuccinoy l-*sn*-glycero-3-phosphocholine (OChemsPC), 1-hexadecyl snglycero-3-phosphocholine (C16 Lyso PC), 1,2-dilinolenoyl-*sn*-glycero-3-phosphocholine, 1,2-diarachidonoyl-*sn*-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-*sn*-glycero-3-phosphocholine, 1,2-diphytanoyl-*sn*-glycero-3-phosphoethanolamine (ME 16.0 PE), 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-*sn*-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-*sn*-glycero-3-

phosphoethanolamine, 1,2-diarachidonoyl-*sn*-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-*sn*-glycero-3-phosphoethanolamine, 1,2-dioleoyl-*sn*-glycero-3-phospho-rac-(1 -glycerol) sodium salt (DOPG), dipalmitoylphosphatidylglycerol (DPPG), palmitoyloleoylphosphatidylethanolamine (POPE), distearoyl-phosphatidyl-ethanolamine (DSPE), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), 1-stearoyl-2-oleoyl-phosphatidy ethanolamine (SOPE), 1-stearoyl-2 oleoylphosphatidylcholine (SOPC), sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyloleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidylethanolamine (LPE), or combinations thereof. In some embodiments, a phospholipid is DSPC. In some embodiments, a phospholipid is DMPC.

[0352] In some embodiments, the phospholipid comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-(succinyl) (succinyl PE), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl) (succinyl-DPPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), or a combination thereof.

G. Diameter

[0353] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that have an average hydrodynamic diameter from about 30 to about 220 nm. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have an average hydrodynamic diameter that is about 30 nm, 35 nm,40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, 150 nm, 155 nm, 160 nm, 165 nm, 170 nm, 175 nm, 180 nm, 185 nm, 190 nm, 195 nm, 200 nm, 205 nm, 210 nm, 215 nm, 220 nm, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have an average hydrodynamic diameter from between 50 nm to 200 nm.

[0354] In some embodiments, lipid nanoparticles described herein have an average hydrodynamic diameter from about 30 to about 220 nm. In some embodiments, lipid nanoparticles described herein have an average hydrodynamic diameter that is about 30 nm, 35 nm,40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, 150 nm, 155 nm, 160 nm, 165 nm, 170 nm, 175 nm, 180 nm, 185 nm, 190 nm, 195 nm, 200 nm, 205 nm, 210 nm, 215 nm, 220 nm, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, lipid nanoparticles described herein have an average hydrodynamic diameter from between 50 nm to 200 nm.

H. Polydispersity

[0355] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that have a polydispersity index (PDI) of about 0.01 to about 0.3. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have a PDI that is about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.15, 0.2, 0.25, 0.3, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have a PDI from about 0.05 to about 0.2, about 0.06 to about 0.1, or about 0.07 to about 0.09.

[0356] In some embodiments, lipid nanoparticles described herein have a PDI from about 0.01 to about 0.3. In some embodiments, lipid nanoparticles described herein have a PDI that is about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.15, 0.2, 0.25, 0.3, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, lipid nanoparticles described herein have a PDI from about 0.05 to about 0.2, about 0.06 to about 0.1, or about 0.07 to about 0.09.

I. Encapsulation efficiency

[0357] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials, wherein encapsulation effiency of provided compositions, preparations, nanoparticles, and/or nanomaterials is from about 80% to about 100%. In some embodiments, encapsulation effiency of compositions, preparations, nanoparticles, and/or

nanomaterials described herein is about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5%, 100%, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, encapsulation effiency of compositions, preparations, nanoparticles, and/or nanomaterials described herein is from about 90% to about 100%, about 95% to about 100%, about 95% to about 98%, or about 95.5% to about 97.5%. In some embodiments, encapsulation effiency of compositions, preparations, nanoparticles, and/or nanomaterials described herein is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

[0358] In some embodiments, encapsulation effiency of lipid nanoparticles described herein is from about 80% to about 100%. In some embodiments, encapsulation effiency of lipid nanoparticles described herein is about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5%, 100%, or any range having endpoints defined by any two of the aforementioned values. For example, in some embodiments, encapsulation effiency of lipid nanoparticles described herein is from about 90% to about 100%, about 95% to about 100%, about 95% to about 98%, or about 95.5% to about 97.5%. In some embodiments, encapsulation effiency of lipid nanoparticles described herein is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

J. pKa

[0359] Among other things, the present disclosure describes compositions, preparations, nanoparticles, and/or nanomaterials that have a pKa from about 5 to about 9. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have a pKa that is about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, or any range having endpoints defined by any two of the aforementioned values. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein have a pKa that is about 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, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, or any range having endpoints defined by any two of the aforementioned values.

[0360] In some embodiments, lipid nanoparticles described herein have a pKa from about 5 to about 9. In some embodiments, lipid nanoparticles described herein have a pKa that is about 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, or any range having endpoints defined by any two of the

aforementioned values. In some embodiments, lipid nanoparticles described herein have a pKa that is about 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, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, or any range having endpoints defined by any two of the aforementioned values.

II. Exemplary LNP Preparations

[0361] The present invention provides for compositions, preparations, nanoparticles, and/or nanomaterials that comprise lipid nanoparticles. In some embodiments, a lipid nanoparticle preparation comprises about 30 mole percent to about 70 mole percent ionizable lipid, about 5 mole percent to about 25 mole percent phospholipid, about 25 mole percent to about 45 mole percent cholesterol, and about 0 mole percent to about 5 mole percent conjugate-linker lipid.

[0362] In some embodiments, a lipid nanoparticle preparation comprises about 45 mole percent ionizable lipid, about 9 mole percent phospholipid, about 44 mole percent cholesterol, and about 2 mole percent conjugate-linker lipid. In some embodiments, a lipid nanoparticle preparation comprises about 50 mole percent ionizable lipid, about 9 mole percent phospholipid, about 38 mole percent cholesterol, and about 3 mole percent conjugate-linker lipid.

[0363] In some embodiments, a lipid nanoparticle preparation comprises about 40 mole percent to about 60 mole percent ionizable lipid of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*, about 5 mole percent to about 15 mole percent 1-2-distearoyl-sn-glycero-3-phosphocholine, about 1 mole percent to about 5 mole percent C14PEG2000, and about 30 mole percent to about 47 mole percent cholesterol, based on the total moles of these four ingredients.

[0364] In some embodiments, a lipid nanoparticle (LNP) preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):mRNA from about 2:1 and 50:1. In some embodiments, a LNP preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):mRNA of about 2:1, about 3:1, about 4:1, about 5:1, about 6:1, about 7:1, about 8:1, about 9:1, about 10:1, about 11:1, about 12:1, about 13:1, about 14:1, about 15:1, about 16:1, about 17:1, about 18:1, about 19:1, about 20:1, about 21:1, about 22:1, about 23:1, about 24:1, about 25:1, about 26:1, about 27:1, about 28:1, about 29:1, about 30:1, about 31:1, about 32:1, about 33:1, about 34:1, about 35:1, about 36:1, about 37:1, about 38:1, about 39:1,

about 40:1, about 41:1, about 42:1, about 43:1, about 44:1, about 45:1, about 46:1, about 47:1, about 48:1, about 49:1, about 50:1. In some embodiments, a lipid nanoparticle (LNP) preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):mRNA of about 11.7:1 and 19:1.

[0365] In some embodiments, a lipid nanoparticle preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):siRNA from about 2:1 and 50:1. In some embodiments, a LNP preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):mRNA of about 2:1, about 3:1, about 4:1, about 5:1, about 6:1, about 7:1, about 8:1, about 9:1, about 10:1, about 11:1, about 12:1, about 13:1, about 14:1, about 15:1, about 16:1, about 17:1, about 18:1, about 19:1, about 20:1, about 21:1, about 22:1, about 23:1, about 24:1, about 25:1, about 26:1, about 27:1, about 28:1, about 29:1, about 30:1, about 31:1, about 32:1, about 33:1, about 34:1, about 35:1, about 36:1, about 37:1, about 38:1, about 39:1, about 40:1, about 41:1, about 42:1, about 43:1, about 44:1, about 45:1, about 46:1, about 47:1, about 48:1, about 49:1, about 50:1. In some embodiments, a lipid nanoparticle (LNP) preparation comprises a mass ratio of (ionizable lipid, cholesterol, lipid-PEG, and phospholipid):mRNA of about 11.7:1 and 19:1.

III. Pharmaceutical compositions

[0366] The present invention provides for compositions, preparations, nanoparticles, and/or nanomaterials that comprise pharmaceutical compositions. Among other things, in some embodiments, pharmaceutical compositions comprise lipid nanoparticles and lipid nanoparticle preparations described herein. For example, in some embodiments, lipid nanoparticles and lipid nanoparticle preparations described herein can be formulated in whole or in part as pharmaceutical compositions.

[0367] In some embodiments, pharmaceutical compositions may include one or more nanoparticle compositions described herein. For example, a pharmaceutical composition may comprise one or more nanoparticle compositions including one or more different therapeutic and/or prophylactics including but not limited to one or more nucleic acids of different types or encode different agents. In some embodiments, a pharmaceutical composition comprises one or more pharmaceutically acceptable excipients or accessory ingredients including but not limited to a pharmaceutically acceptable carrier.

[0368] A pharmaceutical composition may be administered to a subject. In some embodiments, a pharmaceutical composition is administered as described herein. In some *in vivo* approaches, the nanoparticle compositions disclosed herein are administered to a subject in a therapeutically effective amount as described herein.

[0369] In some embodiments, the ordinary skilled worker, considering the therapeutic context, age, and general health of the recipient, will be able to devise an appropriate dosage level and dosing regimen using the pharmaceutical compositions described herein for treatment of various conditions in various patients. For example, in some embodiments, a selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment desired. In some embodiments, generally dosage levels of about 0.001 mg to about 5 mg of nucleic acid per kg of body weight are administered each dosage to mammals. More specifically, in some embodiments, a preferential dose for nucleic acids within the disclosed nanoparticles is about 0.1 mg / kg to about 1.0 mg/kg. For the disclosed nanoparticles, generally dosage levels of about 0.2 mg to about 100 mg of four components (ionizable lipid, cholesterol, conjugate-linker conjugate, and phospholipid) / kg of body weight are administered to mammals. More specifically, in some embodiments, a preferential dose of the disclosed nanoparticles is about 0.5 mg / kg to about 5 mg / kg of the four components / kg of body weight.

[0370] In some embodiments, a pharmaceutical composition described herein is administered locally, for example by injection directly into a site to be treated. Typically, the injection causes an increased localized concentration of the composition which is greater than that which can be achieved by systemic administration. In some embodiments, a pharmaceutical composition described herein can be combined with a matrix as described herein to assist in creating an increased localized concentration of the polypeptide compositions by reducing the passive diffusion of the polypeptides out of the site to be treated.

A. Preparations for parenteral administration

[0371] In some embodiments, the compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein, including those containing lipid nanoparticles, are administered in an aqueous solution, by parenteral injection. In some embodiments, a preparation may also be in the form of a suspension or emulsion. In general, pharmaceutical compositions are provided including effective amounts of a lipid nanoparticle, and optionally include pharmaceutically acceptable

diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions optionally include one or more for the following: diluents, sterile water, buffered saline of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; and additives such as detergents and solubilizing agents (e.g., TWEEN 20 (polysorbate-20), TWEEN 80 (polysorbate-80)), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), and preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Formulations may be lyophilized and redissolved/resuspended immediately before use. A formulation may be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions.

B. Controlled delivery polymeric matrices

[0372] In some embodiments, the compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein can also be administered in controlled release formulations. In some embodiments, controlled release polymeric devices can be made for long term release systemically following implantation of a polymeric device (such as a rod, cylinder, film, disk) or injection (such as microparticles). In some embodiments, a matrix can be in the form of microparticles such as microspheres. In some embodiments, an agent is dispersed within a solid polymeric matrix or microcapsules. In some embodiments, a core is of a different material than a polymeric shell of any of the described compositions, preparations, nanoparticles, and/or nanomaterials. In some embodiments, a peptide is dispersed or suspended in a core, which may be liquid or solid in nature, of any of the described compositions, preparations, nanoparticles, and/or nanomaterials. Unless specifically defined herein, microparticles, microspheres, and microcapsules are used interchangeably. In some embodiments, a polymer may be cast as a thin slab or film, ranging from nanometers to four centimeters, a powder produced by grinding or other standard techniques, or even a gel such as a hydrogel.

[0373] In some embodiments, non-biodegradable matrices are used for delivery of the described compositions, preparations, nanoparticles, and/or nanomaterials. In some embodiments, biodegradable matrices are used for delivery of the described compositions, preparations, nanoparticles, and/or nanomaterials. In some embodiments, biodegradable matrices are preferred.

In some embodiments, biodegradable matrices comprise natural or synthetic polymers. In some embodiments, synthetic polymers are preferred due to the better characterization of degradation and release profiles. In some embodiments, a polymer is selected based on the period over which release is desired. In some embodiments, linear release may be most useful, although in others a pulse release or "bulk release" may provide more effective results. In some embodiments, a polymer may be in the form of a hydrogel (typically in absorbing up to about 90% by weight of water), and can optionally be crosslinked with multivalent ions or polymers.

[0374] The matrices can be formed by solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art. Bioerodible microspheres can be prepared using any of the methods developed for making microspheres for drug delivery, for example, as described by Mathiowitz and Langer, J. Controlled Release, 5:13-22 (1987); Mathiowitz, et al., Reactive Polymers, 6:275-283 (1987); and Mathiowitz, et al., J. Appl. Polymer Sci., 35:755-774 (1988), the disclosure of which is hereby incorporated by reference in its entirety herein.

[0375] In some embodiments, the described compositions, preparations, nanoparticles, and/or nanomaterials can be formulated for local release to treat the area of implantation or injection – which will typically deliver a dosage that is much less than the dosage for treatment of an entire body – or systemic delivery. These can be implanted or injected subcutaneously, into the muscle, fat, or swallowed.

C. Cargo

[0376] Among other things, the present invention provides for compositions, preparations, nanoparticles, and/or nanomaterials that comprise cargo as described herein. In some embodiments, the compositions, preparations, nanoparticles, and/or nanomaterials include a therapeutic or prophylactic agent for delivery to a subject. In some embodiments, a therapeutic or prophylactic agent is encapsulated by a lipid nanoparticle. In some embodiments, a lipid nanoparticle is loaded with one or more nucleic acids.

D. Therapeutic and/or prophylactic agents

[0377] Cargo delivered via a LNP composition may be a biologically active agent. In some embodiments, the cargo is or comprises one or more biologically active agents, such as mRNA, guide RNA (gRNA), nucleic acid, RNA-guided DNA-binding agent, expression vector, template

nucleic acid, antibody (e.g. , monoclonal, chimeric, humanized, nanobody, and fragments thereof etc.), cholesterol, hormone, peptide, protein, chemotherapeutic and other types of antineoplastic agent, low molecular weight drug, vitamin, co-factor, nucleoside, nucleotide, oligonucleotide, enzymatic nucleic acid, antisense nucleic acid, triplex forming oligonucleotide, antisense DNA or RNA composition, chimeric DNA:RNA composition, allozyme, aptamer, ribozyme, decoys and analogs thereof, plasmid and other types of vectors, and small nucleic acid molecule, RNAi agent, short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA) and "self-replicating RNA" (encoding a replicase enzyme activity and capable of directing its own replication or amplification *in vivo*) molecules, peptide nucleic acid (PNA), a locked nucleic acid ribonucleotide (LNA), morpholino nucleotide, threose nucleic acid (TNA), glycol nucleic acid (GNA), sisiRNA (small internally segmented interfering RNA), and iRNA (asymmetrical interfering RNA). The above list of biologically active agents is exemplary only, and is not intended to be limiting. Such compounds may be purified or partially purified, and may be naturally occurring or synthetic, and may be chemically modified.

[0378] Cargo delivered via a LNP composition may be an RNA, such as an mRNA molecule encoding a protein of interest. For example, in some embodiments, an mRNA for expressing a protein such as green fluorescent protein (GFP), an RNA-guided DNA-binding agent, or a Cas nuclease is described herein. LNP compositions that include a Cas nuclease mRNA, for example a Class 2 Cas nuclease mRNA that allows for expression in a cell of a Class 2 Cas nuclease such as a Cas9 or Cpfl protein are provided. Further, cargo may contain one or more guide RNAs or nucleic acids encoding guide RNAs. A template nucleic acid, e.g., for repair or recombination, may also be included in the composition or a template nucleic acid may be used in the methods described herein. In some embodiments, cargo comprises an mRNA that encodes a *Streptococcus pyogenes* Cas9, optionally and an *S. pyogenes* gRNA. In some embodiments, cargo comprises an mRNA that encodes a *Neisseria meningitidis* Cas9, optionally and an *nme* gRNA.

[0379] "mRNA" refers to a polynucleotide and comprises an open reading frame that can be translated into a polypeptide (i.e., can serve as a substrate for translation by a ribosome and amino-acylated tRNAs). mRNA can comprise a phosphate-sugar backbone including ribose residues or analogs thereof, e.g., 2'-methoxy ribose residues. In some embodiments, the sugars of an mRNA phosphate-sugar backbone consist essentially of ribose residues, 2'-methoxy ribose residues, or a

combination thereof. In general, mRNAs do not contain a substantial quantity of thymidine residues (e.g., 0 residues or fewer than 30, 20, 10, 5, 4, 3, or 2 thymidine residues; or less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 4%, 3%, 2%, 1%, 0.5%, 0.2%, or 0.1% thymidine content). An mRNA can contain modified uridines at some or all of its uridine positions.

E. CRISPR/Cas Cargo

[0380] In some embodiments, the disclosed compositions, preparations, nanoparticles, and/or nanomaterials comprise an mRNA encoding an RNA-guided DNA-binding agent, such as a Cas nuclease. In particular embodiments, the disclosed compositions, preparations, nanoparticles, and/or nanomaterials comprise an mRNA encoding a Class 2 Cas nuclease, such as S. pyogenes Cas9.

[0381] As used herein, an "RNA-guided DNA binding agent" means a polypeptide or complex of polypeptides having RNA and DNA binding activity, or a DNA-binding subunit of such a complex, wherein the DNA binding activity is sequence-specific and depends on the sequence of the RNA. Exemplary RNA-guided DNA binding agents include Cas cleavases/nickases and inactivated forms thereof ("dCas DNA binding agents"). "Cas nuclease", as used herein, encompasses Cas cleavases, Cas nickases, and dCas DNA binding agents. Cas cleavases/nickases and dCas DNA binding agents include a Csm or Cmr complex of a type III CRISPR system, the CaslO, Csml, or Cmr2 subunit thereof, a Cascade complex of a type I CRISPR system, the Cas3 subunit thereof, and Class 2 Cas nucleases. As used herein, a"Class 2 Cas nuclease" is a single chain polypeptide with RNA-guided DNA binding activity. Class 2 Cas nucleases include Class 2 Cas cleavases/nickases (e.g., H840A, D10A, or N863 A variants), which further have RNA-guided DNA cleavases or nickase activity, and Class 2 dCas DNA binding agents, in which cleavase/nickase activity is inactivated. Class 2 Cas nucleases include, for example, Cas9, Cpfl, C2cl, C2c2, C2c3, HF Cas9 (e.g., N497A, R661A, Q695A, Q926A variants), HypaCas9 (e.g., N692A, M694A, Q695A, H698A variants), eSPCas9(1.0) (e.g., K810A, K1003A, R1060A variants), and eSPCas9(1.1) (e.g., K848A, K1003A, R1060A variants) proteins and modifications thereof. Cpfl protein, Zetsche et al., Cell, 163: 1-13 (2015), is homologous to Cas9, and contains a RuvC-like nuclease domain. Cpfl sequences of Zetsche are incorporated by reference in their entirety herein. See, e.g., Zetsche, Tables Sl and S3. See, e.g, Makarova et al., Nat Rev Microbiol,

13(11): 722-36 (2015); Shmakov et al., Molecular Cell, 60:385-397 (2015), the contents of which are hereby incorporated in its entirety herein.

[0382] As used herein, "ribonucleoprotein" (RNP) or "RNP complex" refers to a guide RNA together with an RNA-guided DNA binding agent, such as a Cas nuclease, e.g., a Cas cleavase, Cas nickase, or dCas DNA binding agent (e.g., Cas9). In some embodiments, the guide RNA guides the RNA-guided DNA binding agent such as Cas9 to a target sequence, and the guide RNA hybridizes with and the agent binds to the target sequence; in cases where the agent is a cleavase or nickase, binding can be followed by cleaving or nicking.

[0383] In some embodiments, cargo for a LNP composition includes at least one guide RNA comprising guide sequences that direct an RNA-guided DNA binding agent, which can be a nuclease (e.g., a Cas nuclease such as Cas9), to a target DNA. gRNA may guide the Cas nuclease or Class 2 Cas nuclease to a target sequence on a target nucleic acid molecule. In some embodiments, a gRNA binds with and provides specificity of cleavage by a Class 2 Cas nuclease. In some embodiments, a gRNA and a Cas nuclease may form a ribonucleoprotein (RNP), e.g., a CRISPR/Cas complex such as a CRISPR/Cas9 complex. In some embodiments, a CRISPR/Cas complex may be a Type-II CRISPR/Cas9 complex. In some embodiments, a CRISPR/Cas complex may be a Type-V CRISPR/Cas complex, such as a Cpfl/guide RNA complex. Cas nucleases and cognate gRNAs may be paired. A gRNA scaffold structures that pair with each Class 2 Cas nuclease vary with the specific CRISPR/Cas system.

[0384] "Guide RNA", "gRNA", and simply "guide" are used herein interchangeably to refer to either a crRNA (also known as CRISPR RNA), or the combination of a crRNA and a trRNA (also known as tracrRNA). Guide RNAs can include modified RNAs as described herein. The crRNA and trRNA may be associated as a single RNA molecule (single guide RNA, sgRNA) or in two separate RNA molecules (dual guide RNA, dgRNA). "Guide RNA" or "gRNA" refers to each type. trRNA may be a naturally-occurring sequence, or a trRNA sequence with modifications or variations compared to naturally-occurring sequences.

[0385] As used herein, a "guide sequence" refers to a sequence within a guide RNA that is complementary to a target sequence and functions to direct a guide RNA to a target sequence for binding or modification (e.g., cleavage) by an RNA-guided DNA binding agent. A "guide sequence" may also be referred to as a "targeting sequence," or a "spacer sequence." A guide sequence can be 20 base pairs in length, e.g., in the case of Streptococcus pyogenes (i.e., Spy Cas9)

and related Cas9 homologs/orthologs. Shorter or longer sequences can also be used as guides, e.g., 15-, 16-, 17-, 18-, 19-, 21-, 22-, 23-, 24-, or 25-nucleotides in length. In some embodiments, a target sequence is in a gene or on a chromosome, for example, and is complementary to a guide sequence. In some embodiments, a degree of complementarity or identity between a guide sequence and its corresponding target sequence may be about or at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, a guide sequence and the target region may be 100% complementary or identical over a region of at least 15, 16, 17, 18, 19, or 20 contiguous nucleotides. In other embodiments, a guide sequence and a target region may contain at least one mismatch. For example, a guide sequence and a target sequence may contain 1, 2, 3, or 4 mismatches, where the total length of the target sequence is at least 17, 18, 19, 20 or more base pairs. In some embodiments, a guide sequence and a target region may contain 1-4 mismatches where a guide sequence comprises at least 17, 18, 19, 20 or more nucleotides. In some embodiments, a guide sequence and the target region may contain 1, 2, 3, or 4 mismatches where the guide sequence comprises 20 nucleotides.

[0386] Target sequences for RNA-guided DNA binding proteins such as Cas proteins include both the positive and negative strands of genomic DNA (i.e., the sequence given and the sequence's reverse compliment), as a nucleic acid substrate for a Cas protein is a double stranded nucleic acid. Accordingly, where a guide sequence is said to be "complementary to a target sequence", it is to be understood that the guide sequence may direct a guide RNA to bind to the reverse complement of a target sequence. Thus, in some embodiments, where the guide sequence binds the reverse complement of a target sequence, the guide sequence is identical to certain nucleotides of the target sequence (e.g., the target sequence not including the PAM) except for the substitution of U for T in the guide sequence.

[0387] The length of the targeting sequence may depend on the CRISPR/Cas system and components used. For example, different Class 2 Cas nucleases from different bacterial species have varying optimal targeting sequence lengths. Accordingly, the targeting sequence may comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, or more than 50 nucleotides in length. In some embodiments, the targeting sequence length is 0, 1, 2, 3, 4, or 5 nucleotides longer or shorter than the guide sequence of a naturally-occurring nucleotide sequence.

[0388] CRISPR/Cas system. In certain embodiments, a Cas nuclease and gRNA scaffold will be derived from the same CRISPR/Cas system. In some embodiments, a targeting sequence may comprise or consist of 18-24 nucleotides. In some embodiments, a targeting sequence may comprise or consist of 19-21 nucleotides. In some embodiments, the targeting sequence may comprise or consist of 20 nucleotides.

[0389] In some embodiments, a sgRNA is a "Cas9 sgRNA" capable of mediating RNA-guided DNA cleavage by a Cas9 protein. In some embodiments, a sgRNA is a "Cpfl sgRNA" capable of mediating RNA-guided DNA cleavage by a Cpfl protein. In some embodiments, a gRNA comprises a crRNA and tracr RNA sufficient for forming an active complex with a Cas9 protein and mediating RNA-guided DNA cleavage. In some embodiments, a gRNA comprises a crRNA sufficient for forming an active complex with a Cpfl protein and mediating RNA-guided DNA cleavage. See Zetsche 2015.

[0390] Certain embodiments of the invention also provide nucleic acids, e.g., expression cassettes, encoding the gRNA described herein. A "guide RNA nucleic acid" is used herein to refer to a guide RNA (e.g. an sgRNA or a dgRNA) and a guide RNA expression cassette, which is a nucleic acid that encodes one or more guide RNAs.

[0391] Certain embodiments of the present disclosure also provide delivery of adenine base editors ("ABEs") using the LNPs compositions, preparations, nanoparticles, and/or nanomaterials described herein. ABEs and methods of their use are described, e.g. in U.S. Patent No. 10,113,163 and U.S. Patent Publication No. 2021/0130805, the contents of each of which are hereby incorporated by reference in their entireties.

[0392] Certain embodiments of the present disclosure also provide delivery of cytosine base editors ("CBEs") using the LNPs compositions, preparations, nanoparticles, and/or nanomaterials described herein. ABEs and methods of their use are described, e.g. in U.S. Patent Nos. 10,167,457 and 9,840,699, the contents of each of which are hereby incorporated by reference in their entireties.

[0393] The term "base editor (BE)," or "nucleobase editor (NBE)" refers to an agent comprising a polypeptide that is capable of making a modification to a base (e.g., A, T, C, G, or U) within a nucleic acid sequence (e.g., DNA or RNA). In some embodiments, the base editor is capable of deaminating a base within a nucleic acid. In some embodiments, the base editor is capable of deaminating a base within a DNA molecule. In some embodiments, the base editor is capable of

deaminating an adenine (A) in DNA. . In some embodiments, the deaminase is a cytosine deaminase or a cytidine deaminase. In some embodiments, the base editor is a fusion protein comprising a nucleic acid programmable DNA binding protein (napDNAbp) fused to an adenosine deaminase. In some embodiments, the base editor is a Cas9 protein fused to an adenosine deaminase. In some embodiments, the base editor is a Cas9 nickase (nCas9) fused to an adenosine deaminase. In some embodiments, the base editor is a nuclease-inactive Cas9 (dCas9) fused to an adenosine deaminase. In some embodiments, the base editor is fused to an inhibitor of base excision repair, for example, a UGI domain, or a dISN domain. In some embodiments, the fusion protein comprises a Cas9 nickase fused to a deaminase and an inhibitor of base excision repair, such as a UGI or dISN domain. The term "nucleic acid programmable DNA binding protein" or "napDNAbp" refers to a protein that associates with a nucleic acid (e.g., DNA or RNA), such as a guide nuclic acid, that guides the napDNAbp to a specific nucleic acid sequence. For example, a Cas9 protein can associate with a guide RNA that guides the Cas9 protein to a specific DNA sequence that has complementary to the guide RNA. In some embodiments, the napDNAbp is a class 2 microbial CRISPR-Cas effector. In some embodiments, the napDNAbp is a Cas9 domain, for example a nuclease active Cas9, a Cas9 nickase (nCas9), or a nuclease inactive Cas9 (dCas9). Examples of nucleic acid programmable DNA binding proteins include, without limitation, Cas9 (e.g., dCas9 and nCas9), CasX, CasY, Cpf1, C2c1, C2c2, C2C3, and Argonaute. It should be appreciated, however, that nucleic acid programmable DNA binding proteins also include nucleic acid programmable proteins that bind RNA. For example, the napDNAbp may be associated with a nucleic acid that guides the napDNAbp to an RNA. Other nucleic acid programmable DNA binding proteins are also within the scope of this disclosure, though they may not be specifically listed in this disclosure.

F. Modified RNAs

[0394] In certain embodiments, the disclosed compositions, preparations, nanoparticles, and/or nanomaterials comprise modified nucleic acids, including modified RNAs.

[0395] Modified nucleosides or nucleotides can be present in an RNA, for example a gRNA or mRNA. A gRNA or mRNA comprising one or more modified nucleosides or nucleotides, for example, is called a "modified" RNA to describe the presence of one or more non-naturally and/or naturally occurring components or configurations that are used instead of or in addition to the

canonical A, G, C, and U residues. In some embodiments, a modified RNA is synthesized with a non-canonical nucleoside or nucleotide, here called "modified."

[0396] Modified nucleosides and nucleotides can include one or more of: (i) alteration, e.g., replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone linkage (an exemplary backbone modification); (ii) alteration, e.g., replacement, of a constituent of the ribose sugar, e.g. , of the 2' hydroxyl on the ribose sugar (an exemplary sugar modification); (iii) wholesale replacement of the phosphate moiety with "dephospho" linkers (an exemplary backbone modification); (iv) modification or replacement of a naturally occurring nucleobase, including with a non-canonical nucleobase (an exemplary base modification); (v) replacement or modification of the ribose-phosphate backbone (an exemplary backbone modification); (vi) modification of the 3' end or 5' end of the oligonucleotide, e.g. , removal, modification or replacement of a terminal phosphate group or conjugation of a moiety, cap or linker (such 3' or 5' cap modifications may comprise a sugar and/or backbone modification); and (vii) modification or replacement of the sugar (an exemplary sugar modification). Certain embodiments comprise a 5' end modification to an mRNA, gRNA, or nucleic acid. Certain embodiments comprise a 3' end modification to an mRNA, gRNA, or nucleic acid. A modified RNA can contain 5' end and 3' end modifications. A modified RNA can contain one or more modified residues at non-terminal locations. In certain embodiments, a gRNA includes at least one modified residue. In certain embodiments, an mRNA includes at least one modified residue.

[0397] Unmodified nucleic acids can be prone to degradation by, e.g., intracellular nucleases or those found in serum. For example, nucleases can hydrolyze nucleic acid phosphodiester bonds. Accordingly, in one aspect the RNAs (e.g. mRNAs, gRNAs) described herein can contain one or more modified nucleosides or nucleotides, e.g., to introduce stability toward intracellular or serum-based nucleases. In some embodiments, the modified gRNA molecules described herein can exhibit a reduced innate immune response when introduced into a population of cells, both *in vivo* and *ex vivo*. The term "innate immune response" includes a cellular response to exogenous nucleic acids, including single stranded nucleic acids, which involves the induction of cytokine expression and release, particularly the interferons, and cell death.

[0398] Accordingly, in some embodiments, RNA or nucleic acids in the disclosed the disclosed compositions, preparations, nanoparticles, and/or nanomaterials comprise at least one modification

which confers increased or enhanced stability to the nucleic acid, including, for example, improved resistance to nuclease digestion *in vivo*. As used herein, the terms "modification" and "modified" as such terms relate to the nucleic acids provided herein, include at least one alteration which preferably enhances stability and renders the RNA or nucleic acid more stable (e.g., resistant to nuclease digestion) than the wild-type or naturally occurring version of the RNA or nucleic acid. As used herein, the terms "stable" and "stability" as such terms relate to the nucleic acids of the present invention, and particularly with respect to the RNA, refer to increased or enhanced resistance to degradation by, for example nucleases (i.e., endonucleases or exonucleases) which are normally capable of degrading such RNA. Increased stability can include, for example, less sensitivity to hydrolysis or other destruction by endogenous enzymes (e.g., endonucleases or exonucleases) or conditions within the target cell or tissue, thereby increasing or enhancing the residence of such RNA in the target cell, tissue, subject and/or cytoplasm. The stabilized RNA molecules provided herein demonstrate longer half-lives relative to their naturally occurring, unmodified counterparts (e.g. the wild-type version of the mRNA). Also contemplated by the terms "modification" and "modified" as such terms related to the mRNA of the LNP compositions disclosed herein are alterations which improve or enhance translation of mRNA nucleic acids, including for example, the inclusion of sequences which function in the initiation of protein translation (e.g., the Kozac consensus sequence). (Kozak, M., Nucleic Acids Res 15 (20): 8125-48 (1987), the contents of which are hereby incorporated by reference herein in its entirety).

[0399] In some embodiments, an RNA or nucleic acid of the disclosed compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein have undergone a chemical or biological modification to render it more stable. Exemplary modifications to an RNA include the depletion of a base (e.g., by deletion or by the substitution of one nucleotide for another) or modification of a base, for example, the chemical modification of a base. The phrase "chemical modifications" as used herein, includes modifications which introduce chemistries which differ from those seen in naturally occurring RNA, for example, covalent modifications such as the introduction of modified nucleotides, (e.g., nucleotide analogs, or the inclusion of pendant groups which are not naturally found in such RNA molecules).

[0400] In some embodiments of a backbone modification, the phosphate group of a modified residue can be modified by replacing one or more of the oxygens with a different substituent. Further, the modified residue, e.g., modified residue present in a modified nucleic acid, can include

the wholesale replacement of an unmodified phosphate moiety with a modified phosphate group as described herein. In some embodiments, the backbone modification of the phosphate backbone can include alterations that result in either an uncharged linker or a charged linker with unsymmetrical charge distribution. Examples of modified phosphate groups include, phosphorothioate, phosphoroselenates, borano phosphates, borano phosphate esters, hydrogen phosphonates, phosphoroamidates, alkyl or aryl phosphonates and phosphotriesters. The phosphorous atom in an unmodified phosphate group is achiral. However, replacement of one of the non-bridging oxygens with one of the above atoms or groups of atoms can render the phosphorous atom chiral. The stereogenic phosphorous atom can possess either the "R" configuration (herein Rp) or the "S" configuration (herein Sp). The backbone can also be modified by replacement of a bridging oxygen, (i.e., the oxygen that links the phosphate to the nucleoside), with nitrogen (bridged phosphoroamidates), sulfur (bridged phosphorothioates) and carbon (bridged methylenephosphonates). The replacement can occur at either linking oxygen or at both of the linking oxygens. The phosphate group can be replaced by non-phosphorus containing connectors in certain backbone modifications. In some embodiments, the charged phosphate group can be replaced by a neutral moiety. Examples of moieties which can replace the phosphate group can include, without limitation, e.g., methyl phosphonate, hydroxylamino, siloxane, carbonate, carboxymethyl, carbamate, amide, thioether, ethylene oxide linker, sulfonate, sulfonamide, thioformacetal, formacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo and methyleneoxymethylimino.

G. mRNA

[0401] In some embodiments, the disclosed compositions, preparations, nanoparticles, and/or nanomaterials comprise an mRNA comprising an open reading frame (ORF) encoding an RNA-guided DNA binding agent, such as a Cas nuclease, or Class 2 Cas nuclease as described herein. In some embodiments, an mRNA comprising an ORF encoding an RNA-guided DNA binding agent, such as a Cas nuclease or Class 2 Cas nuclease, is provided, used, or administered. An mRNA may comprise one or more of a 5' cap, a 5' untranslated region (UTR), a 3' UTRs, and a polyadenine tail. The mRNA may comprise a modified open reading frame, for example to encode a nuclear localization sequence or to use alternate codons to encode the protein.

[0402] mRNA in the disclosed compositions, preparations, nanoparticles, and/or nanomaterials may encode, for example, a secreted hormone, enzyme, receptor, polypeptide, peptide or other protein of interest that is normally secreted. In one embodiment of the invention, the mRNA may optionally have chemical or biological modifications which, for example, improve the stability and/or half-life of such mRNA or which improve or otherwise facilitate protein production.

[0403] In addition, suitable modifications include alterations in one or more nucleotides of a codon such that the codon encodes the same amino acid but is more stable than the codon found in the wild-type version of the mRNA. For example, an inverse relationship between the stability of RNA and a higher number cyti dines (C's) and/or uridines (U's) residues has been demonstrated, and RNA devoid of C and U residues have been found to be stable to most RNases (Heidenreich, et al. J Biol Chem 269, 2131-8 (1994), the disclosure of which is hereby incorporated by reference herein in its entirety). In some embodiments, the number of C and/or U residues in an mRNA sequence is reduced. In another embodiment, the number of C and/or U residues is reduced by substitution of one codon encoding a particular amino acid for another codon encoding the same or a related amino acid. Contemplated modifications to the mRNA nucleic acids of the present invention also include the incorporation of pseudouridines. The incorporation of pseudouridines into the mRNA nucleic acids of the present invention may enhance stability and translational capacity, as well as diminishing immunogenicity *in vivo*. See, e.g., Kariko, K., et al., Molecular Therapy 16 (11): 1833-1840 (2008), the contents of which is hereby incorporated by reference herein in its entirety. Substitutions and modifications to the mRNA of the present invention may be performed by methods readily known to one or ordinary skill in the art.

[0404] The constraints on reducing the number of C and U residues in a sequence will likely be greater within the coding region of an mRNA, compared to an untranslated region, (i.e., it will likely not be possible to eliminate all of the C and U residues present in the message while still retaining the ability of the message to encode the desired amino acid sequence). The degeneracy of the genetic code, however presents an opportunity to allow the number of C and/or U residues that are present in the sequence to be reduced, while maintaining the same coding capacity (i.e., depending on which amino acid is encoded by a codon, several different possibilities for modification of RNA sequences may be possible).

[0405] The term modification also includes, for example, the incorporation of non-nucleotide linkages or modified nucleotides into the mRNA sequences of the present invention (e.g.,

modifications to one or both the 3' and 5' ends of an mRNA molecule encoding a functional secreted protein or enzyme). Such modifications include the addition of bases to an mRNA sequence (e.g., the inclusion of a poly A tail or a longer poly A tail), the alteration of the 3' UTR or the 5' UTR, complexing the mRNA with an agent (e.g., a protein or a complementary nucleic acid molecule), and inclusion of elements which change the structure of an mRNA molecule (e.g., which form secondary structures).

[0406] The poly A tail is thought to stabilize natural messengers. Therefore, in one embodiment a long poly A tail can be added to an mRNA molecule thus rendering the mRNA more stable. Poly A tails can be added using a variety of art-recognized techniques. For example, long poly A tails can be added to synthetic or *in vitro* transcribed mRNA using poly A polymerase (Yokoe, et al. Nature Biotechnology. 1996; 14: 1252-1256, the contents of which is hereby incorporated by reference herein in its entirety). A transcription vector can also encode long poly A tails. In addition, poly A tails can be added by transcription directly from PCR products. In one embodiment, the length of the poly A tail is at least about 90, 200, 300, 400 at least 500 nucleotides. In one embodiment, the length of the poly A tail is adjusted to control the stability of a modified mRNA molecule of the invention and, thus, the transcription of protein. For example, since the length of the poly A tail can influence the half-life of an mRNA molecule, the length of the poly A tail can be adjusted to modify the level of resistance of the mRNA to nucleases and thereby control the time course of protein expression in a cell. In one embodiment, the stabilized mRNA molecules are sufficiently resistant to *in vivo* degradation (e.g., by nucleases), such that they may be delivered to the target cell without a transfer vehicle.

[0407] In some embodiment embodiments, an mRNA can be modified by the incorporation 3' and/or 5' untranslated (UTR) sequences which are not naturally found in the wild-type mRNA. In one embodiment, 3' and/or 5' flanking sequence which naturally flanks an mRNA and encodes a second, unrelated protein can be incorporated into the nucleotide sequence of an mRNA molecule encoding a therapeutic or functional protein in order to modify it. For example, 3' or 5' sequences from mRNA molecules which are stable (e.g., globin, actin, GAPDH, tubulin, histone, or citric acid cycle enzymes) can be incorporated into the 3' and/or 5' region of a sense mRNA nucleic acid molecule to increase the stability of the sense mRNA molecule. See, e.g., US2003/0083272, the contents of which is hereby incorporated by reference herein in its entirety. More detailed

descriptions of the mRNA modifications can be found in US2017/0210698A1, at pages 57-68, which content is incorporated herein by reference in its entirety.

H. Template nucleic acid

[0408] The compositions, preparations, nanoparticles, and/or nanomaterials and methods disclosed herein may include a template nucleic acid. A template may be used to alter or insert a nucleic acid sequence at or near a target site for an RNA-guided DNA binding protein such as a Cas nuclease, e.g., a Class 2 Cas nuclease. In some embodiments, the methods comprise introducing a template to the cell. In some embodiments, a single template may be provided. In some embodiments, two or more templates may be provided such that editing may occur at two or more target sites. For example, different templates may be provided to edit a single gene in a cell, or two different genes in a cell.

[0409] In some embodiments, a template may be used in homologous recombination. In some embodiments, the homologous recombination may result in the integration of the template sequence or a portion of the template sequence into the target nucleic acid molecule. In some embodiments, a template may be used in homology-directed repair, which involves DNA strand invasion at the site of the cleavage in the nucleic acid. In some embodiments, homology-directed repair may result in including the template sequence in the edited target nucleic acid molecule. In some embodiments, a template may be used in gene editing mediated by non-homologous end joining. In some embodiments, a template sequence has no similarity to the nucleic acid sequence near the cleavage site. In some embodiments, a template or a portion of the template sequence is incorporated. In some embodiments, a template includes flanking inverted terminal repeat (ITR) sequences.

[0410] In some embodiments, a template sequence may correspond to, comprise, or consist of an endogenous sequence of a target cell. It may also or alternatively correspond to, comprise, or consist of an exogenous sequence of a target cell. As used herein, the term "endogenous sequence" refers to a sequence that is native to the cell. The term "exogenous sequence" refers to a sequence that is not native to a cell, or a sequence whose native location in the genome of the cell is in a different location. In some embodiments, the endogenous sequence may be a genomic sequence of the cell.

[0411] In some embodiments, the endogenous sequence may be a chromosomal or extrachromosomal sequence. In some embodiments, an endogenous sequence may be a plasmid sequence of the cell.

[0412] In some embodiments, a template contains ssDNA or dsDNA containing flanking invert-terminal repeat (ITR) sequences. In some embodiments, a template is provided as a vector, plasmid, minicircle, nanocircle, or PCR product.

[0413] In some embodiments, a nucleic acid is purified. In some embodiments, a nucleic acid is purified using a precipitation method (e.g., LiCl precipitation, alcohol precipitation, or an equivalent method, e.g., as described herein). In some embodiments, a nucleic acid is purified using a chromatography-based method, such as an HPLC-based method or an equivalent method (e.g., as described herein). In some embodiments, a nucleic acid is purified using both a precipitation method (e.g, LiCl precipitation) and an HPLC-based method. In some embodiments, the nucleic acid is purified by tangential flow filtration (TFF).

IV. Methods of manufacturing LNPs

[0414] Methods of manufacturing lipid nanoparticles are known in the art. In some embodiments, the described compositions, preparations, nanoparticles, and/or nanomaterials are manufactured using microfluidics. For instance, exemplary methods of using microfluidics to form lipid nanoparticles are described by Leung, A.K.K, et al., *J Phys Chem*, 116:18440-18450 (2012), Chen, D., et al., *J Am Chem Soc*, 134:6947-6951 (2012), and Belliveau, N.M., et al., *Molecular Therapy-Nucleic Acids*, 1: e37 (2012), the disclosures of which are hereby incorporated by reference in their entireties.

[0415] Briefly, a cargo, such as a cargo described herein, is prepared in a first buffer solution. The other lipid nanoparticle components (such as ionizable lipid, conjugate-linker lipids, cholesterol, and phospholipid) are prepared in a second buffer solution. In some embodiments, a syringe pump introduces the two solutions into a microfluidic device. The two solutions come into contact within the microfluidic device to form lipid nanoparticles encapsulating the cargo.

[0416] Methods of screening the disclosed lipid nanoparticles are described in International Patent Application No. PCT/US2018/058171, which is incorporated by reference in its entirety herein. In some embodiments, the screening methods characterize vehicle delivery preparations to identify preparations with a desired tropism and that deliver functional cargo to the cytoplasm of specific

cells. In some embodiments, the screening method uses a reporter that has a functionality that can be detected when delivered to the cell. For example, detecting a functional reporter in a cell indicates that the LNP preparation delivers functional cargo to the cell. Among other things, in some embodiments, a chemical composition identifier is included in each different delivery vehicle formulation to keep track of the chemical composition specific for each different delivery vehicle formulation. In some embodiments, a chemical composition identifier is a nucleic acid barcode. In some embodiments, a sequence of the nucleic acid barcode is paired to which chemical components were used to formulate the LNP preparation in which it is loaded so that when the nucleic acid barcode is sequenced, the chemical composition of the delivery vehicle that delivered the barcode is identified. Representative barcodes include, but are not limited to, barcodes described by Sago, 2018 PNAS, Sago, JACS 2018, the disclosure of which is hereby incorporated by reference in its entirety. Representative reporters include, but are not limited to siRNA, mRNA, nuclease protein, nuclease mRNA, small molecules, epigenetic modifiers, and phenotypic modifiers. DNA (genomic and DNA barcodes) can be isolated using QuickExtract (Lucigen) and sequenced using Illumina MiniSeq as described by Sago et al. PNAS 2018, Sago et al. JACs 2018, Sago, Lokugamage et al. Nano Letters 2018, the disclosures of which are hereby incorporated by reference in their entireties).

V. Methods of use

[0417] Among other things, the present disclosure describes methods of using compositions, preparations, nanoparticles, and/or nanomaterials described herein. For example, in some embodiments, the present disclosure describes methods of using compositions, preparations, nanoparticles, and/or nanomaterials to deliver cargo to specific cells, tissues, or organs, as described herein. As another example, in some embodiments, the present disclosure describes methods of treatment and/or delaying and/or arresting progression of a disease or disorder using compositions, preparations, nanoparticles, and/or nanomaterials as described herein. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein are for use in medicine.

[0418] In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials described herein deliver therapeutic or prophylactic agents to specific cells or organs in a subject in need thereof. In some embodiments, the compositions, preparations, nanoparticles, and/or

nanomaterials deliver therapeutic or prophylactic agents to specific cells or organs in a subject in need thereof in the absence of a targeting ligand. In some embodiments, the compositions, preparations, nanoparticles, and/or nanomaterials are useful to treat or prevent diseases in a subject in need thereof.

A. Methods of delivering cargo to cells, tissue, or organs

[0419] Among other things, in some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein target a particular type or class of cells (e.g., cells of a particular organ or system thereof), tissues, and/organs. In some embodiments, the present disclosure provides methods of delivering one or more cargos described herein to a subject in need thereof. In some embodiments, such methods comprise *in vivo* and/or *in vitro* delivery. In some embodiments, such methods comprise *in vivo* delivery. In some embodiments, such methods comprise *in vitro* delivery. In some embodiments, the present disclosure provides for methods of delivering one or more therapeutic and/or prophylactic nucleic acids to a subject in need thereof are described herein.

[0420] In some embodiments, a composition, preparation, nanoparticle, and/or nanomaterial comprises a therapeutic and/or prophylactic of interest that may be specifically delivered to liver cells in the subject. Exemplary liver cells include but are not limited to hepatocytes.

[0421] In some embodiments, a composition, preparation, nanoparticle, and/or nanomaterial comprises a therapeutic and/or prophylactic of interest that may be specifically delivered to spleen cells in the subject. Exemplary spleen cells include but are not limited to splenic monocytes, splenic T cells, splenic memory B cells, or splenic B cells.

[0422] In some embodiments, a composition, preparation, nanoparticle, and/or nanomaterial comprises a therapeutic and/or prophylactic of interest that may be specifically delivered to bone marrow cells in the subject. Exemplary bone marrow cells include but are not limited to bone marrow monocytes, bone marrow B cells, bone marrow memory B cells, or bone marrow T cells.

[0423] In some embodiments, a composition, preparation, nanoparticle, and/or nanomaterial comprises a therapeutic and/or prophylactic of interest that may be specifically delivered to immune cells in the subject. Exemplary immune cells include but are not limited to CD8+, CD4+, or CD8+CD4+ cells.

[0424] In some embodiments, a composition, preparation, nanoparticle, and/or nanomaterial comprises a therapeutic and/or prophylactic of interest that may be specifically delivered to hematopoietic stem cells in the subject. Unless otherwise specified, it is understood that the terms "hematopoietic stem cells (HSCs)" and "hematopoietic stem and progenitor cells (HSPCs)" are used interchangeably in the present disclosure.

[0425] In some embodiments, the lipid nanoparticles can be formulated to be delivered in the absence of a targeting ligand to a mammalian liver hepatocytes, liver immune cells, spleen T cells, or lung endothelial cells. Specific delivery to a particular class or type of cells indicates that a higher proportion of lipid nanoparticles are delivered to target type or class of cells. In some embodiments, specific delivery may result in a greater than 2 fold, 5 fold, 10 fold, 15 fold, or 20 fold compared to delivery using a conventional nanoparticle system (e.g., MC3-containing LNPs).

B. Methods of producing a polypeptide

[0426] Among other things, in some embodiments, methods of using compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein are used for methods of producing a polypeptide. Among other things, in some embodiments, lipid nanoparticles described herein can be used for producing a polypeptide in a target cell in a subject in need thereof. For example, in some embodiments, lipid nanoparticles described herein can be used for producing a polypeptide in a target cell in a subject in need thereof. In some embodiments, compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein comprise one or more nucleic sequences to be delivered to a cell.

[0427] In some embodiments, one or more nucleic acids are expressed in a cell. In some embodiments, expression of a nucleic acid sequence involves one or more of the following: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing, editing, 5' cap formation, and/or 3' end formation); (3) translation of an RNA into a polypeptide or protein; and/or (4) post-translational modification of a polypeptide or protein.

C. Methods of gene regulation

[0428] Among other things, in some embodiments, methods of using compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein are used for gene regulation. Among other

things, in some embodiments, lipid nanoparticles described herein can be used for reducing and/or increasing gene expression in a target cell in a subject in need thereof. For example, in some embodiments, lipid nanoparticles described herein can deliver one or more nucleic acids to a target cell in the subject without a targeting ligand. In some embodiments, a nucleic acid is an inhibitor nucleic acid. In some embodiments, an inhibitory nucleic acid is an siRNA. In some embodiments, a nucleic acid is a nucleic acid described herein. As another example, in some embodiments, lipid nanoparticles described herein can deliver cargo to a target cell in the subject without a targeting ligand. In some embodiments, cargo is any cargo described herein.

[0429] Among other things, in some embodiments, methods of using compositions, preparations, nanoparticles, and/or nanomaterials disclosed herein for editing of a gene in a cell in a subject in need thereof.

[0430] In some embodiments, a cell that is targeted for gene regulation is an immune cell. The immune cell can be a T cell, such as CD8+ T cell, CD4+ T cell, or T regulatory cell. Other exemplary immune cells for gene editing include but are not limited to macrophages, dendritic cells, B cells or natural killer cells. In some embodiments, the cell that is targeted for gene regulation in a hepatocyte.

[0431] Exemplary genes that can be targeted include but are not limited to T cell receptors, B cell receptors, CTLA4, PD1, FOXO1, FOXO3, AKTs, CCR5, CXCR4, LAG3, TIM3, Killer immunoglobulin-like receptors, GITR, BTLA, LFA-4, T4, LFA-1, Bp35, CD27L receptor, TNFRSF8, TNFRSF5, CD47, CD52, ICAM-1, LFA-3, L-selectin, Ki-24, MB1, B7, B70, M-CSFR, TNFR-II, IL-7R, OX-40, CD137, CD137L, CD30L, CD40L, FasL, TRAIL, CD257, LIGHT, TRAIL-R1, TRAILR2, TRAIL-R4, TWEAK-R, TNFR, BCMA, B7DC, BTLA, B7-H1, B7-H2, B7-H3, ICOS, VEGFR2, NKG2D, JAG1, GITR, CD4, CCR2, GATA-3, MTORC1, MTORC2, RAPTOR, GATOR, FOXP3, NFAT, IL2R, and IL7. Other exemplary genes that can be targeted include but are not limited to OCT, G6Pase, Mut, PCCA, PCCB, PCSK9, ALAS1, and PAH. Exemplary tumor-associated antigens that can be recognized by T cells and are contemplated for targeting, include but are not limited to MAGE1, MAGE3, MAGE6, BAGE, GAGE, NYESO-1, MART1/Melan A, MC1R, GP100, tyrosinase, TRP-1, TRP-2, PSA, CEA, Cyp-B, Her2/Neu, hTERT, MUC1, PRAME, WT1, RAS, CDK-4, MUM-1, KRAS, MSLN and β-catenin.

D. Subjects to be treated

[0432] In some embodiments, subjects who are treated are mammals experiencing cancer, autoimmune disease, infections disease, organ transplant, organ failure, protein deficiency, or a combination thereof. In some embodiments, a subject is a human. In some embodiments, methods described herein may cause hepatocytes to translate certain proteins. In some embodiments, methods described herein may be used to deliver one or more DNA, mRNA, sgRNA, or siRNA to a hepatocyte. In some embodiments, methods described herein may be used to deliver one or more DNA, mRNA, sgRNA, or siRNA to a splenic T cell. In some embodiments, methods described herein may be used to deliver one or more DNA, mRNA, sgRNA, or siRNA to a splenic B cell. In some embodiments, methods described herein may be used to deliver one or more DNA, mRNA, sgRNA, or siRNA to a splenic monocyte. In some embodiments, methods described herein may be used to deliver one or more DNA, mRNA, sgRNA, or siRNA to a bone marrow cell.

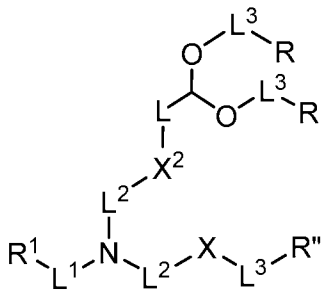
[0433] It should be understood that the order of steps or order for performing certain action is immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

[0434] While the invention has been particularly shown and described with reference to specific preferred embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

Exemplary Embodiments

[0435] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the present disclosure:

1. A compound of Formula A':



A'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

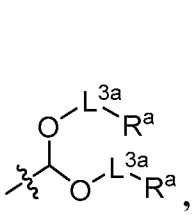
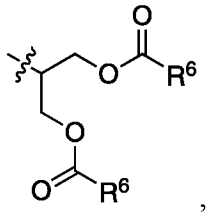
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

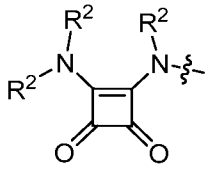
R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each of R and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl

each of L^3 and L^{3a} is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$,

$-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or



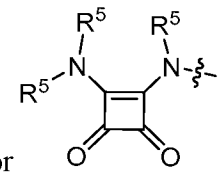
R^1 is , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

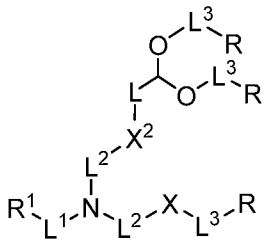
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

2. A compound of Formula A:



A

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

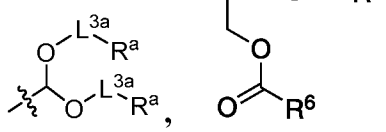
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

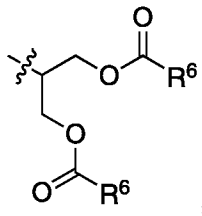
each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

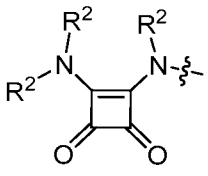
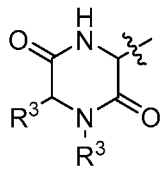
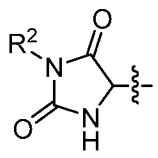
X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each L^{3a} is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

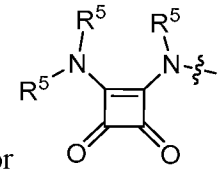
R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

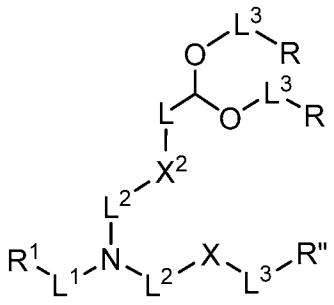
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

3. A compound of Formula I":



I"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

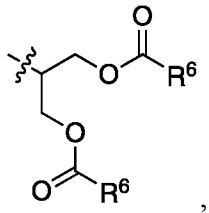
each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

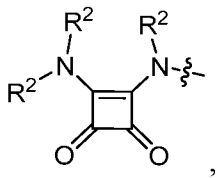
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

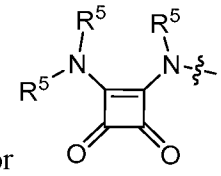
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

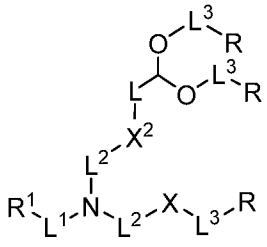
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

4. A compound of Formula I':



I'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

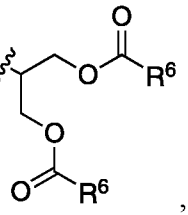
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

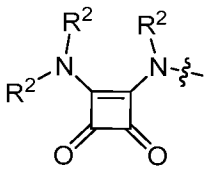
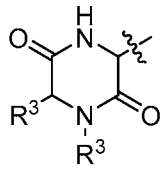
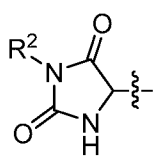
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

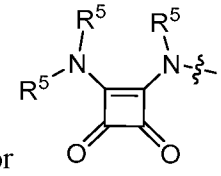
R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, -CN, -NO_2, -OR^4, -$S(O)_2R^4$, -$S(O)_2N(R^4)_2$, -$(CH_2)_n$-R^4, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently -$(CH_2)_n$-R^4, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, -OR^5, -$N(R^5)_2$, -$OC(O)R^5$, -$OC(O)OR^5$, -CN, -$C(O)N(R^5)_2$, -$NR^5C(O)R^5$, -$OC(O)N(R^5)_2$, -$N(R^5)C(O)OR^5$, -$NR^5S(O)_2R^5$, -$NR^5C(O)N(R^5)_2$, -$NR^5C(S)N(R^5)_2$, -$NR^5C(NR^5)N(R^5)_2$, or  ;

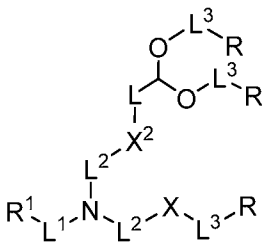
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

5. A compound of Formula I:



I

or its N-oxide, or a salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

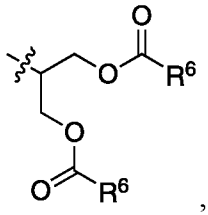
each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

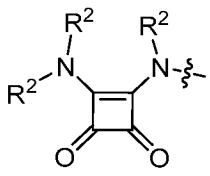
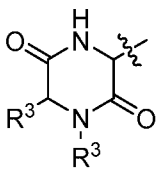
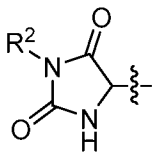
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, a 3- to 7-membered cycloaliphatic ring, a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

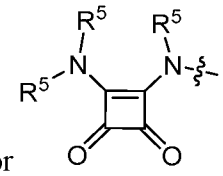
each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, a 3- to 7-membered cycloaliphatic

ring, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

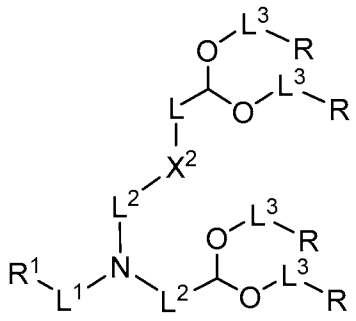
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

6. A compound of Formula II":



II"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

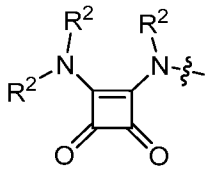
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$;

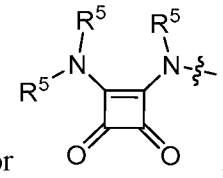
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

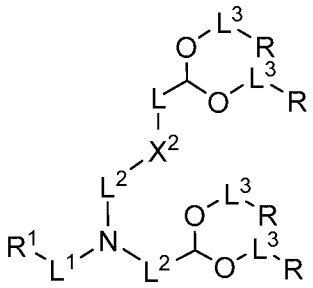
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

7. A compound of Formula II':



II'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

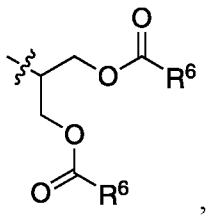
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

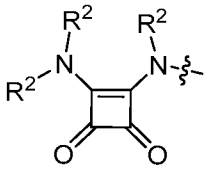
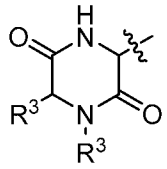
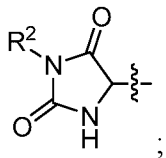
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$,

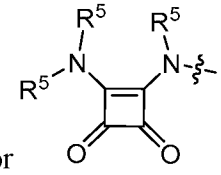
-C(NR^2)R^2, -C(O)N(R^2)OR^2, -C(R^2)N(R^2)$_2$C(O)OR^2,  , -CR^2(OR^2)R^3, ,  , or  ;

each R^2 is independently hydrogen, -CN, -NO$_2$, -OR^4, -S(O)$_2$R^4, -S(O)$_2$N(R^4)$_2$, -(CH$_2$)$_n$-R^4, or an optionally substituted group selected from C$_{1-6}$ aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently -(CH$_2$)$_n$-R^4, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, -OR^5, -N(R^5)$_2$, -OC(O)R^5, -OC(O)OR^5, -CN, -C(O)N(R^5)$_2$, -NR^{5}C(O)R^5, -OC(O)N(R^5)$_2$, -N(R^5)C(O)OR^5, -NR^{5}S(O)$_2$R^5, -NR^{5}C(O)N(R^5)$_2$, -NR^{5}C(S)N(R^5)$_2$, -NR^{5}C(NR^5)N(R^5)$_2$, or  ;

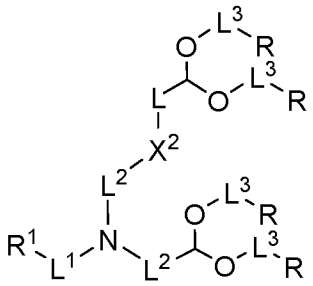
each R^5 is independently hydrogen, optionally substituted C$_{1-6}$ aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C$_{4-12}$ aliphatic; and

each n is independently 0 to 4.

8. A compound of Formula II:



II

or its N-oxide, or a salt thereof, wherein

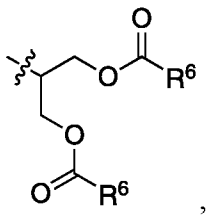
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

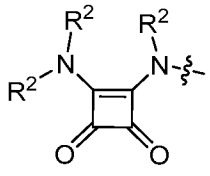
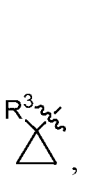
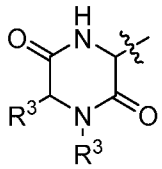
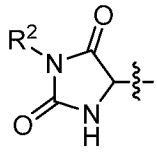
L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, a 3- to 7-membered cycloaliphatic ring, a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$,

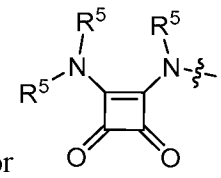
-C(O)N(R^2)OR^2, -C(R^2)N(R^2)$_2$C(O)OR^2,  , -CR^2(OR^2)R^3,  ,  ,  , or ;

each R^2 is independently hydrogen, -CN, -NO_2, -OR^4, -S(O)$_2$$R^4$, -S(O)$_2$N($R^4$)$_2$, -($CH_2$)$_n$-$R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, a 3- to 7-membered cycloaliphatic ring, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently -(CH_2)$_n$-R^4, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, -OR^5, -N(R^5)$_2$, -OC(O)R^5, -OC(O)OR^5, -CN, -C(O)N(R^5)$_2$, -NR^5C(O)R^5, -OC(O)N(R^5)$_2$, -N(R^5)C(O)OR^5, -NR^5S(O)$_2$$R^5$, -N$R^5$C(O)N($R^5$)$_2$, -N$R^5$C(S)N($R^5$)$_2$, -N$R^5$C(N$R^5$)N($R^5$)$_2$, or  ;

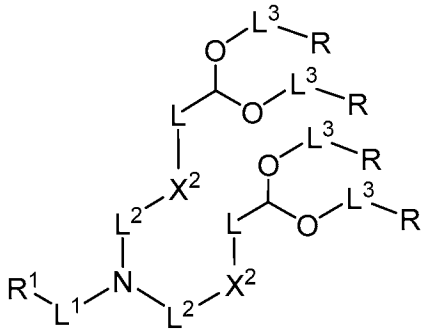
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

9. A compound of Formula III':



III'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

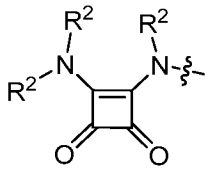
each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$,

$-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or



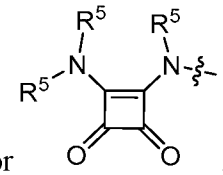
R^1 is , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

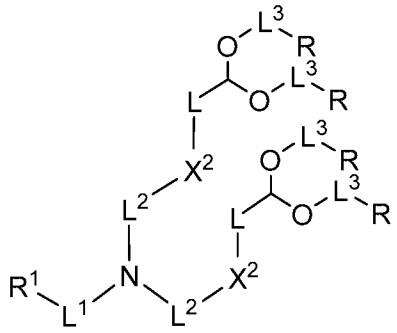
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

10. A compound of Formula III:



III

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

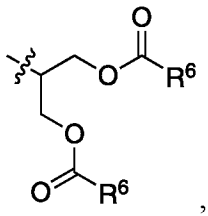
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently C_{2-10} alkylenyl, or C_{3-10} heteroalkylenyl;

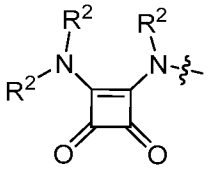
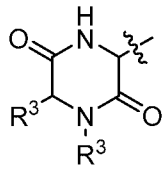
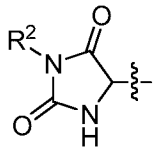
each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each L^3 is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-;

each R is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, C_{6-20} haloaliphatic, a 3- to 7-membered cycloaliphatic ring, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, an optionally substituted 3- to 7-membered cycloaliphatic ring, an optionally substituted 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an optionally substituted 8- to 10-membered bicyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$,

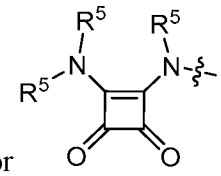
$-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$,  , $-CR^2(OR^2)R^3$, ,  , or  ;

each R^2 is independently hydrogen, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3- to 7-membered cycloaliphatic ring, a 5- to 6-membered monocyclic heteroaryl ring comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 3- to 7-membered heterocyclic ring comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$, or

two occurrences of R^3, taken together with the atoms to which they are attached, form an optionally substituted 5- to 6-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

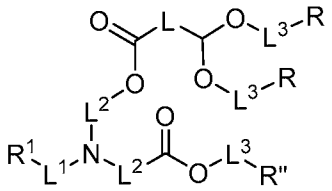
each R^5 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form an optionally substituted 4- to 7-membered heterocyclic ring comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

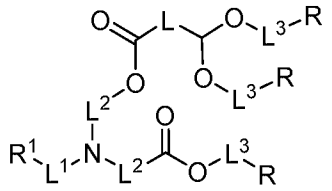
11. The compound according to embodiment 1 or 3, wherein the compound is of Formula I"-a:



I"-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

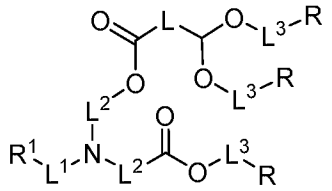
12. The compound according to embodiment 2 or 4, wherein the compound is of Formula I'-a:



I'-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

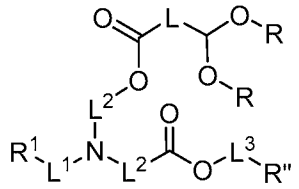
13. The compound according to embodiment 5, wherein the compound is of Formula I-a:



I-a

or its N-oxide, or a salt thereof.

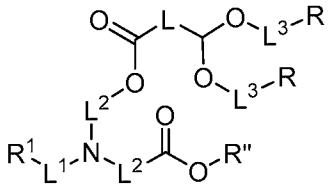
14. The compound according to any one of embodiments 1, 3, and 11, wherein the compound is of Formula I"-a-*i*:



I"-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

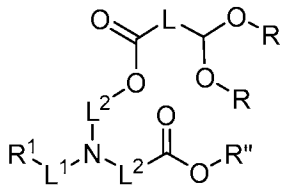
15. The compound according to any one of embodiments 1, 3, and 11, wherein the compound is of Formula I"-a-*ii*:



I"-a-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

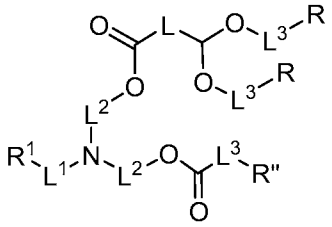
16. The compound according to any one of embodiments 1, 3, 11, 14, and 15, wherein the compound is of Formula I"-a-*iii*:



I"-a-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

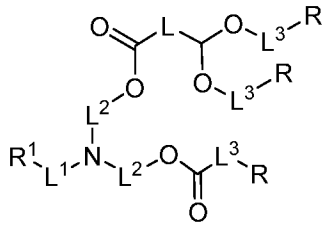
17. The compound according to embodiment 1 or 3, wherein the compound is of Formula I"-b:



I"-b

or its N-oxide, or a pharmaceutically acceptable salt thereof.

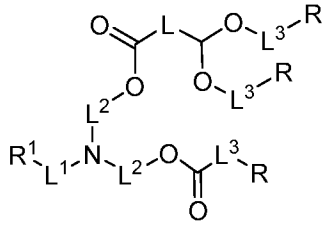
18. The compound according to embodiment 2 or 4, wherein the compound is of Formula I'-b:



I'-b

or its N-oxide, or a pharmaceutically acceptable salt thereof.

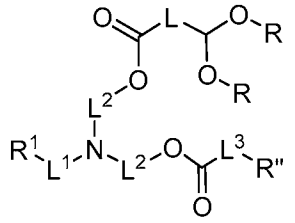
19. The compound according to embodiment 5, wherein the compound is of Formula I-b:



I-b

or its N-oxide, or a salt thereof.

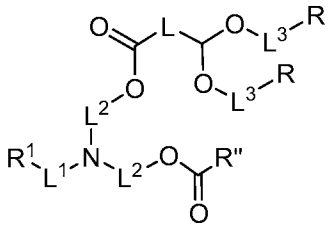
20. The compound according to any one of embodiments 1, 3, and 17, wherein the compound is of Formula I"-b-*i*:



I"-b-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

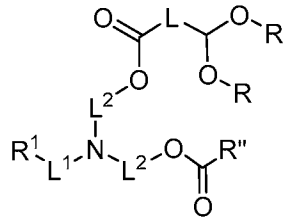
21. The compound according to any one of embodiments 1, 3, and 17, wherein the compound is of Formula I"-b-*ii*:



I"-b-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

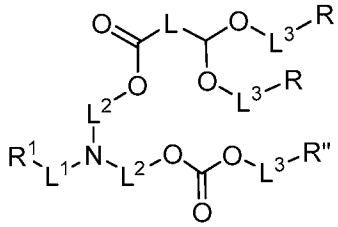
22. The compound according to any one of embodiments 1, 3, 17, 20, and 21, wherein the compound is of Formula I"-b-*iii*:



I"-b-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

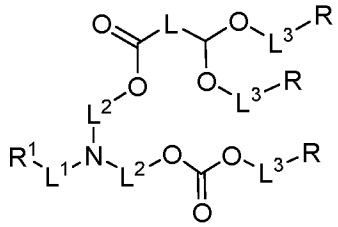
23. The compound according to embodiment 1 or 3, wherein the compound is of Formula I"-c:



I"-c

or its N-oxide, or a pharmaceutically acceptable salt thereof.

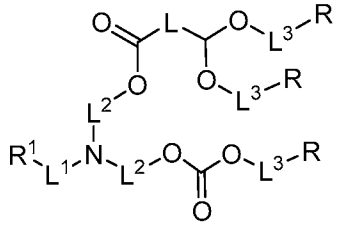
24. The compound according to embodiment 2 or 4, wherein the compound is of Formula I'-c:



I'-c

or its N-oxide, or a pharmaceutically acceptable salt thereof.

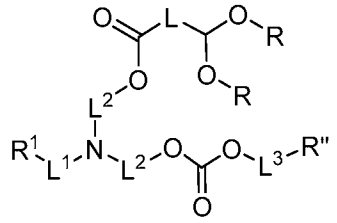
25. The compound according to embodiment 5, wherein the compound is of Formula I-c:



I-c

or its N-oxide, or a salt thereof.

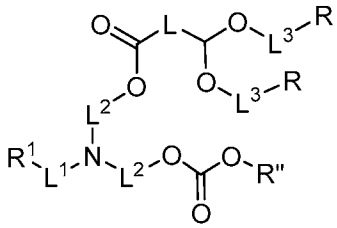
26. The compound according to any one of embodiments 1, 3, and 23, wherein the compound is of Formula I"-c-*i*:



I"-c-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

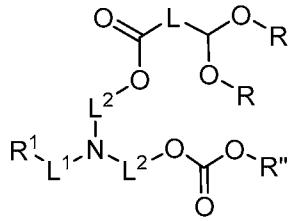
27. The compound according to any one of embodiments 1, 3, and 23, wherein the compound is of Formula I"-c-*ii*:



I"-c-*ii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

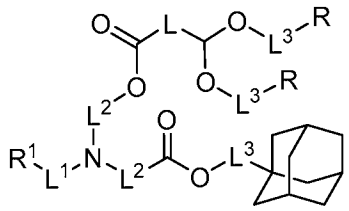
28. The compound according to any one of embodiments 1, 3, 23, 26, and 27, wherein the compound is of Formula I"-c-*iii*:



I"-c-*iii*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

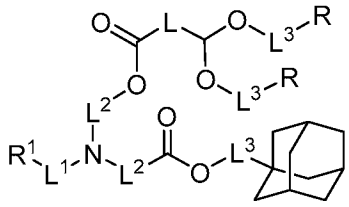
29. The compound according to any one of embodiments 1-4, wherein the compound is of Formula I'-d:



I'-d

or its N-oxide, or a pharmaceutically acceptable salt thereof.

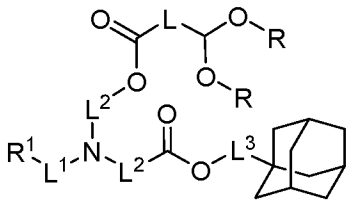
30. The compound according to embodiment 5, wherein the compound is of Formula I-d:



I-d

or its N-oxide, or a salt thereof.

31. The compound according to any one of embodiments 1-5, 29, and 30, wherein the compound is of Formula I'-d-*i*:

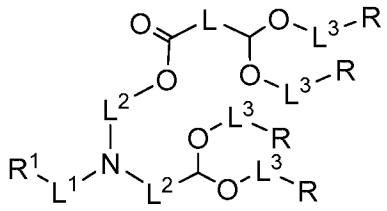


I'-d-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

32. The compound according to any one of embodiments5, 8, 13, 19, 25, and 30, wherein a salt thereof is a pharmaceutically salt thereof.

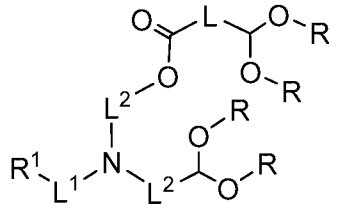
33. The compound according to any one of embodiments 1, 2, and 6-8, wherein the compound is of Formula II-a:



II-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

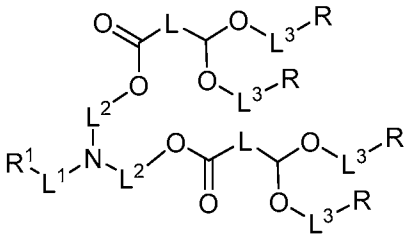
34. The compound according to any one of embodiments 1, 2, 6-8, and 33, wherein the compound is of Formula II-a-*i*:



II-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

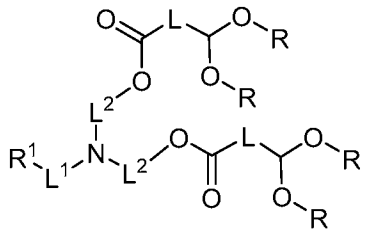
35. The compound according to any one of embodiments 1, 2, 9, and 10, wherein the compound is of Formula III-a:



III-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

36. The compound according to any one of embodiments 1, 2, 9, 10, and 35, wherein the compound is of Formula III-a-*i*:



III-a-*i*

or its N-oxide, or a pharmaceutically acceptable salt thereof.

37. The compound according to any one of embodiments 1-10, wherein each X^2 is independently -OC(O)-.

38. The compound according to any one of embodiments 1-10, wherein each X^2 is independently -C(O)O-.

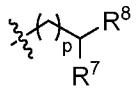
39. The compound according to any one of embodiments 1-10, wherein each X^2 is independently -OC(O)O-.

40. The compound according to any one of embodiments 1-5, wherein X is -OC(O)-.

41. The compound according to any one of embodiments 1-5, wherein X is -C(O)O-.

42. The compound according to any one of embodiments 1-5, wherein X is -OC(O)O-.

43. The compound according to any one of embodiments 1-42, wherein

each of $-L^3-R''$, $-L^3-R$ and $-L^{3a}-R^a$ is independently  ;

R^7 is optionally substituted C_{6-10} aliphatic or C_{6-10} haloaliphatic;

R^8 is optionally substituted C_{2-8} aliphatic or C_{2-8} haloaliphatic; and

p is 0 or 1.

44. The compound according to any one of embodiments 1-43, wherein L^1 is absent, C_{2-5} alkylenyl, or C_{2-5} heteroalkylenyl.

45. The compound according to embodiment 44, wherein L^1 is absent.

46. The compound according to embodiment 44, wherein L^1 is C_{2-5} alkylenyl.

47. The compound according to any one of embodiments 1-43, wherein L^1 is absent, C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

48. The compound according to embodiment 47, wherein L^1 is C_{1-5} alkylenyl.

49. The compound according to embodiment 47 or 48, wherein L^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2-$.

50. The compound according to any one of embodiments 1-49, wherein each L^2 is independently C_{4-8} alkylenyl or C_{4-8} heteroalkylenyl.

51. The compound according to embodiment 50, wherein each L^2 is independently C_{4-8} alkylenyl.

52. The compound according to embodiment 50 or 51, wherein each L^2 is independently $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2-$.

53. The compound according to embodiment 50, wherein each L^2 is independently C_{4-8} heteroalkylenyl.

54. The compound according to any one of embodiments 1-49, wherein each L^2 is independently optionally substituted C_{2-9} alkylenyl, or optionally substituted C_{3-9} heteroalkylenyl.

55. The compound according to embodiment 54, wherein each L^2 is independently optionally substituted C_{2-9} alkylenyl.

56. The compound according to embodiment 54, wherein each L^2 is independently optionally substituted C_{3-9} heteroalkylenyl.

57. The compound according to any one of embodiments 1-56, wherein each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl.

58. The compound according to embodiment 57, wherein each L is independently C_{1-10} alkylenyl.

59. The compound according to any one of embodiments 1-57, wherein each L is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

60. The compound according to embodiment 57, 58, or 59, wherein each L is independently C_{1-5} alkylenyl.

61. The compound according to embodiment 59 or 60, wherein each L is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2CH_2-$.

62. The compound according to embodiment 57, wherein each L is independently C_{2-10} heteroalkylenyl.

63. The compound according to embodiment 57, 59, or 62, wherein each L is independently C_{2-5} heteroalkylenyl.

64. The compound according to any one of embodiments 1, 3, 6, 9, 11-42 and 44-63, wherein each of L^3 and L^{3a} is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl.

65. The compound according to any one of embodiments 1-42 and 44-64, wherein each of L^3 and L^{3a} is independently absent, C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl.

66. The compound according to embodiment 65, wherein each of L^3 and L^{3a} is absent.

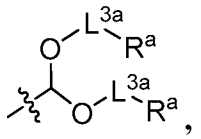
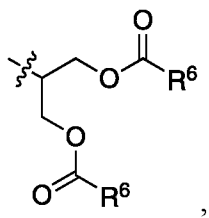
67. The compound according to embodiment 65, wherein each of L^3 and L^{3a} is independently C_{1-10} alkylenyl.

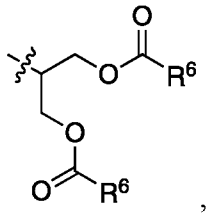
68. The compound according to embodiment 65, wherein each L^3 and L^{3a} is independently C_{2-10} heteroalkylenyl.

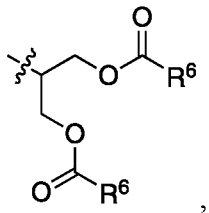
69. The compound according to embodiment 65, wherein each of L^3 and L^{3a} is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

70. The compound according to embodiment 69, wherein each of L^3 and L^{3a} is independently C_{1-5} alkylenyl.

71. The compound according to embodiment 69, wherein each of L^3 and L^{3a} is independently C_{2-5} heteroalkylenyl.

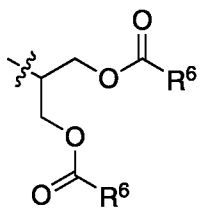
72. The compound according to any one of embodiments 1, 3, 11, 14-17, 20-23, 26-28, 37-71, wherein R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

73. The compound according to embodiment 72, wherein R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

74. The compound according to embodiment 73, wherein R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl.

75. The compound according to embodiment 74, wherein R" is hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl.

76. The compound according to any one of embodiments 72-75, wherein R" is hydrogen.

77. The compound according to any one of embodiments 72-74, wherein R" is 
.

78. The compound according to any one of embodiments 72-75, wherein R" is optionally substituted C_{6-20} aliphatic.

79. The compound according to embodiment 78, wherein R" is optionally substituted C_{6-20} alkyl.

80. The compound according to embodiment 78, wherein R" is optionally substituted C_{6-20} alkenyl.

81. The compound according to embodiment 78, wherein R" is optionally substituted C_{6-20} alkynyl.

82. The compound according to embodiment 78, wherein R" is C_{6-20} haloaliphatic.

83. The compound according to embodiment 82, wherein R" is C_{6-20} haloalkyl comprising 1-7 fluorine atoms.

84. The compound according to any one of embodiments 72-75, wherein R" is optionally substituted 3- to 12-membered cycloaliphatic.

85. The compound according to embodiment 84, wherein R" is optionally substituted 3- to 7-membered cycloaliphatic.

86. The compound according to embodiment 85, wherein R" is optionally substituted cyclohexyl.

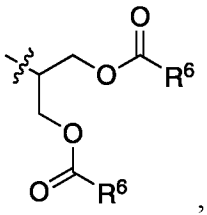
87. The compound according to any one of embodiments 72-75, wherein R" is optionally substituted 1-adamantyl.

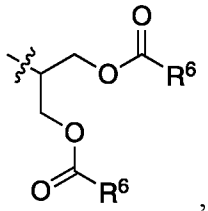
88. The compound according to any one of embodiments 72-75, wherein R" is optionally substituted phenyl.

89. The compound according to any one of embodiments 1-42 and 44-88, wherein each of R and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic,

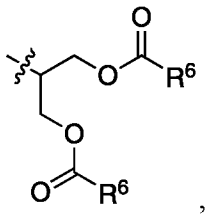
3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

90. The compound according to embodiment 89, wherein each of R, and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl.

91. The compound according to any one of embodiments 1-42 and 44-88, wherein each of R and R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 7-membered cycloaliphatic, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl.

92. The compound according to embodiment 91, wherein each of R and R^a is independently hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 7-membered cycloaliphatic, 1-adamantyl, and phenyl.

93. The compound according to any one of embodiments 89-92, wherein each of R and R^a is hydrogen.

94. The compound according to embodiment 91 or 92, wherein each of R and R^a is independently  , wherein each R^6 is independently C_{4-12} aliphatic.

95. The compound according to any one of embodiments 89-92, wherein each of R and R^a is independently optionally substituted C_{6-20} aliphatic.

96. The compound according to embodiment 95, wherein each of R and R^a is independently optionally substituted C_{6-20} alkyl.

97. The compound according to embodiment 95, wherein each of R and R^a is independently optionally substituted C_{6-20} alkenyl.

98. The compound according to embodiment 95, wherein each of R and R^a is independently optionally substituted C_{6-20} alkynyl.

99. The compound according to any one of embodiments 89-92 and 95, wherein each of R and R^a is independently optionally substituted C_{6-20} haloaliphatic.

100. The compound according to embodiment 99, wherein each of R and R^a is independently C_{6-20} haloaliphatic.

101. The compound according to embodiment 99, wherein each of R and R^a is independently optionally substituted C_{6-20} haloalkyl comprising 1-7 fluorine atoms.

102. The compound according to embodiment 99, wherein each of R and R^a is independently C_{6-20} haloalkyl comprising 1-7 fluorine atoms.

103. The compound according to any one of embodiments 89-92, wherein each of R and R^a is independently optionally substituted 3- to 12-membered cycloaliphatic.

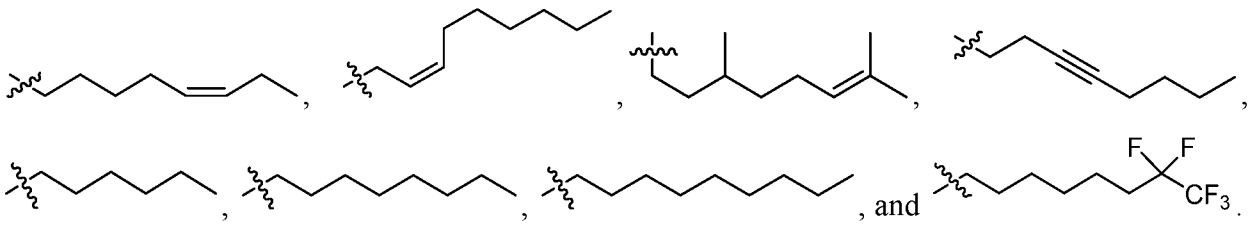
104. The compound according to embodiment 103, wherein each of R and R^a is independently optionally substituted 3- to 7-membered cycloaliphatic.

105. The compound according to embodiment 104, wherein each of R and R^a is independently optionally substituted cyclohexyl.

106. The compound according to any one of embodiments 89-92, wherein each of R and R^a is independently optionally substituted 1-adamantyl.

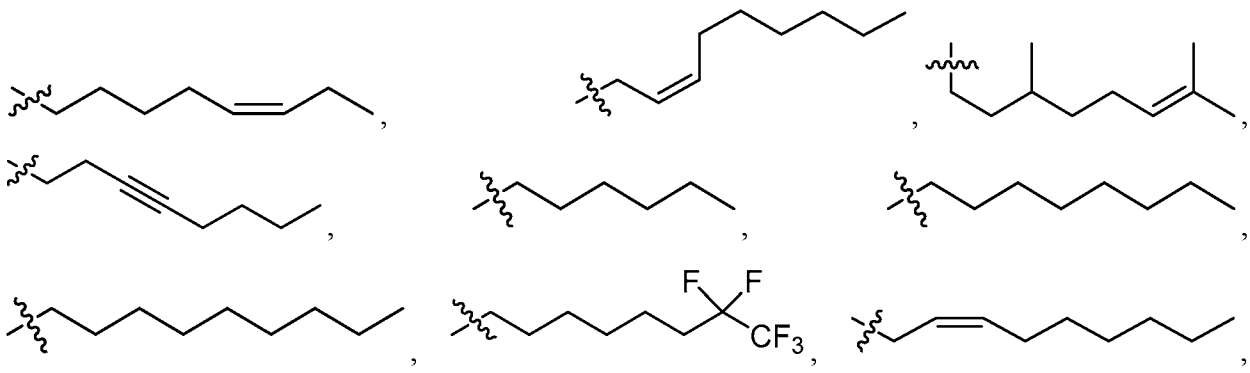
107. The compound according to any one of embodiments 89-92, wherein each of R and R^a is independently optionally substituted phenyl.

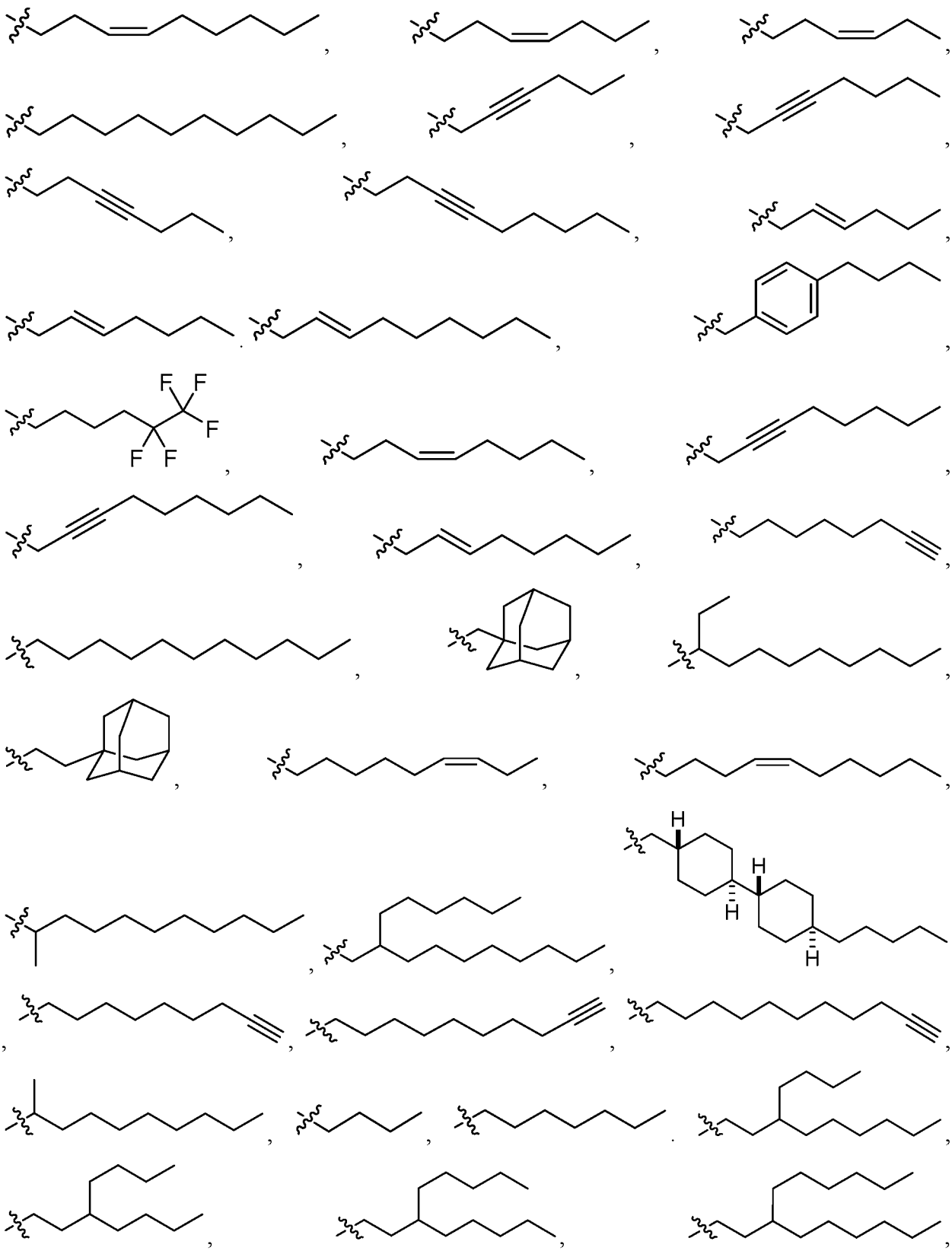
108. The compound according to any one of embodiments 1-107, wherein each of $-L^3-R''$, $-L^3-R$, and $-L^{3a}-R^a$ is independently selected from the group consisting of

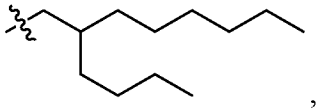


, and .

109. The compound according to any one of embodiments 1-107, wherein each of $-L^3-R''$, $-L^3-R$, and $-L^{3a}-R^a$ is independently selected from the group consisting of



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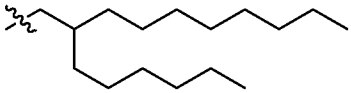
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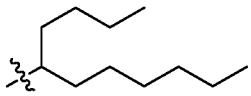
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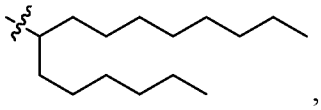
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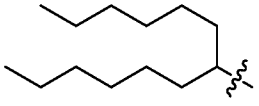
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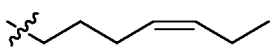
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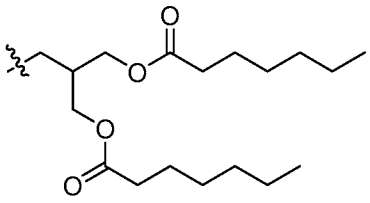
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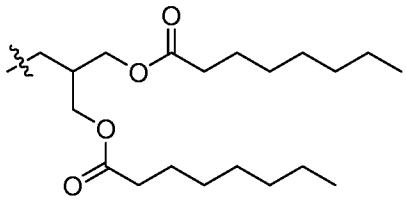
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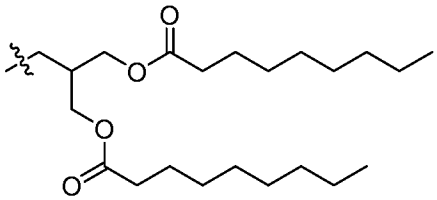
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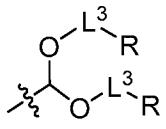
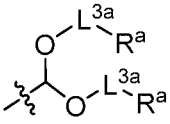
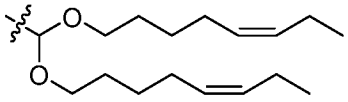
110. The compound according to any one of embodiments 1-107, wherein each of  and  is independently selected from the group consisting of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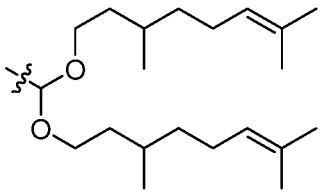
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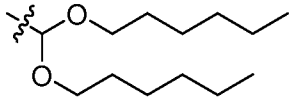
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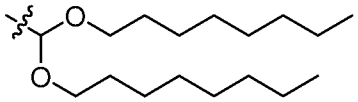
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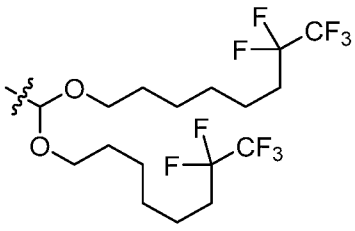
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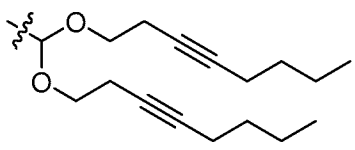
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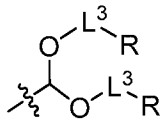
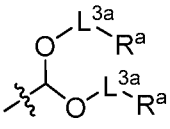
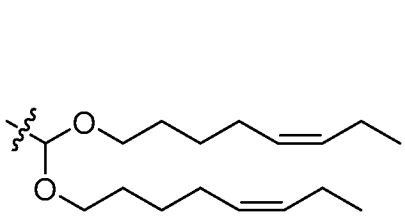
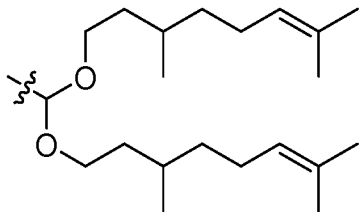
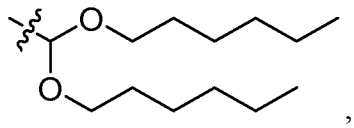
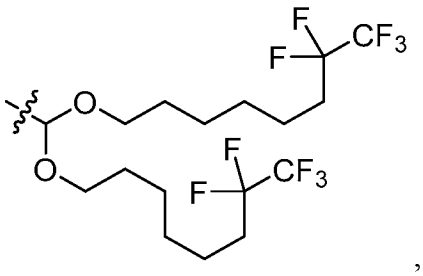
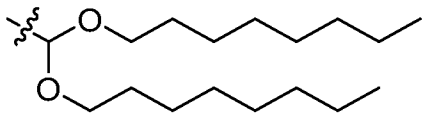
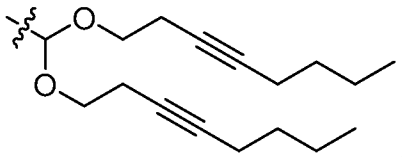
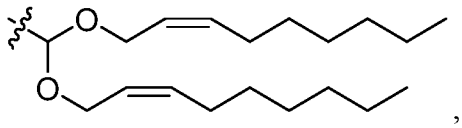
111. The compound according to any one of embodiments 1-107, wherein each of  and  is independently selected from the group consisting of

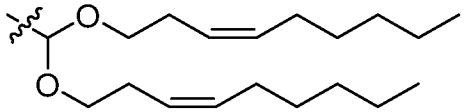
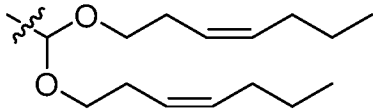
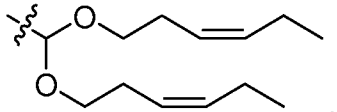
 ,  ,  ,

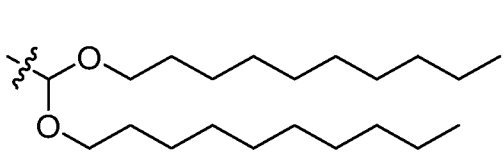
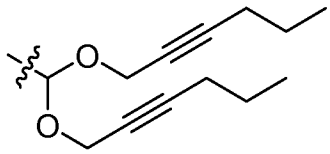
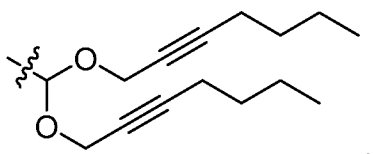


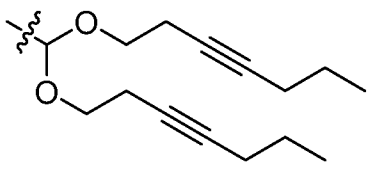
 ,

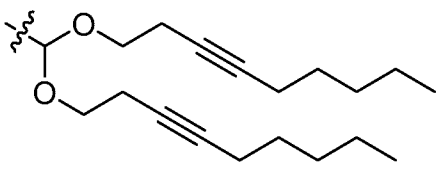
 ,

 ,

 ,  ,  ,

 ,  ,  ,



 ,

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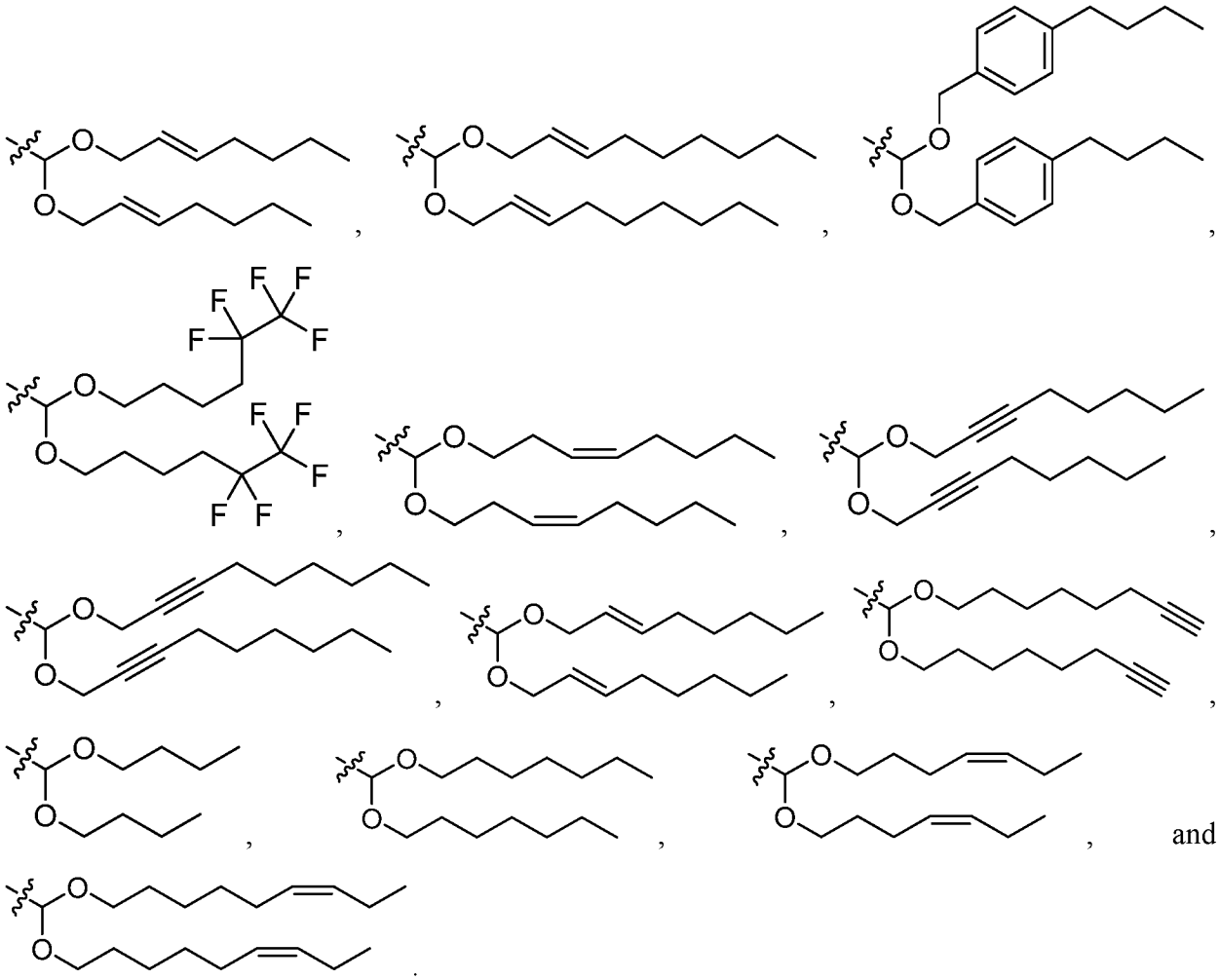
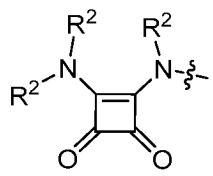


112. The compound according to any one of embodiments 1-111, wherein R^1 is $-OR^2$.

113. The compound according to any one of embodiments 1-111, wherein R^1 is $-NR^2C(O)N(R^2)_2$.

114. The compound according to any one of embodiments 1-111, wherein R^1 is  .

115. The compound according to any one of embodiments 1-111, wherein R^1 is $-NR^2C(O)R^2$.

116. The compound according to any one of embodiments 1-111, wherein R^1 is $-NR^2S(O)_2R^2$.

117. The compound according to any one of embodiments 1-111, wherein R^1 is $-C(O)OR^2$.

118. The compound according to any one of embodiments 1-111, wherein R^1 is $-C(O)SR^2$.

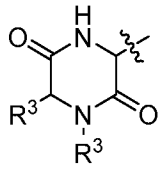
119. The compound according to any one of embodiments 1-111, wherein R^1 is $-C(O)N(R^2)_2$.

120. The compound according to any one of embodiments 112-119, wherein each R^2 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or $-(CH_2)_nN(R^5)_2$, wherein R^5 is hydrogen or optionally substituted C_{1-6} aliphatic.

121. The compound according to any one of embodiments 1-111, wherein R^1 is $-CR^2(OR^2)R^3$.

122. The compound according to embodiment 121, wherein R^1 is $-CH(OH)R^3$.

123. The compound according to any one of embodiments 1-111, wherein R^1 is .

124. The compound according to any one of embodiments 1-111, wherein R^1 is  .

125. The compound according to embodiment 124, wherein each R^3 is independently $-(CH_2)_n-R^4$, wherein R^4 is hydrogen and n is 0.

126. The compound according to any one of embodiments 121-124, wherein each R^3 is independently $-CH_2-R^4$.

127. The compound according to any one of embodiments 121-124, wherein each R^3 is independently -$(CH_2)_3$-R^4.

128. The compound according to embodiment 126 or 127, wherein each R^4 is independently -OR^5.

129. The compound according to embodiment 128, wherein each R^4 is independently -OH.

130. The compound according to embodiment 126 or 127, wherein each R^4 is independently -$C(O)N(R^5)_2$.

131. The compound according to embodiment 130, wherein each R^4 is independently -$C(O)NH_2$.

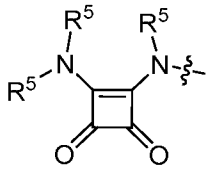
132. The compound according to embodiment 126 or 127, wherein each R^4 is independently -$NR^5C(O)R^5$.

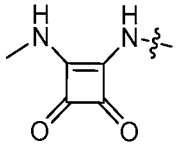
133. The compound according to embodiment 132, wherein each R^4 is independently -$NHC(O)CH_3$.

134. The compound according to embodiment 126 or 127, wherein each R^4 is independently -$NR^5C(S)N(R^5)_2$.

135. The compound according to embodiment 134, wherein each R^4 is independently -$NHC(S)NHCH_3$.

136. The compound according to embodiment 126 or 127, wherein each R^4 is independently



137. The compound according to embodiment 136, wherein each R^4 is independently  .

138. The compound according to any one of embodiments 1-111, wherein R^1 is optionally substituted phenyl.

139. The compound according to any one of embodiments 1-111, wherein R^1 is optionally substituted 3- to 7-membered cycloaliphatic.

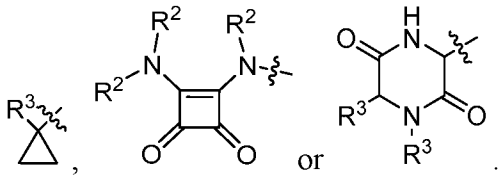
140. The compound according to any one of embodiments 1-111, wherein R^1 is optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

141. The compound according to any one of embodiments 1-111, wherein R^1 is optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

142. The compound according to any one of embodiments 1-111, wherein R^1 is optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

143. The compound according to any one of embodiments 1-111, wherein R^1 is $-OR^2$, $-OC(O)OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, or $-CR^2(OR^2)R^3$.

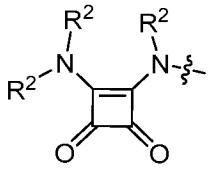
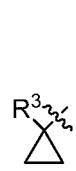
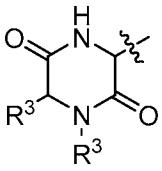
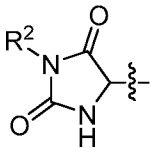
144. The compound according to any one of embodiments 1-111, wherein R^1 is $-CR^2(OR^2)R^3$,

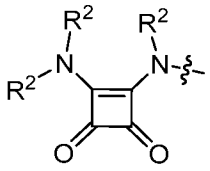
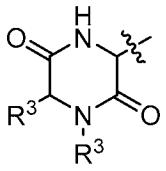


or .

145. The compound according to any one of embodiments 1-111, wherein R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$.

146. The compound according to any one of embodiments 1-111, wherein R^1 is hydrogen, optionally substituted phenyl, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, $-P(O)(OR^2)_2$, or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups.

147. The compound according to any one of embodiments 1-111, wherein R^1 is  ,  ,  , or  .

148. The compound according to embodiment 147, wherein R^1 is  , or  .

149. The compound according to any one of embodiments 145-148 , wherein each R^2 is independently hydrogen, oxo, $-(CH_2)_n-R^4$, or an optionally substituted group selected from phenyl, and 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

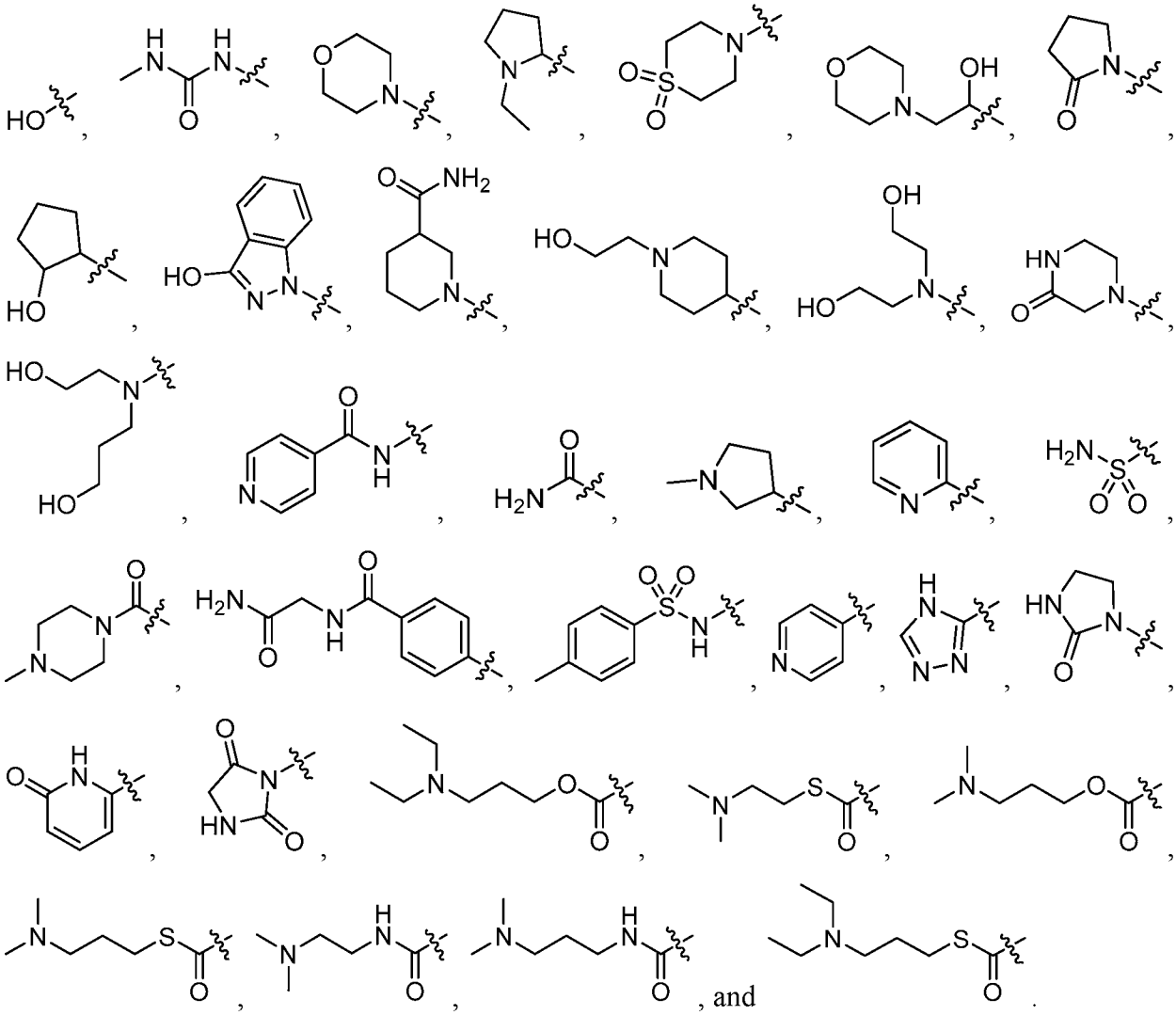
150. The compound according to any one of embodiments 145-148, wherein each R^3 is independently $-(CH_2)_n-R^4$.

151. The compound according to embodiment 149 or 150, wherein each R^4 is independently $-OR^5$ or $-N(R^5)_2$.

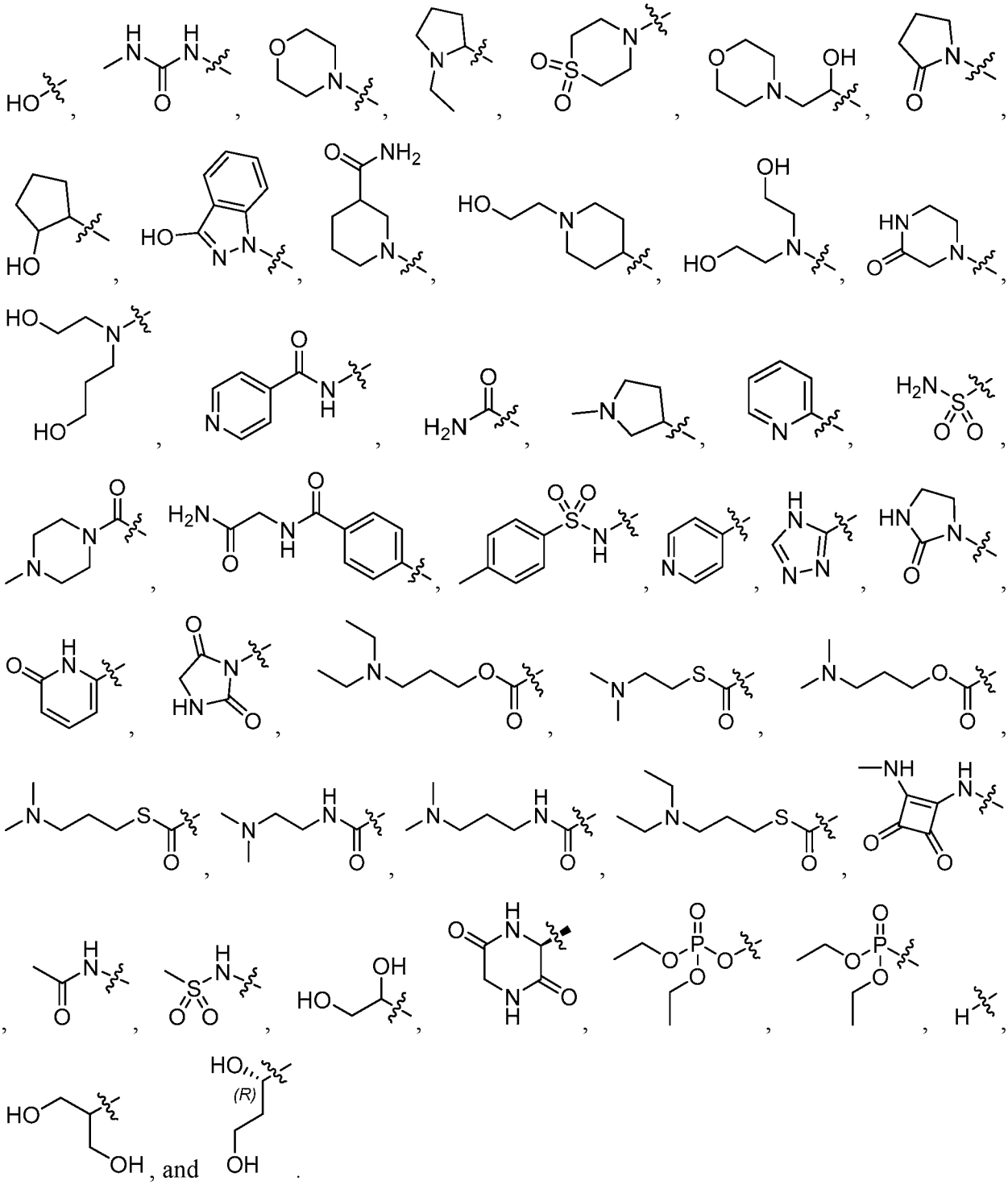
152. The compound according to embodiment 151, wherein each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic.

153. The compound according to embodiment 77 or 94, wherein each R^6 is independently C_{6-8} aliphatic.

154. The compound according to any one of embodiments 1-111, 145, and 146, wherein R^1 is selected from the group consisting of



155. The compound according to any one of embodiments 1-111, 145, and 146, wherein R^1 is selected from the group consisting of



156. The compound according to any one of embodiments 1-5, wherein the compound is selected from the group consisting of compounds 7-1 to 7-16, or a pharmaceutically acceptable salt thereof.

157. The compound according to any one of embodiments 1, 2, 9, and 10, wherein the compound is selected from the group consisting of compounds 8-1 to 8-66, or a pharmaceutically acceptable salt thereof.

158. The compound according to embodiment 1, wherein the compound is selected from Table 1, or a pharmaceutically acceptable salt thereof.

159. A lipid nanoparticle (LNP) preparation comprising an ionizable lipid according to any one of embodiments 1-158.

160. A lipid nanoparticle (LNP) preparation comprising:
an ionizable lipid according to any one of embodiments 1-158;
a phospholipid;
a sterol; and
a conjugate-linker lipid (e.g., polyethylene glycol lipid).

161. The LNP preparation of embodiment 160, further comprising one or more contaminants and/or degradants.

162. The LNP preparation of embodiment 160, excluding one or more contaminants and/or degradants.

163. The LNP preparation of embodiment 159 or 160, further comprising a therapeutic and/or prophylactic agent.

164. The LNP preparation of embodiment 163, wherein the therapeutic and/or prophylactic agent is or comprises one or more nucleic acids.

165. The LNP preparation of embodiment 164, wherein the one or more nucleic acids is or comprises RNA.

166. The LNP preparation of embodiment 165, wherein the RNA is or comprises mRNA, antisense RNA, siRNA, shRNA, miRNA, gRNA, or a combination thereof.

167. The LNP preparation of embodiment 164, wherein the one or more nucleic acids is or comprises DNA.

168. The LNP preparation of any one of embodiments 164-167, wherein the one or more nucleic acids comprises both RNA and DNA.

169. The LNP preparation of any one of embodiments 163-168, wherein the LNP preparation is formulated to deliver the therapeutic and/or prophylactic agent to target cells.

170. The LNP preparation of embodiment 169, wherein the target cells are or comprise spleen cells (e.g., splenic B cells, splenic T cells, splenic monocytes), liver cells (e.g., hepatocytes), bone marrow cells (e.g., bone marrow monocytes), immune cells, kidney cells, muscle cells, heart cells, or cells in the central nervous system.

171. The LNP preparation of embodiment 169, wherein the target cells are or comprise hematopoietic stem cells (HSCs).

172. The LNP preparation of any one of embodiments 159-171, wherein the ionizable lipid is or comprises a compound according to any one of embodiments 1-59, or a combination thereof.

173. The LNP preparation of any one of embodiments 159-172, wherein the LNP preparation comprises about 70 mol percent or less of the ionizable lipid.

174. The LNP preparation of any one of embodiments 159-173, wherein the LNP preparation comprises from about 30 mol percent to about 70 mol percent ionizable lipid.

175. The LNP preparation of any one of embodiments 159-174, wherein the LNP preparation comprises about 50 mol percent ionizable lipid.

176. The LNP preparation of any one of embodiments 159-174, wherein the LNP preparation comprises about 34.7 mol percent ionizable lipid.

177. The LNP preparation of any one of embodiments 159-174, wherein the LNP preparation comprises about 38.5 mol percent ionizable lipid.

178. The LNP preparation of any one of embodiments 160-177, wherein the phospholipid comprises 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-(succinyl) (succinyl PE), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl) (succinyl-DPPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), or a combination thereof.

179. The LNP preparation of any one of embodiments 160-178, wherein the phospholipid is or comprises DSPC.

180. The LNP preparation of any one of embodiments 160-179, wherein the LNP preparation comprises from about 10 mol percent to about 65 mol percent phospholipid.

181. The LNP preparation of any one of embodiments 160-180, wherein the LNP preparation comprises about 9 mol percent phospholipid.

182. The LNP preparation of any one of embodiments 160-180, wherein the LNP preparation comprises about 10 mol percent phospholipid.

183. The LNP preparation of any one of embodiments 160-180, wherein the LNP preparation comprises about 30 mol percent phospholipid.

184. The LNP preparation of any one of embodiments 160-183, wherein the conjugate-linker lipid comprises a polyethylene glycol lipid.

185. The LNP preparation of any one of embodiments 160-184, wherein the conjugate-linker lipid comprises DiMystyrlGlycerol (DMG), 1,2-Dipalmitoyl-rac-glycerol, 1,2-Dipalmitoyl-rac-glycerol, methoxypolyethylene Glycol (DPG-PEG), 1,2-Distearoyl-rac-glycero-3-methylpolyoxyethylene (DSG – PEG), or any combination thereof.

186. The LNP preparation of any one of embodiments 160-185, wherein the conjugate-linker lipid has an average molecular mass from about 500 Da to about 5000 Da.

187. The LNP preparation of any one of embodiments 160-186, wherein the conjugate-linker lipid has an average molecular mass of about 2000 Da.

188. The LNP preparation of any one of embodiments 160-187, wherein the LNP preparation comprises from about 0 mol percent to about 5 mol percent conjugate-linker lipid.

189. The LNP preparation of any one of embodiments 160-188, wherein the LNP preparation comprises about 1.5 mol percent conjugate-linker lipid.

190. The LNP preparation of any one of embodiments 160-188, wherein the LNP preparation comprises about 3 mol percent conjugate-linker lipid.

191. The LNP preparation of any one of embodiments 160-190, wherein the LNP preparation comprises from about 20 mol percent to about 50 mol percent sterol.

192. The LNP preparation of any one of embodiments 160-191, wherein the LNP preparation comprises about 33.8 mol percent sterol.

193. The LNP preparation of any one of embodiments 160-191, wherein the LNP preparation comprises about 38 mol percent sterol.

194. The LNP preparation of any one of embodiments 160-191, wherein the LNP preparation comprises about 38.5 mol percent sterol.

195. The LNP preparation of any one of embodiments 160-194, wherein the sterol is a cholesterol, or a variant or derivative thereof.

196. The LNP preparation of any one of embodiments 160-195, wherein the cholesterol is an oxidized cholesterol.

197. The LNP preparation of any one of embodiments 160-195, wherein the cholesterol is an esterified cholesterol.

198. The LNP preparation of any one of embodiments 160-194, wherein the sterol is a phytosterol.

199. A pharmaceutical composition comprising a LNP preparation of any one of embodiments 159-198 and a pharmaceutically acceptable excipient.

200. The pharmaceutical composition of embodiment 199, which is in a liquid formulation.

201. The pharmaceutical composition of embodiment 199, which is in a frozen formulation.

202. A method for administering a therapeutic and/or prophylactic agent to a subject in need thereof, the method comprising administering the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199, to the subject.

203. A method for treating a disease or a disorder in a subject in need thereof, the method comprising administering the LNP preparation of any one of embodiments 159-198, or the

pharmaceutical composition of embodiment 199, to the subject, wherein the therapeutic and/or prophylactic agent is effective to treat the disease.

204. A method for delaying and/or arresting progression a disease or a disorder in a subject in need thereof, the method comprising administering the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199, to the subject, wherein the therapeutic and/or prophylactic agent is effective to treat the disease.

205. A method of delivering a therapeutic and/or prophylactic agent to a mammalian cell derived from a subject, the method comprising contacting the cell of the subject having been administered the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199.

206. The method of embodiment 205, comprising administering to the subject the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199.

207. A method of producing a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199, wherein the therapeutic and/or prophylactic agent is or comprises an mRNA, and wherein the mRNA encodes the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide of interest.

208. A method of inhibiting production of a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199, wherein the therapeutic and/or prophylactic agent is or comprises an RNA, whereby the RNA is capable of inhibiting production of the polypeptide of interest.

209. The method of embodiment 208, wherein the RNA comprises an antisense RNA, a miRNA, a shRNA, a siRNA, or a gRNA.

210. A method of specifically delivering a therapeutic and/or prophylactic agent to a mammalian organ, the method comprising contacting a mammalian organ with the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199, whereby the therapeutic and/or prophylactic agent is delivered to the organ.

211. The method of embodiment 210, comprising administering to a subject the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199 to the subject.

212. A method of preparing a LNP preparation of any one of embodiments 159-198, or a pharmaceutical composition of embodiment 199.

213. A method of manufacturing a LNP preparation of any one of embodiments 159-198, or a pharmaceutical composition of embodiment 199.

214. A method of manufacturing an intermediate (e.g., any intermediate that may be stored or shipped) of any one of embodiments 159-199.

215. A method of characterizing a compound according to any one of embodiments 1-158.

216. A method of characterizing a LNP preparation of any one of embodiments 159-198, or a pharmaceutical composition of embodiment 199.

217. A method of providing a LNP preparation of any one of embodiments 159-198, or a pharmaceutical composition of embodiment 199, comprising assessing one or more characteristics

of the LNP preparation and establishing one or more characteristics of the LNP preparation (e.g., compared to a reference sample).

218. A method of vaccinating by administering the LNP preparation of any one of embodiments 159-198, or the pharmaceutical composition of embodiment 199.

219. The method of embodiment 218, wherein the step of administering comprises administering at least one dose.

220. The method of embodiment 219, wherein the step of administering comprises administering at least two doses.

221. The method of any one of embodiments 218-220, wherein the step of administering is via intramuscular injection.

222. A method of inducing an adaptive immune response in a subject, comprising administering to the subject an effective amount of a composition comprising at least one RNA; wherein the composition comprises a LNP preparation comprising a compound of any of Formulae A', A, I", I', I, II", II', II, III', III, I"-a, I'-a, I-a, I"-a-*i*, I"-a-*ii*, I"-a-*iii*, I"-b, I'-b, I-b, I"-b-*i*, I"-b-*ii*, I"-b-*iii*, I"-c, I'-c, I-c, I"-c-*i*, I"-c-*ii*, I"-c-*iii*, I'-d, I-d, I'-d-*i*, II-a, II-a-*i*, III-a, and III-a-*i*, or any one of embodiments 1-158, or a pharmaceutically acceptable salt thereof.

Exemplification

[0436] The present disclosure exemplifies compositions, preparations, formulations, nanoparticles, and/or nanomaterials described herein. The present disclosure also exemplifies methods of preparing, characterizing, and validating compositions, preparations, formulations, nanoparticles, and/or nanomaterials described herein.

Example 1: Materials and Methods

[0437] The present Example provides exemplary materials and methods of preparing, characterizing, and validating compositions, preparations, nanoparticles, and/or nanomaterials described herein.

LNP preparations

[0438] Among other things, the present Example provides for exemplary LNP preparations.

[0439] Lipid nanoparticle components were dissolved in 100% ethanol at specified lipid component molar ratios. Nucleic acid (NA) cargo was dissolved in 10 mM citrate, 100 mM NaCl, pH 4.0, resulting in a concentration of NA cargo of approximately 0.22 mg/mL. In some embodiments, NA cargos include both a functional NA and a reporter DNA barcode mixed at mass ratios of 1:10 to 10:1 functional NA to barcode. As described herein, a NA can be a siRNA, an anti-sense, an expressing DNA, or mRNA.

[0440] LNPs were prepared with a total lipid to NA mass ratio of 11.7. LNPs were formed by microfluidic mixing of the lipid and NA solutions using a Precision Nanosystems NanoAssemblr Spark or Benchtop series Instruments, according to the manufacturers protocol. A ratio of aqueous to organic solvent of approximately 2:1 or 3:1 was maintained during mixing using differential flow rates. After mixing, LNPs were collected, diluted in PBS (approximately 1:1 v/v). Further buffer exchange was conducted using dialysis in PBS at 4°C for 4 to 24 hours against a 20kDa filter. After this initial dialysis, each individual LNP preparation was characterized via dynamic light scattering (DLS) to measure the size (e.g., diameter) and polydispersity. In addition, pKa of a subpopulation of LNPs was measured via a 2-(p-toluidino)-6-napthalene sulfonic acid (TNS) assay. LNPs falling within specific diameter and polydispersity ranges were pooled, and further dialyzed against phosphate buffer saline (PBS) at 4°C for 1 to 4 hours against a 100kDa dialysis cassette. After the second dialysis, LNPs were sterile filtered using 0.22μM filter and stored at 4°C for further use.

LNP characterization

[0441] DLS - LNP hydrodynamic diameter and polydispersity index (PDI) were measured using high throughput dynamic light scattering (DLS) (DynaPro plate reader II, Wyatt). LNPs were diluted 1X PBS to an appropriate concentration and analyzed.

Concentration & Encapsulation Efficiency

[0442] Concentration of NA was determined by Qubit microRNA kit (for siRNA) or HS RNA kit (for mRNA) per manufacturer's instructions. Encapsulation efficiency was determined by measuring nucleic acid concentration in unlysed and lysed LNPs.

pKa

[0443] A stock solution of 10 mM HEPES (Sigma Aldrich), 10 mM MES (Sigma Aldrich), 10 mM sodium acetate (Sigma), and 140 nM sodium chloride (Sigma Aldrich) was prepared, and pH was adjusted using hydrogen chloride and sodium hydroxide to a range of about pH 4-10. Using four replicates for each pH value, 140 µL pH-adjusted buffer was added to a 96-well plate, followed by the addition 5 µL of 2-(p-toluidino)-6- napthalene sulfonic acid (60 µg/ mL). 5µL of LNP was added to each well. After 5 min of incubation under gentle shaking, fluorescence was measured using an excitation wavelength of 325 nm and emission wavelength of 435 nm (BioTek Synergy H4 Hybrid).

LNP Administration

[0444] Male and female mice aged approximately 8-12 weeks were used for the studies described by the present Example. Each mouse was temporarily restrained, and pooled LNP was administered intravenously (IV) via tail vein injection in up to five animals per experiment. Age-matched mice were also used to administer vehicle (1X PBS) via tail vein injection in up to three animals per experiment. At 72 hours post-dose, tissues including liver, spleen, bone marrow, kidney, lung, muscle, and blood were collected for analysis.

Flow

[0445] Liver, kidney, lung, and muscle tissues were mechanically, and then enzymatically digested using a mixture of proteinases, then passed through a 70uM filter to generate single cell suspensions. Spleen tissues were mechanically digested to generate single cell suspensions. All tissues were treated with (Ammonium-Chloride-Potassium) ACK buffer to lyse red blood cells, and then stained with fluorescently-labeled antibodies for flow cytometry and fluorescence-activated cell sorting (FACS). Commercially available antibodies were used. Using a BD FACSMelody (Becton Dickinson), samples were acquired via flow cytometry to generate gates prior to sorting. In general, gating structure is size → singlet cells → live cells → cells of interest. T cells were defined as CD45+CD3+, monocytes are defined as CD45+CD11b+, and B cells are defined as CD45+CD19+. Endothelial cells were defined as CD31+, monocytes and Kupffer cells as CD45+CD11b+ and hepatocytes as CD31-/CD45-. For siRNA studies, downregulation of the target gene was gated. For mRNA studies, upregulation of the target gene was gated. Tissues from vehicle-dosed mice were used to set the gates for sorting. Up to 1 million cells of each cell subset with the correct phenotype were sorted into PBS. After sorting, cells were pelleted via

centrifugation and DNA is extracted using Quick Extract DNA Extraction Solution (Lucigen) according to manufacturer's protocol. Following DNA extraction, DNA was stored at -20°C.

Barcoding Sequencing

[0446] DNA (genomic and DNA barcodes) were isolated using QuickExtract (Lucigen) and sequenced using Illumina MiniSeq as described herein, normalizing frequency DNA barcode counts in FACS isolated samples to frequency in injected input. These data were plotted as 'Normalized Fold Above Input' (data not shown).

Confirmation

[0447] Structural and functional features of the provided LNPs were confirmed based on protocols described herein.

LNP Preparation

[0448] Lipid nanoparticle components were dissolved in 100% ethanol at specified lipid component molar ratios. Nucleic acid (NA) cargo was dissolved in 10 mM citrate, 100 mM NaCl, pH 4.0, resulting in a concentration of NA cargo of approximately 0.22 mg/mL. In some embodiments, NA cargos include both a functional NA and a reporter DNA barcode mixed at mass ratios of 1:10 to 10:1 functional NA to barcode. LNPs were formulated with a total lipid to NA mass ratio of 11.7. LNPs were formed by microfluidic mixing of the lipid and NA solutions using a Precision Nanosystems NanoAssemblr Spark or Benchtop series Instruments, according to the manufacturers protocol. A 2:1 or 3:1 ratio of aqueous to organic solvent was maintained during mixing using differential flow rates. After mixing, LNPs were collected, diluted in PBS (approximately 1:1 v/v), and further buffer exchange was conducted using dialysis in PBS at 4°C for 8 to 24 hours against a 20kDa filter. After this initial dialysis, each individual LNP formulation was characterized via DLS to measure the size and polydispersity, and the pKa of a subpopulation of LNPs was measured via TNS assay. A fter dialysis, LNPs are sterile filtered using 0.22 micron sterile filter and stored at 4°C for further use.

LNP Characterization

DLS

[0449] LNP hydrodynamic diameter and polydispersity index (PDI) were measured using high throughput dynamic light scattering (DLS) (DynaPro plate reader II, Wyatt). LNPs were diluted 1X PBS to an appropriate concentration and analyzed.

Concentration & Encapsulation Efficiency

[0450] Concentration of NA was determined by Qubit microRNA kit (for siRNA) or HS RNA kit (for mRNA) per manufacturer's instructions. Encapsulation efficiency was determined by measuring unlysed and lysed LNPs.

pKa

[0451] A stock solution of 10 mM HEPES (Sigma Aldrich), 10 mM MES (Sigma Aldrich), 10 mM sodium acetate (Sigma), and 140 nM sodium chloride (Sigma Aldrich) was prepared and pH adjusted using hydrogen chloride and sodium hydroxide to a range of about pH 4-10. Using four replicates for each pH, 140 μL pH-adjusted buffer was added to a 96-well plate, followed by the addition 5 μL of 2-(p-toluidino)-6- napthalene sulfonic acid (60 μg/ mL). 5μL of LNP was added to each well. After 5 min of incubation under gentle shaking, fluorescence was measured using an excitation wavelength of 325 nm and emission wavelength of 435 nm (BioTek Synergy H4 Hybrid).

LNP Administration

[0452] Male and female mice aged approximately 8-12 weeks were used for studies described by the present Example. Each mouse was temporarily restrained, and pooled LNP was administered IV via tail vein injection in up to five animals per experiment. Age-matched mice was also used to administer vehicle (1X PBS) via tail vein injection in up to three animals per experiment. Additional routes of administration can also be conducted including intracerebral ventricular (ICV), intracisterna manga (ICM), intrathecal (IT), intramuscular (IM), nebulization, intranasal (IN), subcutaneous (SC), intraarticular, and intradermal (ID). At 72 hours post-dose, tissues including liver, spleen, bone marrow and blood were collected for analysis.

Flow

[0453] Liver, kidney, lung, and muscle (e.g. skeletal and cardiac) tissues were mechanically, and then enzymatically digested using a mixture of proteinases, then passed through a 70uM filter to generate single cell suspensions. Spleen tissues were mechanically digested to generate single cell suspensions. Tissues were treated with ACK buffer to lyse red blood cells, and then stained with fluorescently-labeled antibodies for flow cytometry and fluorescence-activated cell sorting (FACS). Commercially available antibodies were used in the present example. Using a BD FACSMelody (Becton Dickinson), samples were acquired via flow cytometry to generate gates prior to sorting. In general, the gating structure was size → singlet cells → live cells → cells of interest. T cells were defined as CD45+CD3+, monocytes are defined as CD45+CD11b+, and B

cells are defined as CD45+CD19+. Endothelial cells were defined as CD31+, monocytes and Kupffer cells as CD45+CD11b+ and hepatocytes and myocytes were defined as CD31-/CD45- in the liver and muscle, respectively. Tissues from vehicle-dosed mice were used to set the gates for sorting.

hEPO Expression

[0454] For human EPO (hEPO) protein expression, mice were temporarily restrained and bled at 6 hours post-administration (via tail vein). Blood was collected in heparin tubes, processed to plasma, and stored at -80°C until ready to use. Appropriate dilutions of plasma were used to measure hEPO protein using R&D systems ELISA kit (DuoSet; DY286-05) according to manufacturer's instructions.

Tolerability

ALT / AST Quantification

[0455] For rat Aspartate Transaminase (AST) and Alanine Transaminase (ALT) quantification, rats were temporarily restrained and bled at 2, 4, 6, 24, 48, and 72 hrs hours post-administration. Blood was collected in heparin tubes, processed to plasma, and stored at -80°C until ready to use. AST is quantified using AST/GOT reagent (ThermoFisher, TR70121) and ALT is quantified using ALT/GPT reagent (ThermoFisher, TR71121) according to manufacturer's instructions.

Rat MCP-1 ELISA

[0456] For Rat Monocype Chemoattractant Protein-1 (MCP-1) protein expression, rats were temporarily restrained and bled at 2, 4, 6, 24, 48, and 72 hrs hours post-administration. Blood was collected in heparin tubes, processed to plasma, and stored at -80°C until ready to use. Appropriate dilutions of plasma were used to measure MCP-1 protein using R&D systems ELISA kit (DuoSet; DY3144-05) according to manufacturer's instructions.

Screening Experiments

[0457] As described herein, a plurality of LNPs (for example, more than 300 LNP preparations) can be simultaneously tested in a single screening experiment. In some embodiments, more than 300 LNPs are screened in a single mouse. In some embodiments, more than 850 LNPs are screened in a single mouse (see FIG. 1 and FIG. 2). Screening experiments were used to measure mRNA or siRNA delivery to cells and tissues as described herein.

[0458] For mRNA delivery, each LNP preparation was formulated to carry Cre mRNA and a barcode as described herein. Each LNP preparation was administered to LSL-tdTom mouse

(Ai14) (see FIG. 1) in accordance with the methods described herein (see also FIG. 1). Referring to FIG. 1, a library of LNP preparations each comprising one or more components, a barcode sequence, and Cre mRNA was administered into a Cre-LoxP reporter mouse. As described herein, mouse cells were sorted using FACS based on whether the cells were tdTom- or tdTom+. Sorted tDTom+ cells were then sequenced as descried herein.

[0459] For siRNA delivery, each LNP preparation was formulated to carry siGFP and barcodes, as described herein. Each LNP preparation was administered to a GFP mouse (see FIG. 2) in accordance with the methods described herein (see also FIG. 2). Referring to FIG. 2, a library of LNP preparations each comprising one or more components, a barcode sequence, and siGFP was administered into a GFP reporter mouse. As described herein, cells were sorted using FACS based on GFP expression. Sorted cells were then sequenced as descried herein.

[0460] About 454 LNP preparations were formulated using compounds described herein and compounds developed by Applicant that are described in U.S. Provisional Application Nos. 63/128,685 and 63/128,682. About 20 LNP preparations were formulated using MC3 as a control. The following measurements were made: LNP preparation diameter, LNP preparation polydispersity, "normalized delivery efficiency" to any combination of cell- and tissue- types (e.g., about 27 per screen), LNP preparation pKA (which is related to, but not the same as lipid pKA), lipid pKA, and LNP preparation ionizability. Encapsulation efficiency and delivery potency were also measured for each pool of LNP preparations. hEPO expression and Cre expression measurements were performed as described herein.

Example 2: Potency per screen

[0461] The present Example provides exemplary compositions, preparations, nanoparticles, and/or nanomaterials, and materials and methods for screening potency of such compositions, preparations, nanoparticles, and/or nanomaterials described herein.

[0462] FIG. 3 depicts a bar graph that shows overall potency of three exemplary LNP screens as described in Example 1 (Screen 33, Screen 35, Screen 36). Screen 33 contains compounds of the present disclosure, while Screens 35 and 36 contain compounds described in U.S. Provisional Application Nos. 63/128,685 and 63/128,682. The present example demonstrates that each pool of LNPs (in some cases up to 384 LNPs per mouse) was highly potent across many tissues (including bone marrow, spleen, liver; kidney and muscle data not shown) (see FIG. 3).

Example 3: Exemplary LNP preparations with potent delivery to various cell types

[0463] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials for potent delivery to various cell types described herein.

[0464] Based on the results derived from Screen 33, several lipids exemplary LNP preparations (Exemplary Lipid 7, Exemplary Lipid 5, Exemplary Lipid 6, Exemplary Lipid 1, which are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16) were identified for use in splenic delivery, and in particular, for use in B cell delivery. These identified lipids were formulated into LNP preparations and screened using a Cre reporter system described herein. Three Ai14 mice were used per group. Payloads comprised 0.3 mg/kg Cre mRNA. Data was collected at 168 hours post-injection. Results were compared to an MC3-LNP preparation as a control (see FIG. 4). Unexpectedly, representative data in FIG. 4 shows that the screening platforms described herein can correctly identify unique LNP preparations with potent delivery to various cell-types, for example, splenic B cells and T cells.

[0465] Exemplary Lipids 7, 5, 6, and 1 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16. Accordingly, the present example demonstrates that in some embodiments, lipids characterized by including an ester-linked acetal feature show potent delivery to various cell-types, for example splenic B cells and T cells.

Example 4: Exemplary LNP preparations are delivered to various cell types

[0466] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[0467] Four LNP preparations (Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-16) were selected to confirm efficacy results using a Cre reporter system and Ai14 mouse model described herein (see FIG. 5). FIG. 5 also includes data for Exemplary Lipids 2, 3, and 4, which are exemplary compounds described in U.S. Provisional Application Nos. 63/128,685 and 63/128,682. FIG. 5 shows % tdTomato+ cells across a variety of cell-types (bone marrow B cells, bone marrow memory B cells, bone marrow T cells, bone marrow monocytes, spleen monocytes, spleen T cells, spleen B cells, and spleen memory B cells) using four exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 2,

Exemplary Lipid 3, Exemplary Lipid 4) containing 1 mg/kg Cre mRNA compared to a saline control. Data was also collected for liver delivery but is not shown. Three Ai14 mice per group were used in each experiment. Data was collected 72 hours post-injection. Unexpectedly, representative data in FIG. 5 shows that the screening platforms described herein can identify several highly potent LNP preparations to determine what type of LNP preparation would be most potent for a particular cell type.

[0468] Exemplary Lipid 1 is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-16. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having an ester-linked acetal feature show potent delivery across various cell types, including bone marrow B cells, bone marrow memory B cells, bone marrow monocytes, spleen monocytes, spleen B cells, and spleen memory B cells.

Example 5: Exemplary LNP preparations deliver functional mRNA

[0469] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials that deliver functional mRNA to various cell types.

[0470] Three exemplary LNP preparations (Exemplary Lipid 7, Exemplary Lipid 5, Exemplary Lipid 1, which are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16) were selected to determine each preparation's ability to deliver functional mRNA in mice. LNP preparations each carried 0.15 mg/kg hEPO mRNA and was administered at a mass ratio of 11.7 and 19 in 2-3 C57BL6 mice. hEPO expression in plasma was measured six hours post injection of LNP preparations (see FIG. 6).

[0471] Exemplary Lipids 7, 5, and 1 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16. Accordingly, in some embodiments, the present example demonstrates lipids characterized by having an ester-linked acetal are able to deliver functional mRNA in mice.

Example 6: Tolerability and efficacy experiments

[0472] The present Example provides exemplary materials and methods of preparing, characterizing, and validating compositions, preparations, nanoparticles, and/or nanomaterials described herein.

[0473] Two exemplary LNP preparations (Exemplary Lipid 5 and Exemplary Lipid 1, which are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16) were selected to determine tolerability and efficacy of hEPO mRNA delivery in rats as described herein. Each LNP preparation containing 1.0 mg/kg hEPO mRNA was injected into Sprague-Dawley rats (N=2). FIG. 7 shows amount of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) collected from rat plasma (U/L) at 24 hours post-injection for each exemplary LNP preparation. FIG. 8 shows amount of monocyte chemoattractant protein-1 (MCP-1) collected from rat plasma (ng/mL) at 6 hours post-injection for each LNP preparation. Saline was used as a control. FIG. 9 shows amount of hEPO collected from rat plasma (ng/mL) after administering a vehicle (control) and the two exemplary LNP preparations across various time points post-injection (0, 2, 4, 6, 24, 48, 96 hours).

[0474] Exemplary Lipids 1 and 5 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-16. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having an ester-linked acetal feature are able to deliver functional mRNA in mice.

Example 7: Synthesis of Ionizable lipids

[0475] The present Example provides exemplary materials and methods of preparing, characterizing, and validating ionizable lipids as described herein. As described in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods and other methods known to one of ordinary skill in the art can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[0476] General notes: All reactions were run using anhydrous grade solvents under an atmosphere of nitrogen in flasks or vials with magnetic stirring, unless otherwise noted. Anhydrous solvents were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed using a Biotage Selekt or Teledyne-Isco Combiflash Nextgen300+ with prepacked silica gel cartridges. Thin layer chromatography was performed using Merck silica gel 60 plates, and compounds were visualized using iodine. Nuclear magnetic resonance (NMR) spectroscopy was performed either using a Varian INOVA 500 MHz or a Bruker AVANCE 400 MHz

spectrometer; chemical shifts are reported in δ parts per million (ppm) referenced to tetramethylsilane at δ = 0.00 ppm for $CDCl_3$ samples, and residual solvent peak (δ = 2.50 ppm) for DMSO samples. Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) was performed using a Waters Acquity UPLC H-class Plus with QDa detector (ESI^+) using one of the following methods.

[0477] Method A: 6 min run, Column: BEH C18 (2.1 x 50 mm), 1.7 μM, mobile phase: initially 90% [0.1% HCOOH in water] and 10% ACN; then to 5% [0.1% HCOOH in water] and 95% ACN over 3 min, held this mobile phase composition for 2 min, and finally back to initial condition over 1 min, i.e; 90% [0.1% HCOOH in water] and 10% ACN. Flow =0.5 mL/min.

[0478] Method B: 5 min run, Column: XTERRA RP 18 (4.6 x 50 mm), 5 μm, mobile phase: initially 50% [0.1% HCOOH in water] and 50% [0.1% HCOOH in (70:30) ACN: THF]; then to 2% [0.1% HCOOH in water] and 98% [0.1% HCOOH in (70:30) ACN: THF] in 2.65 min, held this mobile phase composition up to 3.75 min, and finally back to initial condition, i.e; 50% [0.1% HCOOH in water] and 50% [0.1% HCOOH in (70:30) ACN: THF] in 4.90 min, held this mobile phase composition up to 5.10 min. Flow =1.2 mL/min.

[0479] Method C: 12 min run, Column: XTERRA RP 18 (4.6 x 50 mm), 5 μm, (mobile phase: initially 80% [0.1% HCOOH in water] and 20% [0.1% HCOOH in (70:30) ACN: THF]; held this initial condition for 0.75 min; then to 65% [0.1% HCOOH in water] and 35% [0.1% HCOOH in (70:30) ACN: THF] in 3.0 min, then to 2% [0.1% HCOOH in water] and 98% [0.1% HCOOH in (70:30) ACN: THF] in 6.0 min, held this mobile phase composition up to 9.0 min, and finally back to initial condition, i.e.; 80% [0.1% HCOOH in WATER] and 20% [0.1% HCOOH in (70:30) ACN: THF] in 11.00 min, held this mobile phase composition up to 12.10 min. Flow =1.2 ml/min

List of abbreviations

ACN: acetonitrile

d: doublet

DCC: N,N'-dicyclohexylcarbodiimide

DCM: dichloromethane

DIPEA: N,N-diisopropylethylamine

DMAP: 4-(dimethylamino)pyridine

DMSO: dimethyl sulfoxide

EDC: *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

Eq: equivalents

Et: ethyl

i-Pr: isopropyl

m: multiplet

Me: methyl

p: pentet

PPTS: pyridinium p-toluenesulfonate

q: quartet

Rt: retention time

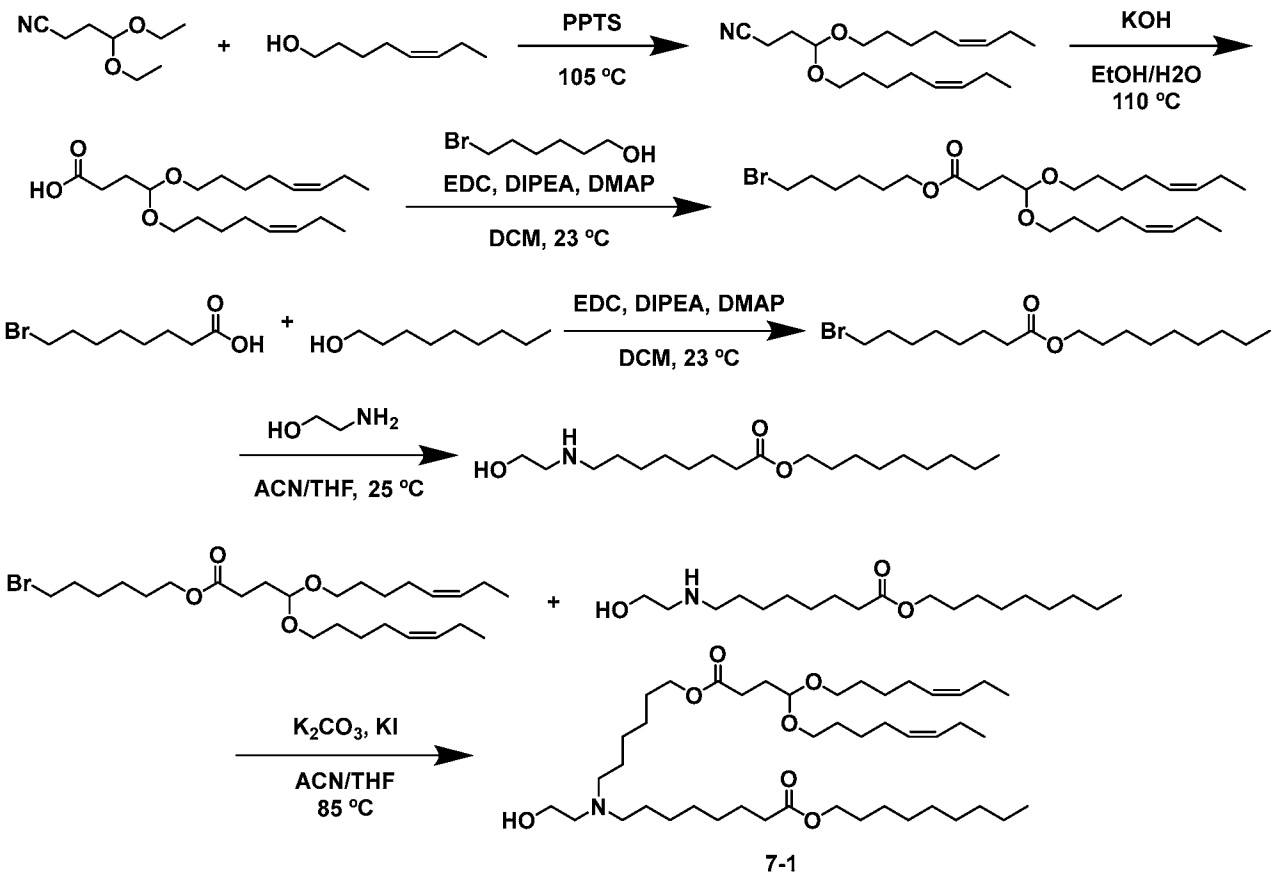
s: singlet

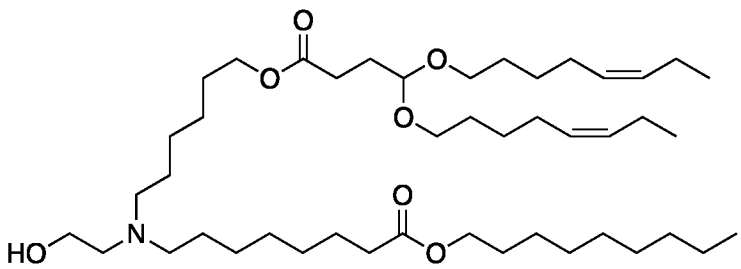
t: triplet

TEA: triethylamine

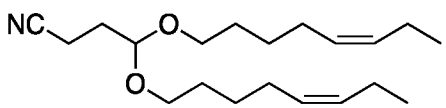
THF: tetrahydrofuran

[0480] The following example lipids were prepared according to the below synthetic scheme, using Example 7-1 as an illustration.





Example 7-1: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

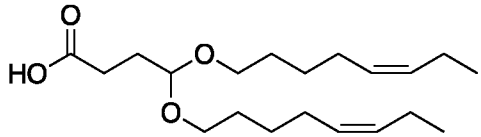


Step 1: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanenitrile

General Procedure A:

[0481] To a vial containing pyridinium *p*-toluene sulfonate (0.12 g, 0.48 mmol, 0.05 Eq) was added 4,4-diethoxybutanenitrile (1.5 g, 9.5 mmol, 1 Eq) and cis-5-octen-1-ol (3.7 g, 29 mmol, 3 Eq). The vial was tightly capped, and the resulting mixture was heated at 105 °C for 72 h. After this time, the mixture was allowed to cool to room temperature. The crude material was purified

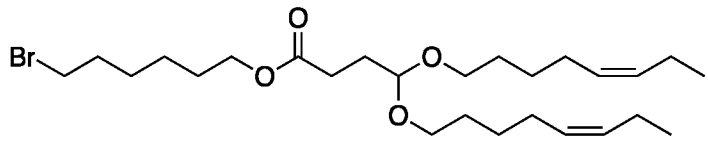
by flash column chromatography (100 g silica, 0 to 100% dichloromethane in hexanes over 20 minutes). Obtained 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile (1.14 g, 37%) as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.43 – 5.27 (m, 4H), 4.56 (t, *J* = 5.3 Hz, 1H), 3.61 (dt, *J* = 9.3, 6.6 Hz, 2H), 3.44 (dt, *J* = 9.3, 6.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.91 (m, 9H), 1.66 – 1.54 (m, 5H), 1.49 – 1.36 (m, 4H), 0.96 (t, *J* = 7.6 Hz, 6H).



Step 2: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid

General Procedure B:

[0482] To a vial containing 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile (1.14 g, 3.54 mmol, 1 Eq) was added potassium hydroxide (0.60 g, 10.6 mmol, 3 Eq) followed by ethanol (3.5 mL) and water (3.5 mL). The vial was tightly capped, and the reaction mixture was heated to 110 °C for 18 h. After this time, the mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate (20 mL), and the pH was adjusted to ~5 by the addition of 1M HCl. The resulting biphasic mixture was separated, and the aqueous phase was extracted two more times with ethyl acetate (2 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated to afford 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid (1.16 g, 96% yield) as a sticky white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.41 – 5.24 (m, 4H), 4.45 (t, *J* = 5.6 Hz, 1H), 3.51 (dt, *J* = 9.0, 6.7 Hz, 2H), 3.39 (dt, *J* = 9.0, 6.7 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 2.08 – 1.98 (m, 8H), 1.81 (q, *J* = 7.3 Hz, 2H), 1.59 – 1.52 (m, 4H), 1.44 – 1.32 (m, 4H), 0.94 (t, *J* = 7.5 Hz, 6H).

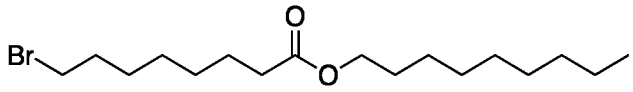


Step 3: 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

General Procedure C:

[0483] To a solution of 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid (508 mg, 1 Eq, 1.49 mmol) in DCM (13 mL) was added 6-bromohexan-1-ol (270 mg, 195 µL, 1 Eq, 1.49 mmol), DIPEA (964 mg, 1.29 mL, 5 Eq, 7.46 mmol) , and DMAP (36.4 mg, 0.2 Eq, 298 µmol). Added EDC (429 mg, 1.5 Eq, 2.24 mmol) last, stirred at 23 °C for 18 h. After this time, the reaction

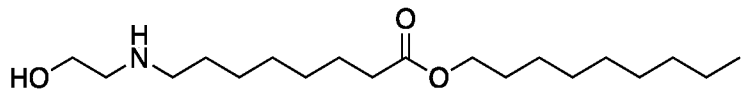
mixture was concentrated and purified by flash column chromatography (50 g silica, 0 to 50% ethyl acetate in hexanes). Obtained 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (397 mg, 53%) as a colorless oil.



Step 4: nonyl 8-bromooctanoate

General Procedure D:

[0484] To a stirred solution of 8-bromooctanoic acid (3.0 g, 13.4 mmol, 1 eq) in DCM (20 mL) were added DCC (3.35 g, 17.5 mmol, 1.3 eq), DMAP (0.174 g, 1.3 mmol, 0.1 eq) and 1-nonanol (2.13 g, 14.8 mmol, 1.1 eq). The reaction mixture was stirred at 23 °C for 16 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (15 mL ×3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by combiflash column chromatography, eluted with 10% ethyl acetate-hexane to afford nonyl 8-bromooctanoate (3.2 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.20 – 1.38 (m, 16H), 1.38 – 1.48 (m, 2H), 1.54 – 1.68 (m, 4H), 1.78 – 1.90 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).



Step 5: nonyl 8-((2-hydroxyethyl)amino)octanoate

General Procedure E:

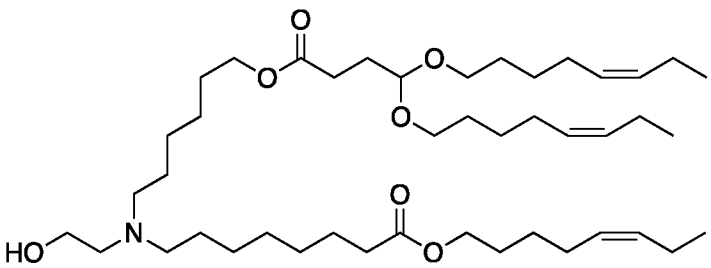
[0485] To a stirred solution of nonyl 8-bromooctanoate (500.0 mg, 0.93 mmol, 1 eq) in ACN/THF (1:1) (0.5 mL) was added ethanolamine (1.7 mL, 28.04 mmol, 30 eq) under nitrogen atmosphere and stirred at 25 °C for 16 h. Upon completion, the reaction mixture was concentrated in vacuo and diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude material thus obtained was purified by combi flash column chromatography, eluted with 0-15% MeOH-DCM gradient to afford nonyl 8-((2-hydroxyethyl)amino)octanoate (320 mg, 68%) as a light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.23 – 1.33 (m, 22H), 1.44 – 1.51 (m, 2H), 1.57 – 1.64

(m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 5.2 Hz, 2H), 3.62 (t, *J* = 5.5 Hz, 2H), 4.04 (t, *J* = 6.8 Hz, 2H).

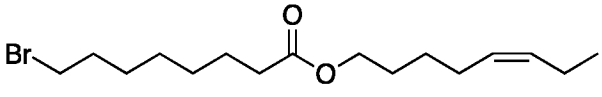
Step 6: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-1)

General Procedure F:

[0486] To a solution of 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (305 mg, 1 Eq, 606 µmol) in ACN (3 mL) and THF (3 mL) was added potassium carbonate (251 mg, 3 Eq, 1.82 mmol), potassium iodide (121 mg, 1.2 Eq, 727 µmol), and nonyl 8-((2-hydroxyethyl)amino)octanoate (200 mg, 1 Eq, 606 µmol). The resulting mixture was stirred at 85°C for 18 h. After this time, the mixture was filtered through a pad of celite and concentrated. The residue was partitioned between ethyl acetate and water, and the organic layer washed twice with water and once with brine. The organics were combined, dried over sodium sulfate and concentrated. The resulting residue was purified by flash column chromatography (50 g silica, 0 to 10% methanol in DCM). Obtained nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (0.308 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 – 5.25 (m, 4H), 4.49 (t, *J* = 5.6 Hz, 1H), 4.05 (t, *J* = 6.7 Hz, 4H), 3.67 (d, *J* = 5.3 Hz, 2H), 3.57 (dt, *J* = 9.4, 6.6 Hz, 2H), 3.40 (dt, *J* = 9.3, 6.6 Hz, 2H), 2.74 (m, 2H), 2.62 (m, 3H), 2.37 (t, *J* = 8.6, 6.4 Hz, 3H), 2.28 (dd, *J* = 8.6, 6.4 Hz, 3H), 2.10 – 1.97 (m, 8H), 1.95 – 1.89 (m, 2H), 1.64 – 1.53 (m, 14H), 1.45 – 1.18 (m, 27H), 0.95 (t, *J* = 7.5 Hz, 6H), 0.90 – 0.83 (t, *J* = 7.5 Hz, 3H). UPLC-MS (Method A): Rt 3.56 min, m/z calculated [M+H]: 752.63, found 752.62.

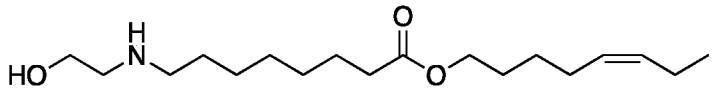


Example 7-2: (Z)-oct-5-en-1-yl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-oct-5-en-1-yl 8-bromooctanoate

[0487] Prepared according to General Procedure D, substituting (*Z*)-oct-5-en-1-ol for 1-nonanol. Isolated 815 mg, 52%.

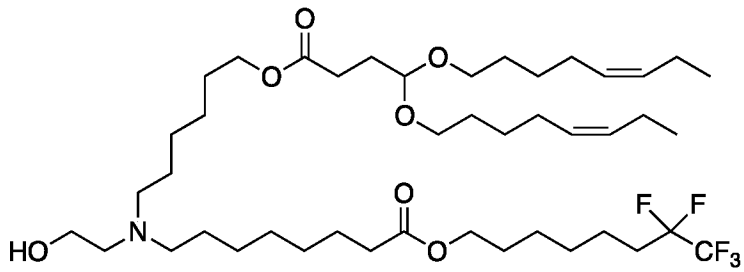


Step 2: (Z)-oct-5-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

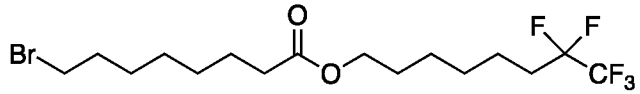
[0488] Prepared according to General Procedure E, substituting (*Z*)-oct-5-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 210 mg, 57%. UPLC-MS (Method A): Rt 2.38 min, m/z calculated [M+H]: 314.26, found 314.41.

Step 3: (Z)-oct-5-en-1-yl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-2)

[0489] Prepared according to General Procedure F, substituting (*Z*)-oct-5-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 63 mg, 36%. UPLC-MS (Method A): Rt 3.40 min, m/z calculated [M+H]: 736.60, found 736.62.

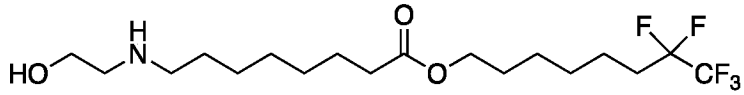


Example 7-3: 7,7,8,8,8-pentafluorooctyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 7,7,8,8,8-pentafluorooctyl 8-bromooctanoate

[0490] Prepared according to General Procedure D, substituting 7,7,8,8,8-pentafluoro-1-octanol for 1-nonanol. Isolated 1.1 g, 58%.

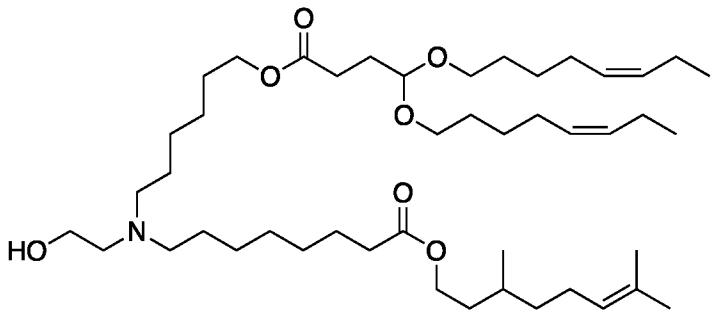


Step 2: 7,7,8,8,8-pentafluorooctyl 8-((2-hydroxyethyl)amino)octanoate

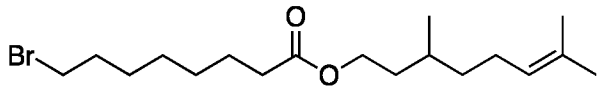
[0491] Prepared according to General Procedure E, substituting 7,7,8,8,8-pentafluorooctyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 444 mg, 93%. UPLC-MS (Method A): Rt 2.49 min, m/z calculated [M+H]: 406.23, found 406.36.

Step 3: 7,7,8,8,8-pentafluorooctyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-3)

[0492] Prepared according to General Procedure F, substituting 7,7,8,8,8-pentafluorooctyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 99 mg, 65%. UPLC-MS (Method A): Rt 3.40 min, m/z calculated [M+H]: 828.57, found 828.61.

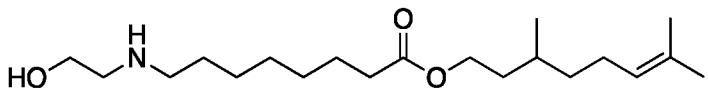


Example 7-4: 3,7-dimethyloct-6-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 3,7-dimethyloct-6-en-1-yl 8-bromooctanoate

[0493] Prepared according to General Procedure D, substituting (+/-)-β-citronellol for 1-nonanol. Isolated 1.07 g, 66%.

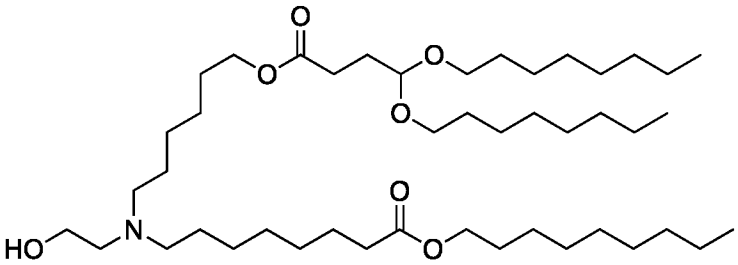


Step 2: 3,7-dimethyloct-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

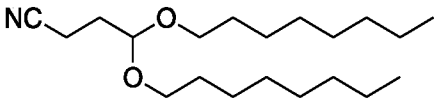
[0494] Prepared according to General Procedure E, substituting 3,7-dimethyloct-6-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 470 mg, 99%. UPLC-MS (Method A): Rt 2.40 min, m/z calculated [M+H]: 342.29, found 342.47.

Step 3: 3,7-dimethyloct-6-en-1-yl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-4)

[0495] Prepared according to General Procedure F, substituting 3,7-dimethyloct-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 40 mg, 24%. UPLC-MS (Method A): Rt 3.49 min, m/z calculated [M+H]: 764.63, found 764.70.

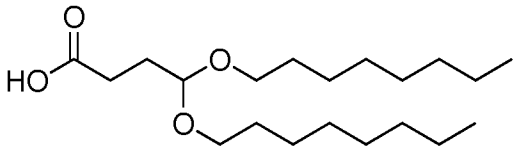


Example 7-5: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



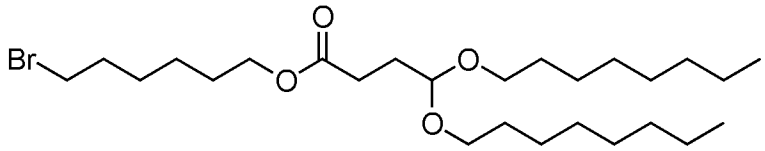
Step 1: 4,4-bis(octyloxy)butanenitrile

[0496] Prepared according to General Procedure A, substituting 1-octanol for cis-5-octen-1-ol. Isolated 1.45 g, 39%. ^{1}H NMR (400 MHz, CDCl3) δ 0.87 (d, *J* = 6.9 Hz, 6H), 1.21-1.30 (m, 20H), 1.53-1.58 (m, 4H), 1.90 (q, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.39-3.44 (m, 2H), 3.56-3.61 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H).



Step 2: 4,4-bis(octyloxy)butanoic acid

[0497] Prepared according to General Procedure B, substituting 4,4-bis(octyloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 1.8 g, 84%. ^{1}H NMR (400 MHz, DMSO-d6) δ 0.85 (d, *J* = 6.8 Hz, 6H), 1.21-1.30 (m, 20H), 1.43-1.48 (m, 4H), 1.69 (q, *J* = 6.8 Hz, 2H), 2.21 (t, *J* = 7.2 Hz, 2H), 3.35-3.39 (m, 2H), 3.44-3.50 (m, 2H), 4.44 (t, *J* = 5.5 Hz, 1H), 12.06 (bs, 1H).

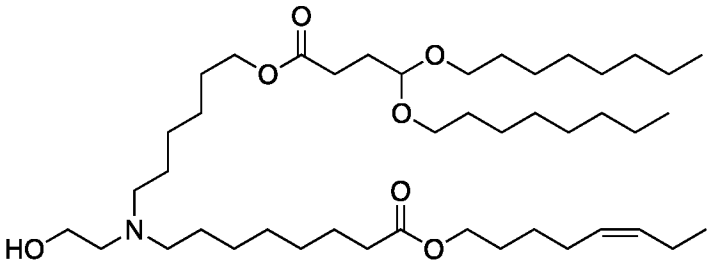


Step 3: 6-bromohexyl 4,4-bis(octyloxy)butanoate

[0498] Prepared according to General Procedure C, substituting 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 878 mg, 63%.

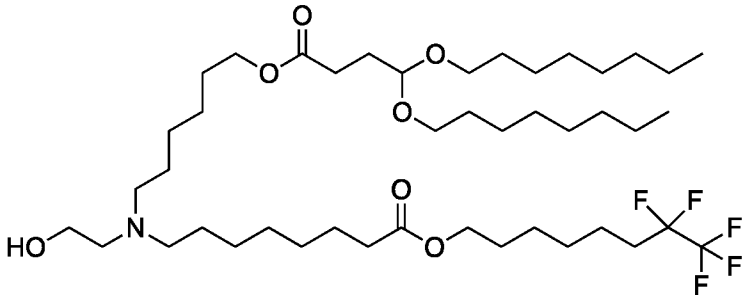
Step 4: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-5)

[0499] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Isolated 87 mg, 51%. UPLC-MS (Method A): Rt 3.83 min, m/z calculated [M+H]: 756.66, found 756.65.



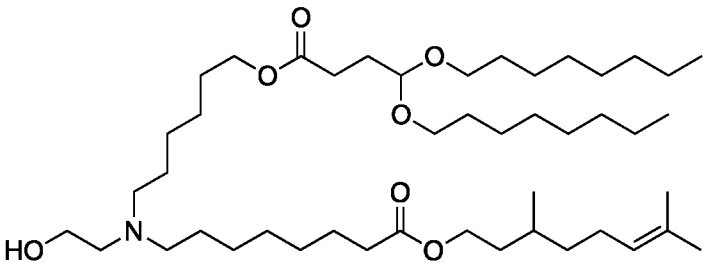
Example 7-6: (*Z*)-oct-5-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0500] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-oct-5-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 104 mg, 59%. UPLC-MS (Method A): Rt 3.65 min, m/z calculated [M+H]: 740.63, found 740.64.



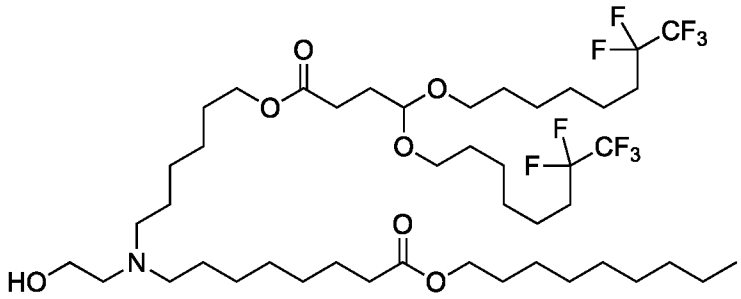
Example 7-7: 7,7,8,8,8-pentafluorooctyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0501] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 7,7,8,8,8-pentafluorooctyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 99 mg, 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (t, *J* = 5.6 Hz, 1H), 4.05 (td, *J* = 6.7, 4.2 Hz, 4H), 3.75 (m, 2H) 3.56 (dt, *J* = 9.3, 6.7 Hz, 2H), 3.40 (dt, *J* = 9.3, 6.7 Hz, 2H), 2.73 (m, 2H), 2.60 (m, 3H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 3H), 2.11 – 1.88 (m, 4H), 1.68 – 1.49 (m, 16H), 1.46 – 1.19 (m, 35H), 0.91 – 0.82 (m, 6H). UPLC-MS (Method A): Rt 3.51 min, m/z calculated [M+H]: 832.60, found 832.60.

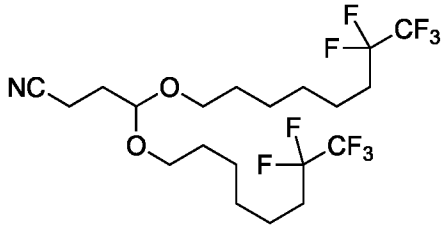


Example 7-8: 3,7-dimethyloct-6-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0502] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3,7-dimethyloct-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 102 mg, 60%. UPLC-MS (Method A): Rt 3.72 min, m/z calculated [M+H]: 768.66, found 768.72.

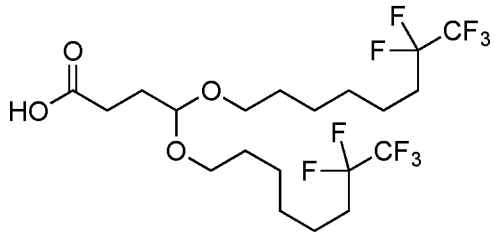


Example 7-9: nonyl 8-((6-((4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



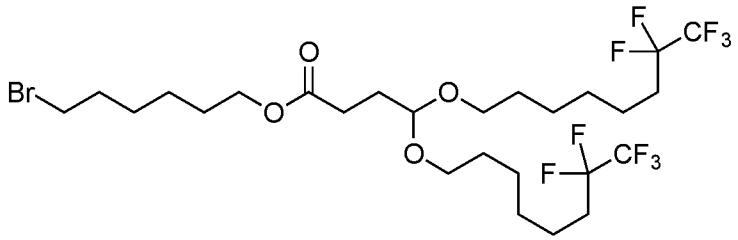
Step 1: 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanenitrile

[0503] Prepared according to General Procedure A, substituting 7,7,8,8,8-pentafluoro-1-octanol for cis-5-octen-1-ol. Isolated 4.74 g, 40%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.57 (t, *J* = 5.3 Hz, 1H), 3.61 (dt, *J* = 9.2, 6.5 Hz, 2H), 3.45 (dt, *J* = 9.3, 6.5 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.09 – 1.91 (m, 6H), 1.65 – 1.53 (m, 8H), 1.47 – 1.35 (m, 8H).



Step 2: 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoic acid

[0504] Prepared according to General Procedure B, substituting 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 1.6 g, 96%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.50 (t, *J* = 5.5 Hz, 1H), 3.57 (dt, *J* = 9.4, 6.6 Hz, 2H), 3.41 (dt, *J* = 9.4, 6.6 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.08 – 1.87 (m, 6H), 1.69 – 1.51 (m, 8H), 1.41 – 1.38 (m, *J* = 3.5 Hz, 8H).

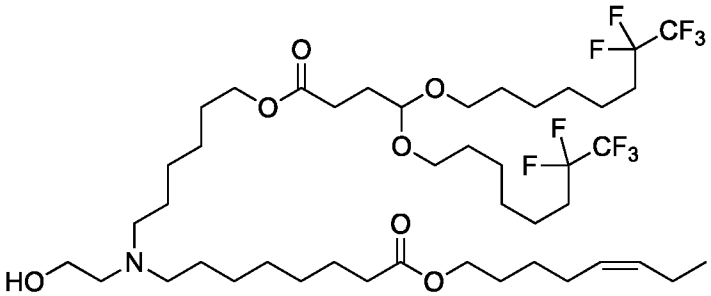


Step 3: 6-bromohexyl 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoate

[0505] Prepared according to General Procedure C, substituting 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 1.01 g, 53%.

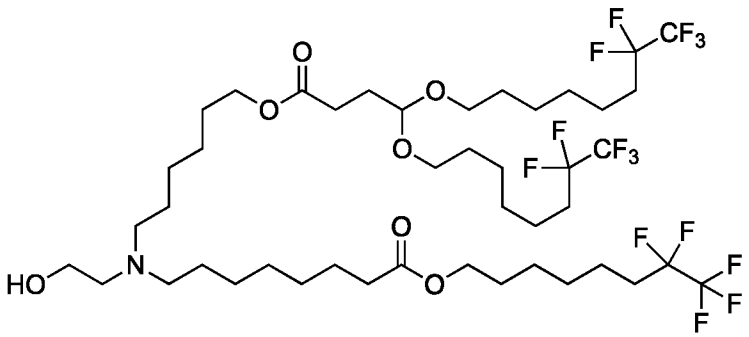
Step 4: nonyl 8-((6-((4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-9)

[0506] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Isolated 82 mg, 39%. UPLC-MS (Method A): Rt 3.57 min, m/z calculated [M+H]: 936.57, found 936.59.



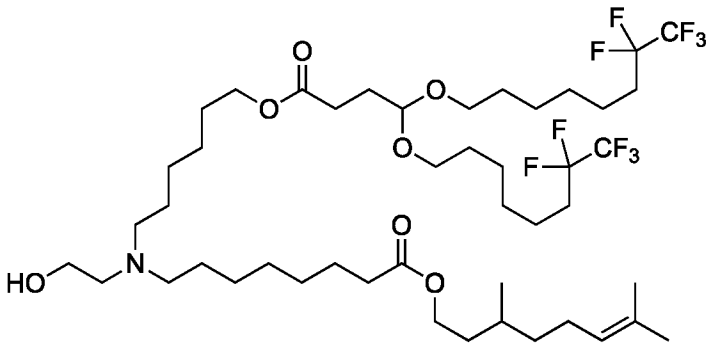
Example 7-10: (*Z*)-oct-5-en-1-yl 8-((6-((4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0507] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-oct-5-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 121 mg, 55%. UPLC-MS (Method A): Rt 3.42 min, m/z calculated [M+H]: 920.54, found 920.59.



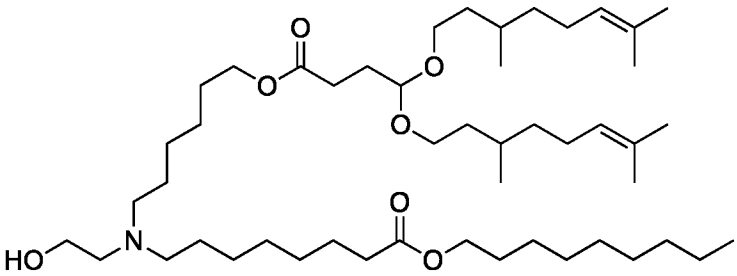
Example 7-11: 7,7,8,8,8-pentafluorooctyl 8-((6-((4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0508] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 7,7,8,8,8-pentafluorooctyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 131 mg, 70%. UPLC-MS (Method A): Rt 3.28 min, m/z calculated [M+H]: 1012.50, found 1012.57.

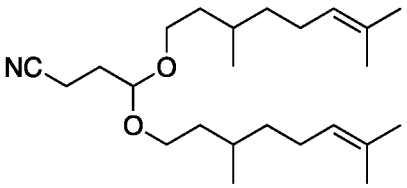


Example 7-12: 3,7-dimethyloct-6-en-1-yl 8-((6-((4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0509] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((7,7,8,8,8-pentafluorooctyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3,7-dimethyloct-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 144 mg, 69%. UPLC-MS (Method A): Rt 3.45 min, m/z calculated [M+H]: 948.57, found 948.67.

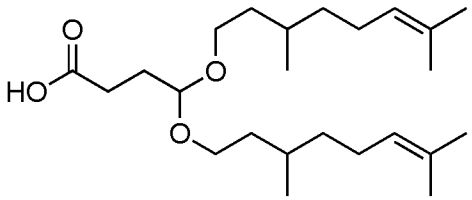


Example 7-13: nonyl 8-((6-((4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



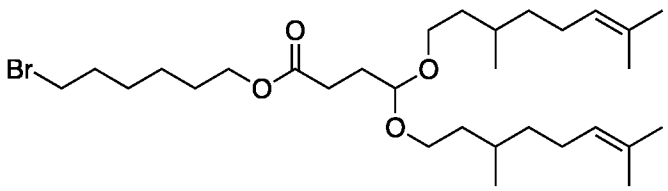
Step 1: 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanenitrile

[0510] Prepared according to General Procedure A, substituting (+/-)-β-citronellol for cis-5-octen-1-ol. Isolated 866 mg, 24%.



Step 2: 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoic acid

[0511] Prepared according to General Procedure B, substituting 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 880 mg, 97%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.09 (dddd, *J* = 7.1, 5.7, 2.9, 1.4 Hz, 2H), 4.51 (t, *J* = 5.5 Hz, 1H), 3.62 (dddd, *J* = 16.2, 14.0, 6.9, 1.5 Hz, 2H), 3.45 (ddt, *J* = 16.7, 9.2, 6.7 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.06 – 1.89 (m, 6H), 1.68 (d, *J* = 1.4 Hz, 6H), 1.66 – 1.52 (m, 8H), 1.42 – 1.29 (m, 5H), 1.16 (dddd, *J* = 13.4, 9.8, 7.8, 5.8 Hz, 3H), 0.89 (dd, *J* = 6.6, 1.7 Hz, 6H).

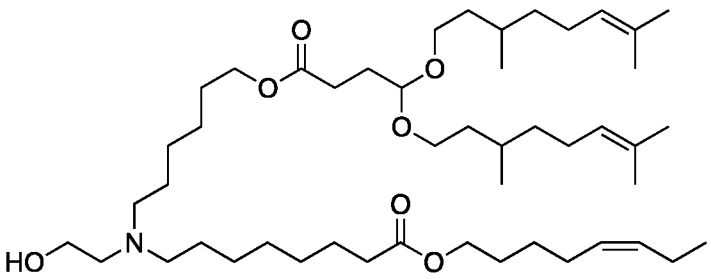


Step 3: 6-bromohexyl 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoate

[0512] Prepared according to General Procedure C, substituting 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 596 mg, 66%.

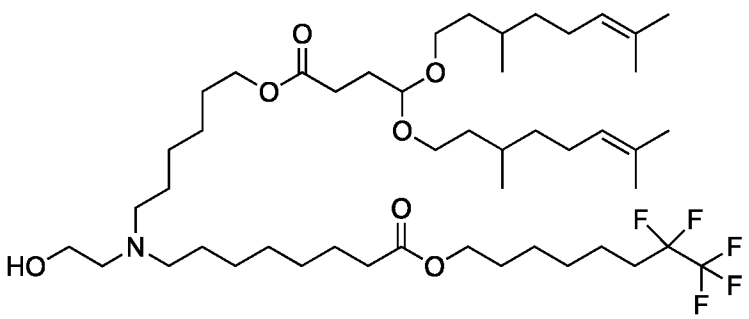
Step 4: nonyl 8-((6-((4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-13)

[0513] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Isolated 65 mg, 45%. UPLC-MS (Method A): Rt 3.73 min, m/z calculated [M+H]: 808.70, found 808.80.



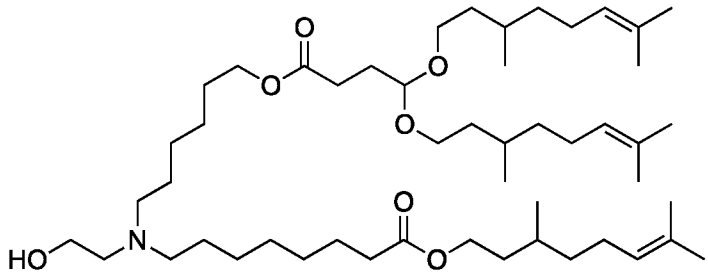
Example 7-14: (*Z*)-oct-5-en-1-yl 8-((6-((4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0514] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-oct-5-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 57 mg, 40%. UPLC-MS (Method A): Rt 3.54 min, m/z calculated [M+H]: 792.66, found 792.70.



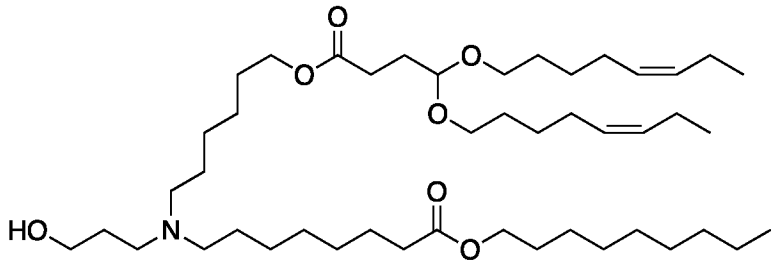
Example 7-15: 7,7,8,8,8-pentafluorooctyl 8-((6-((4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0515] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 7,7,8,8,8-pentafluorooctyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 95 mg, 60%. UPLC-MS (Method A): Rt 3.51 min, m/z calculated [M+H]: 884.63, found 884.79.

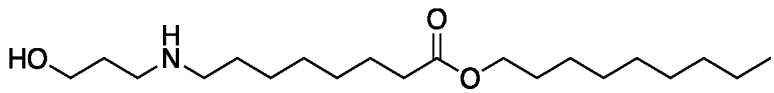


Example 7-16: 3,7-dimethyloct-6-en-1-yl 8-((6-((4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0516] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((3,7-dimethyloct-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3,7-dimethyloct-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 128 mg, 71%. UPLC-MS (Method A): Rt 3.75 min, m/z calculated [M+H]: 820.70, found 820.75.



Example 7-17: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

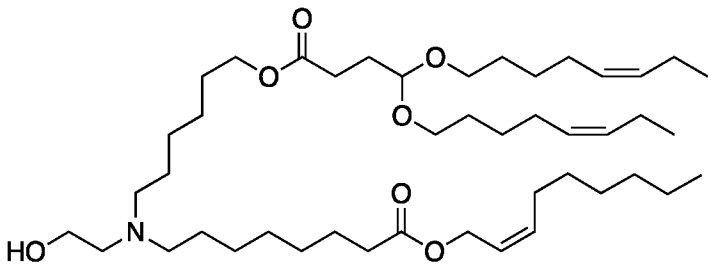


Step 1: nonyl 8-((3-hydroxypropyl)amino)octanoate

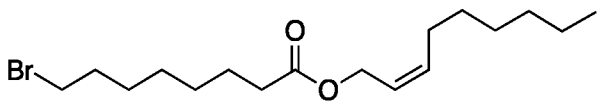
[0517] Prepared according to General Procedure E, substituting 3-aminopropan-1-ol for ethanolamine. Isolated 218 mg, 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 6.7 Hz, 3H), 1.17 – 1.42 (m, 22H), 1.45 – 1.60 (m, 6H), 2.26 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.54 (d, J = 6.9 Hz, 2H), 3.44 (t, J = 6.2 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H).

Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate (Example 7-17)

[0518] Prepared according to General Procedure F, substituting nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 75 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-d) δ 0.87 (t, J = 6.7 Hz, 3H), 0.94 (t, J = 7.5 Hz, 6H), 1.20 – 1.46 (m, 33H), 1.54 – 1.70 (m, 6H), 1.75 – 1.87 (m, 4H), 1.86 – 1.96 (m, 2H), 1.96 – 2.10 (m, 8H), 2.29 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.6 Hz, 2H), 3.06 (s, 4H), 3.22 (s, 2H), 3.35 – 3.45 (m, 2H), 3.52 – 3.65 (m, 2H), 3.85 (t, J = 5.4 Hz, 2H), 4.00 – 4.09 (m, 4H), 4.48 (t, J = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 1.99 min, m/z calculated [M+H]: 767.2, found 767.4.

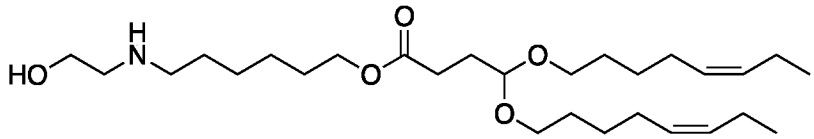


Example 7-18: (*Z*)-non-2-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-non-2-en-1-yl 8-bromooctanoate

[0519] Prepared according to General Procedure D, substituting (*Z*)-non-2-en-1-ol for (*Z*)-oct-5-en-1-ol. Isolated 140 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-d) δ 0.87 (t, J = 6.8 Hz, 3H), 1.17 – 1.38 (m, 5H), 1.36 – 1.47 (m, 2H), 1.52 – 1.68 (m, 2H), 1.73 (dd, J = 4.3, 9.1 Hz, 3H), 1.79 – 1.95 (m, 5H), 2.09 (q, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 3.11 – 3.28 (m, 1H), 3.39 (t, J = 6.8 Hz, 2H), 4.61 (d, J = 6.8 Hz, 2H), 5.46 – 5.56 (m, 1H), 5.58 – 5.69 (m, 1H).

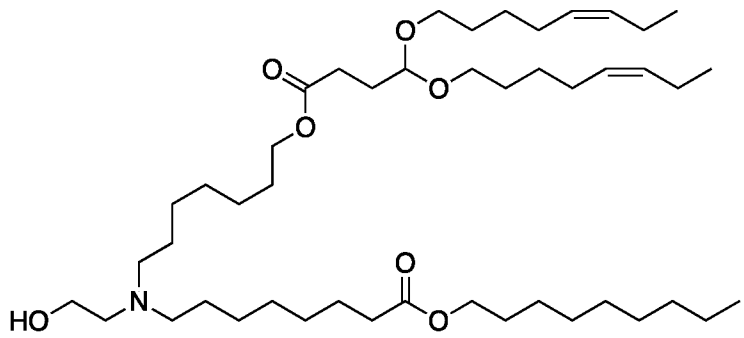


Step 2: 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

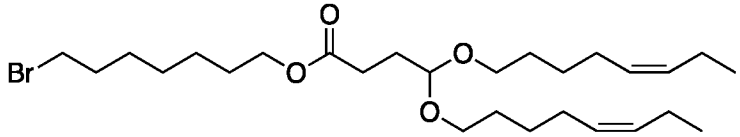
[0520] Prepared according to General Procedure E, substituting 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 2.1 g, 83%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.32 – 1.44 (m, 8H), 1.46 – 1.66 (m, 10H), 1.88 – 1.95 (m, 2H), 1.97 – 2.08 (m, 8H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.76 – 2.79 (m, 2H), 3.35 – 3.45 (m, 2H), 3.52 – 3.60 (m, 2H), 3.60 – 3.67 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).

Step 3: (Z)-non-2-en-1-yl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-18)

[0521] Prepared according to General Procedure F, substituting (Z)-non-2-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 33 mg, 28%. UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 750.62, found 750.86.



Example 7-19: nonyl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

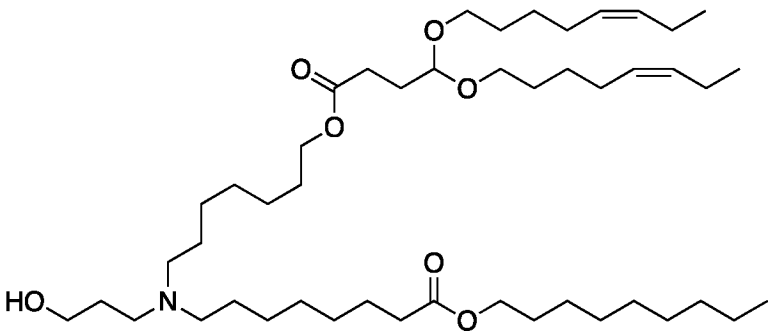


Step 1: 7-bromoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0522] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol. Isolated 203 mg, 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 – 5.27 (m, 4H), 4.56 (t, *J* = 5.3 Hz, 1H), 3.61 (dt, *J* = 9.3, 6.6 Hz, 2H), 3.44 (dt, *J* = 9.3, 6.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.91 (m, 9H), 1.66 – 1.54 (m, 5H), 1.49 – 1.36 (m, 4H), 0.96 (t, *J* = 7.6 Hz, 6H).

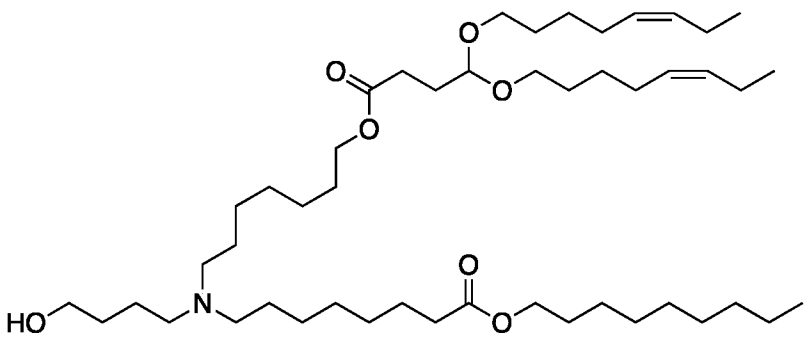
Step 2: nonyl 8-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate (Example 7-19)

[0523] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Isolated 66 mg, 63%. UPLC-MS (Method A): Rt 3.54 min, m/z calculated [M+H]: 766.65, found 766.71.

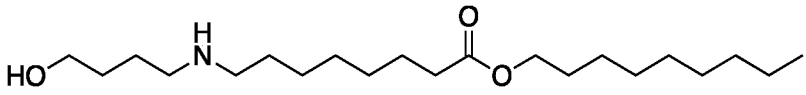


Example 7-20: nonyl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

[0524] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 69 mg, 65%. UPLC-MS (Method A): Rt 3.52 min, m/z calculated [M+H]: 780.66, found 780.71.



Example 7-21: nonyl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(4-hydroxybutyl)amino)octanoate

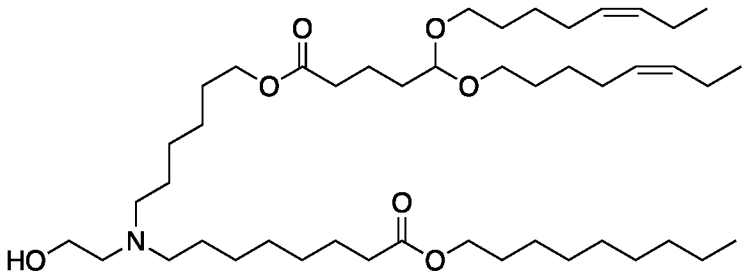


Step 1: nonyl 8-((4-hydroxybutyl)amino)octanoate

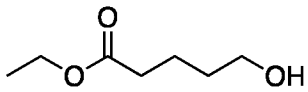
[0525] Prepared according to General Procedure E, substituting 4-aminobutan-1-ol for ethanolamine. Isolated 123 mg, 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 6.5 Hz, 3H), 1.17 – 1.33 (m, 20H), 1.32 – 1.47 (m, 8H), 1.46 – 1.59 (m, 4H), 2.26 (t, J = 7.2 Hz, 2H), 2.43 – 2.48 (m, 2H), 3.33 – 3.44 (m, 2H), 3.99 (t, J = 6.5 Hz, 2H).

Step 2: nonyl 8-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(4-hydroxybutyl)amino)octanoate (Example 7-21)

[0526] Prepared according to General Procedure F, substituting nonyl 8-((4-hydroxybutyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 71 mg, 71%. UPLC-MS (Method A): Rt 3.51 min, m/z calculated [M+H]: 794.68, found 794.80.



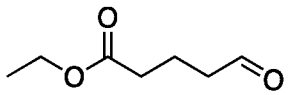
Example 7-22: nonyl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: ethyl 5-hydroxypentanoate

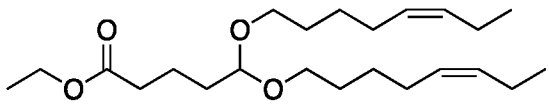
[0527] To a stirred solution of tetrahydro-2*H*-pyran-2-one (1 g, 10 mmol) in ethanol (15 mL) was added NaOH (0.44 g,11 mmol). The reaction mixture was heated at 80 °C for 30 min, then allowed to cool to 25 °C for 2 h. Excess solvent was then removed under reduced pressure. The crude material was diluted with DMF (20 mL), and to it was added ethyl iodide (1.4 mL, 17.2 mmol) drop wise and allowed to stir at 25 °C for 16 h. Upon completion, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (2 x 15 mL). The organic layer was dried over

anhydrous Na_2SO_4 and then concentrated under reduced pressure to afford ethyl 5-hydroxypentanoate (820 mg, 59%) as yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.56 – 1.74 (m, 5H), 2.31 – 2.35 (t, 7.2 Hz 3H), 3.64 (t, *J* = 6.3 Hz, 2H), 4.09-4.14 (q, *J* = 7.2 Hz, 2H).



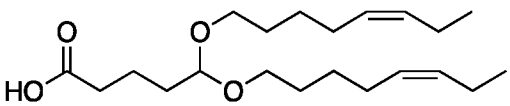
Step 2: ethyl 5-oxopentanoate

[0528] Pyridinium chlorochromate (1.1 g, 5.13 mmol) was suspended in dry DCM (10 mL) at 25 °C. Then a solution of ethyl 5-hydroxypentanoate (500 mg, 3.42 mmol) in DCM (5 mL) was added to the reaction mixture, and the resulting mixture was stirred at 25 °C for 2 h. After this time, diethyl ether (15 mL) was added, and the dark reaction mixture was allowed to stand for 2 h. The solid was filtered off and washed with ethyl ether (2 x 20 mL). The combined solvents were removed, and the residue was purified by combiflash chromatography, eluted with 5% EtOAc-hexane to afford ethyl 5-oxopentanoate (300 mg, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.90 – 2.01 (m, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.47 – 2.56 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 9.77 (s, 1H).



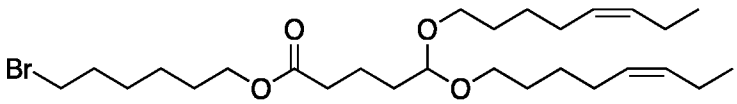
Step 3: ethyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

[0529] Sodium sulfate (591 mg, 4.16 mmol) was taken into a flame-dried two-neck 100 mL round-bottom flash under vacuum for 15 minutes. Then a solution of ethyl 5-oxopentanoate (200 mg, 1.38 mmol) in DCM (5.0 mL) was added at 25 °C followed by cis-5-octenol (0.63 mL, 4.16 mmol) and $KHSO_4$ (57 mg, 0.42 mmol). The resulting mixture was stirred for 12 h. Upon completion, solid was separated by filtration and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash chromatography, eluted with 5% EtOAc-hexane to afford ethyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate (320 mg, 60%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.47 (m, 4H), 1.49 – 1.74 (m, 8H), 1.90 – 2.09 (m, 8H), 2.31 (t, *J* = 7.0 Hz, 2H), 3.34 – 3.44 (m, 2H), 3.50 – 3.68 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 5.24 – 5.43 (m, 4H).



Step 4: 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoic acid

[0530] To a stirred solution of ethyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate (700 mg, 1.83 mmol) in THF (6 mL), and added NaOH (147 mg, 3.66 mmol) was dissolved in water (2 mL). The reaction mixture was stirred at 25 °C for 6 h. Upon completion, was added water (15 mL) and acidified with saturated citric acid solution (30 mL) and extracted with DCM (3x25 mL), washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoic acid (630 mg, 97%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 6H), 1.29 – 1.41 (m, 4H), 1.42 – 1.54 (m, 8H), 1.92 – 2.07 (m, 8H), 2.15 – 2.26 (m, 2H), 3.29 – 3.40 (m, 2H), 3.43 – 3.54 (m, 2H), 4.43 (s, 1H), 5.23 – 5.40 (m, 4H), 11.96 (s, 1H).

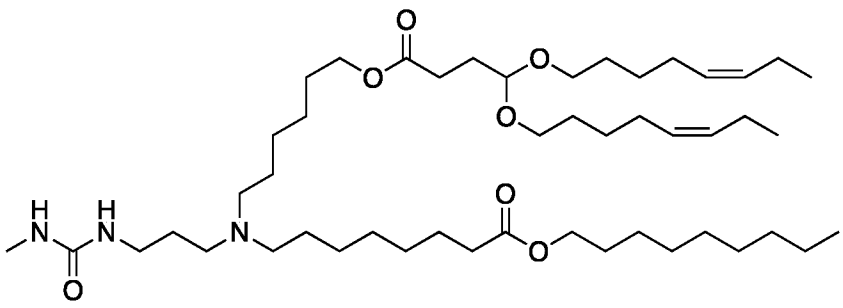


Step 5: 6-bromohexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

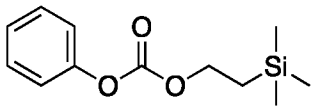
[0531] Prepared according to General Procedure C, substituting 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 110 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, J = 7.3 Hz, 6H), 1.24 (t, J = 6.8 Hz, 1H), 1.31 – 1.50 (m, 11H), 1.58 – 1.75 (m, 6H), 1.79 – 1.93 (m, 2H), 1.93 – 2.14 (m, 8H), 2.31 (d, J = 8.2 Hz, 2H), 3.40 (dd, J = 5.2, 8.2 Hz, 4H), 3.55 (dd, J = 6.9, 9.9 Hz, 2H), 4.05 (t, J = 6.5 Hz, 2H), 4.35 – 4.54 (m, 1H), 5.15 – 5.53 (m, 4H).

Step 6: nonyl 8-((6-((5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-22)

[0532] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 43 mg, 43%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 752.7, found 752.9.

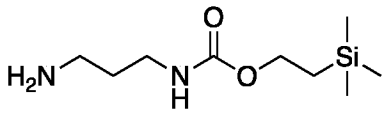


Example 7-23: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate



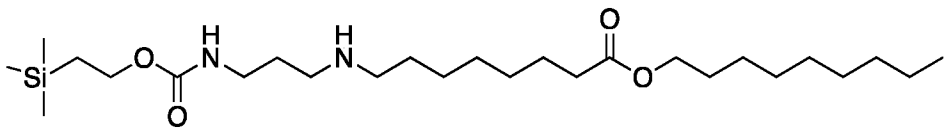
Step 1: phenyl (2-(trimethylsilyl)ethyl) carbonate

[0533] To a solution of 2-(trimethylsilyl)ethan-1-ol (500 mg, 4.23 mmol) in DCM (10 mL) was added pyridine (0.5 mL, 5.50 mmol) at 25 °C. A condenser was fitted and phenyl chloroformate (0.5 mL, 4.23 mmol) was added to the reaction mixture over 20 min. After stirring at 25 °C for 2 h, the reaction mixture was diluted with water (20 mL) and extracted with DCM (30 mL × 2). The organic layer was separated, washed with 2N H_2SO_4 (20 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated to afford phenyl (2-(trimethylsilyl)ethyl) carbonate (910 mg, 90%) as a colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.06 (s, 9H), 1.13 (t, *J* = 8.7 Hz, 2H), 4.29 – 4.38 (m, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.18 – 7.26 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 2H).



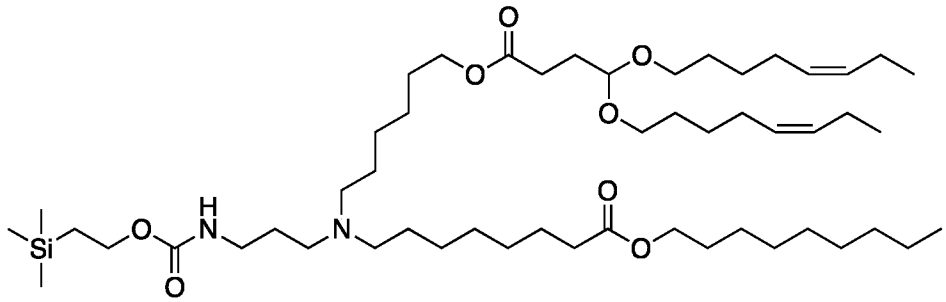
Step 2: 2-(trimethylsilyl)ethyl (3-aminopropyl)carbamate

[0534] Phenyl (2-(trimethylsilyl)ethyl) carbonate (200.0 mg, 0.84 mmol) was added to a stirring solution of 1,3-propanediamine (0.07 mL, 0.84 mmol) in absolute ethanol (3.0 mL) at 25 °C. After stirring for 12h, ethanol was evaporated and the reaction mixture was diluted with water (10 mL × 2). Then the pH of the solution was adjusted to 2-3 with 2N HCl and the aqueous phase was extracted with DCM (20 mL × 2). The organic layer was separated and the aqueous phase was made with 2N NaOH solution. The aqueous phase was extracted with DCM (20 mL × 2). The organic layer was washed with 2N aqueous NaOH, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afforded 2-(trimethylsilyl)ethyl (3-aminopropyl)carbamate (170 mg, 93%) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.02 (s, 9H), 0.95 (d, *J* = 8170/218/15.9 Hz, 2H), 1.58 – 1.72 (m, 2H), 1.80 – 1.96 (m, 2H), 2.80 (t, *J* = 6.3 Hz, 2H), 3.16 – 3.34 (m, 2H), 4.14 (d, *J* = 8.6 Hz, 2H), 5.08 (s, 1H).



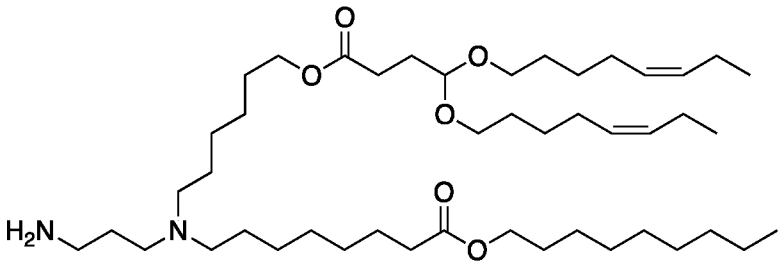
Step 3: nonyl 2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate

[0535] To a stirred solution of 2-(trimethylsilyl)ethyl (3-aminopropyl)carbamate (50 mg, 0.3 mmol) in DMF (1.0 mL), TEA (0.07 mL, 0.458 mmol) and nonyl 8-bromooctanoate (40.0 mg, 0.115 mmol) were added to the solution. The solution was stirred for 16 h at 25 °C. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL × 2). The organic layer was washed with ice water (20 mL). Next, organic part was dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure. The organic residue was purified by combiflash column chromatography (eluted by 0-5% MeOH/DCM) to afford nonyl 2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate (30 mg, 25%) as a yellow liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.03 (s, 9H), 0.86 (d, *J* = 8.3 Hz, 3H), 0.96 (s, 2H), 1.23 – 1.34 (m, 18H), 1.55 – 1.66 (m, 6H), 1.85 (s, 2H), 2.27 (t, *J* = 7.9 Hz, 2H), 2.75 (s, 2H), 2.85 (s, 2H), 3.28 (s, 2H), 4.04 (t, *J* = 7.3 Hz, 2H), 4.13 (s, 2H), 5.41 (s, 1H), 8.55 (s, 1H).



Step 4: nonyl 11-(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)-2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate

[0536] Prepared according to General Procedure F, substituting 2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 250 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.02 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 4H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.17 – 1.45 (m, 28H), 1.45 – 1.69 (m, 20H), 1.91 (d, *J* = 7.1 Hz, 2H), 1.96 – 2.08 (m, 8H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.27 (s, 2H), 3.40 (d, *J* = 8.5 Hz, 2H), 3.56 (d, *J* = 7.9 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 4H), 4.11 (d, *J* = 7.4 Hz, 4H), 4.44 – 4.52 (m, 1H), 5.23 – 5.45 (m, 4H).

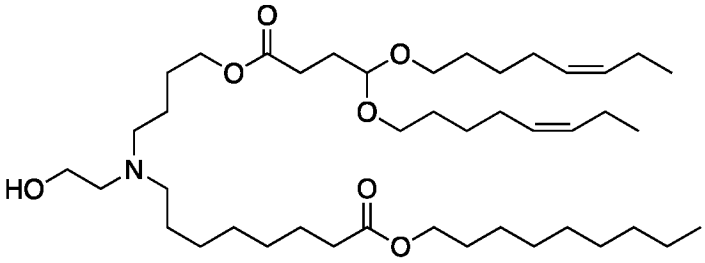


Step 5: nonyl 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate

[0537] A stirred solution of nonyl 11-(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)-2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate (1.0 eqv) in tetrabutylammonium fluoride (1M in THF, 4.0 eqv) was heated at 45 °C for 2 h. After this time, the reaction mixture was concentrated under reduced pressure. Pentane (20 mL) and water (10 mL) were added and stirred vigorously at 25 °C for 15 min. The organic layer was separated and washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford nonyl 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate, which was used in the next step without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.91 (m, 3H), 0.94 (t, *J* = 7.4 Hz, 5H), 1.01 (t, *J* = 7.3 Hz, 5H), 1.21 – 1.37 (m, 20H), 1.35 – 1.53 (m, 6H), 1.52 – 1.73 (m, 12H), 1.86 – 1.97 (m, 2H), 2.03 (d, *J* = 6.7 Hz, 9H), 2.22 – 2.42 (m, 4H), 2.44 – 2.77 (m, 4H), 2.79 – 2.96 (m, 1H), 3.30 – 3.44 (m, 6H), 3.50 – 3.62 (m, 2H), 4.04 (t, *J* = 6.6 Hz, 4H), 4.48 (s, 1H), 5.19 – 5.52 (m, 4H).

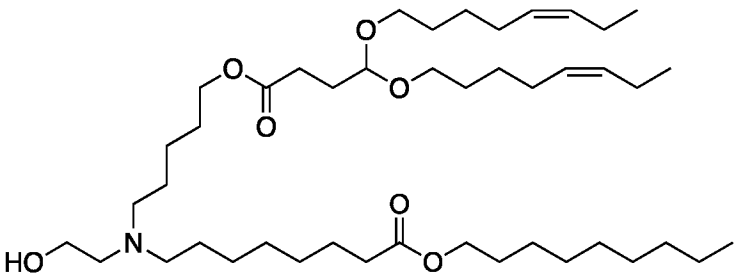
Step 6: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate (Example 7-23)

[0538] To a stirred solution of 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate (41 mg, 0.053 mmol, 1.0 eqv) in DCM (2.0 mL), methylcarbamic chloride (5 mg, 0.053 mmol, 1.0 eqv), TEA (11 mg, 0.11 mmol, 2.0 eqv) and DMAP (11 mg, 0.01 mmol, 0.2 eqv) were added to the solution. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate (21 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (d, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.47 (m, 23H), 1.50 – 1.79 (m, 14H), 1.81 – 2.13 (m, 14H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.74 (d, *J* = 4.6 Hz, 3H), 2.84 – 3.09 (m, 6H), 3.32 (s, 2H), 3.40 (q, *J* = 7.4 Hz, 2H), 3.51 – 3.61 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 4H), 4.48 (t, *J* = 5.5 Hz, 1H), 5.25-5.40 (m, 4H), 5.62 (s, 1H), 6.70 (s, 1H). UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 822.7, found 823.9.



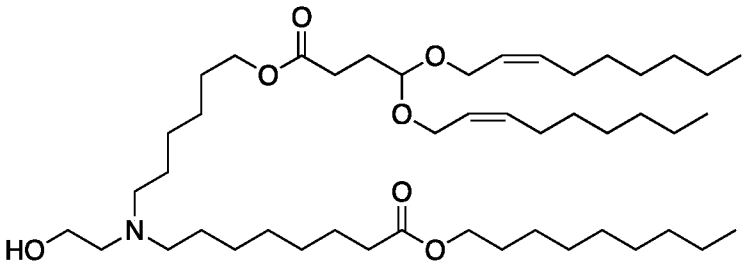
Example 7-24: nonyl 8-((4-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate

[0539] Prepared according to General Procedure F, substituting 4-bromobutyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 36 mg, 55%. UPLC-MS (Method C): Rt 5.04 min, m/z calculated [M+H]: 724.6, found 724.8.

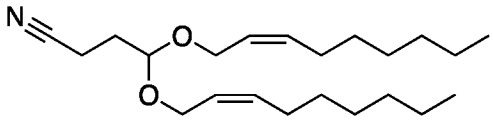


Example 7-25: nonyl 8-((5-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate

[0540] Prepared according to General Procedure F, substituting 5-bromopentyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 33 mg, 72%. UPLC-MS (Method B): Rt 2.03 min, m/z calculated [M+H]: 738.6, found 738.8.

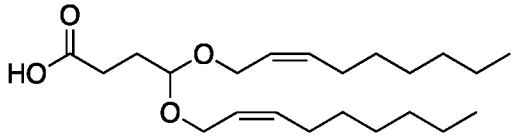


Example 7-26: nonyl 8-((6-((4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



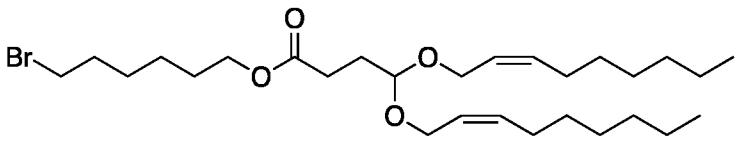
Step 1: 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanenitrile

[0541] Prepared according to General Procedure A, substituting (*Z*)-non-2-en-1-ol for cis-5-octen-1-ol. Isolated 470 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.20 – 1.41 (m, 12H), 1.89 – 1.99 (m, 2H), 2.03 (q, *J* = 6.9 Hz, 4H), 2.32 (q, *J* = 5.9, 6.5 Hz, 4H), 2.41 (t, *J* = 7.4 Hz, 2H), 3.39 – 3.50 (m, 2H), 3.56 – 3.66 (m, 2H), 4.58 (t, *J* = 5.3 Hz, 1H), 5.29 – 5.42 (m, 2H), 5.41 – 5.53 (m, 2H).



Step 2: 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoic acid

[0542] Prepared according to General Procedure B, substituting 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 410 mg, 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 6.7 Hz, 6H), 1.19 – 1.37 (m, 12H), 1.67 – 1.78 (m, 2H), 2.00 (q, *J* = 6.9 Hz, 4H), 2.17 – 2.27 (m, 6H), 3.31 – 3.42 (m, 2H), 3.44 – 3.54 (m, 2H), 4.49 (t, *J* = 5.6 Hz, 1H), 5.30 – 5.47 (m, 4H), 12.07 (s, 1H).

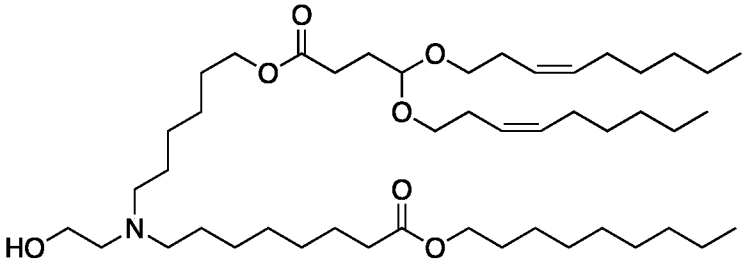


Step 3: 6-bromohexyl 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoate

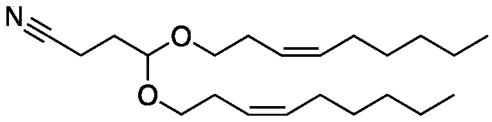
[0543] Prepared according to General Procedure C, substituting 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 230 mg, 64%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.21 – 1.43 (m, 14H), 1.40 – 1.51 (m, 2H), 1.63 (p, *J* = 6.9 Hz, 2H), 1.81 – 1.90 (m, 2H), 1.87 – 1.97 (m, 2H), 2.02 (q, *J* = 7.1 Hz, 4H), 2.30 (q, *J* = 7.0 Hz, 4H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.35 – 3.47 (m, 4H), 3.52 – 3.63 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 4.52 (t, *J* = 5.6 Hz, 1H), 5.29 – 5.51 (m, 4H).

Step 4: nonyl 8-((6-((4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-26)

[0544] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 28 mg, 25%. UPLC-MS (Method B): Rt 2.15 min, m/z calculated [M+H]: 780.7, found 781.1.

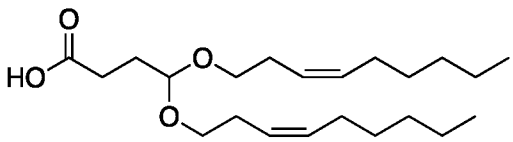


Example 7-27: nonyl 8-((6-((4,4-bis(((*Z*)-non-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



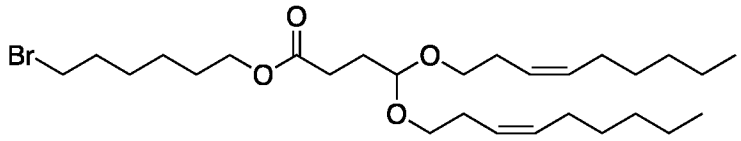
Step 1: 4,4-bis(((Z)-non-3-en-1-yl)oxy)butanenitrile

[0545] Prepared according to General Procedure A, substituting (*Z*)-non-3-en-1-ol for cis-5-octen-1-ol. Isolated 495 mg, 46%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.20 – 1.40 (m, 12H), 1.90 – 1.97 (m, 2H), 2.03 (q, *J* = 7.1 Hz, 4H), 2.32 (q, *J* = 7.0 Hz, 4H), 2.41 (t, *J* = 7.4 Hz, 2H), 3.39 – 3.50 (m, 2H), 3.56 – 3.66 (m, 2H), 4.57 (t, *J* = 5.3 Hz, 1H), 5.29 – 5.40 (m, 2H), 5.41 – 5.53 (m, 2H).



Step 2: 4,4-bis(((Z)-non-3-en-1-yl)oxy)butanoic acid

[0546] Prepared according to General Procedure B, substituting 4,4-bis(((*Z*)-non-3-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 450 mg, 86%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.86 (t, *J* = 6.7 Hz, 6H), 1.18 – 1.37 (m, 12H), 1.73 (q, *J* = 7.5 Hz, 2H), 2.00 (q, *J* = 6.9 Hz, 4H), 2.17 – 2.27 (m, 6H), 3.27 – 3.42 (m, 2H), 3.44 – 3.54 (m, 2H), 4.49 (t, *J* = 5.6 Hz, 1H), 5.30 – 5.47 (m, 4H), 12.04 (s, 1H).

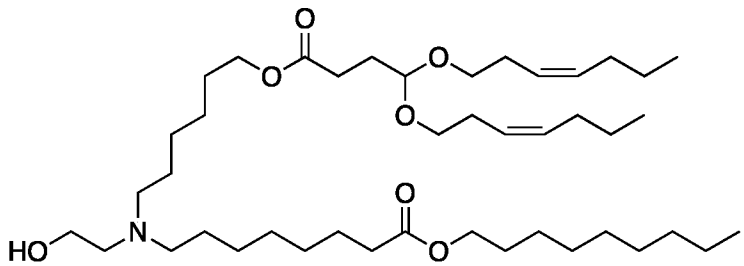


Step 3: 6-bromohexyl 4,4-bis(((Z)-non-3-en-1-yl)oxy)butanoate

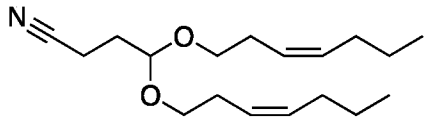
[0547] Prepared according to General Procedure C, substituting 4,4-bis(((*Z*)-non-3-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 210 mg, 58%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.85 (t, *J* = 6.8 Hz, 6H), 1.18 – 1.46 (m, 16H), 1.50 – 1.62 (m, 2H), 1.71 – 1.83 (m, 4H), 2.00 (q, *J* = 7.0 Hz, 4H), 2.22 (q, *J* = 6.8 Hz, 4H), 2.30 (t, *J* = 7.4 Hz, 2H), 3.26 – 3.41 (m, 2H), 3.44 – 3.56 (m, 4H), 3.99 (t, *J* = 6.6 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.29 – 5.47 (m, 4H).

Step 4: nonyl 8-((6-((4,4-bis(((Z)-non-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-27)

[0548] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-3-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 34 mg, 29%. UPLC-MS (Method B): Rt 2.15 min, m/z calculated [M+H]: 780.7, found 781.1.

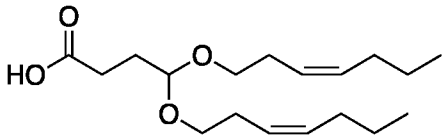


Example 7-28: nonyl 8-((6-((4,4-bis(((*Z*)-non-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



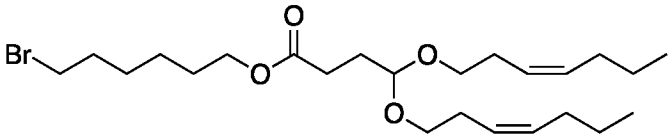
Step 1: 4,4-bis(((Z)-hept-3-en-1-yl)oxy)butanenitrile

[0549] Prepared according to General Procedure A, substituting (*Z*)-hept-3-en-1-ol for cis-5-octen-1-ol. Isolated 460 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.4 Hz, 6H), 1.30 – 1.44 (m, 4H), 1.88 – 1.98 (m, 2H), 2.01 (q, *J* = 7.3 Hz, 4H), 2.32 (q, *J* = 7.0 Hz, 4H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.39 – 3.50 (m, 2H), 3.56 – 3.66 (m, 2H), 4.58 (t, *J* = 5.3 Hz, 1H), 5.31 – 5.42 (m, 2H), 5.42 – 5.54 (m, 2H).



Step 2: 4,4-bis(((Z)-hept-3-en-1-yl)oxy)butanoic acid

[0550] Prepared according to General Procedure B, substituting 4,4-bis(((*Z*)-hept-3-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 440 mg, 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 7.4 Hz, 6H), 1.26 – 1.40 (m, 4H), 1.72 (q, *J* = 7.2 Hz, 2H), 1.99 (q, *J* = 7.0 Hz, 4H), 2.18 – 2.28 (m, 6H), 3.26 – 3.42 (m, 2H), 3.44 – 3.55 (m, 2H), 4.49 (t, *J* = 5.7 Hz, 1H), 5.31 – 5.47 (m, 4H), 12.05 (s, 1H).

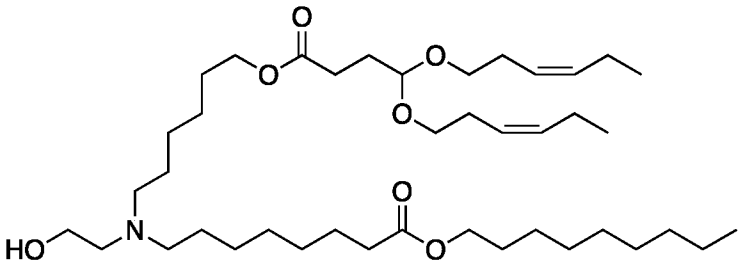


Step 3: 6-bromohexyl 4,4-bis(((Z)-hept-3-en-1-yl)oxy)butanoate

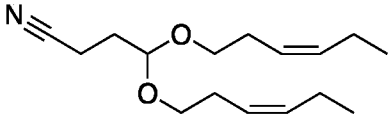
[0551] Prepared according to General Procedure C, substituting 4,4-bis(((*Z*)-hept-3-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 200 mg, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.4 Hz, 6H), 1.29 – 1.50 (m, 8H), 1.63 (p, *J* = 6.7 Hz, 2H), 1.85 (q, *J* = 7.0 Hz, 2H), 1.92 (q, *J* = 7.3 Hz, 2H), 2.01 (q, *J* = 7.2 Hz, 4H), 2.31 (q, *J* = 6.8 Hz, 4H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.35 – 3.47 (m, 4H), 3.52 – 3.63 (m, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 4.52 (t, *J* = 5.6 Hz, 1H), 5.23 – 5.52 (m, 4H).

Step 4: nonyl 8-((6-((4,4-bis(((Z)-hept-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-28)

[0552] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*Z*)-hept-3-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 28 mg, 27%. UPLC-MS (Method B): Rt 1.83 min, m/z calculated [M+H]: 724.6, found 724.9.

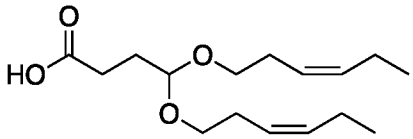


Example 7-29: nonyl 8-((6-((4,4-bis(((*Z*)-hex-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



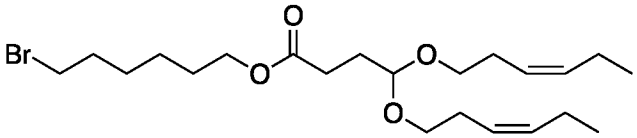
Step 1: 4,4-bis(((Z)-hex-3-en-1-yl)oxy)butanenitrile

[0553] Prepared according to General Procedure A, substituting (*Z*)-hex-3-en-1-ol for cis-5-octen-1-ol. Isolated 320 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.5 Hz, 6H), 1.88 – 1.98 (m, 2H), 1.98 – 2.11 (m, 4H), 2.31 (q, *J* = 6.8 Hz, 4H), 2.41 (t, *J* = 7.4 Hz, 2H), 3.39 – 3.50 (m, 2H), 3.56 – 3.67 (m, 2H), 4.57 (t, *J* = 5.3 Hz, 1H), 5.26 – 5.38 (m, 2H), 5.41 – 5.54 (m, 2H).



Step 2: 4,4-bis(((Z)-hex-3-en-1-yl)oxy)butanoic acid

[0554] Prepared according to General Procedure B, substituting 4,4-bis(((*Z*)-hex-3-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 310 mg, 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, *J* = 7.5 Hz, 6H), 1.73 (q, *J* = 7.2 Hz, 2H), 1.95 – 2.08 (m, 4H), 2.17 – 2.28 (m, 6H), 3.32 – 3.42 (m, 2H), 3.45 – 3.55 (m, 2H), 4.49 (t, *J* = 5.6 Hz, 1H), 5.27 – 5.38 (m, 2H), 5.36 – 5.48 (m, 2H), 12.05 (s, 1H).

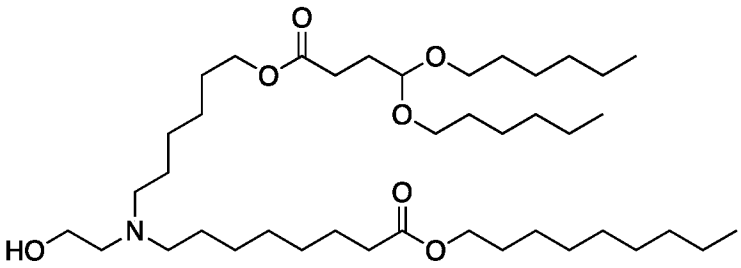


Step 3: 6-bromohexyl 4,4-bis(((Z)-hex-3-en-1-yl)oxy)butanoate

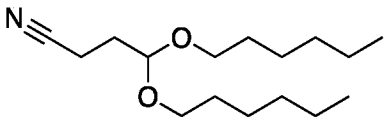
[0555] Prepared according to General Procedure C, substituting 4,4-bis(((*Z*)-hex-3-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 210 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.5 Hz, 6H), 1.32 – 1.51 (m, 4H), 1.62 (q, *J* = 7.1 Hz, 2H), 1.80 – 1.97 (m, 4H), 1.98 – 2.11 (m, 4H), 2.30 (q, *J* = 6.8 Hz, 4H), 2.38 (t, *J* = 7.6 Hz, 2H), 3.35 – 3.47 (m, 4H), 3.52-3.63 (m, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 4.52 (t, *J* = 5.6 Hz, 1H), 5.27 – 5.39 (m, 2H), 5.41 – 5.50 (m, 2H).

Step 4: nonyl 8-((6-((4,4-bis(((Z)-hex-3-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-29)

[0556] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*Z*)-hex-3-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 44 mg, 42%. UPLC-MS (Method B): Rt 1.72 min, m/z calculated [M+H]: 696.6, found 696.9.

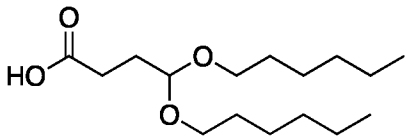


Example 7-30: nonyl 8-((6-((4,4-bis(hexyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



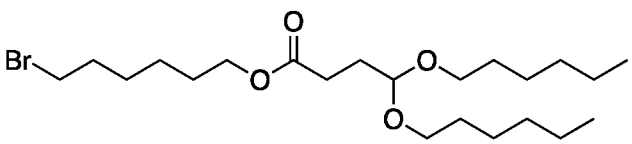
Step 1: 4,4-bis(hexyloxy)butanenitrile

[0557] Prepared according to General Procedure A, substituting 1-hexanol for cis-5-octen-1-ol. Isolated 440 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.22 – 1.40 (m, 12H), 1.50 – 1.61 (m, 4H), 1.88 – 1.98 (m, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.37 – 3.48 (m, 2H), 3.54 – 3.65 (m, 2H), 4.55 (t, *J* = 5.3 Hz, 1H).



Step 2: 4,4-bis(hexyloxy)butanoic acid

[0558] Prepared according to General Procedure B, substituting 4,4-bis(hexyloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 440 mg, 93%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.84 (t, *J* = 6.8 Hz, 6H), 1.22 – 1.26 (m, 14H), 1.45 (t, 4H), 1.69 (m, 2H), 2.19 (t, *J* = 7.2 Hz, 2H), 3.31 – 3.37(m, 4H), 3.45 – 3.51(m, 2H), 4.43 (t, *J* = 5.3 Hz, 1H).

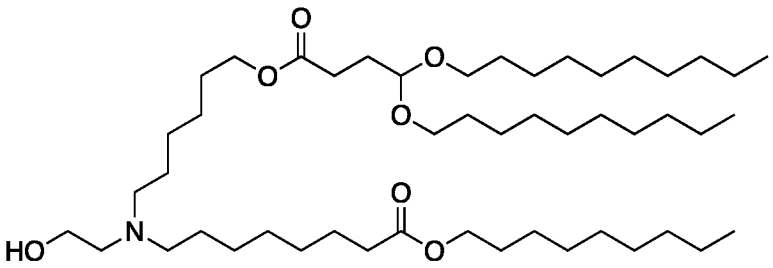


Step 3: 6-bromohexyl 4,4-bis(hexyloxy)butanoate

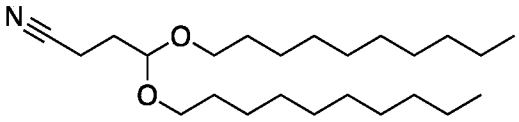
[0559] Prepared according to General Procedure C, substituting 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 76 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.4 Hz, 6H), 1.38 – 1.21 (m, 12H), 1.59-1.54 (m, 4H), 1.92 (q, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 3.45-3.39 (m, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 3.45 – 3.39 (m, 2H), 3.62-3.56 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H)

Step 4: nonyl 8-((6-((4,4-bis(hexyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-30)

[0560] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 33 mg, 32%. UPLC-MS (Method B): Rt 1.91 min, m/z calculated [M+H]: 700.6, found 701.2.

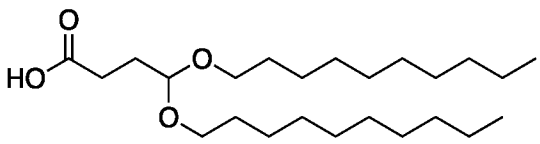


Example 7-31: nonyl 8-((6-((4,4-bis(decyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis(decyloxy)butanenitrile

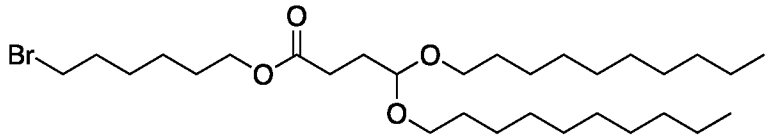
[0561] Prepared according to General Procedure A, substituting 1-decanol for cis-5-octen-1-ol. Isolated 480 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 6H), 1.23 – 1.37 (m, 12H), 1.50 – 1.62 (m, 4H), 1.88 – 1.98 (m, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 3.37 – 3.47 (m, 2H), 3.53 – 3.64 (m, 2H), 4.54 (t, *J* = 5.3 Hz, 1H).



Step 2: 4,4-bis(decyloxy)butanoic acid

[0562] Prepared according to General Procedure B, substituting 4,4-bis(decyloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 450 mg, 91%. ^{1}H NMR (400 MHz, DMSO-

d_6) δ 0.85 (t, J = 6.6 Hz, 6H), 1.14 – 1.35 (m, 28H), 1.47 (t, J = 6.8 Hz, 4H), 1.72 (q, J = 6.9 Hz, 2H), 2.21 (t, J = 7.4 Hz, 2H), 3.31 – 3.40 (m, 2H), 3.42 – 3.53 (m, 2H), 4.44 (t, J = 5.6 Hz, 1H), 12.04 (s, 1H).

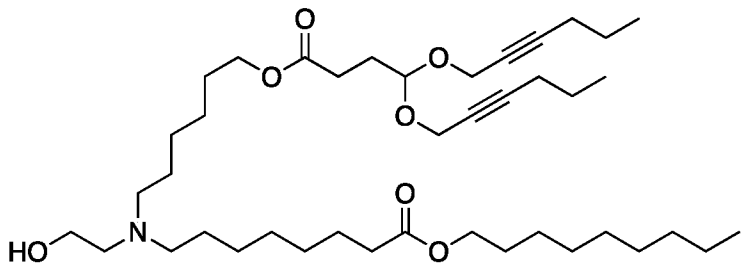


Step 3: 6-bromohexyl 4,4-bis(decyloxy)butanoate

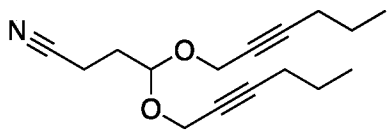
[0563] Prepared according to General Procedure C, substituting 4,4-bis(decyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 210 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, J = 6.7 Hz, 6H), 1.18 – 1.51 (m, 34H), 1.52 (d, J = 6.8 Hz, 1H), 1.57 (d, J = 7.2 Hz, 1H), 1.57 – 1.69 (m, 2H), 1.80 – 1.97 (m, 4H), 2.37 (t, J = 7.5 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.50 – 3.61 (m, 2H), 4.06 (t, J = 6.7 Hz, 2H), 4.48 (t, J = 5.6 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(decyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-31)

[0564] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(decyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 29 mg, 32%. UPLC-MS (Method B): Rt 2.41 min, m/z calculated [M+H]: 812.7, found 813.5.



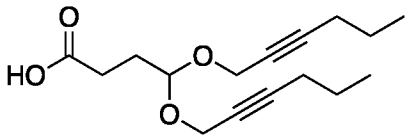
Example 7-32: nonyl 8-((6-((4,4-bis(hex-2-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis(hex-2-yn-1-yloxy)butanenitrile

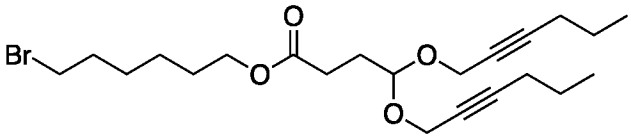
[0565] Prepared according to General Procedure A, substituting hex-2-yn-1-ol for cis-5-octen-1-ol. Isolated 250 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, J = 7.2 Hz, 6H), 1.50 –

1.56 (m, 4H), 1.99 (t, *J* = 7.2 Hz, 2H), 2.17 (m, 4H), 2.45 (t, *J* = 7.3 Hz, 2H), 4.24 (s, 4H), 4.91 (d, *J* = 4.9 Hz, 1H).



Step 2: 4,4-bis(hex-2-yn-1-yloxy)butanoic acid

[0566] Prepared according to General Procedure B, substituting 4,4-bis(hex-2-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 180 mg, 73%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.93 (t, *J* = 7.4 Hz, 6H), 1.46 (q, *J* = 7.2 Hz, 4H), 1.78 (q, *J* = 6.8 Hz, 2H), 2.13 – 2.23 (m, 4H), 2.25 (t, *J* = 7.4 Hz, 2H), 4.11 – 4.25 (m, 4H), 4.74 (t, *J* = 5.5 Hz, 1H), 11.99 – 12.25 (m, 1H).

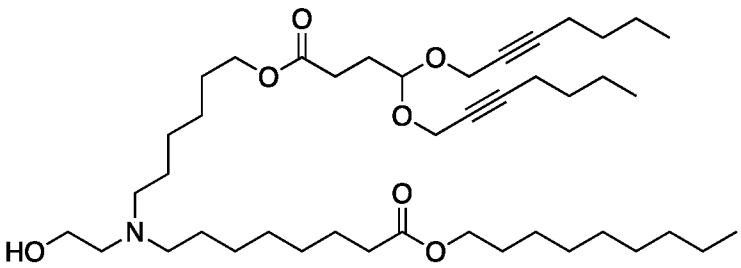


Step 3: 6-bromohexyl 4,4-bis(hex-2-yn-1-yloxy)butanoate

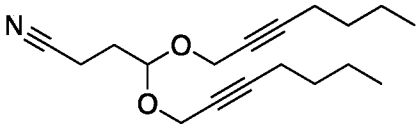
[0567] Prepared according to General Procedure C, substituting 4,4-bis(hex-2-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 105 mg, 37%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.97 (t, *J* = 7.4 Hz, 6H), 1.32 – 1.51 (m, 4H), 1.47 – 1.56 (m, 4H), 1.55 – 1.69 (m, 2H), 1.80 – 1.92 (m, 2H), 1.93 – 2.03 (m, 2H), 2.13 – 2.23 (m, 4H), 2.42 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 4.22 (t, *J* = 2.2 Hz, 4H), 4.83 (t, *J* = 5.5 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(hex-2-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-32)

[0568] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(hex-2-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 35 mg, 33%. UPLC-MS (Method B): Rt 1.81 min, m/z calculated [M+H]: 692.5, found 692.8.

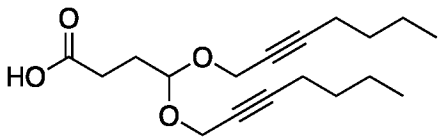


Example 7-33: nonyl 8-((6-((4,4-bis(hept-2-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



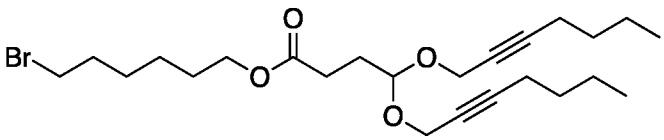
Step 1: 4,4-bis(hept-2-yn-1-yloxy)butanenitrile

[0569] Prepared according to General Procedure A, substituting hept-2-yn-1-ol for cis-5-octen-1-ol. Isolated 385 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.2 Hz, 6H), 1.35 – 1.46 (m, 4H), 1.43 – 1.54 (m, 4H), 1.97 – 2.07 (m, 2H), 2.15 – 2.27 (m, 4H), 2.47 (t, *J* = 7.5 Hz, 2H), 4.24 (s, 4H), 4.92 (t, *J* = 5.2 Hz, 1H).



Step 2: 4,4-bis(hept-2-yn-1-yloxy)butanoic acid

[0570] Prepared according to General Procedure B, substituting 4,4-bis(hept-2-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 325 mg, 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, *J* = 7.1 Hz, 6H), 1.28 – 1.49 (m, 8H), 1.72 – 1.82 (m, 2H), 2.14 – 2.29 (m, 6H), 4.10 – 4.23 (m, 4H), 4.72 (t, *J* = 5.5 Hz, 1H), 12.08 (s, 1H).

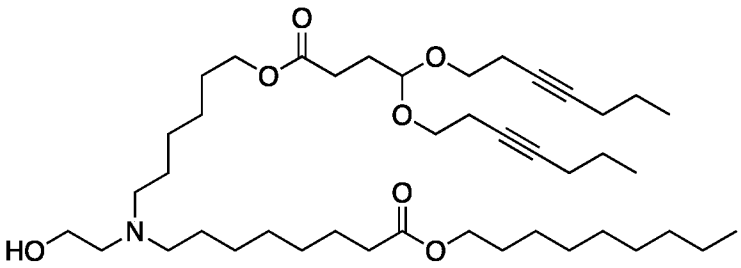


Step 3: 6-bromohexyl 4,4-bis(hept-2-yn-1-yloxy)butanoate

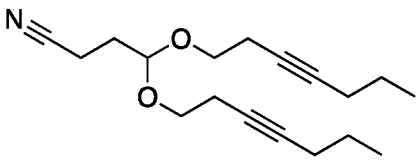
[0571] Prepared according to General Procedure C, substituting 4,4-bis(hept-2-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 195 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, *J* = 7.2 Hz, 6H), 1.29 – 1.53 (m, 12H), 1.57 – 1.69 (m, 2H), 1.80 – 1.92 (m, 2H), 1.98 (q, *J* = 7.8 Hz, 2H), 2.16 – 2.25 (m, 4H), 2.42 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 4.21 (t, *J* = 2.2 Hz, 4H), 4.82 (t, *J* = 5.5 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(hept-2-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-33)

[0572] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(hept-2-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 57 mg, 56%. UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 720.6, found 721.2.

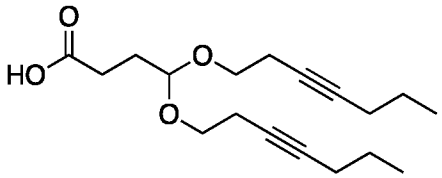


Example 7-34: nonyl 8-((6-((4,4-bis(hept-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



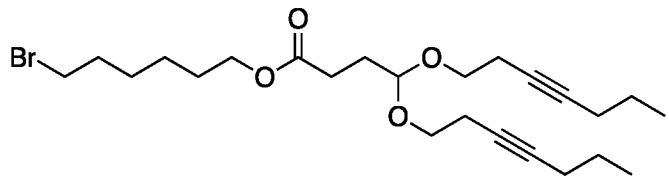
Step 1: 4,4-bis(hept-3-yn-1-yloxy)butanenitrile

[0573] Prepared according to General Procedure A, substituting hept-3-yn-1-ol for cis-5-octen-1-ol. Isolated 412 mg, 37%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.3 Hz, 6H), 1.42 – 1.56 (m, 4H), 1.92 – 2.02 (m, 2H), 2.06 – 2.16 (m, 4H), 2.38 – 2.49 (m, 6H), 3.51 – 3.62 (m, 2H), 3.64 – 3.75 (m, 2H), 4.67 (t, *J* = 5.4 Hz, 1H).



Step 2: 4,4-bis(hept-3-yn-1-yloxy)butanoic acid

[0574] Prepared according to General Procedure B, substituting 4,4-bis(hept-3-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 493 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.3 Hz, 6H), 1.42 – 1.54 (m, 4H), 1.91 – 2.01 (m, 2H), 2.06 – 2.16 (m, 4H), 2.37 – 2.52 (m, 6H), 3.50 – 3.61 (m, 2H), 3.63 – 3.73 (m, 2H), 4.64 (t, *J* = 5.6 Hz, 1H).

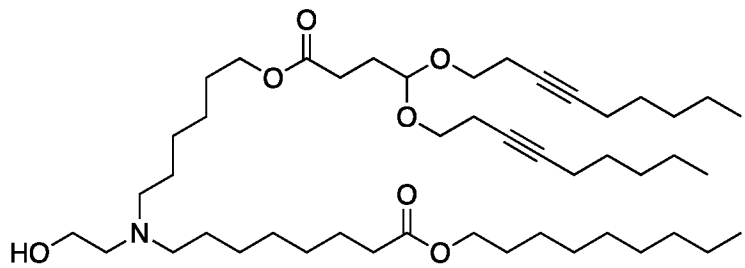


Step 3: 6-bromohexyl 4,4-bis(hept-3-yn-1-yloxy)butanoate

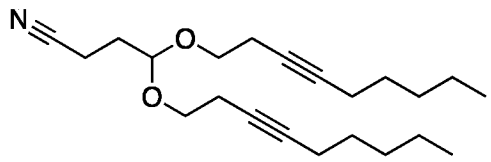
[0575] Prepared according to General Procedure C, substituting 4,4-bis(hept-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 165 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.4 Hz, 6H), 1.30 – 1.43 (m, 2H), 1.38 – 1.56 (m, 6H), 1.57 – 1.69 (m, 2H), 1.80 – 1.92 (m, 2H), 1.89 – 1.99 (m, 2H), 2.06 – 2.16 (m, 4H), 2.35 – 2.46 (m, 6H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.49 – 3.60 (m, 2H), 3.61 – 3.72 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(hept-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-34)

[0576] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(hept-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 80 mg, 53%. UPLC-MS (Method B): Rt 1.88 min, m/z calculated [M+H]: 720.6, found 720.9.



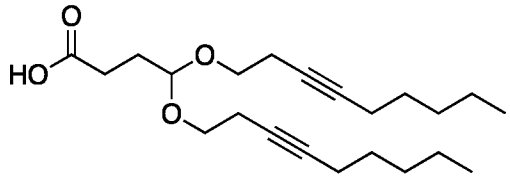
Example 7-35: nonyl 8-((6-((4,4-bis(non-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis(non-3-yn-1-yloxy)butanenitrile

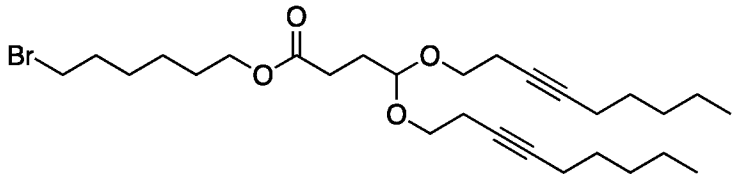
[0577] Prepared according to General Procedure A, substituting non-3-yn-1-ol for cis-5-octen-1-ol. Isolated 542 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 6H), 1.25 –

1.37 (m, 8H), 1.46 (q, *J* = 7.0 Hz, 4H), 1.92 – 2.02 (m, 2H), 2.08 – 2.20 (m, 4H), 2.38 – 2.49 (m, 6H), 3.50 – 3.61 (m, 2H), 3.63 – 3.75 (m, 2H), 4.67 (t, *J* = 5.4 Hz, 1H).



Step 2: 4,4-bis(non-3-yn-1-yloxy)butanoic acid

[0578] Prepared according to General Procedure B, substituting 4,4-bis(non-3-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 453 mg, 92%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.20 – 1.40 (m, 9H), 1.40 – 1.53 (m, 4H), 1.95 (q, *J* = 6.9 Hz, 2H), 2.07 – 2.17 (m, 4H), 2.37 – 2.51 (m, 6H), 3.49 – 3.60 (m, 2H), 3.62 – 3.73 (m, 2H), 4.63 (t, *J* = 5.6 Hz, 1H).

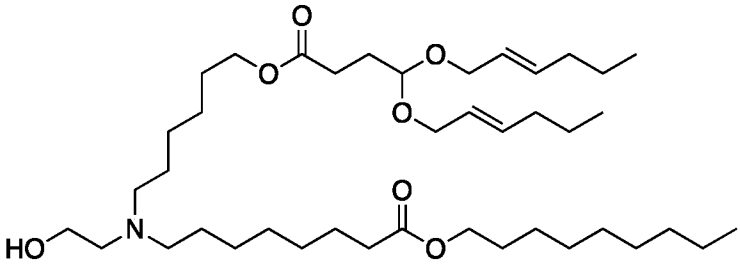


Step 3: 6-bromohexyl 4,4-bis(non-3-yn-1-yloxy)butanoate

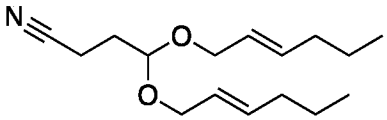
[0579] Prepared according to General Procedure C, substituting 4,4-bis(non-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 91 mg, 46%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.8 Hz, 6H), 1.22 – 1.41 (m, 8H), 1.42 – 1.53 (m, 4H), 1.57 – 1.69 (m, 2H), 1.80 – 1.90 (m, 2H), 1.89 – 1.99 (m, 2H), 2.08 – 2.17 (m, 2H), 2.35 – 2.46 (m, 4H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.49 – 3.60 (m, 2H), 3.61 – 3.72 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 4.60 (t, *J* = 5.8 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(non-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-35)

[0580] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(non-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 76 mg, 54%. UPLC-MS (Method B): Rt 1.87 min, m/z calculated [M+H]: 776.6, found 777.3.

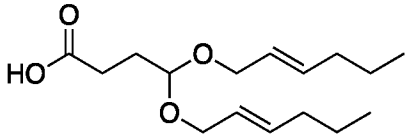


Example 7-36: nonyl 8-((6-((4,4-bis(((*E*)-hex-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



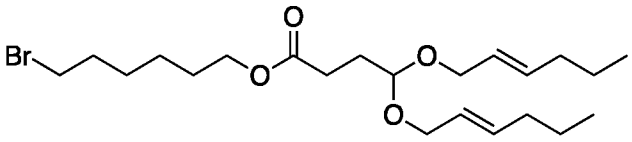
Step 1: 4,4-bis(((E)-hex-2-en-1-yl)oxy)butanenitrile

[0581] Prepared according to General Procedure A, substituting (*E*)-hex-2-en-1-ol for cis-5-octen-1-ol. Isolated 432 mg, 36%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, *J* = 7.4 Hz, 6H), 1.33 – 1.47 (m, 4H), 1.92 – 1.98 (m, 2H), 2.02 (q, *J* = 6.9 Hz, 4H), 2.42 (t, *J* = 7.4 Hz, 2H), 3.91 – 4.01 (m, 2H), 4.02 – 4.12 (m, 2H), 4.65 (t, *J* = 5.3 Hz, 1H), 5.46 – 5.59 (m, 2H), 5.64 – 5.76 (m, 2H).



Step 2: 4,4-bis(((E)-hex-2-en-1-yl)oxy)butanoic acid

[0582] Prepared according to General Procedure B, substituting 4,4-bis(((*E*)-hex-2-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 352 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.3 Hz, 6H), 1.32-1.49 (m, 5H), 1.91 – 2.05 (m, 6H), 2.45 (t, *J* = 7.3 Hz, 2H), 3.95 (dd, *J* = 6.4, 11.8 Hz, 2H), 4.05 (dd, *J* = 6.0, 11.8 Hz, 2H), 4.61 (t, *J* = 5.5 Hz,1H), 5.47 – 5.59 (m, 2H), 5.63 – 5.75 (m, 2H).



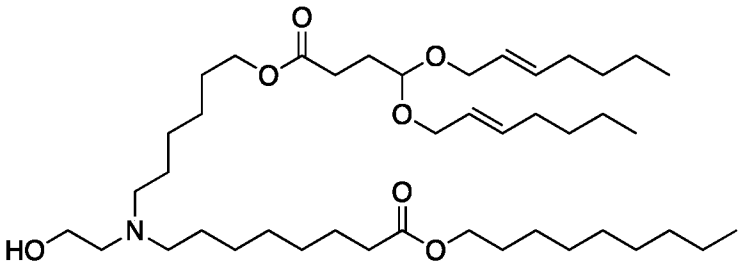
Step 3: 6-bromohexyl 4,4-bis(((E)-hex-2-en-1-yl)oxy)butanoate

[0583] Prepared according to General Procedure C, substituting 4,4-bis(((*E*)-hex-2-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 134 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.3 Hz, 6H), 1.30 – 1.50 (m, 8H), 1.63 (t, *J* = 7.3 Hz, 2H), 1.86 (t, *J* = 7.2 Hz, 2H), 1.90-2.05 (m, 6H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* = 6.8 Hz,

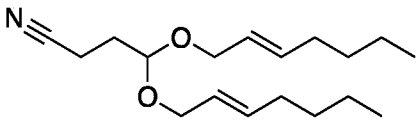
2H), 3.94 (dd, *J* = 6.4, 11.8 Hz, 2H), 3.99 – 4.09 (m, 4H), 4.59 (t, *J* = 5.5 Hz, 1H), 5.48 – 5.59 (m, 2H), 5.62 – 5.74 (m, 2H).

Step 4: nonyl 8-((6-((4,4-bis(((E)-hex-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-36)

[0584] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*E*)-hex-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 80 mg, 53%. UPLC-MS (Method B): Rt 1.93 min, m/z calculated [M+H]: 696.6, found 696.9.

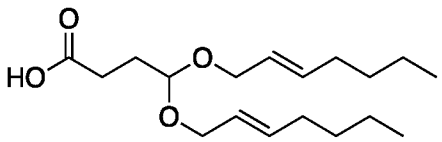


Example 7-37: nonyl 8-((6-((4,4-bis(((*E*)-hept-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis(((E)-hept-2-en-1-yl)oxy)butanenitrile

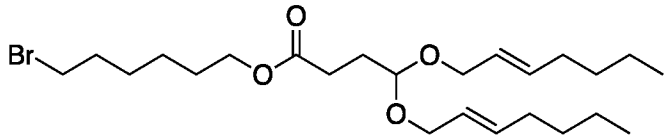
[0585] Prepared according to General Procedure A, substituting (*E*)-hept-2-en-1-ol for cis-5-octen-1-ol. Isolated 451 mg, 34%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 6H), 1.22 – 1.43 (m, 8H), 1.90 – 2.00 (m, 2H), 2.05 (q, *J* = 6.9 Hz, 4H), 2.42 (t, *J* = 7.4 Hz, 2H), 3.95 (dd, *J* = 6.5, 11.8 Hz, 2H), 4.07 (dd, *J* = 6.0, 11.8 Hz, 2H), 4.64 (t, *J* = 5.3 Hz, 1H), 5.46 – 5.59 (m, 2H), 5.64 – 5.76 (m, 2H).



Step 2: 4,4-bis(((E)-hept-2-en-1-yl)oxy)butanoic acid

[0586] Prepared according to General Procedure B, substituting 4,4-bis(((*E*)-hept-2-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 321 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 6H), 1.19 – 1.42 (m, 9H), 1.90 – 2.09 (m,

6H), 2.45 (t, *J* = 7.3 Hz, 2H), 3.94 (dd, *J* = 6.5, 11.8 Hz, 2H), 4.05 (dd, *J* = 6.1, 11.8 Hz, 2H), 4.61 (t, *J* = 5.4 Hz, 1H), 5.46 – 5.58 (m, 2H), 5.63 – 5.75 (m, 2H).

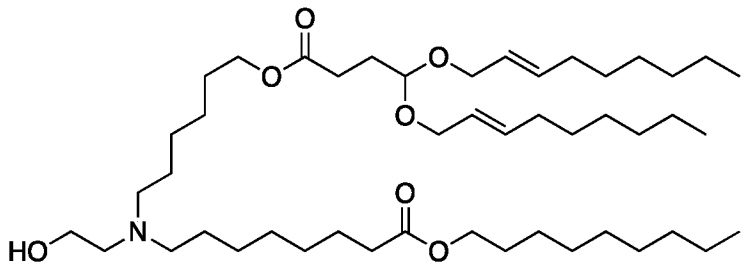


Step 3: 6-bromohexyl 4,4-bis(((E)-hept-2-en-1-yl)oxy)butanoate

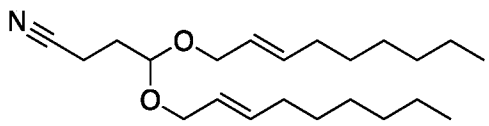
[0587] Prepared according to General Procedure C, substituting 4,4-bis(((*E*)-hept-2-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 54 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 6H), 1.25 – 1.41 (m, 10H), 1.42 – 1.51 (m, 2H), 1.63 (t, *J* = 7.3 Hz, 2H), 1.80 – 1.94 (m, 2H), 1.94 (q, *J* = 6.9 Hz, 2H), 2.03 (q, *J* = 6.9 Hz, 4H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.93 (dd, *J* = 6.4, 11.7 Hz, 2H), 3.97 – 4.11 (m, 4H), 4.58 (t, *J* = 5.6 Hz, 1H), 5.46 – 5.58 (m, 2H), 5.62 – 5.74 (m, 2H).

Step 4: nonyl 8-((6-((4,4-bis(((E)-hept-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-37)

[0588] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*E*)-hept-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 24 mg, 32%. UPLC-MS (Method B): Rt 2.01 min, m/z calculated [M+H]: 724.6, found 725.0.



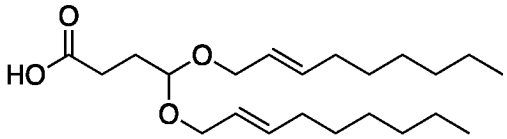
Example 7-38: nonyl 8-((6-((4,4-bis(((*E*)-non-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis(((E)-non-2-en-1-yl)oxy)butanenitrile

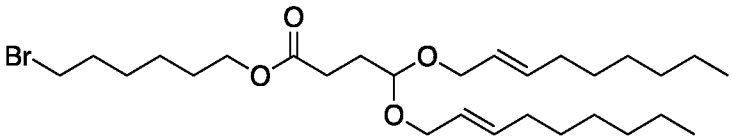
[0589] Prepared according to General Procedure A, substituting (*E*)-non-2-en-1-ol for cis-5-octen-1-ol. Isolated 721 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.4 Hz, 6H), 1.20 – 1.41 (m, 16H), 1.90 – 2.00 (m, 2H), 2.04 (q, *J* = 6.9 Hz, 4H), 2.42 (t, *J* = 7.4 Hz, 2H), 3.95 (dd, *J*

= 6.5, 11.7 Hz, 2H), 4.06 (dd, *J* = 6.1, 11.6 Hz, 2H), 4.64 (t, *J* = 5.2 Hz, 1H), 5.45 – 5.59 (m, 2H), 5.63 – 5.76 (m, 2H).



Step 2: 4,4-bis(((E)-non-2-en-1-yl)oxy)butanoic acid

[0590] Prepared according to General Procedure B, substituting 4,4-bis(((*E*)-non-2-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 295 mg, 93%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 6H), 1.17 – 1.45 (m, 16H), 1.95 (q, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 7.0 Hz, 4H), 2.45 (t, *J* = 7.3 Hz, 2H), 3.71 (q, *J* = 7.0 Hz, 1H), 3.94 (dd, *J* = 6.5, 11.8 Hz, 2H), 4.04 (dd, *J* = 6.1, 11.7 Hz, 2H), 4.61 (t, *J* = 5.4 Hz, 1H), 5.46 – 5.58 (m, 2H), 5.63 – 5.75 (m, 2H).

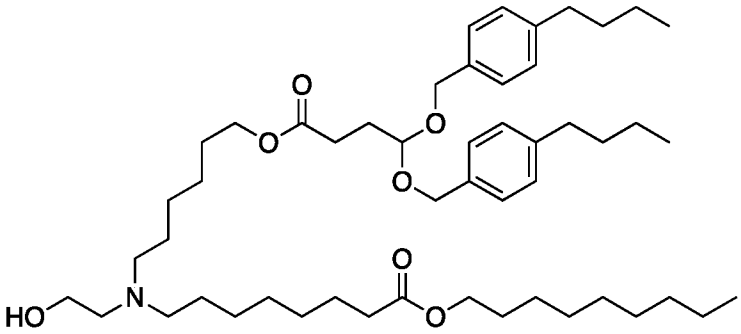


Step 3: 6-bromohexyl 4,4-bis(((E)-non-2-en-1-yl)oxy)butanoate

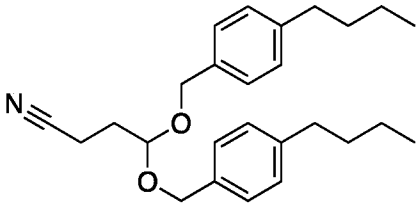
[0591] Prepared according to General Procedure C, substituting 4,4-bis(((*E*)-non-2-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 231 mg, 49%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.18 – 1.43 (m, 18H), 1.40 – 1.52 (m, 2H), 1.58 – 1.68 (m, 2H), 1.81 – 1.90 (m, 2H), 1.91 – 1.97 (m, 2H), 2.03 (q, *J* = 7.2 Hz, 4H), 2.38 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.93 (dd, *J* = 6.4, 11.8 Hz, 2H), 3.98 – 4.09 (m, 4H), 4.58 (t, *J* = 5.6 Hz, 1H), 5.46 – 5.58 (m, 2H), 5.62 – 5.75 (m, 2H).

Step 4: nonyl 8-((6-((4,4-bis(((E)-non-2-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-38)

[0592] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*E*)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 87 mg, 61%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 780.7, found 781.4. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.5 Hz, 6H), 1.17 – 1.47 (m, 47H), 1.78 – 1.90 (m, 4H), 1.89 – 1.99 (m, 2H), 1.97 – 2.08 (m, 6H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.00 – 3.27 (m, 6H), 3.88 – 4.11 (m, 9H), 4.58 (t, *J* = 5.5 Hz, 1H), 5.46 – 5.62 (m, 2H), 5.62 – 5.76 (m, 2H).

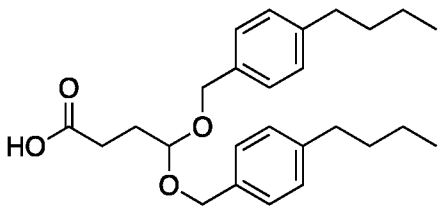


Example 7-39: nonyl 8-((6-((4,4-bis((4-butylbenzyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4,4-bis((4-butylbenzyl)oxy)butanenitrile

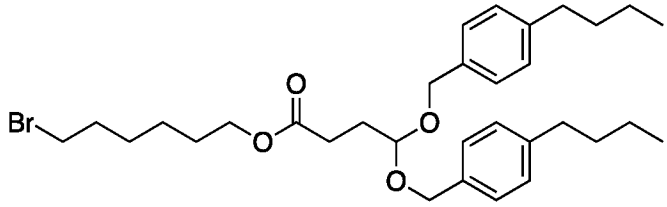
[0593] Prepared according to General Procedure A, substituting (4-butylphenyl)methanol for cis-5-octen-1-ol. Isolated 634 mg, 36%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.92 (t, *J* = 7.3 Hz, 6H), 1.29 – 1.40 (m, 4H), 1.52 – 1.65 (m, 4H), 1.97 – 2.07 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.7 Hz, 4H), 4.51 (d, *J* = 11.5 Hz, 2H), 4.64 (d, *J* = 11.4 Hz, 2H), 4.78 (t, *J* = 5.1 Hz, 1H), 7.14 – 7.18 (m, 4H), 7.19 – 7.27 (m, 4H).



Step 2: 4,4-bis((4-butylbenzyl)oxy)butanoic acid

[0594] Prepared according to General Procedure B, substituting 4,4-bis((4-butylbenzyl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 305 mg, 97%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.3 Hz, 6H), 1.27 – 1.41 (m, 4H), 1.51 – 1.64 (m, 4H), 2.05 (q, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.4 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 4H), 3.71 (q, *J*

= 7.0 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 2H), 4.62 (d, *J* = 11.4 Hz, 2H), 4.76 (t, *J* = 5.4 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 4H), 7.20 – 7.26 (m, 4H).

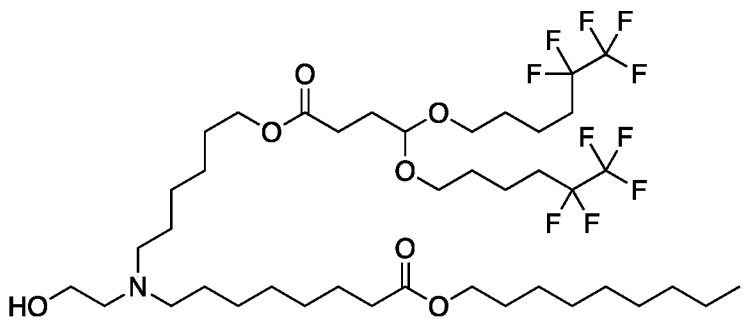


Step 3: 6-bromohexyl 4,4-bis((4-butylbenzyl)oxy)butanoate

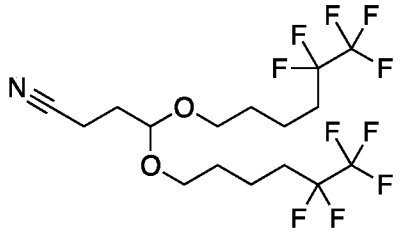
[0595] Prepared according to General Procedure C, substituting 4,4-bis((4-butylbenzyl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 256 mg, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.3 Hz, 6H), 1.27 – 1.41 (m, 6H), 1.38 – 1.51 (m, 2H), 1.55 – 1.66 (m, 6H), 1.78 – 1.91 (m, 2H), 2.01 – 2.11 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 4H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.02 (t, *J* = 6.7 Hz, 2H), 4.50 (d, *J* = 11.5 Hz, 2H), 4.61 (d, *J* = 11.5 Hz, 2H), 4.74 (t, *J* = 5.6 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 4H), 7.21 – 7.26 (m, 4H).

Step 4: nonyl 8-((6-((4,4-bis((4-butylbenzyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-39)

[0596] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((4-butylbenzyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 96 mg, 64%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 824.6, found 825.4. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.97 (m, 9H), 1.18 – 1.46 (m, 26H), 1.55 – 1.70 (m, 11H), 1.84 (s, 4H), 2.05 (q, *J* = 7.0 Hz, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 4H), 2.98 – 3.22 (m, 6H), 3.93 – 4.10 (m, 6H), 4.50 (d, *J* = 11.5 Hz, 2H), 4.61 (d, *J* = 11.4 Hz, 2H), 4.74 (t, *J* = 5.5 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 4H), 7.22 (d, *J* = 7.7 Hz, 4H).

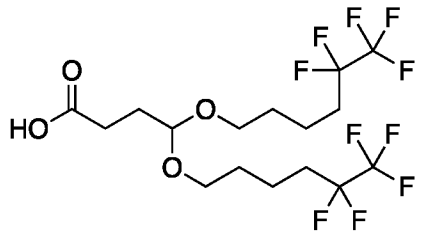


Example 7-40: nonyl 8-((6-((4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



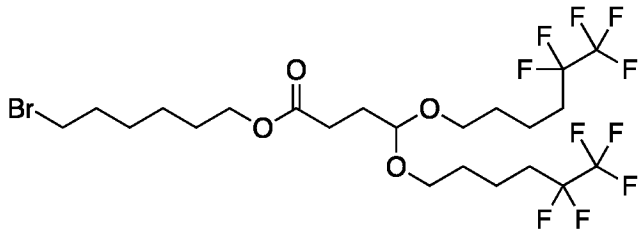
Step 1: 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanenitrile

[0597] Prepared according to General Procedure A, substituting 5,5,6,6,6-pentafluorohexan-1-ol for cis-5-octen-1-ol. Isolated 545 mg, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.60 – 1.72 (m, 8H), 1.89 – 1.99 (m, 2H), 1.98 – 2.13 (m, 4H), 2.41 (t, *J* = 7.2 Hz, 2H), 3.42 – 3.52 (m, 2H), 3.62 (dd, *J* = 5.2, 9.0 Hz, 2H), 4.57 (t, *J* = 5.3 Hz, 1H).



Step 2: 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoic acid

[0598] Prepared according to General Procedure B, substituting 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 345 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.58 – 1.75 (m, 9H), 1.86 – 2.15 (m, 6H), 2.43 (t, *J* = 7.3 Hz, 2H), 3.39 – 3.51 (m, 2H), 3.55 – 3.65 (m, 2H), 4.52 (t, *J* = 5.4 Hz, 1H).



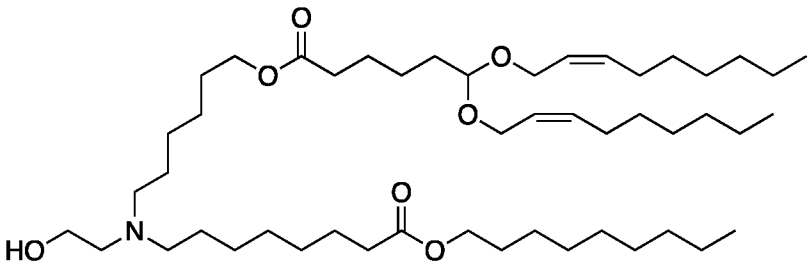
Step 3: 6-bromohexyl 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoate

[0599] Prepared according to General Procedure C, substituting 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 143 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.32 – 1.51 (m, 2H), 1.57 – 1.74 (m, 12H), 1.79 –

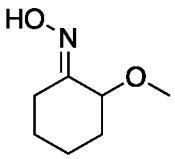
2.00 (m, 4H), 1.97 – 2.13 (m, 4H), 2.36 (t, *J* = 7.5 Hz, 2H), 3.35 – 3.50 (m, 4H), 3.54 – 3.69 (m, 2H), 4.06 (t, *J* = 6.7 Hz, 2H), 4.50 (t, *J* = 5.5 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-40)

[0600] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis((5,5,6,6,6-pentafluorohexyl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 22 mg, 24%. UPLC-MS (Method C): Rt 4.95 min, m/z calculated [M+H]: 880.5, found 881.2.

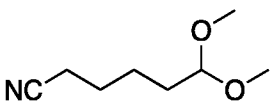


Example 7-41: nonyl 8-((6-((6,6-bis(((*Z*)-non-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



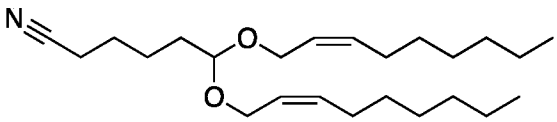
Step 1: 2-methoxycyclohexan-1-one oxime

[0601] To a stirred solution of 2-methoxycyclohexan-1-one (5 g, 39.0 mmol) in MeOH-H_2O (150 ml, 1:2) was added sodium acetate (6.41 g, 78.1 mmol) followed by the addition of hydroxylamine hydrochloride (5.43 g, 78.1 mmol). The resulting mixture was heated at 70 °C in a sealed tube for 16 h. After that time, MeOH was evaporated and the mixture was diluted with water, extracted with ethyl acetate (3 x 50 mL), washed with brine and dried over sodium sulfate and concentrated under reduced pressure. The crude thus obtained was purified by flash column chromatography eluting with 3% ethyl acetate in hexane to afford 2-methoxycyclohexan-1-one oxime (4.1 g, 88%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17-1.32 (m, 1H), 1.40-1.56 (m, 2H), 1.59-1.82 (m, 3H), 1.92-1.99 (m, 1H), 2.93-3.01 (m, 1H), 3.11 (s, 3H), 3.63 (s, 1H), 10.61 (s, 1H).



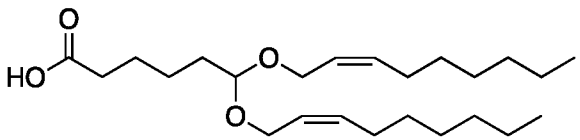
Step 2: 6,6-dimethoxyhexanenitrile

[0602] To a stirred solution of 2-methoxycyclohexan-1-one oxime (2.0 g, 14.0 mmol) in CCl_4 (20 ml) was added thionyl chloride (1.2 ml, 16.8 mmol) dropwise at 0 °C and stirred for 10 min. After that time, dry MeOH (20 ml) was added to the reaction mixture at 5-10° C. After addition was complete, the reaction mixture was allowed to reach room temperature and was left for 2 h. The mixture was then diluted with ethyl acetate and washed with brine, dried over sodium sulfate and concentrated to afford 6,6-dimethoxyhexanenitrile (1.6 g, 81%) as light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.44 – 1.56 (m, 2H), 1.57 – 1.75 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 3.31 (s, 6H), 4.34 (t, *J* = 5.5 Hz, 1H).



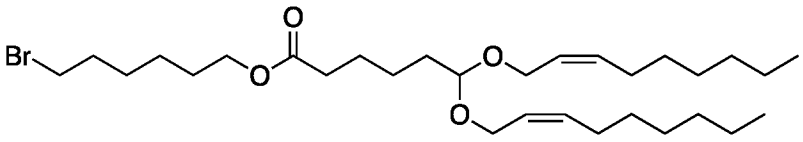
Step 3: 6,6-bis(((Z)-non-2-en-1-yl)oxy)hexanenitrile

[0603] Prepared according to General Procedure A, substituting (*Z*)-non-2-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 250 mg, 28%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.80-0.87 (m, 6H), 1.26-1.38 (m, 18H), 1.52-1.54 (m, 2H), 1.63-1.70 (m, 4H), 2.02-2.07 (m, 4H), 2.33 (t, *J* = 7.12 Hz, 2H), 4.03-4.19 (m, 4H), 4.55 (t, *J* = 5.64 Hz, 1H), 5.47-5.60 (m, 4H).



Step 4: 6,6-bis(((Z)-non-2-en-1-yl)oxy)hexanoic acid

[0604] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-non-2-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 150 mg, 71%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83-0.85 (m, 6H), 1.16-1.24 (m, 20H), 1.46-1.51 (m, 4H), 1.99-2.02 (m, 4H), 2.18 (t, J=7.36 Hz, 2H), 3.96-4.07 (m, 4H), 4.44-4.49 (m, 1H), 5.46-5.50 (m, 4H), 11.96 (bs, 1H).

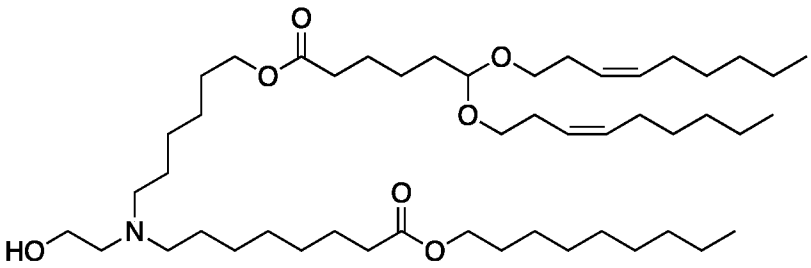


Step 5: 6-bromohexyl 6,6-bis(((Z)-non-2-en-1-yl)oxy)hexanoate

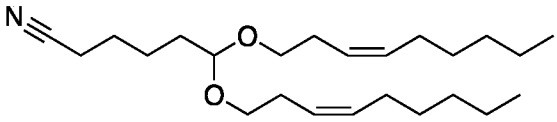
[0605] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-non-2-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 40 mg, 56%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.87 (m ,6H), 1.26-1.38 (m, 20H), 1.42-1.49 (m, 2H), 1.63 (m, 6H), 1.82-1.92 (m, 2H), 2.02-2.11 (m, 4H), 2.31 (t, J=7.56 Hz, 2H), 3.39 (t, J=6.72 Hz, 2H), 4.03-4.18 (m, 6H), 4.54 (t, J=5.72 Hz, 1H), 5.49-5.56 (m, 4H).

Step 6: nonyl 8-((6-((6,6-bis(((Z)-non-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-41)

[0606] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-non-2-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 20 mg, 51%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 808.7, found 809.4.

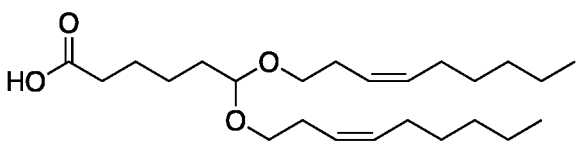


Example 7-42: nonyl 8-((6-((6,6-bis(((*Z*)-non-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



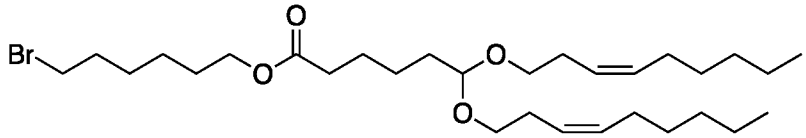
Step 1: 6,6-bis(((Z)-non-3-en-1-yl)oxy)hexanenitrile

[0607] Prepared according to General Procedure A, substituting (*Z*)-non-3-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 320 mg, 33%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.89 (m, 6H), 1.25-1.37 (m, 12H), 1.48-1.54 (m, 2H), 1.60-1.69 (m, 4H), 2.00-2.05 (m, 4H), 2.29-2.34 (m, 6H), 3.38-3.44 (m, 2H), 3.54-3.59 (m, 2H), 4.47 (t, *J* = 5.56 Hz, 1H), 5.32-5.49 (m, 4H).



Step 2: 6,6-bis(((Z)-non-3-en-1-yl)oxy)hexanoic acid

[0608] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-non-3-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 280 mg, 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J=6.96 Hz, 6H), 1.26-1.32 (m, 13H), 1.46-1.50 (m, 4H), 1.97-2.02 (m, 4H), 2.16-2.24 (m, 6H), 3.34-3.37 (m, 2H), 3.46-3.48 (m, 2H), 4.44 (m, 1H), 5.36-5.39 (m, 4H), 11.95 (s, 1H).

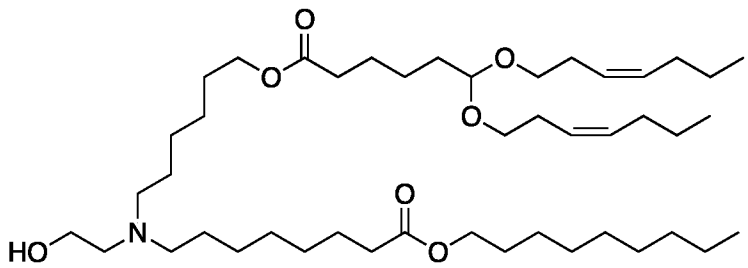


Step 3: 6-bromohexyl 6,6-bis(((Z)-non-3-en-1-yl)oxy)hexanoate

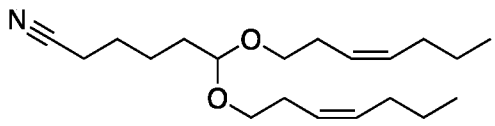
[0609] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-non-3-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 220 mg, 55%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.89 (m ,6H), 1.28-1.37 (m, 18H), 1.44-1.46 (m, 2H), 1.59-1.64 (m, 6H), 1.84-1.87 (m, 2H), 1.97-2.03 (m, 4H), 2.27-2.32 (m, 6H), 3.37-3.43 (m, 4H), 3.52-3.65 (m, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.46-4.51 (m, 1H), 5.35-5.50 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis(((Z)-non-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-42)

[0610] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-non-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 45 mg, 45%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 808.7, found 809.4.

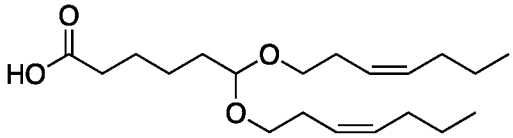


Example 7-43: nonyl 8-((6-((6,6-bis(((*Z*)-hept-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



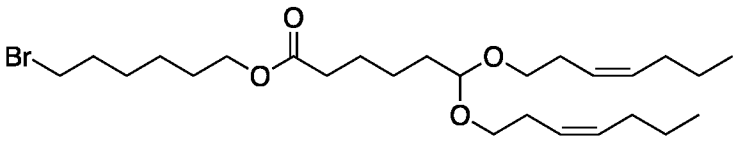
Step 1: 6,6-bis(((Z)-hept-3-en-1-yl)oxy)hexanenitrile

[0611] Prepared according to General Procedure A, substituting (*Z*)-hept-3-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 216 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87-0.91 (m, 6H), 1.32-1.39 (m, 4H), 1.48-1.55 (m, 2H), 1.60-1.69 (m, 4H), 1.98-2.04 (m, 4H), 2.28-2.34 (m, 6H), 3.38-3.44 (m, 2H), 3.54-3.65 (m, 2H), 4.47 (t, *J* = 5.52 Hz, 1H), 5.35-5.47 (m, 4H).



Step 2: 6,6-bis(((Z)-hept-3-en-1-yl)oxy)hexanoic acid

[0612] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-hept-3-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 210 mg, 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83-0.85 (m, 6H), 1.23-1.37 (m, 7H), 1.45-1.52 (m, 4H), 1.96-2.01 (m, 4H), 2.16-2.24 (m, 6H), 3.35-3.39 (m, 2H), 3.45-3.51 (m, 2H), 4.44 (t, J=5.48 Hz, 1H), 5.34-5.44 (m, 4H), 11.95 (bs, 1H).

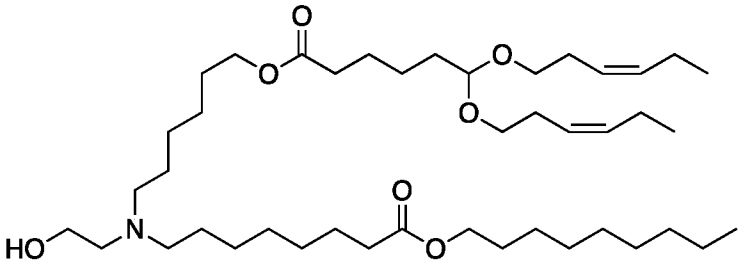


Step 3: 6-bromohexyl 6,6-bis(((Z)-hept-3-en-1-yl)oxy)hexanoate

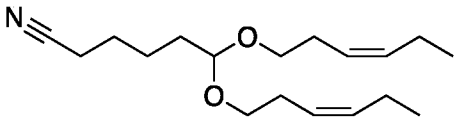
[0613] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-hept-3-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 180 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, J=7.32 Hz, 6H), 1.33-1.39 (m, 8H), 1.44-1.46 (m, 2H), 1.61-1.64 (m, 6H), 1.84-1.89 (m, 2H), 1.98-2.03 (m, 4H), 2.27-2.32 (m, 6H), 3.38-3.44 (m, 4H), 3.52-3.65 (m, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.47 (t, J=5.6 Hz, 1H), 5.34-5.56 (m, 4H).

Step 4: nonyl 8-((6-(((6,6-bis(((Z)-hept-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-43)

[0614] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-hept-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 45 mg, 50%. UPLC-MS (Method C): Rt 5.12 min, m/z calculated [M+H]: 752.6, found 753.3.

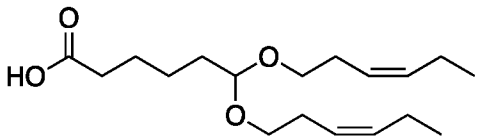


Example 7-44: nonyl 8-((6-((6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



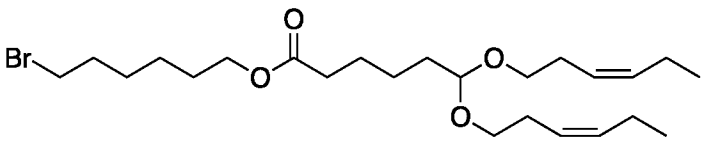
Step 1: 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanenitrile

[0615] Prepared according to General Procedure A, substituting (*Z*)-hex-3-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 350 mg, 31%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.93-0.97 (m, 6H), 1.48-1.54 (m, 4H), 1.60-1.71 (m, 4H), 2.00-2.08 (m, 4H), 2.27-2.34 (m, 6H), 3.38-3.44 (m, 2H), 3.53-3.59 (m, 2H), 4.47 (t, *J* = 5.56 Hz, 1H), 5.29-5.47 (m, 4H).



Step 2: 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoic acid

[0616] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 340 mg, 91%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.93 (t, J=7.92 Hz, 6H), 1.23-1.31 (m, 2H), 1.45-1.52 (m, 4H), 1.94-2.04 (m, 4H), 2.16-2.24 (m, 6H), 3.33-3.39 (m, 2H), 3.45-3.51 (m, 2H), 4.44 (t, J=5.48 Hz, 1H), 5.29-5.44 (m, 4H), 11.94 (bs, 1H).



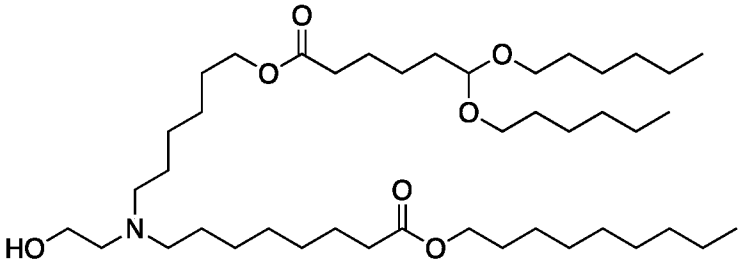
Step 3: 6-bromohexyl 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoate

[0617] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 280 mg, 54%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.93-0.97 (m, 6H), 1.34-1.40 (m, 4H), 1.44-1.48 (m, 2H), 1.55-

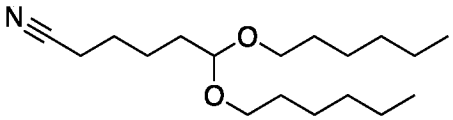
1.64 (m, 9H), 1.83-1.87 (m, 2H), 2.02-2.06 (m, 4H), 2.27-2.32 (m, 6H), 3.37-3.43 (m, 4H), 3.52-3.58 (m, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.47 (t, J=5.6 Hz, 1H), 5.31-5.46 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-44)

[0618] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 56 mg, 57%. UPLC-MS (Method B): Rt 1.91 min, m/z calculated [M+H]: 724.6, found 725.2.

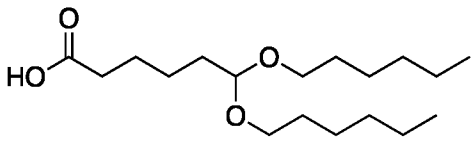


Example 7-45: nonyl 8-((6-((6,6-bis(hexyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



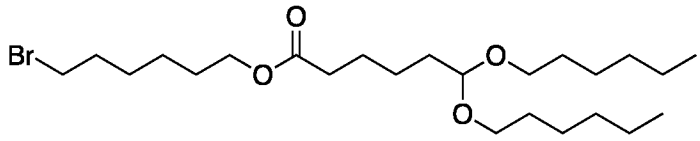
Step 1: 6,6-bis(hexyloxy)hexanenitrile

[0619] Prepared according to General Procedure A, substituting hexan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 210 mg, 29%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86-0.89 (m, 6H), 1.29-1.31 (m, 12H), 1.50-1.54 (m, 6H), 1.63-1.71 (m, 4H), 2.33 (t, *J* = 7.12 Hz, 2H), 3.36-3.41 (m, 2H), 3.52-3.58 (m, 2H), 4.44 (t, *J* = 5.48 Hz, 1H).



Step 2: 6,6-bis(hexyloxy)hexanoic acid

[0620] Prepared according to General Procedure B, substituting 6,6-bis(hexyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 245 mg, 92%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.85 (t, J=6.92 Hz, 6H), 1.26 (m, 15H), 1.43-1.54 (m, 8H), 2.17 (t, J=7.32 Hz, 2H), 3.31-3.36 (m, 2H), 3.44-3.50 (m, 2H), 4.40 (t, J=5.64 Hz, 1H), 11.95 (bs, 1H).

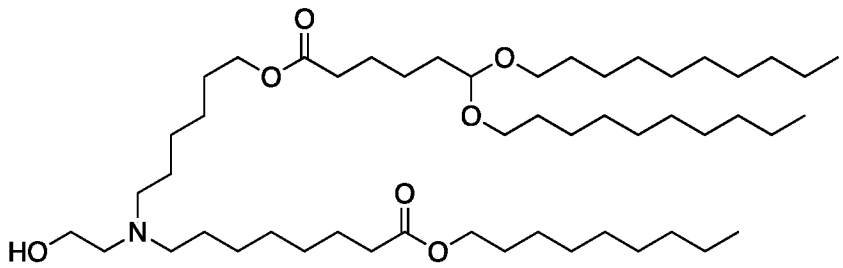


Step 3: 6-bromohexyl 6,6-bis(hexyloxy)hexanoate

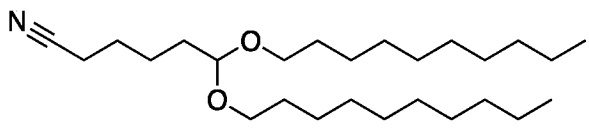
[0621] Prepared according to General Procedure C, substituting 6,6-bis(hexyloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 190 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.89 (m, 6H), 1.28-1.38 (m, 15H), 1.44-1.46 (m, 2H), 1.50-1.65 (m, 13H), 1.83-1.87 (m, 2H), 2.29 (t, J=7.6 Hz, 2H), 3.37-3.41 (m, 4H), 3.51-3.55 (m, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.43 (m, 1H).

Step 4: nonyl 8-((6-((6,6-bis(hexyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-45)

[0622] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(hexyloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 55 mg, 55%. UPLC-MS (Method B): Rt 2.01 min, m/z calculated [M+H]: 728.6, found 729.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (m, 6H), 1.26-1.31 (m, 24 H), 1.44-1.58 (m, 12H), 2.25-2.29 (m, 3H), 3.05-3.28 (m, 4H), 3.44-3.50 (m, 2H), 3.69 (bs, 1H), 3.97-4.01 (m, 3H), 4.40 (t, J=5.72 Hz, 1H).



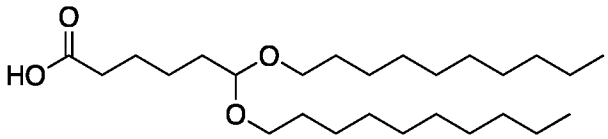
Example 7-46: nonyl 8-((6-((6,6-bis(decyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 6,6-bis(decyloxy)hexanenitrile

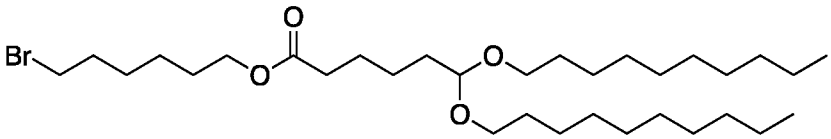
[0623] Prepared according to General Procedure A, substituting decan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 260 mg, 25%. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 0.84-0.88 (m, 6H), 1.25-1.28 (m, 28H), 1.46-1.54 (m, 5H), 1.58-1.71 (m, 4H), 2.33 (t, *J* = 7.12 Hz, 2H), 3.35-3.41 (m, 2H), 3.52-3.57 (m, 2H), 4.44 (t, *J* = 5.56 Hz, 1H).



Step 2: 6,6-bis(decyloxy)hexanoic acid

[0624] Prepared according to General Procedure B, substituting 6,6-bis(decyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 250 mg, 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83-0.86 (m, 6H), 1.24 (m, 30H), 1.47-1.48 (m, 8H), 2.17 (t, J=7.32 Hz, 1H), 3.33-3.36 (m, 2H), 3.43-3.48 (m, 2H), 4.39 (t, J=5.44 Hz, 1H), 11.94 (bs, 1H).

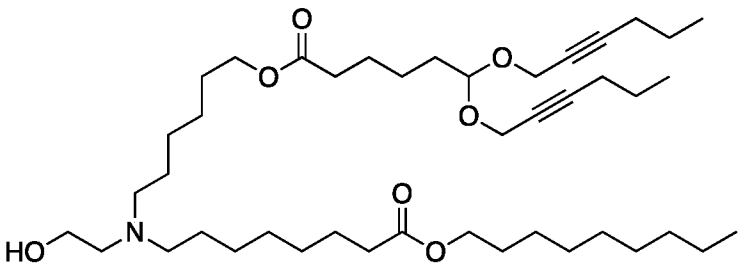


Step 3: 6-bromohexyl 6,6-bis(decyloxy)hexanoate

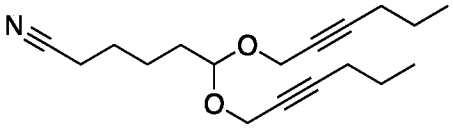
[0625] Prepared according to General Procedure C, substituting 6,6-bis(decyloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 180 mg, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.88 (m, 6H), 1.25-1.38 (m, 34H), 1.42-1.48 (m, 2H), 1.59-1.63 (m, 6H), 1.82-1.87 (m, 2H), 2.29 (t, J=7.4 Hz, 2H), 3.35-3.41 (m, 4H), 3.51-3.56 (m, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.43 (t, J=5.64 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(decyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-46)

[0626] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(decyloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 56 mg, 56%. UPLC-MS (Method B): Rt 2.34 min, m/z calculated [M+H]: 840.8, found 841.5.

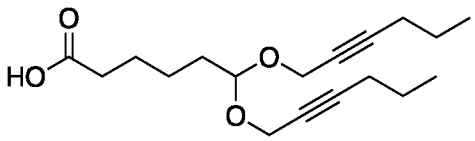


Example 7-47: nonyl 8-((6-((6,6-bis(hex-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



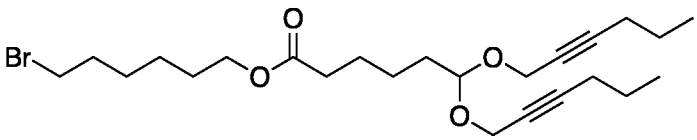
Step 1: 6,6-bis(hex-2-yn-1-yloxy)hexanenitrile

[0627] Prepared according to General Procedure A, substituting hex-2-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 250 mg, 34%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95-0.98 (t, *J* = 7.32 Hz, 6H), 1.48-1.58 (m, 9H), 1.66-1.71 (m, 4H), 2.16-2.20 (m, 4H), 2.33 (t, *J* = 7.08 Hz, 2H), 4.21-4.24 (m, 4H), 4.80 (t, *J* = 5.4 Hz, 1H).



Step 2: 6,6-bis(hex-2-yn-1-yloxy)hexanoic acid

[0628] Prepared according to General Procedure B, substituting 6,6-bis(hex-2-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 150 mg, 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J=7.4 Hz, 6H), 1.23-1.33 (m, 2H), 1.41-1.57 (m, 8H), 2.16-2.20 (m, 6H), 4.12-4.21 (m, 4H), 4.69 (t, J=5.56 Hz, 1H), 11.96 (bs, 1H).

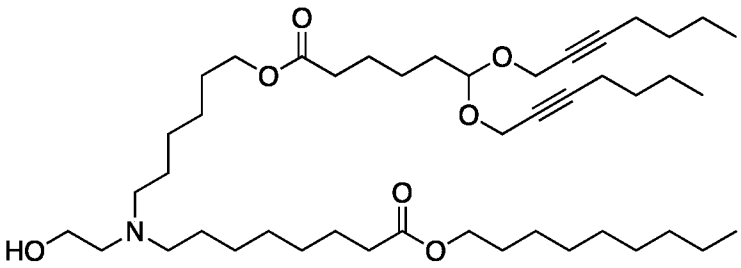


Step 3: 6-bromohexyl 6,6-bis(hex-2-yn-1-yloxy)hexanoate

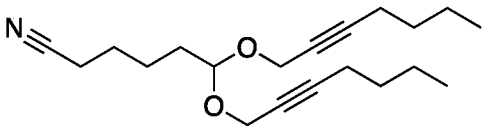
[0629] Prepared according to General Procedure C, substituting 6,6-bis(hex-2-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 150 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.88 (m, 6H), 1.43-1.53 (m, 11H), 1.59-1.69 (m, 7H), 1.82-1.89 (m, 2H), 2.15-2.20 (m, 4H), 2.29 (t, J=7.4 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 4.05 (t, J=6.52 Hz, 2H), 4.20-4.21 (m, 4H), 4.77 (t, J=5.68 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(hex-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-47)

[0630] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(hex-2-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 27 mg, 46%. UPLC-MS (Method C): Rt 4.89 min, m/z calculated [M+H]: 720.6, found 720.9.

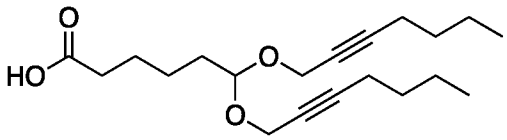


Example 7-48: nonyl 8-((6-((6,6-bis(hept-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



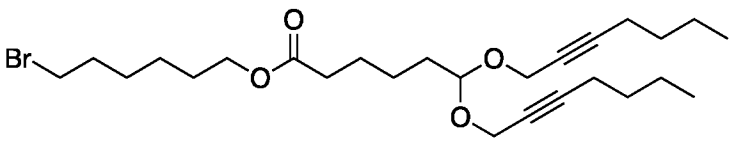
Step 1: 6,6-bis(hept-2-yn-1-yloxy)hexanenitrile

[0631] Prepared according to General Procedure A, substituting hept-2-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 230 mg, 29%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.24 Hz, 6H), 1.36-1.50 (m, 8H), 1.66-1.73 (m, 4H), 2.19-2.22 (m, 4H), 2.28-2.35 (m, 2H), 3.65 (s, 1H), 4.20-4.21 (m, 4H), 4.79 (t, *J* = 5.28 Hz, 1H).



Step 2: 6,6-bis(hept-2-yn-1-yloxy)hexanoic acid

[0632] Prepared according to General Procedure B, substituting 6,6-bis(hept-2-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 140 mg, 68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J=7.4 Hz, 6H), 1.27-1.57 (m, 14H), 2.17-2.22 (m, 6H), 4.11-4.20 (m, 4H), 4.68 (t, J=5.56 Hz, 1H), 11.96 (bs, 1H).

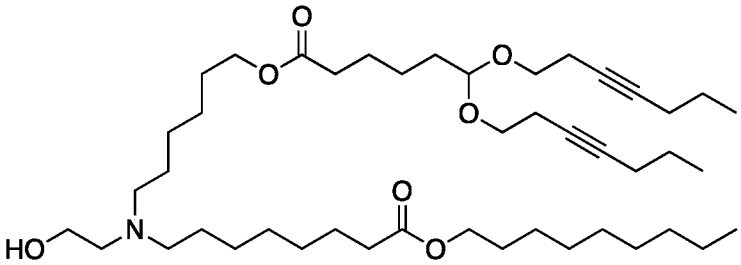


Step 3: 6-bromohexyl 6,6-bis(hept-2-yn-1-yloxy)hexanoate

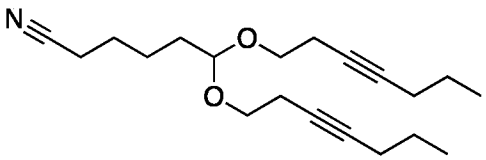
[0633] Prepared according to General Procedure C, substituting 6,6-bis(hept-2-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 140 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, J=7.32 Hz, 6H), 1.34-1.51 (m, 14H), 1.60-1.68 (m, 6H), 1.82-1.89 (m, 2H), 2.18-2.20 (m, 4H), 2.29 (t, J=7.4 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 4.04 (t, J=6.64 Hz, 2H), 4.19 (s, 4H), 4.76 (t, J=5.56 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(hept-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-48)

[0634] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(hept-2-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 40 mg, 52%. UPLC-MS (Method C): Rt 4.99 min, m/z calculated [M+H]: 748.6, found 748.9.

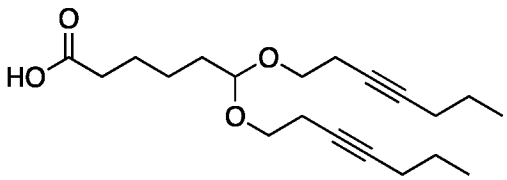


Example 7-49: nonyl 8-((6-((6,6-bis(hept-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



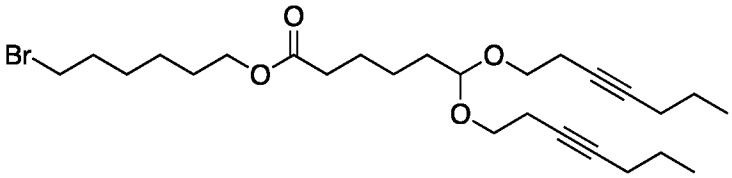
Step 1: 6,6-bis(hept-3-yn-1-yloxy)hexanenitrile

[0635] Prepared according to General Procedure A, substituting hept-3-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 220 mg, 28%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.36 Hz, 6H), 1.37-1.55 (m, 5H), 1.62-1.72 (m, 4H), 2.09-2.012 (m, 4H), 2.28-2.35 (m, 2H), 2.40-2.43 (m, 4H), 3.51-3.56 (m, 2H), 3.63-3.68 (m, 2H), 4.56 (t, *J* = 5.6 Hz, 1H).



Step 2: 6,6-bis(hept-3-yn-1-yloxy)hexanoic acid

[0636] Prepared according to General Procedure B, substituting 6,6-bis(hept-3-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 145 mg, 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J=7.36 Hz, 6H), 1.26-1.30 (m, 3H), 1.39-1.51 (m, 8H), 2.07-2.11 (m, 4H), 2.18 (t, J=7.32 Hz, 2H), 2.33-2.36 (m, 4H), 3.30-3.57 (m, 4H), 4.52 (t, J=5.68 Hz, 1H), 11.95 (bs, 1H).

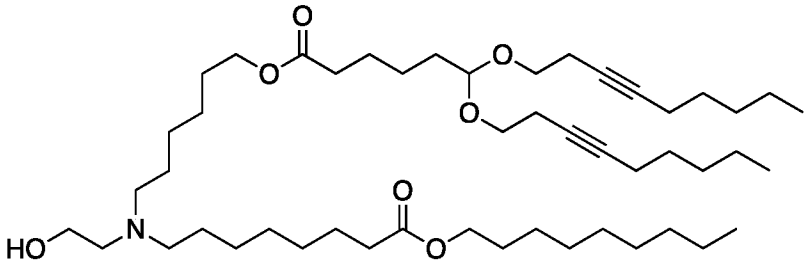


Step 3: 6-bromohexyl 6,6-bis(hept-3-yn-1-yloxy)hexanoate

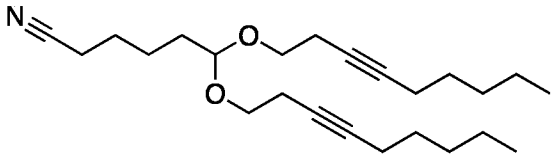
[0637] Prepared according to General Procedure C, substituting 6,6-bis(hept-3-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 85 mg, 40%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, J=7.32 Hz, 6H), 1.36-1.55 (m, 10H), 1.62 (m, 6H), 1.82-1.93 (m, 2H), 2.09-2.12 (m, 4H), 2.28 (t, J=7.64 Hz, 2H), 2.39-2.43 (m, 4H), 3.39 (t, J=6.76 Hz, 2H), 3.50-3.56 (m, 2H), 3.62-3.67 (m, 2H), 4.05 (t, J=6.56 Hz, 2H), 4.55 (t, J=5.64 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(hept-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-49)

[0638] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(hept-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 29 mg, 50%. UPLC-MS (Method B): Rt 1.88 min, m/z calculated [M+H]: 748.6, found 748.9.

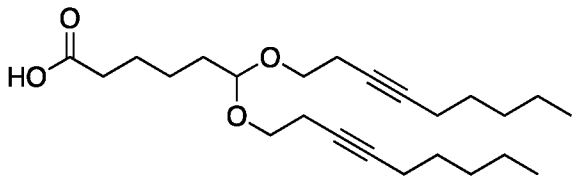


Example 7-50: nonyl 8-((6-((6,6-bis(non-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



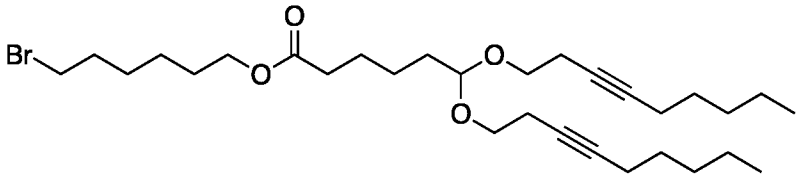
Step 1: 6,6-bis(non-3-yn-1-yloxy)hexanenitrile

[0639] Prepared according to General Procedure A, substituting non-3-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 220 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.36Hz, 6H), 1.37-1.55 (m, 5H), 1.62-1.72 (m, 4H), 2.09-2.12 (m, 4H), 2.28-2.35 (m, 2H), 2.40-2.43 (m, 4H), 3.51-3.56 (m, 2H), 3.63-3.68 (m, 2H), 4.56 (t, *J* = 5.6Hz, 1H).



Step 2: 6,6-bis(non-3-yn-1-yloxy)hexanoic acid

[0640] Prepared according to General Procedure B, substituting 6,6-bis(non-3-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 150 mg, 60%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84-0.87 (m, 6H), 1.28-1.29 (m, 10H), 1.38-1.50 (m, 7H), 2.08-2.12 (m, 4H), 2.18 (t, J=7.32 Hz, 2H), 2.29-2.41 (m, 4H), 3.42-3.58 (m, 4H), 4.52 (t, J=5.68 Hz, 1H), 11.98 (bs, 1H).

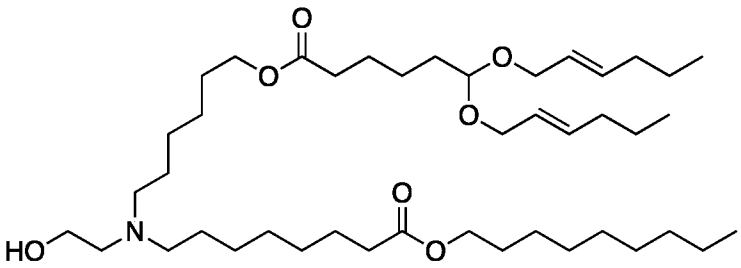


Step 3: 6-bromohexyl 6,6-bis(non-3-yn-1-yloxy)hexanoate

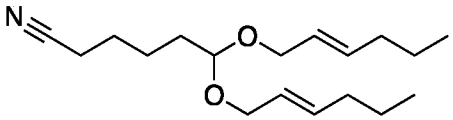
[0641] Prepared according to General Procedure C, substituting 6,6-bis(non-3-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 90 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, J=6.96 Hz, 6H), 1.29-1.48 (m, 16H), 1.60-1.63 (m, 5H), 1.86 (m, 2H), 2.09-2.14 (m, 4H), 2.28 (t, J=7.6 Hz, 2H), 2.39-2.42 (m, 3H), 3.39 (t, J=6.76 Hz, 2H), 3.52-3.54 (m, 2H), 3.63-3.65 (m, 2H), 4.05 (t, J=6.56 Hz, 2H), 4.54 (t, J=5.64 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(non-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-50)

[0642] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(non-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 33 mg, 46%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 804.7, found 805.2.

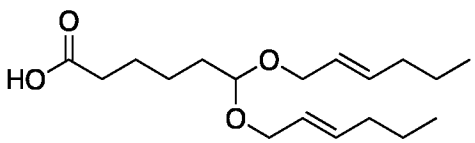


Example 7-51: nonyl 8-((6-((6,6-bis(((*E*)-hex-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



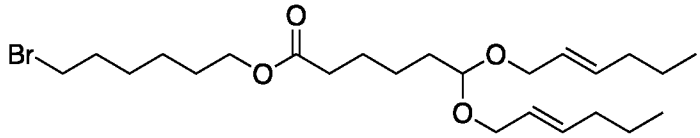
Step 1: 6,6-bis(((E)-hex-2-en-1-yl)oxy)hexanenitrile

[0643] Prepared according to General Procedure A, substituting (*E*)-hex-2-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 210 mg, 28%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.36 Hz, 6H), 1.35-1.44 (m, 4H), 1.49-1.55 (m, 3H), 1.62-1.69 (m, 3H), 1.99-2.04 (m, 4H), 2.31-2.52 (m, 2H), 3.91-3.95 (m, 1H), 4.01-4.08 (m, 2H), 4.55 (t, *J* = 5.6 Hz, 1H), 5.51-5.55 (m, 1H), 5.64-5.70 (m, 2H).



Step 2: 6,6-bis(((E)-hex-2-en-1-yl)oxy)hexanoic acid

[0644] Prepared according to General Procedure B, substituting 6,6-bis(((*E*)-hex-2-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 120 mg, 72%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.86 (t, J=7.36 Hz, 6H), 1.26-1.39 (m, 8H), 1.46-1.49 (m, 4H), 1.95-2.00 (m, 4H), 2.18 (t, J=7.32 Hz, 2H), 3.85-3.98 (m, 4H), 4.47 (t, J=5.44 Hz, 1H), 5.45-5.52 (m, 2H), 5.59-5.67 (m, 2H), 11.97 (bs, 1H).

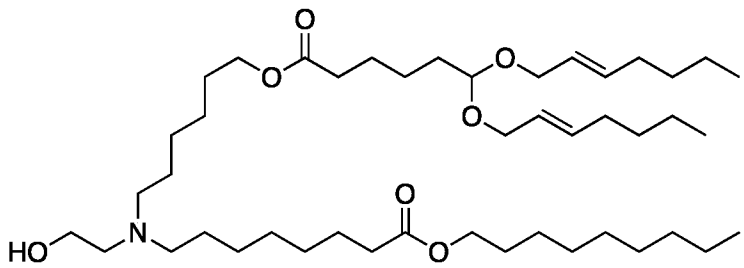


Step 3: 6-bromohexyl 6,6-bis(((E)-hex-2-en-1-yl)oxy)hexanoate

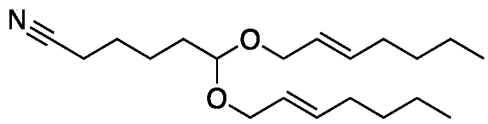
[0645] Prepared according to General Procedure C, substituting 6,6-bis(((*E*)-hex-2-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 70 mg, 38%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, J=7.4 Hz, 6H), 1.34-1.48 (m, 9H), 1.59-1.66 (m, 6H), 1.82-1.87 (m, 2H), 1.98-2.04 (m, 4H), 2.29 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 3.90-3.95 (m, 2H), 4.00-4.08 (m, 4H), 4.54 (t, J=5.68 Hz, 1H), 5.49-5.56 (m, 2H), 5.63-5.71 (m, 2H).

Step 4: nonyl 8-((6-((6,6-bis(((E)-hex-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-51)

[0646] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*E*)-hex-2-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 23 mg, 35%. UPLC-MS (Method B): Rt 1.92 min, m/z calculated [M+H]: 724.6, found 725.1.

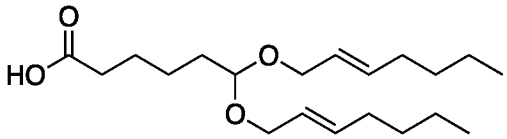


Example 7-52: nonyl 8-((6-((6,6-bis(((*E*)-hept-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



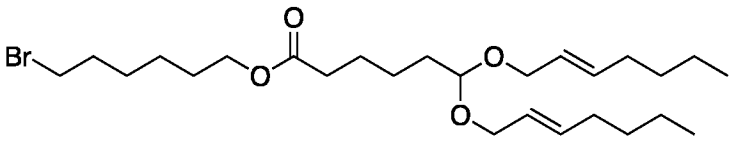
Step 1: 6,6-bis(((E)-hept-2-en-1-yl)oxy)hexanenitrile

[0647] Prepared according to General Procedure A, substituting (*E*)-hept-2-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 220 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.91Hz, 6H), 1.29-1.36 (m, 8H), 1.50-1.71 (m, 6H), 2.01-2.04 (m, 4H), 2.32 (t, *J* = 7.12 Hz, 2H), 3.90-3.95 (m, 2H), 4.00-4.06 (m, 2H), 4.54 (t, *J* = 5.52 Hz, 1H), 5.47-5.56 (m, 2H), 5.65-5.70 (m, 2H).



Step 2: 6,6-bis(((E)-hept-2-en-1-yl)oxy)hexanoic acid

[0648] Prepared according to General Procedure B, substituting 6,6-bis(((*E*)-hept-2-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 130 mg, 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (m, 6H), 1.26-1.37 (m, 10H), 1.41-1.52 (m, 4H), 1.99-2.00 (m, 4H), 2.18 (t, J=7.36 Hz, 2H), 3.84-4.03 (m, 4H), 4.47 (t, J=5.44 Hz, 1H), 5.45-5.51 (m, 2H), 5.59-5.66 (m, 2H), 11.98 (bs, 1H).

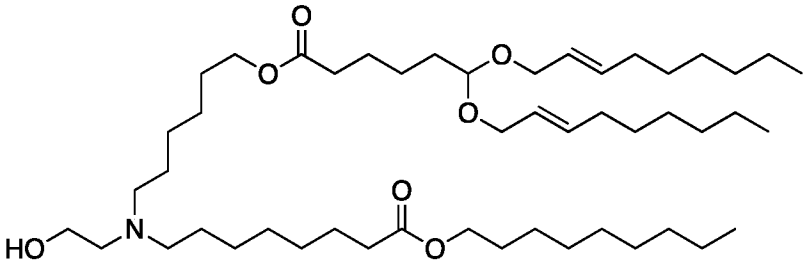


Step 3: 6-bromohexyl 6,6-bis(((E)-hept-2-en-1-yl)oxy)hexanoate

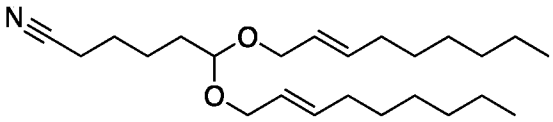
[0649] Prepared according to General Procedure C, substituting 6,6-bis(((*E*)-hept-2-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 86 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, J=7.04 Hz, 6H), 1.20-1.48 (m, 13H), 1.56-1.65 (m, 5H), 1.82-1.87 (m, 2H), 2.00-2.05 (m, 3H), 2.28 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 3.89-3.94 (m, 2H), 3.99-4.06 (m, 4H), 4.53 (t, J=5.68 Hz, 1H), 5.49-5.56 (m, 2H), 5.64-5.71 (m, 2H).

Step 4: nonyl 8-((6-(((6,6-bis(((E)-hept-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-52)

[0650] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*E*)-hept-2-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 23 mg, 40%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 752.6, found 753.2.

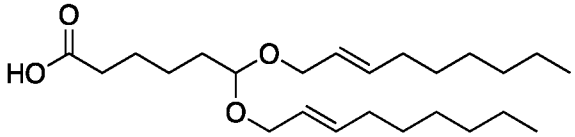


Example 7-53: nonyl 8-((6-((6,6-bis(((*E*)-non-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



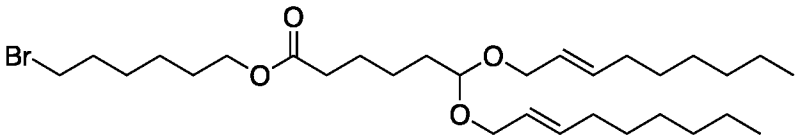
Step 1: 6,6-bis(((E)-non-2-en-1-yl)oxy)hexanenitrile

[0651] Prepared according to General Procedure A, substituting (*E*)-non-2-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 230 mg, 24%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-00.87 (m, 6H), 1.26-1.42 (m, 18H), 1.63-1.76 (m, 4H), 2.00-2.03 (m, 4H), 2.33 (t, *J* = 7.16 Hz, 2H), 3.90-4.07 (m, 4H), 4.54 (t, *J* = 5.52 Hz, 1H), 5.50-5.55 (m, 2H), 5.65-5.72 (m, 2H).



Step 2: 6,6-bis(((E)-non-2-en-1-yl)oxy)hexanoic acid

[0652] Prepared according to General Procedure B, substituting 6,6-bis(((*E*)-non-2-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 130 mg, 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83-0.85 (m, 3H), 1.24 (m, 11H), 1.46-1.49 (m, 2H), 1.96-2.00 (m, 2H), 2.17 (t, J=7.36 Hz, 1H), 3.80-3.97 (m, 2H), 4.47 (t, J=5.44 Hz, 1H), 5.44-5.53 (m, 1H), 5.59-5.75 (m, 1H), 11.96 (bs, 1H).



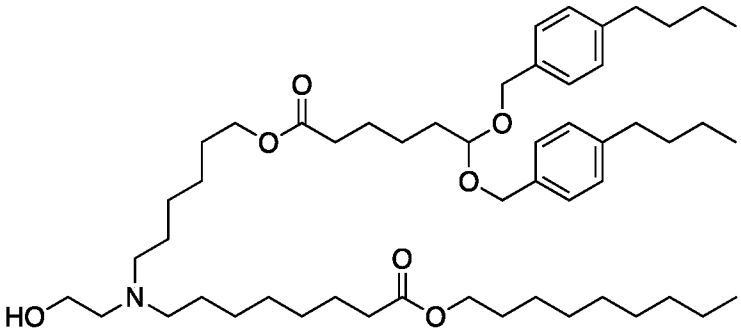
Step 3: 6-bromohexyl 6,6-bis(((E)-non-2-en-1-yl)oxy)hexanoate

[0653] Prepared according to General Procedure C, substituting 6,6-bis(((*E*)-non-2-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 110 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (m, 6H), 1.26-1.49 (m, 20H), 1.60-1.64 (m, 5H), 1.82-1.89

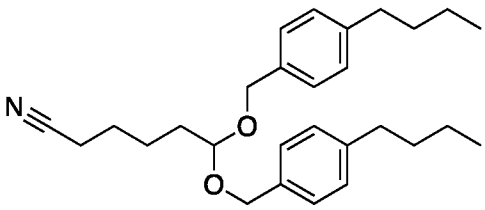
(m, 2H), 1.99-2.03 (m, 4H), 2.28 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 3.90-3.94 (m, 2H), 3.99-4.06 (m, 4H), 4.54 (t, J=5.48 Hz, 1H), 5.50-5.55 (m, 2H), 5.62-5.70 (m, 2H).

Step 4: nonyl 8-((6-((6,6-bis(((E)-non-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-53)

[0654] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*E*)-non-2-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 39 mg, 53%. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 808.7, found 809.2.

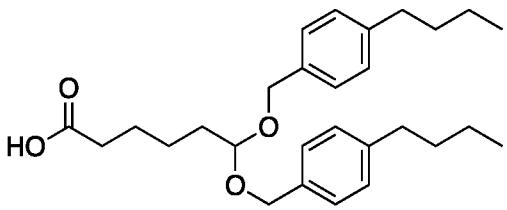


Example 7-54: nonyl 8-((6-((6,6-bis((4-butylbenzyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



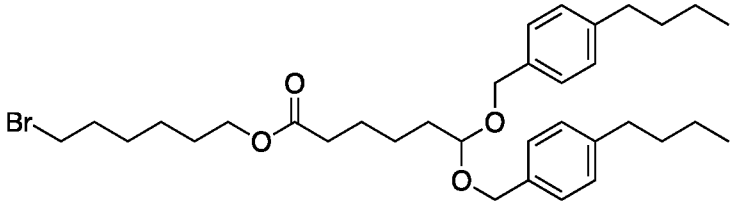
Step 1: 6,6-bis((4-butylbenzyl)oxy)hexanenitrile

[0655] Prepared according to General Procedure A, substituting (4-butylphenyl)methanol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 260 mg, 25%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.28 Hz, 6H), 1.29-1.38 (m, 4H), 1.55-1.77 (m, 12H), 2.29 (t, *J* = 7.04 Hz, 2H), 2.59 (t, *J* = 7.76 Hz, 4H), 4.48-4.51 (d, *J* = 11.48 Hz, 2H), 4.59-4.64 (m, 2H), 4.69 (t, *J* = 5.52 Hz, 1H), 7.14-7.16 (m, 4H), 7.22-7.24 (m, 4H).



Step 2: 6,6-bis((4-butylbenzyl)oxy)hexanoic acid

[0656] Prepared according to General Procedure B, substituting 6,6-bis((4-butylbenzyl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 150 mg, 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J=7.36 Hz, 6H), 1.17-1.33 (m, 8H), 1.41-1.64 (m, 8H), 2.17 (t, J=7.36 Hz, 2H), 2.49-2.66 (m, 4H), 4.43-4.46 (d, J=12.04 Hz, 2H), 4.53-4.56 (d, J=11.6 Hz, 2H), 4.66 (t, J=5.4 Hz, 1H), 7.14-7.22 (m, 8H), 11.97 (bs, 1H).

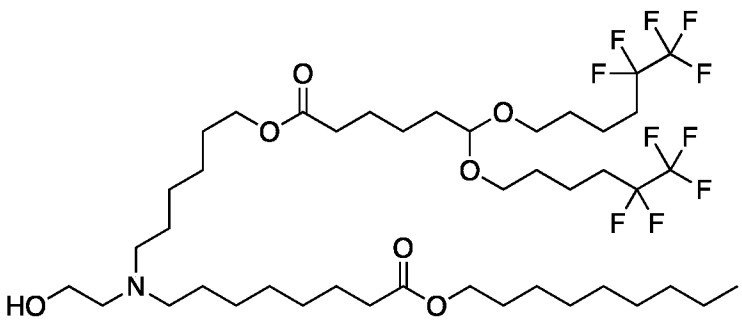


Step 3: 6-bromohexyl 6,6-bis((4-butylbenzyl)oxy)hexanoate

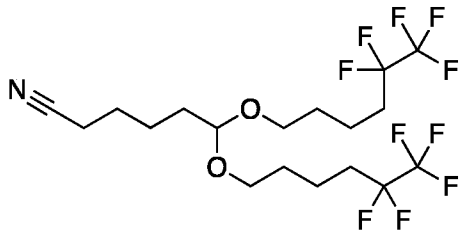
[0657] Prepared according to General Procedure C, substituting 6,6-bis((4-butylbenzyl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 82 mg, 46%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.84-0.92 (m, 6H), 1.21-1.43 (m, 10H), 1.53-1.75 (m, 12H), 1.81-1.90 (m, 4H), 2.27 (t, J=7.4 Hz, 2H), 2.59 (t, J=7.72 Hz, 4H), 3.38 (t, J=6.72 Hz, 2H), 4.04 (t, J=6.64 Hz, 2H), 4.48-4.61 (m, 4H), 4.70 (t, J=5.72 Hz, 1H), 7.13-7.15 (m, 4H), 7.22-7.24 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis((4-butylbenzyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-54)

[0658] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis((4-butylbenzyl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 22 mg, 35%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 852.7, found 853.2.

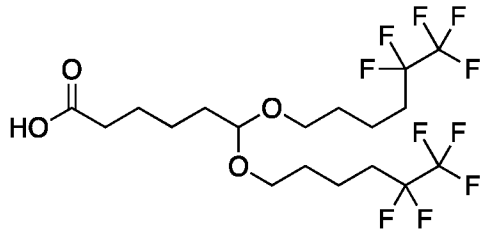


Example 7-55: nonyl 8-((6-((6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



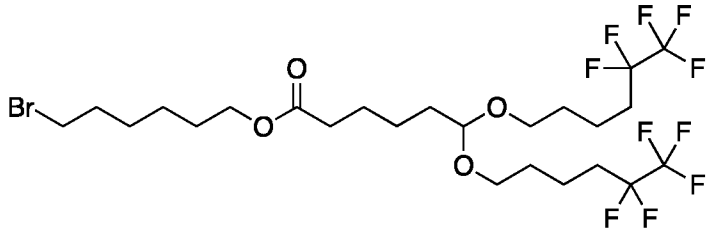
Step 1: 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanenitrile

[0659] Prepared according to General Procedure A, substituting 5,5,6,6,6-pentafluorohexan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 208 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.50-1.53 (m, 2H), 1.68 (m, 12H), 1.98-2.09 (m, 4H), 2.37 (t, *J* = 4.76 Hz, 2H), 3.41-3.48 (m, 2H), 3.57-3.64 (m, 2H), 3.69-3.70 (m, 1H), 4.45 (t, *J* = 5.48 Hz, 1H).



Step 2: 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoic acid

[0660] Prepared according to General Procedure B, substituting 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 220 mg, 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.27 (m, 2H), 1.50-1.57 (m, 8H), 2.17-2.19 (m, 4H), 3.40-3.52 (m, 4H), 4.44 (m, 1H), 12.0 (bs, 1H).

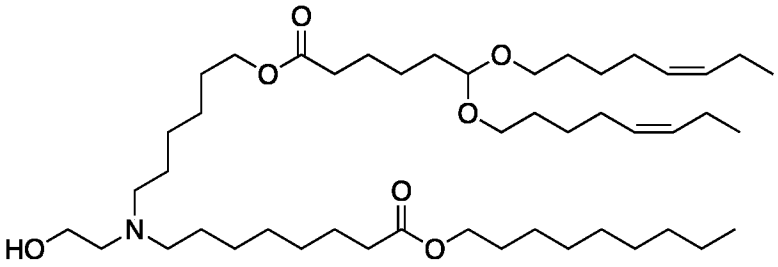


Step 3: 6-bromohexyl 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoate

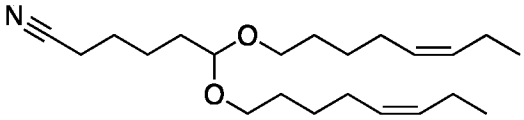
[0661] Prepared according to General Procedure C, substituting 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 80 mg, 40%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.36-1.37 (m, 4H), 1.46-1.49 (m, 4H), 1.65 (m, 20H), 1.82-1.87 (m, 2H), 1.99-2.06 (m, 6H), 2.27-2.32 (m, 3H), 2.45 (m, 1H), 3.39-3.47 (m, 4H), 3.56-3.60 (m, 2H), 3.65-3.70 (m, 2H), 4.03-4.08 (m, 2H), 4.44 (t, J=5.44 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-55)

[0662] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis((5,5,6,6,6-pentafluorohexyl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 27 mg, 32%. UPLC-MS (Method C): Rt 5.14 min, m/z calculated [M+H]: 908.5, found 908.6.

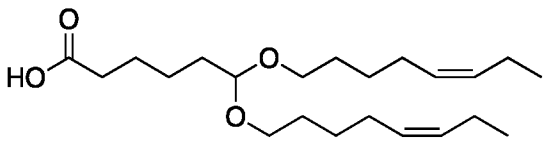


Example 7-56: nonyl 8-((6-((6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



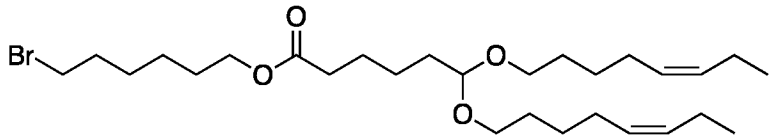
Step 1: 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanenitrile

[0663] Prepared according to General Procedure A, substituting 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 220 mg, 24%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.56 Hz, 6H), 1.24 (t, *J* = 6.72 Hz, 1H), 1.38-1.69 (m, 13H), 1.98-2.06 (m, 8H), 2.33 (t, *J* = 7.12 Hz, 2H), 3.36-3.58 (m, 4H), 4.44 (t, *J* = 5.52 Hz, 1H), 5.28-5.37 (m, 4H).



Step 2: 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoic acid

[0664] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 190 mg, 75%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.90 (t, J=7.52 Hz, 6H), 1.27-1.36 (m, 7H), 1.47 (m, 8H), 1.97-2.01 (m, 8H), 2.16 (t, J=9.4 Hz, 2H), 3.46 (m, 2H), 4.40 (m, 1H), 5.30-5..39 (m, 4H), 11.95 (bs, 1H).

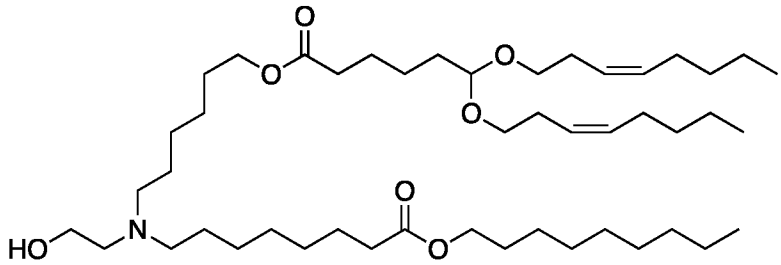


Step 3: 6-bromohexyl 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate

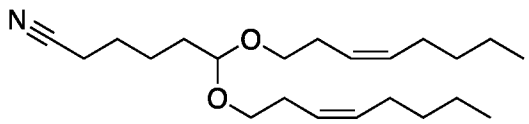
[0665] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 120 mg, 60%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, J=4.76 Hz, 6H), 1.34-1.45 (m, 10H), 1.52-1.64 (m, 10H), 1.85 (m, 2H), 2.00-2.06 (m, 8H), 2.29 (t, J=7.6 Hz, 2H), 3.37-3.41 (m, 4H), 3.51-3.58 (m, 2H), 4.04 (t, J=6.68 Hz, 2H), 4.43 (t, J=5.68 Hz, 1H), 5.31-5.36 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-56)

[0666] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 31 mg, 53%. UPLC-MS (Method B): Rt 2.16 min, m/z calculated [M+H]: 780.7, found 780.9.

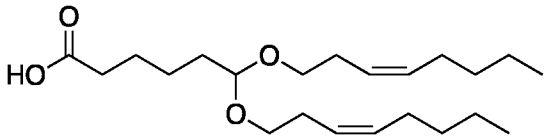


Example 7-57: nonyl 8-((6-((6,6-bis(((*Z*)-oct-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



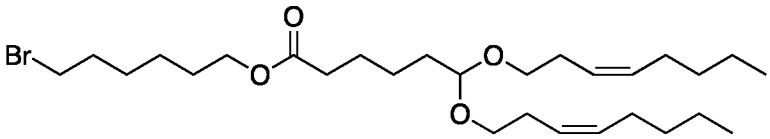
Step 1: 6,6-bis(((Z)-oct-3-en-1-yl)oxy)hexanenitrile

[0667] Prepared according to General Procedure A, substituting (*Z*)-oct-3-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 350 mg, 40%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86-0.90 (m, 6H), 1.26-1.33 (m, 8H), 1.47-1.53 (m, 2H), 1.60-1.71 (m, 4H), 2.01-2.05 (m, 4H), 2.28-2.34 (m, 6H), 3.40-3.44 (m, 2H), 3.53-3.59 (m, 2H), 4.47 (t, *J* = 5.52 Hz, 1H), 5.32-5.48 (m, 4H).



Step 2: 6,6-bis(((Z)-oct-3-en-1-yl)oxy)hexanoic acid

[0668] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-oct-3-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 95 mg, 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (m, 6H), 1.27-1.28 (m, 11H), 1.46-1.50 (m, 4H), 1.98-2.01 (m, 5H), 2.16-2.32 (m, 6H), 3.31-3.50 (m, 4H), 5.32-5.42 (m, 4H), 11.97 (bs, 1H).

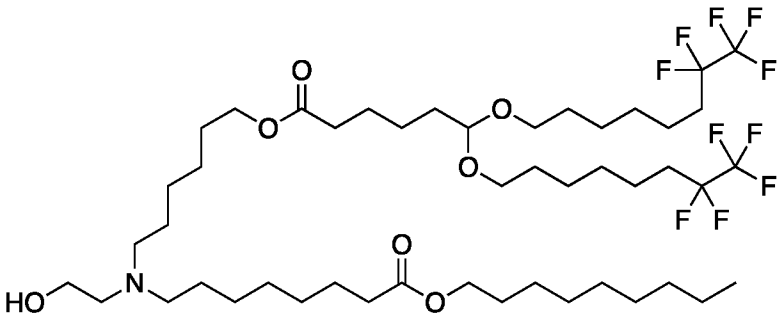


Step 3: 6-bromohexyl 6,6-bis(((Z)-oct-3-en-1-yl)oxy)hexanoate

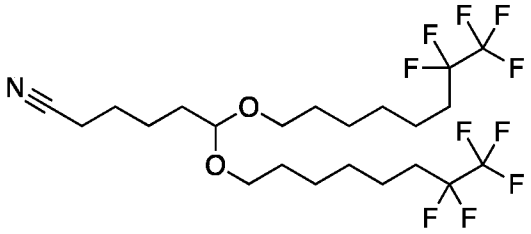
[0669] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-oct-3-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 80 mg, 40%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (m, 6H), 1.31-1.45 (m, 15H), 1.62 (m, 7H), 1.84-1.85 (m, 2H), 2.02-2.04 (m, 4H), 2.29-2.31 (m, 5H), 3.39-3.41 (m, 4H), 3.52-3.63 (m, 3H), 4.05 (m, 2H), 4.47-4.48 (m, 1H), 5.36-5.43 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis(((Z)-oct-3-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-57)

[0670] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*Z*)-oct-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 16 mg, 34%. UPLC-MS (Method C): Rt 5.29 min, m/z calculated [M+H]: 780.7, found 780.8.

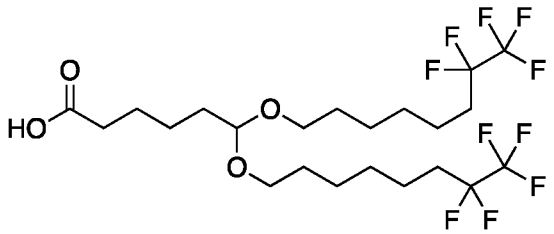


Example 7-58: nonyl 8-((6-((6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



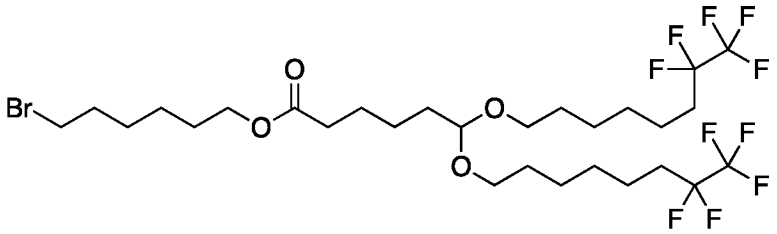
Step 1: 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanenitrile

[0671] Prepared according to General Procedure A, substituting 7,7,8,8,8-pentafluorooctan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 230 mg, 16%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.39 (m, 9H), 1.50-1.69 (m, 14H), 1.93-2.06 (m, 4H), 2.33 (t, J=4Hz, 2H), 3.36-3.42 (m, 2H), 3.53-3.56 (m, 2H), 4.44 (t, J=5.2Hz, 1H).



Step 2: 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoic acid

[0672] Prepared according to General Procedure B, substituting 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanenitrilefor 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 160 mg, 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.35 (m, 11H), 1.40-1.49 (m, 12H), 2.09-2.22 (m, 6H), 3.31-3.39 (m, 4H), 3.43-3.50 (m, 2H), 4.41 (t, J=5.56 Hz, 1H), 12.00 (bs, 1H).

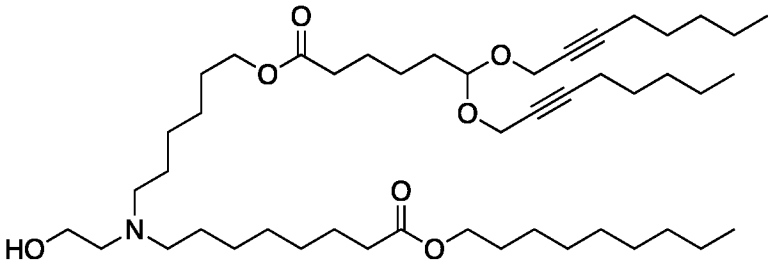


Step 3: 6-bromohexyl 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoate

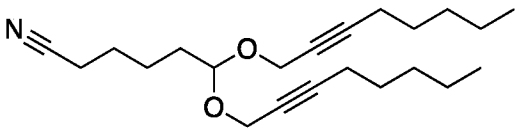
[0673] Prepared according to General Procedure C, substituting 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 120 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.38-1.49 (m, 14H), 1.56 (m, 10H), 1.81-1.88 (m, 1H), 1.92-2.06 (m, 4H), 2.29 (t, J=7.6 Hz, 2H), 3.35-3.41 (m, 3H), 3.51-3.57 (m, 2H), 4.04 (t, J=6.56 Hz, 2H), 4.43 (t, J=5.56 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-58)

[0674] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis((7,7,8,8,8-pentafluorooctyl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 41 mg, 45%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 964.6, found 964.8.

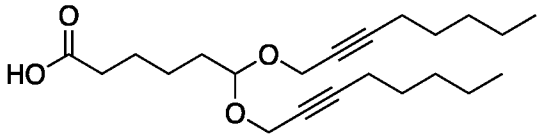


Example 7-59: nonyl 8-((6-((6,6-bis(oct-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



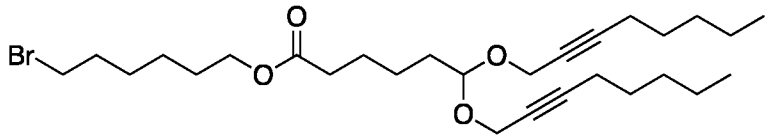
Step 1: 6,6-bis(oct-2-yn-1-yloxy)hexanenitrile

[0675] Prepared according to General Procedure A, substituting oct-2-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 210 mg, 19%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87-0.90 (t, J=7.00 Hz, 6H), 1.29-1.32 (m, 8H), 1.54 (m, 5H), 1.67-1.71 (m, 3H), 2.20-2.21 (m, 4H), 2.31-2.35 (m, 2H), 4.21 (s, 4H), 4.79-4.80 (m, 1H).



Step 2: 6,6-bis(oct-2-yn-1-yloxy)hexanoic acid

[0676] Prepared according to General Procedure B, substituting 6,6-bis(oct-2-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 120 mg, 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (m, 6H), 1.23-1.36 (m, 10H), 1.38-1.57 (m, 8H), 2.16-2.21 (m, 6H), 4.11-4.20 (m, 4H), 4.68 (t, J=5.44 Hz, 1H), 11.97 (bs, 1H).

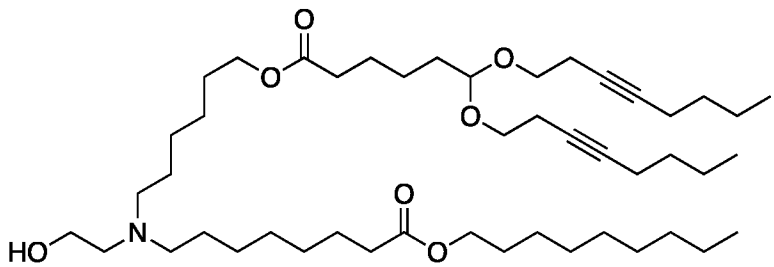


Step 3: 6-bromohexyl 6,6-bis(oct-2-yn-1-yloxy)hexanoate

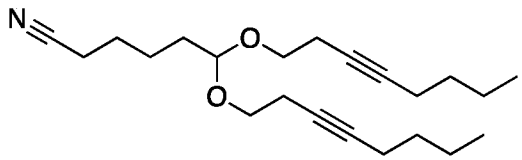
[0677] Prepared according to General Procedure C, substituting 6,6-bis(oct-2-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 70 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, J=6.92 Hz, 6H), 1.15-1.51 (m, 23H), 1.63-1.64 (m, 6H), 1.82-1.87 (m, 2H), 2.17-2.21 (m, 4H), 2.29 (t, J=7.56 Hz, 2H), 3.39 (t, J=6.64 Hz, 2H), 4.04 (t, J=6.64 Hz, 2H), 4.19 (s, 4H), 4.76 (t, J=5.48 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(oct-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-59)

[0678] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(oct-2-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 32 mg, 35%. UPLC-MS (Method C): Rt 5.16 min, m/z calculated [M+H]: 776.6, found 776.7.

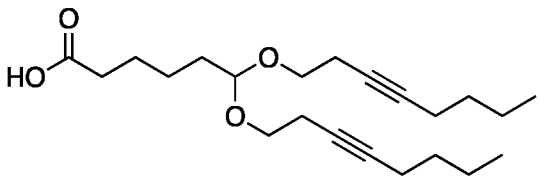


Example 7-60: nonyl 8-((6-((6,6-bis(oct-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



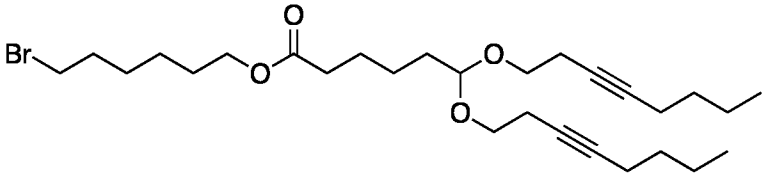
Step 1: 6,6-bis(oct-3-yn-1-yloxy)hexanenitrile

[0679] Prepared according to General Procedure A, substituting oct-3-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 210 mg, 17%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87-0.90 (t, J=7.00 Hz, 6H), 1.12-1.70 (m, 18H), 2.11-2.13 (m, 4H), 2.31-2.34 (t, J=7.04 Hz, 2H), 2.41 (m, 4H), 3.50-3.56 (m, 2H), 3.62-3.68 (m, 2H), 4.56 (t, J=5.76 Hz, 1H).



Step 2: 6,6-bis(oct-3-yn-1-yloxy)hexanoic acid

[0680] Prepared according to General Procedure B, substituting 6,6-bis(oct-3-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 160 mg, 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J=7.05 Hz, 6H), 1.23-1.51 (m, 16H), 2.09-2.13 (m, 4H), 2.16 (t, J=9.4 Hz, 2H), 2.31-2.50 (m, 4H), 3.44-3.57 (m, 4H), 4.52 (m, 1H), 11.96 (bs, 1H).

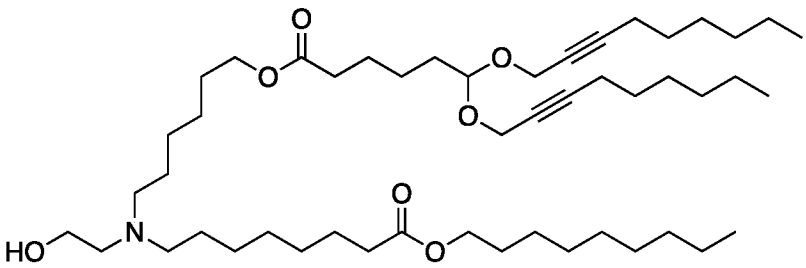


Step 3: 6-bromohexyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate

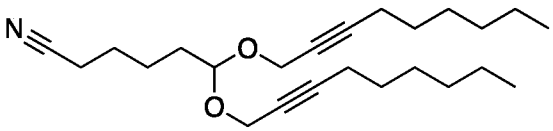
[0681] Prepared according to General Procedure C, substituting 6,6-bis(oct-3-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 90 mg, 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, J=6.92 Hz, 6H), 1.20-1.24 (m, 2H), 1.36-1.46 (m, 16H), 1.62 (ill. res. m, 6H), 1.82-1.87 (m, 2H), 2.11-2.13 (m, 4H), 2.28 (t, J=7.6 Hz, 2H), 2.40-2.42 (m, 4H), 3.39 (t, J=6.72 Hz, 2H), 3.49-3.55 (m, 2H), 3.61-3.67 (m, 2H), 4.04 (t, J=6.68 Hz, 2H), 4.54 (t, J=5.28 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(oct-3-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-60)

[0682] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 52 mg, 44%. UPLC-MS (Method C): Rt 5.09 min, m/z calculated [M+H]: 776.6, found 776.8.

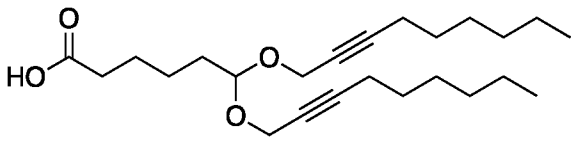


Example 7-61: nonyl 8-((6-((6,6-bis(non-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



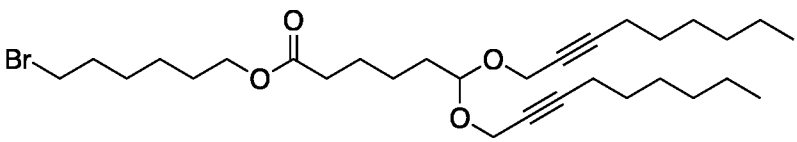
Step 1: 6,6-bis(non-2-yn-1-yloxy)hexanenitrile

[0683] Prepared according to General Procedure A, substituting non-2-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 230 mg, 19%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87-0.90 (t, J=7.00 Hz, 6H), 1.25-1.40 (m, 12H), 1.46-1.73 (m, 13H), 2.18-2.21 (m, 4H), 2.31-2.35 (t, J=7.12 Hz, 2H), 4.17-4.24 (m, 4H), 4.77-4.80 (t, J=5.4 Hz, 1H).



Step 2: 6,6-bis(non-2-yn-1-yloxy)hexanoic acid

[0684] Prepared according to General Procedure B, substituting 6,6-bis(non-2-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 190 mg, 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J=7.058 Hz, 6H), 1.19-1.58 (m, 22H), 2.06-2.21 (m, 6H), 4.11-4.20 (m, 4H), 4.68 (t, J=5.52 Hz, 1H).

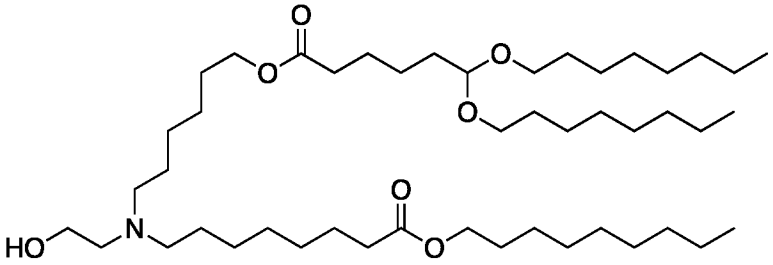


Step 3: 6-bromohexyl 6,6-bis(non-2-yn-1-yloxy)hexanoate

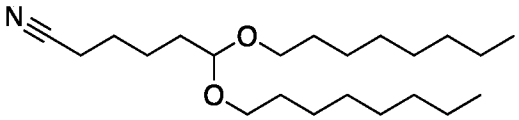
[0685] Prepared according to General Procedure C, substituting 6,6-bis(non-2-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 95 mg, 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, J=7.04 Hz, 6H), 1.24-1.68 (m, 32H), 1.84-1.87 (m, 2H), 2.17-2.21 (m, 4H), 2.29 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 4.05 (t, J=6.6 Hz, 2H), 4.19 (m, 4H), 4.76 (t, J=5.68 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(non-2-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-61)

[0686] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(non-2-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 32 mg, 32%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 804.7, found 804.8.

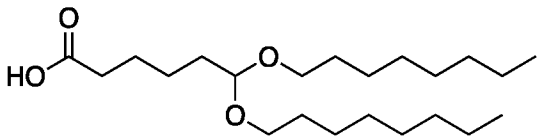


Example 7-62: nonyl 8-((6-((6,6-bis(octyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



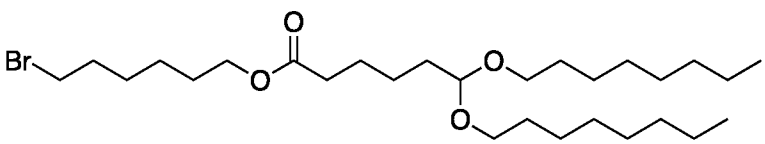
Step 1: 6,6-bis(octyloxy)hexanenitrile

[0687] Prepared according to General Procedure A, substituting octan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 210 mg, 18%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85-0.88 (m, 6H), 1.34 (m, 20H), 1.46-1.72 (m, 8H), 2.31-2.35 (t, J=7.12 Hz, 2H), 3.36-3.41 (m, 2H), 3.52-3.58 (m, 2H), 4.44 (t, J=5.52 Hz, 1H).



Step 2: 6,6-bis(octyloxy)hexanoic acid

[0688] Prepared according to General Procedure B, substituting 6,6-bis(octyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 180 mg, 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83-0.86 (m, 6H), 1.24 (m, 22H), 1.44-1.49 (m, 8H), 2.17 (t, J=7.32 Hz, 2H), 3.30-3.49 (m, 6H), 4.40 (t, J=5.52 Hz, 1H), 11.99 (bs, 1H).

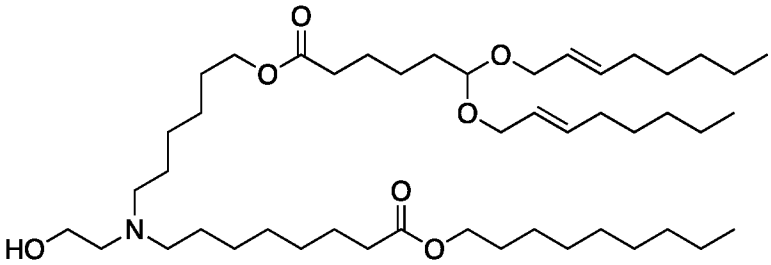


Step 3: 6-bromohexyl 6,6-bis(octyloxy)hexanoate

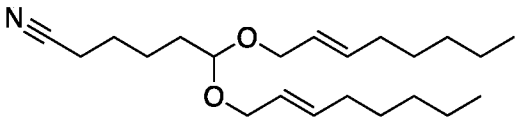
[0689] Prepared according to General Procedure C, substituting 6,6-bis(octyloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 90 mg, 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (t, J=6.96 Hz, 6H), 1.26-1.46 (m, 27H), 1.48-1.66 (m, 12H), 1.82-1.89 (m, 2H), 2.29 (t, J=7.6 Hz, 2H), 3.35-3.41 (m, 4H), 3.51-3.56 (m, 2H), 4.05 (t, J=6.68 Hz, 2H), 4.43 (t, J=5.64 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(octyloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-62)

[0690] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(octyloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 38 mg, 39%. UPLC-MS (Method B): Rt 2.23 min, m/z calculated [M+H]: 784.7, found 784.8.

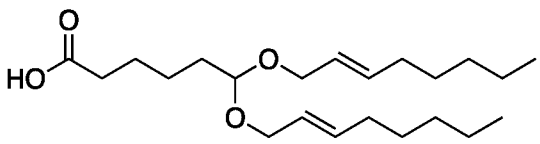


Example 7-63: nonyl 8-((6-((6,6-bis(((*E*)-oct-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



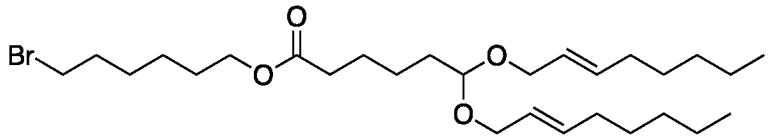
Step 1: 6,6-bis(((E)-oct-2-en-1-yl)oxy)hexanenitrile

[0691] Prepared according to General Procedure A, substituting (*E*)-oct-2-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 230 mg, 25%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (m, 6H), 1.28-1.38 (m, 12H), 1.51-1.75 (m, 5H), 2.01-2.03 (m, 4H), 2.30-2.34 (t, J=7.04 Hz, 2H), 3.90-4.04 (m, 4H), 4.50-4.55 (m, 1H), 5.50-5.54 (m, 2H), 5.65-5.72 (m, 2H).



Step 2: 6,6-bis(((E)-oct-2-en-1-yl)oxy)hexanoic acid

[0692] Prepared according to General Procedure B, substituting 6,6-bis(((*E*)-oct-2-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 190 mg, 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85-0.87 (m, 6H), 1.26-1.49 (m, 19H), 1.98-2.00 (m, 4H), 2.18 (t, J=7.32 Hz, 2H), 3.85-4.05 (m, 4H), 4.47 (t, J=5.52 Hz, 1H), 5.46-5.50 (m, 2H), 5.55-5.66 (m, 2H), 11.96 (bs, 1H).

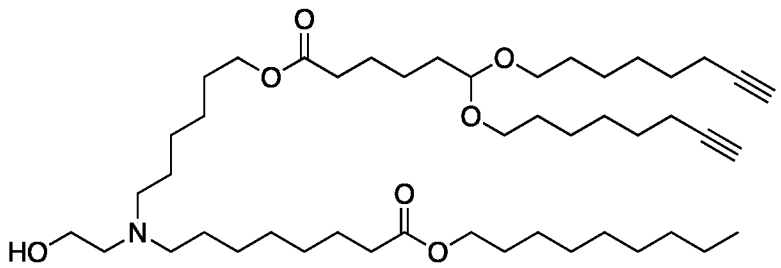


Step 3: 6-bromohexyl 6,6-bis(((E)-oct-2-en-1-yl)oxy)hexanoate

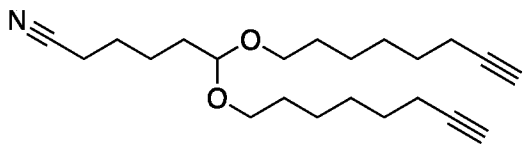
[0693] Prepared according to General Procedure C, substituting 6,6-bis(((*E*)-oct-2-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 70 mg, 40%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, J=6.96 Hz, 6H), 1.20-1.48 (m, 18H), 1.50-1.62 (m, 5H), 1.64-1.85 (m, 2H), 1.87-2.05 (m, 4H), 2.28 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.76 Hz, 2H), 3.90-3.94 (m, 2H), 3.99-4.06 (m, 3H), 4.54 (t, J=5.64 Hz, 1H), 5.49-5.72 (m, 4H).

Step 4: nonyl 8-((6-((6,6-bis(((E)-oct-2-en-1-yl)oxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-63)

[0694] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(((*E*)-oct-2-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 19 mg, 28%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 780.7, found 780.7.

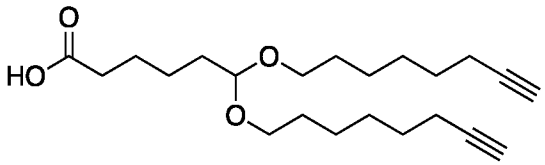


Example 7-64: nonyl 8-((6-((6,6-bis(oct-7-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



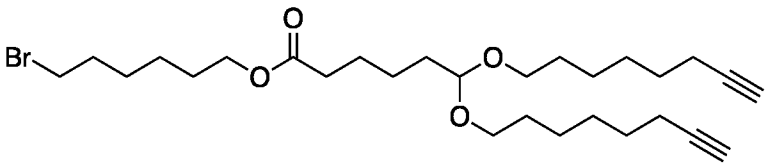
Step 1: 6,6-bis(oct-7-yn-1-yloxy)hexanenitrile

[0695] Prepared according to General Procedure A, substituting oct-7-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 200 mg, 22%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.35-1.38 (m, 8H), 1.50-1.69 (m, 17H), 1.91-1.93 (m, 2H), 2.15-2.19 (m, 4H), 2.33 (t, J=7.12 Hz, 2H), 3.30-3.41 (m, 2H), 3.52-3.58 (m, 2H), 4.43 (t, J=5.6 Hz, 1H).



Step 2: 6,6-bis(oct-7-yn-1-yloxy)hexanoic acid

[0696] Prepared according to General Procedure B, substituting 6,6-bis(oct-7-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 170 mg, 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16-1.48 (m, 30H), 2.12-2.20 (m, 8H), 2.66-2.72 (m, 2H), 3.31-3.39 (m, 6H), 3.46-3.48 (m, 3H), 4.40 (m, 1H), 12.01 (m, 1H).

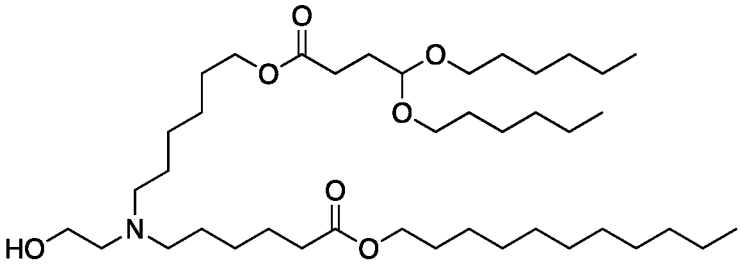


Step 3: 6-bromohexyl 6,6-bis(oct-7-yn-1-yloxy)hexanoate

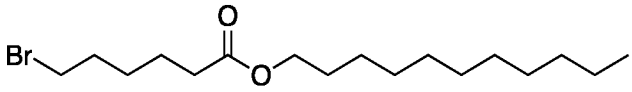
[0697] Prepared according to General Procedure C, substituting 6,6-bis(oct-7-yn-1-yloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 90 mg, 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.46-1.53 (m, 15H), 1.57-1.67 (m, 9H), 1.82-1.89 (m, 2H), 1.93-1.92 (m, 2H), 2.15-2.19 (m, 4H), 2.29 (t, J=7.64 Hz, 2H), 3.35-3.41 (m, 4H), 3.51-3.57 (m, 2H), 4.05 (t, J=6.56 Hz, 2H), 4.43 (t, J=5.6 Hz, 1H).

Step 4: nonyl 8-((6-((6,6-bis(oct-7-yn-1-yloxy)hexanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-64)

[0698] Prepared according to General Procedure F, substituting 6-bromohexyl 6,6-bis(oct-7-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 26 mg, 38%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 776.6, found 776.7.

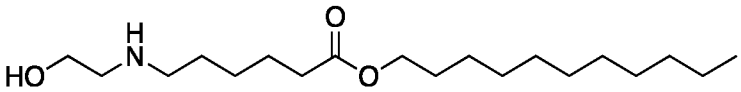


Example 7-65: undecyl 6-((6-((4,4-bis(hexyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate



Step 1: undecyl 6-bromohexanoate

[0699] Prepared according to General Procedure D, substituting 1-undecanol for 1-nonanol and 6-bromohexanoic acid for 8-bromooctanoic acid. Isolated 1.22 g, 68%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.23 – 1.37 (m, 16H), 1.40 – 1.53 (m, 2H), 1.52 – 1.69 (m, 4H), 1.83 – 1.93 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 3.40 (t, *J* = 6.7 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).

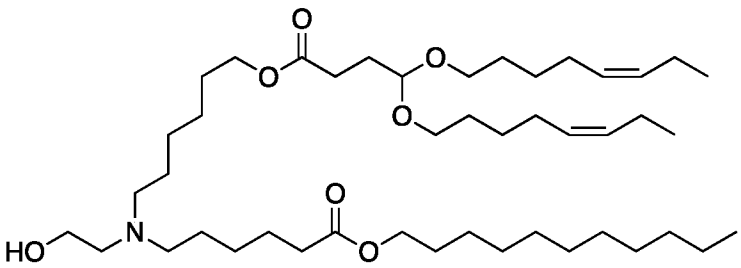


Step 2: undecyl 6-((2-hydroxyethyl)amino)hexanoate

[0700] Prepared according to General Procedure E, substituting undecyl 6-bromohexanoate for nonyl 8-bromooctanoate. Isolated 220 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.5 Hz, 3H), 1.15 – 1.42 (m, 20H), 1.50 – 1.72 (m, 6H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.78 – 2.86 (m, 2H), 3.64 – 3.72 (m, 2H), 4.04 (t, *J* = 6.9 Hz, 2H).

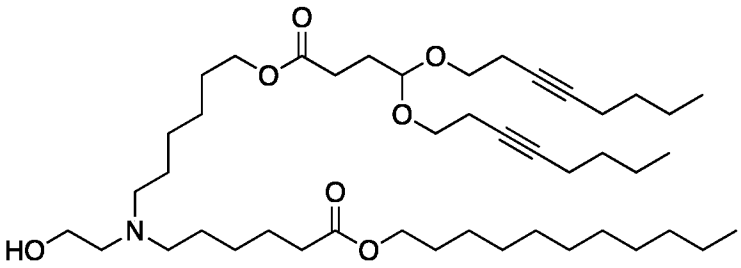
Step 3: undecyl 6-((6-((4,4-bis(hexyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate (Example 7-65)

[0701] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 16 mg, 20%. UPLC-MS (Method B): Rt 1.96 min, m/z calculated [M+H]: 701.6, found 701.0.

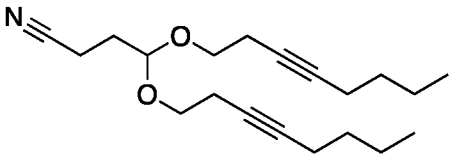


Example 7-66: undecyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate

[0702] Prepared according to General Procedure F, substituting undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 28 mg, 43%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 752.6, found 753.1.

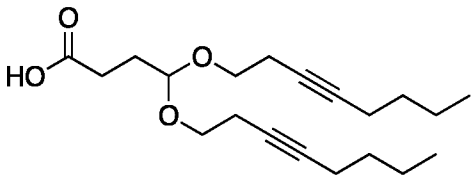


Example 7-67: undecyl 6-((6-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate



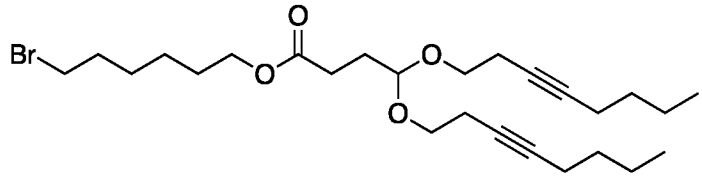
Step 1: 4,4-bis(oct-3-yn-1-yloxy)butanenitrile

[0703] Prepared according to General Procedure A, substituting oct-3-yn-1-ol for cis-5-octen-1-ol. Isolated 732 mg, 25%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 6H), 1.31 – 1.51 (m, 8H), 1.98 (q, *J* = 6.9 Hz, 2H), 2.09 – 2.18 (m, 4H), 2.38 – 2.49 (m, 6H), 3.50 – 3.61 (m, 2H), 3.64 – 3.74 (m, 2H), 4.67 (t, *J* = 5.2 Hz, 1H).



Step 2: 4,4-bis(oct-3-yn-1-yloxy)butanoic acid

[0704] Prepared according to General Procedure B, substituting 4,4-bis(oct-3-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 450 mg, 72%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.0 Hz, 6H), 1.31 – 1.51 (m, 8H), 1.91 – 2.01 (m, 2H), 2.07 – 2.18 (m, 4H), 2.36 – 2.53 (m, 6H), 3.50 – 3.60 (m, 2H), 3.62 – 3.73 (m, 2H), 4.63 (t, *J* = 5.6 Hz, 1H).

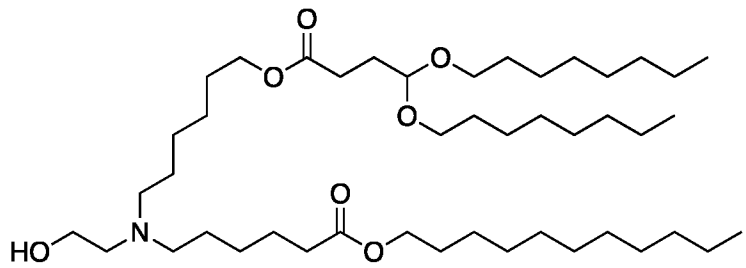


Step 3: 6-bromohexyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

[0705] Prepared according to General Procedure C, substituting 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 453 mg, 46%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.0 Hz, 6H), 1.31 – 1.52 (m, 12H), 1.57 – 1.67 (m, 2H), 1.80 – 1.92 (m, 2H), 1.89 – 1.99 (m, 2H), 2.08 – 2.18 (m, 4H), 2.35 – 2.46 (m, 6H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.72 (m, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

Step 4: nonyl 8-((6-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-67)

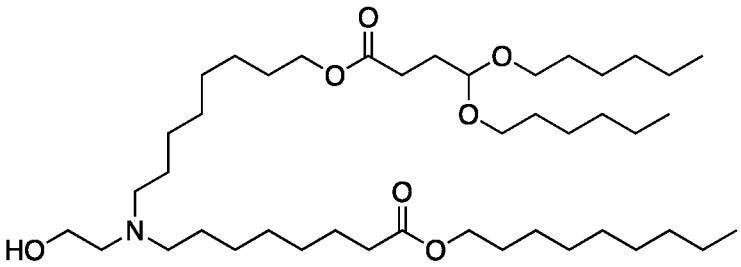
[0706] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 43 mg, 32%. UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 748.6, found 749.0.



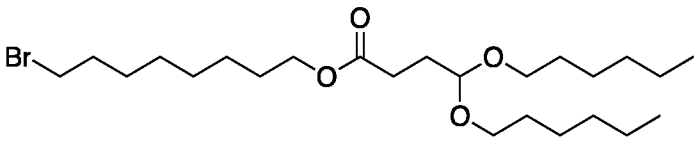
Example 7-68: undecyl 6-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate

[0707] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-

((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 24 mg, 46%. UPLC-MS (Method B): Rt 2.27 min, m/z calculated [M+H]: 756.7, found 756.9.



Example 7-69: undecyl 6-((6-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate

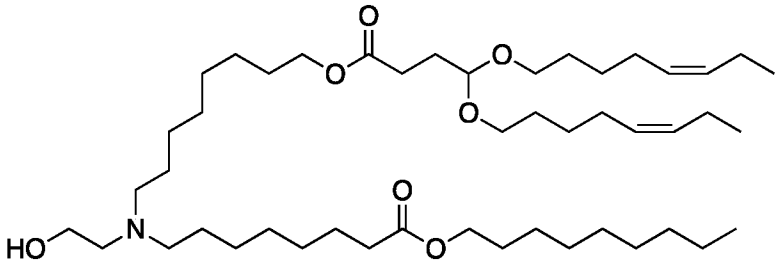


Step 1: 8-bromooctyl 4,4-bis(hexyloxy)butanoate

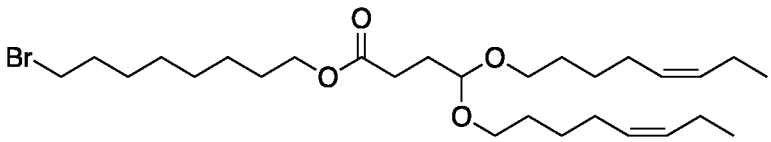
[0708] Prepared according to General Procedure C, substituting 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid and 8-bromooctan-1-ol for 6-bromohexan-1-ol. Isolated 180 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (m, 6H), 1.28 – 1.31 (m, 18H), 1.82 – 1.94 (m, 4H), 2.36 (t, *J* = 7.6 Hz, 2H), 3.39-3.41 (m, 4H), 3.53 – 3.58 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 6.2 Hz, 1H), 4.49 –4.50 (m, 1H).

Step 2: nonyl 8-((8-((4,4-bis(hexyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate (Example 7-69)

[0709] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 26 mg, 52%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 728.6, found 729.2.



Example 7-70: nonyl 8-((8-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate

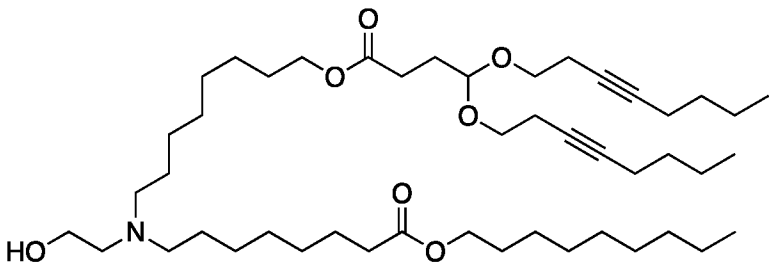


Step 1: 8-bromooctyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

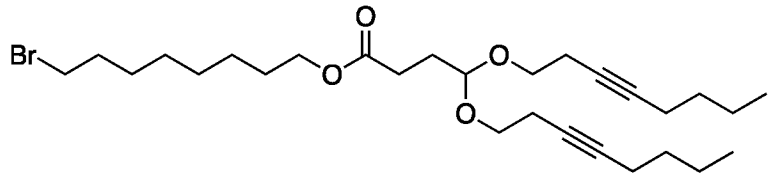
[0710] Prepared according to General Procedure C, substituting 8-bromooctan-1-ol for 6-bromohexan-1-ol. Isolated 200 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.26 – 1.46 (m, 17H), 1.57 – 1.70 (m, 2H), 1.79 – 1.97 (m, 4H), 1.98 – 2.07 (m, 7H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 8.1 Hz, 4H), 3.51 – 3.62 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 6.2 Hz, 1H), 5.10 – 5.53 (m, 4H).

Step 2: nonyl 8-((8-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate (Example 7-70)

[0711] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 23 mg, 48%. UPLC-MS (Method B): Rt 2.04 min, m/z calculated [M+H]: 780.7, found 781.4.



Example 7-71: nonyl 8-((8-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate

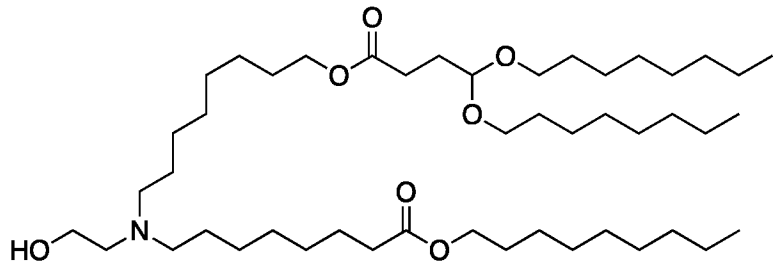


Step 1: 8-bromooctyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

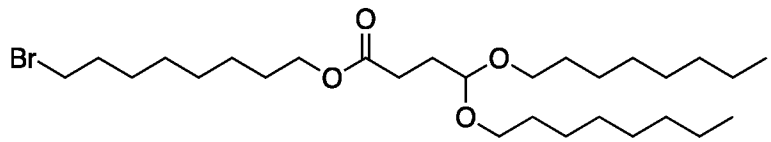
[0712] Prepared according to General Procedure C, substituting 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid and 8-bromooctan-1-ol for 6-bromohexan-1-ol. Isolated 130 mg, 56%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.31 – 1.46 (m, 14H), 1.53 – 1.60 (m, 2H), 1.82 – 1.96 (m, 3H), 2.11 – 2.15 (m, 4H),2.37-2.43 (m, 6H), 3.39 (t, *J* = 6.8 Hz, 2H), 3.50 – 3.55 (m, 2H), 3.56 – 3.67 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.60 (t, *J* = 6.2 Hz, 1H).

Step 2: nonyl 8-((8-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate (Example 7-71)

[0713] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 33 mg, 56%. UPLC-MS (Method B): Rt 1.88 min, m/z calculated [M+H]: 776.6, found 777.3.



Example 7-72: nonyl 8-((8-((4,4-bis(octyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate



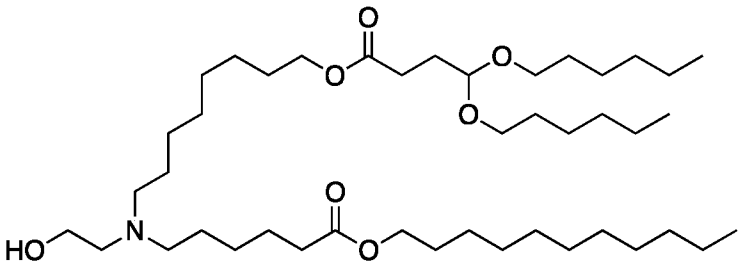
Step 1: 8-bromooctyl 4,4-bis(octyloxy)butanoate

[0714] Prepared according to General Procedure C, substituting 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid and 8-bromooctan-1-ol for 6-bromohexan-1-ol. Isolated 110 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (t, *J* = 7.1 Hz, 6H), 1.26 – 1.31

(m, 27H), 1.40 – 1.41 (m, 2H),1.52 – 1.62 (m, 2H), 1.82 – 1.94 (m, 3H), 2.36 (t, *J* = 7.6 Hz, 2H), 3.37-3.40 (m,4H), 3.41 – 3.56 (m, 2H), 4.02 (t, *J* = 6.7 Hz, 2H), 4.46 (t, *J* = 6.2 Hz, 1H).

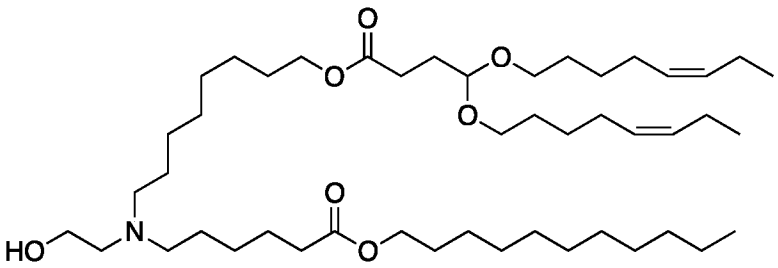
Step 2: nonyl 8-((8-((4,4-bis(octyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate (Example 7-72)

[0715] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 52 mg, 62%. UPLC-MS (Method C): Rt 5.30 min, m/z calculated [M+H]: 784.7, found 785.4.



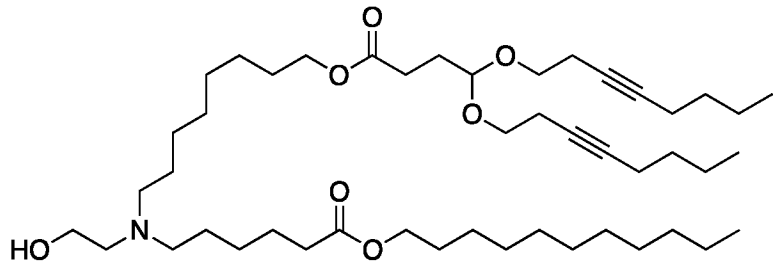
Example 7-73: undecyl 6-((8-((4,4-bis(hexyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)hexanoate

[0716] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 34 mg, 67%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 728.6, found 729.2.



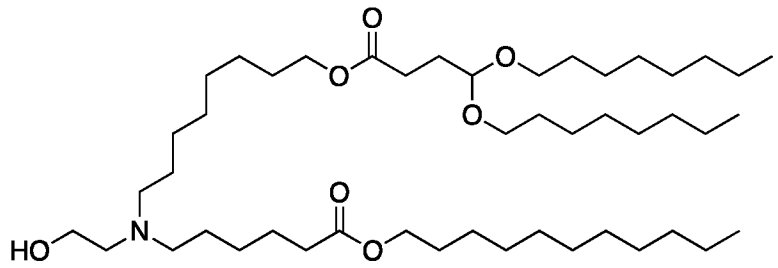
Example 7-74: undecyl 6-((8-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)hexanoate

[0717] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 41 mg, 63%. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 780.7, found 781.4.



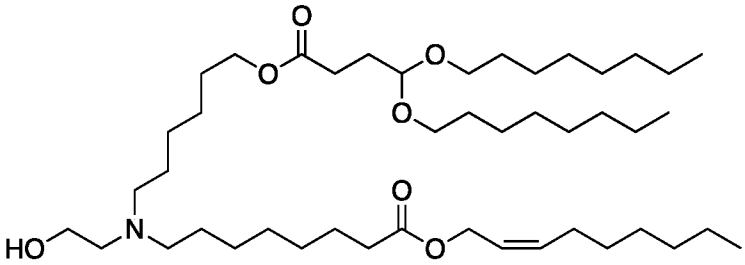
Example 7-75: undecyl 6-((8-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)hexanoate

[0718] Prepared according to General Procedure F, substituting 8-bromooctyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 37 mg, 54%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 776.6, found 777.3.

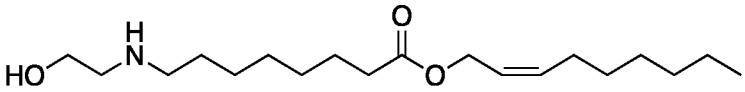


Example 7-76: undecyl 6-((8-((4,4-bis(octyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)hexanoate

[0719] Prepared according to General Procedure F, substituting nonyl 8-((8-((4,4-bis(octyloxy)butanoyl)oxy)octyl)(2-hydroxyethyl)amino)octanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 51%. UPLC-MS (Method B): Rt 2.22 min, m/z calculated [M+H]: 784.7, found 784.9.



Example 7-77: (*Z*)-non-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

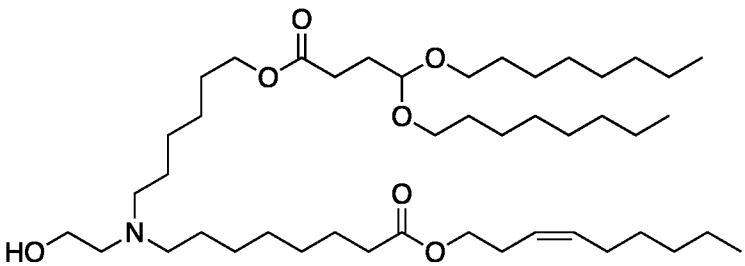


Step 1: (Z)-non-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

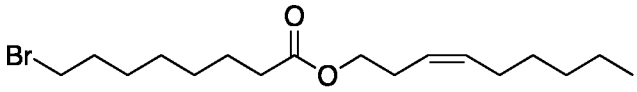
[0720] Prepared according to General Procedure E, substituting (Z)-non-2-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 150 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.19 – 1.39 (m, 24H), 2.01 – 2.13 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 1H), 2.59 (t, *J* = 7.2 Hz, 1H), 2.72 – 2.83 (m, 1H), 3.58 – 3.66 (m, 1H), 4.18 (d, *J* = 6.1 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 5.45 – 5.69 (m, 2H).

Step 2: (Z)-non-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-77)

[0721] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 41 mg, 44%. UPLC-MS (Method B): Rt 2.14 min, m/z calculated [M+H]: 754.7, found 755.1.

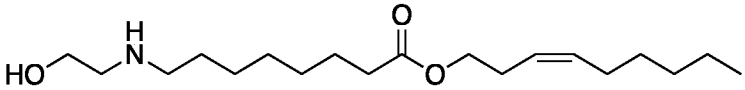


Example 7-78: (*Z*)-non-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-non-3-en-1-yl 8-bromooctanoate

[0722] Prepared according to General Procedure D, substituting (*Z*)-non-3-en-1-ol for 1-nonanol. Isolated 450 mg, 58%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.21 – 1.47 (m, 12H), 1.61 (t, *J* = 7.3 Hz, 2H), 1.71 – 1.90 (m, 2H), 2.03 (q, *J* = 7.4 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.36 (q, *J* = 7.1 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.06 (t, *J* = 6.9 Hz, 2H), 5.26 – 5.37 (m, 1H), 5.41 – 5.58 (m, 1H).

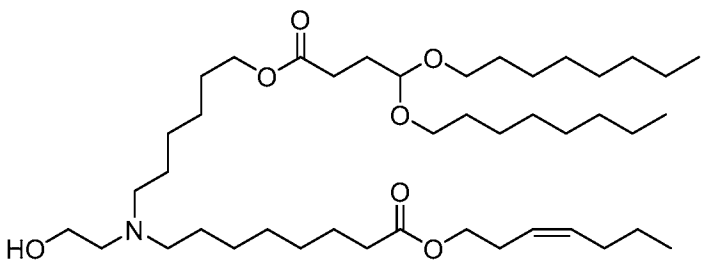


Step 2: (Z)-non-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

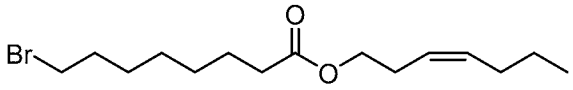
[0723] Prepared according to General Procedure E, substituting (Z)-non-3-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 155 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.15 – 1.41 (m, 20H), 1.47 – 1.67 (m, 2H), 1.97 – 2.11 (m, 2H), 2.23 – 2.39 (m, 3H), 2.66 (t, *J* = 7.2 Hz, 1H), 2.82 (t, *J* = 5.2 Hz, 1H), 3.59 – 3.72 (m, 2H), 4.05 (t, *J* = 6.9 Hz, 1H), 5.29 – 5.39 (m, 1H), 5.43 – 5.63 (m, 1H).

Step 3: (Z)-non-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-78)

[0724] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 16 mg, 17%. UPLC-MS (Method C): Rt 5.17 min, m/z calculated [M+H]: 754.7, found 755.3.

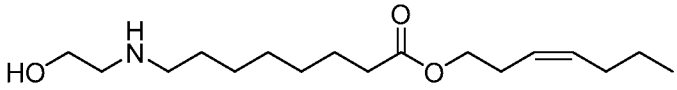


Example 7-79: (*Z*)-hept-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-hept-3-en-1-yl 8-bromooctanoate

[0725] Prepared according to General Procedure D, substituting (*Z*)-hept-3-en-1-ol for 1-nonanol. Isolated 350 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.21 – 1.47 (m, 8H), 1.55 – 1.66 (m, 2H), 1.71 – 1.88 (m, 2H), 2.02 (q, *J* = 7.6 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (q, *J* = 7.1 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 1H), 3.52 (t, *J* = 6.7 Hz, 1H), 4.06 (t, *J* = 7.0 Hz, 2H), 5.27 – 5.41 (m, 1H), 5.44 – 5.55 (m, 1H).

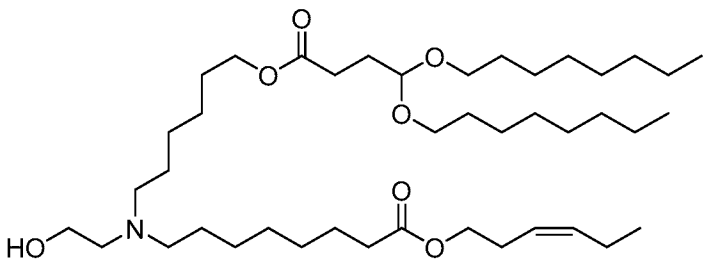


Step 2: (Z)-hept-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

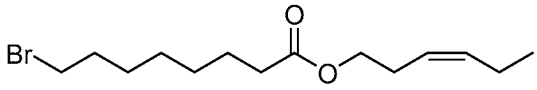
[0726] Prepared according to General Procedure E, substituting (Z)-hept-3-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 142 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.94 (m, 3H), 1.17 – 1.53 (m, 18H), 1.68 (s, 2H), 1.97 – 2.06 (m, 2H), 2.28 (t, *J* = 7.3 Hz, 1H), 2.36 (q, *J* = 7.2 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 1H), 2.77 (t, *J* = 5.2 Hz, 1H), 3.63 (t, *J* = 5.2 Hz, 1H), 4.05 (t, *J* = 6.9 Hz, 1H), 5.31 – 5.39 (m, 1H), 5.49 (d, *J* = 10.4 Hz, 1H).

Step 3: (Z)-hept-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-79)

[0727] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-hept-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 31 mg, 32%. UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 726.6, found 727.3.

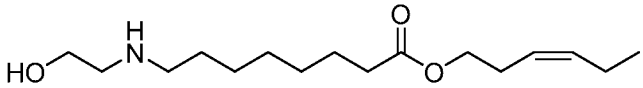


Example 7-80: (*Z*)-hex-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-hex-3-en-1-yl 8-bromooctanoate

[0728] Prepared according to General Procedure D, substituting (*Z*)-hex-3-en-1-ol for 1-nonanol. Isolated 440 mg, 64%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.21 – 1.36 (m, 4H), 1.42 (t, *J* = 7.5 Hz, 2H), 1.61 (t, *J* = 7.3 Hz, 2H), 1.79 – 1.89 (m, 2H), 2.00 – 2.09 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.36 (q, *J* = 7.1 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.06 (t, *J* = 6.9 Hz, 2H), 5.24 – 5.36 (m, 1H), 5.44 – 5.55 (m, 1H).

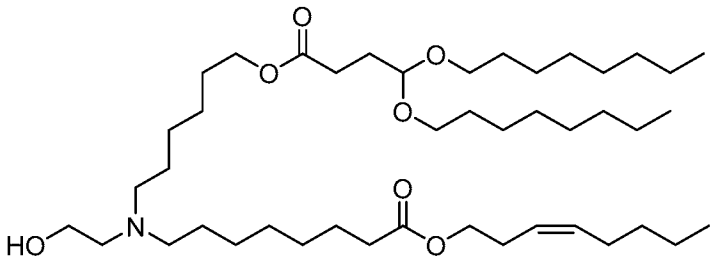


Step 2: (Z)-hex-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

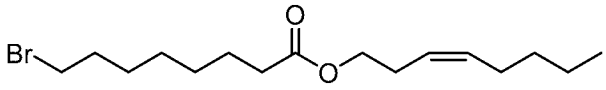
[0729] Prepared according to General Procedure E, substituting (Z)-hex-3-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 150 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.25 – 1.39 (m, 10H), 1.47 (t, *J* = 6.8 Hz, 2H), 1.99 – 2.11 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.36 (q, *J* = 6.9 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 4.05 (t, *J* = 6.9 Hz, 2H), 5.26 – 5.35 (m, 1H), 5.49 (q, *J* = 7.8 Hz, 1H).

Step 3: (Z)-hex-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-80)

[0730] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-hex-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 51 mg, 45%. UPLC-MS (Method B): Rt 1.88 min, m/z calculated [M+H]: 712.6, found 713.2. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.91 (m, 6H), 0.96 (t, *J* = 7.5 Hz, 3H), 1.17 – 1.45 (m, 16H), 1.48 – 1.68 (m, 16H), 1.80 – 1.96 (m, 6H), 2.00 – 2.09 (m, 2H), 2.24 – 2.41 (m, 8H), 3.07 – 3.16 (m, 5H), 3.17 – 3.24 (m, 2H), 3.34 – 3.45 (m, 3H), 3.50 – 3.61 (m, 3H), 3.98 – 4.09 (m, 8H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.37 (m, 1H), 5.44 – 5.56 (m, 1H).

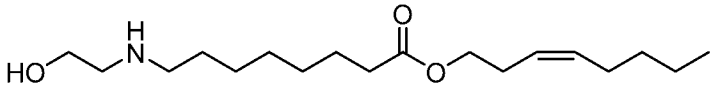


Example 7-81: (*Z*)-oct-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (Z)-oct-3-en-1-yl 8-bromooctanoate

[0731] Prepared according to General Procedure D, substituting (*Z*)-oct-3-en-1-ol for 1-nonanol. Isolated 340 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), δ 1.24 – 1.32 (m, 8H), 1.42 (bs, 2H), 1.61 (t, *J* = 7.0 Hz, 2H), 1.80-1.87 (m, 2H), 2.02 – 2.04 (m, 2H), 2.28 (t, *J* = 7.4 Hz, 2H) 2.36 (q, *J* = 7.2 Hz, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 7.0 Hz, 2H), 5.29-5.35 (m, 1H), 5.45-5.52 (m,1H).

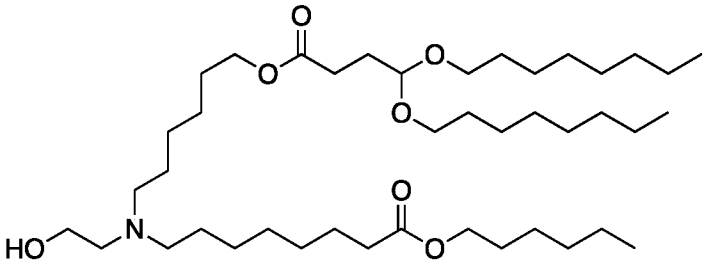


Step 2: (Z)-oct-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

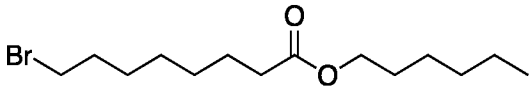
[0732] Prepared according to General Procedure E, substituting (Z)-oct-3-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 250 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.19 – 1.41 (m, 10H), 1.45 – 1.69 (m, 3H), 1.80 – 2.11 (m, 8H), 2.23 – 2.41 (m, 4H), 2.66 (t, *J* = 7.3 Hz, 1H), 2.82 (t, *J* = 5.2 Hz, 1H), 3.59 – 3.72 (m, 2H), 4.05 (t, *J* = 6.9 Hz, 1H), 5.33 (q, *J* = 8.5 Hz, 1H), 5.42 – 5.64 (m, 1H).

Step 3: (Z)-oct-3-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-81)

[0733] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-oct-3-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 49 mg, 41%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 740.6, found 741.3.

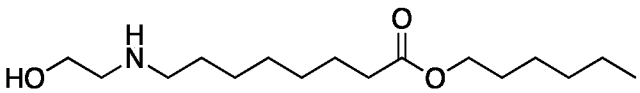


Example 7-82: hexyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: hexyl 8-bromooctanoate

[0734] Prepared according to General Procedure D, substituting hexan-1-ol for 1-nonanol. Isolated 420 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.21 – 1.39 (m, 10H), 1.37 – 1.47 (m, 2H), 1.54 – 1.68 (m, 4H), 1.79 – 1.89 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).

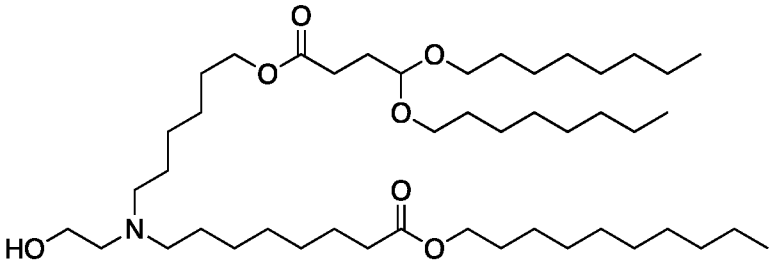


Step 2: hexyl 8-((2-hydroxyethyl)amino)octanoate

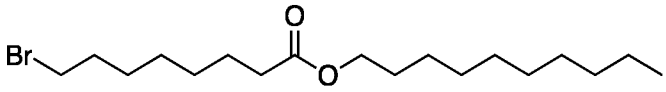
[0735] Prepared according to General Procedure E, substituting hexyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 155 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.22 – 1.39 (m, 14H), 1.39 – 1.52 (m, 2H), 1.61 (q, *J* = 7.1 Hz, 4H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 3.62 (q, *J* = 5.9, 6.6 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 2H).

Step 3: hexyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-82)

[0736] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and hexyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 42 mg, 56%. UPLC-MS (Method B): Rt 1.98 min, m/z calculated [M+H]: 714.6, found 715.3.

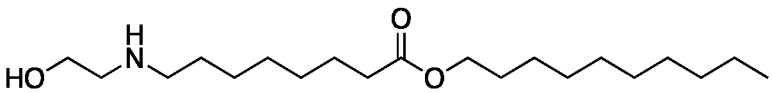


Example 7-83: decyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: decyl 8-bromooctanoate

[0737] Prepared according to General Procedure D, substituting decan-1-ol for 1-nonanol. Isolated 510 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.23 – 1.37 (m, 18H), 1.39 – 1.45 (m, 2H), 1.56 – 1.66 (m, 4H), 1.78 – 1.90 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).

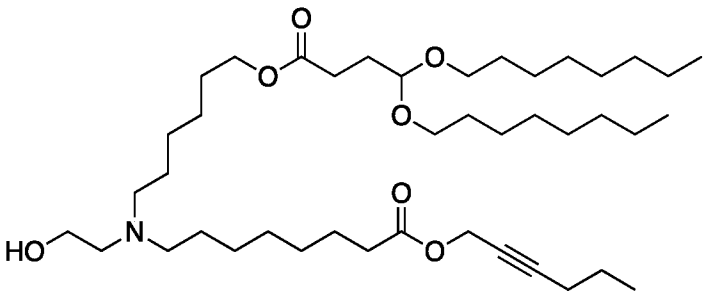


Step 2: decyl 8-((2-hydroxyethyl)amino)octanoate

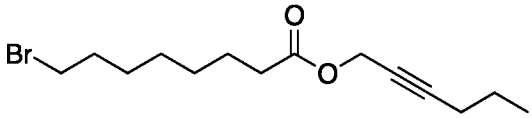
[0738] Prepared according to General Procedure E, substituting decyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 75 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.23 – 1.34 (m, 24H), 1.46 – 1.67 (m, 4H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.76 – 2.84 (m, 2H), 3.63 – 3.72 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H).

Step 3: decyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-83)

[0739] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and decyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 41 mg, 60%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 770.7, found 771.4.

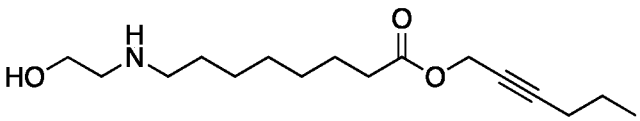


Example 7-84: hex-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: hex-2-yn-1-yl 8-bromooctanoate

[0740] Prepared according to General Procedure D, substituting hex-2-yn-1-ol for 1-nonanol. Isolated 420 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.28 – 1.37 (m, 4H), 1.38 – 1.47 (m, 2H), 1.47 – 1.56 (m, 2H), 1.58 – 1.67 (m, 2H), 1.73 – 1.90 (m, 2H), 2.14 – 2.24 (m, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.63 – 4.69 (m, 2H).

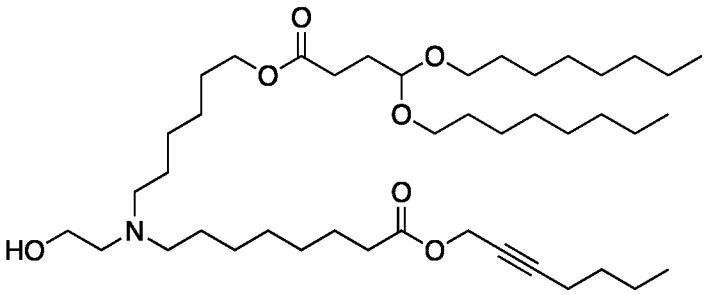


Step 2: hex-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

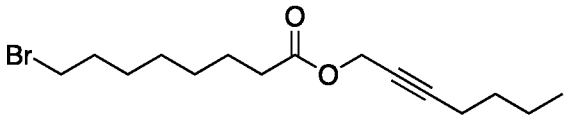
[0741] Prepared according to General Procedure E, substituting hex-2-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 140 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.32 (s, 5H), 1.45 – 1.58 (m, 3H), 1.57 – 1.69 (m, 2H), 1.81 (s, 7H), 2.14 – 2.23 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 1H), 2.79 (t, *J* = 5.2 Hz, 1H), 3.65 (t, *J* = 5.2 Hz, 1H), 4.66 (t, *J* = 2.3 Hz, 2H).

Step 3: hex-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-84)

[0742] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and hex-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 30 mg, 40%. UPLC-MS (Method B): Rt 1.90 min, m/z calculated [M+H]: 710.6, found 711.2.

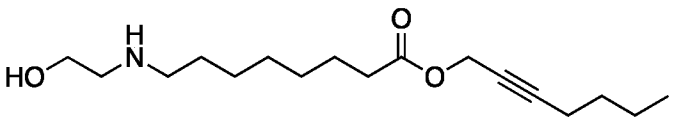


Example 7-85: hept-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: hept-2-yn-1-yl 8-bromooctanoate

[0743] Prepared according to General Procedure D, substituting hept-2-yn-1-ol for 1-nonanol. Isolated 410 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.30 – 1.35 (m, 4H), 1.35 – 1.56 (m, 6H), 1.59 – 1.69 (m, 2H), 1.78 – 1.88 (m, 2H), 2.16 – 2.26 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.65 (t, *J* = 2.2 Hz, 2H).



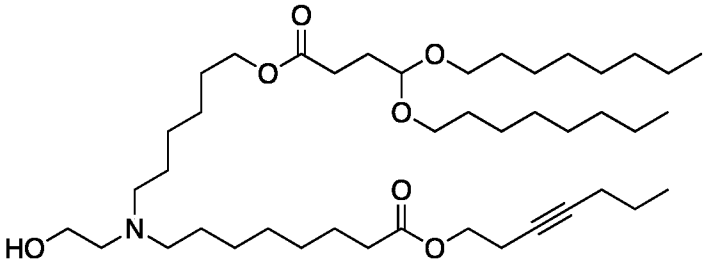
Step 2: hept-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0744] Prepared according to General Procedure E, substituting hept-2-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 110 mg, 83%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.20 – 1.37 (m, 6H), 1.35 – 1.56 (m, 6H), 1.58 – 1.66 (m, 2H), 2.09 – 2.15 (m, 4H), 2.16 – 2.26 (m, 2H), 2.25 – 2.37 (m, 2H), 2.65 (t, *J* = 7.3 Hz, 1H), 2.81 (t, *J* = 5.1 Hz, 1H), 3.67 (t, *J* = 5.2 Hz, 1H), 4.65 (t, *J* = 2.4 Hz, 2H), 5.29 (s, 1H).

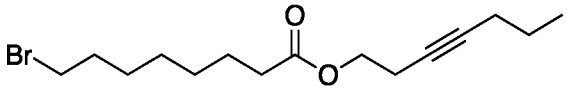
Step 3: hept-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-85)

[0745] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and hept-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate.

Isolated 18 mg, 29%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 724.6, found 725.2.

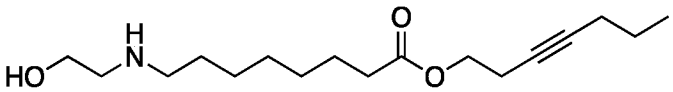


Example 7-86: hept-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: hept-3-yn-1-yl 8-bromooctanoate

[0746] Prepared according to General Procedure D, substituting hept-3-yn-1-ol for 1-nonanol. Isolated 405 mg, 56%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.27 – 1.47 (m, 8H), 1.57 – 1.67 (m, 2H), 1.71 – 1.90 (m, 2H), 2.06 – 2.16 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.43 – 2.52 (m, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.13 (t, *J* = 7.0 Hz, 2H).



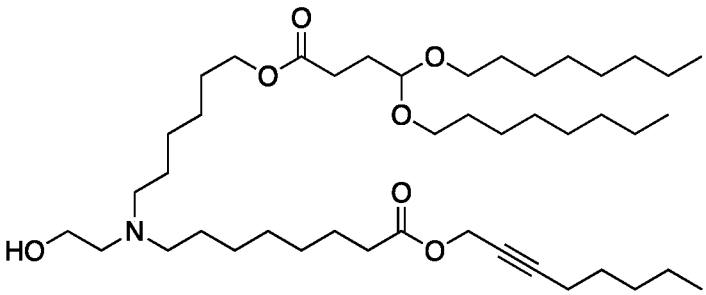
Step 2: hept-3-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0747] Prepared according to General Procedure E, substituting hept-3-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 164 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.28 – 1.38 (m, 6H), 1.39 – 1.56 (m, 4H), 2.02 – 2.15 (m, 6H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.42 – 2.52 (m, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 5.2 Hz, 2H), 3.65 (t, *J* = 5.2 Hz, 2H), 4.12 (t, *J* = 7.0 Hz, 2H).

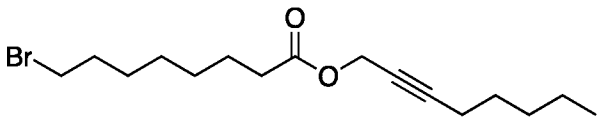
Step 3: hept-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-86)

[0748] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and hept-3-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate.

Isolated 35 mg, 48%. UPLC-MS (Method B): Rt 1.83 min, m/z calculated [M+H]: 724.6, found 725.2.

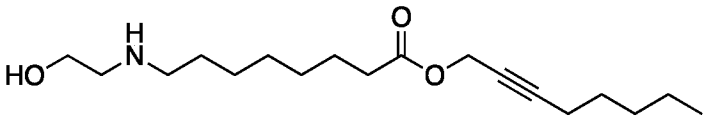


Example 7-87: oct-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: oct-2-yn-1-yl 8-bromooctanoate

[0749] Prepared according to General Procedure D, substituting oct-2-yn-1-ol for 1-nonanol. Isolated 350 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.20 – 1.56 (m, 12H), 1.57 – 1.69 (m, 2H), 1.78 – 1.88 (m, 2H), 2.15 – 2.25 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.66 (t, *J* = 2.2 Hz, 2H).



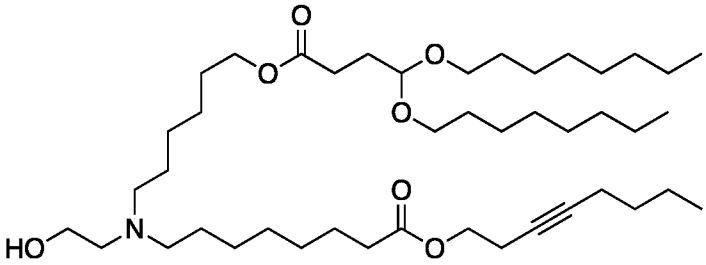
Step 2: oct-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0750] Prepared according to General Procedure E, substituting oct-2-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 70 mg, 74%.^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 6H), 1.19 – 1.41 (m, 10H), 1.45 – 1.68 (m, 5H), 2.14-2.25 (m, 4H), 2.32 (t, *J* = 7.5 Hz, 1H), 2.67 (t, *J* = 7.3 Hz, 1H), 2.83 (t, *J* = 5.1 Hz, 1H), 3.64 – 3.75 (m, 1H), 4.24 (s, 3H), 4.66 (s, 1H).

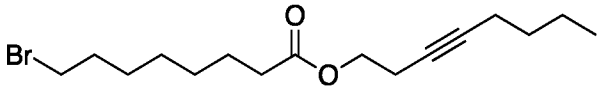
Step 3: oct-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-87)

[0751] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and oct-2-yn-

1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 29%. UPLC-MS (Method B): Rt 1.91 min, m/z calculated [M+H]: 738.6, found 739.3.

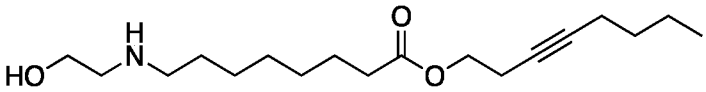


Example 7-88: oct-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: oct-3-yn-1-yl 8-bromooctanoate

[0752] Prepared according to General Procedure D, substituting oct-3-yn-1-ol for 1-nonanol. Isolated 190 mg, 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.49 (m, 10H), 1.58 – 1.68 (m, 2H), 1.69 – 1.90 (m, 2H), 2.08 – 2.18 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.42 – 2.52 (m, 2H), 3.39 (t, *J* = 6.8 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 1H), 4.12 (t, *J* = 6.9 Hz, 2H).



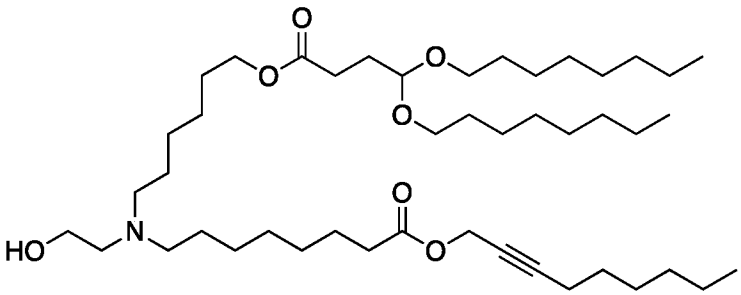
Step 2: oct-3-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0753] Prepared according to General Procedure E, substituting oct-3-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 80 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.53 (m, 14H), 1.57 – 1.67 (m, 2H), 1.69 – 1.81 (m, 1H), 2.09 – 2.22 (m, 2H), 2.23 – 2.35 (m, 2H), 2.39 – 2.51 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 1H), 2.74 – 2.80 (m, 1H), 3.51 (t, *J* = 6.7 Hz, 1H), 3.56 – 3.74 (m, 2H), 4.12 (t, *J* = 7.0 Hz, 2H).

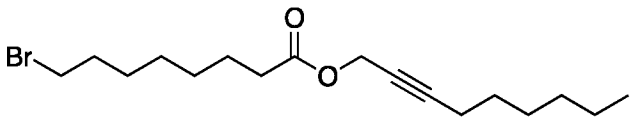
Step 3: oct-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-88)

[0754] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and oct-3-yn-

1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 38 mg, 23%. UPLC-MS (Method C): Rt 5.09 min, m/z calculated [M+H]: 738.6, found 739.0.

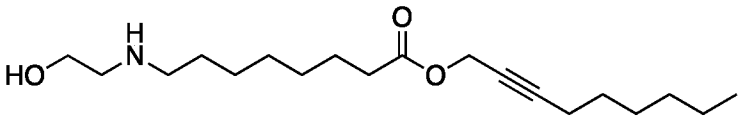


Example 7-89: non-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: non-2-yn-1-yl 8-bromooctanoate

[0755] Prepared according to General Procedure D, substituting non-2-yn-1-ol for 1-nonanol. Isolated 370 mg, 72%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.20 – 1.55 (m, 14H), 1.63 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.89 (m, 2H), 2.15 – 2.25 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.65 (t, *J* = 2.3 Hz, 2H).



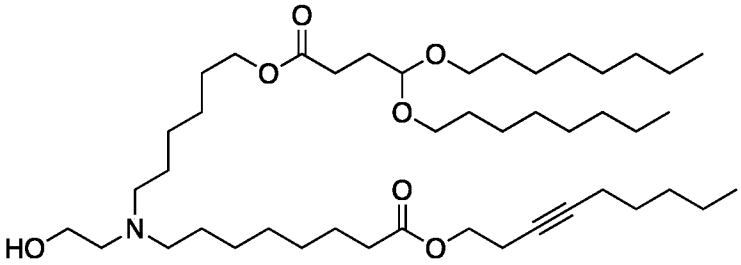
Step 2: non-2-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0756] Prepared according to General Procedure E, substituting non-2-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 80 mg, 70%.^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.19 – 1.45 (m, 19H), 1.44 – 1.68 (m, 4H), 2.13 – 2.25 (m, 3H), 2.32 (t, *J* = 7.5 Hz, 1H), 2.73 – 2.78 (m, 1H), 2.89 – 2.93 (m, 1H), 3.74 – 3.80 (m, 1H), 4.24 (t, *J* = 2.2 Hz, 1H), 4.65 (t, *J* = 2.3 Hz, 1H).

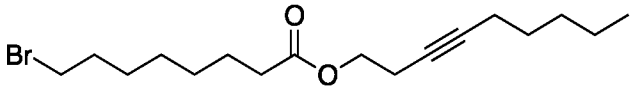
Step 3: non-2-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-89)

[0757] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and non-2-yn-

1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 33 mg, 36%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 752.6, found 753.3.

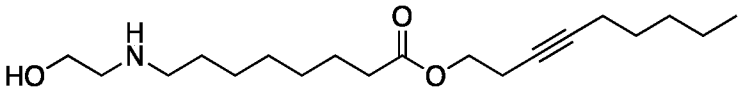


Example 7-90: non-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: non-3-yn-1-yl 8-bromooctanoate

[0758] Prepared according to General Procedure D, substituting non-3-yn-1-ol for 1-nonanol. Isolated 390 mg, 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.23 – 1.39 (m, 8H), 1.38 – 1.52 (m, 4H), 1.62 (t, *J* = 7.3 Hz, 2H), 1.84 (p, *J* = 7.0 Hz, 2H), 2.07 – 2.17 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.42 – 2.52 (m, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.12 (t, *J* = 6.9 Hz, 2H).



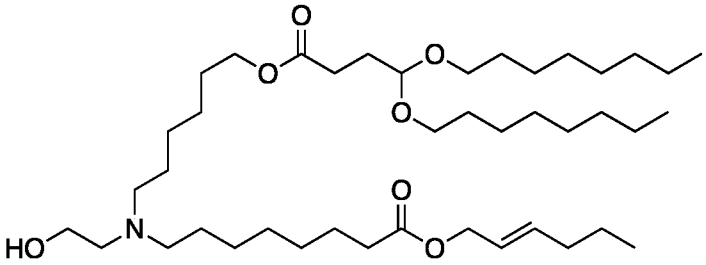
Step 2: non-3-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0759] Prepared according to General Procedure E, substituting non-3-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 155 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.22 – 1.40 (m, 12H), 1.39 – 1.56 (m, 4H), 1.56 – 1.68 (m, 2H), 2.08 – 2.16 (m, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.43 – 2.51 (m, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.81 (t, *J* = 5.2 Hz, 2H), 3.67 (t, *J* = 5.3 Hz, 2H), 4.12 (t, *J* = 7.0 Hz, 2H).

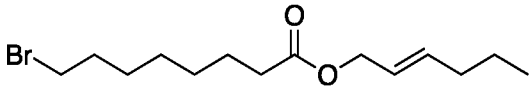
Step 3: non-3-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-90)

[0760] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and non-3-yn-

1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 50 mg, 71%. UPLC-MS (Method C): Rt 5.16 min, m/z calculated [M+H]: 752.6, found 753.3.

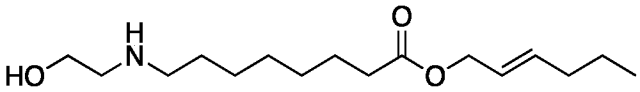


Example 7-91: (*E*)-hex-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (E)-hex-2-en-1-yl 8-bromooctanoate

[0761] Prepared according to General Procedure D, substituting (*E*)-hex-2-en-1-ol for 1-nonanol. Isolated 350 mg, 51%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.28 – 1.38 (m, 4H), 1.35 – 1.47 (m, 4H), 1.56 – 1.68 (m, 2H), 1.78 – 1.90 (m, 2H), 2.02 (q, *J* = 6.9 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.50 (d, *J* = 7.0 Hz, 2H), 5.49 – 5.61 (m, 1H), 5.69 – 5.82 (m, 1H).



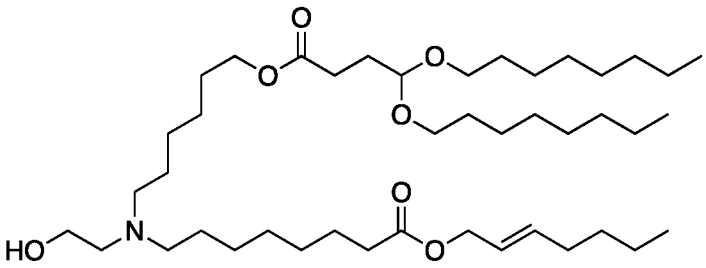
Step 2: (E)-hex-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0762] Prepared according to General Procedure E, substituting (*E*)-hex-2-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 146 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.27 – 1.36 (m, 11H), 1.40 (q, *J* = 7.4 Hz, 2H), 1.50 (t, *J* = 6.9 Hz, 1H), 1.61 (t, *J* = 6.9 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.74 – 2.83 (m, 2H), 3.61 – 3.69 (m, 2H), 4.50 (d, *J* = 6.5 Hz, 2H), 5.48 – 5.61 (m, 1H), 5.69 – 5.81 (m, 1H).

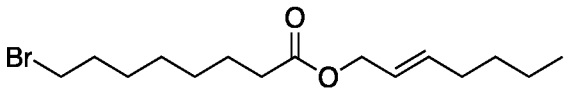
Step 3: (E)-hex-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-91)

[0763] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*E*)-hex-

2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 44 mg, 59%. UPLC-MS (Method B): Rt 1.97 min, m/z calculated [M+H]: 712.6, found 713.2.

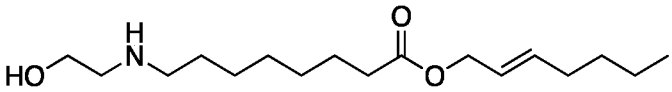


Example 7-92: (*E*)-hept-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (E)-hept-2-en-1-yl 8-bromooctanoate

[0764] Prepared according to General Procedure D, substituting (*E*)-hept-2-en-1-ol for 1-nonanol. Isolated 380 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20 – 1.50 (m, 10H), 1.57 – 1.70 (m, 2H), 1.78 – 1.90 (m, 2H), 2.04 (q, *J* = 6.7 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.50 (d, *J* = 6.5 Hz, 2H), 5.48 – 5.61 (m, 1H), 5.69 – 5.82 (m, 1H).



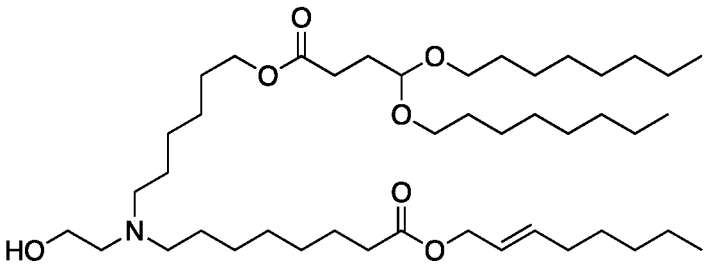
Step 2: (E)-hept-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0765] Prepared according to General Procedure E, substituting (*E*)-hept-2-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 115 mg, 81%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.22 – 1.42 (m, 13H), 1.49 (t, *J* = 7.0 Hz, 1H), 1.61 (t, *J* = 7.2 Hz, 2H), 2.04 (q, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 5.2 Hz, 2H), 3.64 (t, *J* = 5.2 Hz, 2H), 4.50 (d, *J* = 6.5 Hz, 2H), 5.48 – 5.60 (m, 1H), 5.67 – 5.83 (m, 1H).

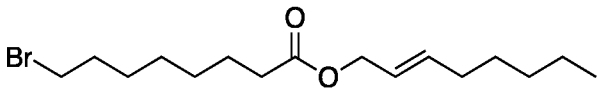
Step 3: (E)-hept-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-92)

[0766] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*E*)-hept-

2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 31 mg, 42%. UPLC-MS (Method B): Rt 1.99 min, m/z calculated [M+H]: 726.6, found 727.3.

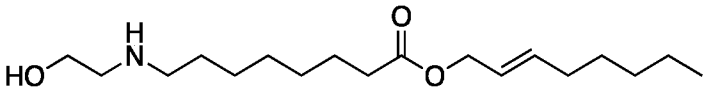


Example 7-93: (*E*)-oct-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (E)-oct-2-en-1-yl 8-bromooctanoate

[0767] Prepared according to General Procedure D, substituting (*E*)-oct-2-en-1-ol for 1-nonanol. Isolated 350 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.21 – 1.47 (m, 12H), 1.58 – 1.66 (m, 2H), 1.78 – 1.90 (m, 2H), 2.04 (q, *J* = 7.1 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.50 (d, *J* = 6.4 Hz, 2H), 5.48 – 5.61 (m, 1H), 5.69 – 5.82 (m, 1H).



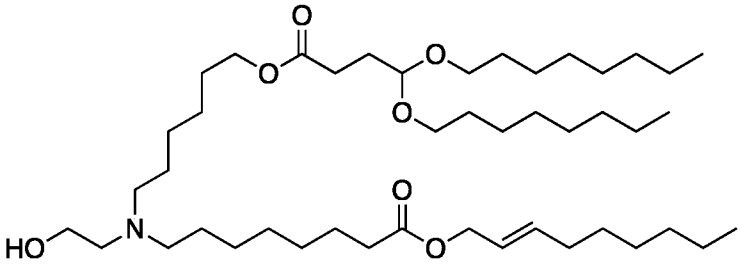
Step 2: (E)-oct-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0768] Prepared according to General Procedure E, substituting (*E*)-oct-2-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 125 mg, 66%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.19 – 1.44 (m, 14H), 1.43 – 1.69 (m, 4H), 2.03 (q, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 5.1 Hz, 2H), 3.58 – 3.72 (m, 2H), 4.50 (d, *J* = 6.5 Hz, 2H), 5.49 – 5.61 (m, 1H), 5.69 – 5.83 (m, 1H).

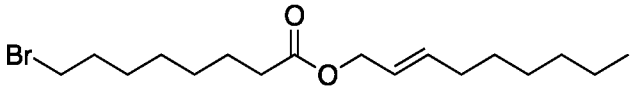
Step 3: (E)-oct-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-93)

[0769] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*E*)-oct-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate.

Isolated 22 mg, 36%. UPLC-MS (Method C): Rt 5.19 min, m/z calculated [M+H]: 740.6, found 741.3.

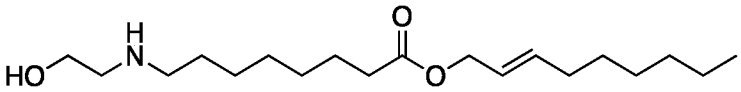


Example 7-94: (*E*)-non-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: (E)-non-2-en-1-yl 8-bromooctanoate

[0770] Prepared according to General Procedure D, substituting (*E*)-non-2-en-1-ol for 1-nonanol. Isolated 275 mg, 58%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.18 – 1.52 (m, 14H), 1.59 – 1.65 (m, 2H), 1.78 – 1.90 (m, 2H), 2.04 (q, *J* = 7.0 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.30 – 3.60 (m, 2H), 4.50 (d, *J* = 6.4 Hz, 2H), 5.48 – 5.61 (m, 1H), 5.70 – 5.82 (m, 1H).



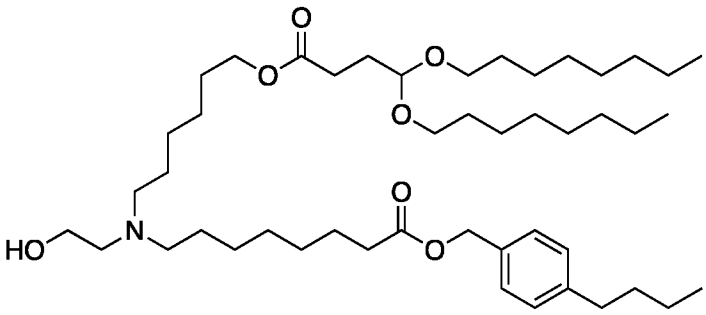
Step 2: (E)-non-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0771] Prepared according to General Procedure E, substituting (*E*)-non-2-en-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 170 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.16 – 1.40 (m, 18H), 1.48 (t, *J* = 7.1 Hz, 1H), 1.56 – 1.65 (m, 1H), 1.85 (s, 3H), 2.03 (q, *J* = 7.3 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 1H), 2.61 (t, *J* = 7.2 Hz, 1H), 2.78 (t, *J* = 5.2 Hz, 1H), 3.64 (t, *J* = 5.2 Hz, 1H), 4.07 (d, *J* = 5.4 Hz, 1H), 4.49 (d, *J* = 6.5 Hz, 1H), 5.48 – 5.60 (m, 1H), 5.60 – 5.71 (m, 1H), 5.68 – 5.81 (m, 1H).

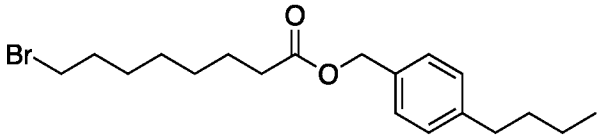
Step 3: (E)-non-2-en-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-94)

[0772] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*E*)-non-

2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 39 mg, 42%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 754.7, found 755.4.

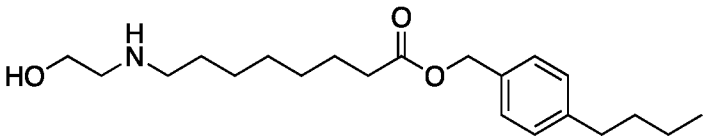


Example 7-95: 4-butylbenzyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 4-butylbenzyl 8-bromooctanoate

[0773] Prepared according to General Procedure D, substituting 4-butylbenzyl alcohol for 1-nonanol. Isolated 280 mg, 56%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.22 – 1.47 (m, 9H), 1.52 – 1.66 (m, 3H), 1.68 – 1.89 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.38 (t, *J* = 6.8 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 1H), 5.07 (s, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H).

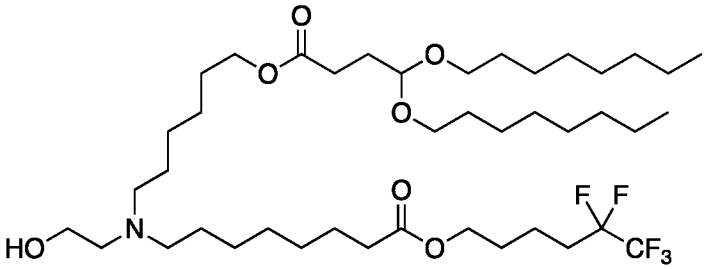


Step 2: 4-butylbenzyl 8-((2-hydroxyethyl)amino)octanoate

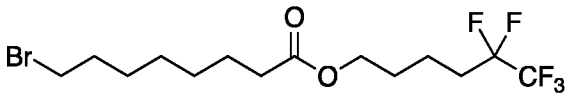
[0774] Prepared according to General Procedure E, substituting 4-butylbenzyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 180 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.19 – 1.45 (m, 13H), 1.52 – 1.70 (m, 7H), 2.60 (t, *J* = 7.7 Hz, 3H), 3.34 – 3.56 (m, 1H), 3.56 – 3.68 (m, 1H), 3.68 – 3.80 (m, 1H), 4.65 (s, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.29 (m, 2H).

Step 3: 4-butylbenzyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-95)

[0775] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 4-butylbenzyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 54 mg, 24%. UPLC-MS (Method B): Rt 2.04 min, m/z calculated [M+H]: 776.6, found 777.2.

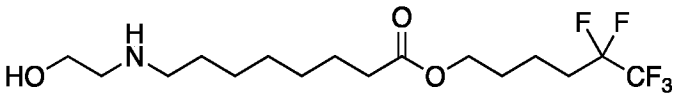


Example 7-96: 5,5,6,6,6-pentafluorohexyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 5,5,6,6,6-pentafluorohexyl 8-bromooctanoate

[0776] Prepared according to General Procedure D, substituting 5,5,6,6,6-pentafluorohexan-1-ol for 1-nonanol. Isolated 450 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.28 – 1.37 (m, 4H), 1.42 (t, *J* = 7.3 Hz, 2H), 1.52 – 1.78 (m, 6H), 1.84 (t, *J* = 7.2 Hz, 2H), 1.97 – 2.12 (m, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.09 (t, *J* = 5.9 Hz, 2H).

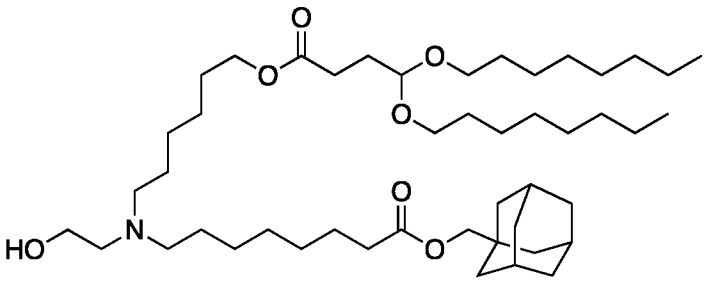


Step 2: 5,5,6,6,6-pentafluorohexyl 8-((2-hydroxyethyl)amino)octanoate

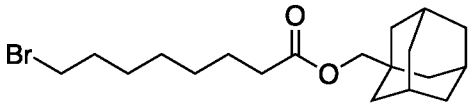
[0777] Prepared according to General Procedure E, substituting 5,5,6,6,6-pentafluorohexyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 280 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.31 (s, 6H), 1.50 (t, *J* = 7.1 Hz, 2H), 1.55 – 1.78 (m, 5H), 1.97 – 2.23 (m, 5H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.79 (t, *J* = 5.2 Hz, 2H), 3.65 (t, *J* = 5.2 Hz, 2H), 4.09 (t, *J* = 5.9 Hz, 2H).

Step 3: 5,5,6,6,6-pentafluorohexyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-96)

[0778] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 5,5,6,6,6-pentafluorohexyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 33 mg, 31%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 804.6, found 805.3.

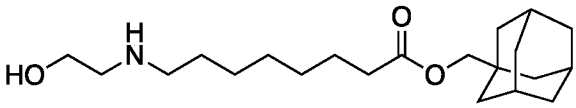


Example 7-97: ((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: ((3r,5r,7r)-adamantan-1-yl)methyl 8-bromooctanoate

[0779] Prepared according to General Procedure D, substituting 1-adamantanemethanol for 1-nonanol. Isolated 380 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.29 – 1.42 (m, 4H), 1.43 (t, *J* = 7.4 Hz, 2H), 1.51 – 1.53 (m, 6H), 1.61 – 1.67 (m, 5H), 1.72 (d, *J* = 12.7 Hz, 3H), 1.76 (s, 0H), 1.77 – 1.90 (m, 2H), 1.97 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 3.66 (s, 2H).



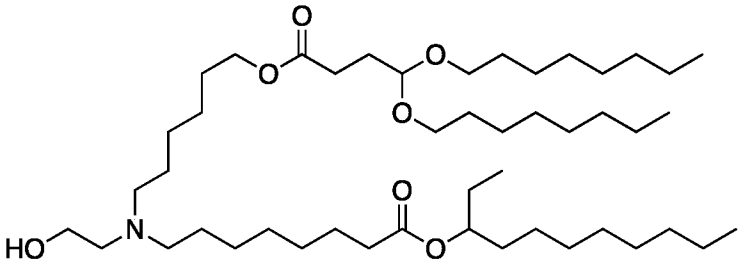
Step 2: ((3r,5r,7r)-adamantan-1-yl)methyl 8-((2-hydroxyethyl)amino)octanoate

[0780] Prepared according to General Procedure E, substituting ((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 310 mg, 88%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.26 – 1.39 (m, 9H), 1.63 (d, *J* = 12.2 Hz, 5H), 1.72 (d, *J* = 12.5 Hz, 4H),

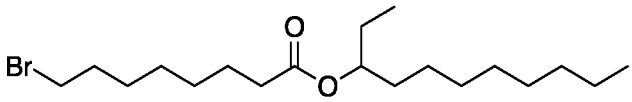
1.81 (s, 6H), 1.97 (s, 3H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 5.2 Hz, 2H), 3.58 – 3.68 (m, 4H).

Step 3: ((3r,5r,7r)-adamantan-1-yl)methyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-97)

[0781] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and ((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 59 mg, 53%. UPLC-MS (Method C): Rt 5.33 min, m/z calculated [M+H]: 778.7, found 779.3.

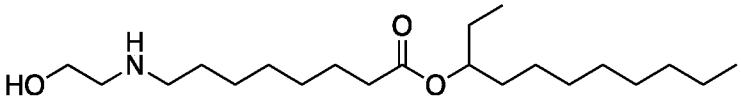


Example 7-98: undecan-3-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: undecan-3-yl 8-bromooctanoate

[0782] Prepared according to General Procedure D, substituting undecane-3-ol for 1-nonanol. Isolated 200 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (t, *J* = 7.4 Hz, 6H), 1.15 – 1.37 (m, 17H), 1.37 – 1.47 (m, 2H), 1.46 – 1.56 (m, 3H), 1.62 (q, *J* = 6.7 Hz, 2H), 1.71 – 1.90 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.45 (dt, *J* = 6.8, 50.1 Hz, 2H), 4.75 – 4.86 (m, 1H).



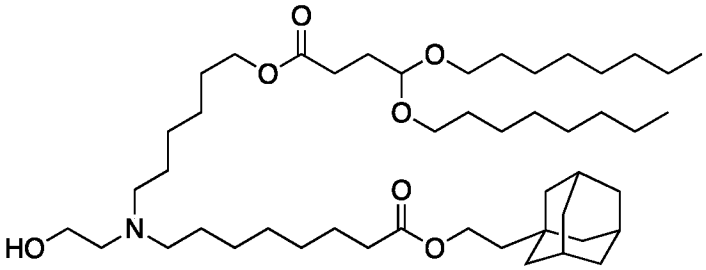
Step 2: undecan-3-yl 8-((2-hydroxyethyl)amino)octanoate

[0783] Prepared according to General Procedure E, substituting undecan-3-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 170 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.90 (m, 6H), 1.16 – 1.39 (m, 20H), 1.43 – 1.81 (m, 10H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.66 (t, *J* = 7.3

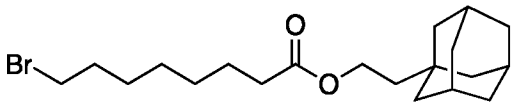
Hz, 1H), 2.82 (t, *J* = 5.1 Hz, 1H), 3.51 (t, *J* = 6.7 Hz, 1H), 3.68 (t, *J* = 5.2 Hz, 1H), 4.63 – 4.94 (m, 1H).

Step 3: undecan-3-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-98)

[0784] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 25%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 784.7, found 785.4. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.79 – 0.95 (m, 12H), 1.17 – 1.43 (m, 41H), 1.45 – 1.69 (m, 14H), 1.78 – 1.97 (m, 6H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 8.1 Hz, 4H), 3.16 (s, 2H), 3.40 (q, *J* = 6.7 Hz, 2H), 3.56 (q, *J* = 6.7 Hz, 2H), 4.04 (dd, *J* = 7.2, 14.2 Hz, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 4.79 (q, *J* = 6.2 Hz, 1H).

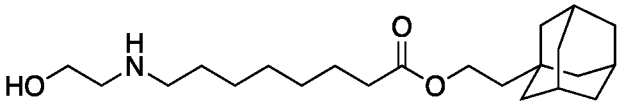


Example 7-99: 2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: 2-((3r,5r,7r)-adamantan-1-yl)ethyl 8-bromooctanoate

[0785] Prepared according to General Procedure D, substituting 2-(adamantan-1-yl)ethan-1-ol for 1-nonanol. Isolated 320 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.28 – 1.47 (m, 14H), 1.58 – 1.65 (m, 4H), 1.66 – 1.74 (m, 4H), 1.78 – 1.90 (m, 2H), 1.94 (s, 3H), 2.27 (t, *J* = 7.5 Hz, 2H), 3.25 – 3.58 (m, 2H), 4.11 (t, *J* = 7.4 Hz, 2H).

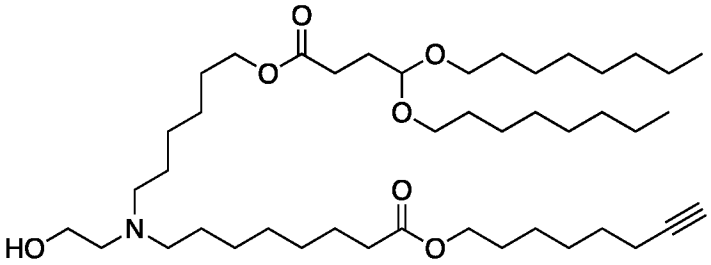


Step 2: 2-((3r,5r,7r)-adamantan-1-yl)ethyl 8-((2-hydroxyethyl)amino)octanoate

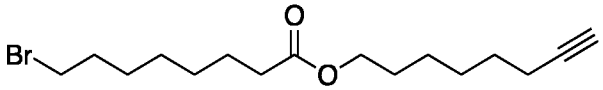
[0786] Prepared according to General Procedure E, substituting 2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethyl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 100 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.28 – 1.35 (m, 6H), 1.40 (t, *J* = 7.3 Hz, 2H), 1.45 – 1.54 (m, 2H), 1.55 – 1.66 (m, 5H), 1.66 – 1.87 (m, 11H), 1.94 (s, 3H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.59 – 2.64 (m, 2H), 2.76 – 2.81 (m, 2H), 3.60 – 3.68 (m, 2H), 4.11 (t, *J* = 7.4 Hz, 2H).

Step 3: 2-((3r,5r,7r)-adamantan-1-yl)ethyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-99)

[0787] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and ((3*r*,5*r*,7*r*)-adamantan-1-yl)methyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 49%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 792.7, found 793.4.

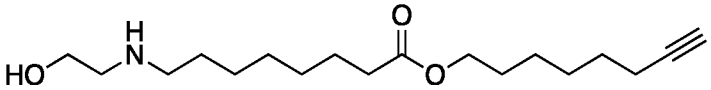


Example 7-100: oct-7-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: oct-7-yn-1-yl 8-bromooctanoate

[0788] Prepared according to General Procedure D, substituting oct-7-yn-1-ol for 1-nonanol. Isolated 200 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.27 – 1.47 (m, 10H), 1.47 – 1.55 (m, 2H), 1.58 – 1.68 (m, 4H), 1.71 – 1.80 (m, 1H), 1.78 – 1.90 (m, 1H), 1.93 (t, *J* = 2.7 Hz, 1H), 2.13 – 2.23 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 3.30 – 3.61 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).

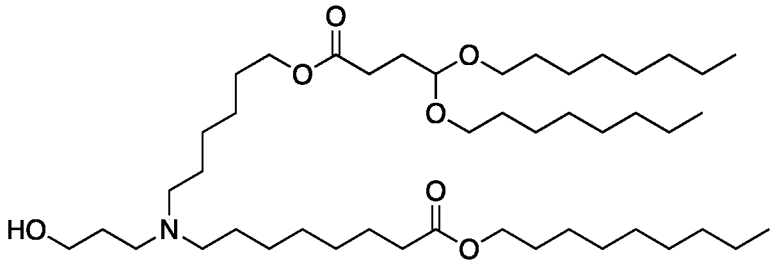


Step 2: oct-7-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate

[0789] Prepared according to General Procedure E, substituting oct-7-yn-1-yl 8-bromooctanoate for nonyl 8-bromooctanoate. Isolated 170 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.24 – 1.48 (m, 13H), 1.45 – 1.57 (m, 3H), 1.55 – 1.68 (m, 4H), 1.69 – 1.80 (m, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 2.09 – 2.23 (m, 2H), 2.23 – 2.33 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 1H), 2.75 – 2.82 (m, 1H), 3.52 (t, *J* = 6.7 Hz, 1H), 3.64 (dd, *J* = 3.7, 6.8 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 2H).

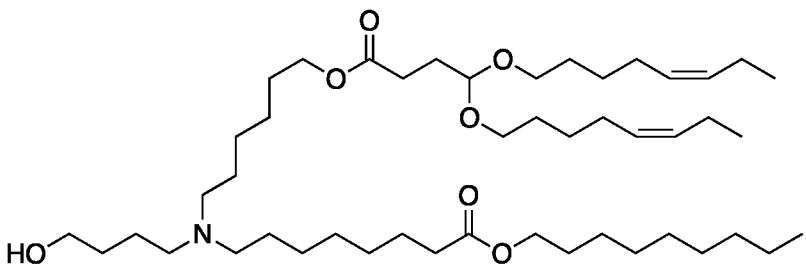
Step 3: oct-7-yn-1-yl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-100)

[0790] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and oct-7-yn-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 23 mg, 20%. UPLC-MS (Method B): Rt 1.89 min, m/z calculated [M+H]: 738.6, found 739.2.

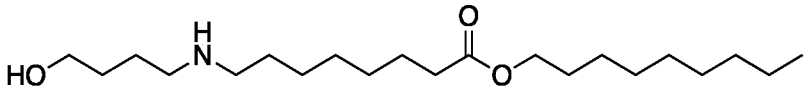


Example 7-101: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0791] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 61 mg, 39%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 770.7, found 771.4.



Example 7-102: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)octanoate

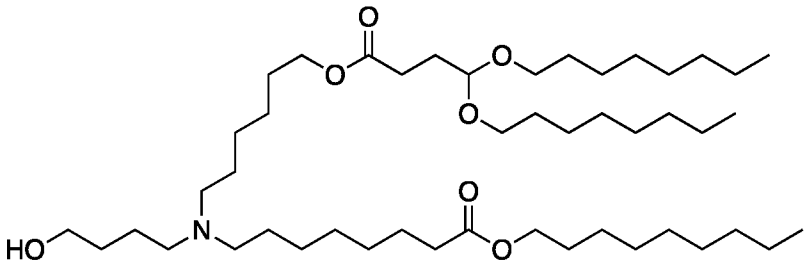


Step 1: nonyl 8-((4-hydroxybutyl)amino)octanoate

[0792] Prepared according to General Procedure E, substituting 4-aminobutan-1-ol for ethanolamine. Isolated 123 mg, 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 6.5 Hz, 3H), 1.17 – 1.33 (m, 20H), 1.32 – 1.47 (m, 8H), 1.46 – 1.59 (m, 4H), 2.26 (t, J = 7.2 Hz, 2H), 2.43 – 2.48 (m, 2H), 3.33 – 3.44 (m, 2H), 3.99 (t, J = 6.5 Hz, 2H).

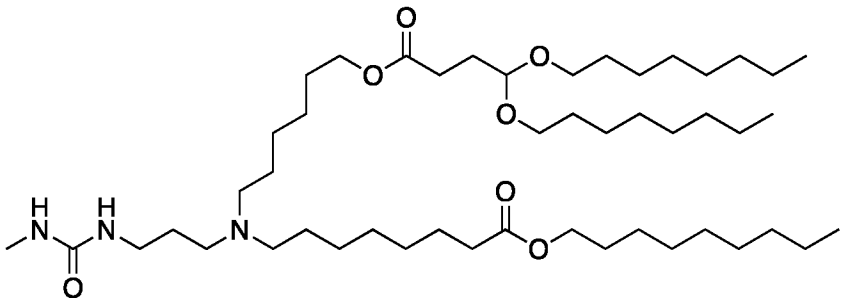
Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)octanoate (Example 7-102)

[0793] Prepared according to General Procedure F, substituting nonyl 8-((4-hydroxybutyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 85 mg, 58%. UPLC-MS (Method B): Rt 1.99 min, m/z calculated [M+H]: 780.7, found 781.4.

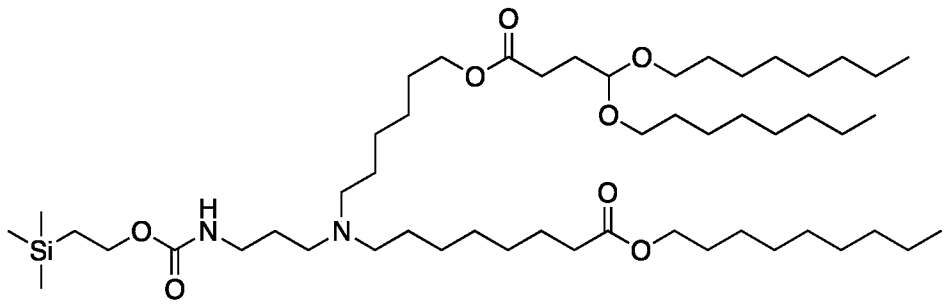


Example 7-103: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0794] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((4-hydroxybutyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 67 mg, 49%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 784.7, found 785.4.

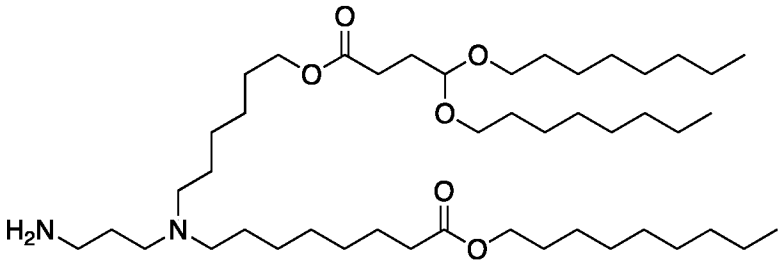


Example 7-104: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate



Step 1: nonyl 11-(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)-2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate

[0795] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 380 mg, 68%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.03 (s, 9H), 0.87 (t, *J* = 6.6 Hz, 9H), 0.91 – 1.02 (m, 2H), 1.18 – 1.40 (m, 50H), 1.41 – 1.59 (m, 11H), 1.91 (q, *J* = 6.9 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.38 – 2.69 (m, 4H), 3.24 (s, 2H), 3.39 (q, *J* = 7.3 Hz, 2H), 3.50 – 3.61 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 4H), 4.09 – 4.17 (m, 2H), 4.48 (t, *J* = 6.0 Hz, 1H).

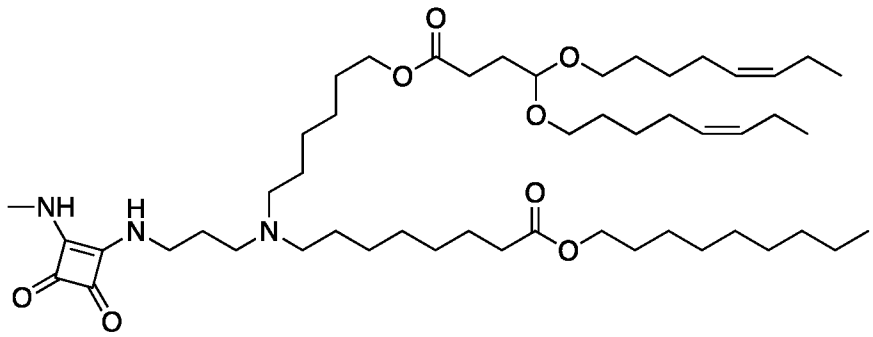


Step 2: nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate

[0796] A stirred solution of nonyl 11-(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)-2,2-dimethyl-6-oxo-5-oxa-7,11-diaza-2-silanonadecan-19-oate (1.0 eqv) in tetrabutylammonium fluoride (1M in THF, 4.0 eqv) was heated at 45 °C for 2 h. After this time, the reaction mixture was concentrated under reduced pressure. Pentane (20 mL) and water (10 mL) were added and stirred vigorously at 25 °C for 15 min. The organic layer was separated and washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate, which was used in the next step without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.95 (m, 9H), 1.00 (t, *J* = 7.3 Hz, 5H), 1.19 – 1.39 (m, 34H), 1.39 – 1.73 (m, 23H), 1.85 – 1.97 (m, 2H), 2.22 – 2.33 (m, 2H), 2.32 – 2.41 (m, 2H), 2.40 – 2.49 (m, 2H), 2.57 – 2.72 (m, 1H), 2.85 – 3.00 (m, 1H), 3.28 – 3.44 (m, 5H), 3.55 (q, *J* = 7.0 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 3H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.29 (s, 1H).

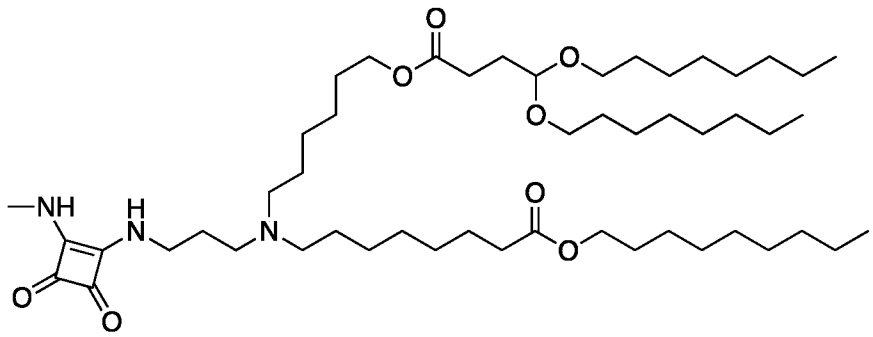
Step 3: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate (Example 7-104)

[0797] To a stirred solution of nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate (48 mg, 0.063 mmol, 1.0 eqv) in DCM (2.0 mL), methylcarbamic chloride (6 mg, 0.063 mmol, 1.0 eqv), TEA (13 mg, 0.12 mmol, 2.0 eqv) and DMAP (13 mg, 0.012 mmol, 0.2 eqv) were added to the solution. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-(3-methylureido)propyl)amino)octanoate (25 mg, 48%) as a colorless oil. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 826.7, found 827.9.



Example 7-105: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)amino)octanoate

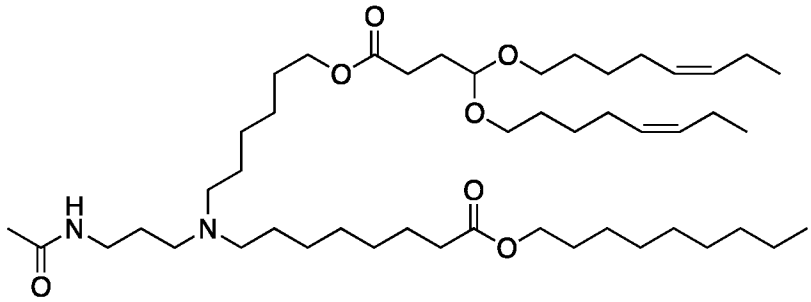
[0798] To a stirred solution of 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in ethanol (5.0 mL) was added 3-ethoxy-4-(methylamino)cyclobut-3-ene-1,2-dione (2.0 eqv). The reaction mixture was stirred at 45 °C for 16 h. The reaction mixture was then concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-7% MeOH/DCM) to afford nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)amino)octanoate (28 mg, 51%) as a colorless oil. UPLC-MS (Method B): Rt 2.01 min, m/z calculated [M+H]: 874.7, found 874.9.



Example 7-106: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)amino)octanoate

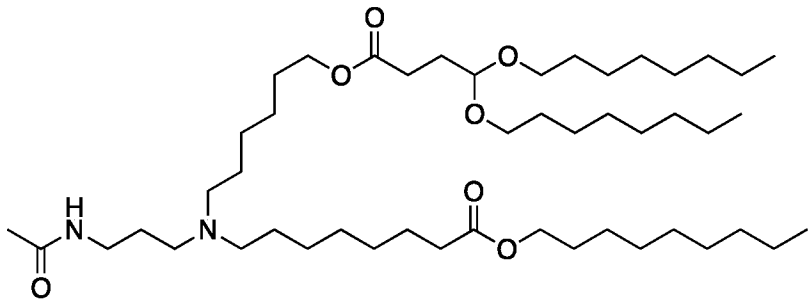
[0799] To a stirred solution of nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in ethanol (5.0 mL) was added 3-ethoxy-4-(methylamino)cyclobut-3-ene-1,2-dione (2.0 eqv). The reaction mixture was stirred at 45 °C for 16 h. The reaction mixture was then concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-7% MeOH/DCM) to

afford nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)amino)octanoate (23 mg, 44%) as a colorless oil. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 878.7, found 879.0.



Example 7-107: nonyl 8-((3-acetamidopropyl)(6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate

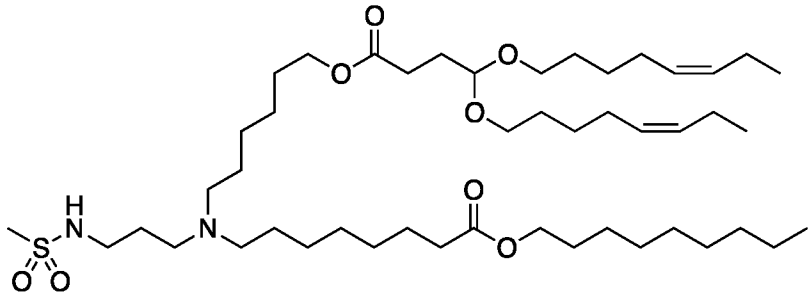
[0800] To a stirred solution of 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in DCM (2.0 mL) was added triethylamine (2.0 eqv) followed by acetic anhydride (1.0 eqv). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((3-acetamidopropyl)(6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate (29 mg, 57%) as a colorless oil. UPLC-MS (Method B): Rt 2.04 min, m/z calculated [M+H]: 807.7, found 808.8.



Example 7-108: nonyl 8-((3-acetamidopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate

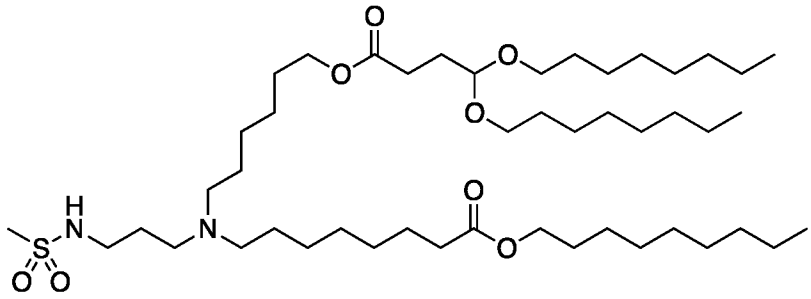
[0801] To a stirred solution of nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in DCM (2.0 mL) was added

triethylamine (2.0 eqv) followed by acetic anhydride (1.0 eqv). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((3-acetamidopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate (19 mg, 40%) as a colorless oil. UPLC-MS (Method B): Rt 2.18 min, m/z calculated [M+H]: 811.7, found 812.9.



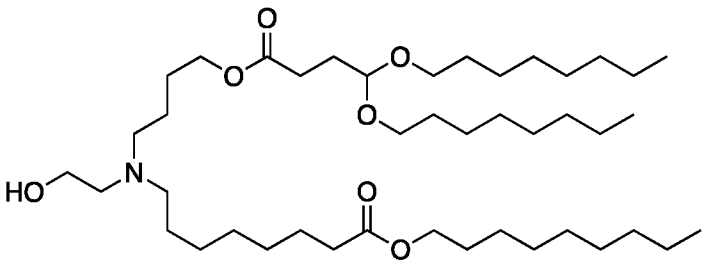
Example 7-109: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(methylsulfonamido)propyl)amino)octanoate

[0802] To a stirred solution of 8-((3-aminopropyl)(6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in DCM (2.0 mL) was added triethylamine (2.0 eqv) followed by methanesulfonyl chloride (1.0 eqv). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(methylsulfonamido)propyl)amino)octanoate (23 mg, 51%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.15 – 1.46 (m, 28H), 1.45 – 1.70 (m, 17H), 1.75 – 1.85 (m, 2H), 1.91 (q, *J* = 7.1 Hz, 2H), 2.03 (q, *J* = 7.7 Hz, 8H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.43 – 2.78 (m, 5H), 2.90 (s, 3H), 3.25 (t, *J* = 5.4 Hz, 2H), 3.34 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 4.04 (t, *J* = 6.9 Hz, 4H), 4.48 (t, *J* = 5.4 Hz, 1H), 5.26-5.40 (m, 4H). UPLC-MS (Method B): Rt 2.09 min, m/z calculated [M+H]: 843.6, found 844.9.

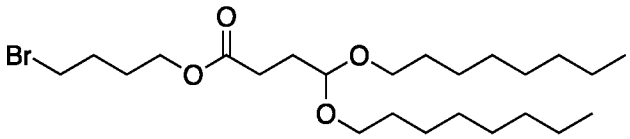


Example 7-110: nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-(methylsulfonamido)propyl)amino)octanoate

[0803] To a stirred solution of nonyl 8-((3-aminopropyl)(6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)amino)octanoate (1.0 eqv) in DCM (2.0 mL) was added triethylamine (2.0 eqv) followed by methanesulfonyl chloride (1.0 eqv). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was then diluted with water (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by combiflash column chromatography (eluted with 0-5% MeOH/DCM) to afford nonyl 8-((6-((4,4-bis(octyloxy)butanoyl)oxy)hexyl)(3-(methylsulfonamido)propyl)amino)octanoate (24 mg, 45%) as a colorless oil. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 847.7, found 848.9.



Example 7-111: nonyl 8-((4-((4,4-bis(octyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate



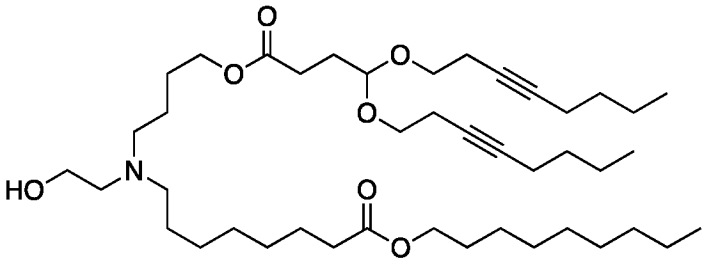
Step 1: 4-bromobutyl 4,4-bis(octyloxy)butanoate

[0804] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic

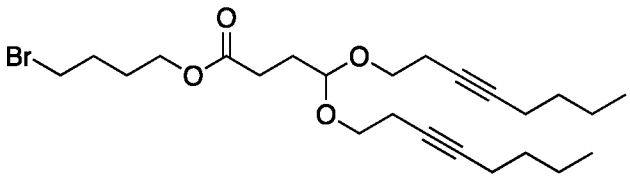
acid. Isolated 130 mg, 46%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 6H), 1.23 – 1.36 (m, 20H), 1.48 – 1.59 (m, 4H), 1.72 – 1.84 (m, 2H), 1.87 – 1.99 (m, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.50 – 3.61 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 2: nonyl 8-((4-((4,4-bis(octyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate (Example 7-111)

[0805] Prepared according to General Procedure F, substituting 4-bromobutyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 28 mg, 43%. UPLC-MS (Method B): Rt 2.09 min, m/z calculated [M+H]: 728.6, found 729.2.



Example 7-112: nonyl 8-((4-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate



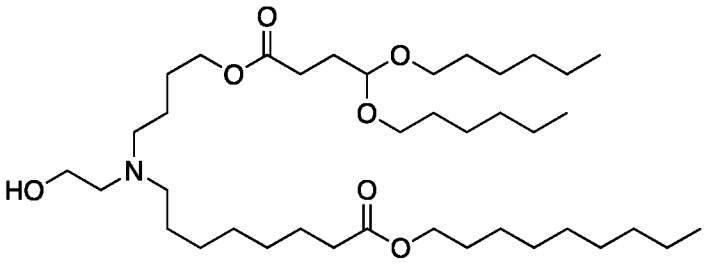
Step 1: 4-bromobutyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

[0806] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 290 mg, 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.32 – 1.50 (m, 8H), 1.79 (q, *J* = 6.8 Hz, 2H), 1.87 – 2.00 (m, 4H), 2.08 – 2.19 (m, 4H), 2.33 – 2.46 (m, 6H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.71 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

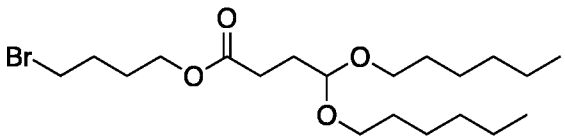
Step 2: nonyl 8-((4-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate (Example 7-112)

[0807] Prepared according to General Procedure F, substituting 4-bromobutyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 32 mg,

61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.1 Hz, 9H), 1.19 – 1.45 (m, 25H), 1.45 – 1.72 (m, 11H), 1.79 (q, J = 7.2 Hz, 2H), 2.07 – 2.17 (m, 4H), 2.28 (t, J = 7.3 Hz, 2H), 2.30 – 2.39 (m, 6H), 2.94 – 3.24 (m, 5H), 3.41 – 3.51 (m, 2H), 3.52 – 3.63 (m, 2H), 3.70 (s, 2H), 3.95 – 4.07 (m, 4H), 4.57 (t, J = 5.6 Hz, 1H), 5.30 (s, 1H), 9.05 (s, 1H). UPLC-MS (Method B): Rt 1.87 min, m/z calculated [M+H]: 720.6, found 721.1.



Example 7-113: nonyl 8-((4-((4,4-bis(hexyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate

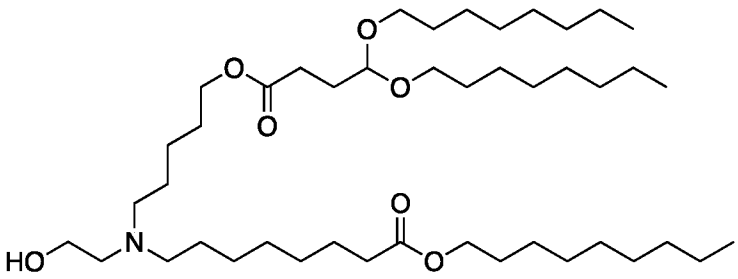


Step 1: 4-bromobutyl 4,4-bis(hexyloxy)butanoate

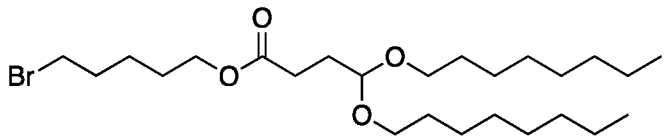
[0808] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 25 mg, 34%. ^{1}H NMR (400 MHz, Chloroform-d) δ 0.88 (t, J = 6.7 Hz, 6H), 1.20 – 1.41 (m, 13H), 1.52 (d, J = 6.9 Hz, 2H), 1.55 – 1.62 (m, 1H), 1.72 – 1.84 (m, 2H), 1.87 – 1.99 (m, 4H), 2.38 (t, J = 7.5 Hz, 2H), 3.34 – 3.47 (m, 4H), 3.51 – 3.61 (m, 2H), 4.09 (t, J = 6.3 Hz, 2H), 4.48 (t, J = 5.6 Hz, 1H).

Step 2: nonyl 8-((4-((4,4-bis(hexyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate (Example 7-113)

[0809] Prepared according to General Procedure F, substituting 4-bromobutyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 18 mg, 40%. UPLC-MS (Method B): Rt 1.90 min, m/z calculated [M+H]: 672.6, found 673.0.



Example 7-114: nonyl 8-((5-((4,4-bis(octyloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate

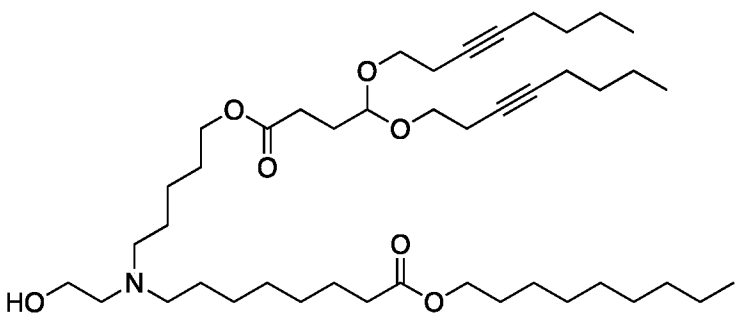


Step 1: 5-bromopentyl 4,4-bis(octyloxy)butanoate

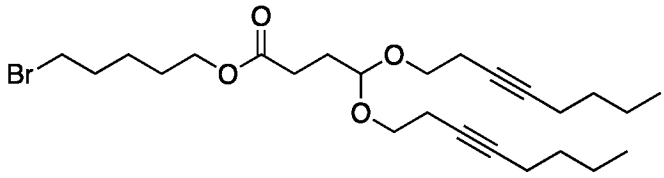
[0810] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 127 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.4 Hz, 6H), 1.23 – 1.36 (m, 20H), 1.43 – 1.60 (m, 6H), 1.59 – 1.70 (m, 2H), 1.82-1.97 (m, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.49 – 3.61 (m, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 2: nonyl 8-((5-((4,4-bis(octyloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate (Example 7-114)

[0811] Prepared according to General Procedure F, substituting 5-bromopentyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 66 mg, 72%. UPLC-MS (Method B): Rt 2.04 min, m/z calculated [M+H]: 742.7, found 743.3.



Example 7-115: nonyl 8-((5-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate

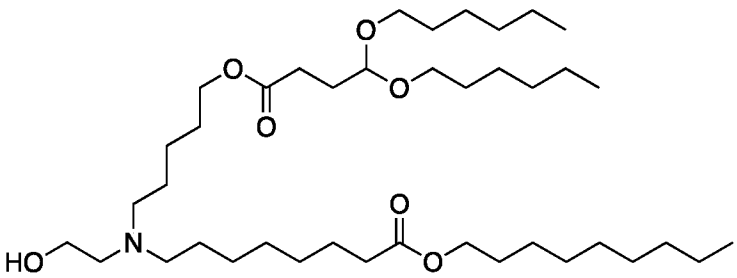


Step 1: 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

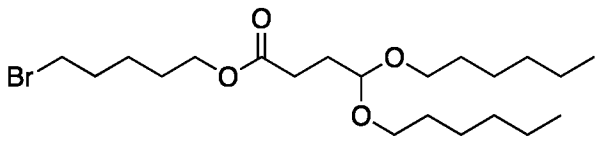
[0812] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 225 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.32 – 1.55 (m, 10H), 1.59 – 1.71 (m, 2H), 1.82 – 1.99 (m, 4H), 2.04 – 2.23 (m, 4H), 2.35 – 2.46 (m, 6H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.72 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

Step 2: nonyl 8-((5-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate (Example 7-115)

[0813] Prepared according to General Procedure F, substituting 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 25 mg, 41%. UPLC-MS (Method B): Rt 1.87 min, m/z calculated [M+H]: 734.6, found 735.1.



Example 7-116: nonyl 8-((5-((4,4-bis(hexyloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate



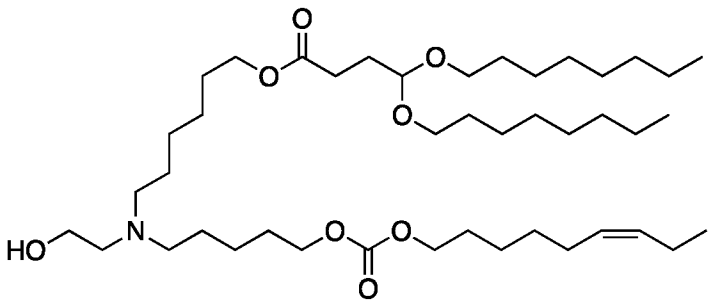
Step 1: 5-bromopentyl 4,4-bis(hexyloxy)butanoate

[0814] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 175 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.18 –

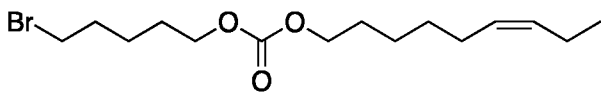
1.41 (m, 14H), 1.44 – 1.55 (m, 2H), 1.54 – 1.61 (m, 2H), 1.61 – 1.70 (m, 2H), 1.82 – 1.97 (m, 4H), 2.38 (t, J = 7.5 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.51 – 3.62 (m, 2H), 4.07 (t, J = 6.5 Hz, 2H), 4.48 (t, J = 5.6 Hz, 1H).

Step 2: nonyl 8-((5-((4,4-bis(hexyloxy)butanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate (Example 7-116)

[0815] Prepared according to General Procedure F, substituting 5-bromopentyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 40 mg, 71%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 – 0.90 (m, 9H), 1.17 – 1.38 (m, 31H), 1.38 – 1.69 (m, 14H), 1.71 – 1.81 (m, 2H), 2.29 (q, J = 7.7 Hz, 4H), 2.95 – 3.20 (m, 5H), 3.33 – 3.38 (m, 2H), 3.43 – 3.54 (m, 2H), 3.69 (s, 2H), 4.00 (q, J = 6.7 Hz, 4H), 4.45 (t, J = 5.5 Hz, 1H), 9.10 (s, 1H). UPLC-MS (Method B): Rt 1.90 min, m/z calculated [M+H]: 686.6, found 687.0.



Example 7-117: (*Z*)-6-((2-hydroxyethyl)(5-(((non-6-en-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate

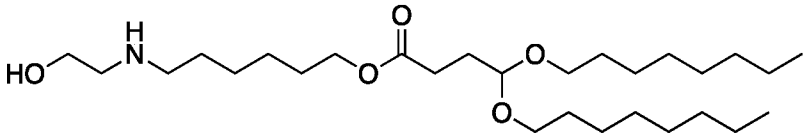


Step 1: (Z)-5-bromopentyl non-6-en-1-yl carbonate

General Procedure H:

[0816] To a stirred solution of 5-bromo-1-pentanol (100 mg, 1 Eq, 0.6 mmol) in DCM (5 mL) at 0 °C were added pyridine (10 mg, 0.01 mL, 0.2 Eq, 0.12 mmol), DMAP (15 mg, 0.2 Eq, 0.12 mmol), and 4-nitrophenyl carbonochloridate (242 mg, 2 Eq, 1.2 mmol). The cooling bath was then removed, and the resulting mixture was stirred at 23 °C for 2 h. After this time, to the mixture was added (Z)-non-6-en-1-ol (256 mg, 3 Eq, 1.8 mmol) and DIPEA (233 mg, 0.31 mL, 3 Eq, 1.8 mmol). The resulting mixture was stirred at 23 °C for 16 h. After completion, the reaction mixture was diluted with DCM (20 mL), washed with 1M sodium carbonate (3 x 15 mL), and washed with

water (20 mL). The resulting dichloromethane layer was dried over sodium sulfate and concentrated. The resulting crude material was purified by flash column chromatography (0 to 5% ethyl acetate in hexanes gradient) to afford (Z)-5-bromopentyl non-6-en-1-yl carbonate (85 mg, 42%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.37 (p, *J* = 3.8 Hz, 4H), 1.52 (d, *J* = 11.5 Hz, 2H), 1.62 – 1.74 (m, 4H), 1.75-1.93 (m, 2H), 1.95 – 2.10 (m, 4H), 3.40 (t, *J* = 6.8 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.12 (q, *J* = 6.4 Hz, 4H), 5.24 – 5.42 (m, 2H).

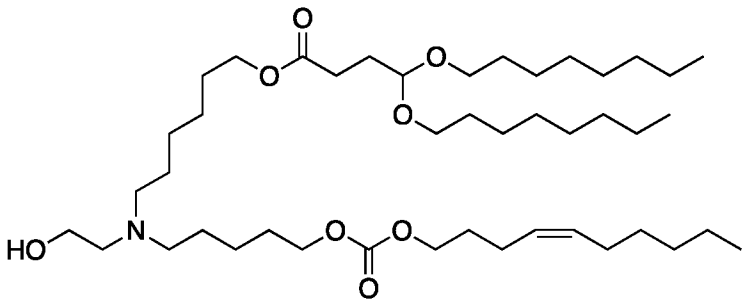


Step 2: 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

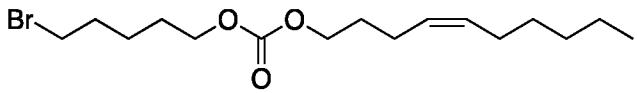
[0817] Prepared according to General Procedure E, substituting 6-bromohexyl 4,4-bis(octyloxy)butanoate for nonyl 8-bromooctanoate. Isolated 460 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.91 (m, 6H), 1.19 – 1.43 (m, 26H), 1.47 – 1.68 (m, 8H), 1.86 – 1.97 (m, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.80 – 2.85 (m, 2H), 3.34 – 3.45 (m, 2H), 3.50 – 3.61 (m, 2H), 3.64 – 3.72 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 3: (Z)-6-((2-hydroxyethyl)(5-(((non-6-en-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-117)

[0818] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl non-6-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 15 mg, 50%. UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 742.6, found 742.9.



Example 7-118: (*Z*)-6-((5-(((dec-4-en-1-yloxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

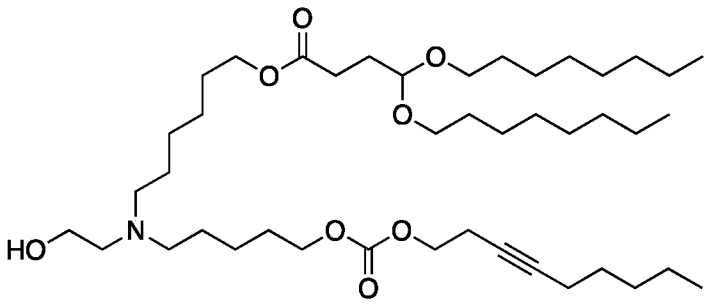


Step 1: (Z)-5-bromopentyl dec-4-en-1-yl carbonate

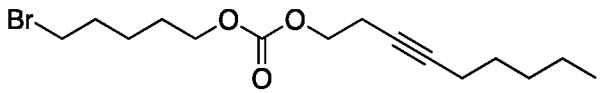
[0819] Prepared according to General Procedure H, substituting (Z)-dec-4-en-1-ol for (Z)-non-6-en-1-ol. Isolated 90 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.22 – 1.40 (m, 11H), 1.45 – 1.61 (m, 2H), 1.64 – 1.78 (m, 1H), 1.75 – 1.91 (m, 2H), 1.95 – 2.23 (m, 4H), 4.08 – 4.17 (m, 1H), 4.28 (t, *J* = 6.6 Hz, 1H), 5.28 – 5.50 (m, 2H), 7.37 (d, *J* = 9.2 Hz, 1H), 8.27 (d, *J* = 9.2 Hz, 1H).

Step 2: (Z)-6-((5-(((dec-4-en-1-yloxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-118)

[0820] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl dec-4-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 65%. UPLC-MS (Method B): Rt 2.22 min, m/z calculated [M+H]: 755.6, found 756.8.



Example 7-119: 6-((2-hydroxyethyl)(5-(((non-3-yn-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate

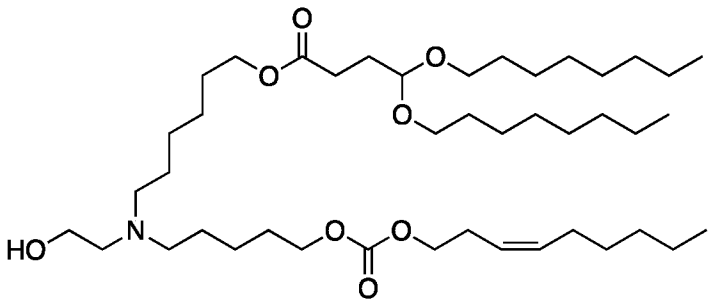


Step 1: 5-bromopentyl non-3-yn-1-yl carbonate

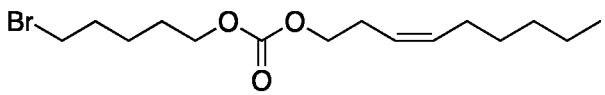
[0821] Prepared according to General Procedure H, substituting non-3-yn-1-ol for (Z)-non-6-en-1-ol. Isolated 92 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.22 – 1.40 (m, 4H), 1.41 – 1.59 (m, 4H), 1.64 – 1.79 (m, 2H), 1.76 – 1.95 (m, 2H), 2.07 – 2.17 (m, 2H), 2.48 – 2.58 (m, 2H), 3.40 (t, *J* = 6.7 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.10 – 4.22 (m, 4H).

Step 2: 6-((2-hydroxyethyl)(5-(((non-3-yn-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-119)

[0822] Prepared according to General Procedure F, substituting 5-bromopentyl non-3-yn-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 26 mg, 58%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 740.5, found 740.8.



Example 7-120: (*Z*)-6-((2-hydroxyethyl)(5-(((non-3-en-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate

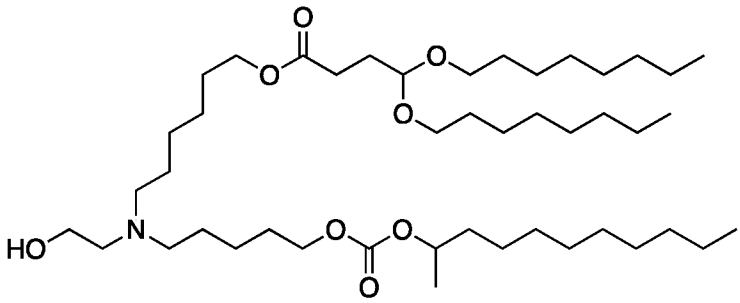


Step 1: (Z)-5-bromopentyl non-3-en-1-yl carbonate

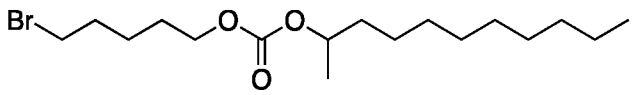
[0823] Prepared according to General Procedure H, substituting (*Z*)-non-3-en-1-ol for (Z)-non-6-en-1-ol. Isolated 88 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.29 (td, *J* = 7.0, 18.1, 19.2 Hz, 8H), 1.69 (q, *J* = 7.2 Hz, 2H), 1.76 – 1.94 (m, 2H), 1.97 – 2.06 (m, 2H), 2.42 (q, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 6.7 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.07 – 4.17 (m, 4H), 5.28 – 5.40 (m, 1H), 5.44 – 5.59 (m, 1H).

Step 2: (Z)-6-((2-hydroxyethyl)(5-(((non-3-en-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-120)

[0824] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl non-3-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 44%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 742.6, found 742.8.



Example 7-121: 6-((2-hydroxyethyl)(5-(((undecan-2-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate

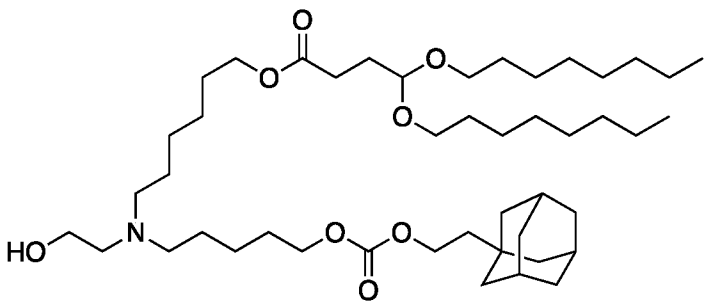


Step 1: 5-bromopentyl undecan-2-yl carbonate

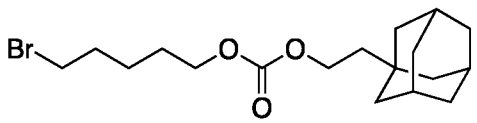
[0825] Prepared according to General Procedure H, substituting undecan-2-ol for (Z)-non-6-en-1-ol. Isolated 100 mg, 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.23 – 1.41 (m, 14H), 1.45 – 1.58 (m, 4H), 1.58 – 1.74 (m, 2H), 1.74 – 1.95 (m, 2H), 3.40 (t, *J* = 6.7 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.12 (t, *J* = 6.5 Hz, 2H), 4.67 – 4.80 (m, 1H), 4.81 – 4.93 (m, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H).

Step 2: 6-((2-hydroxyethyl)(5-(((undecan-2-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-121)

[0826] Prepared according to General Procedure F, substituting 5-bromopentyl undecan-2-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 22 mg, 63%. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 772.6, found 773.0.



Example 7-122: 6-((5-(((2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethoxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

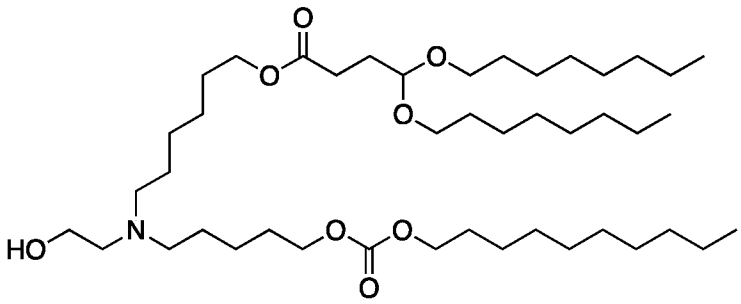


Step 1: 2-((3r,5r,7r)-adamantan-1-yl)ethyl (5-bromopentyl) carbonate

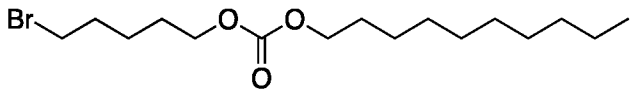
[0827] Prepared according to General Procedure H, substituting 2-(adamantan-1-yl)ethan-1-ol for (Z)-non-6-en-1-ol. Isolated 90 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.43 – 1.58 (m, 11H), 1.59 – 1.75 (m, 6H), 1.77 – 1.92 (m, 1H), 1.96 (d, *J* = 10.7 Hz, 3H), 3.34 – 3.61 (m, 1H), 4.09 – 4.23 (m, 2H), 4.35 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 9.1 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H

Step 2: 6-((5-(((2-((3r,5r,7r)-adamantan-1-yl)ethoxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-122)

[0828] Prepared according to General Procedure F, substituting 2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethyl (5-bromopentyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 63%. UPLC-MS (Method B): Rt 2.16 min, m/z calculated [M+H]: 779.6, found 780.3.



Example 7-123: 6-((5-(((decyloxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

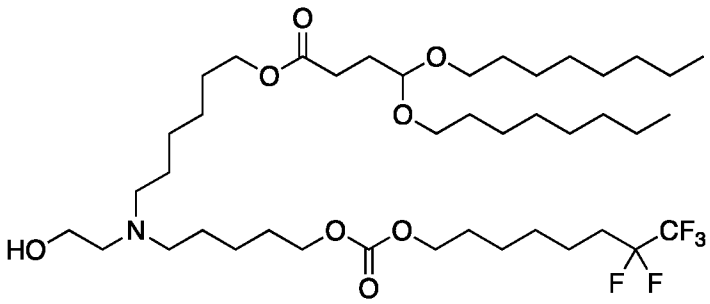


Step 1: 5-bromopentyl decyl carbonate

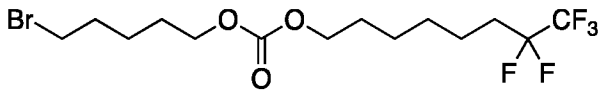
[0829] Prepared according to General Procedure H, substituting decan-1-ol for (Z)-non-6-en-1-ol. Isolated 100 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.22 – 1.39 (m, 15H), 1.46 – 1.55 (m, 1H), 1.59 – 1.75 (m, 4H), 1.76 – 1.95 (m, 2H), 3.40 (t, *J* = 6.7 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.12 (q, *J* = 6.6 Hz, 4H).

Step 2: 6-((5-(((decyloxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-123)

[0830] Prepared according to General Procedure F, substituting 5-bromopentyl decyl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 44%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 758.6, found 758.8.



Example 7-124: 6-((2-hydroxyethyl)(5-((((7,7,8,8,8-pentafluorooctyl)oxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate

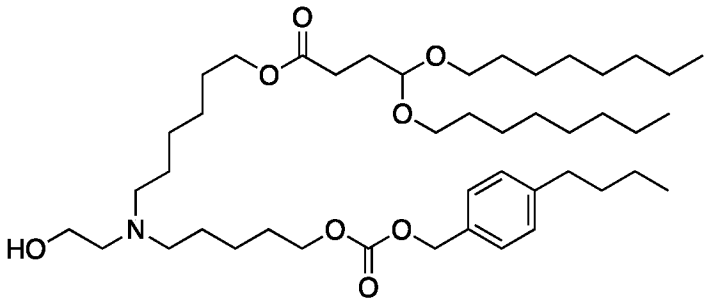


Step 1: 5-bromopentyl (7,7,8,8,8-pentafluorooctyl) carbonate

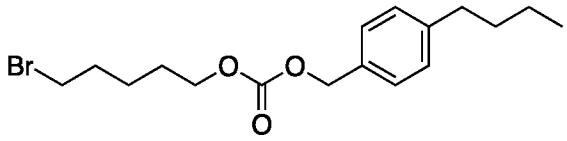
[0831] Prepared according to General Procedure H, substituting 7,7,8,8,8-pentafluorooctan-1-ol for (Z)-non-6-en-1-ol. Isolated 110 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.36 – 1.45 (m, 4H), 1.46 – 1.54 (m, 1H), 1.54 – 1.64 (m, 3H), 1.63 – 1.75 (m, 4H), 1.79 – 2.09 (m, 4H), 3.40 (t, *J* = 6.7 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 1H), 4.13 (td, *J* = 3.5, 6.6 Hz, 4H).

Step 2: 6-((2-hydroxyethyl)(5-((((7,7,8,8,8-pentafluorooctyl)oxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-124)

[0832] Prepared according to General Procedure F, substituting 5-bromopentyl (7,7,8,8,8-pentafluorooctyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 52%. UPLC-MS (Method C): Rt 5.18 min, m/z calculated [M+H]: 820.6, found 820.7.



Example 7-125: 6-((5-((((4-butylbenzyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

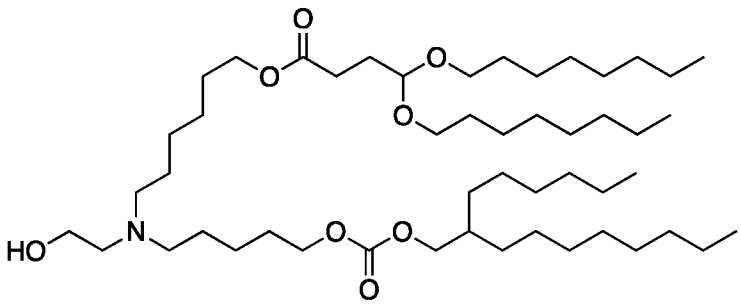


Step 1: 5-bromopentyl (4-butylbenzyl) carbonate

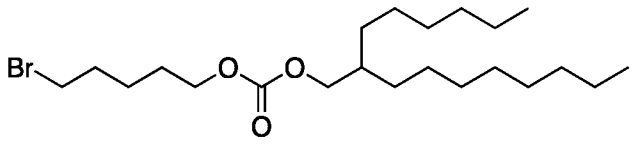
[0833] Prepared according to General Procedure H, substituting 4-butylbenzyl alcohol for (Z)-non-6-en-1-ol. Isolated 100 mg, 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.28 – 1.39 (m, 2H), 1.45 – 1.64 (m, 4H), 1.65 – 1.73 (m, 2H), 1.83 – 1.92 (m, 2H), 2.60 (t, *J* = 7.7 Hz, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 4.14 (t, *J* = 6.5 Hz, 2H), 5.11 (s, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H).

Step 2: 6-((5-((((4-butylbenzyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-125)

[0834] Prepared according to General Procedure F, substituting 5-bromopentyl (4-butylbenzyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 22 mg, 52%. UPLC-MS (Method B): Rt 2.04 min, m/z calculated [M+H]: 764.6, found 764.8.



Example 7-126: 6-((5-((((2-hexyldecyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate



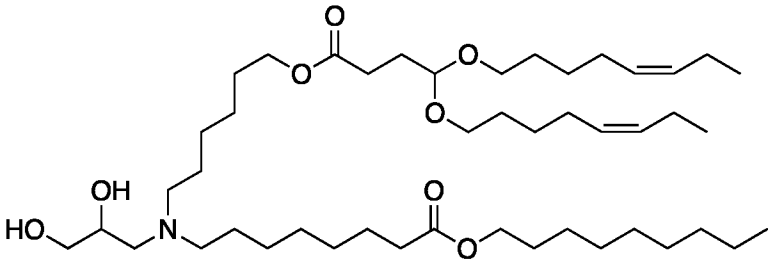
Step 1: 5-bromopentyl (2-hexyldecyl) carbonate

[0835] Prepared according to General Procedure H, substituting 2-hexyldecan-1-ol for (Z)-non-6-en-1-ol. Isolated 80 mg, 42%.^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 (m, 6H), 1.24 – 1.39 (m,

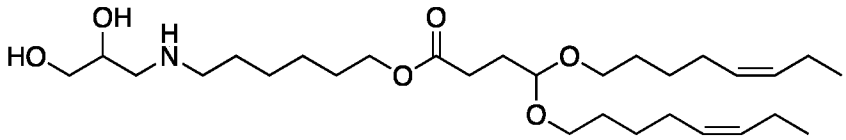
24H), 1.64 – 1.73 (m, 3H), 1.85 – 1.92 (m, 2H), 3.39 (t, *J* = 6.7 Hz, 6H), 4.01 (d, *J* = 5.7 Hz, 2H), 4.12 (t, *J* = 6.4 Hz, 2H).

Step 2: 6-((5-((((2-hexyldecyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate (Example 7-126)

[0836] Prepared according to General Procedure F, substituting 5-bromopentyl (2-hexyldecyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 50%. UPLC-MS (Method B): Rt 2.40 min, m/z calculated [M+H]: 842.6, found 842.7.



Example 7-127: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2,3-dihydroxypropyl)amino)octanoate



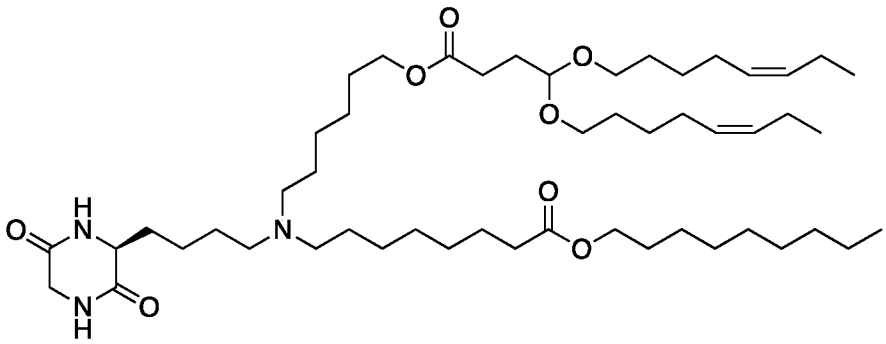
Step 1: 6-((2,3-dihydroxypropyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0837] Prepared according to General Procedure E, substituting 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate and 3-aminopropane-1,2-diol for ethanolamine. Isolated 55 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.32 – 1.46 (m, 6H), 1.49 – 1.69 (m, 6H), 1.71 – 1.83 (m, 2H), 1.85 – 2.11 (m, 12H), 2.32 – 2.41 (m, 2H), 2.86 – 3.17 (m, 4H), 3.35 – 3.45 (m, 3H), 3.51 – 3.69 (m, 4H), 3.71 – 3.83 (m, 1H), 3.97 – 4.19 (m, 3H), 4.48 (s, 2H), 5.21 – 5.45 (m, 4H).

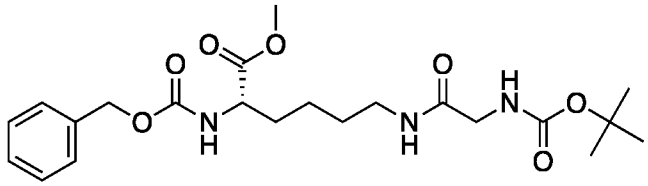
Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2,3-dihydroxypropyl)amino)octanoate (Example 7-127)

[0838] Prepared according to General Procedure F, substituting nonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2,3-dihydroxypropyl)amino)hexyl

4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 27%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 782.6, found 782.5.

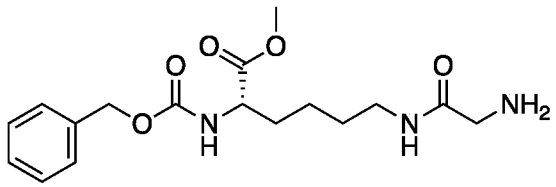


Example 7-128: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-((*S*)-3,6-dioxopiperazin-2-yl)butyl)amino)octanoate



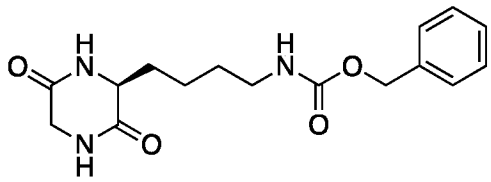
Step 1: methyl N2-((benzyloxy)carbonyl)-N6-((tert-butoxycarbonyl)glycyl)-L-lysinate

[0839] To a stirred solution of methyl ((benzyloxy)carbonyl)-*L*-lysinate hydrochloride (2 g, 5.45 mmol) in DCM: DMF (20 mL), were added DIPEA (4.22 mL, 24.18 mmol), HATU (4.60 g, 12.10 mmol) and (*tert*-butoxycarbonyl)glycine (1.27 g, 7.25 mmol). Reaction mixture was stirred at 25 °C for 16 h. Upon completion, the reaction mixture was evaporated under reduced pressure and diluted with ethyl acetate (60 mL) and washed with cold water (2 × 60 mL) and brine solution (2 × 60 mL). Organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with10% MeOH- DCM to afford methyl N2-((benzyloxy)carbonyl)-N6-((tert-butoxycarbonyl)glycyl)-L-lysinate (1.6 g, 58%) as brown liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.31-1.33 (m, 2H), 1.43 (s, 9H), 1.46-1.49 (m, 2H), 2.78 (s, 1H), 3.15-3.16 (m, 2H), 3.72 (s, 3H), 3.78 (s, 2H), 4.58-4.59 (m, 1H), 5.07 (s, 2H), 5.28 (s, 1H), 6.64 (m, 1H), 7.31-7.34 (m, 5H).



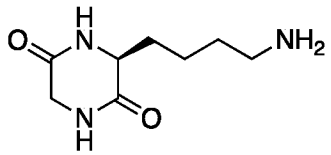
Step 2: methyl N2-((benzyloxy)carbonyl)-N6-glycyl-L-lysinate

[0840] To a stirred solution of N2-((benzyloxy)carbonyl)-N6-((tert-butoxycarbonyl)glycyl)-L-lysinate (2.13 g, 7.58 mmol) in DCM (8 mL), was added TFA (5.8 mL, 75.80 mmol) at 0 °C and the reaction mixture was stirred at 25 °C for 6 h. Upon completion, the reaction mixture was evaporated under reduced pressure and azeotroped with toluene (2×5 mL) to afford methyl N2-((benzyloxy)carbonyl)-N6-glycyl-L-lysinate (1.9 g crude) which was used for the next step without further purification.



Step 3: benzyl (S)-(4-(3,6-dioxopiperazin-2-yl)butyl)carbamate

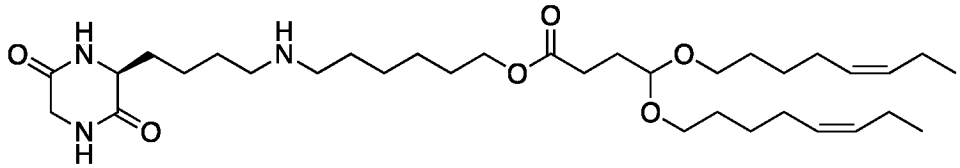
[0841] To a stirred solution of methyl N2-((benzyloxy)carbonyl)-N6-glycyl-L-lysinate (6 g, 13.4 mmol) in 0.1 M AcOH in 2-butanol (48 mL) was added 0.1M N-methylmorpholine in 2-butanol (72 mL) and the reaction mixture was stirred at 120 °C for 16 h. Upon completion, reaction mixture was cooled. Solid was filtered off. The filtrate was evaporated under reduced pressure to get the crude compound. Crude material was triturated with DCM (2×30 mL). Again solid was filtered off. Combined solid was dried under reduced pressure to afford benzyl (S)-(4-(3,6-dioxopiperazin-2-yl)butyl)carbamate (800 mg, 13%) as colorless solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.28-1.40 (m, 4H), 1.63-1.69 (m, 2H), 2.95-3.00 (m, 2H), 3.63-3.69 (m, 3H), 4.99-5.04 (m, 2H), 7.23-7.38 (m, 5H), 7.97 (s, 1H), 8.15 (s, 1H)



Step 4: (S)-3-(4-aminobutyl)piperazine-2,5-dione

[0842] A solution of benzyl (S)-(4-(3,6-dioxopiperazin-2-yl)butyl)carbamate (1.3 g, 3.57 mmol) in methanol (15 mL) and AcOH (15 mL), was degassed with argon for 10 min and then was added 10% Pd-C (50% moist) (600 mg). Reaction mixture was stirred at 25 °C for 16 h under hydrogen atmosphere. upon completion, reaction mixture was filtered, washed with dry methanol (2 × 40 mL) and then evaporated and passed through the bi-carbonate cartridge to afford (S)-3-(4-aminobutyl)piperazine-2,5-dione (300 mg, 45%) as off-white solid. ^{1}H NMR (400 MHz, MeOD)

δ 1.45-1.49 (m, 2H), 1.63-1.69 (m, 2H), 1.81-1.84 (m, 1H), 1.89 (s, 4H), 2.91 (t, J=7.72 Hz, 2H), 3.9-3.93 (m, 2H), 3.98 (t, J=5.16 Hz, 1H).

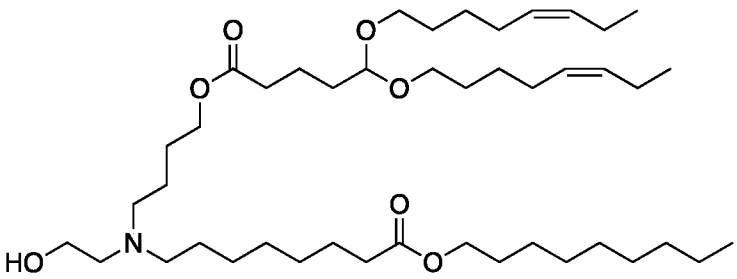


Step 5: 6-((4-((S)-3,6-dioxopiperazin-2-yl)butyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

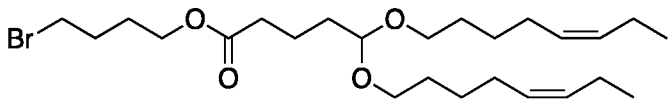
[0843] Prepared according to General Procedure E, substituting 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate and (*S*)-3-(4-aminobutyl)piperazine-2,5-dione for ethanolamine. Isolated 20 mg, 14%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 0.95 (t, *J* = 7.5 Hz, 6H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 8H), 1.50 – 1.60 (m, 4H), 1.69 (dd, *J* = 7.6, 15.0 Hz, 7H), 1.88 (q, *J* = 7.1 Hz, 2H), 1.98 – 2.11 (m, 8H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.94 – 3.02 (m, 5H), 3.38 – 3.48 (m, 2H), 3.54 – 3.65 (m, 2H), 3.92 (d, *J* = 8.0 Hz, 2H), 3.99 (t, *J* = 5.7 Hz, 2H), 4.04 – 4.14 (m, 4H), 5.25 – 5.43 (m, 4H).

Step 6: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-((S)-3,6-dioxopiperazin-2-yl)butyl)amino)octanoate (Example 7-128)

[0844] Prepared according to General Procedure F, substituting nonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((4-((S)-3,6-dioxopiperazin-2-yl)butyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 16 mg, 22%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 876.7, found 877.1.



Example 7-129: nonyl 8-((4-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate

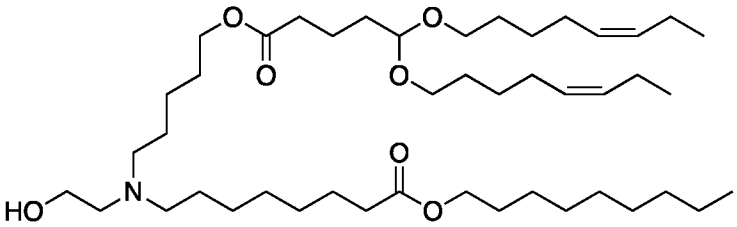


Step 1: 4-bromobutyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

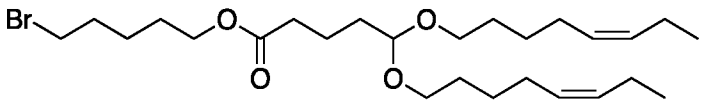
[0845] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 60 mg, 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.4 Hz, 6H), 1.33 – 1.48 (m, 4H), 1.49 – 1.84 (m, 10H), 1.86 – 2.14 (m, 10H), 2.32 (t, *J* = 7.0 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.50 – 3.61 (m, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 4.45 (t, *J* = 5.3 Hz, 1H), 5.24 – 5.42 (m, 4H).

Step 2: nonyl 8-((4-((5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate (Example 7-129)

[0846] Prepared according to General Procedure F, substituting 4-bromobutyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 19 mg, 33%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 738.6, found 739.0.



Example 7-130: nonyl 8-((5-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate

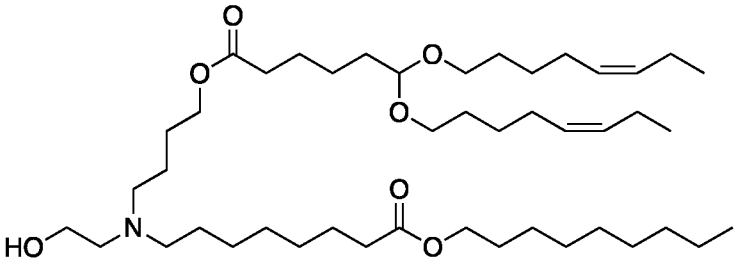


Step 1: 5-bromopentyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

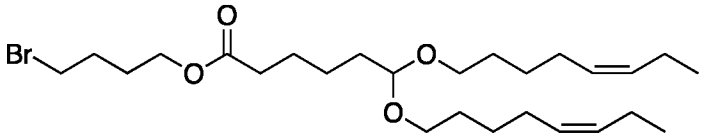
[0847] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 80 mg, 55%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.41 (q, *J* = 7.5 Hz, 4H), 1.52 – 1.72 (m, 12H), 1.82 – 1.94 (m, 2H), 1.96 – 2.09 (m, 8H), 2.32 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 7.0 Hz, 4H), 3.50 – 3.61 (m, 2H), 4.06 (t, *J* = 6.5 Hz, 2H), 4.45 (t, *J* = 4.7 Hz, 1H), 5.24 – 5.40 (m, 4H).

Step 2: nonyl 8-((5-((5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate (Example 7-130)

[0848] Prepared according to General Procedure F, substituting 5-bromopentyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 26 mg, 40%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 752.6, found 752.9.



Example 7-131: nonyl 8-((4-((6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate

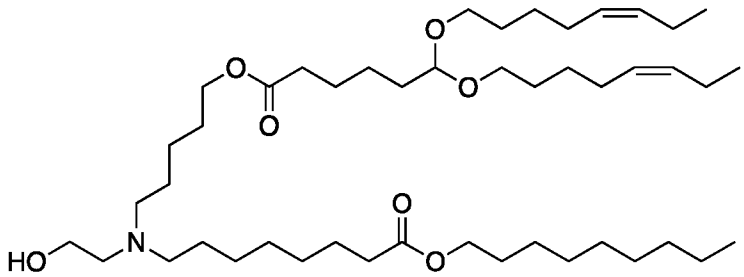


Step 1: 4-bromobutyl 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate

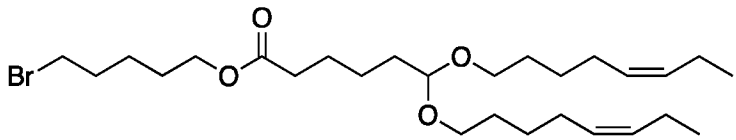
[0849] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 90 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.31 – 1.48 (m, 6H), 1.54 – 1.71 (m, 6H), 1.72 – 1.97 (m, 6H), 1.96 – 2.13 (m, 6H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.33-3.46 (m, 4H), 3.55 (q, *J* = 7.4 Hz, 2H), 3.69 – 3.78 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.44 (t, *J* = 6.9 Hz, 1H), 5.20 – 5.50 (m, 4H).

Step 2: nonyl 8-((4-((6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoyl)oxy)butyl)(2-hydroxyethyl)amino)octanoate (Example 7-131)

[0850] Prepared according to General Procedure F, substituting 4-bromobutyl 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 27 mg, 53%. UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 752.6, found 752.9.



Example 7-132: nonyl 8-((5-((6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate

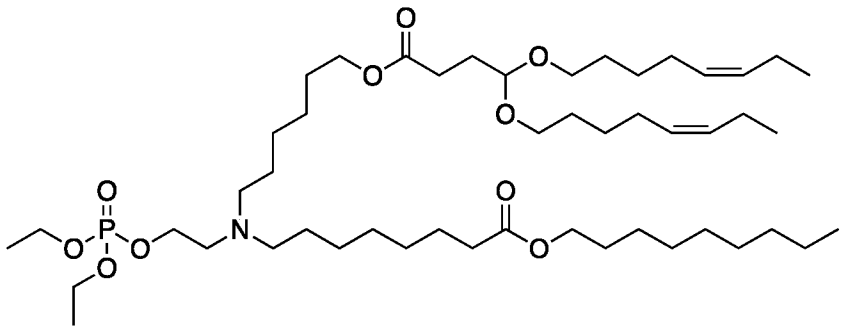


Step 1: 5-bromopentyl 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate

[0851] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 60 mg, 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.30 (m, 3H), 1.41 (q, *J* = 7.7 Hz, 6H), 1.45 – 1.56 (m, 2H), 1.56 – 1.70 (m, 7H), 1.88 (t, *J* = 7.5 Hz, 2H), 1.94 – 2.11 (m, 8H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.35 – 3.45 (m, 4H), 3.49 – 3.60 (m, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 4.44 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.44 (m, 4H).

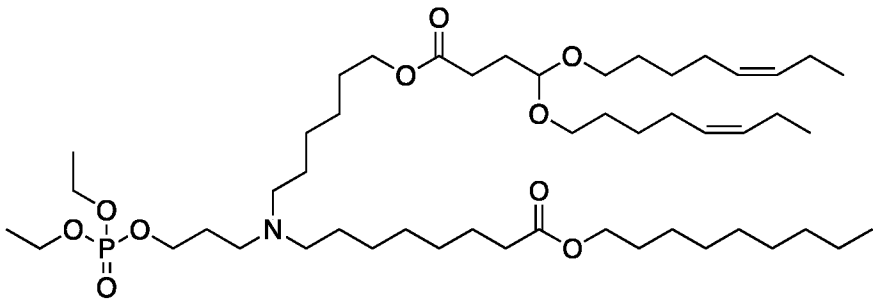
Step 2: nonyl 8-((5-((6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoyl)oxy)pentyl)(2-hydroxyethyl)amino)octanoate (Example 7-132)

[0852] Prepared according to General Procedure F, substituting 5-bromopentyl 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 35 mg, 68%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.98 (m, 9H), 1.23 – 1.46 (m, 30H), 1.50 – 1.71 (m, 15H), 1.96 – 2.09 (m, 8H), 2.24 – 2.34 (m, 4H), 2.84 – 3.12 (m, 6H), 3.34 – 3.44 (m, 2H), 3.50 – 3.60 (m, 2H), 3.91 (s, 2H), 4.05 (q, *J* = 7.0 Hz, 4H), 4.44 (t, *J* = 5.9 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method C): Rt 5.23 min, m/z calculated [M+H]: 766.7, found 766.9.



Example 7-133: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-((diethoxyphosphoryl)oxy)ethyl)amino)octanoate

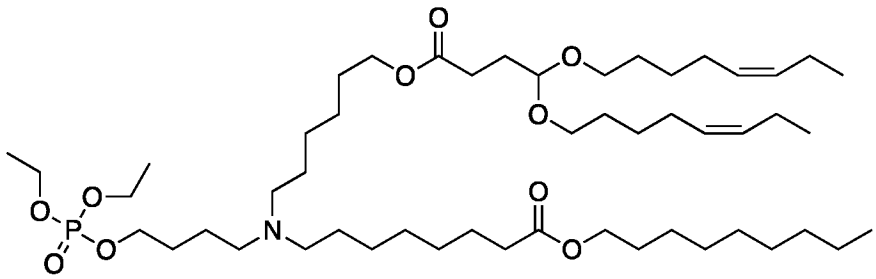
[0853] To a stirred solution of nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (35 mg, 0.046 mmol, 1.0 eqv) in dry DCM (2 mL), were added TEA (12 mg, 0.12 mmol, 2.5 eqv) and DMAP (2 mg, 0.014 mmol, 0.3 eqv) at 0 °C under inert atmosphere. Then was added diethyl chlorophosphate (10 mg, 0.060 mmol, 1.3 eqv) drop wise to the reaction mixture at 0 °C and was stirred at 25 °C for 5 h. Upon completion, reaction mixture was diluted with water (20 mL) and extracted with DCM (3 x 15 mL). Then organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 3-5% MeOH in DCM to afford nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-((diethoxyphosphoryl)oxy)ethyl)amino)octanoate as a light yellow gum (19 mg, 47%). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 888.7, found 889.0.



Example 7-134: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-((diethoxyphosphoryl)oxy)propyl)amino)octanoate

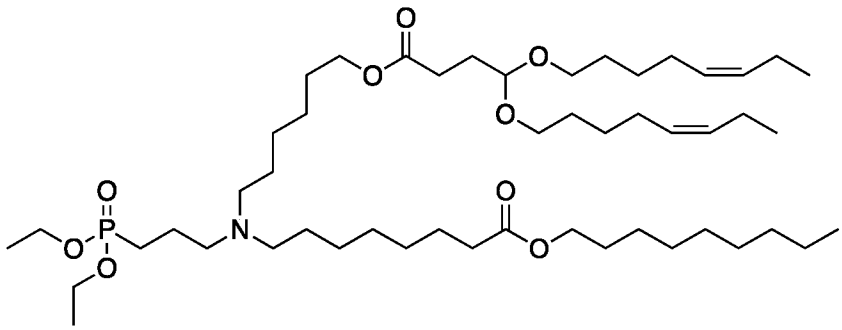
[0854] To a stirred solution of nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate (100 mg, 0.13 mmol, 1.0 eqv) in dry DCM (4 mL), were added TEA (33 mg, 0.33 mmol, 2.5 eqv) and DMAP (5 mg, 0.039 mmol,

0.3 eqv) at 0 °C under inert atmosphere. Then was added diethyl chlorophosphate (29 mg, 0.17 mmol, 1.3 eqv) drop wise to the reaction mixture at 0 °C and was stirred at 25 °C for 5 h. Upon completion, reaction mixture was diluted with water (20 mL) and extracted with DCM (3 x 15 mL). Then organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 3-5% MeOH in DCM to afford nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate as a light brown gum (63 mg, 54%). UPLC-MS (Method B): Rt 2.10 min, m/z calculated [M+H]: 902.7, found 903.0.

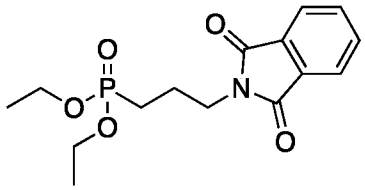


Example 7-135: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-((diethoxyphosphoryl)oxy)butyl)amino)octanoate

[0855] To a stirred solution of nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)octanoate (100 mg, 0.13 mmol, 1.0 eqv) in dry DCM (4 mL), were added TEA (33 mg, 0.33 mmol, 2.5 eqv) and DMAP (5 mg, 0.039 mmol, 0.3 eqv) at 0 °C under inert atmosphere. Then was added diethyl chlorophosphate (29 mg, 0.17 mmol, 1.3 eqv) drop wise to the reaction mixture at 0 °C and was stirred at 25 °C for 5 h. Upon completion, reaction mixture was diluted with water (20 mL) and extracted with DCM (3 x 15 mL). Then organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 3-5% MeOH in DCM to afford nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-((diethoxyphosphoryl)oxy)butyl)amino)octanoateas a light brown gum (56 mg, 47%). UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 916.7, found 916.9.

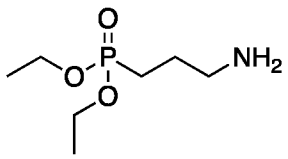


Example 7-136: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(diethoxyphosphoryl)propyl)amino)octanoate



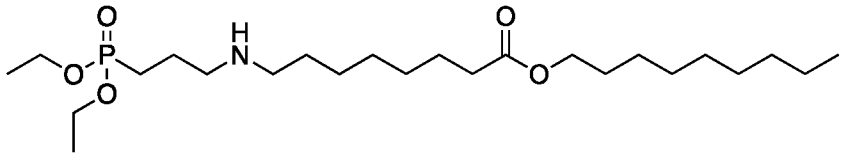
Step 1: diethyl (3-(1,3-dioxoisoindolin-2-yl)propyl)phosphonate

[0856] A stirred solution of 2-(3-bromopropyl)isoindoline-1,3-dione (2 g, 7.46 mmol) in triethylphosphite (6.4 mL, 37.29 mmol) was heated at 140 °C for 48 h in open atmosphere. Upon completion, reaction mixture was cooled to 25 °C and purified directly by combiflash column chromatography, eluted with ethyl acetate to afford diethyl (3-(1,3-dioxoisoindolin-2-yl)propyl)phosphonate (2.2 g, 91%) as viscous oil. 1H NMR (400 MHz, Chloroform-*d*) δ 1.29 (q, *J* = 6.9 Hz, 8H), 1.66 – 1.83 (m, 4H), 1.89 – 2.04 (m, 2H), 3.73 (t, *J* = 7.0 Hz, 2H), 7.67 – 7.74 (m, 2H), 7.79 – 7.85 (m, 2H).



Step 2: diethyl (3-aminopropyl)phosphonate

[0857] To a stirred solution of diethyl (3-(1,3-dioxoisoindolin-2-yl)propyl)phosphonate (200 mg, 0.61 mmol) in toluene (5 mL) was added hydrazine monohydrate (0.4 mL, 6.94 mmol). The resulting mixture was stirred at 25 °C for 16 h, and then heated at 80 °C for 4 h under inert atmosphere. Upon completion, reaction mixture was cooled to 25 °C, filtered through celite bed and washed with toluene (15 mL) and concentrated under reduced pressure to afford diethyl (3-aminopropyl)phosphonate (81 mg, 82%) colorless liquid. 1H NMR (400 MHz, Chloroform-*d*) δ 1.30 (t, *J* = 7.1 Hz, 6H), 1.60 – 1.85 (m, 4H), 2.75 (d, *J* = 6.6 Hz, 2H), 3.98 – 4.17 (m, 4H).

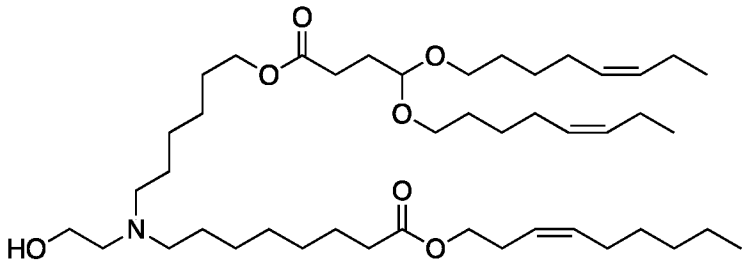


Step 3: nonyl 8-((3-(diethoxyphosphoryl)propyl)amino)octanoate

[0858] Prepared according to General Procedure E, substituting diethyl (3-aminopropyl)phosphonate for ethanolamine. Isolated 210 mg, 79%. 1H NMR (400 MHz, Chloroform-*d*) δ 1.22 – 1.38 (m, 26H), 1.49 – 1.66 (m, 9H), 4.00 – 4.17 (m, 6H), 1.65 – 1.85 (m, 3H), 1.65 – 1.95 (m, 6H), 2.27 (t, *J* = 7.5 Hz, 1H), 2.65 (t, *J* = 7.4 Hz, 1H), 2.77 (q, *J* = 5.8, 6.5 Hz, 1H).

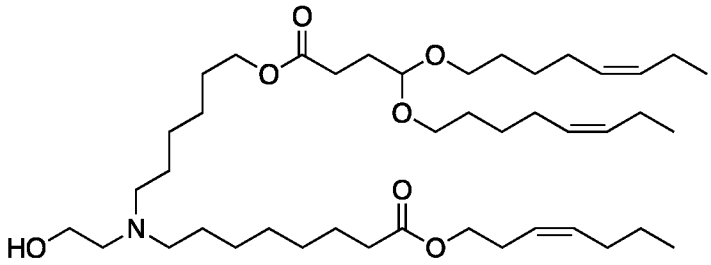
Step 4: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-(diethoxyphosphoryl)propyl)amino)octanoate (Example 7-136)

[0859] Prepared according to General Procedure F, substituting nonyl 8-((3-(diethoxyphosphoryl)propyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 39 mg, 52%. 1H NMR (400 MHz, Chloroform-*d*) δ 0.74 – 1.07 (m, 9H), 1.18 – 1.45 (m, 42H), 1.57 – 1.71 (m, 8H), 1.74 – 1.96 (m, 6H), 1.97 – 2.12 (m, 6H), 2.23 – 2.45 (m, 4H), 2.92 – 3.09 (m, 3H), 3.12 – 3.27 (m, 1H), 3.27– 3.64 (m, 4H), 3.94 – 4.26 (m, 8H), 4.48 (s, 1H), 5.23 – 5.45 (m, 4H). UPLC-MS (Method B): Rt 2.09 min, m/z calculated [M+H]: 886.7, found 887.2.



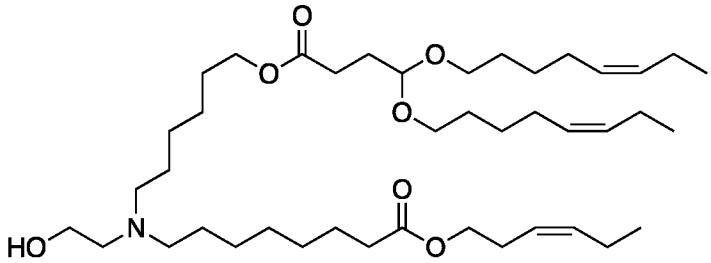
Example 7-137: (*Z*)-non-3-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0860] Prepared according to General Procedure F, substituting (*Z*)-non-3-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 45%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 750.6, found 750.9.



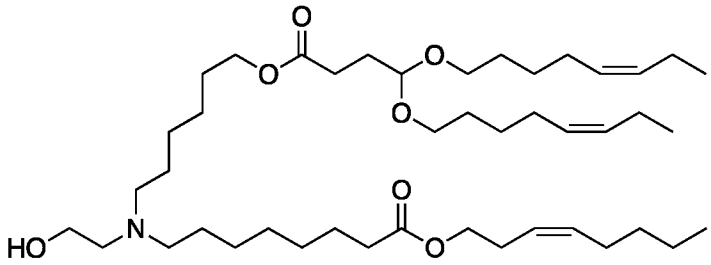
Example 7-138: (*Z*)-hept-3-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0861] Prepared according to General Procedure F, substituting (*Z*)-hept-3-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 22%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 722.6, found 722.9.



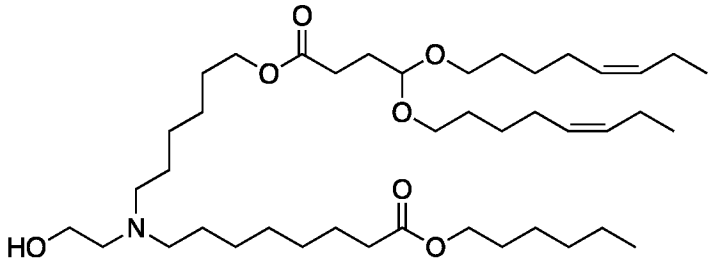
Example 7-139: (*Z*)-hex-3-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0862] Prepared according to General Procedure F, substituting (*Z*)-hex-3-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 14%. UPLC-MS (Method C): Rt 5.02 min, m/z calculated [M+H]: 708.6, found 708.8.



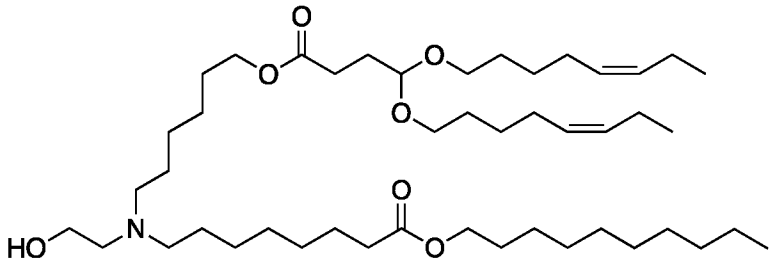
Example 7-140: (*Z*)-oct-3-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0863] Prepared according to General Procedure F, substituting (*Z*)-oct-3-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 72 mg, 44%. UPLC-MS (Method B): Rt 1.97 min, m/z calculated [M+H]: 736.6, found 736.9.



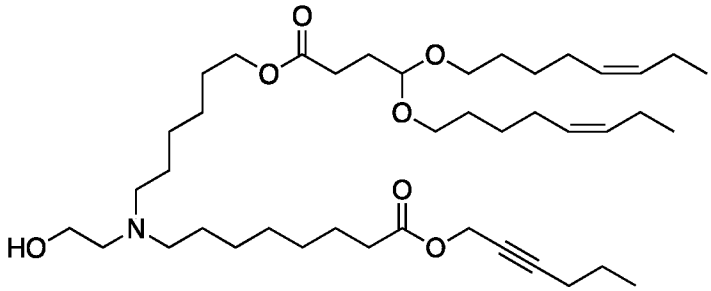
Example 7-141: hexyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0864] Prepared according to General Procedure F, substituting hexyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 51 mg, 37%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86 – 0.90 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.22 – 1.46 (m, 21H), 1.50 – 1.69 (m, 12H), 1.77 – 1.88 (m, 2H), 1.88 – 1.95 (m, 2H), 1.97 – 2.08 (m, 8H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.99 – 3.20 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.96 – 4.09 (m, 6H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 1.93 min, m/z calculated [M+H]: 710.6, found 711.0.



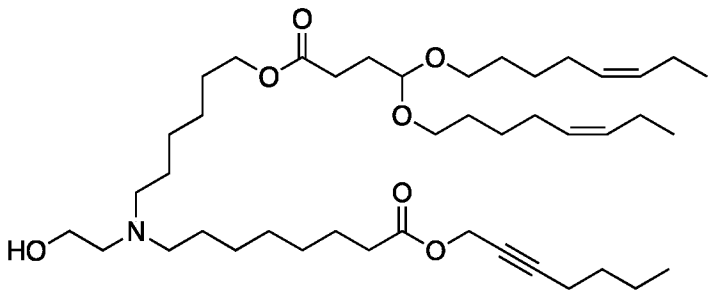
Example 7-142: decyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0865] Prepared according to General Procedure F, substituting decyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 37%. UPLC-MS (Method C): Rt 5.30 min, m/z calculated [M+H]: 766.7, found 767.0.



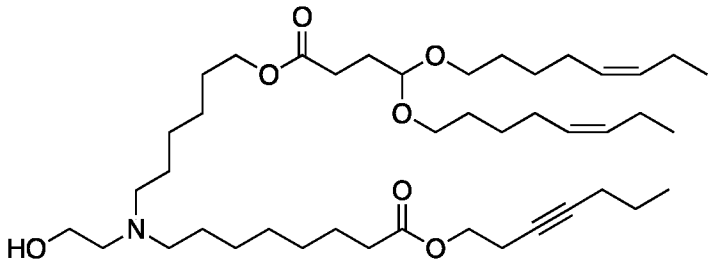
Example 7-143: hex-2-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0866] Prepared according to General Procedure F, substituting hex-2-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 22 mg, 47%. UPLC-MS (Method B): Rt 1.85 min, m/z calculated [M+H]: 706.6, found 706.9.



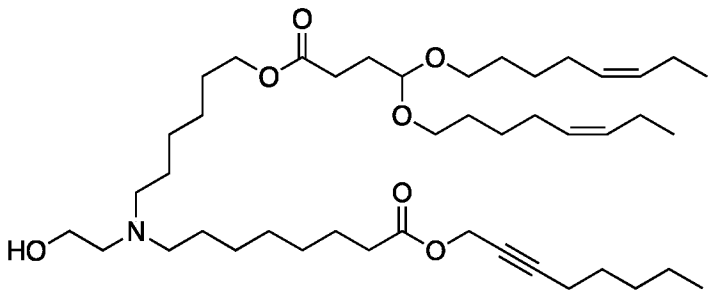
Example 7-144: hept-2-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0867] Prepared according to General Procedure F, substituting hept-2-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 16 mg, 27%. UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 720.6, found 720.9.



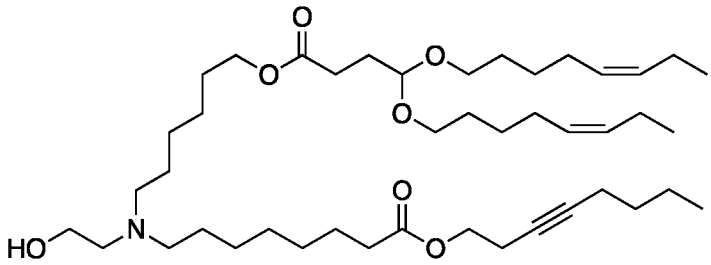
Example 7-145: hept-3-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0868] Prepared according to General Procedure F, substituting hept-3-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 19 mg, 18%. UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 720.6, found 720.9.



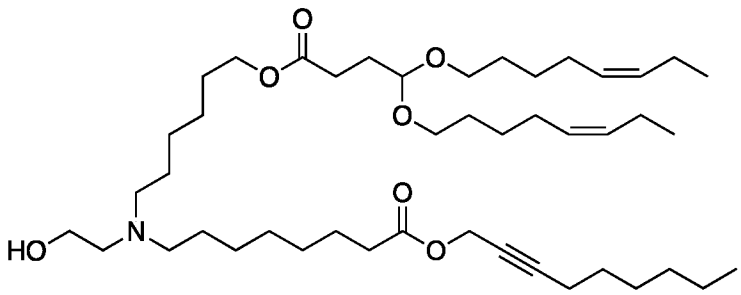
Example 7-146: oct-2-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0869] Prepared according to General Procedure F, substituting oct-2-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 39%. UPLC-MS (Method B): Rt 1.93 min, m/z calculated [M+H]: 734.6, found 735.0.



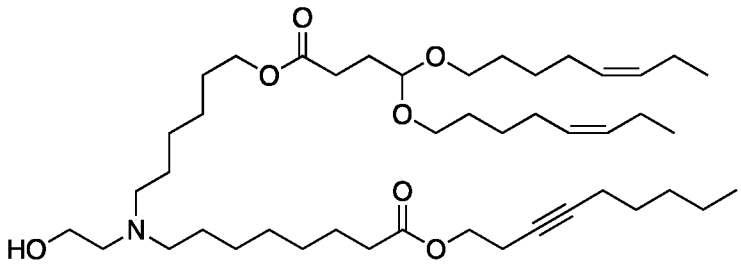
Example 7-147: oct-3-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0870] Prepared according to General Procedure F, substituting oct-3-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 40 mg, 37%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.29 – 1.51 (m, 21H), 1.51 – 1.73 (m, 12H), 1.88 – 1.95 (m, 2H), 1.97 – 2.09 (m, 8H), 2.09 – 2.18 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.42 – 2.52 (m, 2H), 2.98 – 3.22 (m, 6H), 3.35 – 3.46 (m, 2H), 3.51 – 3.62 (m, 2H), 3.97 – 4.16 (m, 6H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 1.93 min, m/z calculated [M+H]: 734.6, found 734.8.



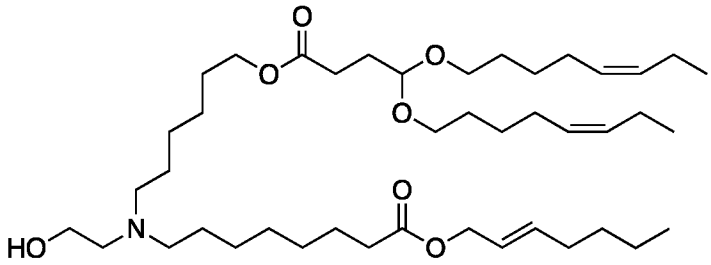
Example 7-148: non-2-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0871] Prepared according to General Procedure F, substituting non-2-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 28 mg, 31%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.46 (m, 16H), 1.45 – 1.71 (m, 14H), 1.77 – 1.96 (m, 6H), 1.96 – 2.09 (m, 8H), 2.15 – 2.25 (m, 2H), 2.29 – 2.41 (m, 5H), 3.00 – 3.21 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.98-4.09 (m, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 4.65 (t, *J* = 2.2 Hz, 2H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 1.98 min, m/z calculated [M+H]: 748.6, found 748.9.



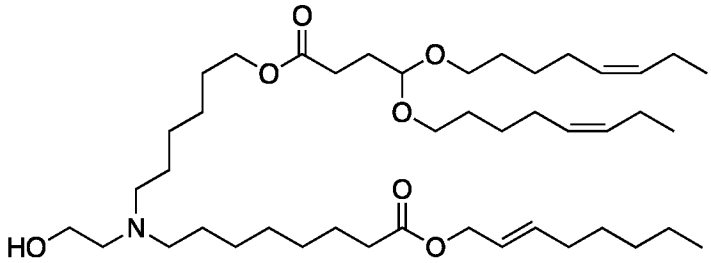
Example 7-149: non-3-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0872] Prepared according to General Procedure F, substituting non-3-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 20%. UPLC-MS (Method B): Rt 2.00 min, m/z calculated [M+H]: 748.6, found 748.9.



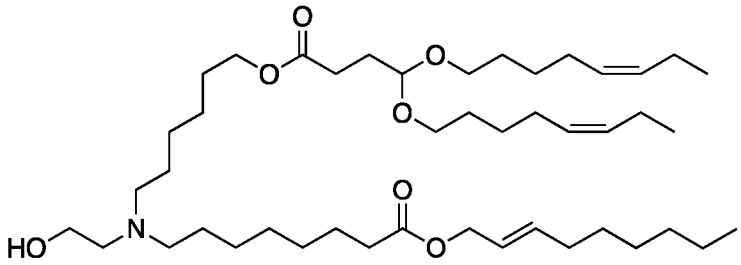
Example 7-150: (*E*)-hept-2-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0873] Prepared according to General Procedure F, substituting (*E*)-hept-2-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 16 mg, 19%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 722.6, found 722.9.



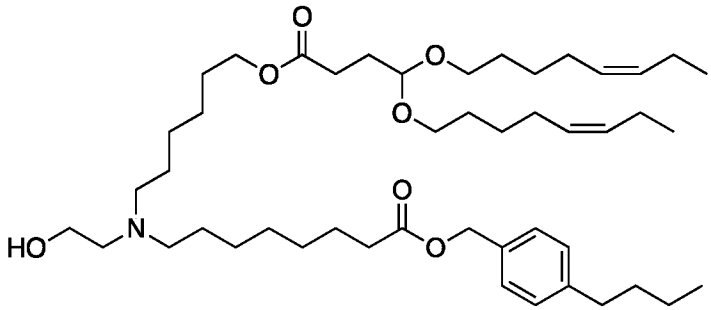
Example 7-151: (*E*)-oct-2-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0874] Prepared according to General Procedure F, substituting (*E*)-oct-2-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 37 mg, 52%. UPLC-MS (Method B): Rt 2.01 min, m/z calculated [M+H]: 736.6, found 736.9.



Example 7-152: (*E*)-non-2-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

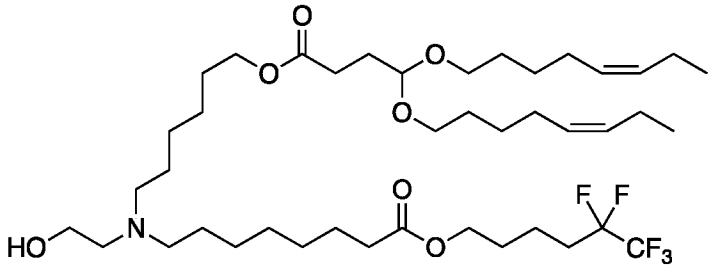
[0875] Prepared according to General Procedure F, substituting (*E*)-non-2-en-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 45 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.22 – 1.45 (m, 19H), 1.50 – 1.67 (m, 16H), 1.86 – 1.97 (m, 2H), 1.96 – 2.09 (m, 10H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.64 – 3.00 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.78 (s, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 4.44 – 4.53 (m, 3H), 5.24 – 5.42 (m, 4H), 5.46 – 5.62 (m, 1H), 5.68 – 5.88 (m, 1H). UPLC-MS (Method C): Rt 5.19 min, m/z calculated [M+H]: 750.6, found 751.0.



Example 7-153: 4-butylbenzyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

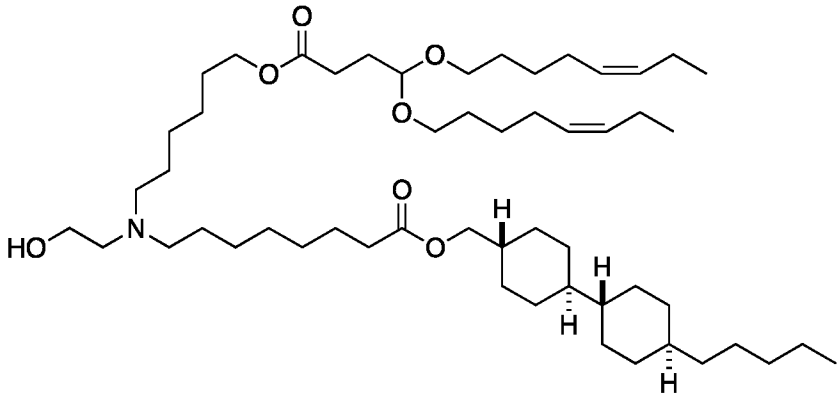
[0876] Prepared according to General Procedure F, substituting 4-butylbenzyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.84 – 0.99 (m, 9H), 1.27 – 1.46 (m, 14H), 1.49 – 1.70 (m, 11H), 1.77 – 1.96 (m, 6H), 1.98 – 2.08 (m, 8H), 2.29 – 2.41 (m, 4H), 2.55 – 2.64 (m, 2H), 3.02 – 3.22 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 4.05 (t, *J* = 6.5 Hz, 4H),

4.48 (t, *J* = 5.6 Hz, 1H), 5.06 (s, 2H), 5.24 – 5.42 (m, 4H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 5.6 Hz, 4H). UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 772.6, found 773.0.



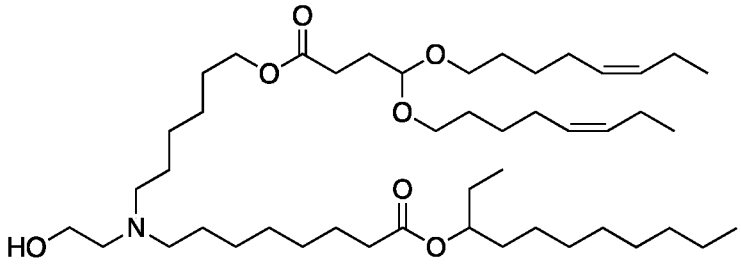
Example 7-154: 5,5,6,6,6-pentafluorohexyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0877] Prepared according to General Procedure F, substituting 5,5,6,6,6-pentafluorohexyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 47 mg, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.27 – 1.45 (m, 18H), 1.51 – 1.79 (m, 15H), 1.87 – 1.95 (m, 2H), 1.96 – 2.14 (m, 8H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.80 – 3.04 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.86 (s, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 1.90 min, m/z calculated [M+H]: 800.5, found 800.9.



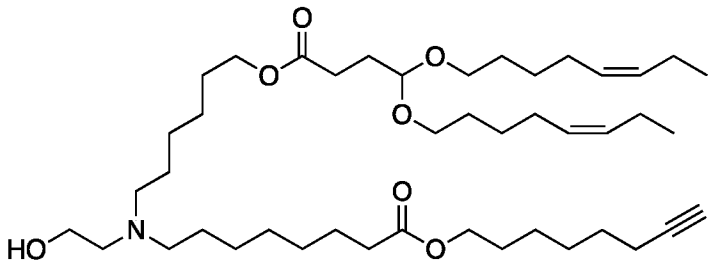
Example 7-155: ((1*r*,1'*s*,4*R*,4'*R*)-4'-pentyl-[1,1'-bi(cyclohexan)]-4-yl)methyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0878] Prepared according to General Procedure F, substituting ((1*r*,1'*s*,4*R*,4'*R*)-4'-pentyl-[1,1'-bi(cyclohexan)]-4-yl)methyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 45 mg, 46%. UPLC-MS (Method B): Rt 2.40 min, m/z calculated [M+H]: 874.7, found 875.1.



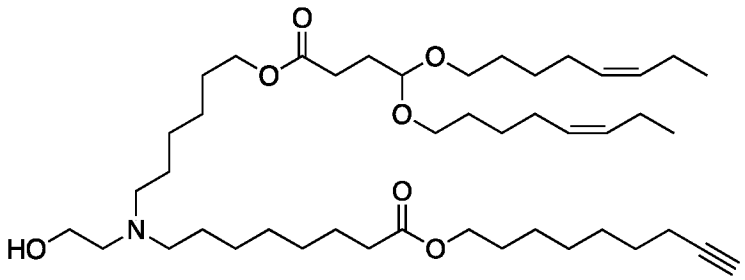
Example 7-156: undecan-3-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0879] Prepared according to General Procedure F, substituting undecan-3-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 26 mg, 25%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 780.7, found 781.0.



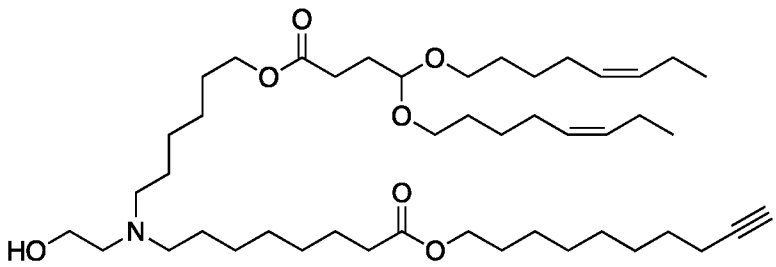
Example 7-157: oct-7-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0880] Prepared according to General Procedure F, substituting oct-7-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 68 mg, 57%. UPLC-MS (Method B): Rt 1.85 min, m/z calculated [M+H]: 734.6, found 734.8.



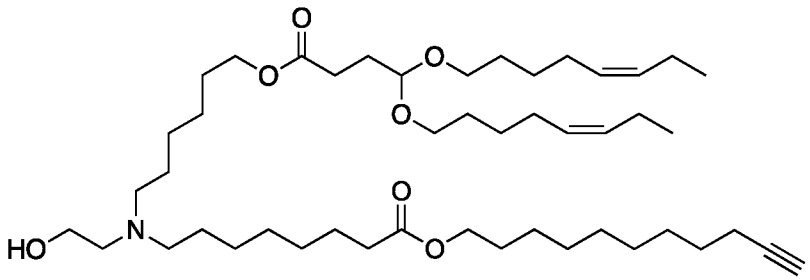
Example 7-158: non-8-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0881] Prepared according to General Procedure F, substituting non-8-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 26%. UPLC-MS (Method C): Rt 5.04 min, m/z calculated [M+H]: 748.6, found 748.9.



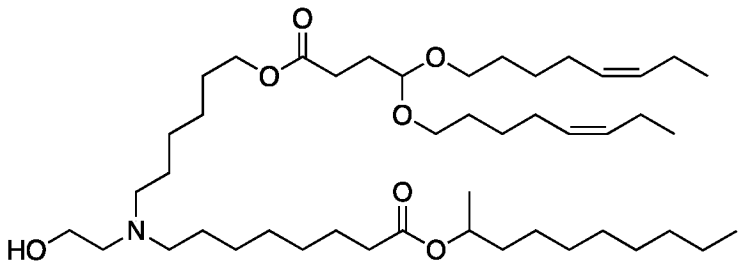
Example 7-159: dec-9-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0882] Prepared according to General Procedure F, substituting dec-9-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 28 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.25 – 1.46 (m, 20H), 1.45 – 1.70 (m, 17H), 1.79 – 1.95 (m, 6H), 1.97 – 2.08 (m, 8H), 2.14 – 2.21 (m, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.05 – 3.21 (m, 6H), 3.32 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.99 – 4.09 (m, 6H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method C): Rt 5.13 min, m/z calculated [M+H]: 762.6, found 763.0.



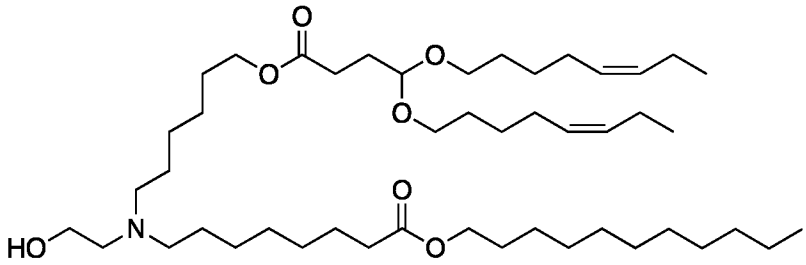
Example 7-160: undec-10-yn-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0883] Prepared according to General Procedure F, substituting undec-10-yn-1-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 35%. UPLC-MS (Method B): Rt 2.03 min, m/z calculated [M+H]: 776.6, found 777.0.



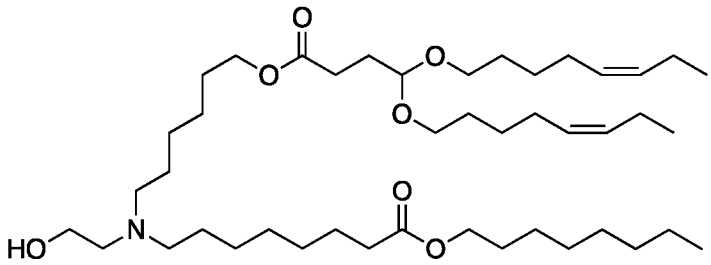
Example 7-161: decan-2-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0884] Prepared according to General Procedure F, substituting decan-2-yl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 25%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.15 – 1.50 (m, 29H), 1.50 – 1.73 (m, 15H), 1.88 – 1.94 (m, 2H), 1.97 – 2.08 (m, 8H), 2.25 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.64 – 2.98 (m, 6H), 3.35 – 3.45 (m, 2H), 3.49 – 3.62 (m, 2H), 3.76 (s, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 4.81 – 4.94 (m, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 2.10 min, m/z calculated [M+H]: 766.7, found 767.0.



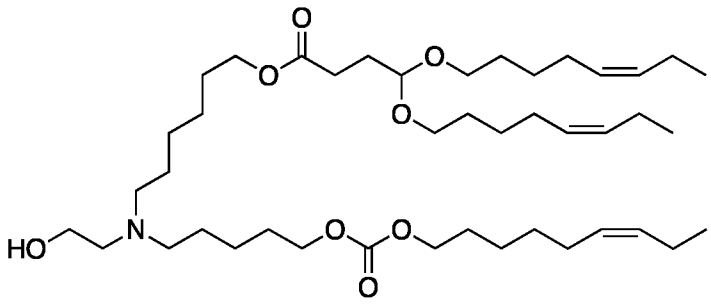
Example 7-162: undecyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0885] Prepared according to General Procedure F, substituting undecyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.20 – 1.45 (m, 22H), 1.50 – 1.70 (m, 18H), 1.79 – 1.96 (m, 6H), 1.98 – 2.08 (m, 9H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.06 – 3.25 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 4.00 – 4.09 (m, 6H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). Isolated 47 mg, 48%. UPLC-MS (Method B): Rt 2.16 min, m/z calculated [M+H]: 780.7, found 781.0.



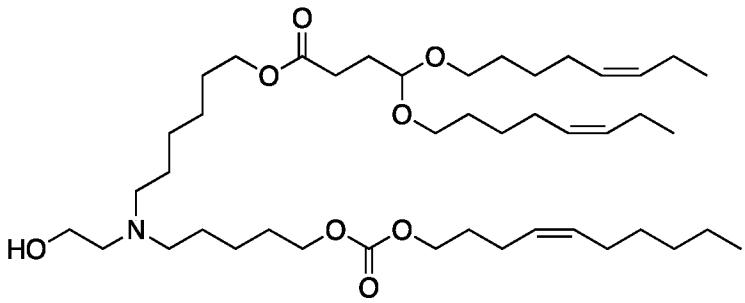
Example 7-163: octyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0886] Prepared according to General Procedure F, substituting octyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 63 mg, 55%. UPLC-MS (Method C): Rt 5.18 min, m/z calculated [M+H]: 738.6, found 738.9.



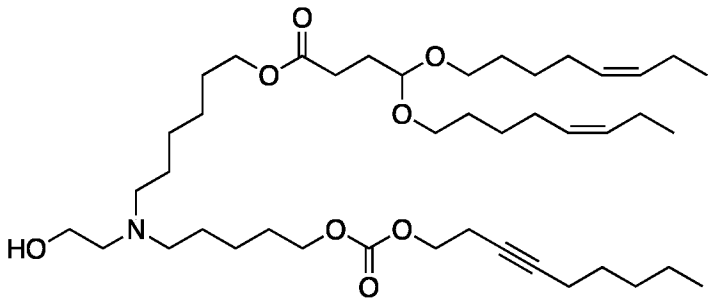
Example 7-164: 6-((2-hydroxyethyl)(5-(((((*Z*)-non-6-en-1-yl)oxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0887] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl non-6-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 52%. UPLC-MS (Method B): Rt 1.94 min, m/z calculated [M+H]: 738.6, found 738.9.



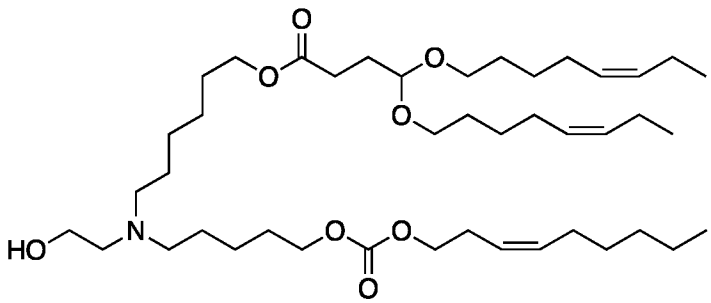
Example 7-165: 6-((5-(((((*Z*)-dec-4-en-1-yl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0888] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl dec-4-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 43%. UPLC-MS (Method C): Rt 5.13 min, m/z calculated [M+H]: 752.6, found 752.7.



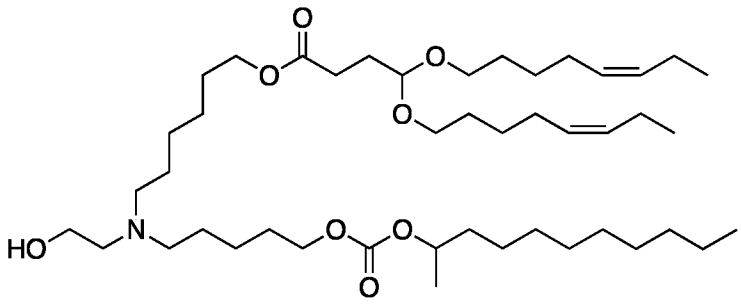
Example 7-166: 6-((2-hydroxyethyl)(5-(((non-3-yn-1-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0889] Prepared according to General Procedure F, substituting 5-bromopentyl non-3-yn-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 15 mg, 42%. UPLC-MS (Method B): Rt 1.88 min, m/z calculated [M+H]: 736.6, found 736.8.



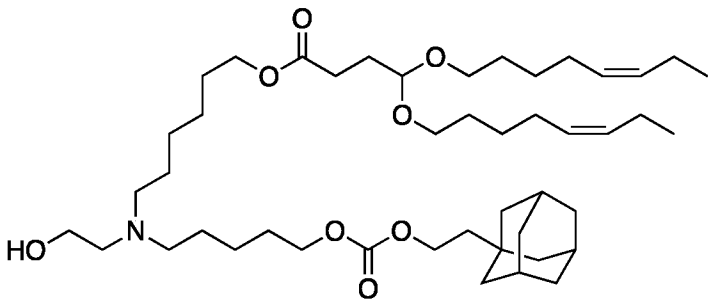
Example 7-167: 6-((2-hydroxyethyl)(5-(((((*Z*)-non-3-en-1-yl)oxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0890] Prepared according to General Procedure F, substituting (*Z*)-5-bromopentyl non-3-en-1-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 51%. UPLC-MS (Method B): Rt 1.95 min, m/z calculated [M+H]: 738.6, found 738.7.



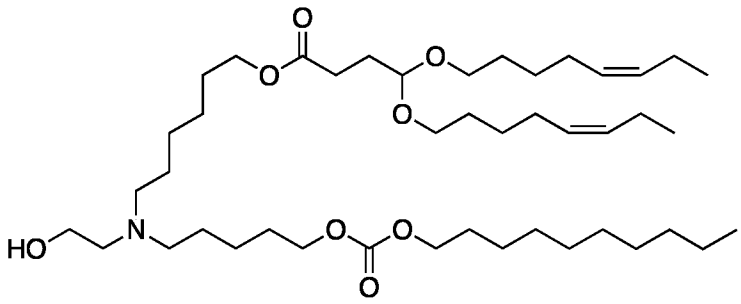
Example 7-168: 6-((2-hydroxyethyl)(5-(((undecan-2-yloxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0891] Prepared according to General Procedure F, substituting 5-bromopentyl undecan-2-yl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 44%. UPLC-MS (Method C): Rt 5.20 min, m/z calculated [M+H]: 768.6, found 768.8.



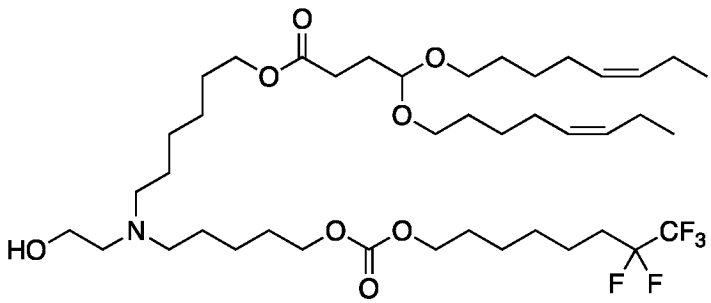
Example 7-169: 6-((5-(((2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethoxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0892] Prepared according to General Procedure F, substituting 2-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethyl (5-bromopentyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 16%. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 776.6, found 776.6.



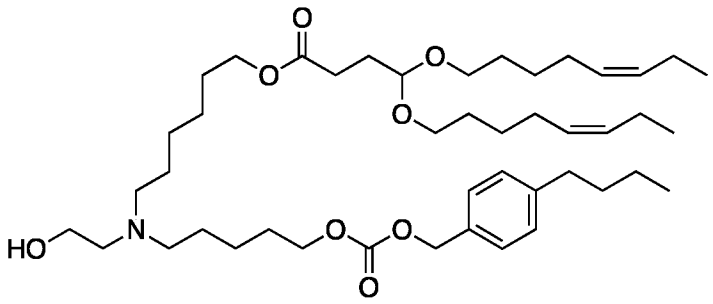
Example 7-170: 6-((5-(((decyloxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0893] Prepared according to General Procedure F, substituting 5-bromopentyl decyl carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 51%. UPLC-MS (Method C): Rt 5.13 min, m/z calculated [M+H]: 754.6, found 754.8.



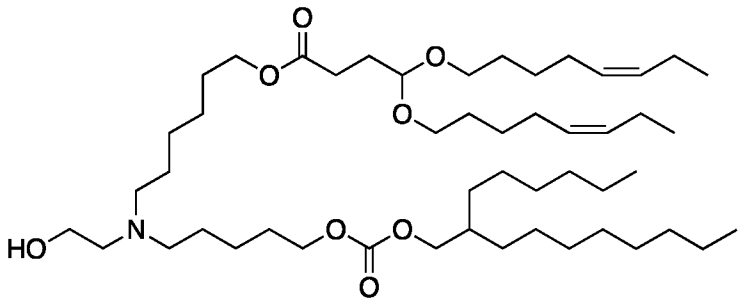
Example 7-171: 6-((2-hydroxyethyl)(5-((((7,7,8,8,8-pentafluorooctyl)oxy)carbonyl)oxy)pentyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0894] Prepared according to General Procedure F, substituting 5-bromopentyl (7,7,8,8,8-pentafluorooctyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 32 mg, 61%. UPLC-MS (Method B): Rt 1.92 min, m/z calculated [M+H]: 816.5, found 816.7.



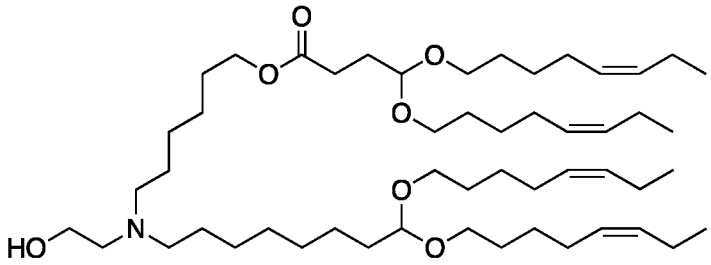
Example 7-172: 6-((5-((((4-butylbenzyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0895] Prepared according to General Procedure F, substituting 5-bromopentyl (4-butylbenzyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 53%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.86-0.95 (m, 10H), 1.10 – 1.34 (m, 16H), 1.39 – 1.45 (m, 14H),1.56 – 1.93 (m, 9H), 2.00 – 2.04 (m, 10H), 2.28 – 2.38 (m, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.99 – 3.12 (m, 6H), 3.37-3.40 (m, 4H), 3.70-4.16 (m, 5H), 4.46-4.47 (m, 1H), 5.11 (s, 2H), 5.29-5.34 (m, 2H), 7.16-7.17 (m, 2H), 7.24-7.28 (m, 2H). UPLC-MS (Method C): Rt 5.01 min, m/z calculated [M+H]: 760.6, found 760.7.

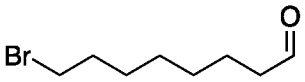


Example 7-173: 6-((5-((((2-hexyldecyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[0896] Prepared according to General Procedure F, substituting 5-bromopentyl (2-hexyldecyl) carbonate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 39%. UPLC-MS (Method B): Rt 2.30 min, m/z calculated [M+H]: 838.7, found 838.6.

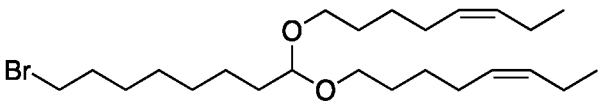


Example 7-174: 6-((5-((((2-hexyldecyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate



Step 1: 8-bromooctanal

[0897] To a stirred solution of 8-bromooctan-1-ol (1 g, 4.80 mmol) in DCM (5 mL) was added pyridinium chlorochromate (2.07 g, 9.61 mmol). The mixture was stirred at 15 °C for 2 h. Upon completion the reaction, reaction mixture was filtered through celite bed and washed by DCM (50 mL). Then filtrate was concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography eluted with 10% EtOAc/hexane to afford 8-bromooctanal (600 mg, 60%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 5H), 1.43 (m, 2H), 1.60-1.64 (m, 2H), 1.80-1.87 (m, 2H), 2.42 (t, J = 7.2 Hz, 2H), 3.39 (t J=8.0Hz, 2H), 9.75 (s, 1H)



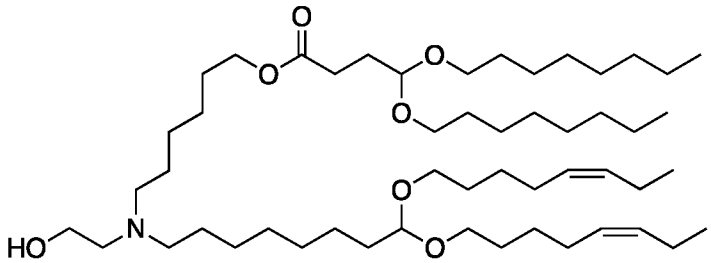
Step 2: (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene

[0898] To a stirred solution of compound 8-bromooctanal (1.0 eqv) in DCM were added (*Z*)-oct-5-en-1-ol (2.5 eqv), followed by Na_2SO_4 (2.7 eqv) and PTSA (0.2 eqv) under inert atmosphere and the reaction mixture was stirred at 15 °C for 2 h. Upon completion the reaction mixture was concentrated in vacuum, dissolved in DCM, and washed with water. Then organic part was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography eluted with 1-2% ethyl acetate-hexane to afford (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene (26 mg, 41%) as colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.21 – 1.29 (m, 2H), 1.28 – 1.35 (m, 6H), 1.35 – 1.48 (m, 6H), 1.54 – 1.65 (m, 5H), 1.84 (t, *J* = 7.2 Hz, 2H), 1.97

– 2.11 (m, 6H), 3.35 – 3.45 (m, 4H), 3.50 – 3.59 (m, 2H), 4.06 – 4.17 (m, 1H), 4.45 (d, *J* = 5.9 Hz, 1H), 5.22 – 5.48 (m, 4H).

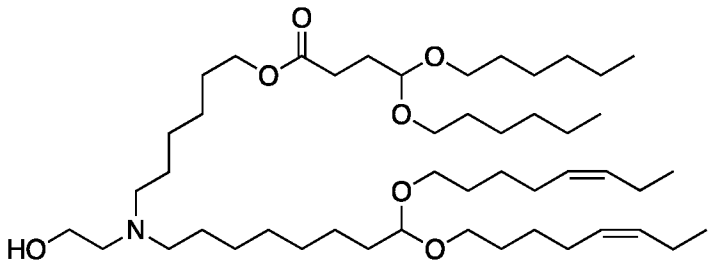
Step 3: 6-((5-((((2-hexyldecyl)oxy)carbonyl)oxy)pentyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (Example 7-174)

[0899] Prepared according to General Procedure F, substituting (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 34%. UPLC-MS (Method B): Rt 2.26 min, m/z calculated [M+H]: 848.7, found 848.5.



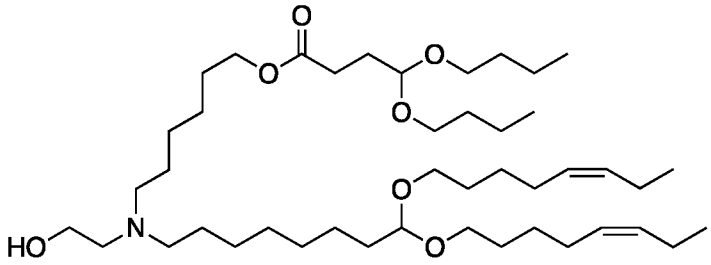
Example 7-175: 6-((8,8-bis(((*Z*)-oct-5-en-1-yl)oxy)octyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate

[0900] Prepared according to General Procedure F, substituting (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(octyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 31%. UPLC-MS (Method B): Rt 2.34 min, m/z calculated [M+H]: 852.8, found 852.6.



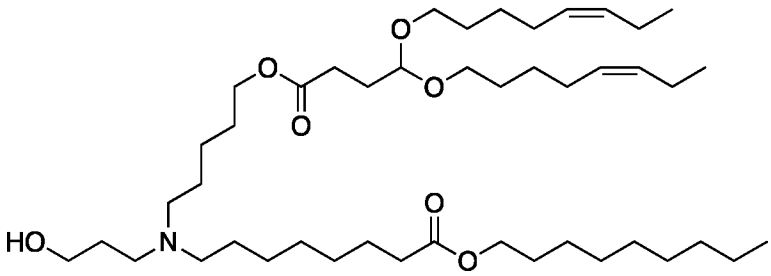
Example 7-176: 6-((8,8-bis(((*Z*)-oct-5-en-1-yl)oxy)octyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(hexyloxy)butanoate

[0901] Prepared according to General Procedure F, substituting (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(hexyloxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 31 mg, 43%. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 796.7, found 796.6.

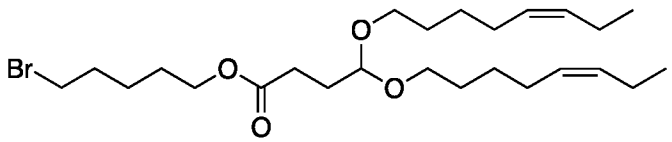


Example 7-177: 6-((8,8-bis(((*Z*)-oct-5-en-1-yl)oxy)octyl)(2-hydroxyethyl)amino)hexyl 4,4-dibutoxybutanoate

[0902] Prepared according to General Procedure F, substituting (Z)-8-((8-bromo-1-(((Z)-oct-5-en-1-yl)oxy)octyl)oxy)oct-3-ene for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-dibutoxybutanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 38 mg, 46%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 740.6, found 740.5.



Example 7-178: nonyl 8-((5-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)pentyl)(3-hydroxypropyl)amino)octanoate

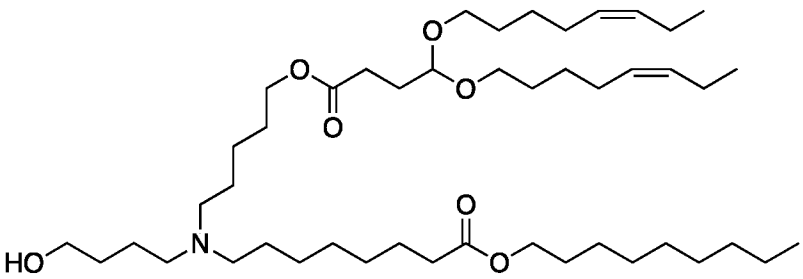


Step 1: 5-bromopentyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0903] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol. Isolated 300 mg, 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.35 – 1.46 (m, 4H), 1.45 – 1.54 (m, 2H), 1.57 – 1.61 (m, 4H), 1.65 (t, *J* = 7.3 Hz, 2H), 1.75 – 1.97 (m, 4H), 1.97 – 2.10 (m, 8H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.36 – 3.46 (m, 4H), 3.50 – 3.61 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.27 – 5.39 (m, 4H).

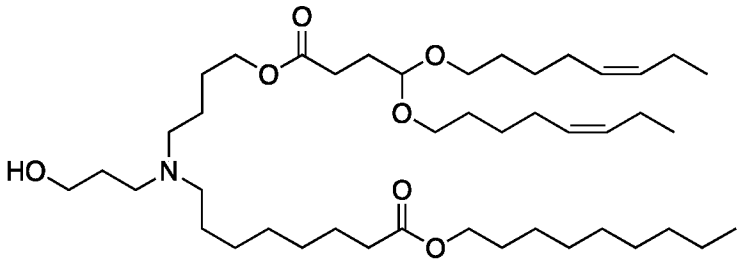
Step 2: nonyl 8-((5-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)pentyl)(3-hydroxypropyl)amino)octanoate (Example 7-178)

[0904] Prepared according to General Procedure F, substituting 5-bromopentyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 27 mg, 27%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 4H), 0.94 (t, *J* = 7.5 Hz, 5H), 1.17 – 1.46 (m, 26H), 1.47 – 1.74 (m, 24H), 1.91 (q, *J* = 7.3 Hz, 2H), 1.96 – 2.09 (m, 7H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.35 – 3.45 (m, 2H), 3.48 – 3.70 (m, 4H), 4.05 (q, *J* = 6.5 Hz, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 752.6, found 753.0.

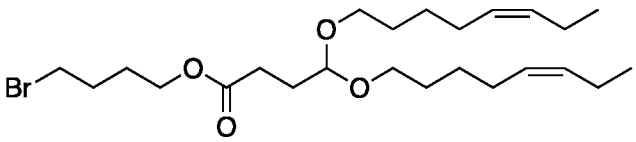


Example 7-179: nonyl 8-((5-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)pentyl)(4-hydroxybutyl)amino)octanoate

[0905] Prepared according to General Procedure F, substituting 5-bromopentyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((4-hydroxybutyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 41 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.7 Hz, 4H), 0.94 (t, *J* = 7.5 Hz, 5H), 1.17 – 1.46 (m, 26H), 1.47 – 1.74 (m, 24H), 1.91 (q, *J* = 7.3 Hz, 2H), 1.96 – 2.09 (m, 7H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.35 – 3.45 (m, 2H), 3.48 – 3.70 (m, 4H), 4.05 (q, *J* = 6.5 Hz, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 766.6, found 767.1.



Example 7-180: nonyl 8-((4-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)butyl)(3-hydroxypropyl)amino)octanoate

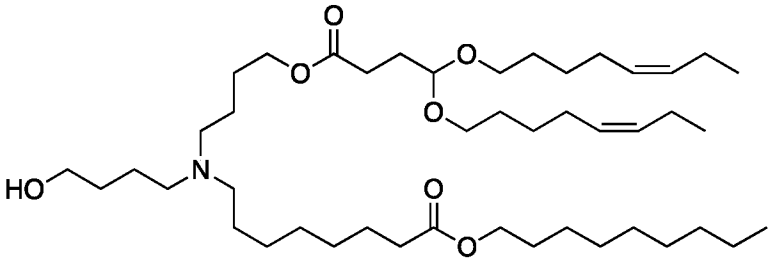


Step 1: 4-bromobutyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0906] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol. Isolated 400 mg, 58%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.33 – 1.46 (m, 4H), 1.48 – 1.64 (m, 4H), 1.72 – 1.84 (m, 2H), 1.87 – 1.97 (m, 4H), 1.96 – 2.12 (m, 8H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.51 – 3.62 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).

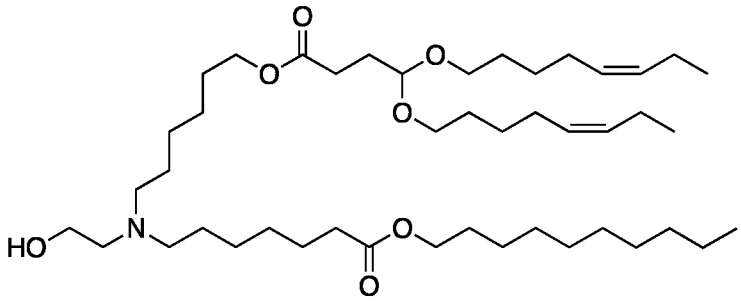
Step 2: nonyl 8-((4-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)butyl)(3-hydroxypropyl)amino)octanoate (Example 7-180)

[0907] Prepared according to General Procedure F, substituting 4-bromobutyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 32 mg, 30%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 4H), 1.15 – 1.35 (m, 39H), 1.33 – 1.46 (m, 5H), 1.60 – 1.73 (m, 3H), 1.70 – 1.84 (m, 2H), 1.92 (q, *J* = 7.1 Hz, 2H), 1.96 – 2.09 (m, 6H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.44 – 2.90 (m, 3H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.79 (t, *J* = 5.3 Hz, 2H), 4.00 – 4.12 (m, 3H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 3H). UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 738.6, found 739.0.



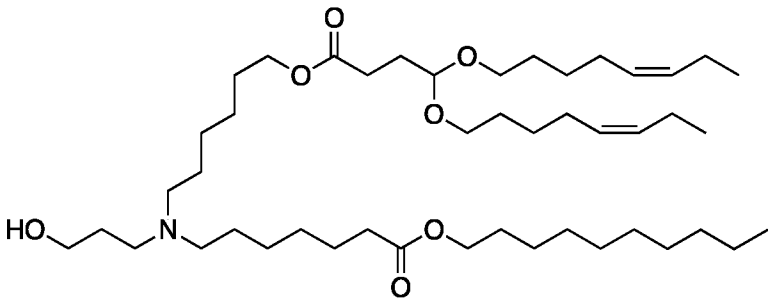
Example 7-181: nonyl 8-((4-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)butyl)(4-hydroxybutyl)amino)octanoate

[0908] Prepared according to General Procedure F, substituting 4-bromobutyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((4-hydroxybutyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 39 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 (t, *J* = 6.6 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 4H), 1.24 – 1.37 (m, 36H), 1.43 (q, *J* = 7.8 Hz, 4H), 1.58 – 1.87 (m, 12H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.99 – 2.11 (m, 5H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.40 (t, *J* = 7.6 Hz, 2H), 2.57 – 2.93 (m, 4H), 3.37 – 3.48 (m, 2H), 3.54 – 3.68 (m, 3H), 4.03 – 4.15 (m, 3H), 4.51 (t, *J* = 5.6 Hz, 1H), 5.29 – 5.43 (m, 3H). UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 752.6, found 753.0.



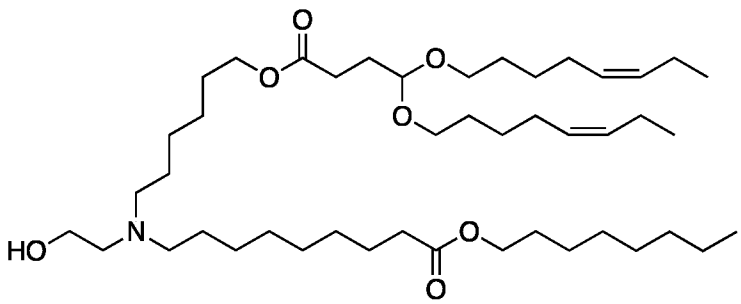
Example 7-182: decyl 7-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)heptanoate

[0909] Prepared according to General Procedure F, substituting decyl 7-((2-hydroxyethyl)amino)heptanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 30%. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 752.6, found 753.1.



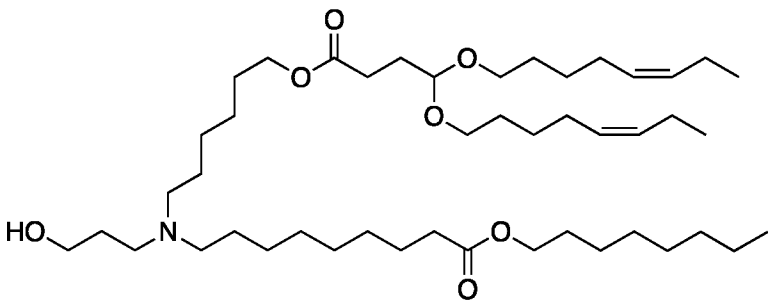
Example 7-183: decyl 7-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)heptanoate

[0910] Prepared according to General Procedure F, substituting decyl 7-((3-hydroxypropyl)amino)heptanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 35%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 766.6, found 767.0.



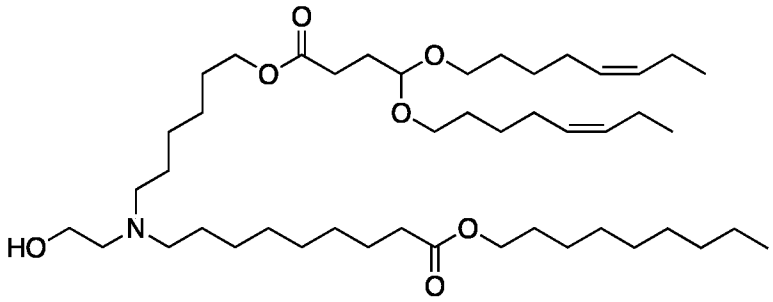
Example 7-184: octyl 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)nonanoate

[0911] Prepared according to General Procedure F, substituting octyl 9-((2-hydroxyethyl)amino)nonanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 34 mg, 32%. UPLC-MS (Method B): Rt 2.14 min, m/z calculated [M+H]: 752.6, found 753.1.



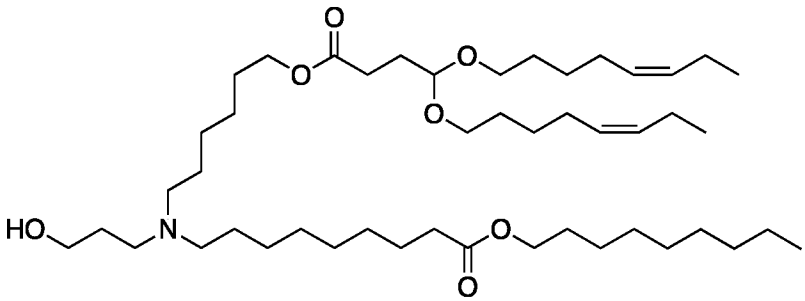
Example 7-185: octyl 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)nonanoate

[0912] Prepared according to General Procedure F, substituting octyl 9-((3-hydroxypropyl)amino)nonanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 26 mg, 30%. UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 766.7, found 767.1.



Example 7-186: nonyl 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)nonanoate

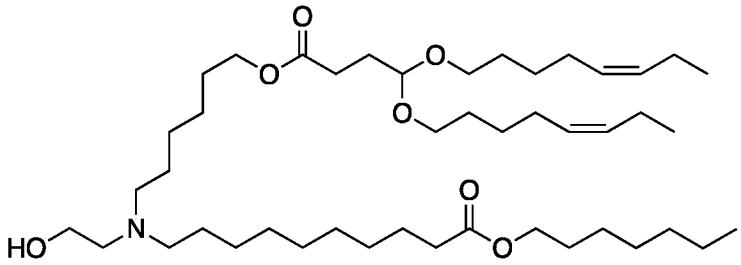
[0913] Prepared according to General Procedure F, substituting nonyl 9-((2-hydroxyethyl)amino)nonanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 39 mg, 34%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.28 (d, *J* = 17.0 Hz, 27H), 1.50 – 1.71 (m, 16H), 1.92 (q, *J* = 7.0 Hz, 2H), 1.96 – 2.08 (m, 8H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.76 (s, 4H), 2.87 (s, 2H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.77 (s, 2H), 4.05 (t, *J* = 6.7 Hz, 4H), 4.48 (t, *J* = 5.5 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 766.7, found 767.0.



Example 7-187: nonyl 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)nonanoate

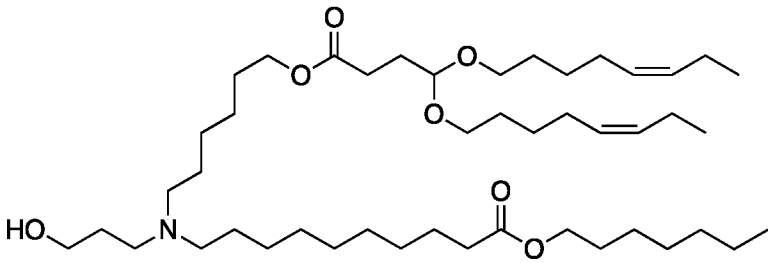
[0914] Prepared according to General Procedure F, substituting nonyl 9-((2-hydroxyethyl)amino)nonanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 49 mg, 45%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.18 – 1.48 (m, 23H), 1.50 – 1.66 (m, 16H), 1.66 – 1.84 (m, 4H), 1.86 – 1.99 (m, 2H), 1.96 – 2.09 (m,

10H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.97 (s, 4H), 3.14 (s, 2H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.83 (t, *J* = 5.4 Hz, 2H), 4.00 – 4.09 (m, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H). UPLC-MS (Method C): Rt 5.22 min, m/z calculated [M+H]: 780.7, found 781.0.



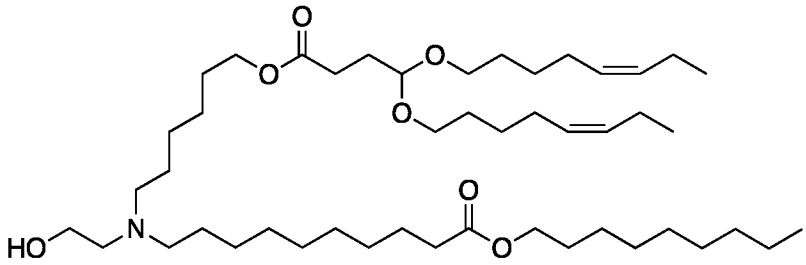
Example 7-188: heptyl 10-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)decanoate

[0915] Prepared according to General Procedure F, substituting heptyl 10-((2-hydroxyethyl)amino)decanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 17 mg, 19%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 752.6, found 753.0.



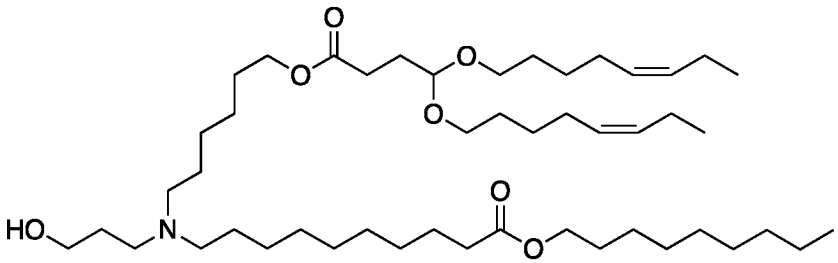
Example 7-189: heptyl 10-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)decanoate

[0916] Prepared according to General Procedure F, substituting heptyl 10-((3-hydroxypropyl)amino)decanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 50 mg, 39%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.20 – 1.46 (m, 27H), 1.50 – 1.65 (m, 14H), 1.91 (q, *J* = 6.9 Hz, 4H), 1.96 – 2.09 (m, 8H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.81 (s, 4H), 2.99 (s, 2H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.82 (t, *J* = 5.3 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 4H), 4.48 (t, *J* = 5.5 Hz, 1H), 5.24-5.42 (m, 4H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 766.7, found 767.1.



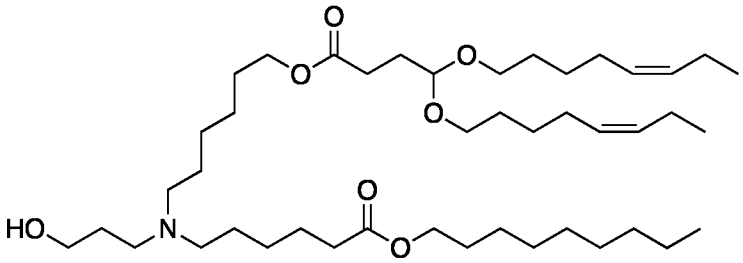
Example 7-190: nonyl 10-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)decanoate

[0917] Prepared according to General Procedure F, substituting nonyl 10-((2-hydroxyethyl)amino)decanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 28%. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 780.7, found 781.1.



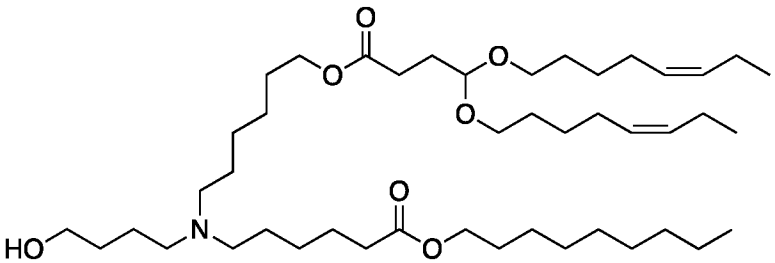
Example 7-191: nonyl 10-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)decanoate

[0918] Prepared according to General Procedure F, substituting nonyl 10-((3-hydroxypropyl)amino)decanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 30 mg, 28%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.20 – 1.48 (m, 26H), 1.50 – 1.68 (m, 16H), 1.71 – 1.84 (m, 4H), 1.92 (q, *J* = 7.1 Hz, 2H), 1.96 – 2.09 (m, 10H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.99 (s, 4H), 3.15 (s, 2H), 3.36 – 3.46 (m, 2H), 3.52 – 3.61 (m, 2H), 3.83 (t, *J* = 5.4 Hz, 2H), 4.04 (t, *J* = 6.4 Hz, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 3H). UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 794.7, found 795.1.



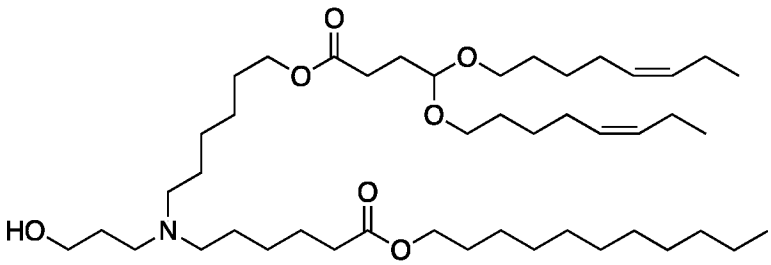
Example 7-192: nonyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)hexanoate

[0919] Prepared according to General Procedure F, substituting nonyl 6-((3-hydroxypropyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 20 mg, 22%. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 738.6, found 739.1.



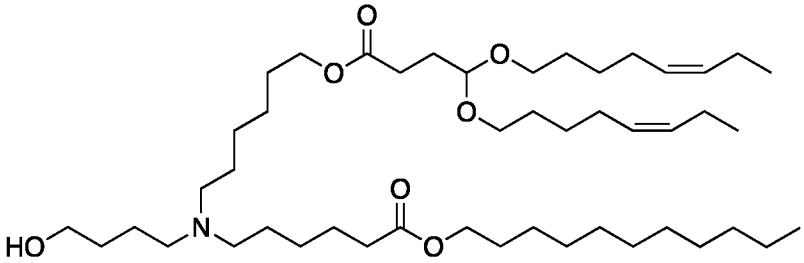
Example 7-193: nonyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)hexanoate

[0920] Prepared according to General Procedure F, substituting nonyl 6-((4-hydroxybutyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 65 mg, 48%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 752.6, found 753.0.



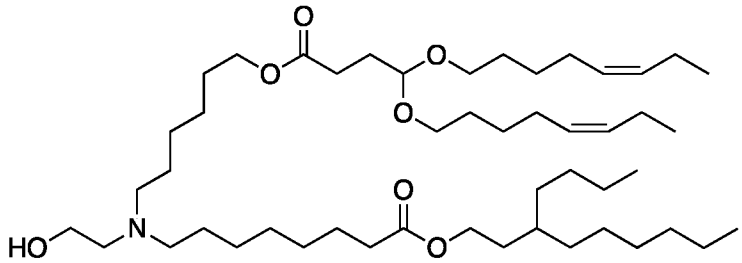
Example 7-194: undecyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)hexanoate

[0921] Prepared according to General Procedure F, substituting undecyl 6-((3-hydroxypropyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 21 mg, 26%. UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 766.7, found 767.1.

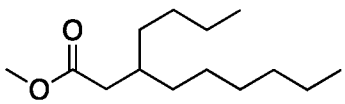


Example 7-195: undecyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)hexanoate

[0922] Prepared according to General Procedure F, substituting undecyl 6-((4-hydroxybutyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 39 mg, 36%. UPLC-MS (Method B): Rt 2.23 min, m/z calculated [M+H]: 780.7, found 781.1.



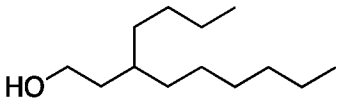
Example 7-196: 3-butylnonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: methyl 3-butylnonanoate

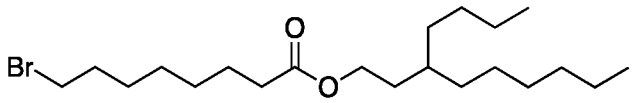
[0923] Copper (I) bromide (0.1 eqv) and lithium chloride (0.2 eqv) were added to a flame dried flask under argon atmosphere. Then was added dry THF (20 mL) and the mixture was stirred for 10 min during which time the solid dissolved. Reaction mixture was placed in an ice bath and stirred for 5 min. After that, were added methyl (*E*)-non-2-enoate (1.0 eqv) and chlorotrimethylsilane (1.1 eqv) and was stirred for 15 min. Then, was added butylmagnesium bromide (18% w/v in THF) (1.4 eqv) drop wise and the reaction was stirred at 0 °C for another 1

h. The solution was poured into saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 1-2% ethyl acetate-hexane to afford methyl 3-butylnonanoate (1.3 g, 69%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.73 – 1.01 (m, 9H), 1.08 – 1.43 (m, 13H), 1.81 – 1.86 (m, 1H), 2.22 (d, *J* = 6.9 Hz, 2H), 3.65 (s, 3H).



Step 2: 3-butylnonan-1-ol

[0924] To a stirred solution of methyl 3-butylnonanoate (1 eqv) in THF (10 mL) was added lithium aluminium hydride (2M in THF) (3.0 eqv) at 0 °C and stirred at 25 °C for 2 h. Then reaction mass was quenched with sodium sulfate decahydrate at 0 °C and filtered through celite. The filtrate was concentrated under reduced pressure, purified by combiflash column chromatography, eluted by 3-5% ethyl acetate-hexane to afford 3-butylnonan-1-ol (540 mg, 67%) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83-0.92 (m, 6H), 1.25 (s, 18H), 1.52 (q, *J* = 6.9 Hz, 2H), 3.66 (t, *J* = 6.9 Hz, 2H).



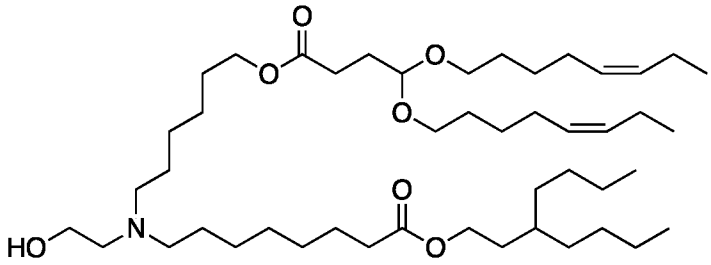
Step 3: 3-butylnonyl 8-bromooctanoate

[0925] Prepared according to General Procedure D, substituting 3-butylnonan-1-ol for nonan-1-ol. Isolated 550 mg, 60%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (td, *J* = 3.0, 6.6 Hz, 6H), 1.24 – 1.41 (m, 25H), 1.54 – 1.61 (m, 3H), 1.77 – 1.87 (m, 2H), 2.27 (t, *J* = 8 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.07 (t, *J* = 7.2 Hz, 2H).

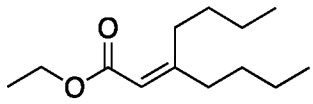
Step 4: 3-butylnonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-196)

[0926] Prepared according to General Procedure F, substituting 3-butylnonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 80 mg, 61%. UPLC-MS (Method B): Rt 2.33 min, m/z calculated [M+H]: 808.7, found 809.2. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.84 – 0.91 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.45 (m, 31H), 1.49 – 1.79 (m, 15H), 1.87 – 1.95 (m, 2H), 1.97 – 2.08 (m, 8H), 2.27 (t, *J* = 7.4 Hz, 2H),

2.37 (t, J = 7.6 Hz, 2H), 2.79 – 3.05 (m, 6H), 3.34 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.84 (s, 2H), 4.00 – 4.11 (m, 4H), 4.48 (t, J = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).

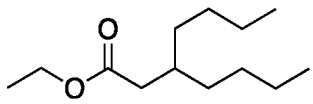


Example 7-197: 3-butylheptyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: ethyl 3-butylhept-2-enoate

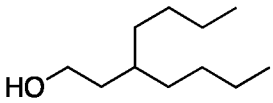
[0927] To a stirred solution of triethyl phosphonoacetate (1.83 g, 9.15 mmol) in dry THF (10 mL) was added NaH (336 mg, 9.15 mmol) portion wise for period of 20 min and stirred for 30 min at 25 °C. Reaction mixture was cooled to 0 °C and was added nonan-5-one (1 g, 7.04 mmol) in portion. The reaction mixture was gradually warmed to 25 °C and heated at 66 °C for 12 h. Upon completion, the reaction mixture was diluted with ethyl acetate (100 mL) and quenched with cold water. Then it was washed with water (2x15 mL) and brine (15 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford ethyl 3-butylhept-2-enoate (1.6 g, crude) as light yellow liquid which was used for next step without any purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.79 – 0.95 (m, 6H), 1.18 – 1.39 (m, 6H), 1.37 – 1.48 (m, 2H), 1.49 – 1.59 (m, 1H), 2.07 – 2.16 (m, 2H), 2.38 (t, J = 7.5 Hz, 2H), 2.53 – 2.62 (m, 2H), 3.98 – 4.35 (m, 2H), 5.60 (s, 1H).



Step 2: ethyl 3-butylheptanoate

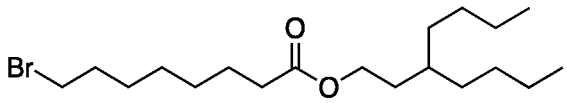
[0928] To a stirred solution of ethyl 3-butylhept-2-enoate (1 g, 4.7 mmol) in EtOH (10 mL), was added $Pd(OH)_2$ (20% w/w) (495 mg, 0.7 mmol). Reaction mixture was stirred at 25 °C for 2 h under H_2 atmosphere. After consumption of starting material, the reaction mixture was filtered through celite bed and concentrated under reduce pressure to afford ethyl 3-butylheptanoate (1.1

g, crude) as colorless liquid which was used directly for the next step. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (q, *J* = 7.1 Hz, 6H), 1.18 – 1.38 (m, 14H), 1.46 – 1.65 (m, 1H), 1.75 – 1.91 (m, 1H), 2.21 (d, *J* = 6.9 Hz, 1H), 2.38 (t, *J* = 7.5 Hz, 1H), 3.90 – 4.42 (m, 2H).



Step 3: 3-butylheptan-1-ol

[0929] To a stirred solution of ethyl 3-butylheptanoate (1.1 g, 5.14 mmol) in THF (10 mL) was added lithium aluminium hydride (2M in THF) (9.1 mL, 18.22 mmol) at 0 °C and stirred at 25 °C for 2 h. Then reaction mass was quenched with $Na_2SO_4.10H_2O$ at 0 °C, and filtered and concentrated under reduced pressure. Crude residue was then purified by combiflash column chromatography, eluted with 2-5% ethyl acetate-hexane to afford 3-butylheptan-1-ol (600 mg, 68%) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.15 (s, 1H), 1.20 – 1.33 (m, 12H), 1.36 – 1.46 (m, 1H), 1.52 (q, *J* = 6.8 Hz, 2H), 3.66 (t, *J* = 7.1 Hz, 2H).

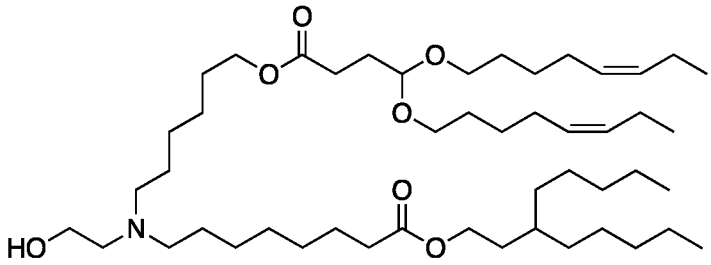


Step 4: 3-butylheptyl 8-bromooctanoate

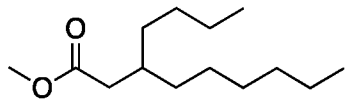
[0930] Prepared according to General Procedure D, substituting 3-butylnonan-1-ol for nonan-1-ol. Isolated 830 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (td, *J* = 3.0, 6.6 Hz, 6H), 1.16 – 1.47 (m, 20H), 1.56 – 1.70 (m, 3H), 1.78 – 1.90 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.07 (t, *J* = 7.0 Hz, 2H).

Step 5: 3-butylheptyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-197)

[0931] Prepared according to General Procedure F, substituting 3-butylheptyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 47 mg, 72%. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 780.7, found 781.1.

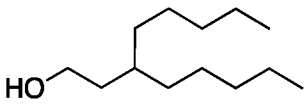


Example 7-198: 3-pentyloctyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



Step 1: methyl 3-pentyloctanoate

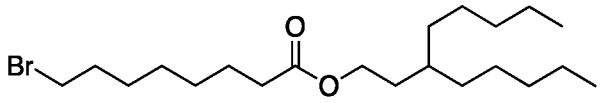
[0932] Copper (I) bromide (0.1 eqv) and lithium chloride (0.2 eqv) were added to a flame dried flask under argon atmosphere. Then was added dry THF (20 mL) and the mixture was stirred for 10 min during which time the solid dissolved. Reaction mixture was placed in an ice bath and stirred for 5 min. After that, were added methyl (*E*)-oct-2-enoate (1.0 eqv) and chlorotrimethylsilane (1.1 eqv) and was stirred for 15 min. Then, was added pentylmagnesium bromide (18% w/v in THF) (1.4 eqv) drop wise and the reaction was stirred at 0 °C for another 1 h. The solution was poured into saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 1-2% ethyl acetate-hexane to afford methyl 3-pentyloctanoate (1.0 g, 68%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.06 – 1.46 (m, 19H), 1.82 (s, 1H), 2.22 (d, *J* = 6.9 Hz, 2H), 3.64 (s, 2H).



Step 2: 3-pentyloctan-1-ol

[0933] To a stirred solution of methyl 3-pentyloctanoate (1 eqv) in THF (10 mL) was added lithium aluminium hydride (2M in THF) (3.0 eqv) at 0 °C and stirred at 25 °C for 2 h. Then reaction mass was quenched with sodium sulfate decahydrate at 0 °C and filtered through celite. The filtrate was concentrated under reduced pressure, purified by combiflash column chromatography, eluted by 3-5% ethyl acetate-hexane to afford 3-pentyloctan-1-ol (580 mg, 65%) as colorless oil. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.9 Hz, 6H), 1.13 (t, *J* = 5.4 Hz, 1H), 1.17 – 1.35 (m, 15H), 1.38 – 1.44 (m, 1H), 1.51 (t, *J* = 6.8 Hz, 2H), 3.65 (q, *J* = 6.5 Hz, 2H), 5.29 (s, 1H).

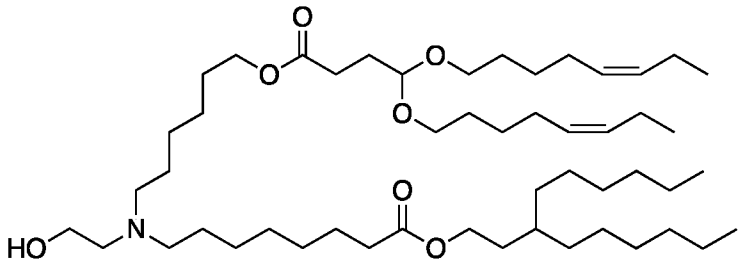


Step 3: 3-pentyloctyl 8-bromooctanoate

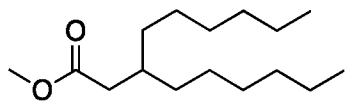
[0934] Prepared according to General Procedure D, substituting 3-pentyloctan-1-ol for nonan-1-ol. Isolated 900 mg, 72%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.14 – 1.49 (m, 19H), 1.49 – 1.68 (m, 8H), 1.78 – 1.90 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.07 (t, *J* = 7.1 Hz, 2H).

Step 4: 3-pentyloctyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-198)

[0935] Prepared according to General Procedure F, substituting 3-pentyloctyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 122 mg, 74%. UPLC-MS (Method B): Rt 2.21 min, m/z calculated [M+H]: 808.7, found 809.1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 7.0 Hz, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.16 – 1.46 (m, 30H), 1.48 – 1.74 (m, 16H), 1.86 – 1.97 (m, 2H), 1.97 – 2.11 (m, 8H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.56 – 2.90 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.70 (s, 2H), 4.00-4.11 (m, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).

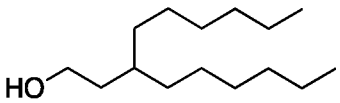


Example 7-199: 3-hexylnonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



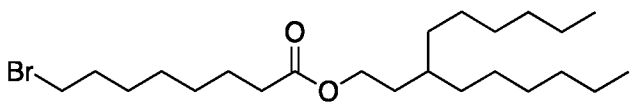
Step 1: methyl 3-hexylnonanoate

[0936] Copper (I) bromide (0.1 eqv) and lithium chloride (0.2 eqv) were added to a flame dried flask under argon atmosphere. Then was added dry THF (20 mL) and the mixture was stirred for 10 min during which time the solid dissolved. Reaction mixture was placed in an ice bath and stirred for 5 min. After that, were added methyl (*E*)-non-2-enoate (1.0 eqv) and chlorotrimethylsilane (1.1 eqv) and was stirred for 15 min. Then, was added pentylmagnesium bromide (18% w/v in THF) (1.4 eqv) drop wise and the reaction was stirred at 0 °C for another 1 h. The solution was poured into saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash column chromatography, eluted with 1-2% ethyl acetate-hexane to afford methyl 3-hexylnonanoate (1.1 g, 67%) as yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.81 – 0.91 (m, 6H), 1.13 – 1.37 (m, 20H), 1.82 (t, *J* = 6.9 Hz, 1H), 2.22 (d, *J* = 6.9 Hz, 2H), 3.65 (s, 3H).



Step 2: 3-hexylnonan-1-ol

[0937] To a stirred solution of methyl 3-hexylnonanoate (1 eqv) in THF (10 mL) was added lithium aluminium hydride (2M in THF) (3.0 eqv) at 0 °C and stirred at 25 °C for 2 h. Then reaction mass was quenched with sodium sulfate decahydrate at 0 °C and filtered through celite. The filtrate was concentrated under reduced pressure, purified by combiflash column chromatography, eluted by 3-5% ethyl acetate-hexane to afford 3-hexylnonan-1-ol (540 mg, 61%) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 6H), 1.12 (t, *J* = 5.2 Hz, 1H), 1.16 – 1.34 (m, 20H), 1.35 – 1.45 (m, 1H), 1.51 (t, *J* = 6.8 Hz, 2H), 3.65 (q, *J* = 6.4 Hz, 2H).

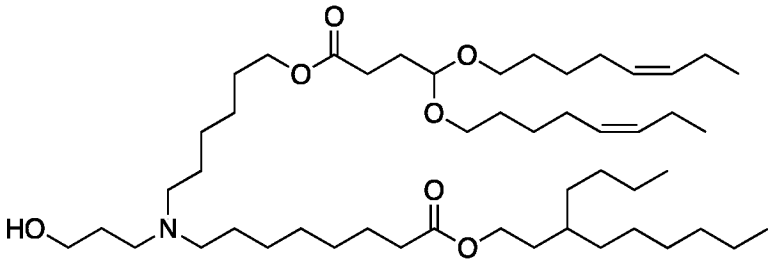


Step 3: 3-hexylnonyl 8-bromooctanoate

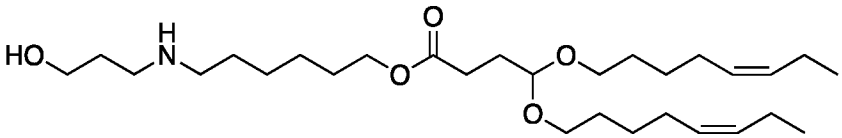
[0938] Prepared according to General Procedure D, substituting 3-hexylnonan-1-ol for nonan-1-ol. Isolated 875 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.2 Hz, 6H), 1.15 – 1.48 (m, 27H), 1.58 (ddd, *J* = 5.5, 10.3, 26.0 Hz, 4H), 1.84 (t, *J* = 7.3 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.07 (t, *J* = 6.9 Hz, 2H).

Step 4: 3-hexylnonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-199)

[0939] Prepared according to General Procedure F, substituting 3-hexylnonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 44 mg, 64%. UPLC-MS (Method B): Rt 2.34 min, m/z calculated [M+H]: 836.7, found 837.1.



Example 7-200: 3-butylnonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

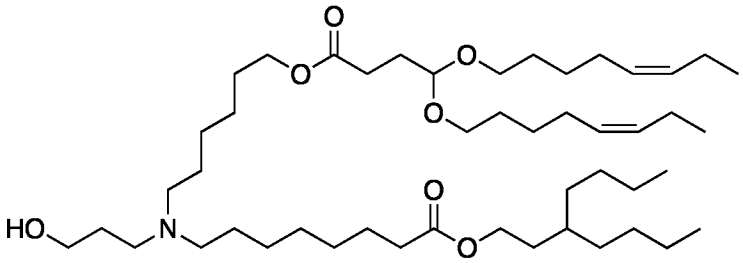


Step 1: 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0940] Prepared according to General Procedure E, substituting 3-aminopropan-1-ol for ethanolamine and 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 835 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.29 – 1.46 (m, 12H), 1.44 – 1.76 (m, 8H), 1.86 – 2.11 (m, 16H), 2.28 (t, *J* = 7.2 Hz, 1H), 2.36 (t, *J* = 7.6 Hz, 1H), 2.61 (t, *J* = 7.1 Hz, 1H), 2.88 (t, *J* = 5.6 Hz, 1H), 3.34 – 3.46 (m, 1H), 3.51 – 3.65 (m, 1H), 3.80 (t, *J* = 5.3 Hz, 1H), 4.04 (t, *J* = 6.8 Hz, 1H), 4.44 – 4.52 (m, 1H), 5.18 – 5.51 (m, 4H).

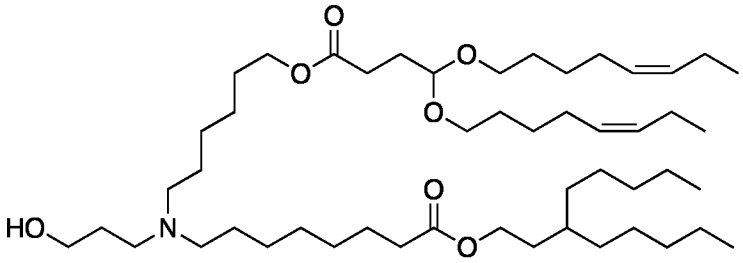
Step 2: 3-butylnonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate (Example 7-200)

[0941] Prepared according to General Procedure F, substituting 3-butylnonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 42 mg, 65%. UPLC-MS (Method B): Rt 2.31 min, m/z calculated [M+H]: 822.7, found 823.1.



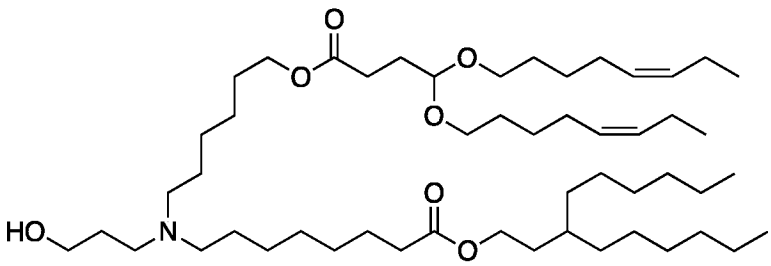
Example 7-201: 3-butylheptyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0942] Prepared according to General Procedure F, substituting 3-butylheptyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 40 mg, 66%. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 794.7, found 795.1.



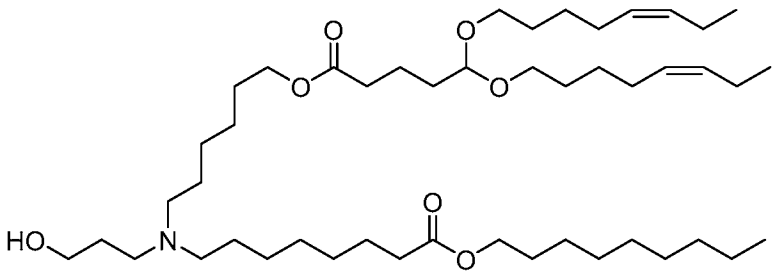
Example 7-202: 3-pentyloctyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0943] Prepared according to General Procedure F, substituting 3-pentyloctyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 40 mg, 62%. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 822.7, found 823.1.



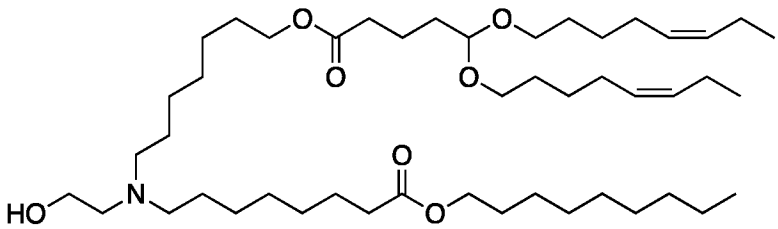
Example 7-203: 3-hexylnonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0944] Prepared according to General Procedure F, substituting 3-hexylnonyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 40 mg, 62%. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 850.7, found 851.2. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85 – 0.90 (m, 6H), 0.94 (t, *J* = 7.6 Hz, 6H), 1.16 – 1.47 (m, 38H), 1.46 – 1.83 (m, 14H), 1.88 – 1.95 (m, 2H), 1.96 – 2.09 (m, 8H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.54 (s, 4H), 2.76 (s, 2H), 3.34 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.78 (t, *J* = 5.2 Hz, 2H), 4.00 – 4.11 (m, 4H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).



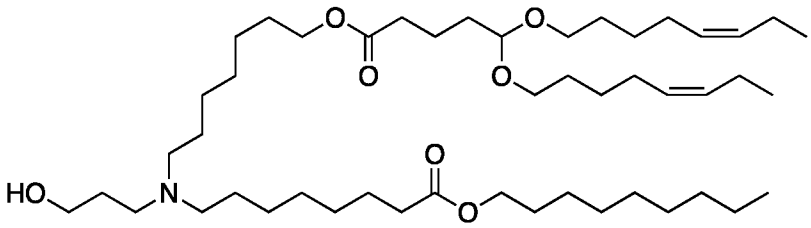
Example 7-204: nonyl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0945] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 106 mg, 56%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 780.7, found 781.1.



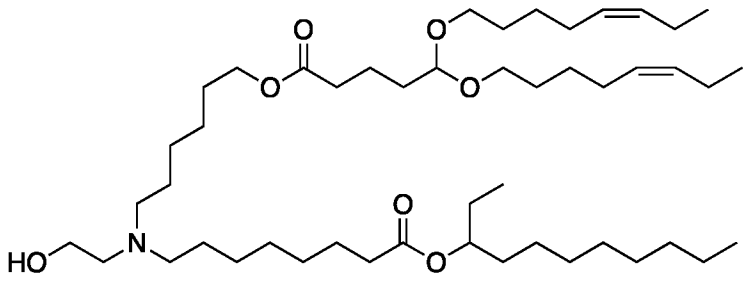
Example 7-205: nonyl 8-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

[0946] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 83 mg, 45%. UPLC-MS (Method B): Rt 2.45 min, m/z calculated [M+H]: 780.7, found 780.9.



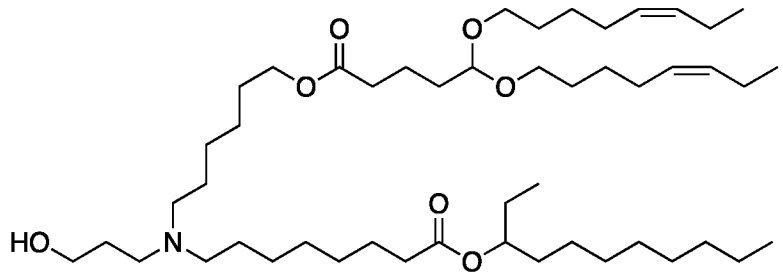
Example 7-206: nonyl 8-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

[0947] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 97 mg, 53%. UPLC-MS (Method B): Rt 2.43 min, m/z calculated [M+H]: 794.7, found 794.8.



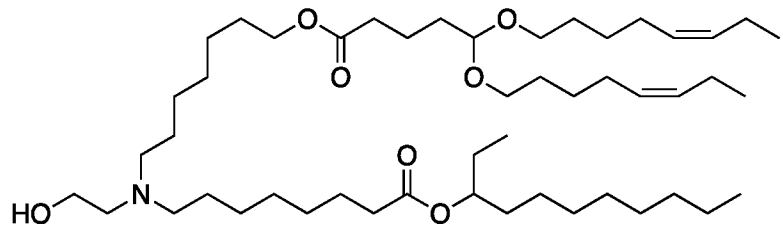
Example 7-207: undecan-3-yl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0948] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 122 mg, 53%. UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 794.7, found 795.1.



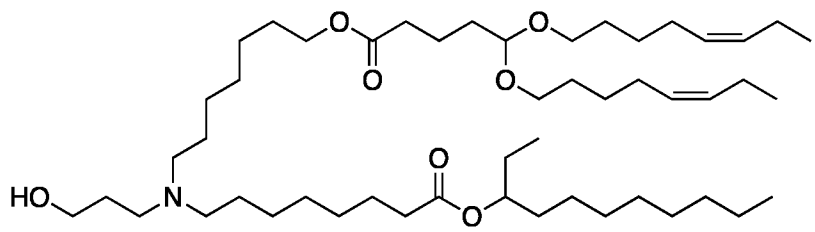
Example 7-208: undecan-3-yl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0949] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 65 mg, 43%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 808.7, found 808.9.



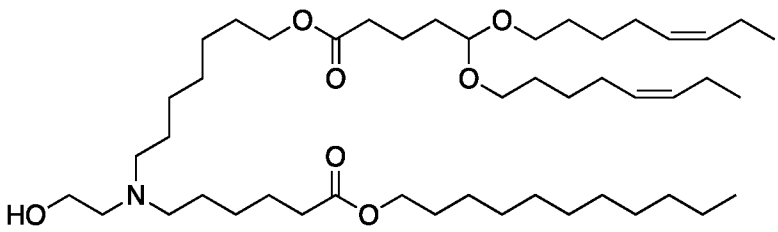
Example 7-209: undecan-3-yl 8-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

[0950] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 64 mg, 47%. UPLC-MS (Method B): Rt 2.22 min, m/z calculated [M+H]: 808.7, found 808.9.



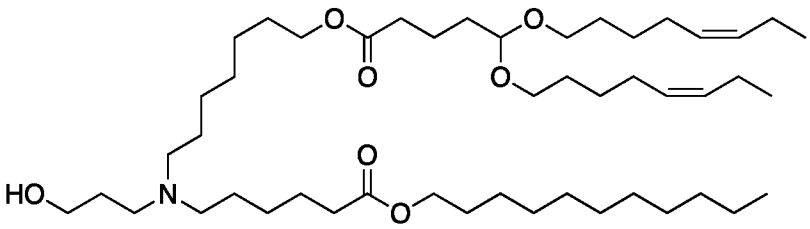
Example 7-210: undecan-3-yl 8-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

[0951] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 45 mg, 37%. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 822.7, found 823.1.



Example 7-211: undecyl 6-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(2-hydroxyethyl)amino)hexanoate

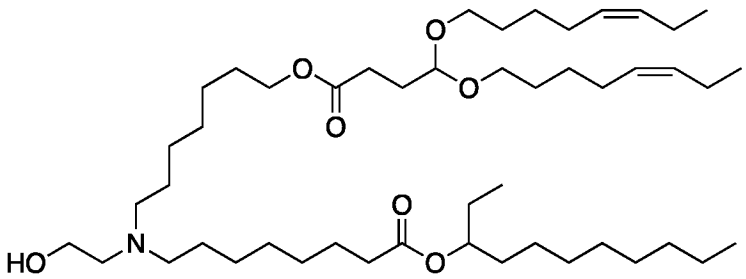
[0952] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 90 mg, 42%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 780.7, found 780.9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.79 – 1.03 (m, 9H), 1.16 – 1.49 (m, 32H), 1.50 – 1.72 (m, 15H), 1.93 – 2.12 (m, 8H), 2.23 – 2.36 (m, 4H), 2.39 – 2.51 (m, 4H), 2.54 – 2.64 (m, 2H), 3.40 (q, *J* = 6.7 Hz, 2H), 3.46 – 3.66 (m, 4H), 4.04 (t, *J* = 6.4 Hz, 4H), 4.46 (d, *J* = 4.7 Hz, 1H), 5.09 – 5.64 (m, 4H).



Example 7-212: undecyl 6-((7-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)heptyl)(3-hydroxypropyl)amino)hexanoate

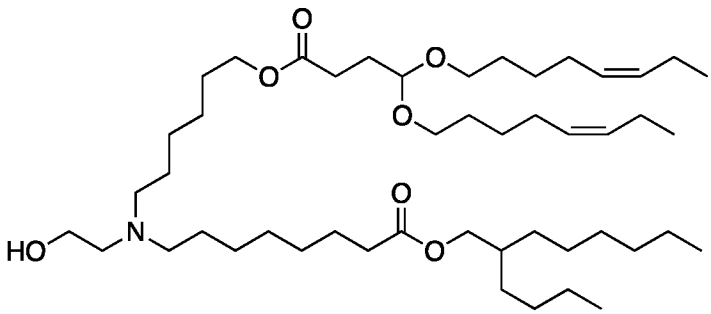
[0953] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecyl 6-((3-hydroxypropyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 75

mg, 34%. UPLC-MS (Method B): Rt 2.20 min, m/z calculated [M+H]: 794.7, found 794.9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 7.1 Hz, 4H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.16 – 1.37 (m, 36H), 1.54 – 1.80 (m, 16H), 1.96 – 2.08 (m, 6H), 2.20 – 2.51 (m, 6H), 2.53 – 2.73 (m, 2H), 3.33 – 3.45 (m, 2H), 3.48 – 3.64 (m, 2H), 3.73 – 3.83 (m, 2H), 3.99 – 4.08 (m, 4H), 4.38 – 4.57 (m, 1H), 5.17 – 5.60 (m, 4H).



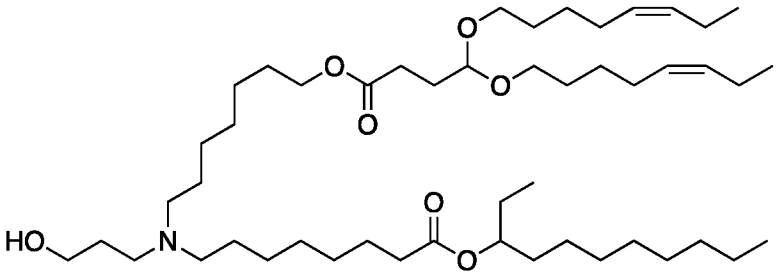
Example 7-213: undecan-3-yl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

[0954] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 58 mg, 38%. UPLC-MS (Method B): Rt 2.14 min, m/z calculated [M+H]: 794.7, found 795.1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.89 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.14 – 1.46 (m, 33H), 1.45 – 1.79 (m, 12H), 1.91 (q, *J* = 7.5 Hz, 2H), 1.95 – 2.11 (m, 8H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.81 – 3.10 (m, 6H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.87 (s, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 4.80 (t, *J* = 6.2 Hz, 1H), 5.24 – 5.42 (m, 4H).



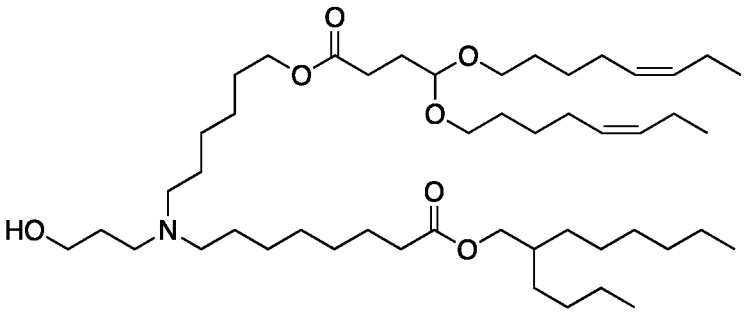
Example 7-214: 2-butyloctyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0955] Prepared according to General Procedure F, substituting 2-butyloctyl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 72 mg, 48%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 794.7, found 795.1.



Example 7-215: undecan-3-yl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

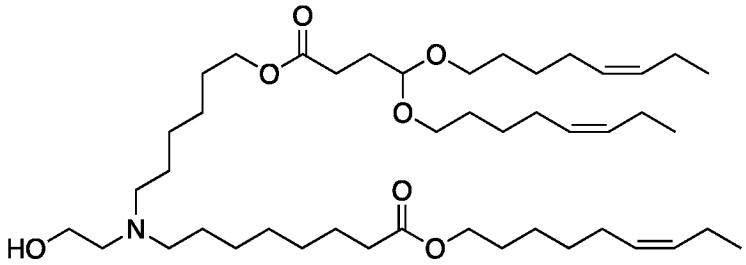
[0956] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and undecan-3-yl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 50 mg, 46%. UPLC-MS (Method B): Rt 2.08 min, m/z calculated [M+H]: 808.7, found 809.1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.91 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.46 (m, 49H), 1.56 – 1.76 (m, 6H), 1.86 – 1.97 (m, 2H), 1.96 – 2.11 (m, 6H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.81 (t, *J* = 5.4 Hz, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 4.48 (t, *J* = 5.7 Hz, 1H), 4.80 (t, *J* = 6.0 Hz, 1H), 5.26 – 5.42 (m, 4H).



Example 7-216: 2-butyloctyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

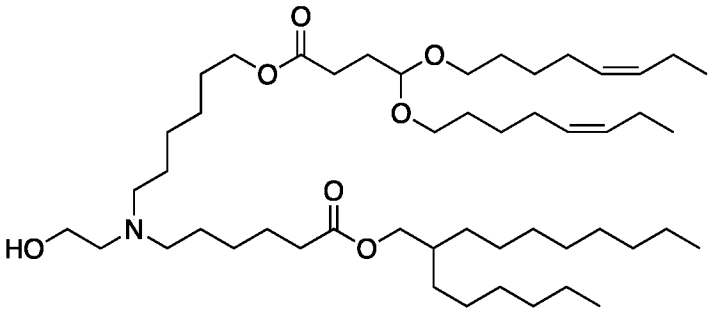
[0957] Prepared according to General Procedure F, substituting 2-butyloctyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 90 mg, 48%. UPLC-MS (Method B): Rt 2.14 min, m/z calculated [M+H]: 808.7, found 809.1. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 0.83 – 0.91 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.19 – 1.46 (m, 30H), 1.66 (s, 12H), 1.68 – 1.86 (m, 4H), 1.87 – 2.09 (m, 11H), 2.29 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.86 – 3.19 (m, 5H), 3.35 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.95 (d, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.15 – 5.52 (m, 4H).



Example 7-217: (*Z*)-non-6-en-1-yl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

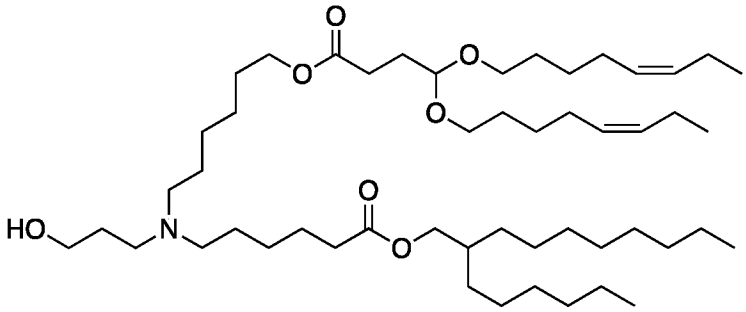
[0958] Prepared according to General Procedure F, substituting (*Z*)-non-6-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 50 mg, 33%. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 750.6, found 751.0. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 9H), 1.21 – 1.78 (m, 33H), 1.88 – 1.96 (m, 2H), 1.98 – 2.10 (m, 12H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.53 – 2.91 (m, 6H), 3.36 – 3.43 (m, 2H), 3.51 – 3.60 (m, 2H), 3.65 – 3.70 (m, 2H), 4.04 (t, *J* = 6.6 Hz, 4H), 4.48 (d, *J* = 5.4 Hz, 1H), 5.09 – 5.62 (m, 6H).



Example 7-218: 2-hexyldecyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexanoate

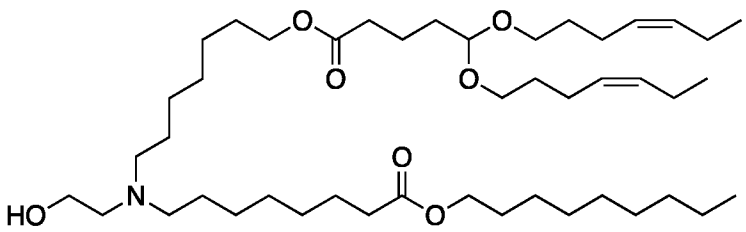
[0959] Prepared according to General Procedure F, substituting 2-hexyldecyl 6-((2-hydroxyethyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 60 mg, 37%. UPLC-MS (Method B): Rt 2.37 min, m/z calculated [M+H]: 822.7, found 823.1. ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 7.0 Hz, 6H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.17 – 1.46 (m, 36H), 1.47 – 1.70 (m, 12H), 1.92 (q, *J* = 7.6 Hz, 3H), 1.96 – 2.11 (m, 8H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.46 – 2.79 (m, 5H), 3.35 – 3.45 (m, 2H), 3.51 – 3.69 (m, 4H), 3.96 (d, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).



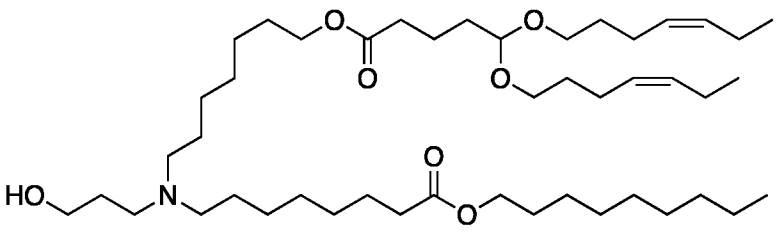
Example 7-219: 2-hexyldecyl 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)hexanoate

[0960] Prepared according to General Procedure F, substituting 2-hexyldecyl 6-((3-hydroxypropyl)amino)hexanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 70 mg, 43%. UPLC-MS (Method B): Rt 2.35 min, m/z calculated [M+H]: 836.7, found 837.2. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.9 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 6H), 1.20 – 1.33 (m, 28H), 1.34 – 1.48 (m, 8H), 1.54 – 1.74 (m, 8H), 1.78 – 1.88 (m, 4H), 1.87 – 2.01 (m, 2H), 1.98 – 2.07 (m, 8H), 2.29 – 2.42 (m, 4H), 2.93 – 3.29 (m, 6H), 3.35 – 3.44 (m, 2H), 3.48 (d, *J* = 4.9 Hz, 1H), 3.53 – 3.61 (m, 2H), 3.84 (t, *J* = 5.0 Hz, 2H), 3.96 (d, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.7 Hz, 1H), 5.27 – 5.39 (m, 4H).



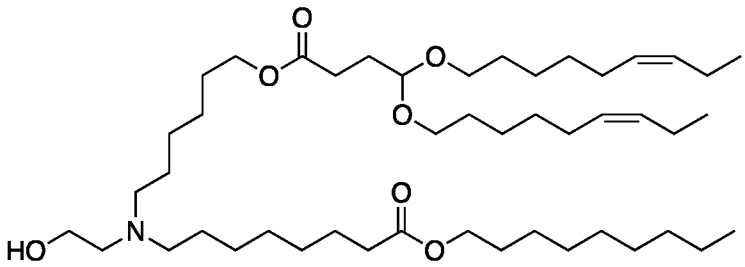
Example 7-220: nonyl 8-((7-((5,5-bis(((*Z*)-hept-4-en-1-yl)oxy)pentanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

[0961] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-hept-4-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 95 mg, 57%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 752.6, found 753.0.

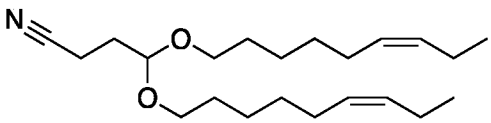


Example 7-221: nonyl 8-((7-((5,5-bis(((*Z*)-hept-4-en-1-yl)oxy)pentanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

[0962] Prepared according to General Procedure F, substituting 7-bromoheptyl 5,5-bis(((*Z*)-hept-4-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and nonyl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 46 mg, 41%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 766.6, found 767.1.

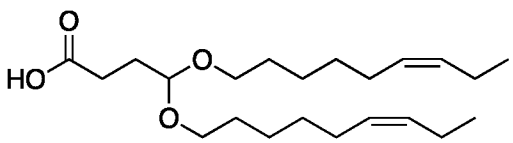


Example 7-222: nonyl 8-((6-((4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate



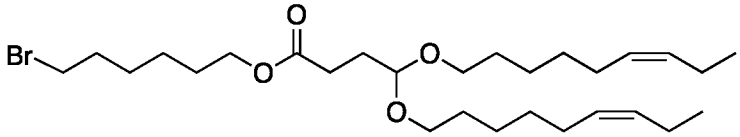
Step 1: 4,4-bis(((Z)-non-6-en-1-yl)oxy)butanenitrile

[0963] Prepared according to General Procedure A, substituting (*Z*)-non-6-en-1-ol for cis-5-octen-1-ol. Isolated 582 mg, 34%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 6H), 1.30 – 1.44 (m, 8H), 1.53 – 1.64 (m, 4H), 1.88 – 2.01 (m, 2H), 1.98 – 2.09 (m, 8H), 2.40 (t, *J* = 7.6 Hz, 2H), 3.32 – 3.47 (m, 2H), 3.54 – 3.64 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H), 5.25 – 5.42 (m, 4H).



Step 2: 4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoic acid

[0964] Prepared according to General Procedure B, substituting 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 180 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.4 Hz, 6H), 1.21 – 1.29 (m, 3H), 1.31 – 1.41 (m, 9H), 1.94 (q, *J* = 7.0 Hz, 2H), 1.97 – 2.07 (m, 9H), 2.44 (t, *J* = 7.2 Hz, 2H), 3.35 – 3.52 (m, 2H), 3.53 – 3.68 (m, 2H), 4.51 (t, *J* = 5.3 Hz, 1H), 5.25 – 5.41 (m, 4H).

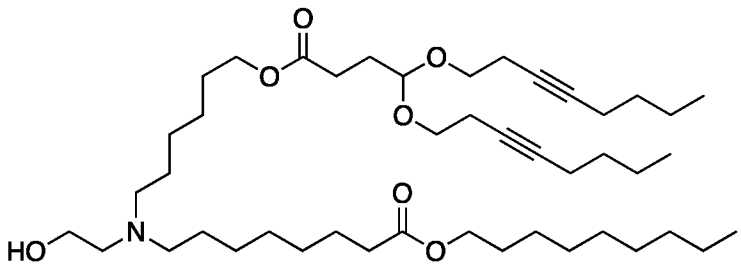


Step 3: 6-bromohexyl 4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoate

[0965] Prepared according to General Procedure C, substituting 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 120 mg, 64%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.6 Hz, 6H), 1.30 – 1.41 (m, 10H), 1.40 – 1.51 (m, 2H), 1.51 – 1.60 (m, 4H), 1.59 – 1.68 (m, 2H), 1.81 – 1.95 (m, 4H), 1.97 – 2.08 (m, 8H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.51 – 3.61 (m, 2H), 4.06 (t, *J* = 6.8 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.25 – 5.41 (m, 4H).

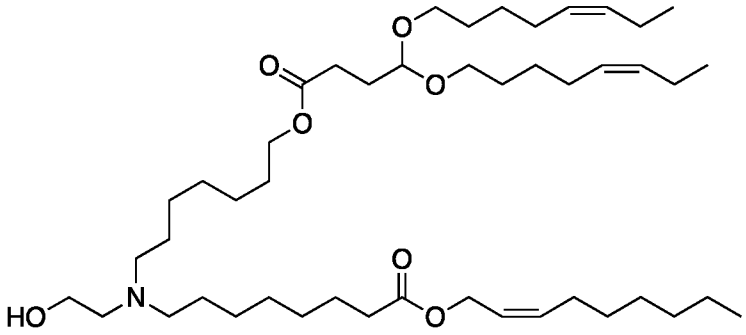
Step 4: nonyl 8-((6-((4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate (Example 7-222)

[0966] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 47 mg, 34%. UPLC-MS (Method B): Rt 2.27 min, m/z calculated [M+H]: 780.7, found 781.1.



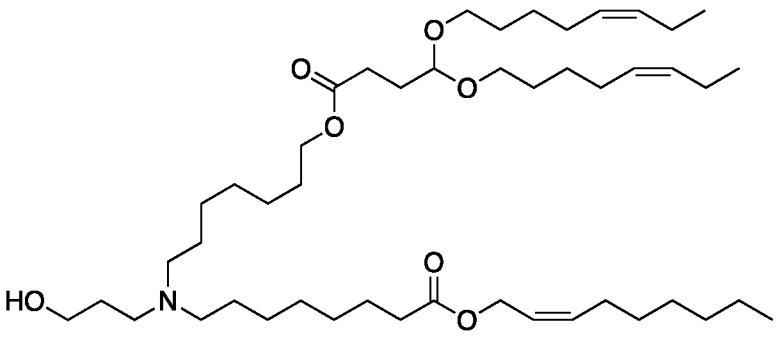
Example 7-223: nonyl 8-((6-((4,4-bis(oct-3-yn-1-yloxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0967] Prepared according to General Procedure F, substituting 6-bromohexyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 43 mg, 32%. UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 748.6, found 749.0.



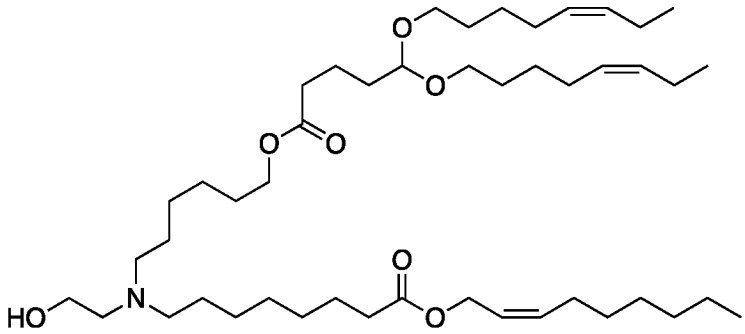
Example 7-224: (*Z*)-non-2-en-1-yl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)octanoate

[0968] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 55 mg, 35%. UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 764.6, found 765.1.



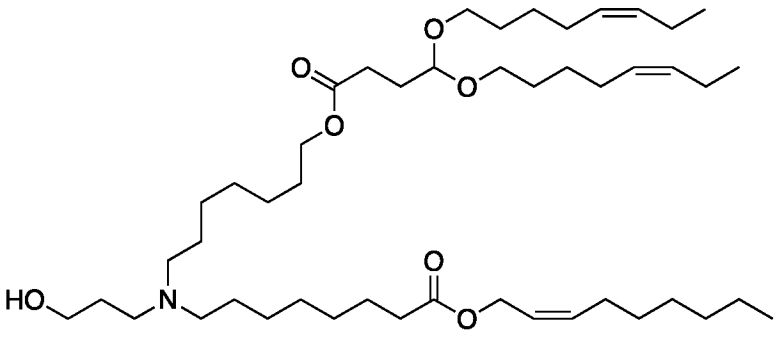
Example 7-225: (*Z*)-non-2-en-1-yl 8-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)octanoate

[0969] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-2-en-1-yl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 18 mg, 24%. UPLC-MS (Method B): Rt 2.16 min, m/z calculated [M+H]: 778.7, found 779.1.



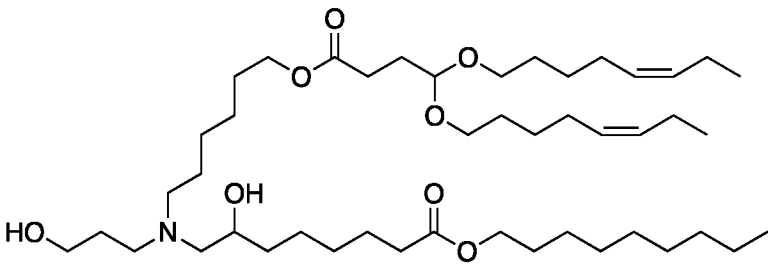
Example 7-226: (*Z*)-non-2-en-1-yl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(2-hydroxyethyl)amino)octanoate

[0970] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-2-en-1-yl 8-((2-hydroxyethyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 36 mg, 46%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 764.6, found 764.8.

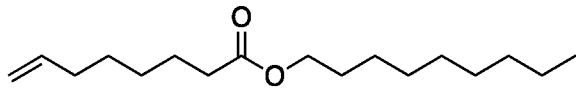


Example 7-227: (*Z*)-non-2-en-1-yl 8-((6-((5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoyl)oxy)hexyl)(3-hydroxypropyl)amino)octanoate

[0971] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and (*Z*)-non-2-en-1-yl 8-((3-hydroxypropyl)amino)octanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 46 mg, 61%. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 778.7, found 778.9.

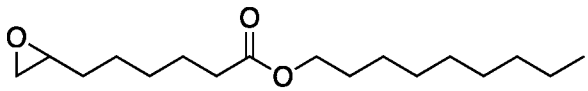


Example 7-228: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate



Step 1: nonyl oct-7-enoate

[0972] To a stirred solution of oct-7-enoic acid (2 g, 14.06 mmol) in DCM (20 mL) was added DCC (4.35 g, 21.09 mmol) and DMAP (515 mg, 4.21 mmol) at 0 °C. Reaction mixture was stirred at 25 °C for 30 min. Then was added nonan-1-ol (2.23 g, 15.47 mmol) to the reaction mixture. Then the reaction mixture was stirred at 25 °C for 16 h. Upon completion, reaction mixture was filtered and evaporated under reduced pressure to get the crude compound. The crude material thus obtained was purified by combiflash column chromatography, eluted with 10% ethyl acetate-hexane to afford nonyl oct-7-enoate (2.5 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85-0.88 (m, 3H), 1.20-1.41 (m, 17H), 1.58-1.65 (m, 4H), 1.72-1.73 (m, 1H), 1.89-1.91 (m, 1H), 2.01-2.06 (m, 2H), 2.28 (t, J =7.52 Hz, 2H), 4.04 (t, J =6.68 Hz, 2H), 4.91-5.00 (m, 2H), 5.73-5.82 (m, 1H).

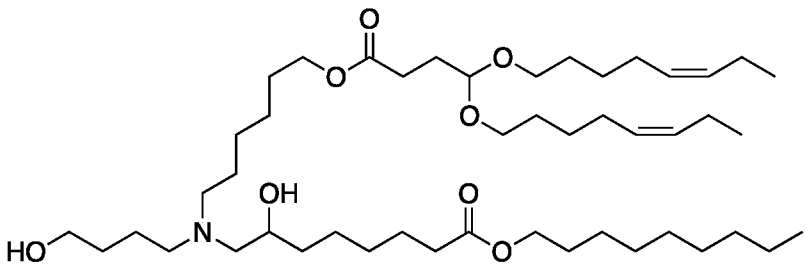


Step 2: nonyl 6-(oxiran-2-yl)hexanoate

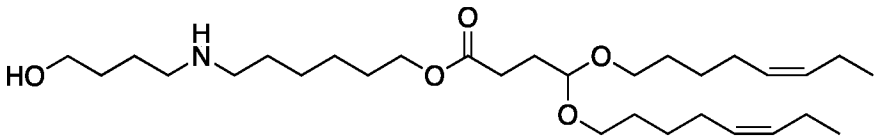
[0973] To a stirred solution of nonyl oct-7-enoate (2.5 g, 9.31 mmol) in DCM (25 mL) was added 3-chloroperbenzoic acid (2.41 g, 13.97 mmol) at 0 °C. Reaction mixture was stirred at 25 °C for 16 h. Upon completion reaction mixture was diluted with DCM (2x50 mL) and washed with saturated solution of sodium bicarbonate (3x100 mL). Combined organic layers were evaporated under reduced pressure. The crude material thus obtained was purified by combiflash column chromatography, eluted with 10% ethyl acetate-hexane to afford nonyl 6-(oxiran-2-yl)hexanoate (2 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J =6.92 Hz, 6H), 1.25-1.29 (m, 24H), 1.35-1.51 (m, 9H), 1.56-1.66 (m, 8H), 2.29 (t, J =7.52 Hz, 4H), 2.44-2.45 (m, 2H), 2.73 (t, J =3.96 Hz, 2H), 2.88 (m, 2H), 4.04 (t, J =6.72 Hz, 4H).

Step 3: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate (Example 7-228)

[0974] A mixture of 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate (50 mg, 0.1 mmol, 1.0 equiv) and nonyl 6-(oxiran-2-yl)hexanoate (31 mg, 0.11 mmol, 1.1 equiv) were heated at 90 °C for 16 h in the absence of solvent. After this time, the mixture was allowed to cool, and the crude material was purified by column chromatography eluting with 0-10% MeOH in DCM gradient to afford nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate (47 mg, 59%). UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 782.6, found 783.2.



Example 7-229: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)-7-hydroxyoctanoate



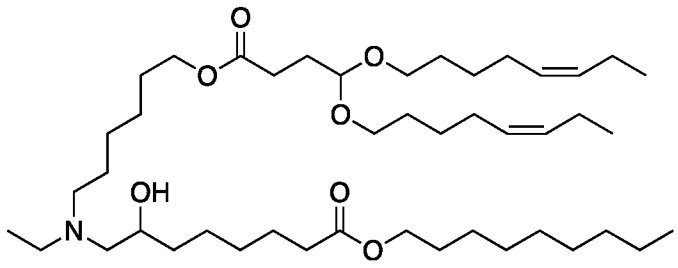
Step 1: 6-((4-hydroxybutyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0975] Prepared according to General Procedure E, substituting 4-aminobutan-1-ol for ethanolamine and 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 188 mg, 92%. UPLC-MS (Method B): Rt 0.58 min, m/z calculated [M+H]: 512.4, found 512.8.

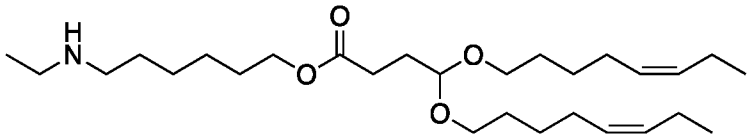
Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(4-hydroxybutyl)amino)-7-hydroxyoctanoate (Example 7-229)

[0976] A mixture of 6-((4-hydroxybutyl)amino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (50 mg, 0.1 mmol, 1.0 equiv) and nonyl 6-(oxiran-2-yl)hexanoate (31 mg, 0.11 mmol, 1.1 equiv) were heated at 90 °C for 16 h in the absence of solvent. After this time, the mixture was allowed to cool, and the crude material was purified by column chromatography eluting with 0-10% MeOH

in DCM gradient to afford nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate (46 mg, 59%). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 796.7, found 797.2.



Example 7-230: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(ethyl)amino)-7-hydroxyoctanoate

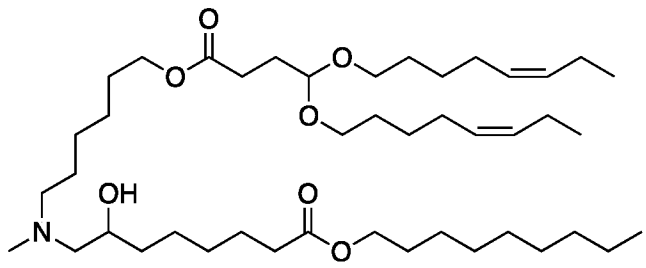


Step 1: 6-(ethylamino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

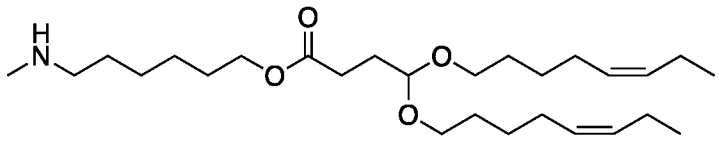
[0977] Prepared according to General Procedure E, substituting ethylamine for ethanolamine and 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 180 mg, 96%. UPLC-MS (Method B): Rt 0.61 min, m/z calculated [M+H]: 468.4, found 468.8.

Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(ethyl)amino)-7-hydroxyoctanoate (Example 7-230)

[0978] A mixture of 6-(ethylamino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (51 mg, 0.11 mmol, 1.0 equiv) and nonyl 6-(oxiran-2-yl)hexanoate (34 mg, 0.12 mmol, 1.1 equiv) were heated at 90 °C for 16 h in the absence of solvent. After this time, the mixture was allowed to cool, and the crude material was purified by column chromatography eluting with 0-10% MeOH in DCM gradient to afford nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate (60 mg, 75%). UPLC-MS (Method B): Rt 2.14 min, m/z calculated [M+H]: 752.6, found 753.2.



Example 7-231: nonyl 8-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(methyl)amino)-7-hydroxyoctanoate

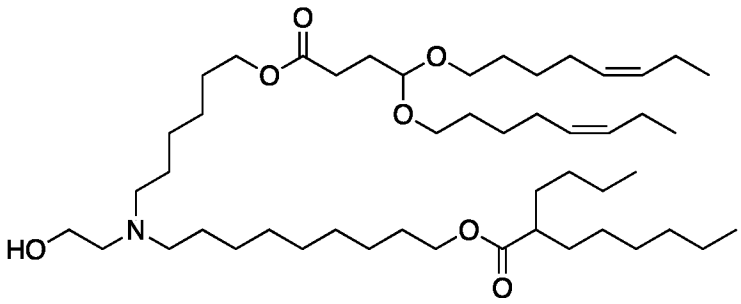


Step 1: 6-(methylamino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

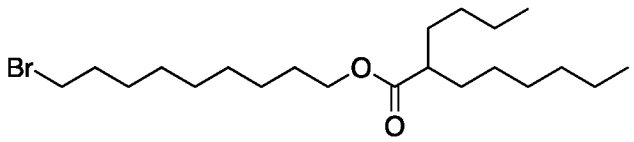
[0979] Prepared according to General Procedure E, substituting methylamine for ethanolamine and 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 170 mg, 94%. UPLC-MS (Method B): Rt 0.59 min, m/z calculated [M+H]: 454.4, found 454.8.

Step 2: nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(methyl)amino)-7-hydroxyoctanoate (Example 7-231)

[0980] A mixture of 6-(methylamino)hexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (50 mg, 0.11 mmol, 1.0 equiv) and nonyl 6-(oxiran-2-yl)hexanoate (34 mg, 0.12 mmol, 1.1 equiv) were heated at 90 °C for 16 h in the absence of solvent. After this time, the mixture was allowed to cool, and the crude material was purified by column chromatography eluting with 0-10% MeOH in DCM gradient to afford nonyl 8-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)-7-hydroxyoctanoate (56 mg, 60%). UPLC-MS (Method B): Rt 2.13 min, m/z calculated [M+H]: 738.6, found 739.0.



Example 7-232: 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)nonyl 2-butyloctanoate

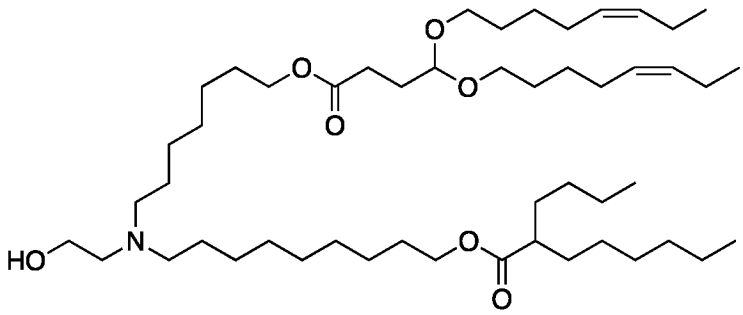


Step 1: 9-bromononyl 2-butyloctanoate

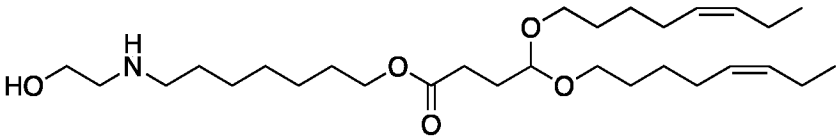
[0981] Prepared according to General Procedure C, substituting 2-butyloctanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid and 9-bromononan-1-ol for 6-bromohexan-1-ol. Isolated 12.8 g, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.91 (m, 6H), 1.17 – 1.37 (m, 21H), 1.38 – 1.45 (m, 4H), 1.55 – 1.65 (m, 3H), 1.78 – 1.90 (m, 2H), 2.23 – 2.38 (m, 1H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 6.5 Hz, 2H).

Step 2: 9-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)nonyl 2-butyloctanoate (Example 7-232)

[0982] Prepared according to General Procedure F, substituting 9-bromononyl 2-butyloctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 90 mg, 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81 – 0.87 (m, 6H), 0.91 (t, *J* = 7.5 Hz, 6H), 1.03 – 1.65 (m, 48H), 1.66 – 1.81 (m, 3H), 1.94 – 2.13 (m, 9H), 2.21 – 2.34 (m, 3H), 3.08 (q, *J* = 6.0 Hz, 1H), 3.26 – 3.40 (m, 4H), 3.43 – 3.55 (m, 4H), 3.95 – 4.05 (m, 4H), 4.36 – 4.52 (m, 1H), 5.25 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 808.7, found 809.1.



Example 7-233: 9-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)nonyl 2-butyloctanoate

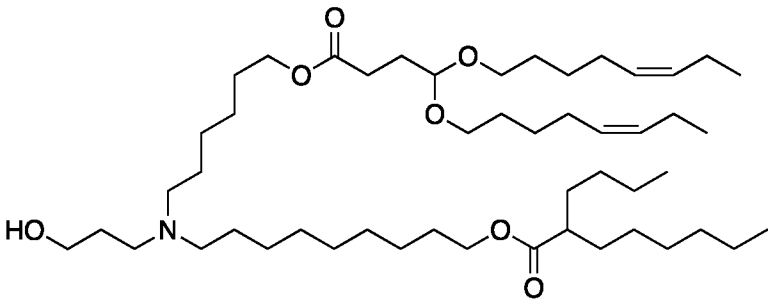


Step 1: 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0983] Prepared according to General Procedure E, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 690 mg, 95% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, J = 7.4 Hz, 6H), 1.20 – 1.42 (m, 13H), 1.42 – 1.57 (m, 6H), 1.77 (q, J = 6.8 Hz, 2H), 1.86 – 2.13 (m, 8H), 2.29 (t, J = 7.1 Hz, 2H), 2.43 – 2.57 (m, 4H), 3.31 – 3.45 (m, 4H), 3.44 – 3.54 (m, 2H), 3.98 (t, J = 6.5 Hz, 2H), 4.24 – 4.60 (m, 1H), 5.23 – 5.40 (m, 4H).

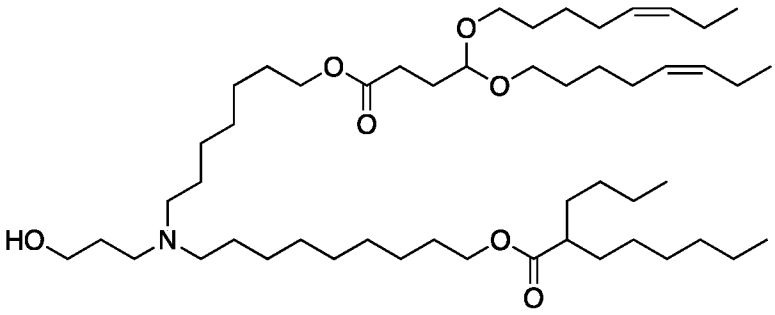
Step 2: 9-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)nonyl 2-butyloctanoate (Example 7-233)

[0984] Prepared according to General Procedure F, substituting 9-bromononyl 2-butyloctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 60 mg, 30%. UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 822.7, found 823.2.

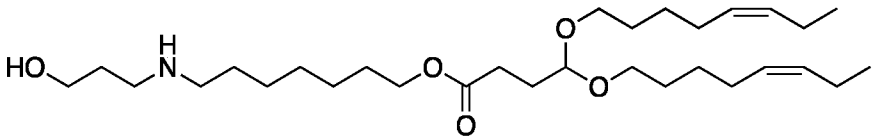


Example 7-234: 9-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)nonyl 2-butyloctanoate

[0985] Prepared according to General Procedure F, substituting 9-bromononyl 2-butyloctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 100 mg, 40%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 – 0.88 (m, 6H), 0.90 (t, J = 7.5 Hz, 6H), 1.08 – 1.66 (m, 55H), 1.76 (q, J = 7.2 Hz, 2H), 1.99 (q, J = 6.9 Hz, 8H), 2.29 (t, J = 7.1 Hz, 3H), 3.31 – 3.40 (m, 2H), 3.39 – 3.55 (m, 4H), 3.95 – 4.05 (m, 4H), 4.44 (t, J = 5.5 Hz, 1H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.26 min, m/z calculated [M+H]: 822.7, found 823.2.



Example 7-235: 9-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)nonyl 2-butyloctanoate



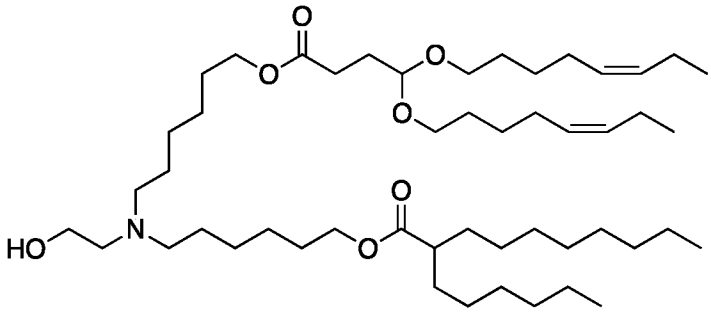
Step 1: 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[0986] Prepared according to General Procedure E, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate and 3-aminopropan-1-ol for ethanolamine. Isolated 950 mg, 96% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 6H), 1.21 – 1.41 (m, 14H), 1.42 – 1.58 (m, 8H), 1.76 (q, J = 7.0 Hz, 2H), 1.93 – 2.05 (m, 8H), 2.29 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 2.53 (d, J = 6.9 Hz, 2H), 3.31 – 3.40 (m, 2H), 3.40 – 3.55 (m, 4H), 3.98 (t, J = 6.6 Hz, 2H), 4.44 (t, J = 5.5 Hz, 1H), 5.23 – 5.40 (m, 4H).

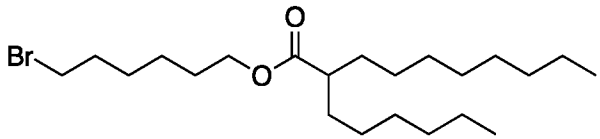
Step 2: 9-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)nonyl 2-butyloctanoate (Example 7-235)

[0987] Prepared according to General Procedure F, substituting 9-bromononyl 2-butyloctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((3-

hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 118 mg, 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 – 0.87 (m, 6H), 0.91 (t, J = 7.5 Hz, 6H), 1.06 – 1.67 (m, 56H), 1.76 (q, J = 6.9 Hz, 2H), 1.88 – 2.06 (m, 9H), 2.29 (t, J = 7.0 Hz, 3H), 3.32 – 3.39 (m, 2H), 3.38 – 3.55 (m, 4H), 3.95 – 4.05 (m, 4H), 4.44 (t, J = 5.5 Hz, 1H), 5.18 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.27 min, m/z calculated [M+H]: 836.7, found 837.2.



Example 7-236: 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexyl 2-hexyldecanoate



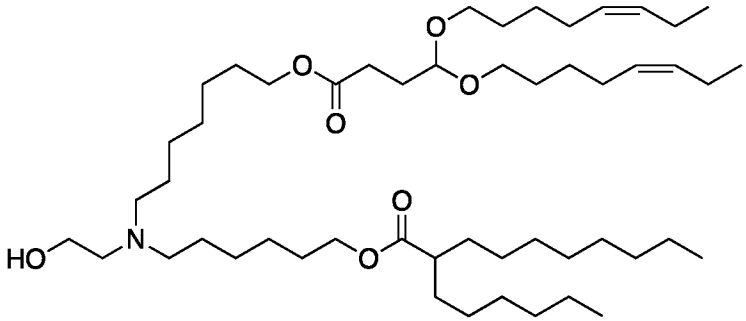
Step 1: 6-bromohexyl 2-hexyldecanoate

[0988] Prepared according to General Procedure C, substituting 2-hexyldecanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 5.7 g, 72%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, J = 6.9 Hz, 6H), 1.18 – 1.31 (m, 19H), 1.31 – 1.53 (m, 6H), 1.54 – 1.70 (m, 4H), 1.80-1.92 (m, 2H), 2.24 – 2.36 (m, 1H), 3.39 (t, J = 6.8 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H), 5.29 (s, 1H).

Step 2: 6-((6-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(2-hydroxyethyl)amino)hexyl 2-hexyldecanoate (Example 7-236)

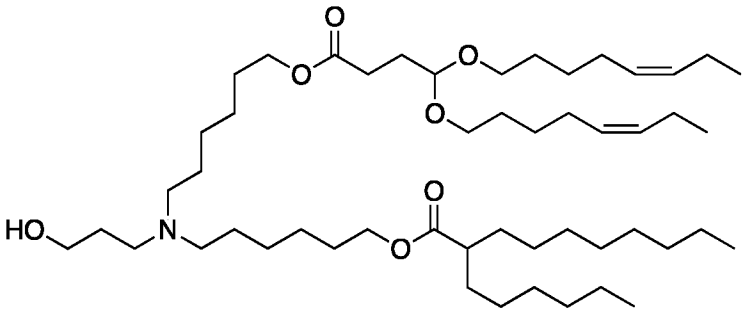
[0989] Prepared according to General Procedure F, substituting 6-bromohexyl 2-hexyldecanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 52 mg, 25%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 – 0.88 (m, 6H), 0.90 (t, J = 6.5 Hz, 6H), 1.06 – 1.63 (m, 53H), 1.76 (q, J = 6.9 Hz, 2H), 1.94 – 2.05 (m, 9H), 2.21 – 2.41 (m, 6H), 3.35 – 3.43

(m, 2H), 3.44 – 3.54 (m, 2H), 3.94 – 4.04 (m, 4H), 4.44 (t, J = 5.5 Hz, 1H), 5.23 – 5.40 (m, J = 6.9 Hz, 4H). UPLC-MS (Method B): Rt 2.38 min, m/z calculated [M+H]: 822.7, found 822.9.



Example 7-237: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)hexyl 2-hexyldecanoate

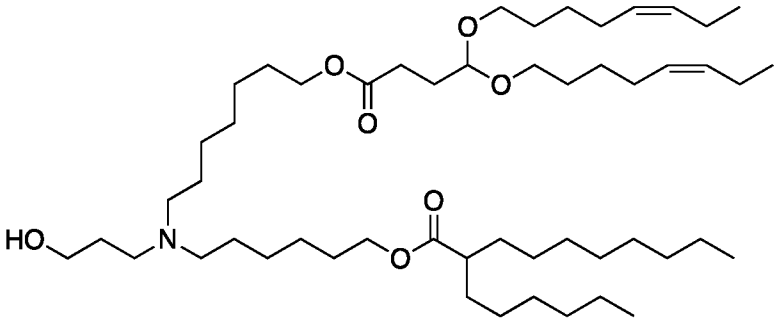
[0990] Prepared according to General Procedure F, substituting 6-bromohexyl 2-hexyldecanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 98 mg, 38%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 – 0.87 (m, 5H), 0.91 (t, J = 7.5 Hz, 6H), 1.06 – 1.65 (m, 59H), 1.76 (q, J = 7.0 Hz, 2H), 1.93 – 2.06 (m, 8H), 2.29 (t, J = 7.0 Hz, 2H), 2.34 – 2.42 (m, 2H), 3.36 (d, J = 6.3 Hz, 2H), 3.44 – 3.55 (m, 2H), 3.94 – 4.05 (m, 4H), 4.44 (t, J = 5.4 Hz, 1H), 5.25 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.35 min, m/z calculated [M+H]: 836.7, found 837.2.



Example 7-238: 6-((6-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)hexyl)(3-hydroxypropyl)amino)hexyl 2-hexyldecanoate

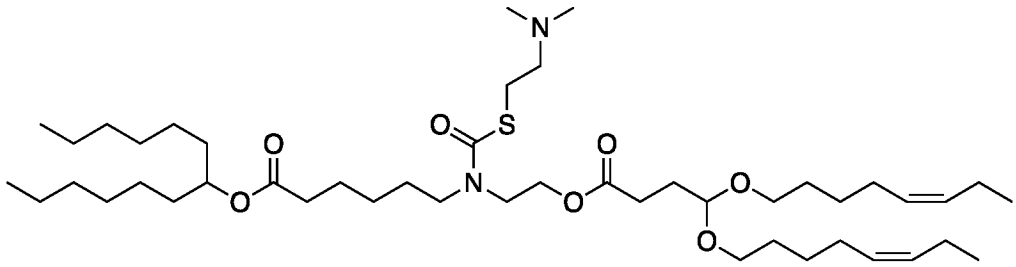
[0991] Prepared according to General Procedure F, substituting 6-bromohexyl 2-hexyldecanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-

hydroxyethyl)amino)octanoate. Isolated 68 mg, 27%. UPLC-MS (Method B): Rt 2.28 min, m/z calculated [M+H]: 836.7, found 836.9.

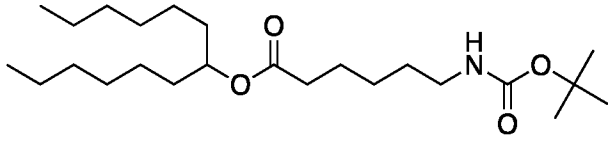


Example 7-239: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)hexyl 2-hexyldecanoate

[0992] Prepared according to General Procedure F, substituting 6-bromohexyl 2-hexyldecanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 80 mg, 32%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 – 0.88 (m, 6H), 0.91 (t, J = 7.5 Hz, 6H), 1.11 – 1.69 (m, 59H), 1.76 (q, J = 6.8 Hz, 2H), 1.93 – 2.06 (m, 8H), 2.28 (t, J = 7.1 Hz, 3H), 3.31 – 3.40 (m, 2H), 3.40 – 3.55 (m, 4H), 3.95 – 4.05 (m, 4H), 4.44 (t, J = 5.5 Hz, 1H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.34 min, m/z calculated [M+H]: 850.7, found 851.2.

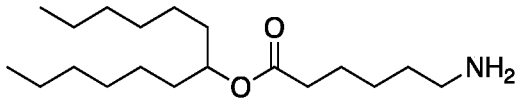


Example 7-240: tridecan-7-yl 6-((2-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)ethyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate



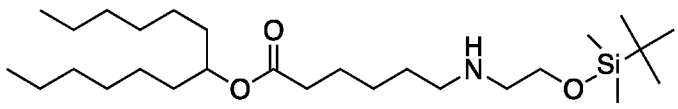
Step 1: tridecan-7-yl 6-((tert-butoxycarbonyl)amino)hexanoate

[0993] To a stirred solution of 6-((*tert*-butoxycarbonyl)amino)hexanoic acid (2.0 g, 8.65 mmol) in DCM (20 mL) were added DCC (2.67 g,12.97 mmol) and DMAP (316 mg, 2.6 mmol) at 25 °C and stirred for 10 min. Then tridecan-7-ol (2.07 g,10.37 mmol) was added portionwise and stirred at 25 °C for 16 h. Upon completion, solvent was evaporated and the residue was taken in water and extracted with DCM (50 mL x 2). Combined organic layers were washed with water (30 mL), saturated $NaHCO_3$ solution (25 mL x 2) and brine (25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude mass thus obtained purified by combiflash column chromatography, eluted with 20% EtOAc/Hexane to afford tridecan-7-yl 6-((tert-butoxycarbonyl)amino)hexanoate (2.37g, 66%) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.17 – 1.40 (m, 18H), 1.40 – 1.54 (m, 15H), 1.63 (p, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 3.10 (q, *J* = 6.8 Hz, 2H), 4.38 – 4.64 (m, 1H), 4.75 – 4.98 (m, 1H).



Step 2: tridecan-7-yl 6-aminohexanoate

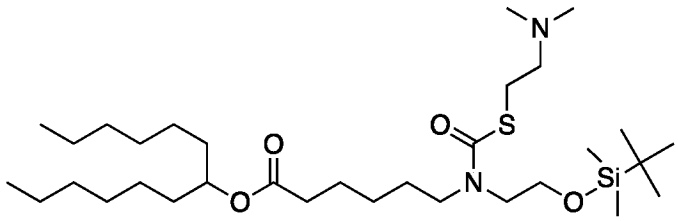
[0994] To a stirred solution of tridecan-7-yl 6-((tert-butoxycarbonyl)amino)hexanoate (3.2 g, 7.73 mmol) in DCM (30 ml) was added TFA (6 mL, 77.36 mmol) at 0 °C. Then the reaction mixture was slowly warmed to 25 °C and stirred for 2 hours. Upon completion of the reaction, excess TFA was evaporated under reduced pressure and the crude was diluted with DCM (60 mL). It was then washed with sat. $NaHCO_3$ solution (2 x 20 mL), brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product tridecan-7-yl 6-aminohexanoate (2.4 g) thus obtained was used for next step without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.86 (t, *J* = 6.8 Hz, 6H), 1.25 (s, 18H), 1.32 – 1.54 (m, 6H), 1.56 – 1.71 (m, 4H), 2.28 (t, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.1 Hz, 2H), 4.73 – 4.95 (m, 1H).



Step 3: tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)hexanoate

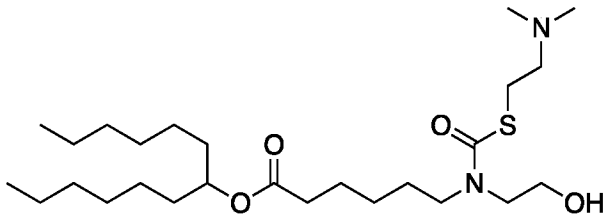
[0995] A solution of (2-bromoethoxy)(*tert*-butyl)dimethylsilane (100 mg, 0.41 mmol) and tridecan-7-yl 6-aminohexanoate (655.29 mg, 2.09 mmol) in ACN-THF (1:1) (2.0 ml) was stirred at 45° C for 16 hours. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 25 ml). The combined organic layers were dried over Na_2SO_4 and

concentrated to get the crude. Crude was subjected to combiflash chromatography (3-5% MeOH-DCM) to get the desired product tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)hexanoate (110 mg, 55%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.05 (s, 6H), 0.82 – 0.91 (m, 15H), 1.14 – 1.34 (m, 18H), 1.33 – 1.43 (m, 2H), 1.49 (q, *J* = 6.2 Hz, 6H), 1.57 – 1.76 (m, 4H),2.28 (t, *J* = 7.4 Hz, 2H), 2.62 – 2.65 (m, 2H), 2.71-2.74 (t, *J* = 6.9 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 4.53 – 5.14 (m, 1H).



Step 4: tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate

[0996] To a stirred solution of tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)hexanoate (110 mg, 0.23 mmol) in DCM (1.0 ml) was added triphosgene (34.58 mg, 0.12 mmol) followed by TEA (0.1 ml, 0.7mmol) at 0°C. Reaction mixture was stirred for 1 h. Then a solution of 2-(dimethylamino)ethane-1-thiol (85 mg,0.82 mmol) in THF (1 ml) was added followed by NaH (39.15 mg, 1.63 mmol) to reaction mixture at 0°C and was stirred for 3h. Reaction mixture was diluted with water (5 mL) and extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude, which was subjected to combiflash chromatography (3-5% MeOH-DCM) to get tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate. ^{1}H NMR (400 MHz, Chloroform-*d*): δ -0.14 – 0.21 (m, 6H), 0.76 – 0.96 (m, 16H), 1.18 – 1.35 (m, 18H), 1.43 – 1.74 (m, 8H), 2.21 – 2.35 (m, 8H), 2.53 (t, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 7.1 Hz, 2H), 3.26 – 3.53 (m, 4H), 3.74 (t, *J* = 5.7 Hz, 2H), 4.71 – 4.97 (m, 1H).

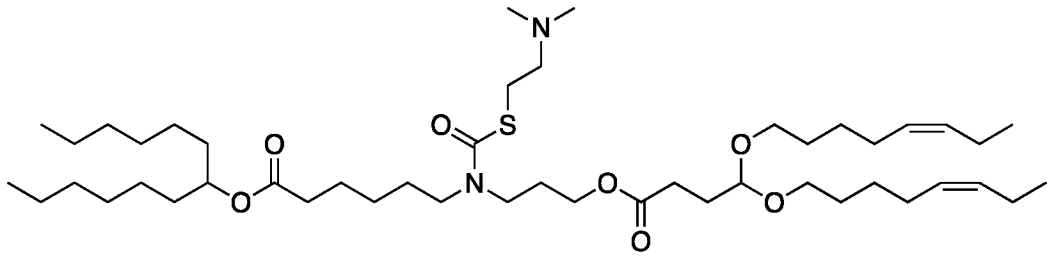


Step 5: tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(2-hydroxyethyl)amino)hexanoate

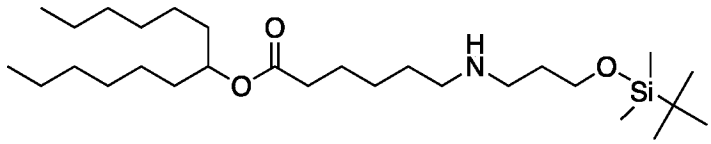
[0997] TBAF (0.13 mL, 1M solution in THF, 0.13 mmol) was added to a solution of tridecan-7-yl 6-((2-((tert-butyldimethylsilyl)oxy)ethyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (40 mg, 0.07 mmol) in 2 mL of THF at 0 °C and stirred for 8h at 25°C. The reaction was quenched by water (1 mL) and extracted with 10% MeOH-DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(2-hydroxyethyl)amino)hexanoate (30 mg) was used for next step without further purification.

Step 6: tridecan-7-yl 6-((2-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)ethyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (Example 7-240)

[0998] Prepared according to General Procedure C, substituting tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(2-hydroxyethyl)amino)hexanoate for 6-bromohexan-1-ol. Isolated 40 mg, 51%. UPLC-MS (Method B): Rt 2.25 min, m/z calculated [M+H]: 811.6, found 811.7.



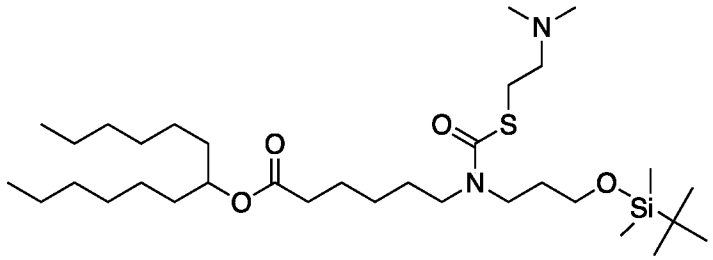
Example 7-241: tridecan-7-yl 6-((3-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)propyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate



Step 1: tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)amino)hexanoate

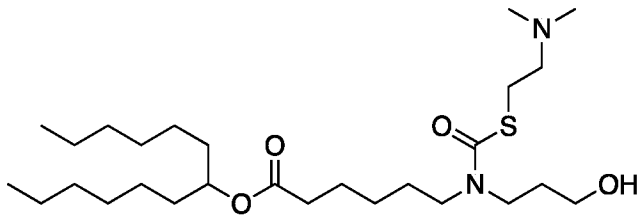
[0999] A solution of (3-bromopropoxy)(*tert*-butyl)dimethylsilane (150 mg, 0.59 mmol) and tridecan-7-yl 6-aminohexanoate (928 mg, 2.96 mmol) in ACN-THF (1:1) (3.0 ml) was stirred at 45° C for 16 hours. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate (2 x 25 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to get the crude. Crude was subjected to combiflash chromatography (3-5% MeOH-

DCM) to get the desired product tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)amino)hexanoate (200 mg, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.05 (s, 6H), 0.82 – 0.91 (m, 15H), 1.14 – 1.34 (m, 18H), 1.33 – 1.43 (m, 2H), 1.49 (q, *J* = 6.2 Hz, 4H), 1.57 – 1.76 (m, 4H), 1.84 – 1.96 (m, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.73 – 2.84 (m, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 4.53 – 5.14



Step 2: tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate

[1000] To a stirred solution of tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)amino)hexanoate (100 mg, 0.206 mmol) in DCM (1.0 ml) was added triphosgene (31 mg, 0.11 mmol) followed by TEA (0.09 ml, 0.62 mmol) at 0°C. Reaction mixture was stirred for 1 h. Then a solution of 2-(dimethylamino)ethane-1-thiol (85 mg, 0.82 mmol) in THF (1 ml) was added followed by NaH (40 mg, 1.65 mmol) to reaction mixture at 0°C and was stirred for 3 h. Reaction mixture was diluted with water (5 mL) and extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude, which was subjected to combiflash chromatography (3-5% MeOH-DCM) to get tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (80 mg, 63%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.82 – 0.91 (m, 13H), 1.15 – 1.38 (m, 17H), 1.42 – 1.70 (m, 18H), 1.71 – 1.87 (m, 2H), 2.24 – 2.31 (m, 8H), 2.54 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 3.19 – 3.46 (m, 4H), 3.61 (t, *J* = 5.6 Hz, 2H), 4.84 (t, *J* = 6.6 Hz, 1H).

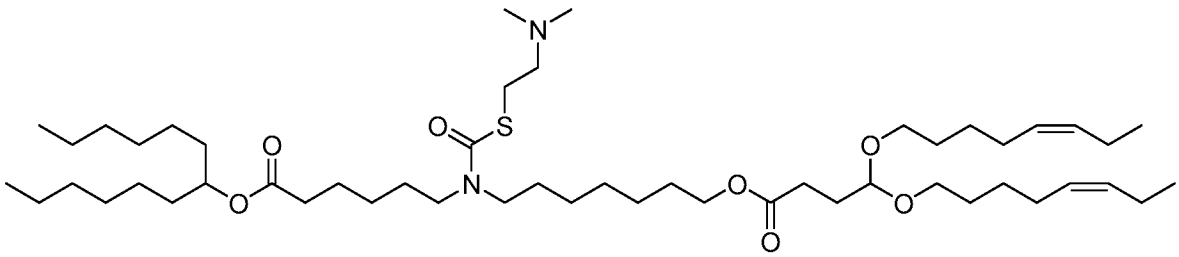


Step 3: tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(3-hydroxypropyl)amino)hexanoate

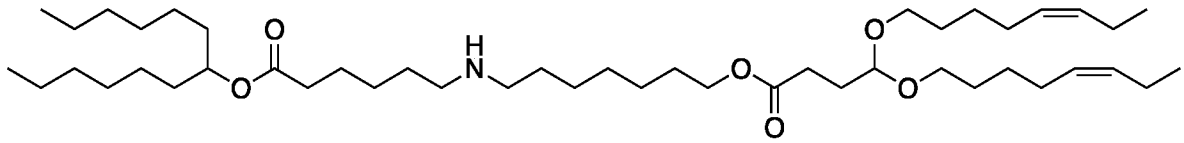
[1001] TBAF (0.26 mL, 1M solution in THF, 0.26 mmol) was added to a solution of tridecan-7-yl 6-((3-((tert-butyldimethylsilyl)oxy)propyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (80 mg, 0.13 mmol) in 5 mL of THF at 0 °C and stirred for 8h at 25°C. The reaction was quenched by water (1 mL) and extracted with 10% MeOH-DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(3-hydroxypropyl)amino)hexanoate (60 mg) was used for next step without further purification.

Step 4: tridecan-7-yl 6-((3-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)propyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (Example 7-241)

[1002] Prepared according to General Procedure C, substituting tridecan-7-yl 6-((((2-(dimethylamino)ethyl)thio)carbonyl)(3-hydroxypropyl)amino)hexanoate for 6-bromohexan-1-ol. Isolated 21 mg, 34%. UPLC-MS (Method B): Rt 2.15 min, m/z calculated [M+H]: 825.6, found 825.7.



Example 7-242: tridecan-7-yl 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate



Step 1: tridecan-7-yl 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)amino)hexanoate

[1003] A mixture of 7-bromoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (110 mg, 0.21 mmol) and tridecan-7-yl 6-aminohexanoate (333 mg, 1.06 mmol) in ACN/THF (1mL:1mL) was stirred at 45°C for 12h. The reaction mixture was concentrated and subjected to combiflash chromatography (5% MeOH-DCM) to afford tridecan-7-yl 6-((7-((4,4-bis(((Z)-oct-5-en-1-

yl)oxy)butanoyl)oxy)heptyl)amino)hexanoate (100 mg, 62%). UPLC-MS (Method B): Rt 1.02 min, m/z calculated [M+H]: 750.6, found 750.8.

Step 2: tridecan-7-yl 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (Example 7-242)

[1004] Triphosgene (10 mg, 0.03 mmol) was added to a solution of tridecan-7-yl 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)amino)hexanoate (30 mg, 0.04 mmol) and Et_3N (0.03 mL, 0.2 mmol) in DCM (1.0 mL) at 0 °C and stirred for 2 h at 23 °C. Then 2-(dimethylamino)ethane-1-thiol (33 mg, 0.23 mmol) was added at 0 °C followed by a mixture of NaH (5 mg, 0.2 mmol) in THF (1 mL) and stirred at 25 °C for 6h. Reaction mixture was diluted with water and extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was subjected to combi flash chromatography (3-5% MeOH-DCM) to afford tridecan-7-yl 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(((2-(dimethylamino)ethyl)thio)carbonyl)amino)hexanoate (35 mg, 26%). UPLC-MS (Method B): Rt 2.38 min, m/z calculated [M+H]: 811.7, found 811.8.

Example 8: Synthesis of Ionizable lipids

[1005] The present Example provides exemplary materials and methods of preparing, characterizing, and validating ionizable lipids as described herein. As described in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present disclosure, the following general methods and other methods known to one of ordinary skill in the art can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[1006] General notes: All reactions were run using anhydrous grade solvents under an atmosphere of nitrogen in flasks or vials with magnetic stirring, unless otherwise noted. Anhydrous solvents were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed using a Biotage Selekt or Teledyne-Isco Combiflash Nextgen300+ with prepacked silica gel cartridges. Thin layer chromatography was performed using Merck silica gel 60 plates, and compounds were visualized using iodine. Nuclear magnetic resonance (NMR) spectroscopy was performed either using a Varian INOVA 500 MHz or a Bruker AVANCE 400 MHz spectrometer; chemical shifts are reported in δ parts per million (ppm) referenced to

tetramethylsilane at δ = 0.00 ppm for $CDCl_3$ samples, and residual solvent peak (δ = 2.50 ppm) for DMSO samples. Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) was performed using a Waters Acquity UPLC H-class Plus with QDa detector (ESI^+) using one of the following methods:

[1007] Method A: 6 min run, Column: BEH C18 (2.1 x 50 mm), 1.7 μM, mobile phase: initially 90% [0.1% HCOOH in water] and 10% ACN; then to 5% [0.1% HCOOH in water] and 95% ACN over 3 min, held this mobile phase composition for 2 min, and finally back to initial condition over 1 min, i.e; 90% [0.1% HCOOH in water] and 10% ACN. Flow =0.5 mL/min.

[1008] Method B: 5 min run, Column: XTERRA RP 18 (4.6 x 50 mm), 5 μm, mobile phase: initially 50% [0.1% HCOOH in water] and 50% [0.1% HCOOH in (70:30) ACN: THF]; then to 2% [0.1% HCOOH in water] and 98% [0.1% HCOOH in (70:30) ACN: THF] in 2.65 min, held this mobile phase composition up to 3.75 min, and finally back to initial condition, i.e; 50% [0.1% HCOOH in water] and 50% [0.1% HCOOH in (70:30) ACN: THF] in 4.90 min, held this mobile phase composition up to 5.10 min. Flow =1.2 mL/min.

[1009] Method C: 12 min run, Column: XTERRA RP 18 (4.6 x 50 mm), 5 μm, (mobile phase: initially 80% [0.1% HCOOH in water] and 20% [0.1% HCOOH in (70:30) ACN: THF]; held this initial condition for 0.75 min; then to 65% [0.1% HCOOH in water] and 35% [0.1% HCOOH in (70:30) ACN: THF] in 3.0 min, then to 2% [0.1% HCOOH in water] and 98% [0.1% HCOOH in (70:30) ACN: THF] in 6.0 min, held this mobile phase composition up to 9.0 min, and finally back to initial condition, i.e.; 80% [0.1% HCOOH in WATER] and 20% [0.1% HCOOH in (70:30) ACN: THF] in 11.00 min, held this mobile phase composition up to 12.10 min. Flow =1.2 ml/min

List of abbreviations

ACN: acetonitrile

d: doublet

DCC: N,N'-dicyclohexylcarbodiimide

DCM: dichloromethane

DIPEA: N,N-diisopropylethylamine

DMAP: 4-(dimethylamino)pyridine

DMSO: dimethyl sulfoxide

EDC: *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

Eq: equivalents

Et: ethyl

i-Pr: isopropyl

m: multiplet

Me: methyl

p: pentet

PPTS: pyridinium p-toluenesulfonate

q: quartet

Rt: retention time

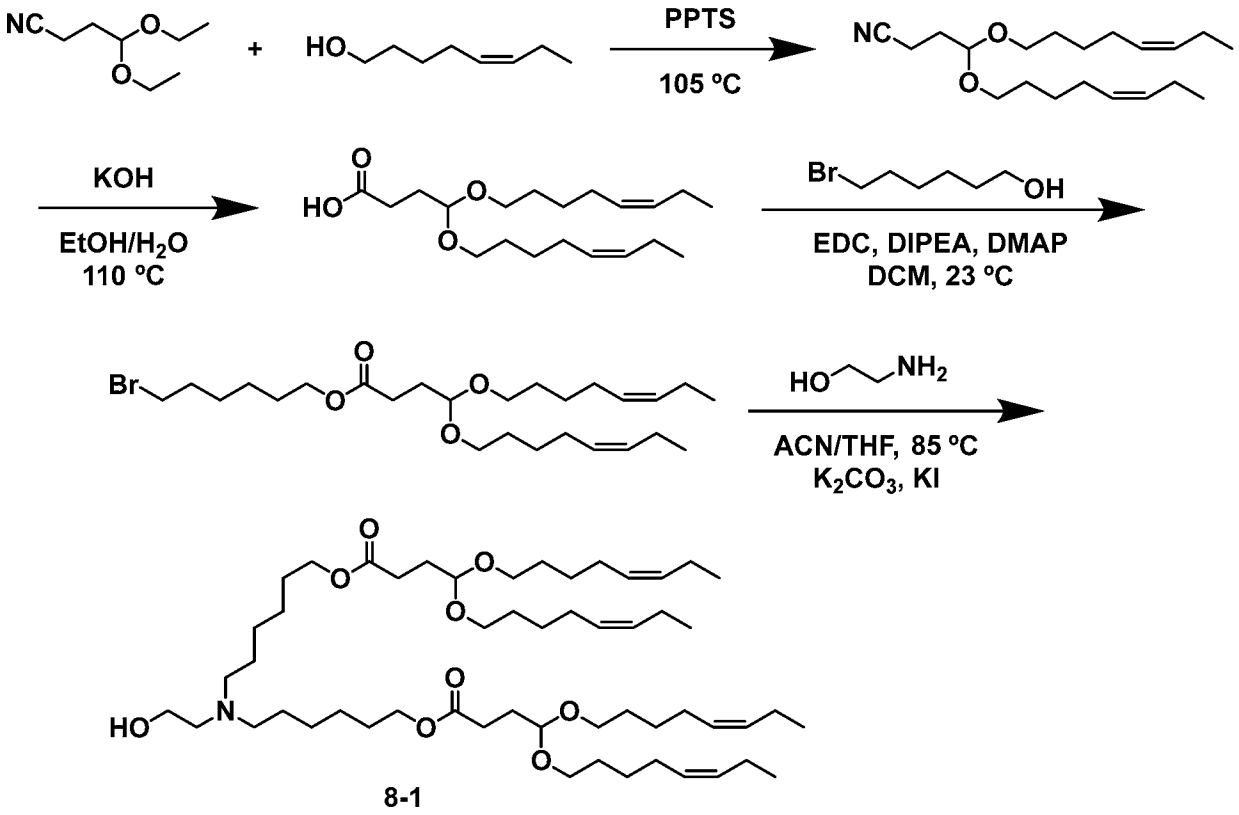
s: singlet

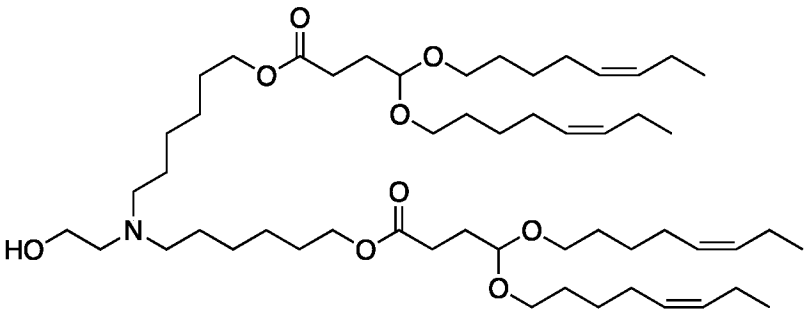
t: triplet

TEA: triethylamine

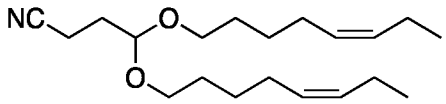
THF: tetrahydrofuran

[1010] The following example lipids were prepared according to the below synthetic scheme, using Example 8-1 as an illustration.





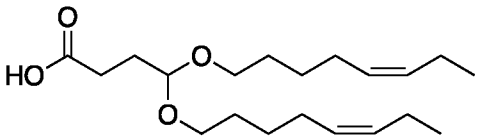
Example 8-1: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)



Step 1: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanenitrile

General Procedure A:

[1011] To a vial containing pyridinium *p*-toluene sulfonate (0.12 g, 0.48 mmol, 0.05 Eq) was added 4,4-diethoxybutanenitrile (1.5 g, 9.5 mmol, 1 Eq) and cis-5-octen-1-ol (3.7 g, 29 mmol, 3 Eq). The vial was tightly capped, and the resulting mixture was heated at 105 °C for 72 h. After this time, the mixture was allowed to cool to room temperature. The crude material was purified by flash column chromatography (100 g silica, 0 to 100% dichloromethane in hexanes over 20 minutes). Obtained 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile (1.14 g, 37%) as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.43 – 5.27 (m, 4H), 4.56 (t, *J* = 5.3 Hz, 1H), 3.61 (dt, *J* = 9.3, 6.6 Hz, 2H), 3.44 (dt, *J* = 9.3, 6.6 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.91 (m, 9H), 1.66 – 1.54 (m, 5H), 1.49 – 1.36 (m, 4H), 0.96 (t, *J* = 7.6 Hz, 6H).

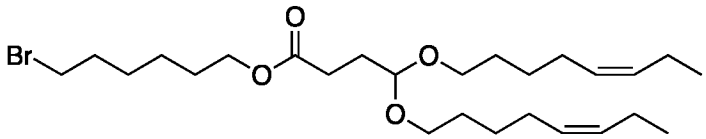


Step 2: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid

General Procedure B:

[1012] To a vial containing 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile (1.14 g, 3.54 mmol, 1 Eq) was added potassium hydroxide (0.60 g, 10.6 mmol, 3 Eq) followed by ethanol (3.5 mL) and water (3.5 mL). The vial was tightly capped, and the reaction mixture was heated to 110 °C for 18 h. After this time, the mixture was allowed to cool to room temperature. The mixture was diluted

with ethyl acetate (20 mL), and the pH was adjusted to ~5 by the addition of 1M HCl. The resulting biphasic mixture was separated, and the aqueous phase was extracted two more times with ethyl acetate (2 x 20 mL). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated to afford 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid (1.16 g, 96% yield) as a sticky white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.41 – 5.24 (m, 4H), 4.45 (t, *J* = 5.6 Hz, 1H), 3.51 (dt, *J* = 9.0, 6.7 Hz, 2H), 3.39 (dt, *J* = 9.0, 6.7 Hz, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 2.08 – 1.98 (m, 8H), 1.81 (q, *J* = 7.3 Hz, 2H), 1.59 – 1.52 (m, 4H), 1.44 – 1.32 (m, 4H), 0.94 (t, *J* = 7.5 Hz, 6H).



Step 3: 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

General Procedure C:

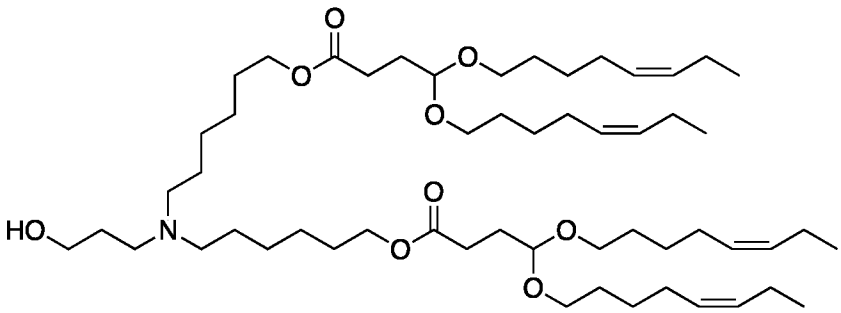
[1013] To a solution of 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid (508 mg, 1 Eq, 1.49 mmol) in DCM (13 mL) was added 6-bromohexan-1-ol (270 mg, 195 µL, 1 Eq, 1.49 mmol), DIPEA (964 mg, 1.29 mL, 5 Eq, 7.46 mmol) , and DMAP (36.4 mg, 0.2 Eq, 298 µmol). Added EDC (429 mg, 1.5 Eq, 2.24 mmol) last, stirred at 23 °C for 18 h. After this time, the reaction mixture was concentrated and purified by flash column chromatography (50 g silica, 0 to 50% ethyl acetate in hexanes). Obtained 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (397 mg, 53%) as a colorless oil.

Step 4: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (Example 8-1)

General Procedure G:

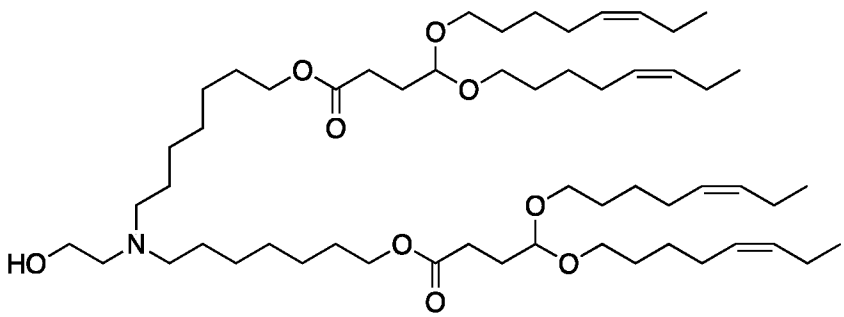
[1014] To a solution of 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (295 mg, 2 Eq, 585 µmol) in ACN (5 mL) and THF (5 mL) was added potassium carbonate (243 mg, 6 Eq, 1.76 mmol), potassium iodide (117 mg, 2.4 Eq, 702 µmol), and 2-aminoethan-1-ol (18 mg, 1 Eq, 293 µmol). The resulting mixture was stirred at 85°C for 18 h. After this time, the mixture was filtered through a pad of celite and concentrated. The residue was partitioned between ethyl acetate and water, and the organic layer washed twice with water and once with brine. The organics were combined, dried over sodium sulfate and concentrated. The resulting residue was purified by flash column chromatography (50 g silica, 0 to 10% methanol in DCM). Obtained ((2-

hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate) (187 mg, 71% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 – 5.27 (m, 8H), 4.49 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 4H), 3.69 (br s, 2H), 3.57 (dt, *J* = 9.3, 6.5 Hz, 4H), 3.41 (dt, *J* = 9.3, 6.6 Hz, 4H), 2.78 (br s, 2H), 2.66 (br s, 4H), 2.37 (t, *J* = 8.0 Hz, 4H), 2.07 – 1.99 (m, 16H), 1.92 (ddd, *J* = 8.3, 7.2, 5.5 Hz, 4H), 1.66 – 1.53 (m, 16H), 1.44 – 1.33 (m, 16H), 0.95 (t, *J* = 7.5 Hz, 12H). UPLC-MS (Method A): Rt 3.61 min, m/z calculated [M+H]: 906.73, found 906.78.

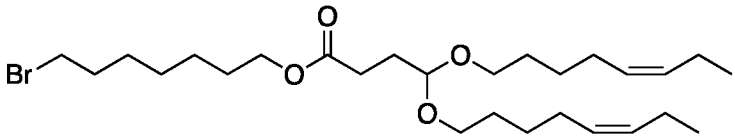


Example 8-2: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1015] Prepared according to General Procedure G, substituting 3-aminopropan-1-ol for 2-aminoethan-1-ol. Obtained 131 mg, 49% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 – 5.27 (m, 8H), 4.49 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 6.7 Hz, 4H), 3.80 (t, *J* = 5.2 Hz, 2H), 3.57 (dt, *J* = 9.3, 6.5 Hz, 4H), 3.40 (dt, *J* = 9.3, 6.6 Hz, 4H), 2.78 (br s, 2H), 2.56 (br s, 4H), 2.37 (t, *J* = 7.7 Hz, 4H), 2.07 – 1.99 (m, 16H), 1.92 (ddd, *J* = 8.3, 7.1, 5.6 Hz, 4H), 1.77 (br s, 2H), 1.66 – 1.53 (m, 16H), 1.44 – 1.32 (m, 16H), 0.95 (t, *J* = 7.5 Hz, 12H). UPLC-MS (Method A): Rt 3.65 min, m/z calculated [M+H]: 920.75, found 920.88.



Example 8-3: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

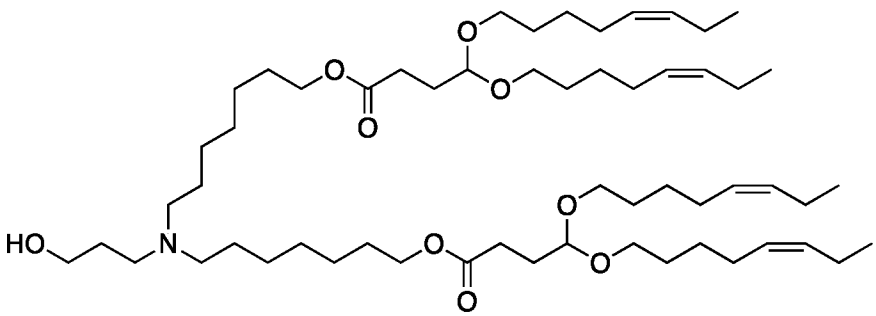


Step 1: 7-bromoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[1016] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol. Obtained 605 mg, 50% yield. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.30 – 1.49 (m, 15H), 1.50 – 1.67 (m, 3H), 1.80 – 1.96 (m, 4H), 1.96 – 2.09 (m, 6H), 2.37 (t, *J* = 7.6 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.50 – 3.62 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.42 (m, 4H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (Example 8-3)

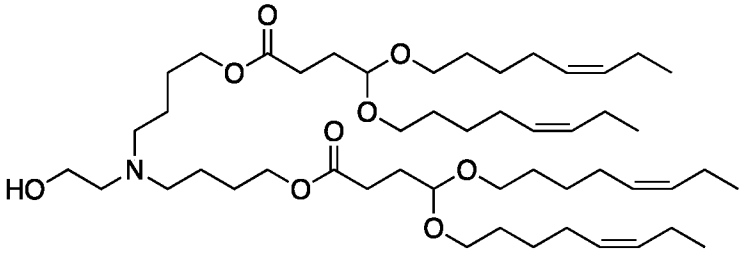
[1017] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 146 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 – 5.21 (m, 8H), 4.49 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 6.8 Hz, 4H), 3.74 (br s, 2H), 3.57 (dt, *J* = 9.3, 6.5 Hz, 4H), 3.41 (dt, *J* = 9.4, 6.6 Hz, 4H), 2.84 (br s, 2H), 2.76 (br s, 4H), 2.37 (t, *J* = 7.7 Hz, 4H), 2.08 – 1.99 (m, 16H), 1.92 (ddd, *J* = 8.3, 7.2, 5.6 Hz, 4H), 1.63 – 1.54 (m, 16H), 1.44 – 1.34 (m, 16H), 0.95 (t, *J* = 7.5 Hz, 12H). UPLC-MS (Method A): Rt 3.69 min, m/z calculated [M+H]: 934.76, found 934.88.



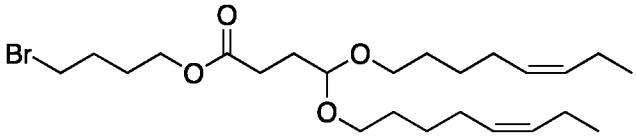
Example 8-4: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1018] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Obtained 129 mg, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 – 5.27 (m, 8H), 4.49 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 6.8 Hz, 4H), 3.80 (t, *J* = 5.2

Hz, 2H), 3.57 (dt, *J* = 9.3, 6.5 Hz, 4H), 3.40 (dt, *J* = 9.3, 6.6 Hz, 4H), 2.78 (br s, 2H), 2.57 (br s, 4H), 2.37 (t, *J* = 7.7 Hz, 2H), 2.07 – 1.99 (m, 16H), 1.92 (td, *J* = 7.6, 5.6 Hz, 4H), 1.77 (br s, 2H), 1.64 – 1.53 (m, 16H), 1.44 – 1.31 (m, 16H), 0.95 (t, *J* = 7.5 Hz, 12H). UPLC-MS (Method A): Rt 3.71 min, m/z calculated [M+H]: 948.78, found 948.98.



Example 8-5: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

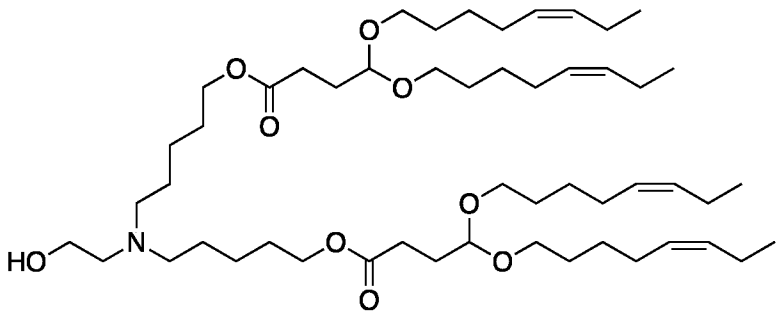


Step 1: 4-bromobutyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

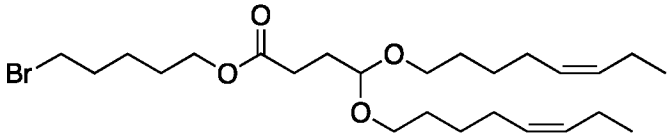
[1019] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol. Obtained 140 mg, 40% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.35 – 1.45 (m, 4H), 1.53 (s, 1H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.74 – 1.84 (m, 2H), 1.88 – 1.95 (m, 4H), 1.97 – 2.09 (m, 8H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.51 – 3.62 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.25 – 5.42 (m, 4H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (Example 8-5)

[1020] Prepared according to General Procedure G, substituting 4-bromobutyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 45 mg, 46% yield. UPLC-MS (Method B): Rt 2.10 min, m/z calculated [M+H]: 850.7, found 850.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, *J* = 7.5 Hz, 12H), 1.29 – 1.40 (m, 11H), 1.41 – 1.52 (m, 11H), 1.56 (d, *J* = 7.6 Hz, 4H), 1.71 – 1.81 (m, 4H), 1.90 – 2.05 (m, 19H), 2.29 (t, *J* = 7.3 Hz, 4H), 2.40 (s, 4H), 3.30 – 3.39 (m, 4H), 3.44 – 3.54 (m, 4H), 4.00 (t, *J* = 6.3 Hz, 4H), 4.44 (t, *J* = 5.5 Hz, 2H), 5.24 – 5.38 (m, 8H).



Example 8-6: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

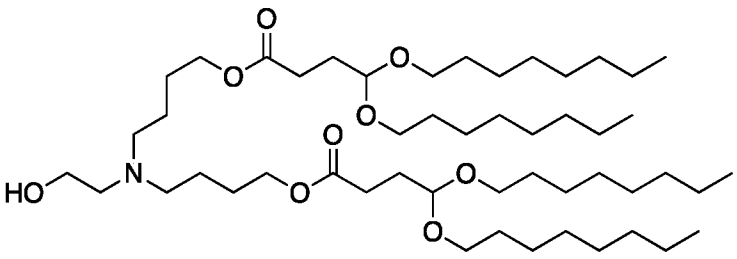


Step 1: 5-bromopentyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

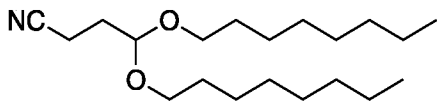
[1021] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol. Obtained 160 mg, 37%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.33 – 1.46 (m, 7H), 1.45 – 1.54 (m, 2H), 1.57 – 1.70 (m, 2H), 1.82 – 2.01 (m, 4H), 2.03 (q, *J* = 7.8 Hz, 8H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.51 – 3.62 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H), 5.29 – 5.43 (m, 5H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (Example 8-6)

[1022] Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 45 mg, 52% yield. UPLC-MS (Method B): Rt 2.15 min, m/z calculated [M+H]: 878.7, found 879.0.

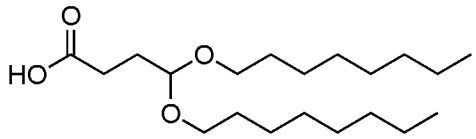


Example 8-7: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(octyloxy)butanoate)



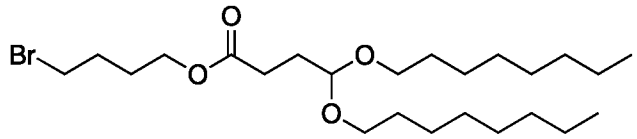
Step 1: 4,4-bis(octyloxy)butanenitrile

[1023] Prepared according to General Procedure A, substituting 1-octanol for cis-5-octen-1-ol. Isolated 1.45 g, 39%. ^{1}H NMR (400 MHz, CDCl3) δ 0.87 (d, *J* = 6.9 Hz, 6H), 1.21-1.30 (m, 20H), 1.53-1.58 (m, 4H), 1.90 (q, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.39-3.44 (m, 2H), 3.56-3.61 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H).



Step 2: 4,4-bis(octyloxy)butanoic acid

[1024] Prepared according to General Procedure B, substituting 4,4-bis(octyloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 1.8 g, 84%. ^{1}H NMR (400 MHz, DMSO-d6) δ 0.85 (d, *J* = 6.8 Hz, 6H), 1.21-1.30 (m, 20H), 1.43-1.48 (m, 4H), 1.69 (q, *J* = 6.8 Hz, 2H), 2.21 (t, *J* = 7.2 Hz, 2H), 3.35-3.39 (m, 2H), 3.44-3.50 (m, 2H), 4.44 (t, *J* = 5.5 Hz, 1H), 12.06 (bs, 1H).

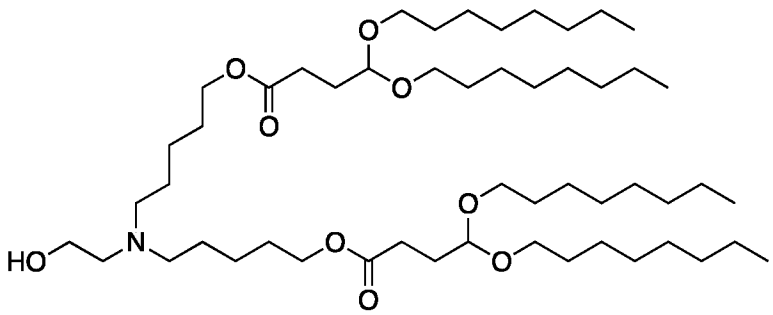


Step 3: 4-bromobutyl 4,4-bis(octyloxy)butanoate

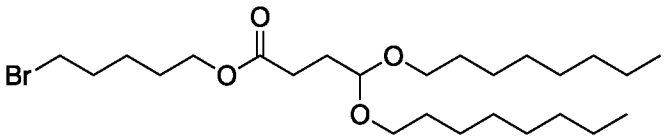
[1025] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 130 mg, 46% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 6H), 1.23 – 1.36 (m, 20H), 1.48 – 1.59 (m, 4H), 1.72 – 1.84 (m, 2H), 1.87 – 1.99 (m, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.50 – 3.61 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 4: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(octyloxy)butanoate) (Example 8-7)

[1026] Prepared according to General Procedure G, substituting 4-bromobutyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 24 mg, 35% yield. UPLC-MS (Method B): Rt 2.30 min, m/z calculated [M+H]: 858.7, found 859.0.



Example 8-8: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(octyloxy)butanoate)

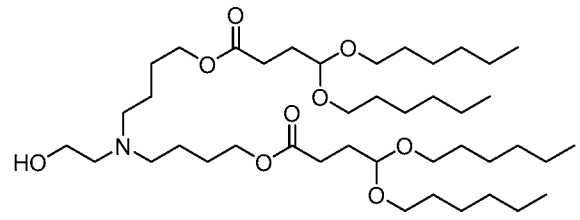


Step 1: 5-bromopentyl 4,4-bis(octyloxy)butanoate

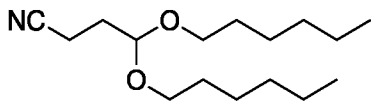
[1027] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 127 mg, 44% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.4 Hz, 6H), 1.23 – 1.36 (m, 20H), 1.43 – 1.60 (m, 6H), 1.59 – 1.70 (m, 2H), 1.82-1.97 (m, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.49 – 3.61 (m, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(octyloxy)butanoate) (Example 8-8)

[1028] Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 32 mg, 44% yield. UPLC-MS (Method B): Rt 2.37 min, m/z calculated [M+H]: 886.8, found 887.0.

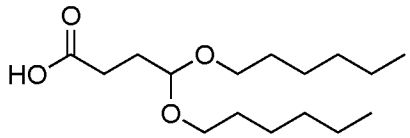


Example 8-9: 4-((4-((4,4-bis(hexyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)butyl 4-(heptyloxy)-4-(hexyloxy)butanoate



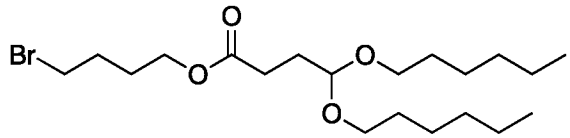
Step 1: 4,4-bis(hexyloxy)butanenitrile

[1029] Prepared according to General Procedure A, substituting 1-hexanol for cis-5-octen-1-ol. Isolated 1.3 g, 31%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.6 Hz, 6H), 1.25 – 1.40 (m, 13H), 1.53 (d, *J* = 7.2 Hz, 2H), 1.55 – 1.64 (m, 2H), 1.88 – 1.98 (m, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.37 – 3.47 (m, 2H), 3.54 – 3.64 (m, 2H), 4.54 (t, *J* = 5.3 Hz, 1H).



Step 2: 4,4-bis(hexyloxy)butanoic acid

[1030] Prepared according to General Procedure B, substituting 4,4-bis(hexyloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 1.29 g, 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 – 0.90 (m, 6H), 1.17 – 1.37 (m, 12H), 1.36 – 1.53 (m, 4H), 1.68 – 1.78 (m, 2H), 2.22 (t, *J* = 7.4 Hz, 2H), 3.29 – 3.40 (m, 2H), 3.43 – 3.54 (m, 2H), 4.45 (t, *J* = 5.6 Hz, 1H), 12.03 (s, 1H).

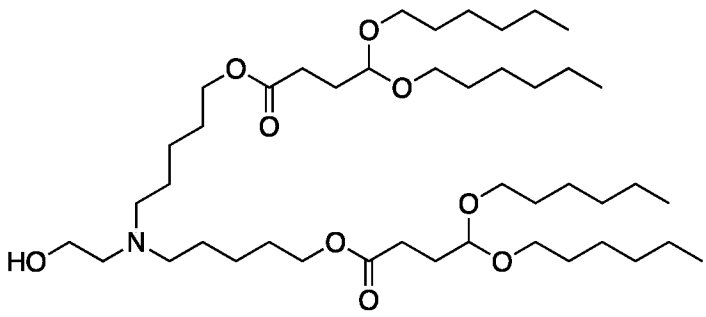


Step 3: 4-bromobutyl 4,4-bis(hexyloxy)butanoate

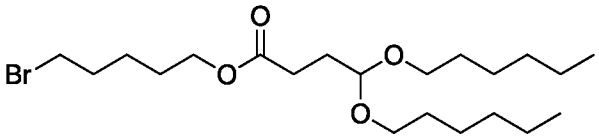
[1031] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 25 mg, 34% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.20 – 1.41 (m, 13H), 1.52 (d, *J* = 6.9 Hz, 2H), 1.55 – 1.62 (m, 1H), 1.72 – 1.84 (m, 2H), 1.87 – 1.99 (m, 4H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.47 (m, 4H), 3.51 – 3.61 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 4: 4-((4-((4,4-bis(hexyloxy)butanoyl)oxy)butyl)(2-hydroxyethyl)amino)butyl 4-(heptyloxy)-4-(hexyloxy)butanoate (Example 8-9)

[1032] Prepared according to General Procedure G, substituting 4-bromobutyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 25 mg, 33% yield. UPLC-MS (Method B): Rt 1.98 min, m/z calculated [M+H]: 746.61, found 746.9.



Example 8-10: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(hexyloxy)butanoate)

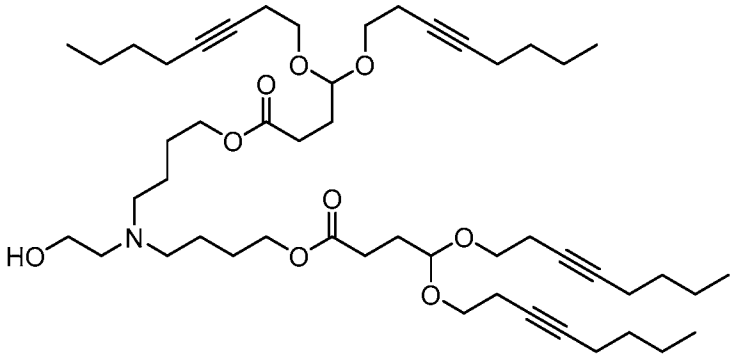


Step 1: 5-bromopentyl 4,4-bis(hexyloxy)butanoate

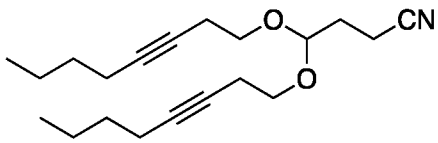
[1033] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(hexyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 175 mg, 39% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.18 – 1.41 (m, 14H), 1.44 – 1.55 (m, 2H), 1.54 – 1.61 (m, 2H), 1.61 – 1.70 (m, 2H), 1.82 – 1.97 (m, 4H), 2.38 (t, *J* = 7.5 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.51 – 3.62 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(hexyloxy)butanoate) (Example 8-10)

[1034] Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(hexyloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 17 mg, 32% yield. UPLC-MS (Method C): Rt 5.03 min, m/z calculated [M+H]: 774.6, found 774.8. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 6.7 Hz, 12H), 1.19 – 1.37 (m, 32H), 1.40 – 1.52 (m, 9H), 1.60 (d, *J* = 6.9 Hz, 6H), 1.71 – 1.81 (m, 4H), 2.29 (t, *J* = 7.3 Hz, 4H), 2.91 – 3.23 (m, 4H), 3.32 – 3.38 (m, 4H), 3.43 – 3.54 (m, 4H), 3.64 – 3.74 (m, 2H), 4.00 (t, *J* = 6.5 Hz, 4H), 4.45 (t, *J* = 5.5 Hz, 2H).

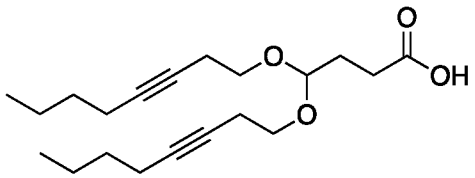


Example 8-11: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)



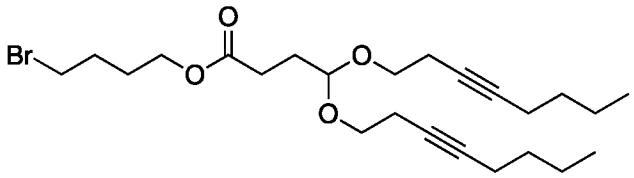
Step 1: 4,4-bis(oct-3-yn-1-yloxy)butanenitrile

[1035] Prepared according to General Procedure A, substituting oct-3-yn-1-ol for cis-5-octen-1-ol, yield 950 mg (39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.0 Hz, 6H), 1.28 – 1.46 (m, 10H), 1.84 (q, J = 7.3 Hz, 2H), 2.07 – 2.17 (m, 4H), 2.33 – 2.42 (m, 4H), 3.44 – 3.55 (m, 2H), 3.55 – 3.66 (m, 2H), 4.62 (t, J = 5.6 Hz, 1H).



Step 2: 4,4-bis(oct-3-yn-1-yloxy)butanoic acid

[1036] Prepared according to General Procedure B, substituting 4,4-bis(oct-3-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile, yield 950 mg (94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.1 Hz, 6H), 1.27 – 1.46 (m, 8H), 1.74 (q, J = 7.2 Hz, 2H), 2.07 – 2.17 (m, 4H), 2.25 (t, J = 7.5 Hz, 2H), 2.30 – 2.40 (m, 4H), 3.42 – 3.51 (m, 2H), 3.52 – 3.64 (m, 2H), 4.56 (t, J = 5.7 Hz, 1H), 12.05 (s, 1H).

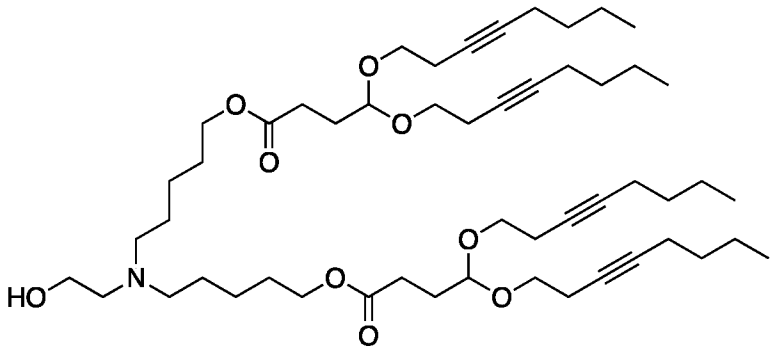


Step 3: 4-bromobutyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

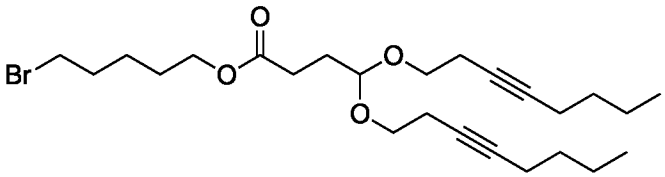
[1037] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 290 mg, 41% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.32 – 1.50 (m, 8H), 1.79 (q, *J* = 6.8 Hz, 2H), 1.87 – 2.00 (m, 4H), 2.08 – 2.19 (m, 4H), 2.33 – 2.46 (m, 6H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.71 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

Step 4: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate) (Example 8-11)

[1038] Prepared according to General Procedure G, substituting 4-bromobutyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 15 mg, 27% yield. UPLC-MS (Method B): Rt 1.90 min, m/z calculated [M+H]: 842.6, found 842.9.



Example 8-12: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)

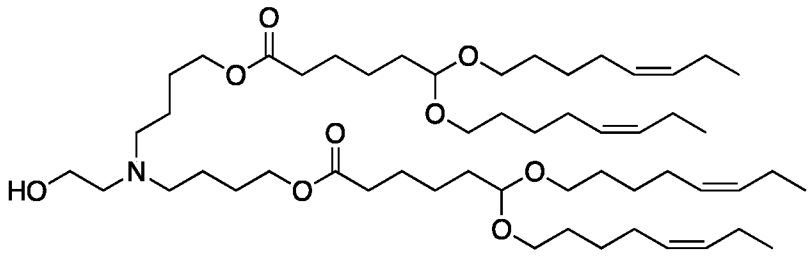


Step 1: 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

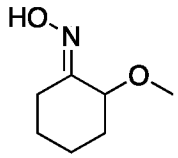
[1039] Prepared according to General Procedure C, substituting 5-bromopentan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 225 mg, 39% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.32 – 1.55 (m, 10H), 1.59 – 1.71 (m, 2H), 1.82 – 1.99 (m, 4H), 2.04 – 2.23 (m, 4H), 2.35 – 2.46 (m, 6H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.72 (m, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 4.60 (t, *J* = 5.7 Hz, 1H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(pentane-5,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate) (Example 8-12)

[1040] Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 23 mg, 33% yield. UPLC-MS (Method B): Rt 2.02 min, m/z calculated [M+H]: 870.6, found 870.8.

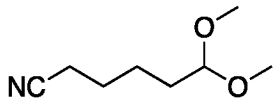


Example 8-13: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate)



Step 1: 2-methoxycyclohexan-1-one oxime

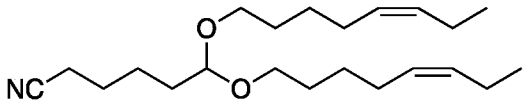
[1041] To a stirred solution of 2-methoxycyclohexan-1-one (5 g, 39.0 mmol) in MeOH-H_2O (150 ml, 1:2) was added sodium acetate (6.41 g, 78.1 mmol) followed by the addition of hydroxylamine hydrochloride (5.43 g, 78.1 mmol). The resulting mixture was heated at 70°C in a sealed tube for 16 h. After that time, MeOH was evaporated and the mixture was diluted with water, extracted with ethyl acetate (3 x 50 mL), washed with brine and dried over sodium sulfate and concentrated under reduced pressure. The crude thus obtained was purified by flash column chromatography eluting with 3% ethyl acetate in hexane to afford 2-methoxycyclohexan-1-one oxime (4.1 g, 88%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17-1.32 (m, 1H), 1.40-1.56 (m, 2H), 1.59-1.82 (m, 3H), 1.92-1.99 (m, 1H), 2.93-3.01 (m, 1H), 3.11 (s, 3H), 3.63 (s, 1H), 10.61 (s, 1H).



Step 2: 6,6-dimethoxyhexanenitrile

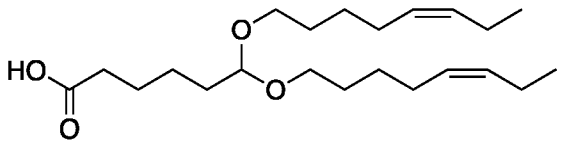
[1042] To a stirred solution of 2-methoxycyclohexan-1-one oxime (2.0 g, 14.0 mmol) in CCl_4 (20 ml) was added thionyl chloride (1.2 ml, 16.8 mmol) dropwise at 0°C and stirred for 10 min. After

that time, dry MeOH (20 ml) was added to the reaction mixture at 5-10° C. After addition was complete, the reaction mixture was allowed to reach room temperature and was left for 2 h. The mixture was then diluted with ethyl acetate and washed with brine, dried over sodium sulfate and concentrated to afford 6,6-dimethoxyhexanenitrile (1.6 g, 81%) as light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.44 – 1.56 (m, 2H), 1.57 – 1.75 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 3.31 (s, 6H), 4.34 (t, *J* = 5.5 Hz, 1H).



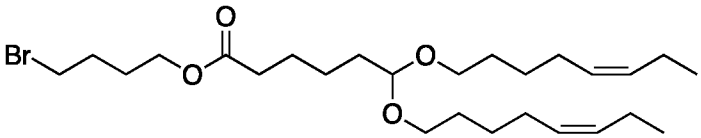
Step 3: 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanenitrile

[1043] Prepared according to General Procedure A, substituting 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Obtained 400 mg, 30% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.34 – 1.46 (m, 4H), 1.44 – 1.74 (m, 11H), 1.96 – 2.10 (m, 8H), 2.33 (t, *J* = 7.1 Hz, 2H), 3.34 – 3.45 (m, 2H), 3.51 – 3.61 (m, 2H), 5.25 – 5.42 (m, 4H).



Step 4: 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoic acid

[1044] Prepared according to General Procedure B substituting 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Obtained 400 mg, 95% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, *J* = 7.5 Hz, 6H), 1.20 – 1.41 (m, 6H), 1.42 – 1.55 (m, 8H), 1.92 – 2.06 (m, 8H), 2.18 (t, *J* = 7.3 Hz, 2H), 3.31 – 3.40 (m, 2H), 3.43 – 3.53 (m, 2H), 4.41 (t, *J* = 5.6 Hz, 1H), 5.23 – 5.42 (m, 4H), 11.96 (s, 1H).



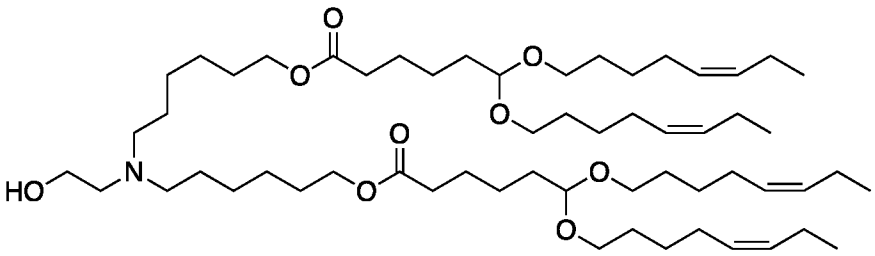
Step 5: 4-bromobutyl 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate

[1045] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 60 mg, 37% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.06 (s, 3H), 0.76 – 0.91 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 6H), 1.30 – 1.46 (m, 4H), 1.50 – 1.70 (m, 5H), 1.72

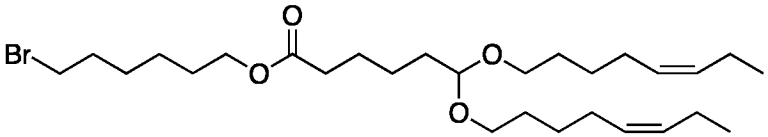
– 1.84 (m, 2H), 1.87 – 1.99 (m, 3H), 1.96 – 2.09 (m, 7H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.34 – 3.46 (m, 4H), 3.50 – 3.60 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.44 (t, *J* = 5.7 Hz, 1H), 5.24 – 5.45 (m, 4H).

Step 6: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate) (Example 8-13)

[1046] Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 16 mg, 32% yield. UPLC-MS (Method C): Rt 5.41 min, m/z calculated [M+H]: 906.7, found 906.6.



Example 8-14: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate)

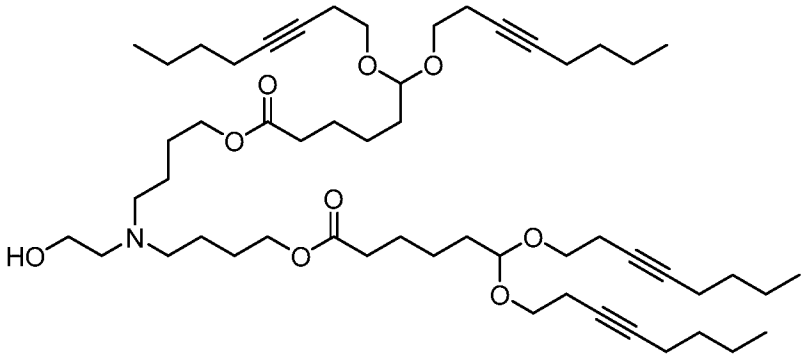


Step 1: 6-bromohexyl 6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate

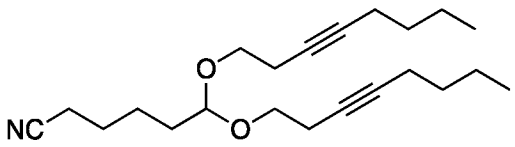
[1047] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 90 mg, 31% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.31 – 1.51 (m, 12H), 1.56 – 1.69 (m, 8H), 1.82 – 1.90 (m, 2H), 1.96 – 2.10 (m, 8H), 2.29 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 4H), 3.50 – 3.60 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.44 (t, *J* = 5.6 Hz, 1H), 5.24 – 5.44 (m, 4H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((Z)-oct-5-en-1-yl)oxy)hexanoate) (Example 8-14)

Prepared according to General Procedure G, substituting 5-bromopentyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 40 mg, 42% yield. UPLC-MS (Method B): Rt 2.29 min, m/z calculated [M+H]: 962.8, found 962.6.

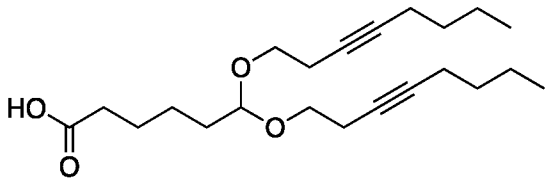


Example 8-15: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(oct-3-yn-1-yloxy)hexanoate)



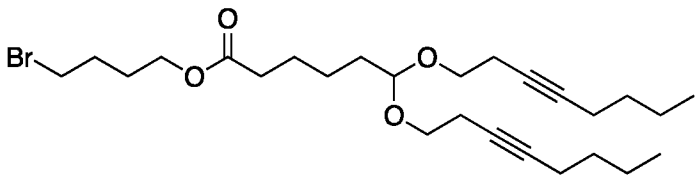
Step 1: 6,6-bis(oct-3-yn-1-yloxy)hexanenitrile

[1048] Prepared according to General Procedure A, substituting oct-3-yn-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Obtained 600 mg, 34% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.33 – 1.49 (m, 8H), 1.42 – 1.55 (m, 2H), 1.58 – 1.76 (m, 4H), 2.09 – 2.18 (m, 4H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.37 – 2.46 (m, 4H), 3.48 – 3.59 (m, 2H), 3.60 – 3.71 (m, 2H), 4.56 (t, *J* = 5.5 Hz, 1H).



Step 2: 6,6-bis(oct-3-yn-1-yloxy)hexanoic acid

[1049] Prepared according to General Procedure B substituting 6,6-bis(oct-3-yn-1-yloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Obtained 550 mg, 87% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, *J* = 7.0 Hz, 6H), 1.23 – 1.45 (m, 10H), 1.44 – 1.56 (m, 4H), 2.09 – 2.14 (m, 4H), 2.19 (t, *J* = 7.3 Hz, 2H), 2.29 – 2.39 (m, 4H), 3.41 – 3.49 (m, 2H), 3.51 – 3.61 (m, 2H), 4.52 (t, *J* = 5.7 Hz, 1H), 11.97 (s, 1H).

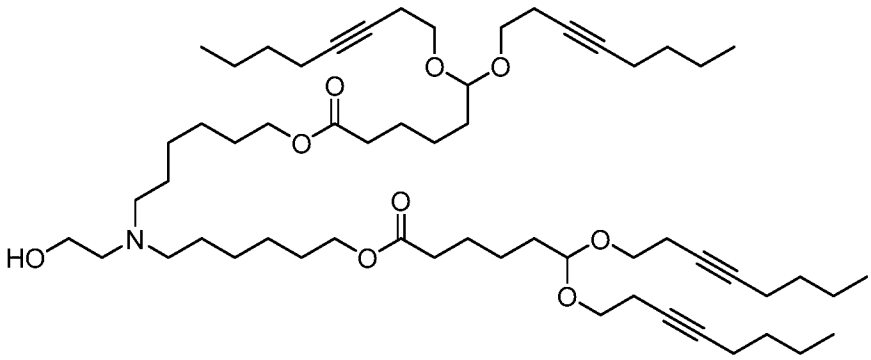


Step 3: 4-bromobutyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate

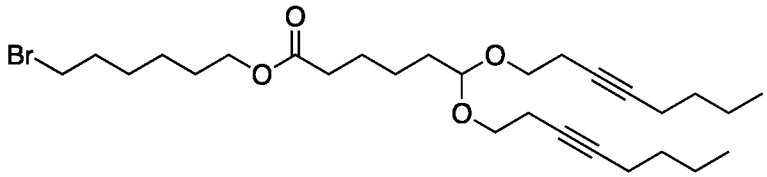
[1050] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 6,6-bis(oct-3-yn-1-yloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 210 mg, 51% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.0 Hz, 6H), 1.31 – 1.50 (m, 10H), 1.58 – 1.68 (m, 4H), 1.78 (t, *J* = 7.3 Hz, 2H), 1.93 (t, *J* = 7.5 Hz, 2H), 2.13 (d, *J* = 7.8 Hz, 4H), 2.30 (t, *J* = 7.7 Hz, 2H), 2.36 – 2.45 (m, 4H), 3.43 (t, *J* = 6.4 Hz, 2H), 3.53 (q, *J* = 7.3 Hz, 2H), 3.65 (q, *J* = 7.8 Hz, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.55 (t, *J* = 5.8 Hz, 1H).

Step 4: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(oct-3-yn-1-yloxy)hexanoate) (Example 8-15)

[1051] Prepared according to General Procedure G, substituting 4-bromobutyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 33 mg, 45% yield. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 898.7, found 898.4.



Example 8-16: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(oct-3-yn-1-yloxy)hexanoate)



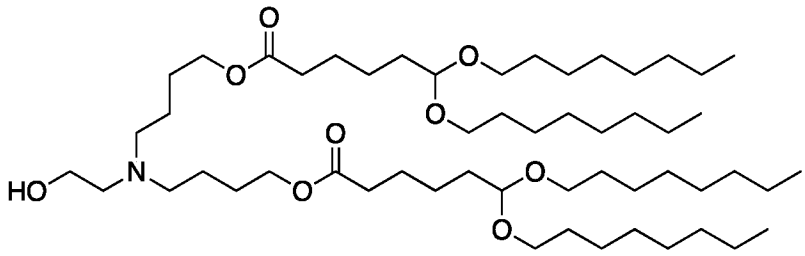
Step 1: 6-bromohexyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate

[1052] Prepared according to General Procedure C, substituting 6,6-bis(oct-3-yn-1-yloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Obtained 150 mg, 41% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.30 – 1.53 (m, 14H), 1.57 – 1.70 (m, 6H), 1.80 – 1.92 (m, 2H), 2.09 – 2.18 (m, 4H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.36 – 2.46 (m,

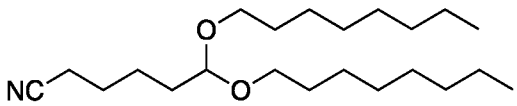
4H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.48 – 3.58 (m, 2H), 3.59 – 3.71 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.55 (t, *J* = 5.8 Hz, 1H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(oct-3-yn-1-yloxy)hexanoate) (Example 8-16)

[1053] Prepared according to General Procedure G, substituting 4-bromobutyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 29 mg, 37% yield. UPLC-MS (Method C): Rt 5.24 min, m/z calculated [M+H]: 954.7, found 954.5.

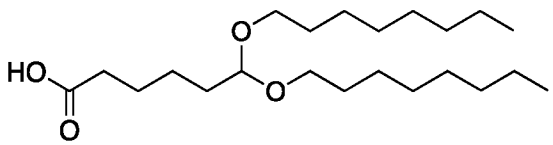


Example 8-17: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(octyloxy)hexanoate)



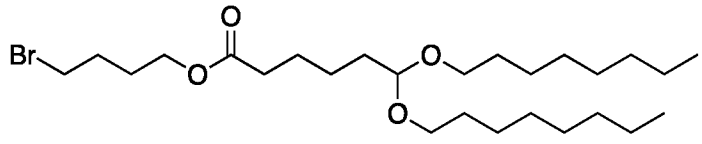
Step 1: 6,6-bis(octyloxy)hexanenitrile

[1054] Prepared according to General Procedure A, substituting 1-octanol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Obtained 800 mg, 39% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.91 (m, 6H), 1.17 – 1.41 (m, 21H), 1.44 – 1.75 (m, 9H), 2.33 (t, *J* = 7.1 Hz, 2H), 3.34 – 3.44 (m, 2H), 3.50 – 3.61 (m, 2H), 4.44 (t, *J* = 5.5 Hz, 1H).



Step 2: 6,6-bis(octyloxy)hexanoic acid

[1055] Prepared according to General Procedure B substituting 6,6-bis(octyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Obtained 780 mg, 88% yield. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 0.85 (t, *J* = 6.6 Hz, 6H), 1.15 – 1.36 (m, 22H), 1.39 – 1.57 (m, 8H), 2.18 (t, *J* = 7.4 Hz, 2H), 3.27 – 3.41 (m, 2H), 3.41 – 3.52 (m, 2H), 4.40 (t, *J* = 5.6 Hz, 1H), 11.96 (s, 1H).

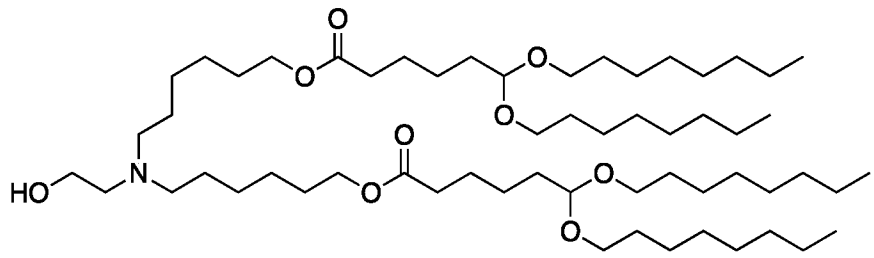


Step 3: 4-bromobutyl 6,6-bis(octyloxy)hexanoate

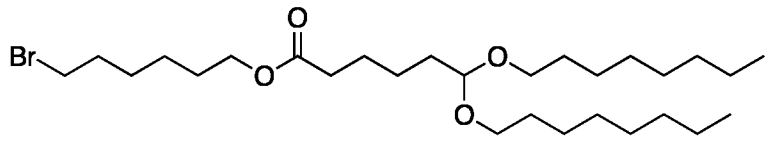
[1056] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 6,6-bis(octyloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 210 mg, 38% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.6 Hz, 6H), 1.16 – 1.45 (m, 22H), 1.46 – 1.71 (m, 8H), 1.72 – 1.84 (m, 2H), 1.86 – 1.99 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.33 – 3.46 (m, 4H), 3.49 – 3.59 (m, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 4.44 (t, *J* = 5.7 Hz, 1H).

Step 4: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(octyloxy)hexanoate) (Example 8-17)

[1057] Prepared according to General Procedure G, substituting 4-bromobutyl 6,6-bis(octyloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 29 mg, 37% yield. UPLC-MS (Method B): Rt 2.38 min, m/z calculated [M+H]: 914.8, found 915.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.70 – 0.75 (m, 4H), 0.85 (t, *J* = 6.5 Hz, 12H), 0.96 – 1.37 (m, 43H), 1.39 – 1.72 (m, 24H), 2.27 (t, *J* = 7.5 Hz, 4H), 3.02 – 3.25 (m, 4H), 3.33 – 3.41 (m, 4H), 3.41 – 3.52 (m, 4H), 3.58 – 3.95 (m, 2H), 4.01 (s, 4H), 4.40 (t, *J* = 5.5 Hz, 2H).



Example 8-18: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(octyloxy)hexanoate)



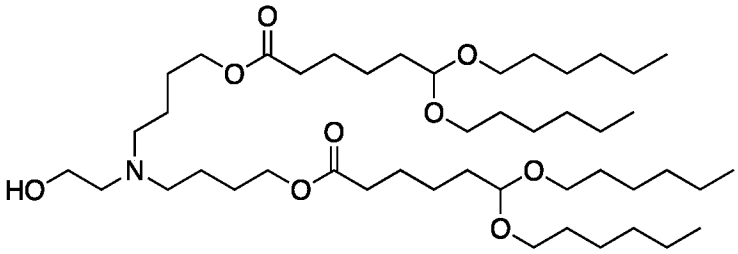
Step 1: 6-bromohexyl 6,6-bis(octyloxy)hexanoate

[1058] Prepared according to General Procedure C, substituting 6,6-bis(octyloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid . Obtained 250 mg, 58% yield. ^{1}H NMR (400

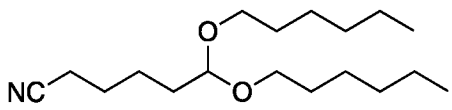
MHz, Chloroform-*d*) δ 0.87 (t, *J* = 6.5 Hz, 6H), 1.17 – 1.43 (m, 29H), 1.40 – 1.51 (m, 2H), 1.58 – 1.69 (m, 6H), 1.80 – 1.92 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 3H), 3.49 – 3.59 (m, 2H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.44 (t, *J* = 5.7 Hz, 1H).

Step 2: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(octyloxy)hexanoate) (Example 8-18)

[1059] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(octyloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 39 mg, 41% yield. UPLC-MS (Method B): Rt 2.43 min, m/z calculated [M+H]: 970.9, found 971.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, *J* = 6.6 Hz, 12H), 1.14 – 1.39 (m, 57H), 1.38 – 1.69 (m, 20H), 2.27 (t, *J* = 7.4 Hz, 4H), 2.96 – 3.21 (m, 6H), 3.31 – 3.42 (m, 4H), 3.41 – 3.52 (m, 4H), 3.70 (s, 2H), 4.00 (t, *J* = 6.6 Hz, 4H), 4.40 (t, *J* = 5.7 Hz, 2H).

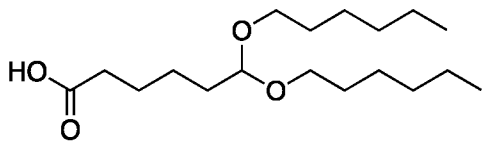


Example 8-19: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(hexyloxy)hexanoate)



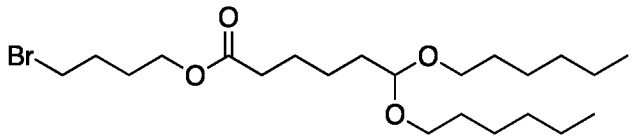
Step 1: 6,6-bis(hexyloxy)hexanenitrile

[1060] Prepared according to General Procedure A, substituting 1-hexanol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Obtained 235 mg, 19% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.6 Hz, 6H), 1.24 – 1.41 (m, 12H), 1.43 – 1.76 (m, 10H), 2.34 (t, *J* = 7.0 Hz, 2H), 3.34 – 3.45 (m, 2H), 3.50 – 3.60 (m, 2H), 4.44 (t, *J* = 5.5 Hz, 1H).



Step 2: 6,6-bis(hexyloxy)hexanoic acid

[1061] Prepared according to General Procedure B substituting 6,6-bis(hexyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Obtained 500 mg, 79% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 6.6 Hz, 6H), 1.17 – 1.36 (m, 18H), 1.41 – 1.55 (m, 7H), 2.18 (t, J = 7.2 Hz, 2H), 3.32 – 3.42 (m, 2H), 3.42 – 3.53 (m, 2H), 4.41 (t, J = 5.5 Hz, 1H), 11.96 (s, 1H).

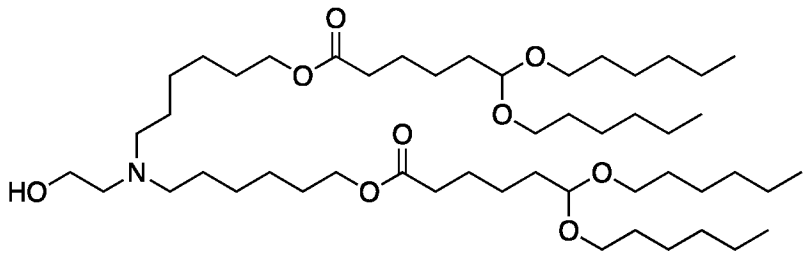


Step 3: 4-bromobutyl 6,6-bis(hexyloxy)hexanoate

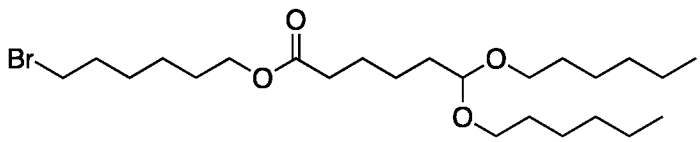
[1062] Prepared according to General Procedure C, substituting 4-bromobutan-1-ol for 6-bromohexan-1-ol and 6,6-bis(hexyloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Obtained 140 mg, 33% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, J = 6.6 Hz, 6H), 1.19 – 1.45 (m, 16H), 1.55 – 1.70 (m, 6H), 1.78 (t, J = 7.4 Hz, 2H), 1.93 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 3.33 – 3.47 (m, 4H), 3.49 – 3.60 (m, 2H), 4.09 (t, J = 6.4 Hz, 2H), 4.44 (t, J = 5.7 Hz, 1H).

Step 4: ((2-hydroxyethyl)azanediyl)bis(butane-4,1-diyl) bis(6,6-bis(hexyloxy)hexanoate) (Example 8-19)

[1063] Prepared according to General Procedure G, substituting 4-bromobutyl 6,6-bis(hexyloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 16 mg, 20% yield. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 802.7, found 802.9.



Example 8-20: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(hexyloxy)hexanoate)

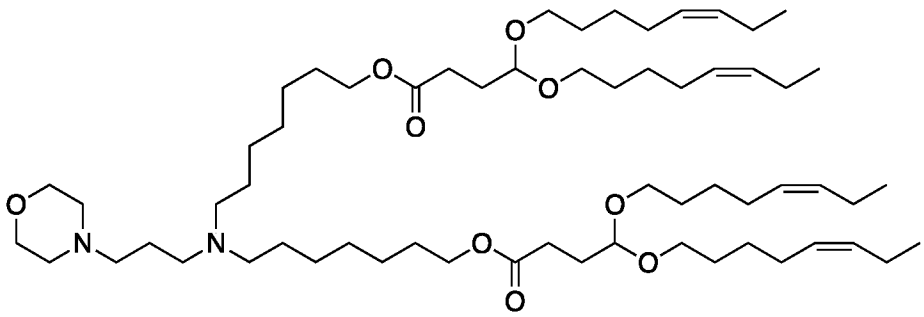


Step 1: 6-bromohexyl 6,6-bis(hexyloxy)hexanoate

[1064] Prepared according to General Procedure C, substituting 6,6-bis(hexyloxy)hexanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Obtained 180 mg, 47% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.92 (m, 6H), 1.21 – 1.41 (m, 20H), 1.41 – 1.51 (m, 2H), 1.56 – 1.70 (m, 6H), 1.86 (t, *J* = 7.4 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 3.33 – 3.44 (m, 4H), 3.49 – 3.59 (m, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 5.7 Hz, 1H).

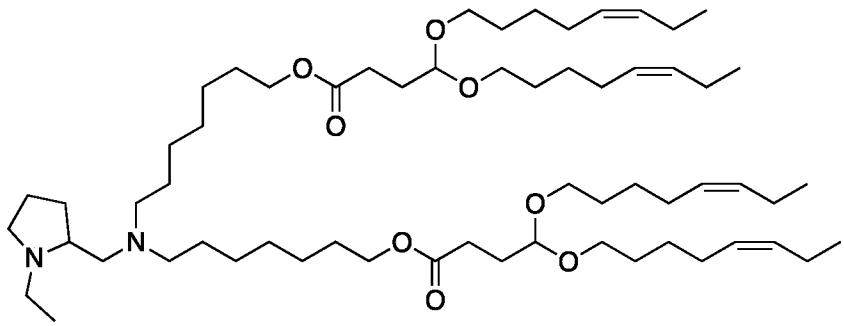
Step 2: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(hexyloxy)hexanoate) (Example 8-20)

[1065] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(hexyloxy)hexanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate. Obtained 20 mg, 29% yield. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 858.7, found 858.8.



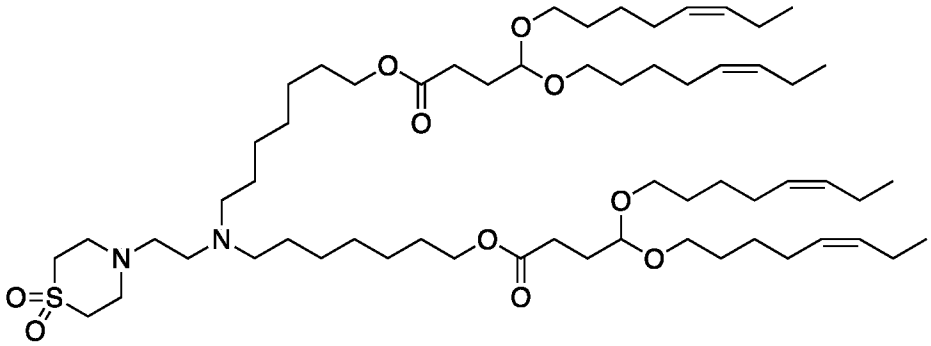
Example 8-21: ((3-morpholinopropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1066] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3-morpholinopropan-1-amine for 2-aminoethan-1-ol. Isolated 51 mg, 73% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1017.8, found 1018.9.



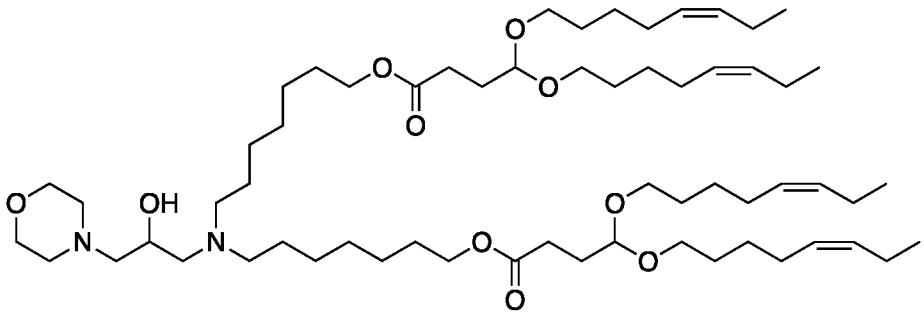
Example 8-22: (((1-ethylpyrrolidin-2-yl)methyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1067] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and (1-ethylpyrrolidin-2-yl)methanamine for 2-aminoethan-1-ol. Isolated 29 mg, 38% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1001.8, found 1003.0



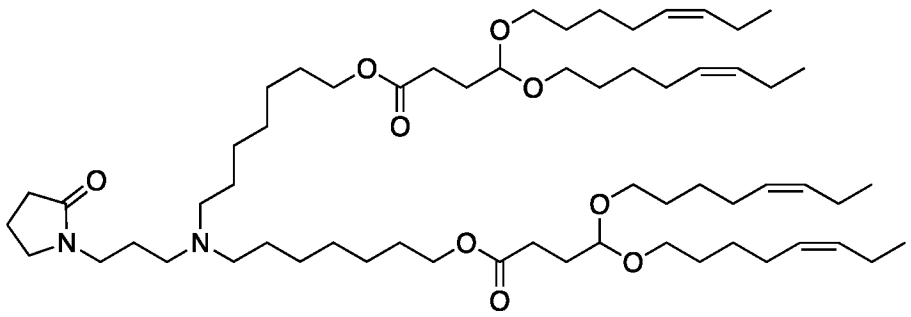
Example 8-23: ((2-(1,1-dioxidothiomorpholino)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1068] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 4-(2-aminoethyl)thiomorpholine 1,1-dioxide for 2-aminoethan-1-ol. Isolated 45 mg, 76% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1051.8, found 1052.8.



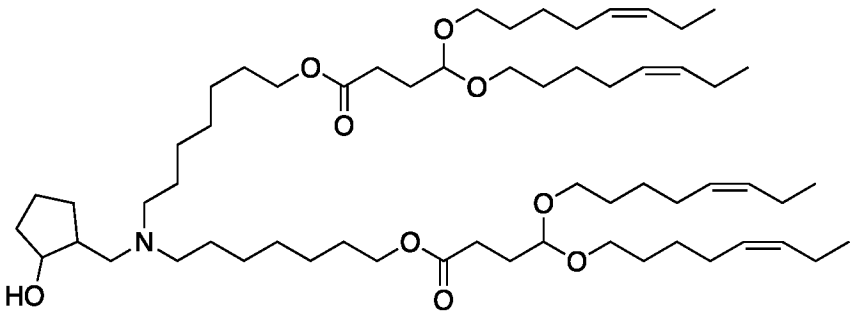
Example 8-24: ((2-hydroxy-3-morpholinopropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1069] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 1-amino-3-morpholinopropan-2-ol for 2-aminoethan-1-ol. Isolated 58 mg, 76% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1033.8, found 1034.9.



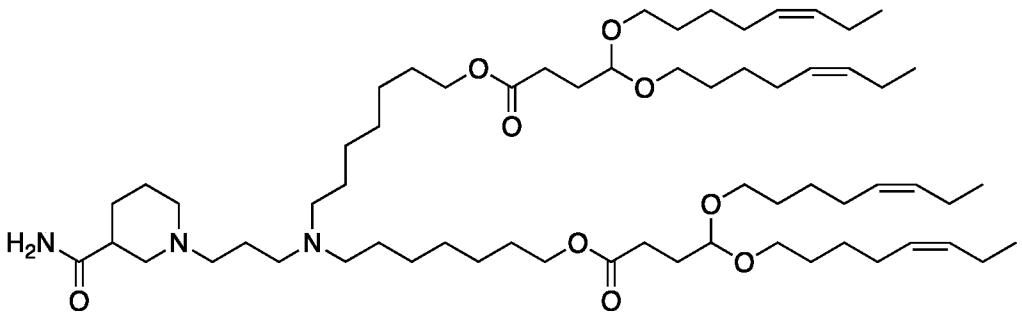
Example 8-25: ((3-(2-oxopyrrolidin-1-yl)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1070] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 1-(3-aminopropyl)pyrrolidin-2-one for 2-aminoethan-1-ol. Isolated 29 mg, 41% yield. UPLC-MS (Method B): Rt 2.32 min, m/z calculated [M+H]: 1015.8, found 1016.9.



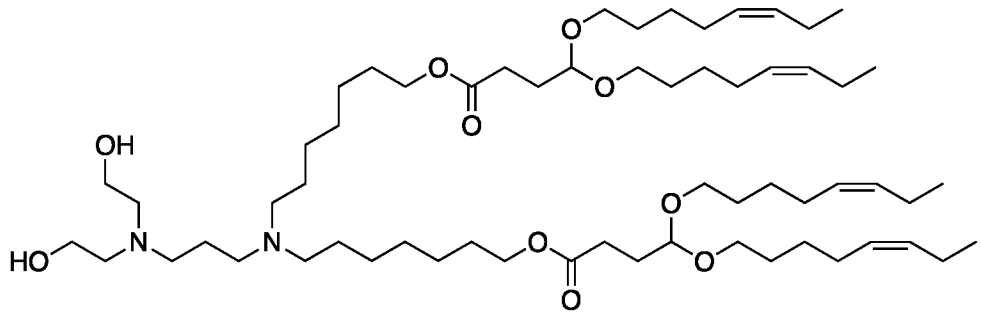
Example 8-26: (((2-hydroxycyclopentyl)methyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1071] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2-(aminomethyl)cyclopentan-1-ol for 2-aminoethan-1-ol. Isolated 23 mg, 54% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 998.8, found 999.9.



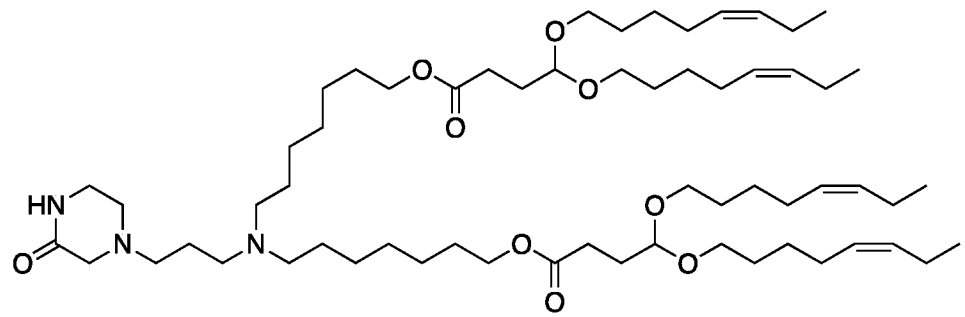
Example 8-28: ((3-(3-carbamoylpiperidin-1-yl)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1072] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and piperidine-3-carboxamide for 2-aminoethan-1-ol. Isolated 25 mg, 52% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1058.8, found 1059.9.



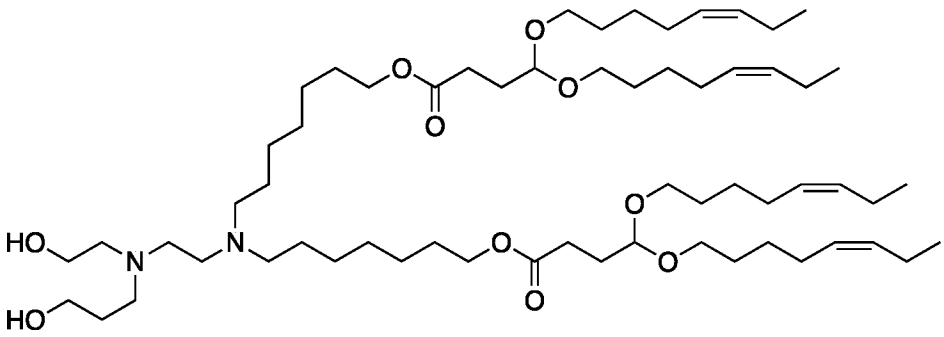
Example 8-30: ((3-(bis(2-hydroxyethyl)amino)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1073] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2,2'-((3-aminopropyl)azanediyl)bis(ethan-1-ol) for 2-aminoethan-1-ol. Isolated 61 mg, 40% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1035.8, found 1036.9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.6 Hz, 12H), 1.31 – 1.47 (m, 23H), 1.50 – 1.65 (m, 15H), 1.91 (q, *J* = 7.4 Hz, 4H), 1.96 – 2.09 (m, 18H), 2.37 (t, *J* = 7.6 Hz, 4H), 2.64 – 2.69 (m, 6H), 2.93 – 3.11 (m, 4H), 3.15 – 3.27 (m, 2H), 3.35 – 3.45 (m, 4H), 3.51 – 3.62 (m, 4H), 3.68 (t, *J* = 5.0 Hz, 4H), 4.04 (t, *J* = 6.7 Hz, 4H), 4.48 (t, *J* = 5.5 Hz, 2H), 5.24 – 5.42 (m, 8H).



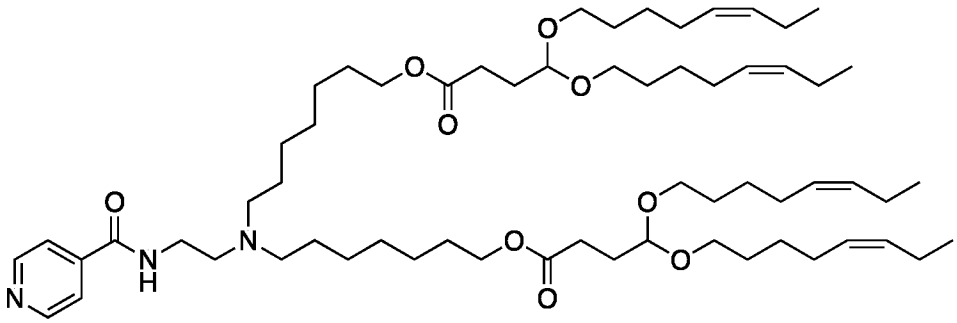
Example 8-31: ((3-(3-oxopiperazin-1-yl)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1074] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 4-(3-aminopropyl)piperazin-2-one for 2-aminoethan-1-ol. Isolated 38 mg, 35% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1030.8, found 1031.9.



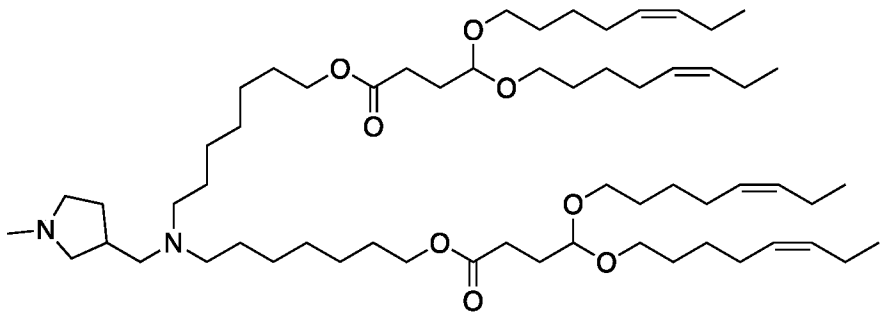
Example 8-32: ((2-((2-hydroxyethyl)(3-hydroxypropyl)amino)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1075] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3-((2-aminoethyl)(2-hydroxyethyl)amino)propan-1-ol for 2-aminoethan-1-ol. Isolated 29 mg, 25% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1035.8, found 1036.9.



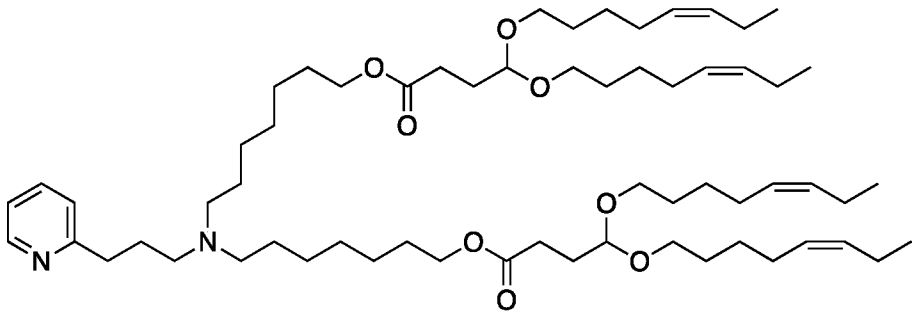
Example 8-33: ((2-(isonicotinamido)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1076] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and *N*-(2-aminoethyl)isonicotinamide for 2-aminoethan-1-ol. Isolated 41 mg, 61% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1038.8, found 1039.9.



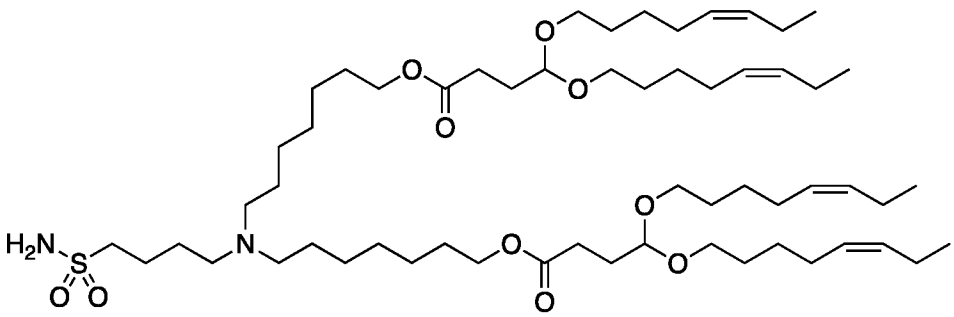
Example 8-35: (((1-methylpyrrolidin-3-yl)methyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1077] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and (1-methylpyrrolidin-3-yl)methanamine for 2-aminoethan-1-ol. Isolated 48 mg, 37% yield. UPLC-MS (Method B): Rt 1.62 min, m/z calculated [M+H]: 987.8, found 987.7.



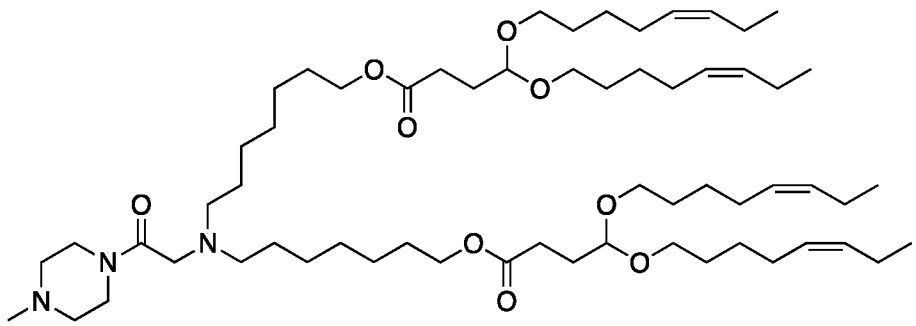
Example 8-36: ((3-(pyridin-2-yl)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1078] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3-(pyridin-2-yl)propan-1-amine for 2-aminoethan-1-ol. Isolated 93 mg, 63% yield. UPLC-MS (Method B): Rt 2.21 min, m/z calculated [M+H]: 1008.8, found 1009.8.



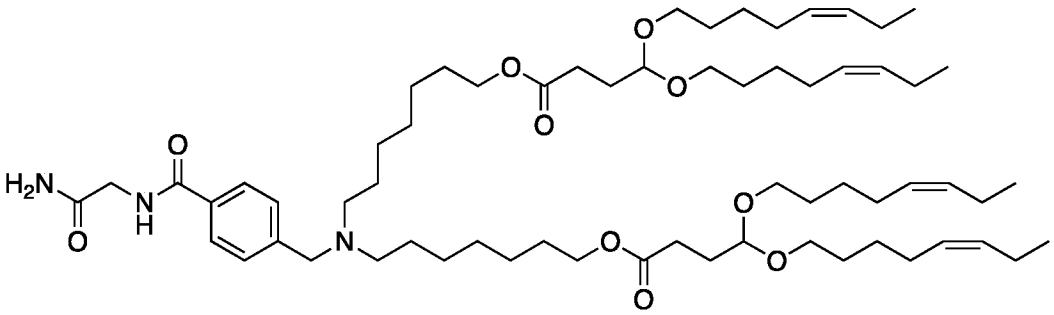
Example 8-37: ((4-sulfamoylbutyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1079] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 4-aminobutane-1-sulfonamide for 2-aminoethan-1-ol. Isolated 46 mg, 43% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1025.8, found 1026.9.



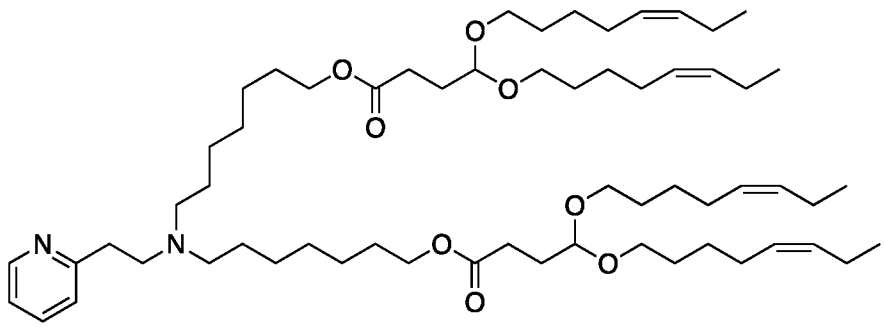
Example 8-38: ((2-(4-methylpiperazin-1-yl)-2-oxoethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1080] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2-amino-1-(4-methylpiperazin-1-yl)ethan-1-one for 2-aminoethan-1-ol. Isolated 44 mg, 37% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1030.8, found 1031.9.



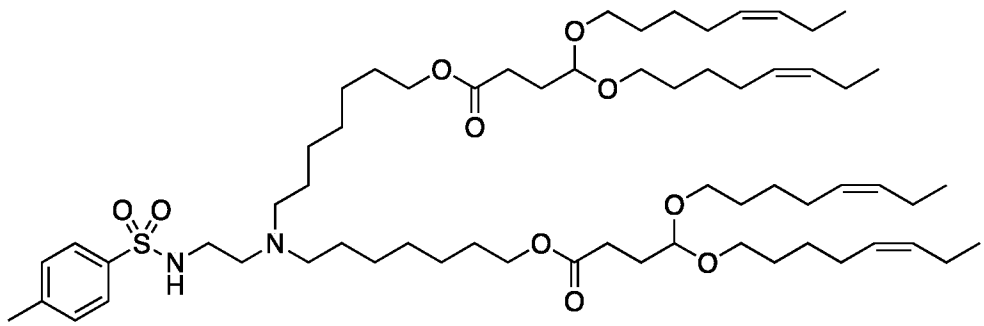
Example 8-39: ((4-((2-amino-2-oxoethyl)carbamoyl)benzyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1081] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and *N*-(2-amino-2-oxoethyl)-4-(aminomethyl)benzamide for 2-aminoethan-1-ol. Isolated 42 mg, 41% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1080.8, found 1081.9. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.5 Hz, 12H), 1.19 – 1.34 (m, 22H), 1.33 – 1.49 (m, 13H), 1.56 – 1.67 (m, 5H), 1.86 – 1.96 (m, 4H), 1.96 – 2.08 (m, 14H), 2.36 (t, *J* = 7.6 Hz, 7H), 3.34 – 3.45 (m, 4H), 3.51 – 3.62 (m, 6H), 4.02 (t, *J* = 6.8 Hz, 4H), 4.14 (d, *J* = 5.2 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 2H), 5.24 – 5.47 (m, 8H), 6.01 (s, 1H), 6.86 – 7.12 (m, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H).



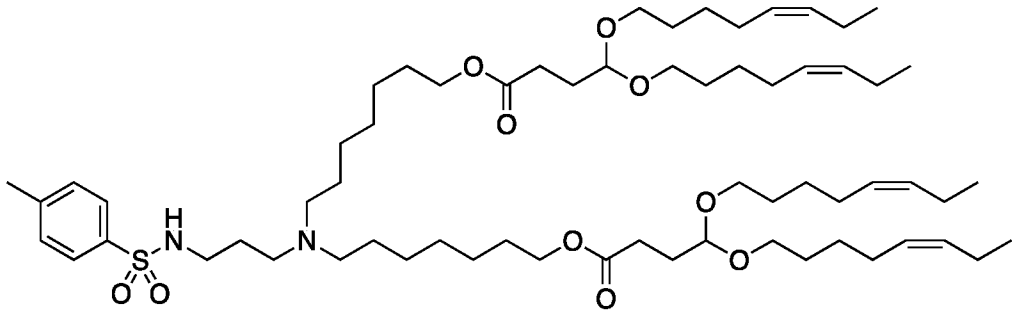
Example 8-40: ((2-(pyridin-2-yl)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1082] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2-(pyridin-2-yl)ethan-1-amine for 2-aminoethan-1-ol. Isolated 92 mg, 63% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 995.8, found 996.8.



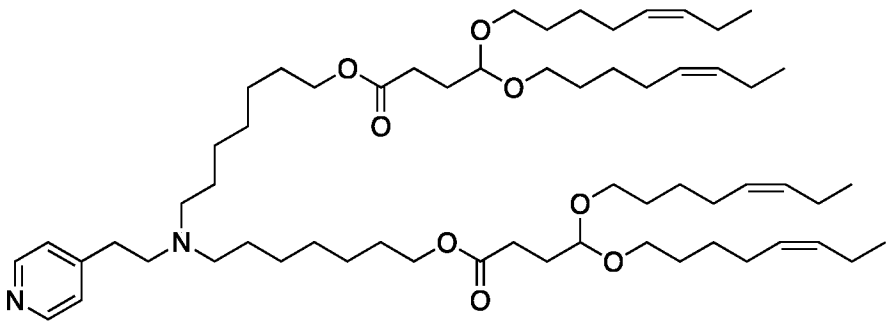
Example 8-41: ((2-((4-methylphenyl)sulfonamido)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1083] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and *N*-(2-aminoethyl)-4-methylbenzenesulfonamide for 2-aminoethan-1-ol. Isolated 31 mg, 36% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1087.8, found 1088.7.



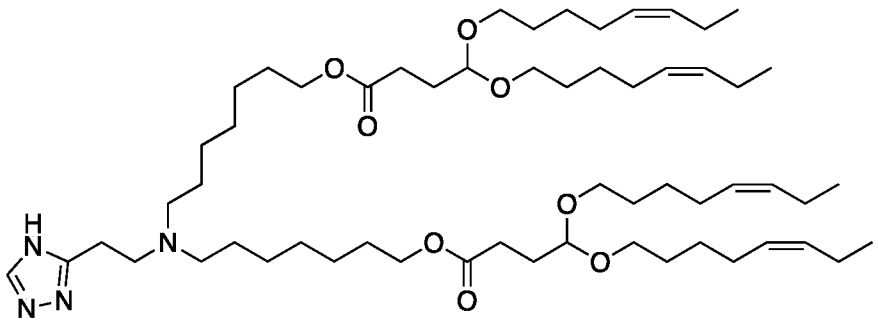
Example 8-42: ((3-((4-methylphenyl)sulfonamido)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1084] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and *N*-(3-aminopropyl)-4-methylbenzenesulfonamide for 2-aminoethan-1-ol. Isolated 29 mg, 31% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 1101.8, found 1102.8.



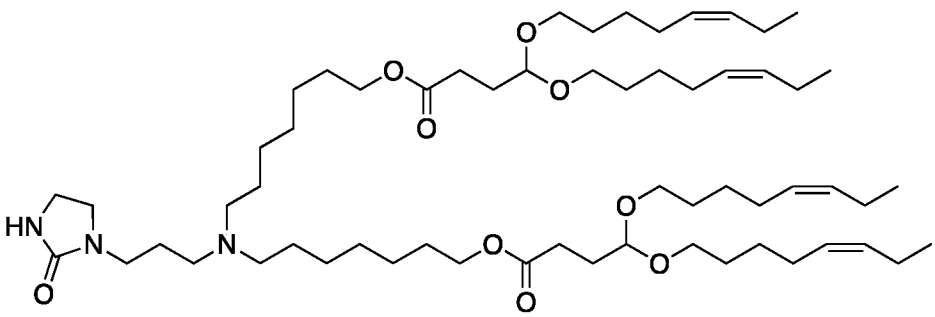
Example 8-43: ((2-(pyridin-4-yl)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1085] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2-(pyridin-4-yl)ethan-1-amine for 2-aminoethan-1-ol. Isolated 28 mg, 24% yield. UPLC-MS (Method B): Rt 2.07 min, m/z calculated [M+H]: 995.8, found 995.7.



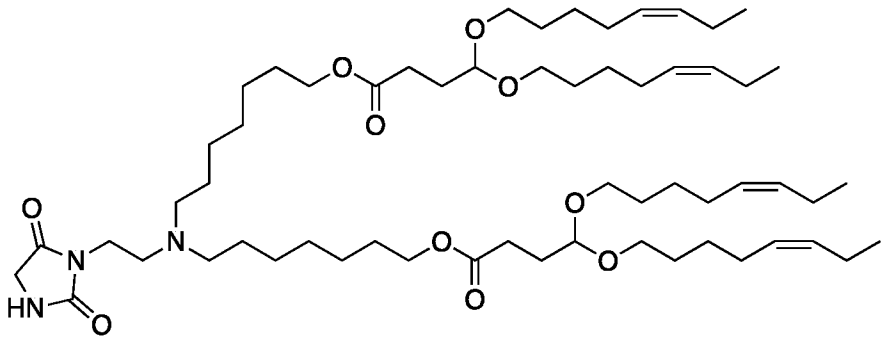
Example 8-44: ((2-(4*H*-1,2,4-triazol-3-yl)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1086] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 2-(4*H*-1,2,4-triazol-3-yl)ethan-1-amine for 2-aminoethan-1-ol. Isolated 40 mg, 23% yield. UPLC-MS (Method B): Rt 2.33 min, m/z calculated [M+H]: 985.8, found 985.9.



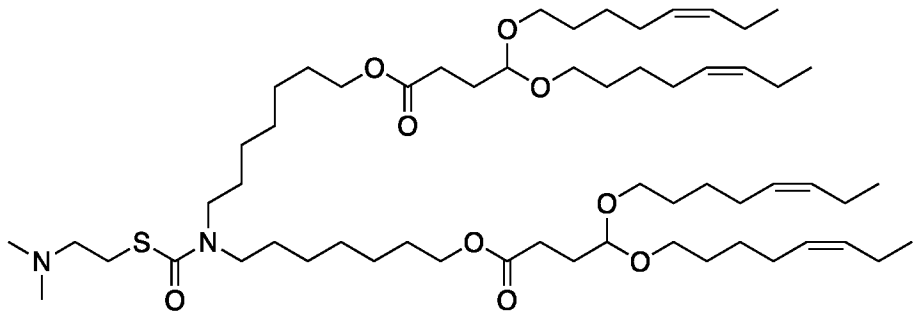
Example 8-45: ((3-(2-oxoimidazolidin-1-yl)propyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1087] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 1-(3-aminopropyl)imidazolidin-2-one for 2-aminoethan-1-ol. Isolated 44 mg, 42% yield. UPLC-MS (Method B): Rt 2.18 min, m/z calculated [M+H]: 1016.8, found 1016.9.

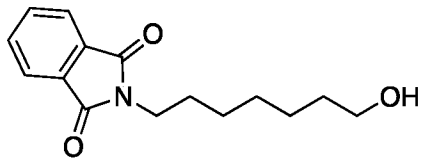


Example 8-47: ((2-(2,5-dioxoimidazolidin-1-yl)ethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1088] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate and 3-(2-aminoethyl)imidazolidine-2,4-dione for 2-aminoethan-1-ol. Isolated 35 mg, 25% yield. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 1016.8, found 1016.9.

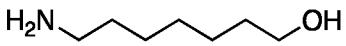


Example 8-49: ((((2-(dimethylamino)ethyl)thio)carbonyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)



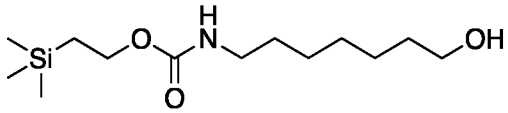
Step 1: 2-(7-hydroxyheptyl)isoindoline-1,3-dione

[1089] Potassium phthalate (2.3 g, 11.27 mmol) and 7-bromoheptan-1-ol (2.0 g, 10.25 mmol) were dissolved in DMF (50 mL). The reaction mixture was heated at 90 °C for 16 h. After this time, the reaction mixture was diluted with water and extracted with ethyl acetate. Combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude which was subjected to combiflash chromatography to get the desired compound 2-(7-hydroxyheptyl)isoindoline-1,3-dione as off white solid (2.0 g, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 1.25 – 1.44 (m, 5H), 1.46 – 1.79 (m, 6H), 3.58 – 3.71 (m, 4H), 7.64 – 7.78 (m, 2H), 7.79 – 7.89 (m, 2H).



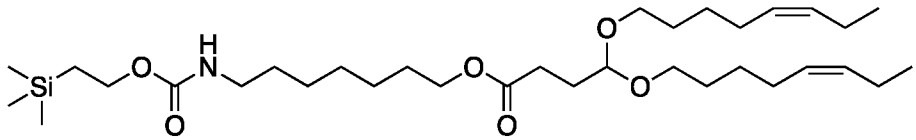
Step 2: 7-aminoheptan-1-ol

[1090] To a solution of 2-(7-hydroxyheptyl)isoindoline-1,3-dione (4.0g, 15.30 mmol) in ethanol (20 ml) was added hydrazine hydrate (3.06 g, 61.23 mmol) and heated at 90°C. Solid appears after 10-20 mins. The reaction mixture was further stirred for 6h. Reaction mixture was filtered and washed with ethyl acetate. Filtrate was evaporated under reduced pressure to get the desire compound 7-aminoheptan-1-ol as colorless liquid (2.0 g, crude). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 1.20 – 1.49 (m, 11H), 1.47 – 1.62 (m, 2H), 2.67 (t, *J* = 6.9 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H).



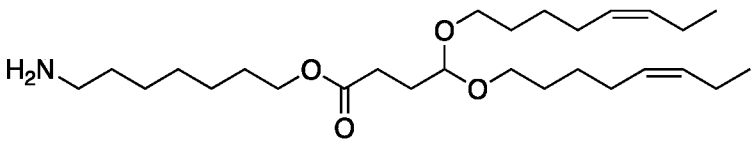
Step 3: 2-(trimethylsilyl)ethyl (7-hydroxyheptyl)carbamate

[1091] To a stirred solution of 7-aminoheptan-1-ol (3.0 g, 22.86 mmol) in DCM (30 ml) was added 1-[2-(Trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (8.89 g, 34.29 mmol) at 0 °C and the reaction mixture was stirred for 16 h. Reaction mixture was evaporated under reduced pressure to get the crude material which was purified by combiflash column chromatography using 50% ethyl acetate in hexane as eluent to get the desired compound 2-(trimethylsilyl)ethyl (7-hydroxyheptyl)carbamate (3.2 g,50% after two steps) as colorless liquid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.02 (s, 9H), 0.83 – 1.07 (m, 2H), 1.20 – 1.41 (m, 7H), 1.43 – 1.58 (m, 4H), 3.03 – 3.25 (m, 2H), 3.53 – 3.75 (m, 2H), 4.00 – 4.24 (m, 2H), 4.43 – 4.69 (m, 1H).



Step 4: 7-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

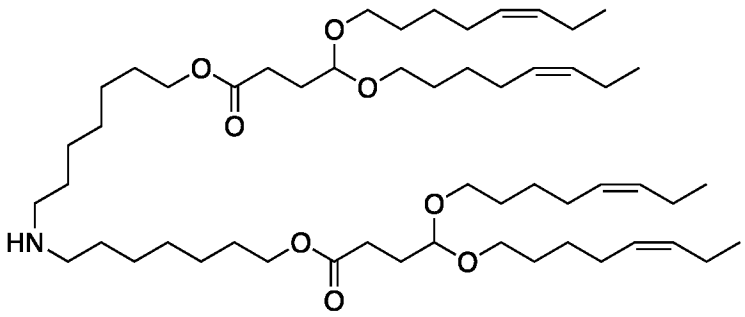
[1092] Prepared according to General Procedure C, substituting 2-(trimethylsilyl)ethyl (7-hydroxyheptyl)carbamate for 6-bromohexan-1-ol. Isolated 4.2 g, 66%. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.02 (s, 9H), 0.89 – 0.99 (m, 8H), 1.25 – 1.51 (m, 18H), 1.89 – 1.96 (m, 2H), 1.98 – 2.09 (m, 8H), 2.36 (t, *J* = 7.2 Hz, 2H), 3.02 – 3.27 (m, 2H), 3.34 – 3.45 (m, 2H), 3.51 – 3.62 (m, 2H), 4.03 (t, *J* = 6.2 Hz, 2H), 4.08 – 4.20 (m, 2H), 4.48 – 4.65 (m, 2H), 5.29 – 5.39 (m, 4H).



Step 5: 7-aminoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[1093] TBAF (3.35 mL, 1M solution in THF, 3.35 mmol) was added to a solution of 7-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (500 mg, 0.84 mmol) in 10 mL of THF at 0 °C and stirred for 8h at 45 °C. The reaction was quenched by water (10 mL) and extracted with 10% MeOH-DCM (2X 30 mL). The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was used for next step without further purification (300 mg, crude). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.93 (t, *J* = 7.5 Hz, 6H), 1.00 (t, *J* = 7.3 Hz, 3H), 1.18 – 1.78 (m, 15H), 1.86 – 1.96 (m, 2H), 1.95 – 2.13 (m, 8H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 3.29 – 3.47

(m, 4H), 3.51 – 3.62 (m, 2H), 4.03 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.5 Hz, 1H), 5.24 – 5.41 (m, 4H).



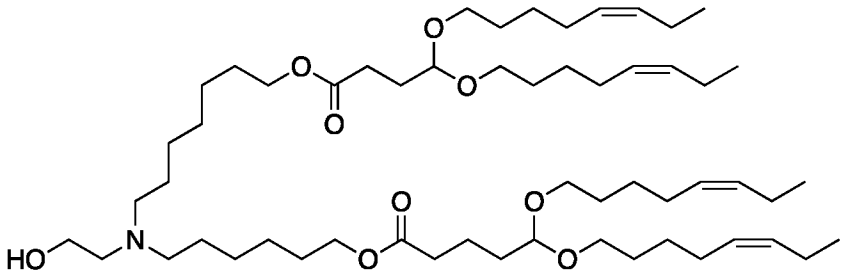
Step 6: azanediylbis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate)

[1094] To a stirred solution of 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate (100 mg, 0.2 mmol) was added 7-aminoheptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate (450.50 mg, 0.99 mmol) in ACN-THF (1:1) (2.0 ml), then the reaction mixture was stirred at 45° C for 16 hours. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. Organic layers were dried over anhydrous Na_2SO_4 and concentrated to get the crude. Crude was subjected to combiflash chromatography (3-5% MeOH-DCM) to get the desired product azanediylbis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (80 mg, 50% two steps). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 0.89 – 1.02 (m, 15H), 1.21 – 1.29 (m, 4H), 1.28 – 1.47 (m, 20H), 1.57 – 1.67 (m, 6H), 1.75 – 1.84 (m, 2H), 1.91 (q, *J* = 7.4 Hz, 6H), 1.96 – 2.09 (m, 16H), 2.36 (t, *J* = 7.6 Hz, 4H), 2.89 – 3.04 (m, 6H), 3.34 – 3.47 (m, 4H), 3.51 – 3.62 (m, 4H), 4.03 (t, *J* = 6.6 Hz, 4H), 4.48 (t, *J* = 5.6 Hz, 2H), 5.24 – 5.42 (m, 6H).

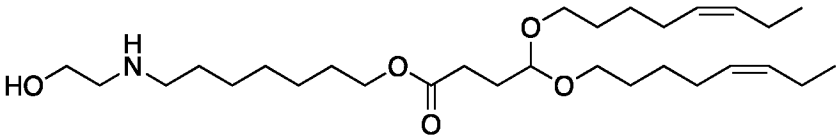
Step 7: ((((2-(dimethylamino)ethyl)thio)carbonyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (Example 8-49)

[1095] To a stirred solution of azanediylbis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate) (100 mg,0.11 mmol) in DCM (1.0 ml) was added triphosgene (18 mg, 0.06 mmol) followed by triethylamine (0.05 ml,0.34 mmol) at 0°C. Reaction mixture was stirred for 2h. Then a solution of 2-(dimethylamino)ethane-1-thiol (14 mg, 0.14 mmol) in THF (1ml) was added followed by NaH (19 mg, 0.8 mmol) at 0°C. Reaction mixture was further stirred for 16h at 45 °C. After completion of reaction, it was diluted with water and extracted with DCM (2 x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to get the crude which was subjected to combiflash chromatography (3-5% MeOH-DCM) to afford ((((2-(dimethylamino)ethyl)thio)carbonyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-5-en-1-

yl)oxy)butanoate) (30 mg, 26%). UPLC-MS (Method B): Rt 2.16 min, m/z calculated [M+H]: 1021.8, found 1021.7.



Example 8-55: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)hexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate

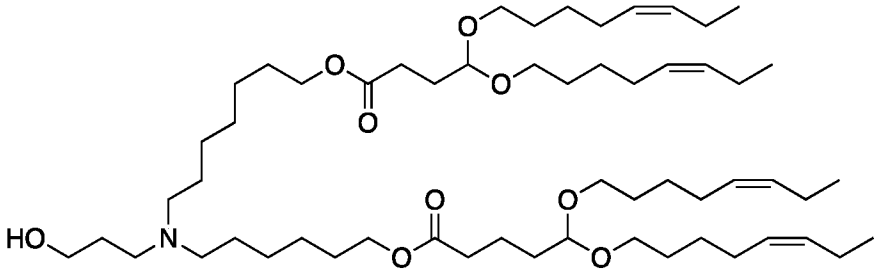


Step 1: 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

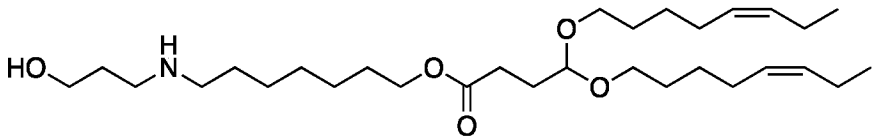
[1096] Prepared according to General Procedure E, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate. Isolated 690 mg, 95% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, J = 7.4 Hz, 6H), 1.20 – 1.42 (m, 13H), 1.42 – 1.57 (m, 6H), 1.77 (q, J = 6.8 Hz, 2H), 1.86 – 2.13 (m, 8H), 2.29 (t, J = 7.1 Hz, 2H), 2.43 – 2.57 (m, 4H), 3.31 – 3.45 (m, 4H), 3.44 – 3.54 (m, 2H), 3.98 (t, J = 6.5 Hz, 2H), 4.24 – 4.60 (m, 1H), 5.23 – 5.40 (m, 4H).

Step 2: 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)hexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate (Example 8-55)

[1097] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 65 mg, 23% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 9H), 1.20 – 1.41 (m, 34H), 1.42 – 1.60 (m, 26H), 1.66 – 1.81 (m, 2H), 1.92 – 2.05 (m, 12H), 2.29 (t, J = 7.2 Hz, 3H), 3.26 – 3.39 (m, 3H), 3.43 – 3.54 (m, 3H), 3.94 – 4.03 (m, 3H), 4.38 – 4.49 (m, 2H), 5.23 – 5.40 (m, 6H). UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 934.8, found 935.0.



Example 8-56: 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)hexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

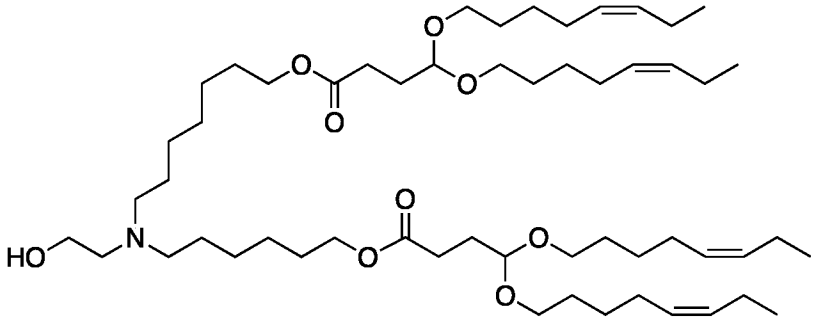


Step 1: 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate

[1098] Prepared according to General Procedure E, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-bromooctanoate and 3-aminopropan-1-ol for ethanolamine. Isolated 950 mg, 96% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 6H), 1.21 – 1.41 (m, 14H), 1.42 – 1.58 (m, 8H), 1.76 (q, J = 7.0 Hz, 2H), 1.93 – 2.05 (m, 8H), 2.29 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 2.53 (d, J = 6.9 Hz, 2H), 3.31 – 3.40 (m, 2H), 3.40 – 3.55 (m, 4H), 3.98 (t, J = 6.6 Hz, 2H), 4.44 (t, J = 5.5 Hz, 1H), 5.23 – 5.40 (m, 4H).

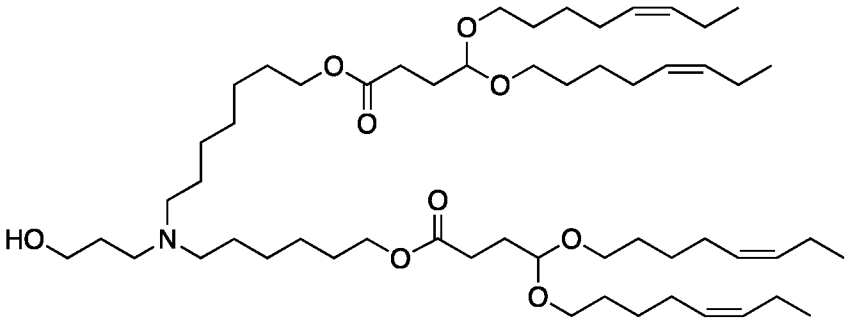
Step 2: 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)hexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate (Example 8-56)

[1099] Prepared according to General Procedure F, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 64 mg, 23% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 12H), 1.19 – 1.64 (m, 45H), 1.71 – 1.82 (m, 3H), 1.93 – 2.05 (m, 16H), 2.29 (t, J = 7.1 Hz, 5H), 3.31 – 3.39 (m, 4H), 3.39 – 3.55 (m, 6H), 3.94 – 4.03 (m, 4H), 4.43 (q, J = 5.5 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 948.8, found 949.0.



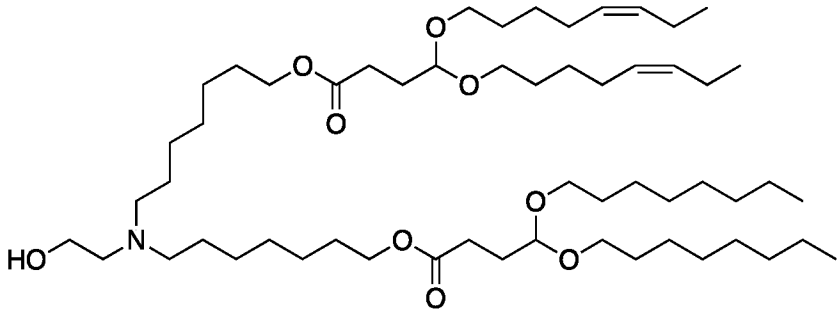
Example 8-57: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[1100] Prepared according to General Procedure F, substituting 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 72 mg, 26% yield. UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 920.8, found 921.0.

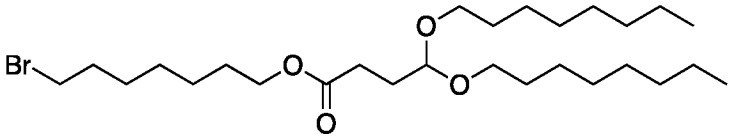


Example 8-58: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)hexyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate

[1101] Prepared according to General Procedure F, substituting 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 87 mg, 32% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.20 – 1.40 (m, 26H), 1.42-1.59 (m, 17H), 1.77 (q, J = 6.9 Hz, 4H), 1.93 – 2.05 (m, 16H), 2.29 (t, J = 7.2 Hz, 4H), 3.31 – 3.40 (m, 4H), 3.39 – 3.54 (m, 6H), 3.99 (t, J = 6.5 Hz, 4H), 4.44 (t, J = 5.4 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 934.8, found 935.1.



Example 8-59: 7-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)heptyl 4,4-bis(octyloxy)butanoate

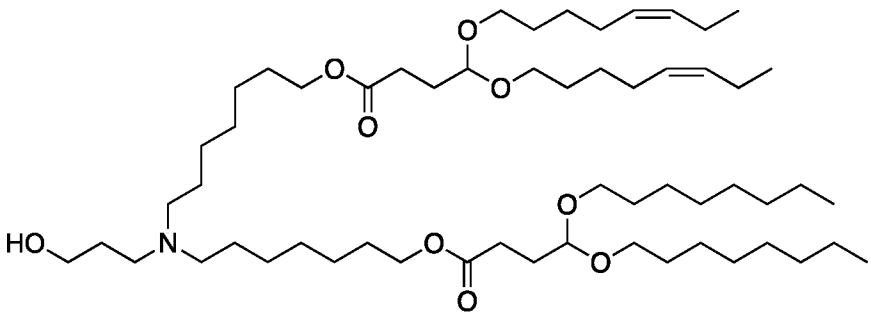


Step 1: 7-bromoheptyl 4,4-bis(octyloxy)butanoate

[1102] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(octyloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 3.1 g, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 6H), 1.14 – 1.49 (m, 28H), 1.56 – 1.71 (m, 4H), 1.76 – 1.99 (m, 4H), 2.37 (t, *J* = 7.4 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.50 – 3.61 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

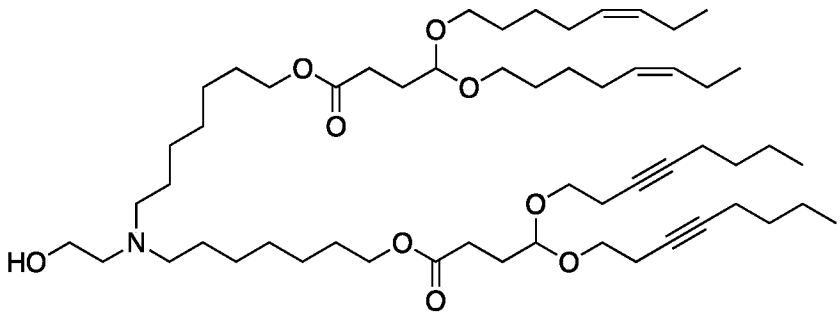
Step 2: 7-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)heptyl 4,4-bis(octyloxy)butanoate (Example 8-59)

[1103] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 135 mg, 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 – 0.87 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 6H), 1.15 – 1.40 (m, 45H), 1.42 – 1.61 (m, 14H), 1.76 (q, *J* = 6.6 Hz, 4H), 1.93 – 2.05 (m, 10H), 2.29 (t, *J* = 7.2 Hz, 4H), 3.27 – 3.39 (m, 4H), 3.42 – 3.54 (m, 4H), 3.98 (t, *J* = 6.5 Hz, 4H), 4.38 – 4.56 (m, 2H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.47 min, m/z calculated [M+H]: 938.8, found 938.9.

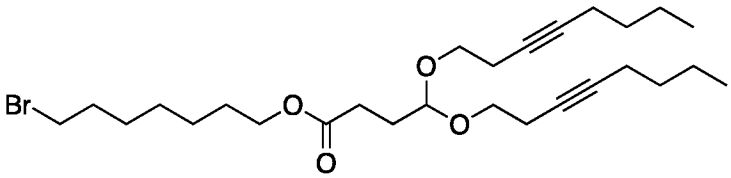


Example 8-60: 7-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)heptyl 4,4-bis(octyloxy)butanoate

[1104] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(octyloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 110 mg, 48% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 – 0.88 (m, 6H), 0.91 (t, J = 7.5 Hz, 6H), 1.15 – 1.40 (m, 47H), 1.40 – 1.53 (m, 12H), 1.76 (q, J = 6.8 Hz, 4H), 1.94 – 2.04 (m, 9H), 2.29 (t, J = 7.2 Hz, 4H), 3.29 – 3.39 (m, 4H), 3.40 – 3.54 (m, 6H), 3.99 (t, J = 6.5 Hz, 4H), 4.33 – 4.52 (m, 2H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.46 min, m/z calculated [M+H]: 952.8, found 952.9.



Example 8-61: 7-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)heptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate



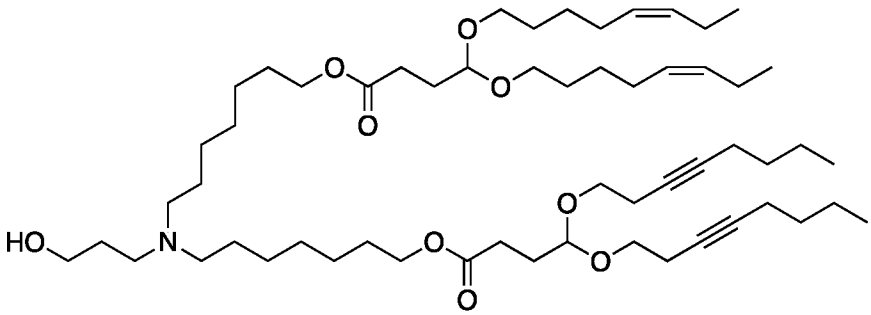
Step 1: 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

[1105] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((*Z*)-oct-5-en-1-

yl)oxy)butanoic acid. Isolated 3.1 g, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 6.9 Hz, 6H), 1.14 – 1.49 (m, 28H), 1.56 – 1.71 (m, 4H), 1.76 – 1.99 (m, 4H), 2.37 (t, *J* = 7.4 Hz, 2H), 3.34 – 3.45 (m, 4H), 3.50 – 3.61 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 2H), 4.48 (t, *J* = 5.6 Hz, 1H).

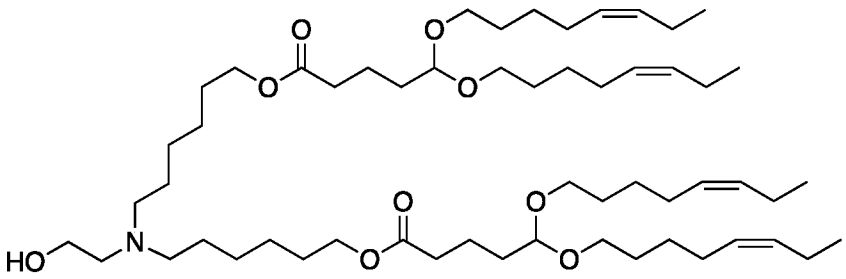
Step 2: 7-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(2-hydroxyethyl)amino)heptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate (Example 8-61)

[1106] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((2-hydroxyethyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 72 mg, 32% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 – 0.95 (m, 12H), 1.19 – 1.43 (m, 35H), 1.42 – 1.61 (m, 8H), 1.71 – 1.83 (m, 4H), 1.93 – 2.06 (m, 8H), 2.07 – 2.16 (m, 4H), 2.24 – 2.39 (m, 10H), 3.32 – 3.38 (m, 2H), 3.40 – 3.63 (m, 6H), 3.94 – 4.06 (m, 4H), 4.36 – 4.69 (m, 2H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 930.7, found 930.8.



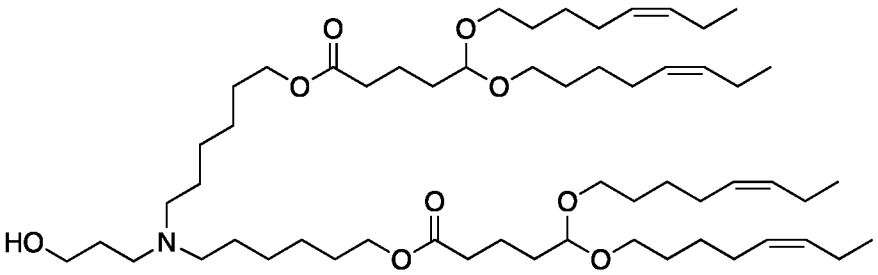
Example 8-62: 7-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(3-hydroxypropyl)amino)heptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

[1107] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 7-((3-hydroxypropyl)amino)heptyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 172 mg, 62% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 – 0.95 (m, 12H), 1.21 – 1.43 (m, 27H), 1.42 – 1.60 (m, 12H), 1.61 – 1.70 (m, 2H), 1.71 – 1.83 (m, 4H), 1.95 – 2.04 (m, 8H), 2.07 – 2.16 (m, 4H), 2.25 – 2.39 (m, 8H), 2.59 – 3.04 (m, 4H), 3.26 – 3.40 (m, 2H), 3.42 – 3.52 (m, 6H), 3.53 – 3.62 (m, 2H), 3.95 – 4.04 (m, 4H), 4.37 – 4.68 (m, 2H), 5.23 – 5.40 (m, 4H). UPLC-MS (Method B): Rt 2.17 min, m/z calculated [M+H]: 944.8, found 944.8.



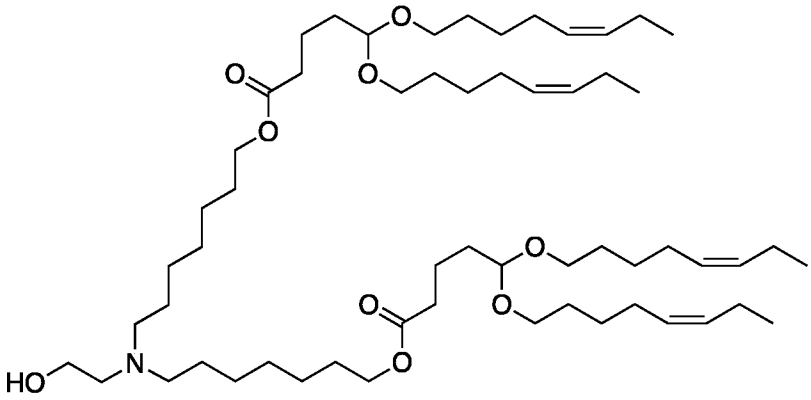
Example 8-63: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate)

[1108] Prepared according to General Procedure G, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 60 mg, 39% yield. UPLC-MS (Method B): Rt 2.27 min, m/z calculated [M+H]: 934.8, found 935.1.



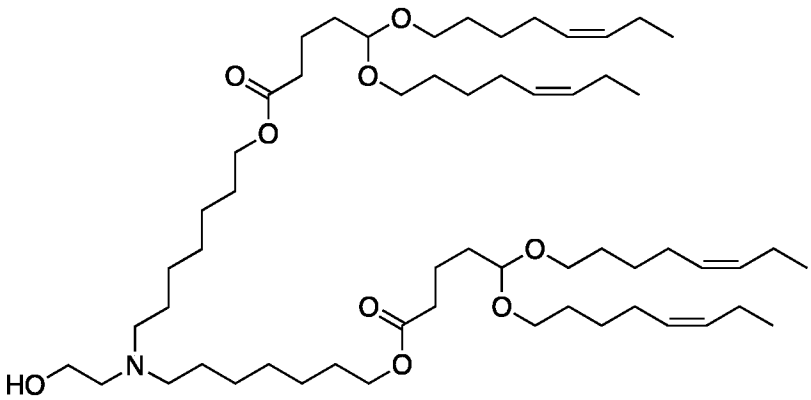
Example 8-64: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate)

[1109] Prepared according to General Procedure G, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 58 mg, 38% yield. UPLC-MS (Method B): Rt 2.26 min, m/z calculated [M+H]: 948.8, found 949.1.



Example 8-65: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate)

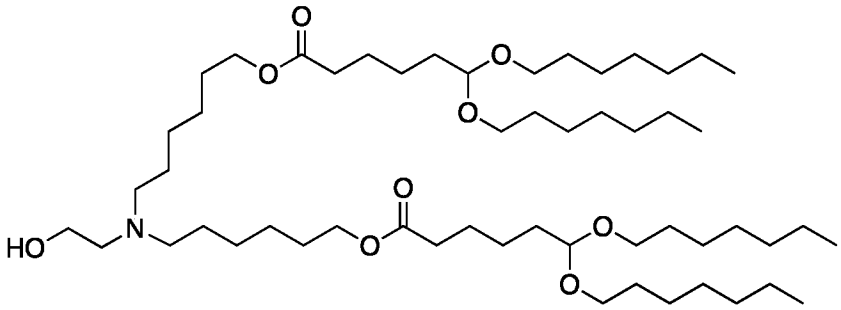
[1110] Prepared according to General Procedure G, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 140 mg, 59% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.19 – 1.41 (m, 27H), 1.42 – 1.62 (m, 26H), 1.93 – 2.05 (m, 16H), 2.24 – 2.33 (m, 4H), 3.30 – 3.39 (m, 4H), 3.43 – 3.53 (m, 4H), 3.99 (t, J = 6.5 Hz, 4H), 4.43 (d, J = 5.2 Hz, 2H), 5.19 – 5.42 (m, 8H). UPLC-MS (Method B): Rt 2.36 min, m/z calculated [M+H]: 962.8, found 963.1.



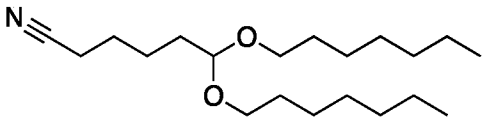
Example 8-66: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate)

[1111] Prepared according to General Procedure G, substituting 7-bromoheptyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 90 mg, 46% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.19 – 1.41 (m, 25H), 1.39 – 1.62 (m, 27H), 1.93 – 2.05 (m, 16H), 2.25 – 2.33 (m, 5H), 3.26 – 3.39 (m, 4H), 3.39 – 3.54 (m, 6H), 3.99 (t, J = 6.5 Hz, 4H), 4.43 (d, J

= 5.1 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.36 min, m/z calculated [M+H]: 976.8, found 977.1.

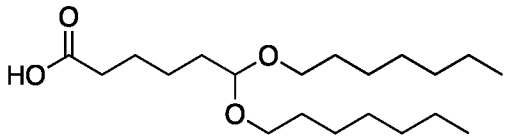


Example 8-67: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(heptyloxy)hexanoate)



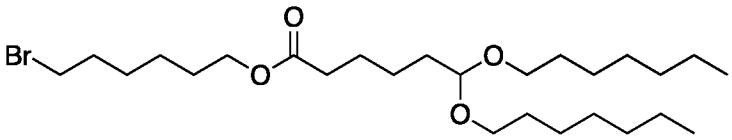
Step 1: 6,6-bis(heptyloxy)hexanenitrile

[1112] Prepared according to General Procedure A, substituting heptan-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 850 mg, 22%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85 – 1.02 (m, 6H), 1.27 – 1.70 (m, 26H), 2.33 (t, *J* = 7.1 Hz, 2H), 3.37 – 3.65 (m, 4H), 4.44 (t, *J* = 5.5 Hz, 1H).



Step 2: 6,6-bis(heptyloxy)hexanoic acid

[1113] Prepared according to General Procedure B, substituting 6,6-bis(heptyloxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 850 mg, 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 – 0.86 (m, 6H), 1.16 – 1.46 (m, 26H), 2.16 – 2.19 (m, 2H), 3.30 – 3.49 (m, 4H), 4.40 – 4.43 (m, 1H), 11.95 (s, 1H).

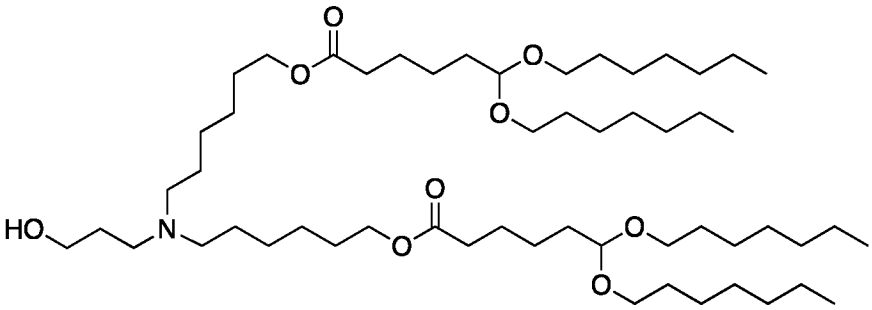


Step 3: 6-bromohexyl 6,6-bis(heptyloxy)hexanoate

[1114] Prepared according to General Procedure C, substituting 6,6-bis(heptyloxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 810 mg, 63%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.80 – 0.90 (m, 6H), 1.20 – 1.90 (m, 35H), 2.20 – 2.40 (m, 2H), 3.29 – 3.56 (m, 6H), 4.04 (t, *J* = 6.5 Hz, 2H), 4.38 – 4.45 (m, 1H).

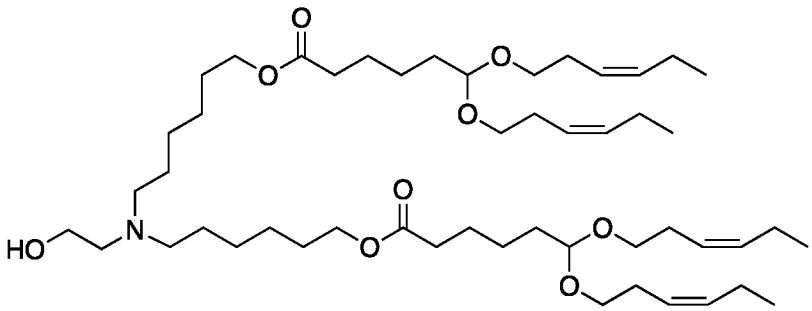
Step 4: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(heptyloxy)hexanoate) (Example 8-67)

[1115] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(heptyloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 90 mg, 40% yield. UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 914.8, found 914.8.

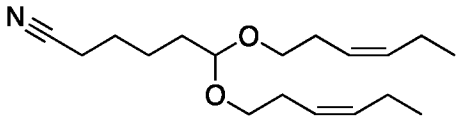


Example 8-68: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(heptyloxy)hexanoate)

[1116] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(heptyloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 142 mg, 57% yield. UPLC-MS (Method B): Rt 2.24 min, m/z calculated [M+H]: 928.8, found 928.8.

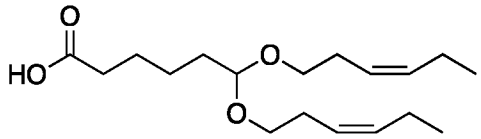


Example 8-69: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoate)



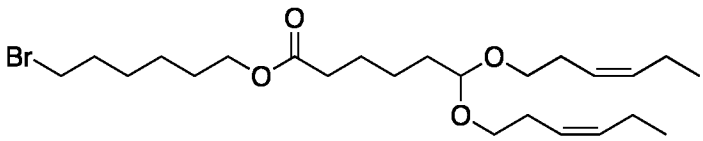
Step 1: 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanenitrile

[1117] Prepared according to General Procedure A, substituting (*Z*)-hex-3-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 1.3 g, 35%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.4 Hz, 6H), 1.34 – 1.71 (m, 6H), 2.02 – 2.34 (m, 10H), 3.29 – 3.65 (m, 4H), 4.42 – 4.49 (m, 1H), 5.29 – 5.48 (m, 4H),



Step 2: 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoic acid

[1118] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 1.2 g, 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 – 0.93 (m, 6H), 1.27 – 1.50 (m, 6H), 1.98 – 2.22 (m, 10H), 3.35 – 3.50 (m, 4H), 4.40 – 4.50 (m, 1H), 5.31 – 5.39 (m, 4H), 11.95 (s, 1H).

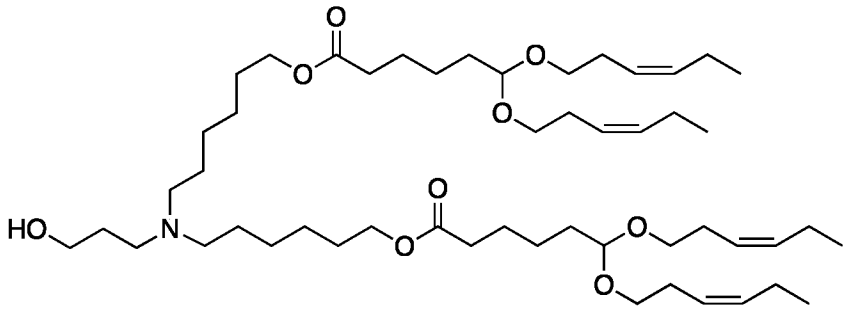


Step 3: 6-bromohexyl 6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoate

[1119] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 570 mg, 58%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.90 – 1.0 (m, 6H), 1.30 – 1.70 (m, 12H), 1.80 – 2.32 (m, 12H), 3.37 – 3.56 (m, 6H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.40 – 4.50 (m, 1H), 5.31 – 5.50 (m, 4H).

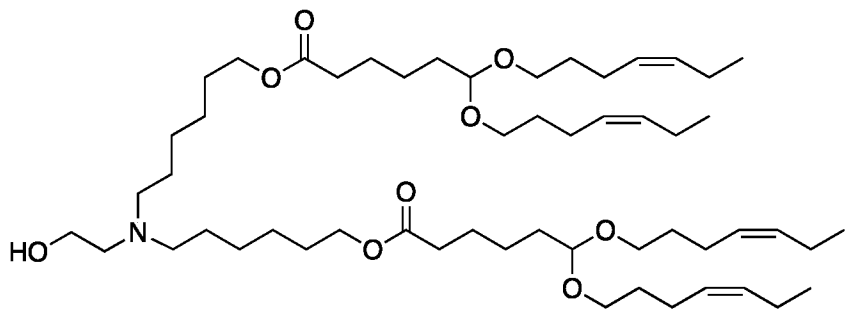
Step 4: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((Z)-hex-3-en-1-yl)oxy)hexanoate)) (Example 8-69)

[1120] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 102 mg, 49% yield. UPLC-MS (Method B): Rt 1.86 min, m/z calculated [M+H]: 850.7, found 850.7.

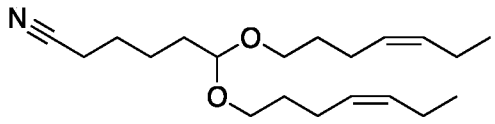


Example 8-70: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoate)

[1121] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(((*Z*)-hex-3-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 83 mg, 48% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 – 0.93 (m, 12H), 1.23 – 1.67 (m, 29H), 1.96 – 2.04 (m, 8H), 2.15 – 2.30 (m, 12H), 3.30 – 3.50 (m, 12H), 3.99 (t, J = 6.6 Hz, 4H), 4.44 (t, J = 5.5 Hz, 2H), 5.28 – 5.44 (m, 8H). UPLC-MS (Method B): Rt 1.87 min, m/z calculated [M+H]: 864.7, found 864.7.

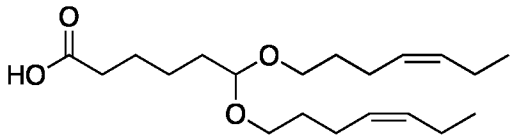


Example 8-71: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanoate)



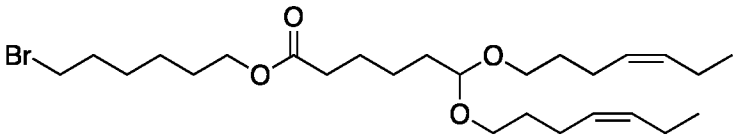
Step 1: 6,6-bis(((Z)-hept-4-en-1-yl)oxy)hexanenitrile

[1122] Prepared according to General Procedure A, substituting (*Z*)-hept-4-en-1-ol for cis-5-octen-1-ol and 6,6-dimethoxyhexanenitrile for 4,4-diethoxybutanenitrile. Isolated 580 mg, 19%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, J = 7.4 Hz, 6H), 1.59 – 1.70 (m, 8H), 2.01 – 2.35 (m, 10H), 3.38 – 3.59 (m, 4H), 4.43 – 4.44 (m, 1H), 5.30 – 5.38 (m, 4H).



Step 2: 6,6-bis(((Z)-hept-4-en-1-yl)oxy)hexanoic acid

[1123] Prepared according to General Procedure B, substituting 6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 520 mg, 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 – 1.00 (m, 6H), 1.15 – 1.59 (m, 11H), 1.97 – 2.32 (m, 10H), 3.45 – 3.50 (m, 2H), 5.26 – 5.47 (m, 4H), 11.96 (s, 1H).

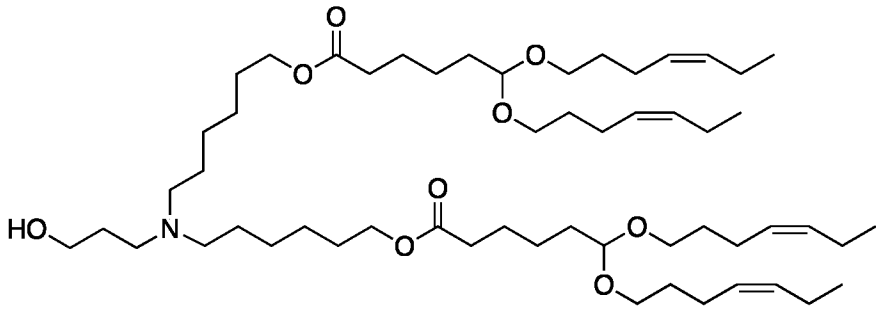


Step 3: 6-bromohexyl 6,6-bis(((Z)-hept-4-en-1-yl)oxy)hexanoate

[1124] Prepared according to General Procedure C, substituting 6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 550 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.4 Hz, 6H), 1.24 – 1.62 (m, 16H), 1.83 – 2.31 (m, 12H), 3.38 – 3.65 (m, 6H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.42 – 4.43 (m, 1H), 5.28 – 5.36 (m, 4H).

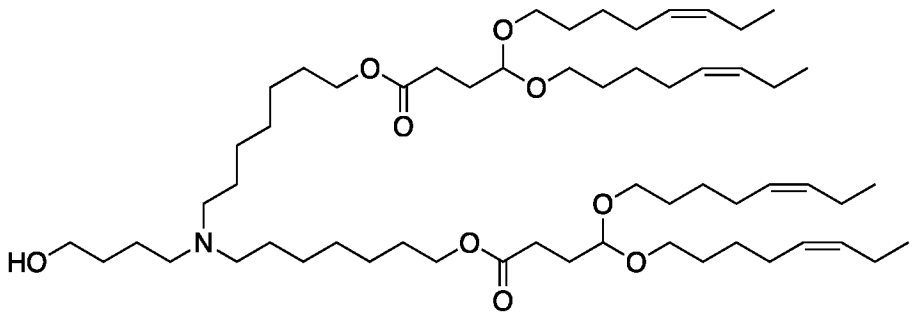
Step 4: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((Z)-hept-4-en-1-yl)oxy)hexanoate) (Example 8-71)

[1125] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 140 mg, 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 – 0.93 (m, 12H), 1.27 – 1.54 (m, 36H), 1.93 – 2.06 (m, 16H), 2.26 (t, *J* = 7.3 Hz, 4H), 2.32 – 2.49 (m, 2H), 3.00 – 3.10 (m, 2H), 3.30 – 3.70 (m, 8H), 3.98 (t, *J* = 6.5 Hz, 4H), 4.10 – 4.30 (m, 1H), 4.39 (t, *J* = 5.5 Hz, 2H), 5.26 – 5.38 (m, 8H). UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 906.7, found 906.7.



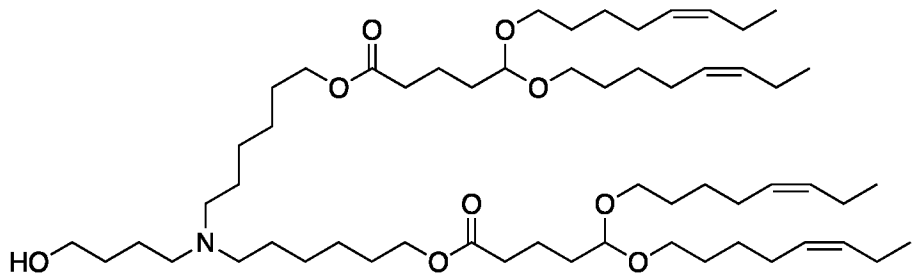
Example 8-72: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanoate)

[1126] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(((*Z*)-hept-4-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 115 mg, 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 – 0.93 (m, 12H), 1.23 – 1.67 (m, 29H), 1.96 – 2.04 (m, 8H), 2.15 – 2.30 (m, 12H), 3.30 – 3.50 (m, 12H), 3.99 (t, J = 6.6 Hz, 4H), 4.44 (t, J = 5.5 Hz, 2H), 5.28 – 5.44 (m, 8H). UPLC-MS (Method B): Rt 2.06 min, m/z calculated [M+H]: 920.8, found 920.7.



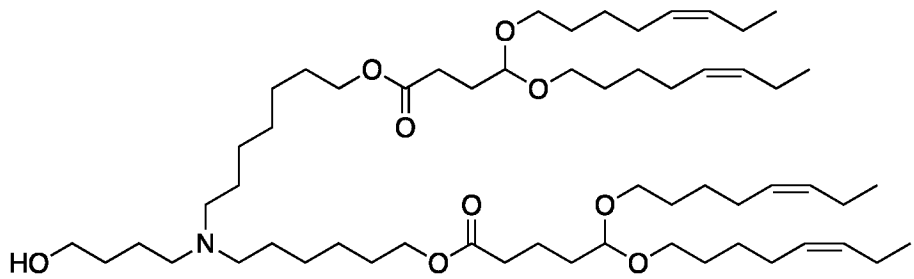
Example 8-73: ((4-hydroxybutyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1127] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 4-aminobutan-1-ol for 2-aminoethan-1-ol. Isolated 80 mg, 37% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.4 Hz, 12H), 1.21 – 1.40 (m, 21H), 1.40 – 1.68 (m, 20H), 1.90 – 2.11 (m, 16H), 2.29 (t, J = 7.3 Hz, 4H), 2.91 – 3.13 (m, 8H), 3.31 – 3.40 (m, 4H), 3.39 – 3.56 (m, 6H), 4.00 (t, J = 6.6 Hz, 4H), 4.44 (t, J = 5.3 Hz, 2H), 4.57 (s, 1H), 5.16 – 5.56 (m, 8H), 8.87 (bs, 1H). UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 962.8, found 962.8.

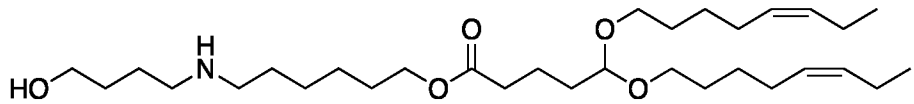


Example 8-74: ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate)

[1128] Prepared according to General Procedure G, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 4-aminobutan-1-ol for 2-aminoethan-1-ol. Isolated 144 mg, 67% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.27 – 1.41 (m, 16H), 1.40 – 1.69 (m, 27H), 1.93 – 2.05 (m, 16H), 2.30 (t, J = 6.3 Hz, 4H), 2.91 – 3.14 (m, 6H), 3.27 – 3.39 (m, 4H), 3.38 – 3.54 (m, 6H), 4.00 (t, J = 6.6 Hz, 4H), 4.40 – 4.45 (m, 2H), 4.57 (s, 1H), 5.23 – 5.40 (m, 8H), 8.90 (bs, 1H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 962.8, found 962.8.



Example 8-75: 6-((7-((4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(4-hydroxybutyl)amino)hexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate

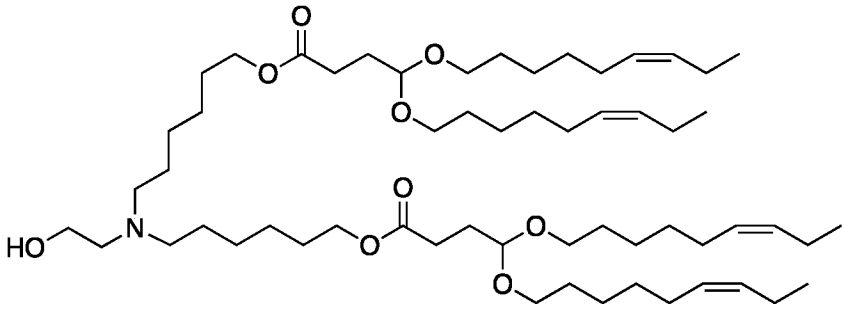


Step 1: 6-((4-hydroxybutyl)amino)hexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate

[1129] Prepared according to General Procedure E, substituting 6-bromohexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for nonyl 8-bromooctanoate and 4-aminobutan-1-ol for 2-aminoethan-1-ol. Isolated 210 mg, 82% yield. UPLC-MS (Method B): Rt 0.69 min, m/z calculated [M+H]: 526.4, found 526.3.

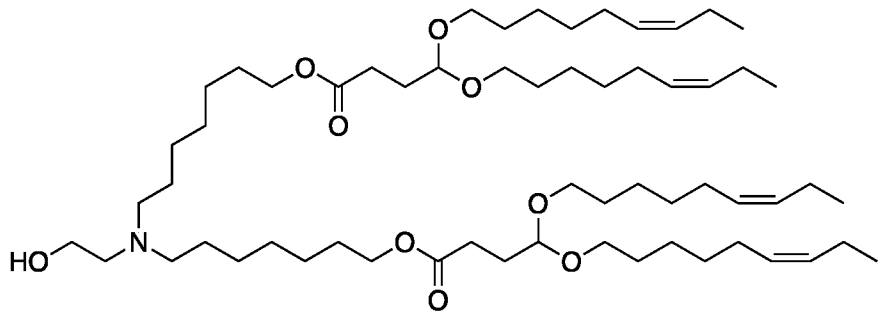
Step 2: 6-((7-((4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoyl)oxy)heptyl)(4-hydroxybutyl)amino)hexyl 5,5-bis(((Z)-oct-5-en-1-yl)oxy)pentanoate (Example 8-75)

[1130] Prepared according to General Procedure F, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 6-((4-hydroxybutyl)amino)hexyl 5,5-bis(((*Z*)-oct-5-en-1-yl)oxy)pentanoate for nonyl 8-((2-hydroxyethyl)amino)octanoate. Isolated 104 mg, 28% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.17 – 1.63 (m, 49H), 1.76 (q, J = 7.3 Hz, 2H), 1.92 – 2.08 (m, 16H), 2.29 (t, J = 7.2 Hz, 5H), 3.33 – 3.43 (m, 5H), 3.43 – 3.54 (m, 4H), 3.94 – 4.03 (m, 4H), 4.43 (q, J = 5.4 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.12 min, m/z calculated [M+H]: 962.8, found 962.8.

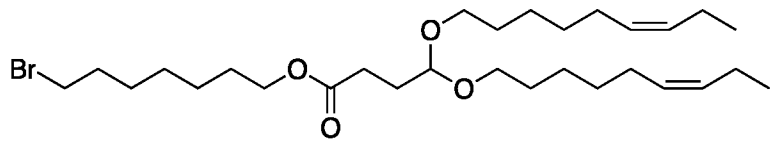


Example 8-76: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate)

[1131] Prepared according to General Procedure G, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 57 mg, 54% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.93 (t, J = 7.5 Hz, 12H), 1.27 – 1.44 (m, 35H), 1.86 – 2.01 (m, 5H), 1.98 – 2.08 (m, 17H), 2.37 (t, J = 7.6 Hz, 5H), 2.47 – 2.85 (m, 6H), 3.34 – 3.44 (m, 5H), 3.50 – 3.61 (m, 5H), 3.62 – 3.70 (m, 2H), 4.05 (t, J = 6.6 Hz, 5H), 4.48 (t, J = 5.5 Hz, 2H), 5.27 – 5.41 (m, 8H). UPLC-MS (Method B): Rt 2.42 min, m/z calculated [M+H]: 962.8, found 963.0.



Example 8-77: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate)

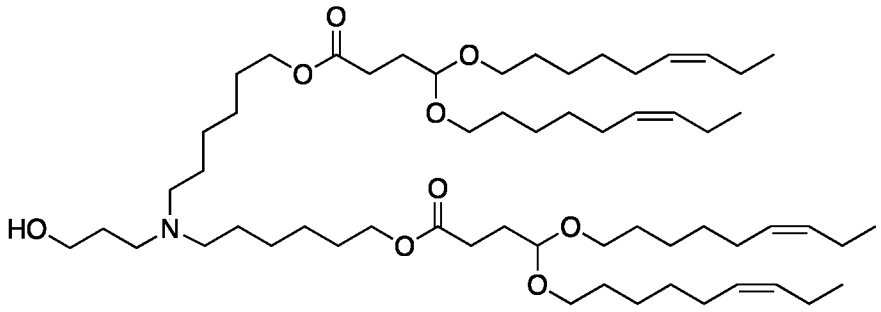


Step 1: 7-bromoheptyl 4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoate

[1132] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 302 mg, 62% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 – 1.01 (m, 6H), 1.26 – 1.48 (m, 16H), 1.53 – 1.69 (m, 4H), 1.76 – 2.11 (m, 12H), 2.37 (t, *J* = 7.5 Hz, 2H), 3.31 – 3.46 (m, 4H), 3.49 – 3.66 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 4.42 – 4.54 (m, 1H), 5.18 – 5.48 (m, 4H).

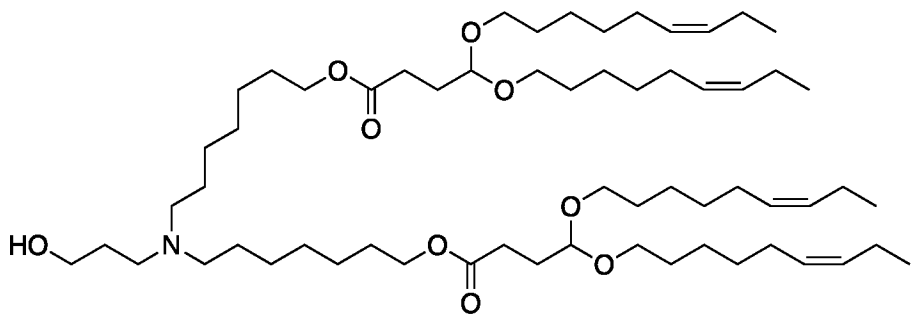
Step 2: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoate) (Example 8-77)

[1133] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((Z)-non-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 52 mg, 56% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.93 (t, *J* = 7.5 Hz, 12H), 1.25 – 1.41 (m, 36H), 1.86 – 2.01 (m, 5H), 1.98 – 2.08 (m, 16H), 2.32 – 2.41 (m, 5H), 2.37 (t, *J* = 7.7 Hz, 4H), 2.50 – 2.88 (m, 6H), 3.34 – 3.44 (m, 5H), 3.50 – 3.61 (m, 5H), 3.63 – 3.73 (m, 2H), 4.04 (t, *J* = 6.7 Hz, 5H), 4.48 (t, *J* = 5.5 Hz, 2H), 5.24 – 5.41 (m, 8H). UPLC-MS (Method C): Rt 5.42 min, m/z calculated [M+H]: 990.8, found 990.9.



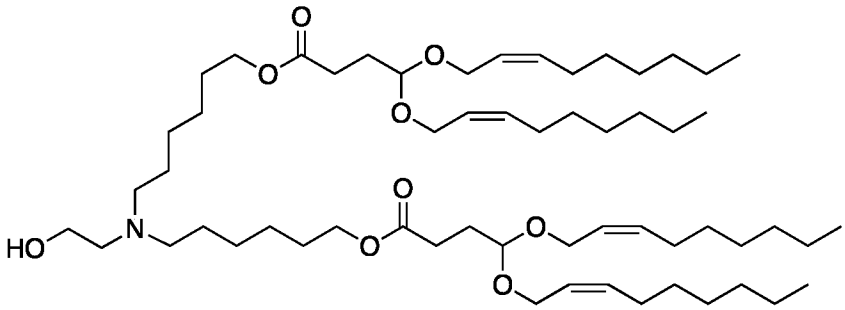
Example 8-78: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate)

[1134] Prepared according to General Procedure G, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 100 mg, 60% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.93 (t, *J* = 7.5 Hz, 12H), 1.29 – 1.44 (m,25H), 1.49 – 1.69 (m, 9H), 1.83 – 1.96 (m, 7H), 1.96 – 2.08 (m, 17H), 2.37 (t, *J* = 7.6 Hz, 5H), 2.50 – 3.19 (m, 7H), 3.34 – 3.44 (m, 5H), 3.50 – 3.61 (m, 5H), 3.80 (t, *J* = 5.2 Hz, 2H), 4.04 (t, *J* = 6.7 Hz, 5H), 4.48 (t, *J* = 5.5 Hz, 2H), 5.24 – 5.41 (m, 8H). UPLC-MS (Method B): Rt 2.41 min, m/z calculated [M+H]: 976.8, found 976.9.



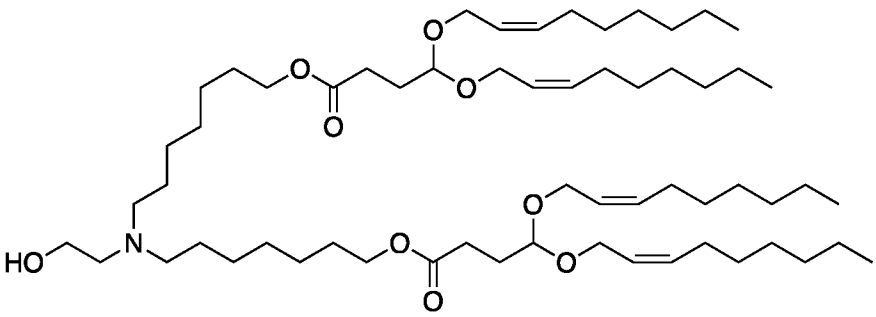
Example 8-79: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate)

[1135] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-non-6-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 62 mg, 56% yield. UPLC-MS (Method B): Rt 2.42 min, m/z calculated [M+H]: 1004.8, found 1004.9.

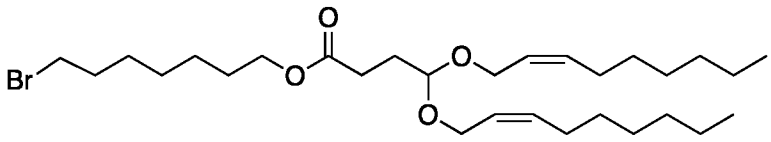


Example 8-80: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate)

[1136] Prepared according to General Procedure G, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 45 mg, 68% yield. UPLC-MS (Method B): Rt 2.44 min, m/z calculated [M+H]: 962.8, found 962.9.



Example 8-81: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate)

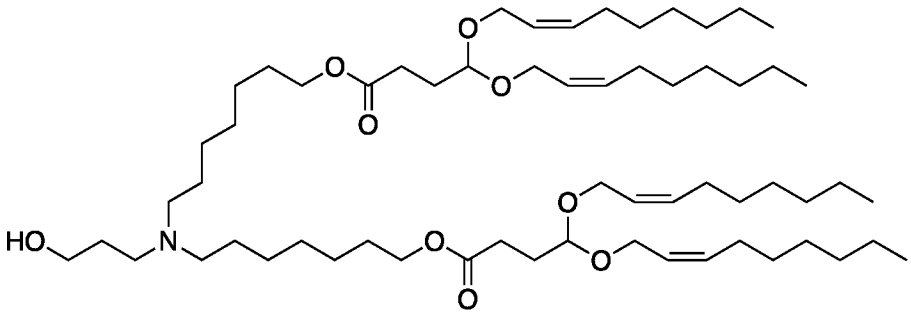


Step 1: 7-bromoheptyl 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoate

[1137] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 231 mg, 52% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.87 (t, *J* = 7.0 Hz, 6H), 1.21 – 1.38 (m, 19H), 1.39 – 1.51 (m, 2H), 1.54 – 1.68 (m, 2H), 1.79 – 1.90 (m, 2H), 1.96 (q, *J* = 7.4 Hz, 2H), 2.05 (q, *J* = 6.7 Hz, 5H), 2.38 (t, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 4.01 – 4.18 (m, 6H), 4.59 (t, *J* = 5.6 Hz, 1H), 5.45 – 5.62 (m, 4H).

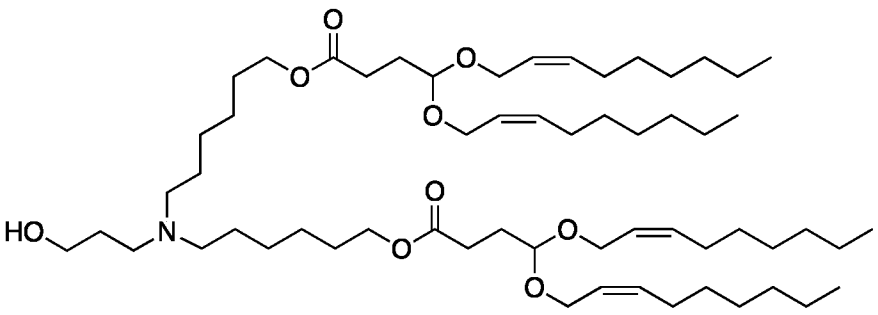
Step 2: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoate) (Example 8-81)

[1138] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((Z)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 52 mg, 55% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.83 – 0.91 (m, 12H), 1.19 – 1.44 (m, 45H), 1.57 – 1.66 (m, 4H), 1.75 – 1.90 (m, 4H), 1.96 (q, *J* = 7.4 Hz, 4H), 2.05 (q, *J* = 6.9 Hz, 8H), 2.38 (t, *J* = 7.5 Hz, 4H), 2.86 – 3.30 (m, 8H), 4.01 – 4.18 (m, 12H), 4.59 (t, *J* = 5.5 Hz, 2H), 5.45 – 5.62 (m, 8H). UPLC-MS (Method B): Rt 2.42 min, m/z calculated [M+H]: 990.8, found 990.9.



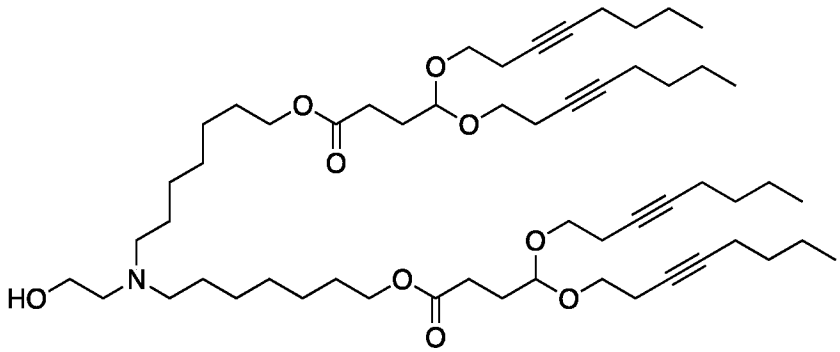
Example 8-82: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate)

[1139] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 51 mg, 54% yield. UPLC-MS (Method B): Rt 2.47 min, m/z calculated [M+H]: 1004.8, found 1004.9.

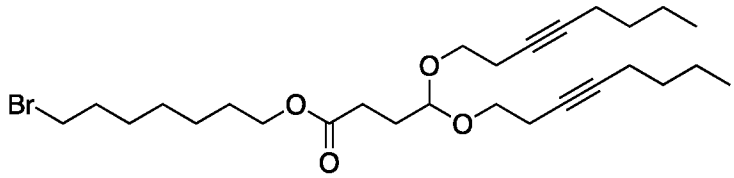


Example 8-83: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate)

[1140] Prepared according to General Procedure G, substituting 6-bromohexyl 4,4-bis(((*Z*)-non-2-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 105 mg, 64% yield. UPLC-MS (Method B): Rt 2.43 min, m/z calculated [M+H]: 976.8, found 976.9.



Example 8-84: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)

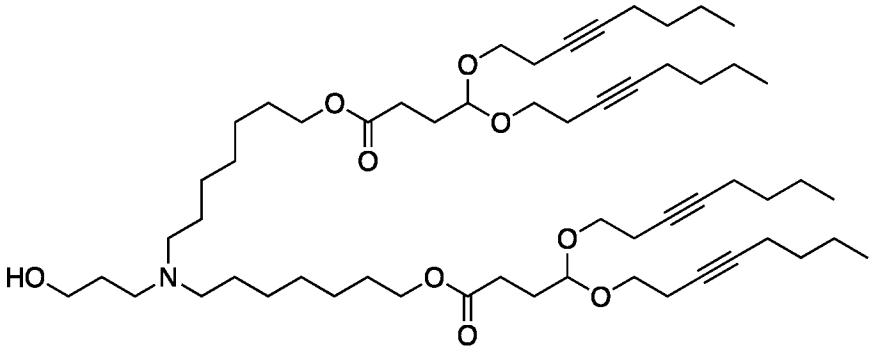


Step 1: 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate

[1141] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 400 mg, 67% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 6H), 1.29 – 1.49 (m, 14H), 1.56 – 1.70 (m, 2H), 1.77 – 1.99 (m, 4H), 2.06 – 2.19 (m, 4H), 2.35 – 2.45 (m, 6H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.59 (m, 2H), 3.61 – 3.72 (m, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.60 (t, *J* = 5.6 Hz, 1H).

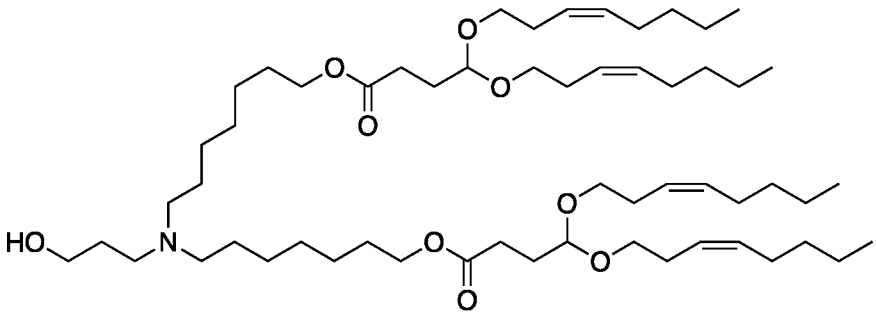
Step 2: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)) (Example 8-84)

[1142] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 97 mg, 65% yield. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 926.7, found 926.8.

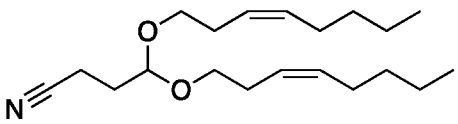


Example 8-85: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)

[1143] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(oct-3-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 90 mg, 72% yield. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 940.7, found 940.9.

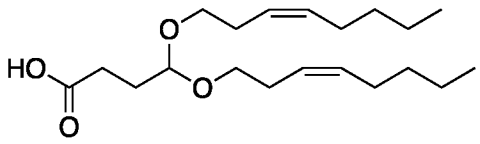


Example 8-86: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-3-en-1-yl)oxy)butanoate)



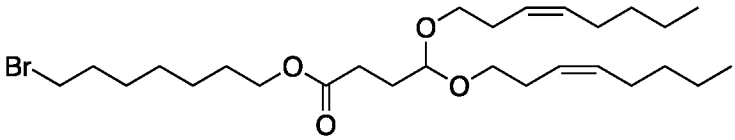
Step 1: 4,4-bis(((Z)-oct-3-en-1-yl)oxy)butanenitrile

[1144] Prepared according to General Procedure A, substituting (*Z*)-oct-3-en-1-ol for cis-5-octen-1-ol. Isolated 715 mg, 29%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 6.8 Hz, 6H), 1.21 – 1.41 (m, 8H), 1.94 (q, *J* = 7.2 Hz, 2H), 1.98 – 2.09 (m, 4H), 2.32 (q, *J* = 6.6 Hz, 4H), 2.41 (t, *J* = 7.3 Hz, 2H), 3.39 – 3.49 (m, 2H), 3.56 – 3.66 (m, 2H), 4.57 (t, *J* = 5.2 Hz, 1H), 5.28 – 5.41 (m, 2H), 5.41 – 5.53 (m, 2H)



Step 2: 4,4-bis(((Z)-oct-3-en-1-yl)oxy)butanoic acid

[1145] Prepared according to General Procedure B, substituting 4,4-bis(((*Z*)-oct-3-en-1-yl)oxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 650 mg, 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.0 Hz, 6H), 1.12 – 1.42 (m, 8H), 1.73 (q, J = 6.9 Hz, 2H), 2.01 (q, J = 6.9 Hz, 4H), 2.12 – 2.27 (m, 6H), 3.31 – 3.43 (m, 2H), 3.44 – 3.54 (m, 2H), 4.49 (t, J = 5.5 Hz, 1H), 5.30 – 5.47 (m, 4H), 12.04 (s, 1H).

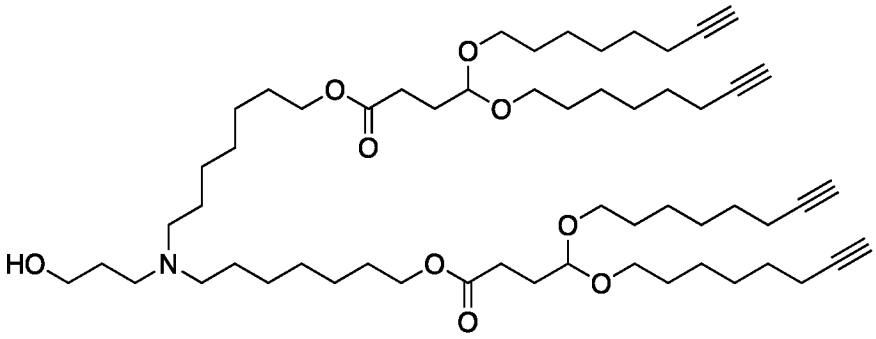


Step 3: 7-bromoheptyl 4,4-bis(((Z)-oct-3-en-1-yl)oxy)butanoate

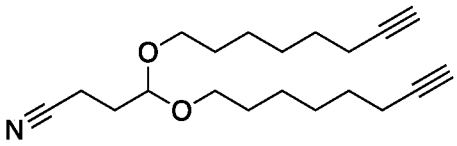
[1146] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-3-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 670 mg, 62% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.82 – 0.94 (m, 6H), 1.22 – 1.40 (m, 12H), 1.39 – 1.48 (m, 2H), 1.56 – 1.67 (m, 2H), 1.74 – 1.97 (m, 4H), 1.98 – 2.08 (m, 4H), 2.25 – 2.42 (m, 6H), 3.35 – 3.47 (m, 4H), 3.52 – 3.63 (m, 2H), 4.04 (t, J = 6.7 Hz, 2H), 4.52 (t, J = 5.6 Hz, 1H), 5.29 – 5.51 (m, 4H).

Step 4: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((Z)-oct-3-en-1-yl)oxy)butanoate) (Example 8-86)

[1147] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-3-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 80 mg, 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.5 Hz, 12H), 1.17 – 1.63 (m, 49H), 1.76 (q, J = 7.3 Hz, 2H), 1.92 – 2.08 (m, 16H), 2.29 (t, J = 7.2 Hz, 5H), 3.33 – 3.43 (m, 5H), 3.43 – 3.54 (m, 4H), 3.94 – 4.03 (m, 4H), 4.43 (q, J = 5.4 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.34 min, m/z calculated [M+H]: 948.8, found 948.8.

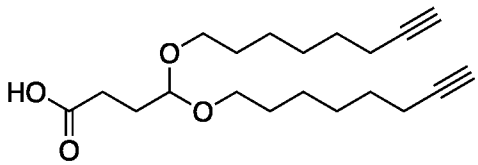


Example 8-87: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-7-yn-1-yloxy)butanoate)



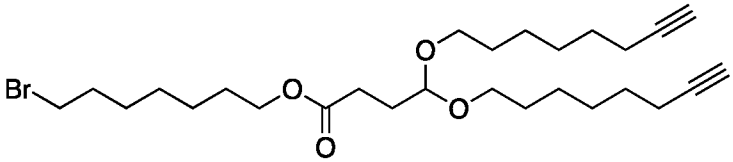
Step 1: 4,4-bis(oct-7-yn-1-yloxy)butanenitrile

[1148] Prepared according to General Procedure A, substituting oct-7-yn-1-ol for cis-5-octen-1-ol. Isolated 350 mg, 28%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.29 – 1.48 (m, 8H), 1.47 – 1.64 (m, 8H), 1.88 – 1.98 (m, 4H), 2.14 – 2.23 (m, 4H), 2.40 (t, *J* = 7.2 Hz, 2H), 3.32 – 3.48 (m, 2H), 3.54 – 3.65 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H).



Step 2: 4,4-bis(oct-7-yn-1-yloxy)butanoic acid

[1149] Prepared according to General Procedure B, substituting 4,4-bis(oct-7-yn-1-yloxy)butanenitrile for 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanenitrile. Isolated 340 mg, 92%. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 1.27 – 1.38 (m, 8H), 1.35 – 1.54 (m, 8H), 1.73 (q, *J* = 7.2 Hz, 2H), 2.09 – 2.19 (m, 4H), 2.21 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 2.4 Hz, 2H), 3.31 – 3.40 (m, 2H), 3.44 – 3.54 (m, 2H), 4.45 (t, *J* = 5.6 Hz, 1H), 12.03 (s, 1H).

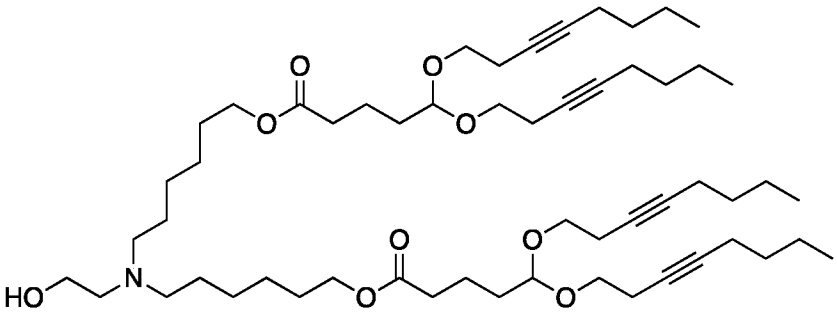


Step 3: 7-bromoheptyl 4,4-bis(oct-7-yn-1-yloxy)butanoate

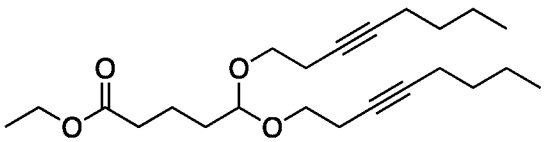
[1150] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 4,4-bis(oct-7-yn-1-yloxy)butanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 330 mg, 64% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.28 – 1.49 (m, 20H), 1.55 – 1.69 (m, 5H), 1.75 – 2.02 (m, 5H), 2.11 – 2.24 (m, 4H), 2.37 (t, *J* = 7.0 Hz, 2H), 3.37 – 3.42 (m, 4H), 3.51 – 3.62 (m, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 4.41 – 4.53 (m, 1H).

Step 4: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-7-yn-1-yloxy)butanoate) (Example 8-87)

[1151] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(oct-7-yn-1-yloxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 90 mg, 72% yield. UPLC-MS (Method B): Rt 2.01 min, m/z calculated [M+H]: 940.7, found 940.8.



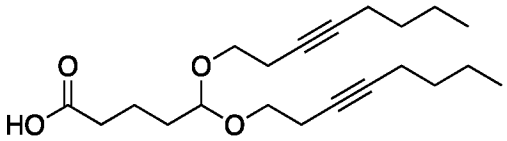
Example 8-88: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(oct-3-yn-1-yloxy)pentanoate)



Step 1: ethyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate

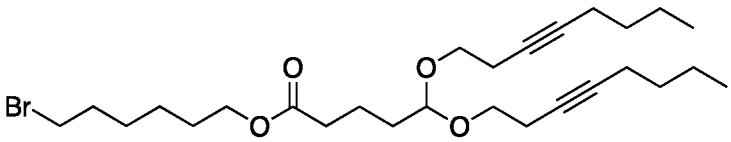
[1152] Sodium sulfate (1.7 g, 12.48 mmol) was taken into a flame-dried two-neck 100 mL round-bottom flask under vacuum for 15 minutes. Then a solution of ethyl 5-oxopentanoate (600 mg, 4.16 mmol) in DCM (10.0 mL) was added at 25 °C followed by oct-3-yn-1-ol (1.5 g, 12.48 mmol) and $KHSO_4$ (170 mg, 1.24 mmol). The resulting mixture was stirred for 12 h. Upon completion, solid was separated by filtration and concentrated under reduced pressure. Crude material thus obtained was purified by combiflash chromatography, eluted with 5% EtOAc-hexane to afford ethyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate (332 mg, 35%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ

0.94 (t, J = 7.8 Hz, 6H), 1.33 – 1.46 (m, 4H), 1.53 – 1.77 (m, 9H), 1.51 – 1.73 (m, 9H), 1.98 – 2.09 (m, 8H), 2.33 (t, J = 7.1 Hz, 2H), 3.34 – 3.45 (m, 2H), 3.51 – 3.61 (m, 2H), 4.44 (t, J = 5.1 Hz, 1H), 5.26 – 5.40 (m, 4H).



Step 2: 5,5-bis(oct-3-yn-1-yloxy)pentanoic acid

[1153] To a stirred solution of ethyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate (2.8 g, 7.40 mmol) in ethanol (20 mL), was added 1M NaOH solution (22 mL, 22 mmol). The reaction mixture was stirred at 25 °C for 6 h. Upon completion, the mixture was neutralized with 1M HCl and extracted with DCM (3x100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 5,5-bis(oct-3-yn-1-yloxy)pentanoic acid (1.8 g, 87%), which was used in the next step without further purification.^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 6.4 Hz, 6H), 1.21 – 1.47 (m, 14H), 2.06 – 2.16 (m, 4H), 2.18 – 2.29 (m, 4H), 3.36 – 3.49 (m, 4H), 4.70 (t, J = 5.4 Hz, 2H).

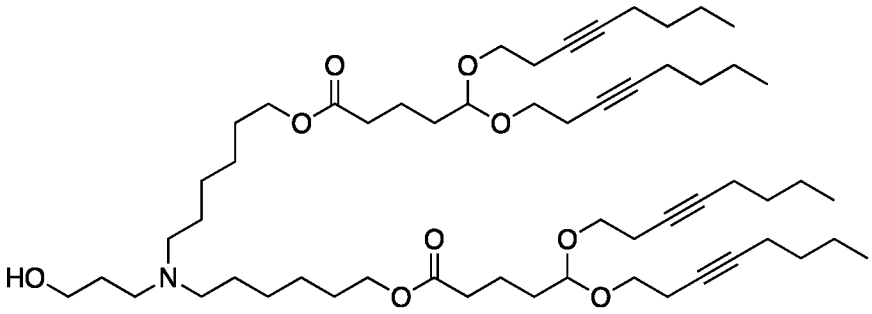


Step 3: 6-bromohexyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate

[1154] Prepared according to General Procedure C, substituting 5,5-bis(oct-3-yn-1-yloxy)pentanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 482 mg, 52% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, J = 6.7 Hz, 6H), 1.12 – 1.29 (m, 2H), 1.30 – 1.51 (m, 16H), 1.58 – 1.78 (m, 4H), 2.05 – 2.21 (m, 4H), 2.26 – 2.54 (m, 6H), 3.32 – 3.60 (m, 2H), 3.60 – 3.71 (m, 2H), 4.12 (t, J = 6.9 Hz, 2H), 4.58 (s, 1H).

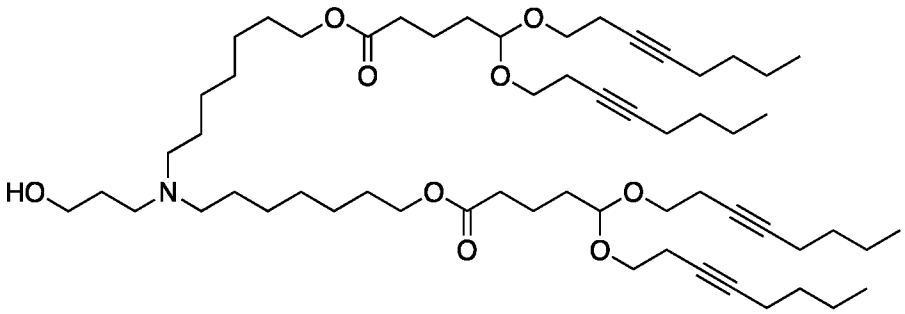
Step 4: ((2-hydroxyethyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(oct-3-yn-1-yloxy)pentanoate) (Example 8-88)

[1155] Prepared according to General Procedure G, substituting 6-bromohexyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 106 mg, 33% yield. UPLC-MS (Method B): Rt 2.03 min, m/z calculated [M+H]: 926.7, found 926.8.

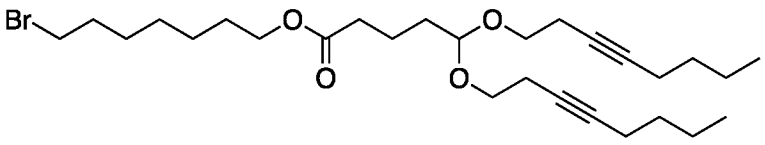


Example 8-89: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(5,5-bis(oct-3-yn-1-yloxy)pentanoate)

[1156] Prepared according to General Procedure G, substituting 6-bromohexyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 106 mg, 37% yield. UPLC-MS (Method B): Rt 1.91 min, m/z calculated [M+H]: 940.7, found 941.2.



Example 8-90: ((3-hydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(5,5-bis(oct-3-yn-1-yloxy)pentanoate)

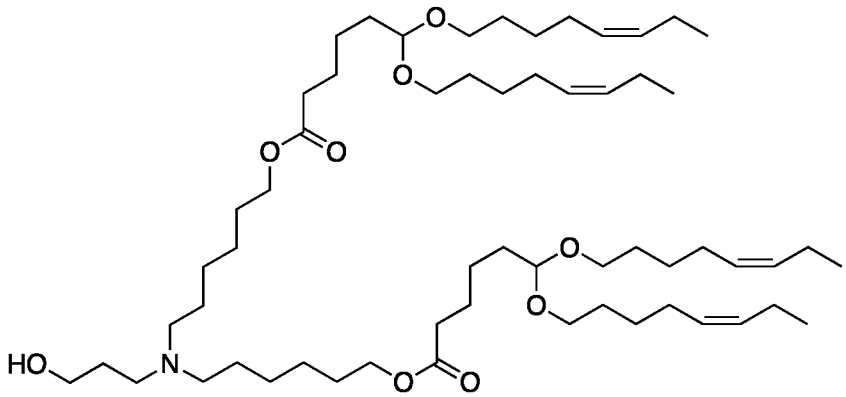


Step 1: 7-bromoheptyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate

[1157] Prepared according to General Procedure C, substituting 7-bromoheptan-1-ol for 6-bromohexan-1-ol and 5,5-bis(oct-3-yn-1-yloxy)pentanoic acid for 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoic acid. Isolated 665 mg, 49% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.0 Hz, 6H), 1.21 (d, *J* = 6.2 Hz, 6H), 1.28 – 1.51 (m, 15H), 1.59 – 1.76 (m, 4H), 2.06 – 2.21 (m, 4H), 2.28 (t, *J* = 7.0 Hz, 2H), 2.36 – 2.48 (m, 4H), 3.54 (q, *J* = 7.0 Hz, 2H), 3.66 (q, *J* = 7.2 Hz, 2H), 4.44 – 4.62 (m, 1H), 4.86 – 5.09 (m, 1H).

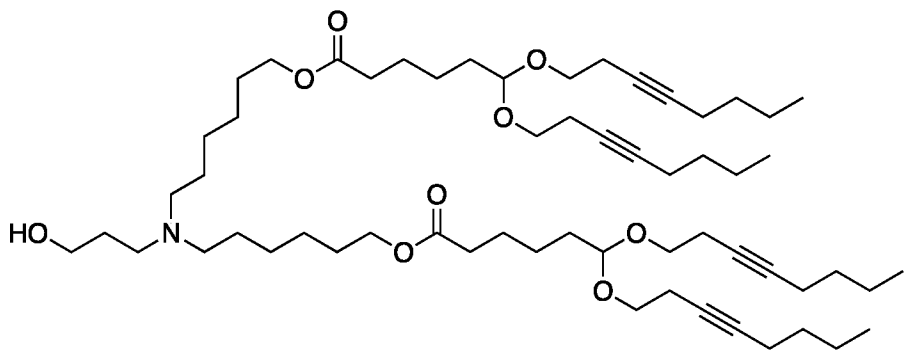
Step 2: ((2-hydroxyethyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(oct-3-yn-1-yloxy)butanoate)) (Example 8-90)

[1158] Prepared according to General Procedure G, substituting 7-bromoheptyl 5,5-bis(oct-3-yn-1-yloxy)pentanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 52 mg, 51% yield. UPLC-MS (Method B): Rt 2.05 min, m/z calculated [M+H]: 968.8, found 968.7.



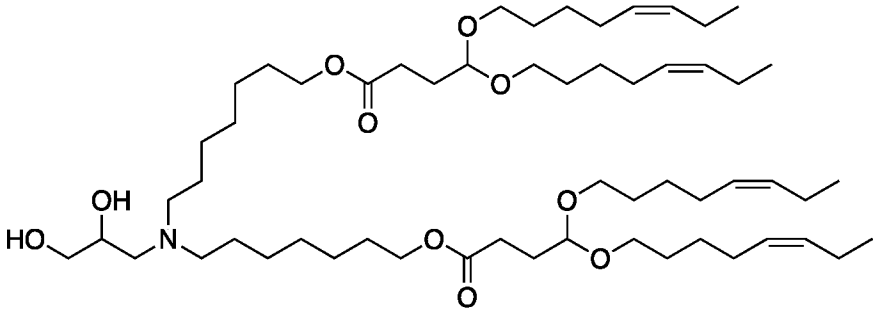
Example 8-91: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate)

[1159] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(((*Z*)-oct-5-en-1-yl)oxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 90 mg, 70% yield. UPLC-MS (Method B): Rt 2.21 min, m/z calculated [M+H]: 976.8, found 976.8.



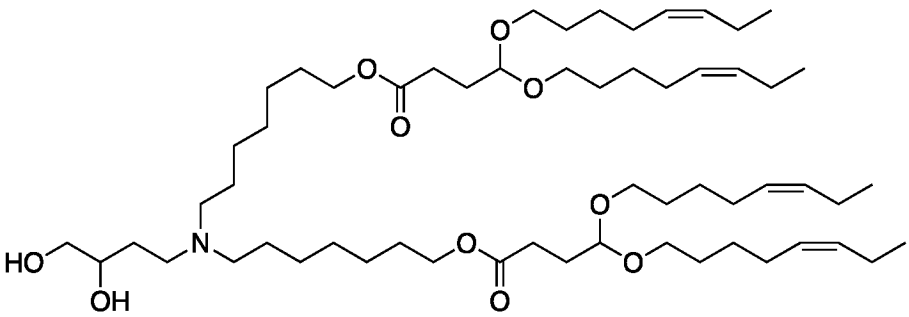
Example 8-92: ((3-hydroxypropyl)azanediyl)bis(hexane-6,1-diyl) bis(6,6-bis(oct-3-yn-1-yloxy)hexanoate)

[1160] Prepared according to General Procedure G, substituting 6-bromohexyl 6,6-bis(oct-3-yn-1-yloxy)hexanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 47 mg, 56% yield. UPLC-MS (Method B): Rt 2.07 min, m/z calculated [M+H]: 968.8, found 968.8.



Example 8-93: ((2,3-dihydroxypropyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

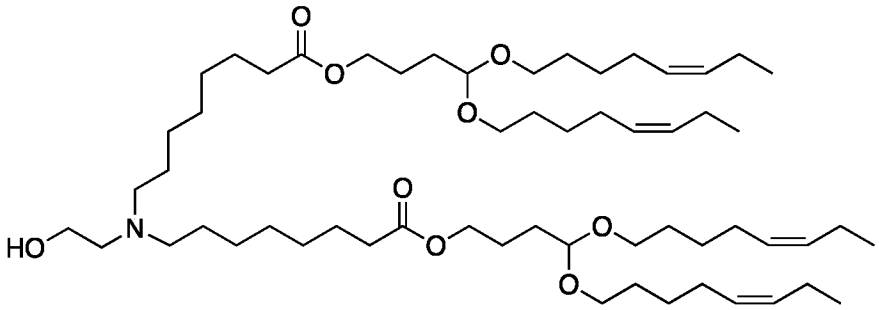
[1161] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropane-1,2-diol for 2-aminoethan-1-ol. Isolated 73 mg, 46% yield. UPLC-MS (Method B): Rt 2.11 min, m/z calculated [M+H]: 964.8, found 964.7.



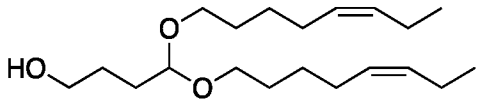
Example 8-94: ((3,4-dihydroxybutyl)azanediyl)bis(heptane-7,1-diyl) bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate)

[1162] Prepared according to General Procedure G, substituting 7-bromoheptyl 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 4-aminobutane-1,2-diol for 2-aminoethan-1-ol. Isolated 69 mg, 49% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 12H), 1.20 – 1.41 (m, 32H), 1.41 – 1.67 (m, 17H), 1.76 (q, J = 7.1 Hz, 4H), 1.91 – 2.08 (m, 16H), 2.24 – 2.37 (m, 4H), 3.31 – 3.40 (m, 4H), 3.44 – 3.55 (m, 4H),

3.99 (t, *J* = 6.4 Hz, 4H), 4.45 (t, *J* = 5.6 Hz, 2H), 5.23 – 5.40 (m, 8H). UPLC-MS (Method B): Rt 2.09 min, m/z calculated [M+H]: 978.8, found 978.7.

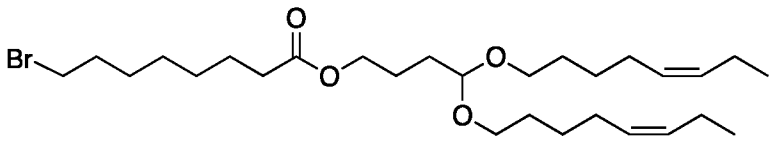


Example 8-95: bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butyl) 8,8'-((2-hydroxyethyl)azanediyl)dioctanoate



Step 1: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butan-1-ol

[1163] To a stirred solution of 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butanoic acid (900 mg, 2.64 mmol) in THF (10 mL) was added $LiAlH_4$ (2.4 M in THF) (2.2 mL, 5.28 mmol) at 0 °C. Reaction mixture was stirred at 25 °C for 2 h. Upon completion, reaction mixture was quenched with saturated solution of ammonium chloride (70 mL) and extracted with ethyl acetate (2x100 mL). Combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Crude material was purified by combiflash column chromatography, eluted with 30% ethyl acetate in hexane to afford 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butan-1-ol (650 mg, 75%). 1H NMR (400 MHz, Chloroform-d) δ 0.91 (t, *J* = 7.52 Hz, 6H), 1.33–1.52 (m, 13H), 1.97-2.02 (m, 8H), 3.33-3.39 (m, 4H), 3.45-3.51 (m, 2H), 4.35 (t, *J* =5.08 Hz, 1H), 4.42 (t, *J* =5.52 Hz, 1H), 5.25-5.37 (m, 4H).



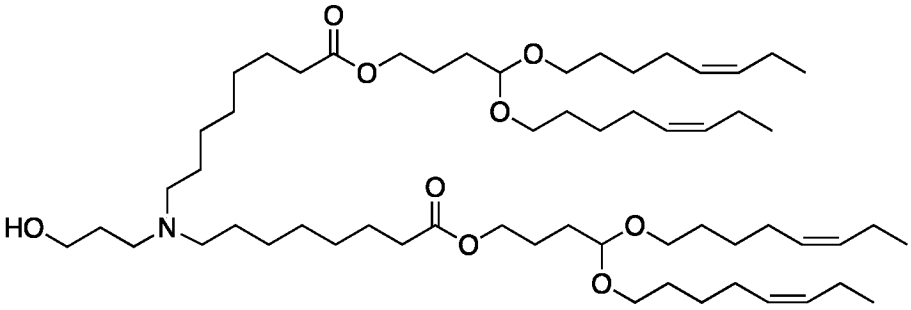
Step 2: 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butyl 8-bromooctanoate

[1164] Prepared according to General Procedure D, substituting 4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butan-1-ol for 1-nonanol. Isolated 470 mg, 49%. 1H NMR (400 MHz, Chloroform-d) δ 0.94 (t, *J* = 7.5 Hz, 6H), 1.20–1.43 (m, 10H), 1.54–1.67 (m, 10H), 1.80–1.85 (m, 2H), 1.98 – 2.04

(m, 8H), 2.28 (t, J = 7.56 Hz, 2H), 3.37–3.42 (m, 4H), 3.53–3.58 (m, 2H), 4.05-4.11 (m, 2H), 4.46 (m, 1H), 5.28–5.39 (m, 4H).

Step 3: bis(4,4-bis(((Z)-oct-5-en-1-yl)oxy)butyl) 8,8'-((2-hydroxyethyl)azanediyl)dioctanoate (Example 8-95)

[1165] Prepared according to General Procedure G, substituting 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate. Isolated 44 mg, 34% yield. UPLC-MS (Method B): Rt 2.19 min, m/z calculated [M+H]: 962.8, found 963.2.



Example 8-96: bis(4,4-bis(((*Z*)-oct-5-en-1-yl)oxy)butyl) 8,8'-((3-hydroxypropyl)azanediyl)dioctanoate

[1166] Prepared according to General Procedure G, substituting 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butyl 8-bromooctanoate for 6-bromohexyl 4,4-bis(((Z)-oct-5-en-1-yl)oxy)butanoate and 3-aminopropan-1-ol for 2-aminoethan-1-ol. Isolated 27 mg, 25% yield. UPLC-MS (Method B): Rt 2.39 min, m/z calculated [M+H]: 976.8, found 977.3.

Example 9: mRNA delivery of LNP preparations across a variety of cell types

[1167] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials that deliver functional mRNA to various cell types.

[1168] Six LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) were selected to determine each preparation's ability to deliver functional mRNA in mice across a variety of cell types (see FIGS. 10-13). LNP preparations each contained 1.0 mg/kg reporter mRNA as described herein. A flow assay as described herein was used to measure reporter surface expression at 24 hours post injection of LNP preparations (see FIGS. 10-13). FIGS. 10-13 also includes data for Exemplary

Lipid 4, which is an exemplary compound described in U.S. Provisional Application No. 63/128,682.

[1169] FIG. 10 depicts a bar graph showing functional delivery of mRNA encoding a reporter using exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to mice across a variety of HSC cell types (Lin-, Sca-1+, LSK cells, LT-HSCs (CD34-Flk2-), and LT-HSCs (CD150+CD48-)), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle). FIG. 11 depicts a bar graph showing functional delivery of mRNA encoding a reporter using exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to mice across a variety of bone marrow (BM) cell types (Live, T cells, B cells, CD11b, Macrophages, NK cells, CD11c), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle). FIG. 12 depicts a bar graph showing functional delivery of mRNA encoding reporter using exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to mice across a variety of spleen cell types (T cells, B cells, CD11b, Macrophages, NK cells, CD11c), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle). FIG. 13 depicts a bar graph that shows functional delivery of mRNA payloads encoding reporter in vivo using six exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11) to mice across a variety of liver cell types (CD31, Hepatocytes, CD45, CD11b, Kupffer cells, NK cells, T cells, B cells), with each LNP preparation containing 1.0 mg/kg reporter mRNA compared to a saline control (vehicle).

[1170] Unexpectedly, representative data in FIGS. 10-13 show that the screening platforms described herein can identify several highly potent LNP preparations for delivery of functional mRNA across a variety of cell types.

[1171] The present Example demonstrates that Exemplary Lipid 1, Exemplary Lipid 8, Exemplary Lipid 4, Exemplary Lipid 9, Exemplary Lipid 10, and Exemplary Lipid 11 effectively deliver mRNA across a variety of cell types in mice. Exemplary Lipids 1 and 8 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25, and Exemplary Lipid 9 is an exemplary compound described in U.S. Provisional Application No. 63/128,682. Accordingly, in some embodiments, the present example demonstrates lipids

characterized by having an ester-linked acetal feature are able to deliver functional mRNA in mice. Exemplary Lipids 10 and 11 are exemplary compound of any of Formulae A', A, III', and III, and exemplary compounds of compounds 8-1 to 8-20. Accordingly, in some embodiments, the present example demonstrates lipids characterized by having at least two ester-linked acetal features are able to deliver functional mRNA in mice. In fact, in some embodiments, Exemplary Lipids 10 and 11 exhibited improved delivery (for example, 1.5-2-fold improvement) of mRNA encoding a reporter to certain cell types (see FIGS. 10-13).

Example 10: mRNA delivery of LNP preparations to Spleen, Liver, and Bone Marrow Cells

[1172] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[1173] Forty LNP preparations (including Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25, and Exemplary Lipids 10 and 11, which are exemplary compounds of any of Formulae A', A, III', and III, and exemplary compounds of compounds 8-1 to 8-20) were selected to confirm efficacy results using a reporter system and C57BL6 mouse models described herein (see FIG. 14). Three C57BL6 mice per group were used in each experiment. Data was collected 24 hours post-injection

[1174] FIG. 14 depicts heat maps showing average median fluorescence of a variety of LNP preparations containing different ionizable lipids normalized to average median fluorescence of an LNP preparation containing Exemplary Lipid 1 across a variety of cell types (bone marrow dendritic cells, splenic B cells, and splenic dendritic cells). Each LNP preparation contained 1.0 mg/kg reporter mRNA. Median normalized fluorescence values referring to Exemplary Lipid 1, Exemplary Lipid 10, and Exemplary Lipid 11 are indicated as "1". "10, and "11", respectively (see FIG. 14, bottom left schematic). "X" indicates a variety of different exemplary lipids that were tested in accordance with the embodiments of the present disclosure. FIG. 14 shows that Exemplary Lipid 11 conferred improved potency compared to Exemplary Lipid 1 in bone marrow dendritic cells and in splenic B cells. FIG. 14 shows that Exemplary Lipids 15 and 16, which are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25, conferred improved potency compared to Exemplary Lipid 1 in splenic dendritic cells.

[1175] FIG. 15 depicts two heat maps showing normalized average % reporter expression (FIG. 15, left) or average normalized median fluorescence (FIG. 15, right) of a variety of LNP preparations containing different ionizable lipids. Average % reporter and average median fluorescence values were normalized to % reporter expression (FIG. 15, left) or average median fluorescence (FIG. 15, right), respectively, of an LNP preparation containing Exemplary Lipid 1 delivered to T cells (bone marrow cells). Stars indicate LNP formulations that resulted in greater average % reporter expression compared to average % reporter expression using an LNP preparation containing Exemplary Lipid 1. Design layout of tested exemplary LNP preparations is depicted in the bottom left schematic of FIG. 14.

[1176] FIG. 16 depicts two heat maps showing normalized average % reporter expression (FIG. 16, left) or average median fluorescence (FIG. 16, right) of a variety of LNP preparations containing different ionizable lipids. Average % reporter and average median fluorescence values were normalized to average % reporter expression (FIG. 16, left) or average median fluorescence (FIG. 16, right), respectively, of an LNP preparation containing Exemplary Lipid 1 delivered to LSK (Lin-Sca-1+c-Kit+) cells. Stars indicate LNP formulations that resulted in greater average % reporter expression compared to average % reporter expression using an LNP preparation containing Exemplary Lipid 1. Design layout of exemplary LNP preparations tested is depicted in the bottom left schematic of FIG. 14.

[1177] FIG. 17 depicts plots showing % reporter expression of Exemplary Lipid 1 compared to Exemplary Lipid 11 in HSPCs and mouse LT-HSCs.

[1178] Unexpectedly, representative data in FIGS. 14-17 show that the screening platforms described herein can identify several highly potent LNP preparations to determine what type of LNP preparation would be most potent for a particular cell type.

[1179] The present Example demonstrates that ionizable lipids tested in this Example, which are exemplary compounds of any of Formulae A', A, I", I', I, III', and III, effectively deliver mRNA across a variety of cell types in mice.

[1180] Exemplary Lipid 1, Exemplary Lipid 15, and Exemplary Lipid 16 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having an ester-linked acetal feature show potent delivery across various cell

types, including bone marrow dendritic cells, bone marrow T cells, splenic B cells, splenic dendritic cells, and LSK (Lin-Sca-1+c-Kit+) cells, HSPCs, and mouse LT-HSCs.

[1181] Exemplary Lipid 10 and 11 are exemplary compounds of any of Formulae A', A, III', and III, and exemplary compounds of compounds 8-1 to 8-20. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having at least two ester-linked acetal features show potent delivery across various cell types, including bone marrow dendritic cells, bone marrow T cells, splenic B cells, splenic dendritic cells, and LSK (Lin-Sca-1+c-Kit+) cells, HSPCs, and mouse LT-HSCs.

Example 11: mRNA delivery of LNP preparations to Balb/C, C57BL6J mouse strains & humanized (NSG-CD34+) immune mice

[1182] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent mRNA delivery to various cell types as described herein.

[1183] Two LNP preparations (including Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25, and Exemplary Lipid 11, which is an exemplary compound of any of Formulae A', A, III', and III, and one of compounds 8-1 to 8-20) were selected to confirm efficacy results using a reporter system and a humanized (NSG-CD34+) mouse model or two mice strains (Balb/C, C57BL6J) mice as described herein (see FIGS. 18-19). Each LNP preparation contained 1.0 mg/kg reporter mRNA.

[1184] FIG. 18 shows bar graphs that each depict delivery of mRNA encoding reporter using exemplary LNP preparations described herein to bone marrow cells (left) and blood cells (right) in humanized (NSG-CD34+) mice. Data for delivery of mRNA encoding reporter using exemplary LNP preparations in accordance with the present disclosure are not shown for all cell types tested (e.g., liver, spleen, other bone marrow cells, lymph nodes, and peyes patch).

[1185] FIG. 19 shows bar graphs that each depict delivery of mRNA encoding reporter using exemplary LNP preparations described herein to blood cells (left), bone marrow (live cells) (middle), and bone marrow (LSK cells) in two mouse strains (Balb/C, C57BL6J mice). Data for delivery of mRNA using exemplary LNP preparations in accordance with the present disclosure are not shown for all cell types tested (e.g., spleen). Data is also not shown for specific subsets of cells (e.g., B cells, T cells, NK cells, monocytes, hepatocytes, or endothelial cells).

[1186] Three Balb/C mice and/or C57BL6J and/or NSG-CD34+ mice per group were used in each experiment. Data was collected 24 hours post-injection. Unexpectedly, representative data in FIGS. 18-19 show that the screening platforms described herein can identify several highly potent LNP preparations to determine what type of LNP preparation would be most potent for a particular cell type.

[1187] The present Example demonstrates that Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25, and Exemplary Lipid 11, which is an exemplary compound of any of Formulae A', A, III', and III, and one of compounds 8-1 to 8-20, effectively deliver mRNA across a variety of cell types in mice. Exemplary Lipid 1 is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having an ester-linked acetal feature show potent delivery across various cell types, including bone marrow live cells, bone marrow CD34+ cells, bone marrow (LSK cells), human LT-HSCs, blood cells (huCD45+), and blood cells (muCD45+). Exemplary Lipid 10 and 11 are exemplary compounds of any of Formulae A', A, III', and III, and exemplary compounds of compounds 8-1 to 8-20. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having at least two ester-linked acetal features show potent delivery across various cell types, bone marrow live cells, bone marrow CD34+ cells, bone marrow (LSK cells), human LT-HSCs, blood cells (huCD45+), and blood cells (muCD45+).

Example 12: LNP preparations for intramuscular mRNA delivery to draining lymph nodes

[1188] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials that deliver mRNA to draining lymph nodes (e.g., for use as mRNA vaccines).

[1189] Ten LNP preparations (including an exemplary lipid characterized as having at least two ester-linked acetal features and exemplary lipids characterized as having an ester-linked acetal feature as described herein) were selected to determine each preparation's ability to intramuscularly deliver functional mRNA in Balb/C mice. Each LNP preparation contained 10 μg of Trilink Fluc mRNA. Six hours post injection, skin-draining lymph nodes (dLN) were isolated and luminescence was measured using standard luminescence assays as described herein (see FIG. 20).

[1190] Unexpectedly, representative data in FIG. 20 shows that the screening platforms described herein can identify several highly potent LNP preparations to determine what type of LNP preparation would be most potent for mRNA delivery to draining lymph nodes (e.g., for use as a mRNA vaccines).

[1191] Representative lipids depicted in FIG. 20 are exemplary compounds of any of Formulae A', A, I", I', I, III', and III. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having one or more ester-linked acetal features show potent delivery to draining lymph nodes.

Example 13: Utilization of LNP preparations for base editing in spleen, liver, and bone marrow

[1192] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials that confer gene editing (e.g., using base editors) in a variety of cell types.

Methods

[1193] Five exemplary LNP preparations (Exemplary Lipid 1, Exemplary Lipid 12, Exemplary Lipid 13, and Exemplary Lipid 14) were selected to determine each preparation's ability to perform base editing in a Balb/C mouse model as described herein.

[1194] Lipid nanoparticle components were dissolved in 100% ethanol at specified lipid component molar ratios. mRNA encoding an adenine base editor and a chemically-modified sgRNA was dissolved at a mass ratio of 1:1 in 10 mM citrate, 100 mM NaCl, pH 4.0, resulting in a concentration of NA cargo of approximately 0.22 mg/mL. LNP preparations were formulated with molar ratios of 50% Ionizable Lipid: 38.5% Cholesterol : 1.5% PEG2000-DMG: 10% DSPC total lipid to NA mass ratio of 11.7 to 33. LNP preparations were formed by microfluidic mixing of the lipid and NA solutions using a Precision Nanosystems NanoAssemblr Spark or Benchtop series Instruments, according to the manufacturers protocol. A 3:1 ratio of aqueous to organic solvent was maintained during mixing using differential flow rates. After mixing, LNP preparations were collected, diluted in PBS (approximately 2:1 v/v), and further buffer exchange was conducted using dialysis in PBS at 4°C for 8 to 24 hours against a 20 kDa filter. After this initial dialysis, each individual LNP preparation was characterized via dynamic light scattering (DLS) to measure size and polydispersity. pKa of a subpopulation of LNP preparations was measured via TNS assay. After dialysis, LNP preparations were sterile filtered using 0.22 micron

sterile filter and stored at 4 °C for further use. In some embodiments, LNP preparations may be concentrated using 100kDa Amicon filters per manufacturers protocol.

LNP Characterization

[1195] DLS - LNP preparation hydrodynamic diameter and polydispersity index (PDI) was measured using high throughput dynamic light scattering (DLS) (DynaPro plate reader II, Wyatt). LNP preparations were diluted 1X PBS to an appropriate concentration and analyzed.

Concentration & Encapsulation Efficiency

[1196] Concentration of NA was determined by Qubit microRNA kit (for siRNA) or HS RNA kit (for mRNA) per manufacturer's instructions. Encapsulation efficiency was determined by measuring unlysed and lysed LNPs.

LNP Administration

[1197] Male Balc/C mice aged approximately 8-12 weeks were used in the experiments described herein. Each mouse is temporarily restrained, and LNP preparations are administered IV via tail vein injection. Age-matched mice are also used to administer vehicle (1X PBS) via tail vein injection as a control. Four to six days post-dose, tissues including liver, spleen, and bone marrow were collected. Genomic DNA was isolated and fragmented and adapter-ligated using the Nextera DNA Flex Library Prep Kit (Illumina) using the 96-well plate Nextera indexing primers (Illumina), according to the manufacturer's instructions. Library size and concentration was confirmed by Fragment Analyzer (Agilent) and sent to Novogene for whole genome sequencing using an Illumina HiSeq.

Base editing

[1198] For base editing, mRNA encoding an adenine base editor (ABE) and a guide RNA (sgRNA) targeting ALAS1 at 1:1 (mass ratio) were coencapsulated in LNP preparations as described herein. LNP preparations were administrated into Balb/c mice through tail vein injections at 3.0 mg/kg total RNA. At 4 days after dosing, mice were euthanized and liver, spleen and bone barrow were harvested. Base editing was determined by performing targeted deep sequencing analysis at the ALAS1 target site using extracted genomic DNA.

Results

[1199] FIGS. 21-23 show bar graphs depicting base editing in bone marrow cells, spleen cells, and liver cells using a variety of LNP preparations containing different exemplary lipids described herein. Results are also shown in Table 2.

Table 2.

Group	Treatment	Dose (mg/kg)	Payload	mRNA:sgRNA	Route	N	Necropsy Date
1	PBS	-	-	-	IV	5	4 days
2	Exemplary Lipid 1, N/P=4.3	3	mRNA encoding Exemplary Adenine Base Editor + Exemplary sgRNA	1:1	IV	5	4 days
3	Exemplary Lipid 12, N/P=4.3	3		1:1	IV	5	4 days
4	Exemplary Lipid 13, N/P=4.3	3		1:1	IV	5	4 days
5	Exemplary Lipid 14, N/P=4.3	3		1:1	IV	5	4 days
6	Exemplary Lipid 11, N/P=4.3	3		1:1	IV	5	4 days

[1200] Unexpectedly, representative data in FIGS. 21-23 show that the screening platforms described herein can identify several highly potent LNP preparations to determine what type of LNP preparation would be most potent for base editing of a variety of cell types *in vivo*. In particular, FIGS. 21 and 22 show that LNP preparations containing Exemplary Lipid 11 edited bone marrow and spleen cells more effectively than LNP preparations containing Exemplary Lipid 1, Exemplary Lipid 12, Exemplary Lipid 13, and Exemplary Lipid 14.

[1201] The present Example demonstrates that Exemplary Lipid 1, Exemplary Lipid 12, Exemplary Lipid 13, Exemplary Lipid 14, which are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25, and Exemplary Lipid 11, which is an exemplary compound of any of Formulae A', A, III', and III, and one of compounds 8-1 to 8-20, effectively can perform base editing of cells in mice.

[1202] Exemplary Lipid 1, Exemplary Lipid 12, Exemplary Lipid 13, and Exemplary Lipid 14 depicted in FIGS. 21-23 are exemplary compounds of any of Formulae A', A, I", I', and I, and exemplary compounds of compounds 7-1 to 7-25. Exemplary Lipid 11 depicted in FIGS. 21-23 is an exemplary compound of any of Formulae A', A, III', and III, and one of compounds 8-1 to

8-20. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having one or more ester-linked acetal features can be used to perform base editing in a variety of cell types, including bone marrow, spleen, and liver. Without wishing to be bound by any theory, the present Example demonstrates that LNP preparations containing an exemplary compound of any of Formulae A', A, I", I', I, III', and III improve delivery of LNP preparations to particular cell types. Moreover, without wishing to be bound by any theory, the present Example demonstrates that mRNA contained with LNP preparations containing an exemplary compound of any of Formulae A', A, I", I', I, III', and III are more stabilized in the LNP during delivery.

Example 14: Exemplary LNP preparations are delivered to mouse HSPCs

[1203] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[1204] One LNP preparation (Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25), having a diameter of 85 nm, a polydispersity index (PDI) of 0.08, and encapsulation efficiency of 96.5%, was selected to confirm efficacy results using a Cre reporter system and Ai14 mouse model described herein at three different doses (0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg; see FIG. 24). FIG. 24 shows % tdTomato+ HSPCs (Lineage negative, Sca-1 positive, cKit positive) isolated from bone marrow 72 hours after LNP administration between 0.1 and 1.0 mg/kg Cre mRNA.

[1205] Exemplary Lipid 1 depicted in FIG. 24 is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having one or more ester-linked acetal features exhibit a dose-dependent increase in particular cell types such as transfected HSPCs.

Example 15: Exemplary LNP preparations are delivered to mouse HSPCs

[1206] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[1207] One LNP preparation (Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25) was selected to confirm efficacy results using a Cre reporter system and Ai14 mouse model described herein by monitoring the

durability of % tdTomato+ in HSPCs at multiple timepoints. FIG. 25A shows % tdTomato+ HSPCs at 2, 8, and 16 weeks post LNP delivery at a dose of 0.3 mg/kg Cre mRNA. FIG. 25B shows % tdTomato+ HSPCs at 2, 8, and 16 weeks post LNP delivery at a dose of 1.0 mg/kg Cre mRNA.

[1208] Having observed durability of the transfected HSPCs, the transfected HSPCs were analyzed to determine their capacity for reconstituting various immune and hematopoietic lineages by measuring the % tdTomato+ abundance in peripheral blood at the 16-week timepoint in monocytes, B cells, T cells, and red blood cells in the mice cohorts administered 0.3 mg/kg and 1.0 mg/kg Cre mRNA (FIG. 25C and FIG. 25D, respectively).

[1209] Exemplary Lipid 1 depicted in FIGS. 25A-25D is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that use of lipids characterized by having one or more ester-linked acetal features result in durable LNP delivery to HSPCs. Moreover, the present Example demonstrates that transfected HSPCs can reconstitute a hematopoietic compartment. Without wishing to be bound by any theory, the present Example demonstrates that LNP preparations containing an exemplary compound of Formula A or I are tolerated and do not impair pluripotency of HSPCs.

Example 16: Exemplary LNP preparations are delivered to human CD34+ HSPCs *in vitro*

[1210] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[1211] One LNP preparation (Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25) was selected to confirm efficacy results in human CD34+ HSPCs *in vitro*.

[1212] Briefly, human CD34+ cells were thawed and then plated in a 48-well tissue culture plate at 40,000 cells/well in a cell culture plate. Cells were incubated for 48 hours to reach homeostasis in StemSpan cell culture media (Stem Cell Technologies) supplemented with 10% Penicillin-Streptomycin and StemSpan CD34+ Expansion Supplement (Stem Cell Technologies). Prior to dosing with 1000 ng reporter mRNA encapsulated in the LNP , cells were centrifuged at 300xG and resuspended in supplemented media, as previously described. To test if ApoE was necessary for LNP uptake, 2 μL of recombinant human apoprotein E3 (ApoE3, R&D Systems) was added to

each well of interest. After 24 hours, cell Fc receptors were blocked with human TruStain FcX (Biolegend), washed with PBS, and fluorescently stained for reporter expression along with phenotyping markers and viability dye.

[1213] At 24 hours, approximately 80% of the CD34+ HSPCs in the LNP + ApoE3 expressed the reporter protein, whereas minimal expression was detected in the absence of ApoE3 (FIG. 26A and FIG. 26B).

[1214] Exemplary Lipid 1 depicted in FIGS. 26A-26B is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that lipids characterized by having one or more ester-linked acetal features result in increased reporter expression when delivered to particular cell types in the presence of ApoE.

Example 17: Exemplary LNP preparations are delivered to non-human primate HSPCs

[1215] The present Example provides exemplary LNP compositions, preparations, nanoparticles, and/or nanomaterials with potent delivery to various cell types as described herein.

[1216] One LNP preparation (Exemplary Lipid 1, which is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25) was selected to confirm efficacy results using a reporter system in non-human primates (NHPs). LNPs were dosed at 0.1, 0.3, and 1.0 mg/kg. FIG. 27 shows delivery of mRNA encoding reporter using exemplary LNP preparation to non-human primate HSPCs (as defined by lineage-negative CD34+ cells within the bone marrow) at 24 hours post-LNP administration.

[1217] Exemplary Lipid 1 depicted in FIG. 27 is an exemplary compound of any of Formulae A', A, I", I', and I, and one of compounds 7-1 to 7-25. Accordingly, in some embodiments, the present example demonstrates that in some embodiments, lipids characterized by including an ester-linked acetal feature show potent delivery to particular cell types in non-human primates (NHPs) across a range of doses.

Equivalents

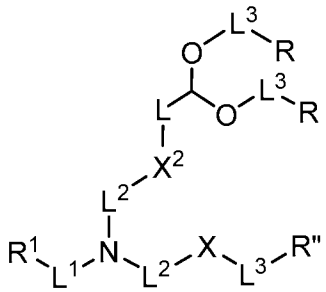
[1218] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the following claims:

Claims

We claim:

1. A compound of Formula A':



A'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

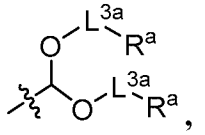
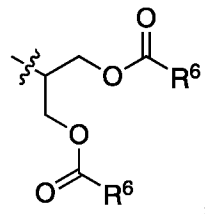
L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

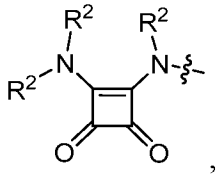
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

R" is hydrogen,  ,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each of R and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl

each of L^3 and L^{3a} is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

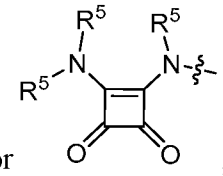
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, $-CN$, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, $-CN$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

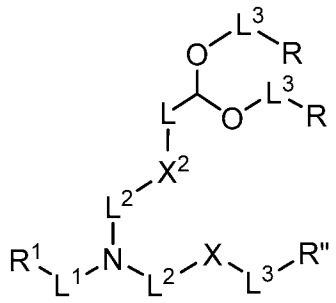
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

2. A compound of Formula I":



I"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

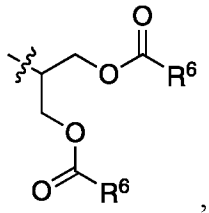
each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

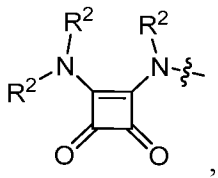
X is absent, -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, $-CN$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

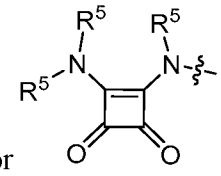
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

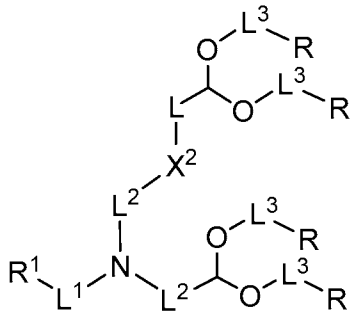
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

3. A compound of Formula II":



II"

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

L is C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

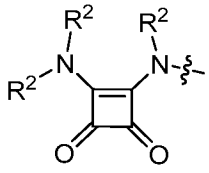
X^2 is -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$, $-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$,

$-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$;

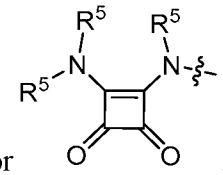
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

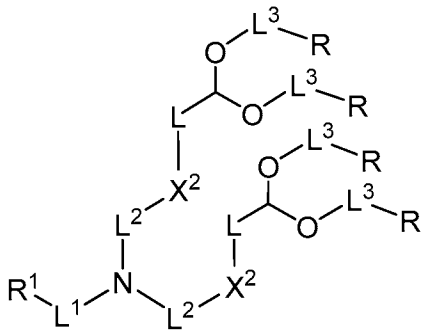
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

4. A compound of Formula III':



III'

or its N-oxide, or a pharmaceutically acceptable salt thereof, wherein

L^1 is absent, C_{1-6} alkylenyl, or C_{2-6} heteroalkylenyl;

each L^2 is independently optionally substituted C_{2-15} alkylenyl, or optionally substituted C_{3-15} heteroalkylenyl;

each L is independently C_{1-10} alkylenyl, or C_{2-10} heteroalkylenyl;

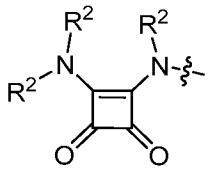
each X^2 is independently -OC(O)-, -C(O)O-, or -OC(O)O-;

each L^3 is independently absent, optionally substituted C_{1-10} alkylenyl, or optionally substituted C_{2-10} heteroalkylenyl;

each R is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 7- to 12-membered bridged bicyclic comprising 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 1-adamantyl, 2-adamantyl, sterolyl, and phenyl;

R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-OC(O)R^2$, $-OC(O)OR^2$, -CN, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-OC(O)N(R^2)_2$, $-N(R^2)C(O)OR^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-NR^2C(S)N(R^2)_2$, $-NR^2C(NR^2)N(R^2)_2$, $-NR^2C(CHR^2)N(R^2)_2$,

$-N(OR^2)C(O)R^2$, $-N(OR^2)S(O)_2R^2$, $-N(OR^2)C(O)OR^2$, $-N(OR^2)C(O)N(R^2)_2$, $-N(OR^2)C(S)N(R^2)_2$, $-N(OR^2)C(NR^2)N(R^2)_2$, $-N(OR^2)C(CHR^2)N(R^2)_2$, $-C(NR^2)N(R^2)_2$, $-C(NR^2)R^2$, $-C(O)N(R^2)OR^2$, $-C(R^2)N(R^2)_2C(O)OR^2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$; or

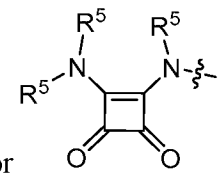
R^1 is  , or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups;

each R^2 is independently hydrogen, oxo, -CN, $-NO_2$, $-OR^4$, $-S(O)_2R^4$, $-S(O)_2N(R^4)_2$, $-(CH_2)_n-R^4$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 3- to 7-membered cycloaliphatic, 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^3 is independently $-(CH_2)_n-R^4$; or

two occurrences of R^3, taken together with the atom(s) to which they are attached, form optionally substituted 5- to 6-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^4 is independently hydrogen, $-OR^5$, $-N(R^5)_2$, $-OC(O)R^5$, $-OC(O)OR^5$, -CN, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-OC(O)N(R^5)_2$, $-N(R^5)C(O)OR^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, $-NR^5C(S)N(R^5)_2$, $-NR^5C(NR^5)N(R^5)_2$, or  ;

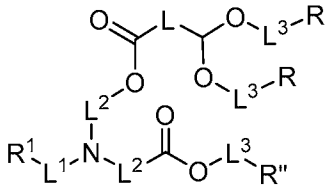
each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic; or

two occurrences of R^5, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur;

each R^6 is independently C_{4-12} aliphatic; and

each n is independently 0 to 4.

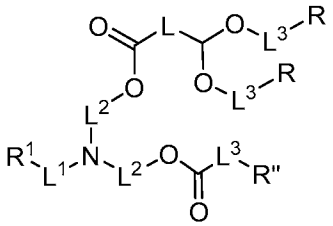
5. The compound according to claim 1 or 2, wherein the compound is of Formula I"-a:



I"-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

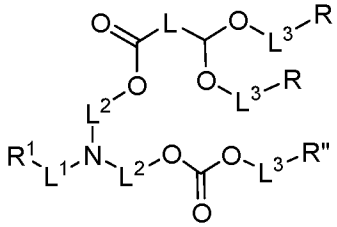
6. The compound according to claim 1 or 2, wherein the compound is of Formula I"-b:



I"-b

or its N-oxide, or a pharmaceutically acceptable salt thereof.

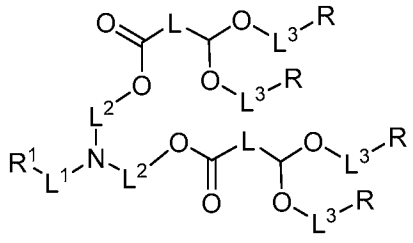
7. The compound according to claim 1 or 2, wherein the compound is of Formula I"-c:



I"-c

or its N-oxide, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1 or 4, wherein the compound is of Formula III-a:



III-a

or its N-oxide, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1-4, wherein each X^2 is -OC(O)-.

10. The compound according to any one of claims 1-4, wherein L^1 is absent, C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

11. The compound according to claim 10, wherein L^1 is C_{1-5} alkylenyl.

12. The compound according to any one of claims 1-4, wherein each L^2 is independently optionally substituted C_{2-9} alkylenyl, or optionally substituted C_{3-9} heteroalkylenyl.

13. The compound according to claim 12, wherein each L^2 is independently optionally substituted C_{2-9} alkylenyl.

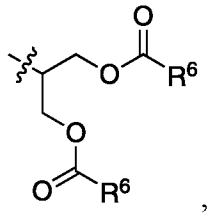
14. The compound according to any one of claims 1-4, wherein each L is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

15. The compound according to claim 14, wherein each L is independently C_{1-5} alkylenyl.

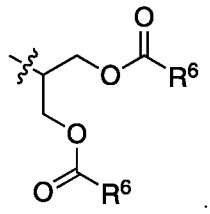
16. The compound according to any one of claims 1-4, wherein each of L^3 and L^{3a} is absent.

17. The compound according to any one of claims 1-4, wherein each of L^3 and L^{3a} is independently C_{1-5} alkylenyl, or C_{2-5} heteroalkylenyl.

18. The compound according to claim 17, wherein each of L^3 and L^{3a} is independently C_{1-5} alkylenyl.

19. The compound according to any one of claims 1-4, wherein R" is hydrogen,  , or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl.

20. The compound according to claim 19, wherein R" is hydrogen.

21. The compound according to claim 19, wherein R" is  .

22. The compound according to claim 19, wherein R" is optionally substituted C_{6-20} aliphatic.

23. The compound according to claim 22, wherein R" is C_{6-20} haloaliphatic.

24. The compound according to claim 19, wherein R" is optionally substituted 3- to 7-membered cycloaliphatic.

25. The compound according to claim 19, wherein R" is optionally substituted 1-adamantyl.

26. The compound according to claim 19, wherein R" is optionally substituted phenyl.

27. The compound according to any one of claims 1-4, wherein each of R and R^a is independently hydrogen, or an optionally substituted group selected from C_{6-20} aliphatic, 3- to 12-membered cycloaliphatic, 1-adamantyl, and phenyl

28. The compound according to claim 27, wherein each of R and R^a is hydrogen.

29. The compound according to claim 27, wherein each of R and R^a is independently optionally substituted C_{6-20} aliphatic.

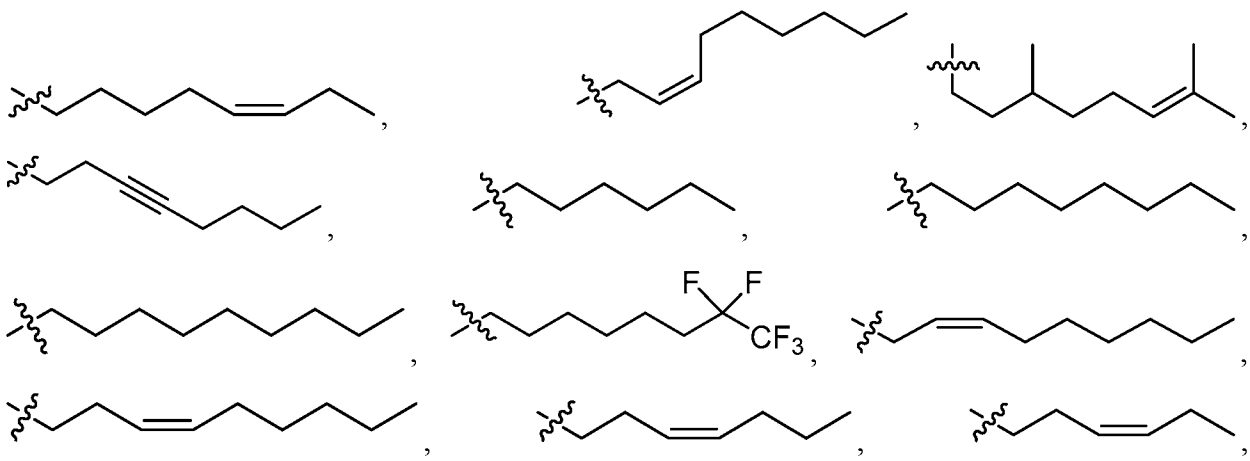
30. The compound according to claim 29, wherein each of R and R^a is independently C_{6-20} haloaliphatic.

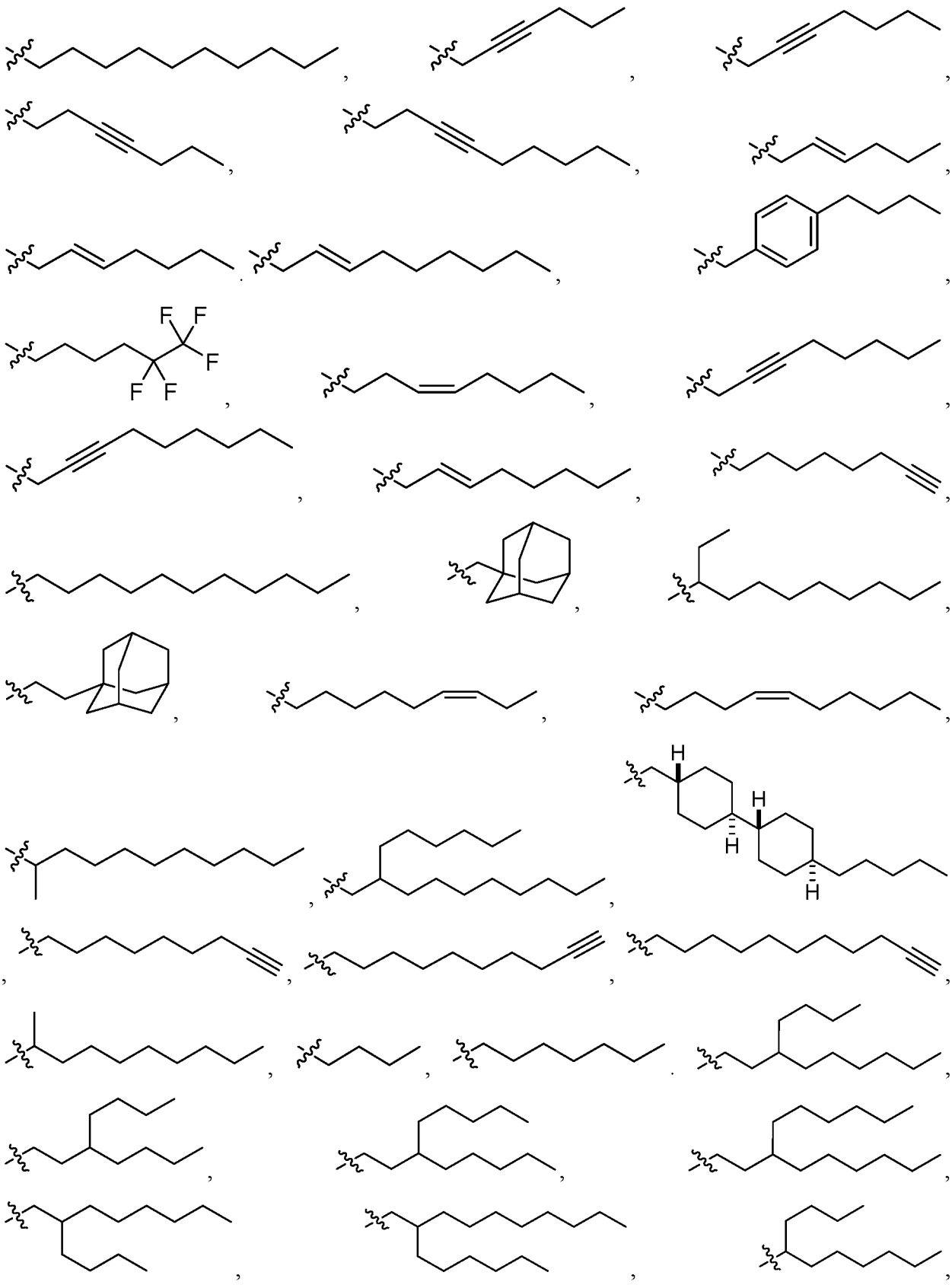
31. The compound according to claim 27, wherein each of R and R^a is independently optionally substituted 3- to 7-membered cycloaliphatic.

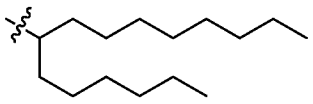
32. The compound according to claim 27, wherein each of R and R^a is independently optionally substituted 1-adamantyl.

33. The compound according to claim 27, wherein each of R and R^a is independently optionally substituted phenyl.

34. The compound according to any one of claims 1-4, wherein each of $-L^3-R''$, $-L^3-R$ and $-L^{3a}-R^a$ is independently selected from the group consisting of




F
F
F
F
F
H
H
H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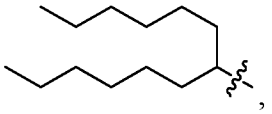
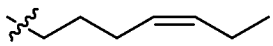

,

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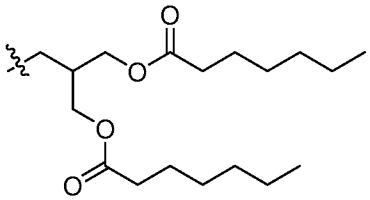
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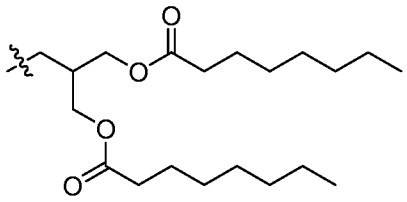
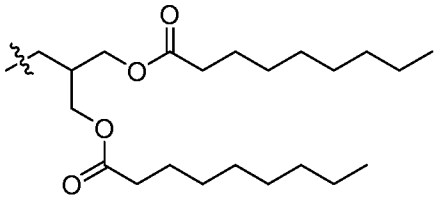

, and

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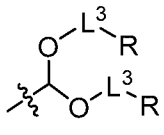
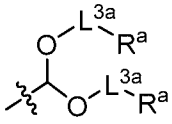
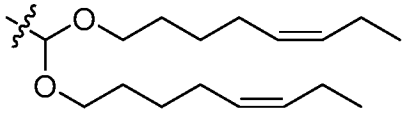
35. The compound according to any one of claims 1-4, wherein each of  and  is independently selected from the group consisting of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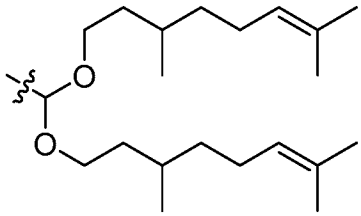
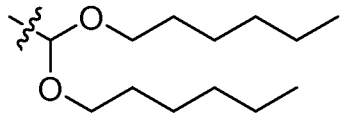

,

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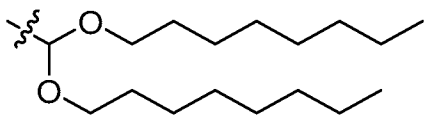
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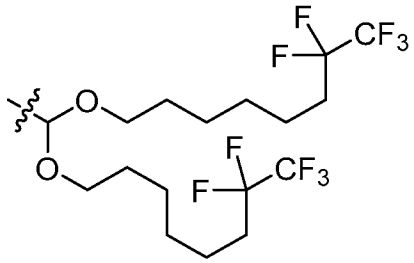
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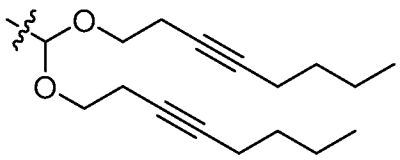
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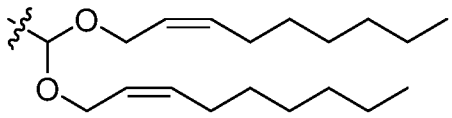
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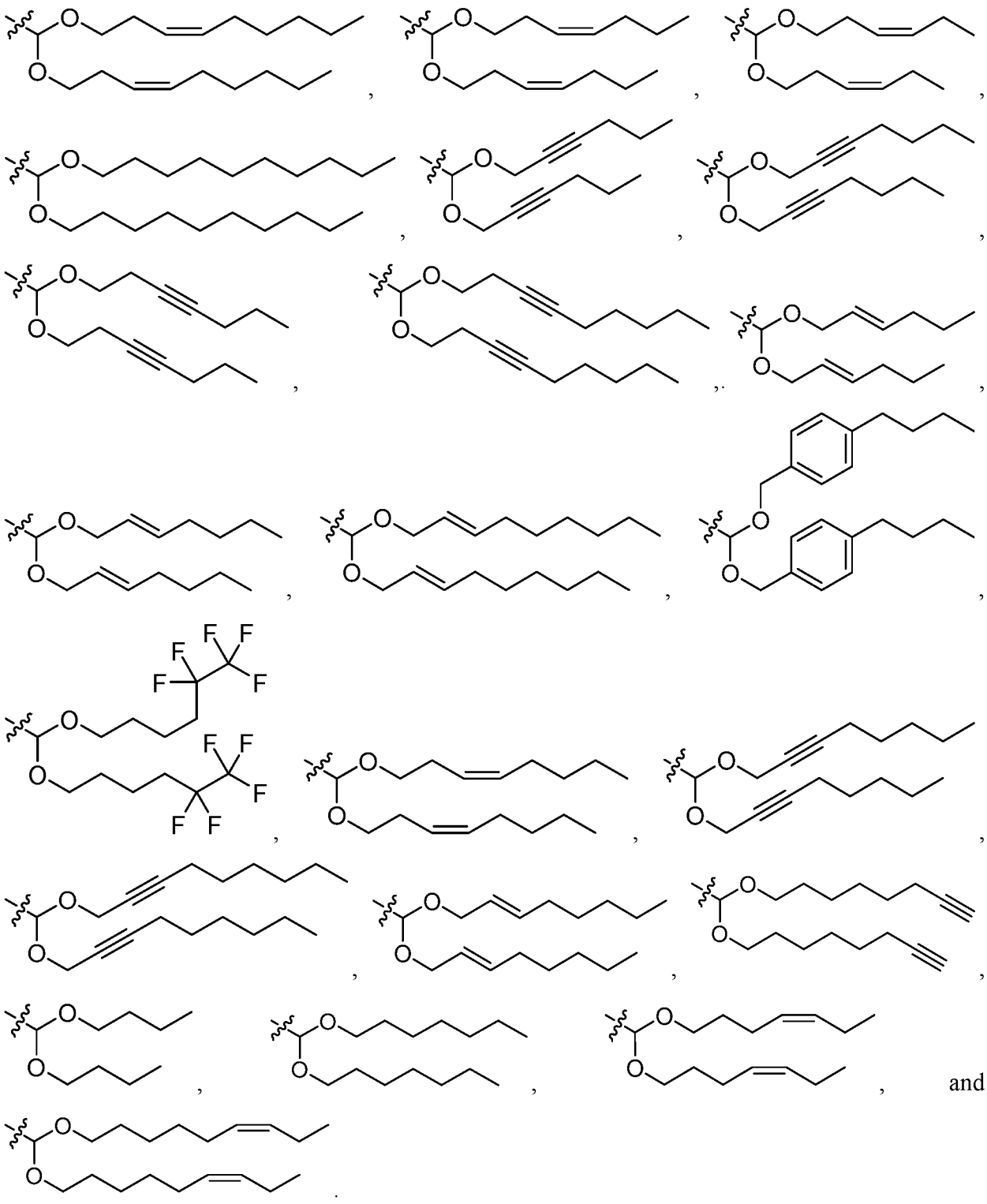


36. The compound according to any one of claims 1-4, wherein R^1 is hydrogen, optionally substituted phenyl, optionally substituted 3- to 7-membered cycloaliphatic, optionally substituted

3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, or $-P(O)(OR^2)_2$.

37. The compound according to any one of claims 1-4, wherein R^1 is hydrogen, optionally substituted phenyl, optionally substituted 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, optionally substituted 8- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, $-OR^2$, $-C(O)OR^2$, $-C(O)SR^2$, $-N(R^2)_2$, $-C(O)N(R^2)_2$, $-S(O)_2N(R^2)_2$, $-NR^2C(O)R^2$, $-NR^2S(O)_2R^2$, $-NR^2C(O)N(R^2)_2$, $-CR^2(R^3)_2$, $-OP(O)(OR^2)_2$, $-P(O)(OR^2)_2$, or a ring selected from 3- to 7-membered cycloaliphatic and 3- to 7-membered heterocyclyl comprising 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the cycloaliphatic or heterocyclyl ring is optionally substituted with 1-4 R^2 or R^3 groups.

38. The compound according to any one of claims 1-4, wherein each R^2 is independently hydrogen, $-(CH_2)_n-R^4$, or an optionally substituted group selected from phenyl, and 5- to 6-membered monocyclic heteroaryl comprising 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two occurrences of R^2, taken together with the atom(s) to which they are attached, form optionally substituted 4- to 7-membered heterocyclyl comprising 0-1 additional heteroatom selected from nitrogen, oxygen, and sulfur.

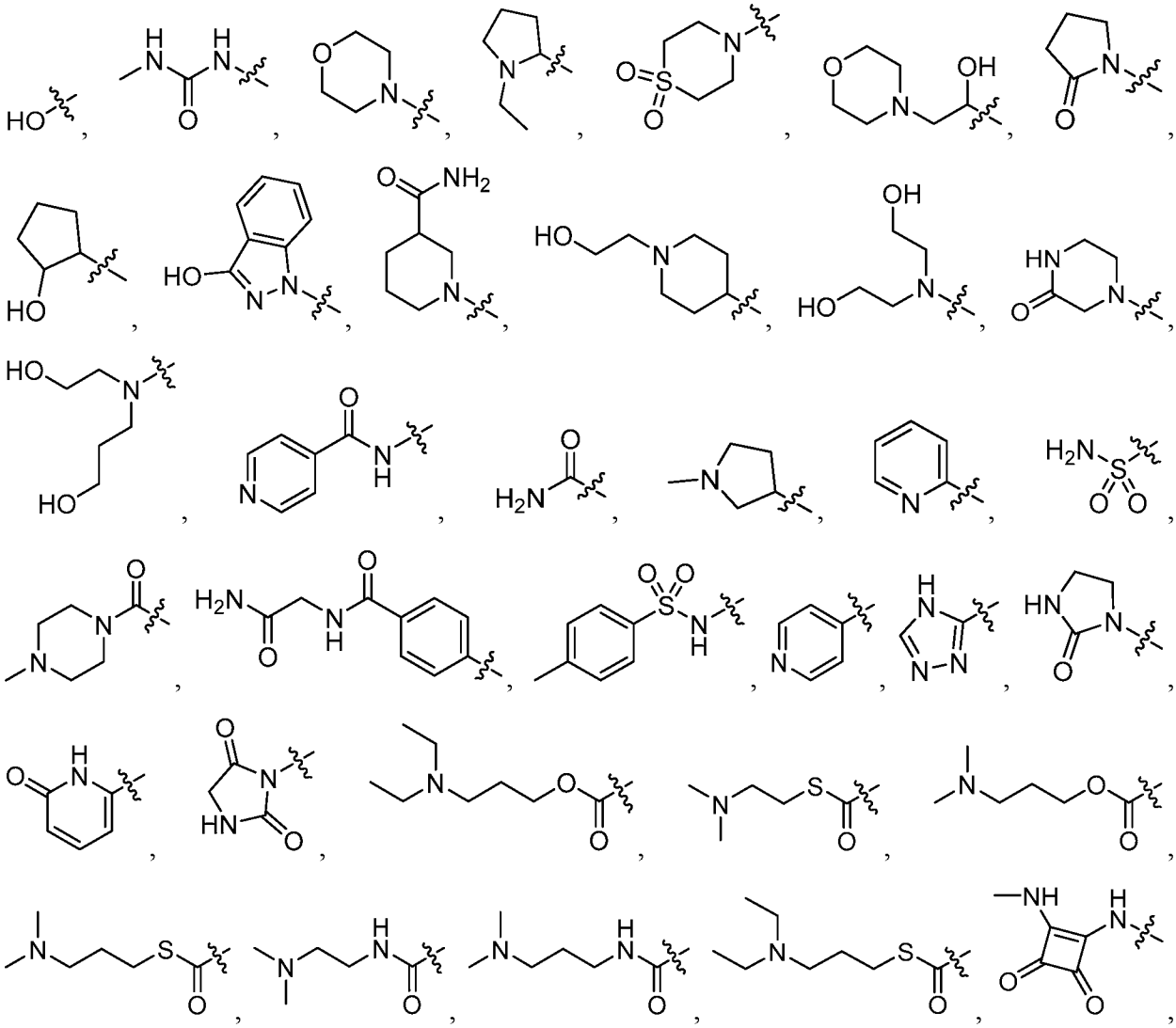
39. The compound according to any one of claims 1-4, wherein each R^3 is independently $-(CH_2)_n-R^4$.

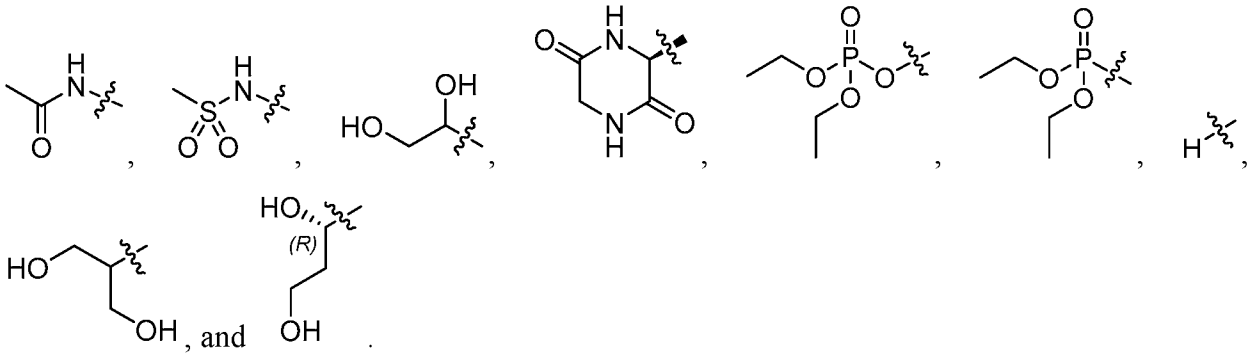
40. The compound according to any one of claims 1-4, wherein each R^4 is independently $-OR^5$ or $-N(R^5)_2$.

41. The compound according to any one of claims 1-4, wherein each R^5 is independently hydrogen, or optionally substituted C_{1-6} aliphatic.

42. The compound according to any one of claims 1-4, wherein each R^6 is independently C_{6-8} aliphatic.

43. The compound according to any one of claims 1-4, wherein R^1 is selected from the group consisting of





44. The compound according to claim 1, wherein the compound is selected from Table 1, or a pharmaceutically acceptable salt thereof.

45. A lipid nanoparticle (LNP) preparation comprising an ionizable lipid according to any one of claims 1-4 and 44.

46. A lipid nanoparticle (LNP) preparation comprising:
an ionizable lipid according to any one of claims 1-4 and 44;
a phospholipid;
a sterol; and
a conjugate-linker lipid (e.g., polyethylene glycol lipid).

47. The LNP preparation of claim 45, further comprising a therapeutic and/or prophylactic agent.

48. The LNP preparation of claim 47, wherein the therapeutic and/or prophylactic agent is or comprises one or more nucleic acids.

49. The LNP preparation of claim 48, wherein the one or more nucleic acids is or comprises RNA.

50. The LNP preparation of claim 49, wherein the one or more nucleic acids is or comprises DNA.

51. The LNP preparation of any one of claims 47-50, wherein the LNP preparation is formulated to deliver the therapeutic and/or prophylactic agent to target cells.

52. The LNP preparation of claim 51, wherein the target cells are or comprise spleen cells (e.g., splenic B cells, splenic T cells, splenic monocytes), liver cells (e.g., hepatocytes), bone marrow cells (e.g., bone marrow monocytes), immune cells, kidney cells, muscle cells, heart cells, or cells in the central nervous system.

53. The LNP preparation of claim 52, wherein the target cells are or comprise hematopoietic stem cells (HSCs).

54. A pharmaceutical composition comprising a LNP preparation of claim 45 and a pharmaceutically acceptable excipient.

55. A method for administering a therapeutic and/or prophylactic agent to a subject in need thereof, the method comprising administering the LNP preparation of claim 45 or the pharmaceutical composition of claim 54 to the subject.

56. A method for treating a disease or a disorder in a subject in need thereof, the method comprising administering the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, to the subject, wherein the therapeutic and/or prophylactic agent is effective to treat the disease.

57. A method for delaying and/or arresting progression a disease or a disorder in a subject in need thereof, the method comprising administering the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, to the subject, wherein the therapeutic and/or prophylactic agent is effective to treat the disease.

58. A method of delivering a therapeutic and/or prophylactic agent to a mammalian cell derived from a subject, the method comprising contacting the cell of the subject having been administered the LNP preparation of claim 45, or the pharmaceutical composition of claim 54.

59. A method of producing a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, wherein the therapeutic and/or prophylactic agent is or comprises an mRNA, and wherein the mRNA encodes the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide of interest.

60. A method of inhibiting production of a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, wherein the therapeutic and/or prophylactic agent is or comprises an RNA, whereby the RNA is capable of inhibiting production of the polypeptide of interest.

61. A method of specifically delivering a therapeutic and/or prophylactic agent to a mammalian organ, the method comprising contacting a mammalian organ with the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, whereby the therapeutic and/or prophylactic agent is delivered to the organ.

62. The method of claim 61, comprising administering to a subject the LNP preparation of claim 45, or the pharmaceutical composition of claim 54, to the subject.

63. A method of vaccinating by administering the LNP preparation of claim 45, or the pharmaceutical composition of claim 54.

64. A method of inducing an adaptive immune response in a subject, comprising administering to the subject an effective amount of a composition comprising at least one RNA; wherein the composition comprises a LNP preparation comprising a compound of any one of claims 1-4 and 44, or a pharmaceutically acceptable salt thereof.

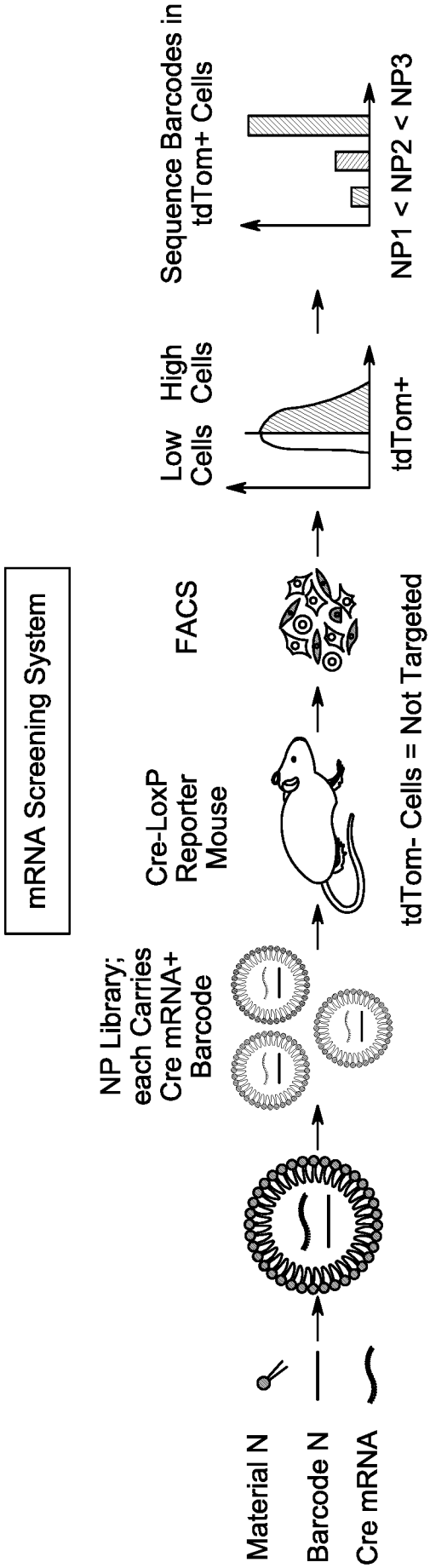

mRNA Screening System
Material N
Barcode N
Cre mRNA
NP Library; each Carries Cre mRNA+ Barcode
Cre-LoxP Reporter Mouse
FACS
tdTom- Cells = Not Targeted
tdTom+ Cells = Targeted
Low Cells
High Cells
tdTom+
Sequence Barcodes in tdTom+ Cells
NP1 < NP2 < NP3

FIG. 1

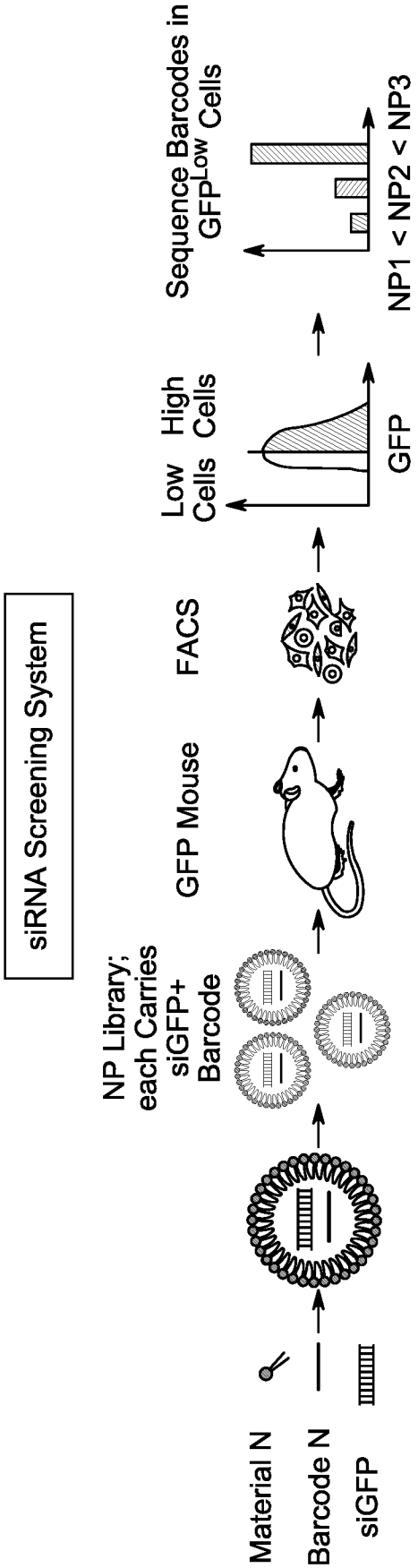

siRNA Screening System
Material N
Barcode N
siGFP
NP Library; each Carries siGFP+ Barcode
GFP Mouse
FACS
Low Cells
High Cells
GFP
GFP^High Cells = Not Targeted
GFP^Low Cells = Targeted
Sequence Barcodes in GFP^Low Cells
NP1 < NP2 < NP3

FIG. 2

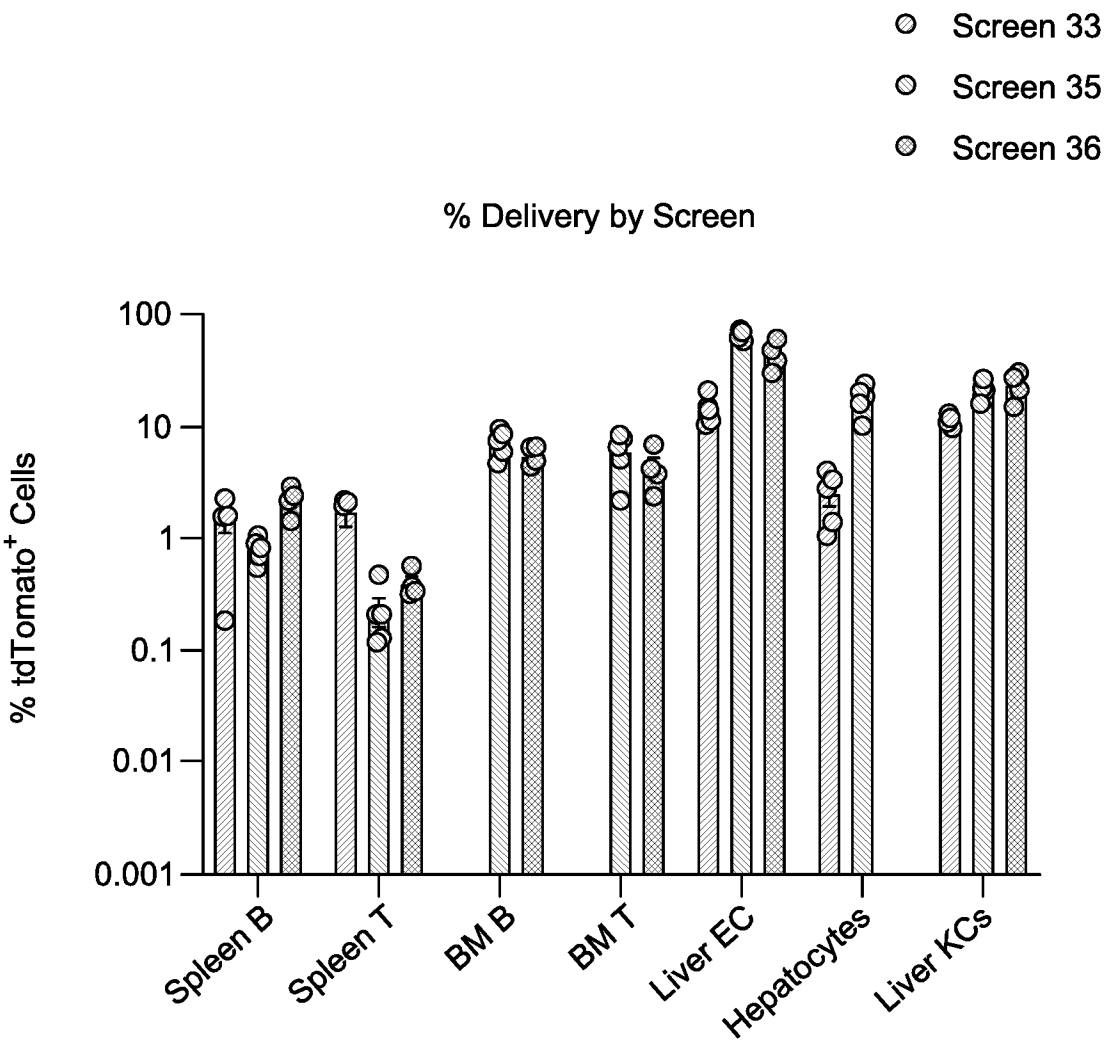

Screen 33
Screen 35
Screen 36
% Delivery by Screen
% tdTomato+ Cells
100
10
1
0.1
0.01
0.001
Spleen B
Spleen T
BM B
BM T
Liver EC
Hepatocytes
Liver KCs

FIG. 3

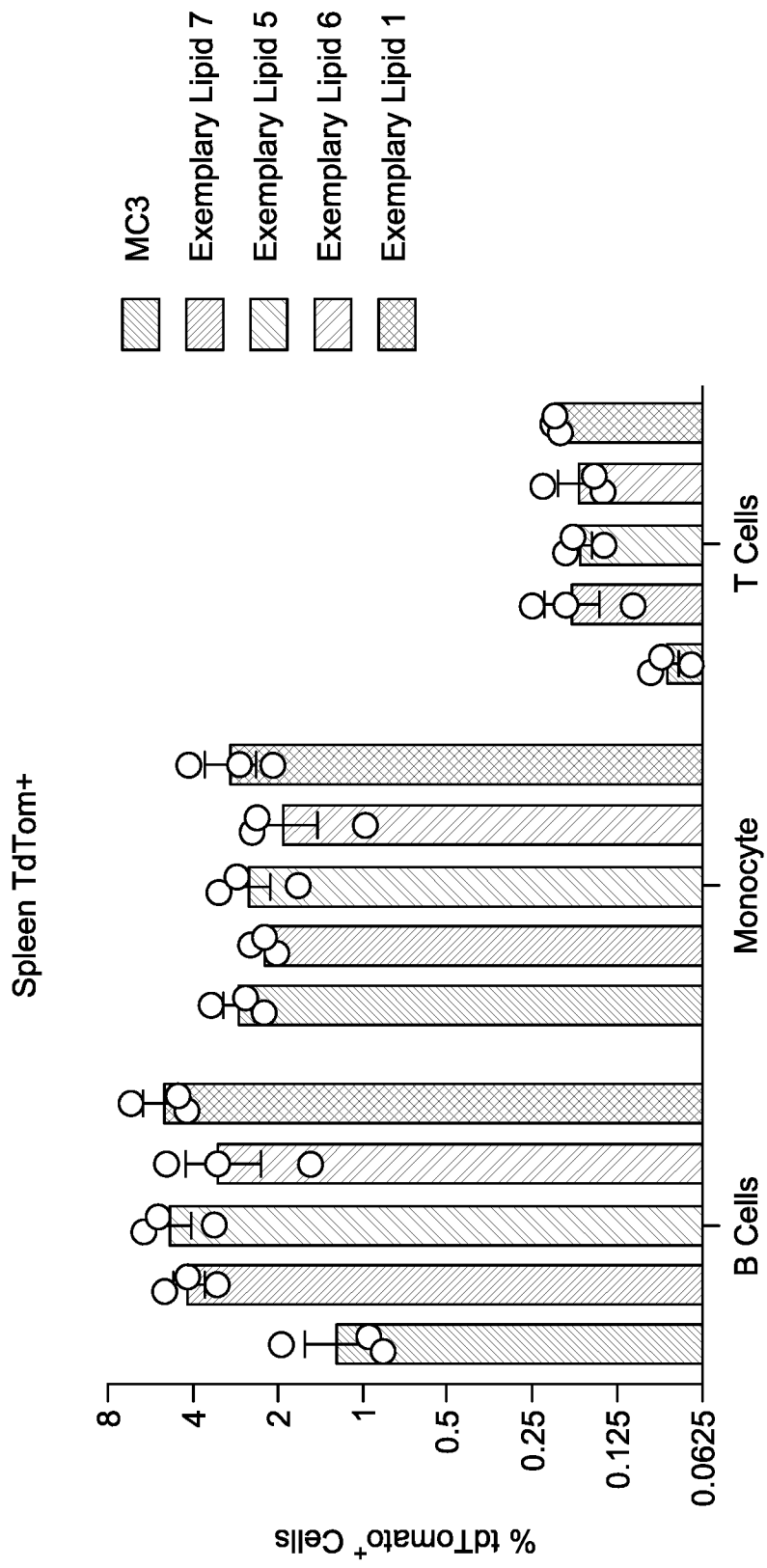

MC3
Exemplary Lipid 7
Exemplary Lipid 5
Exemplary Lipid 6
Exemplary Lipid 1
Spleen TdTom+
% tdTomato+ Cells
8
4
2
1
0.5
0.25
0.125
0.0625
B Cells
Monocyte
T Cells

FIG. 4

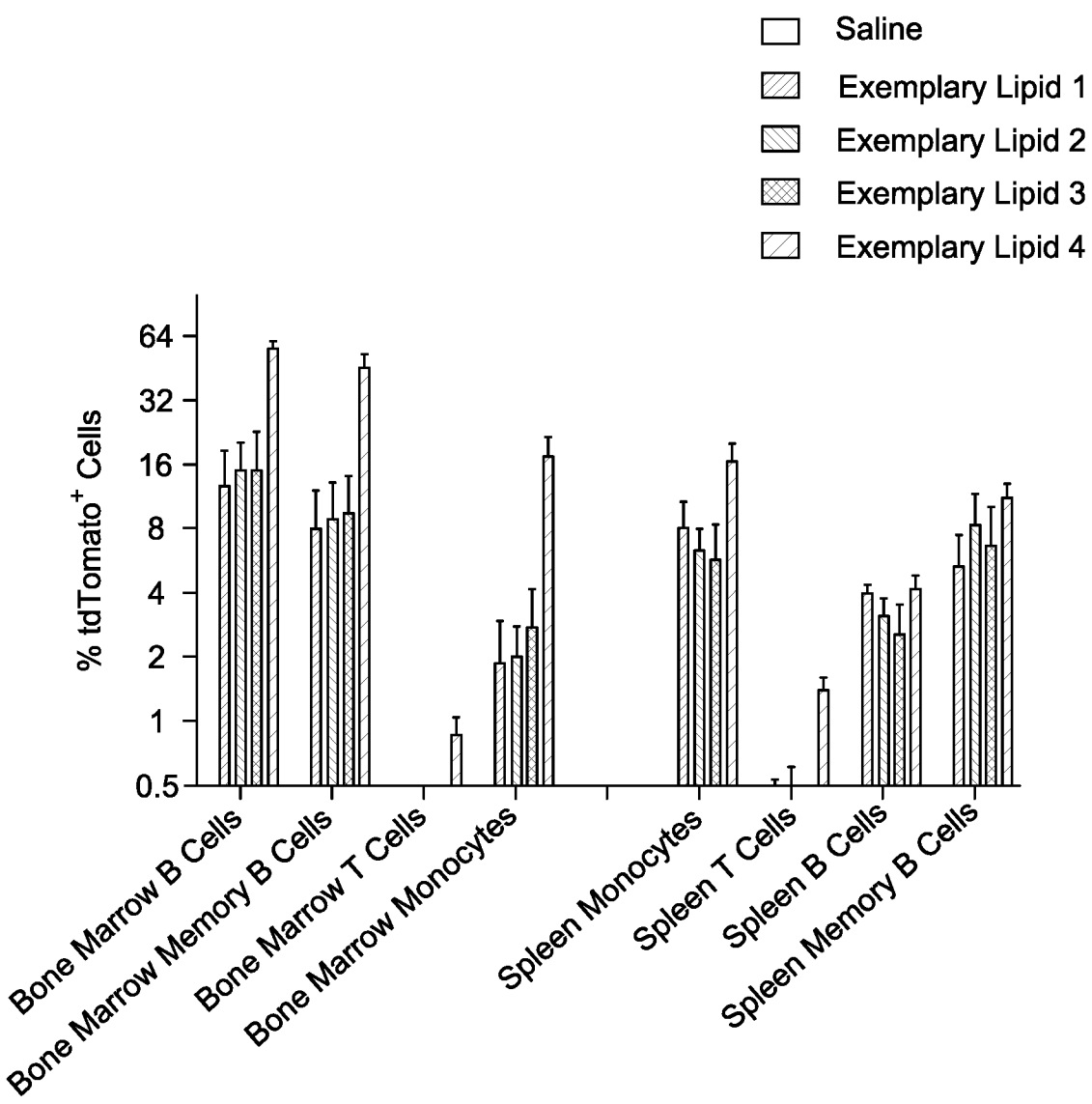

Saline
Exemplary Lipid 1
Exemplary Lipid 2
Exemplary Lipid 3
Exemplary Lipid 4
% tdTomato+ Cells
64
32
16
8
4
2
1
0.5
Bone Marrow B Cells
Bone Marrow Memory B Cells
Bone Marrow T Cells
Bone Marrow Monocytes
Spleen Monocytes
Spleen T Cells
Spleen B Cells
Spleen Memory B Cells

FIG. 5

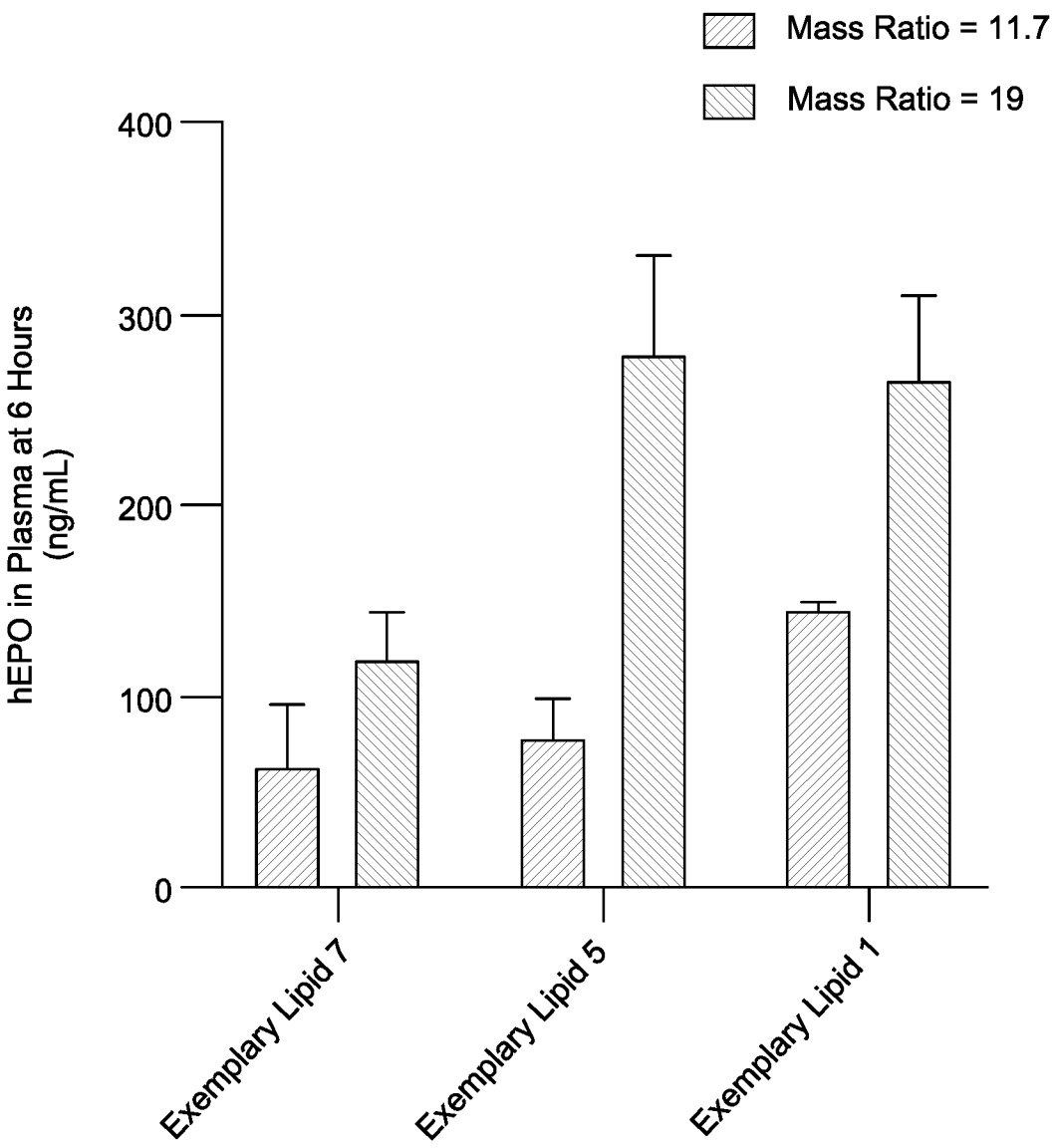

Mass Ratio = 11.7
Mass Ratio = 19
hEPO in Plasma at 6 Hours (ng/mL)
400
300
200
100
0
Exemplary Lipid 7
Exemplary Lipid 5
Exemplary Lipid 1

FIG. 6

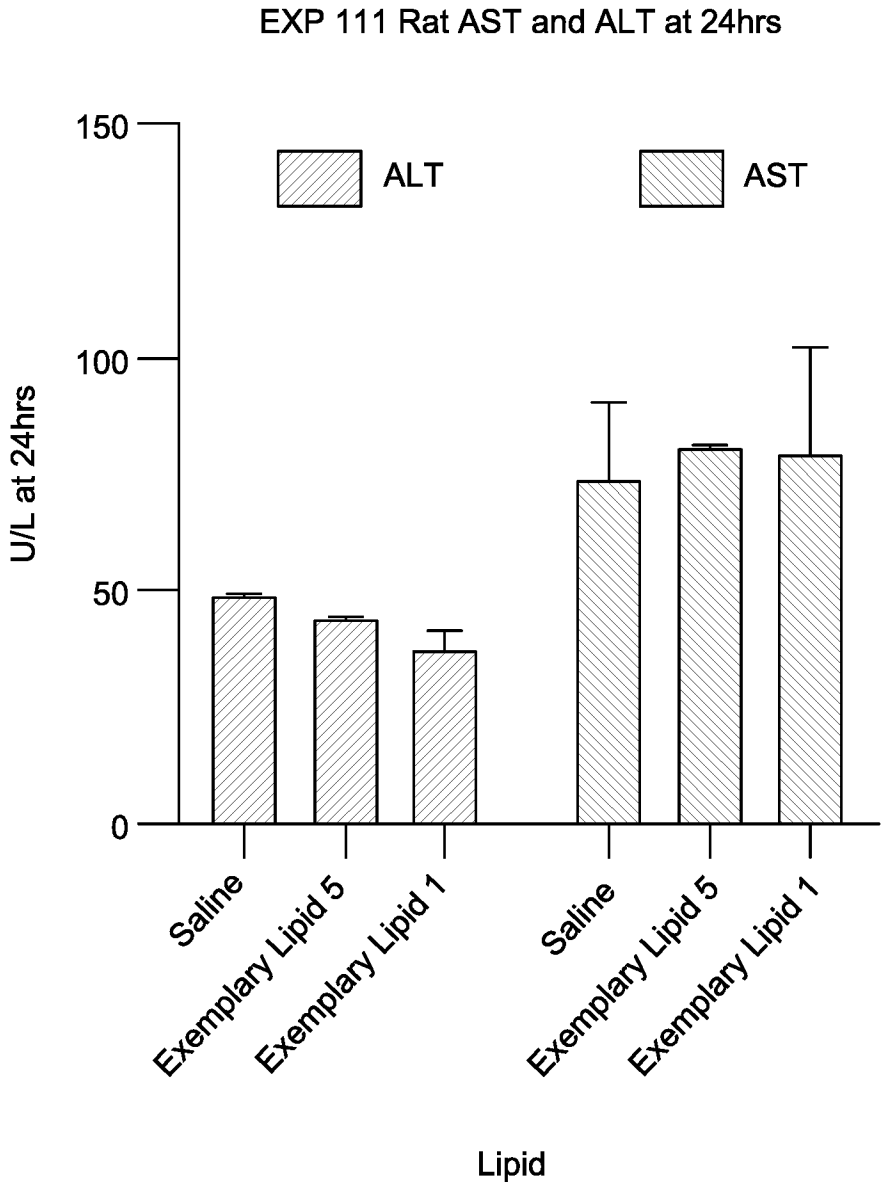

EXP 111 Rat AST and ALT at 24hrs
150
100
50
0
U/L at 24hrs
ALT
AST
Saline
Exemplary Lipid 5
Exemplary Lipid 1
Saline
Exemplary Lipid 5
Exemplary Lipid 1
Lipid

FIG. 7

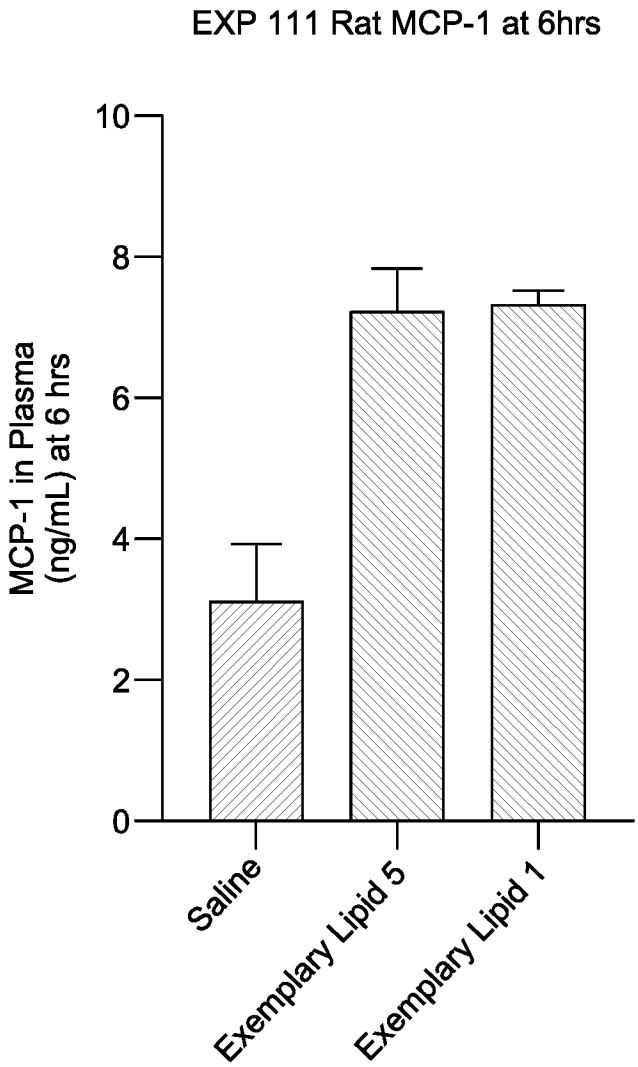

EXP 111 Rat MCP-1 at 6hrs
MCP-1 in Plasma (ng/mL) at 6 hrs
10
8
6
4
2
0
Saline
Exemplary Lipid 5
Exemplary Lipid 1

FIG. 8

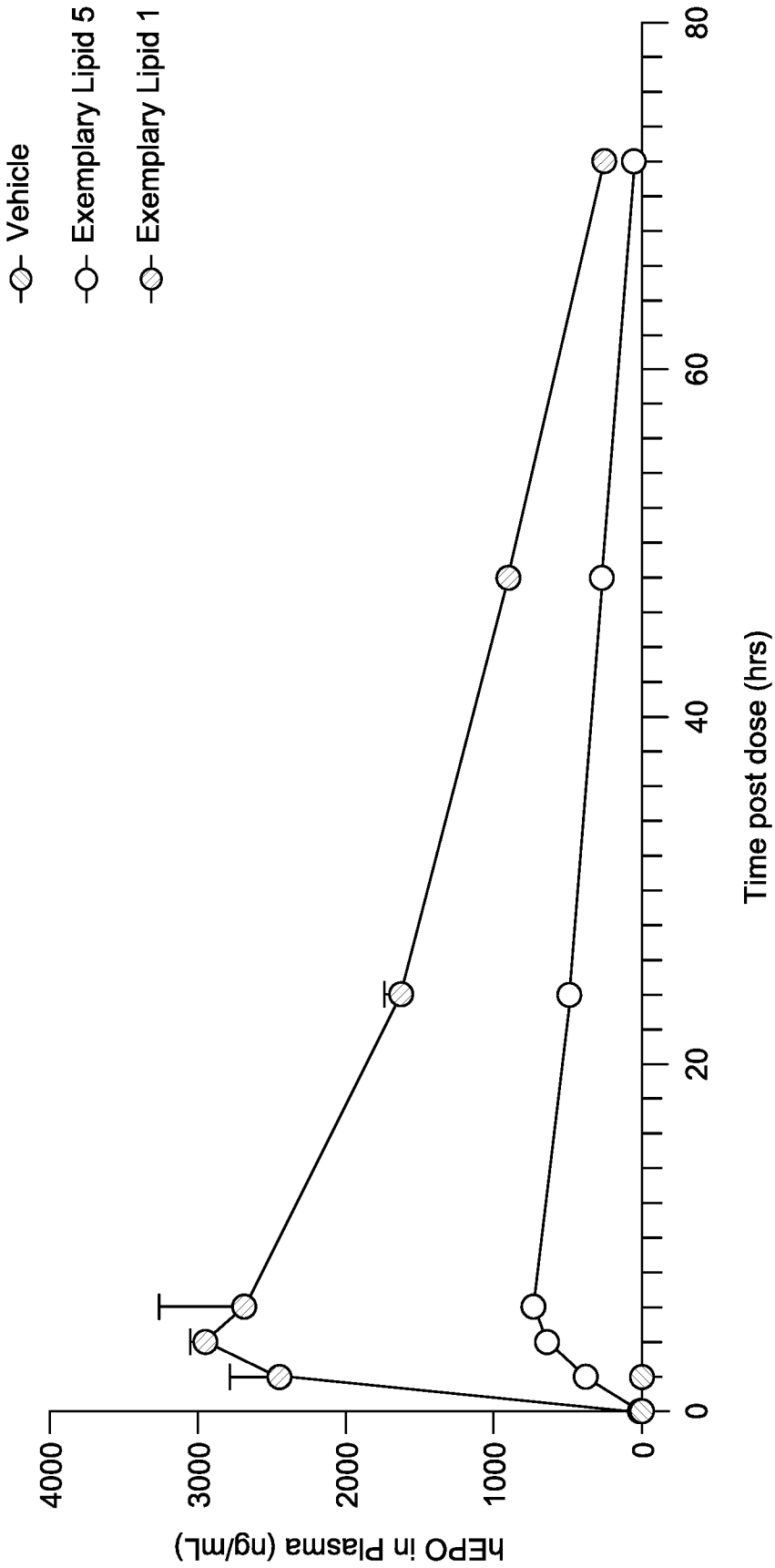

Vehicle
Exemplary Lipid 5
Exemplary Lipid 1
hEPO in Plasma (ng/mL)
4000
3000
2000
1000
0
0
20
40
60
80
Time post dose (hrs)

FIG. 9

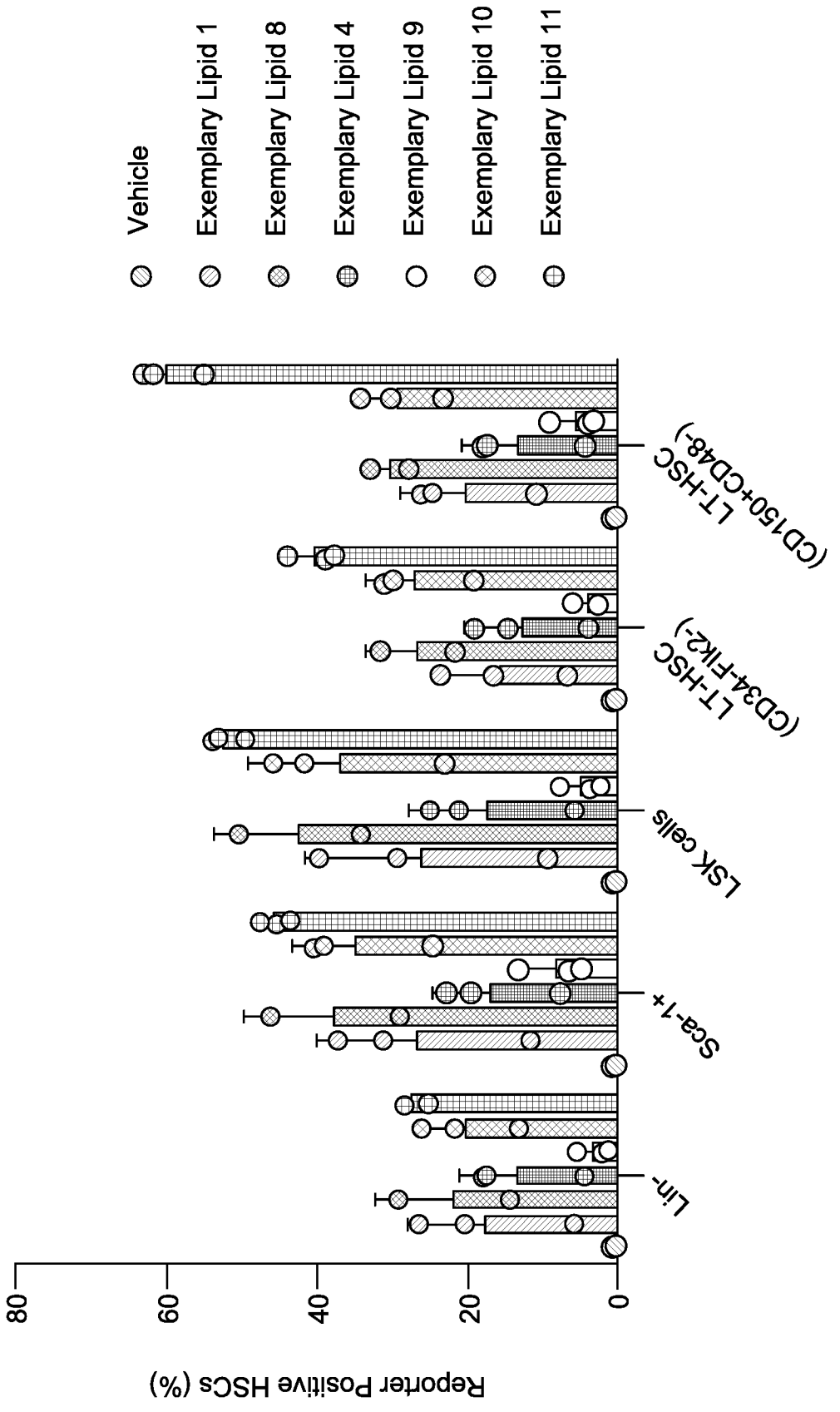

Vehicle
Exemplary Lipid 1
Exemplary Lipid 8
Exemplary Lipid 4
Exemplary Lipid 9
Exemplary Lipid 10
Exemplary Lipid 11
Reporter Positive HSCs (%)
0
20
40
60
80
Lin-
Sca-1+
LSk cells
LT-HSC (CD34-Flk2-)
LT-HSC (CD150+CD48-)

FIG. 10

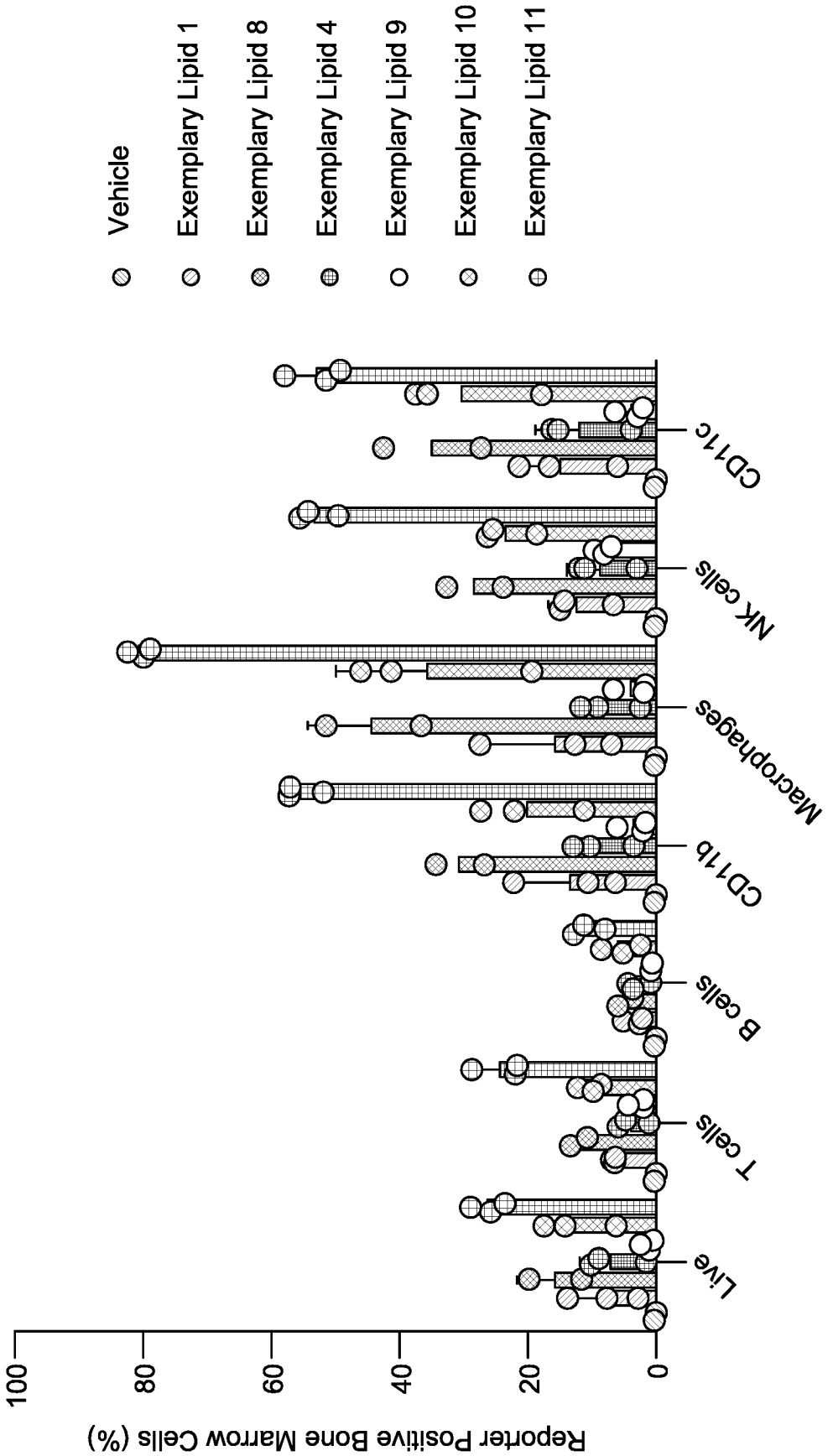

Vehicle
Exemplary Lipid 1
Exemplary Lipid 8
Exemplary Lipid 4
Exemplary Lipid 9
Exemplary Lipid 10
Exemplary Lipid 11
Reporter Positive Bone Marrow Cells (%)
0
20
40
60
80
100
Live
T cells
B cells
CD11b
Macrophages
NK cells
CD11c

FIG. 11

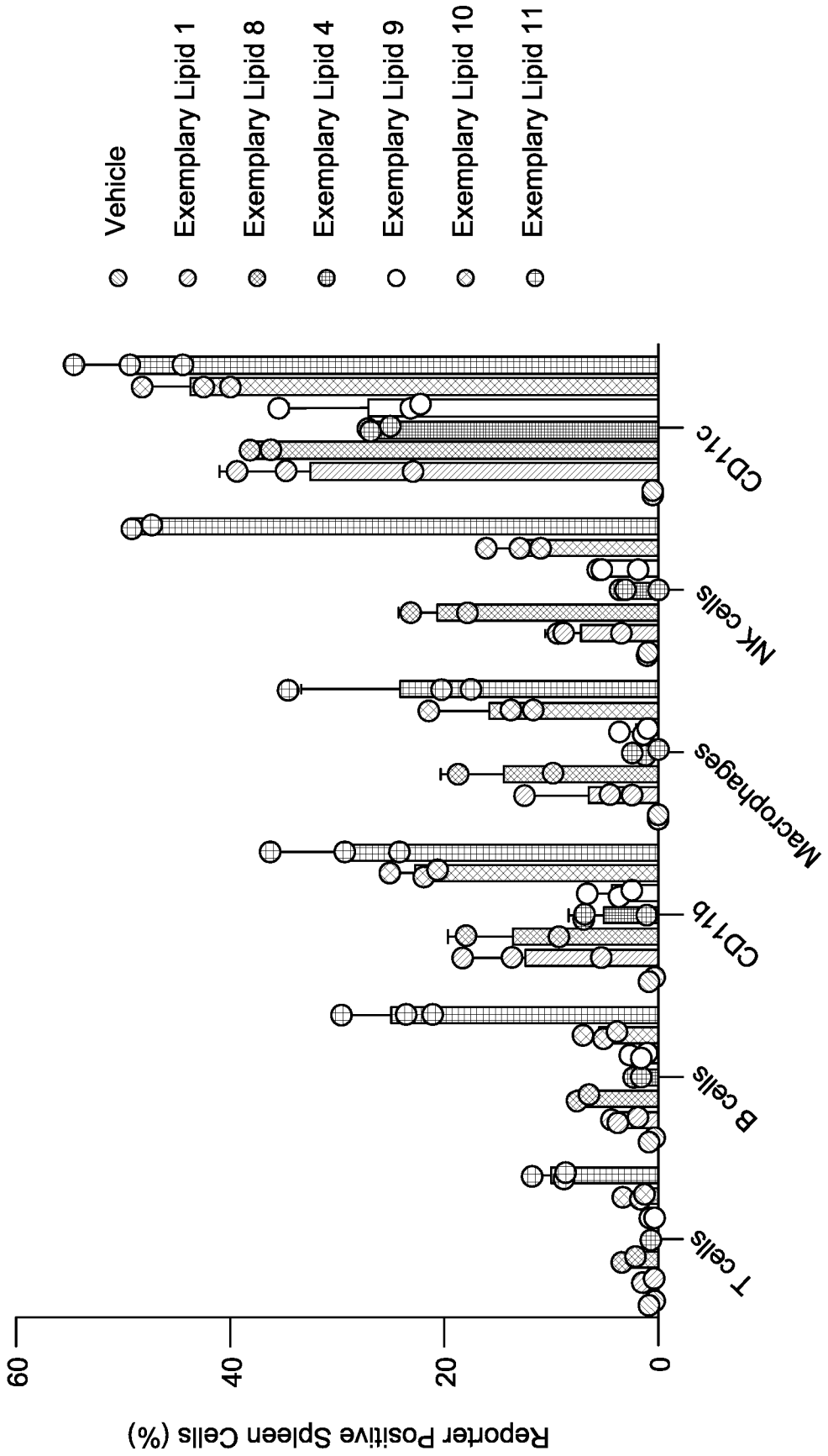

Vehicle
Exemplary Lipid 1
Exemplary Lipid 8
Exemplary Lipid 4
Exemplary Lipid 9
Exemplary Lipid 10
Exemplary Lipid 11
Reporter Positive Spleen Cells (%)
0
20
40
60
T cells
B cells
CD11b
Macrophages
NK cells
CD11c

FIG. 12

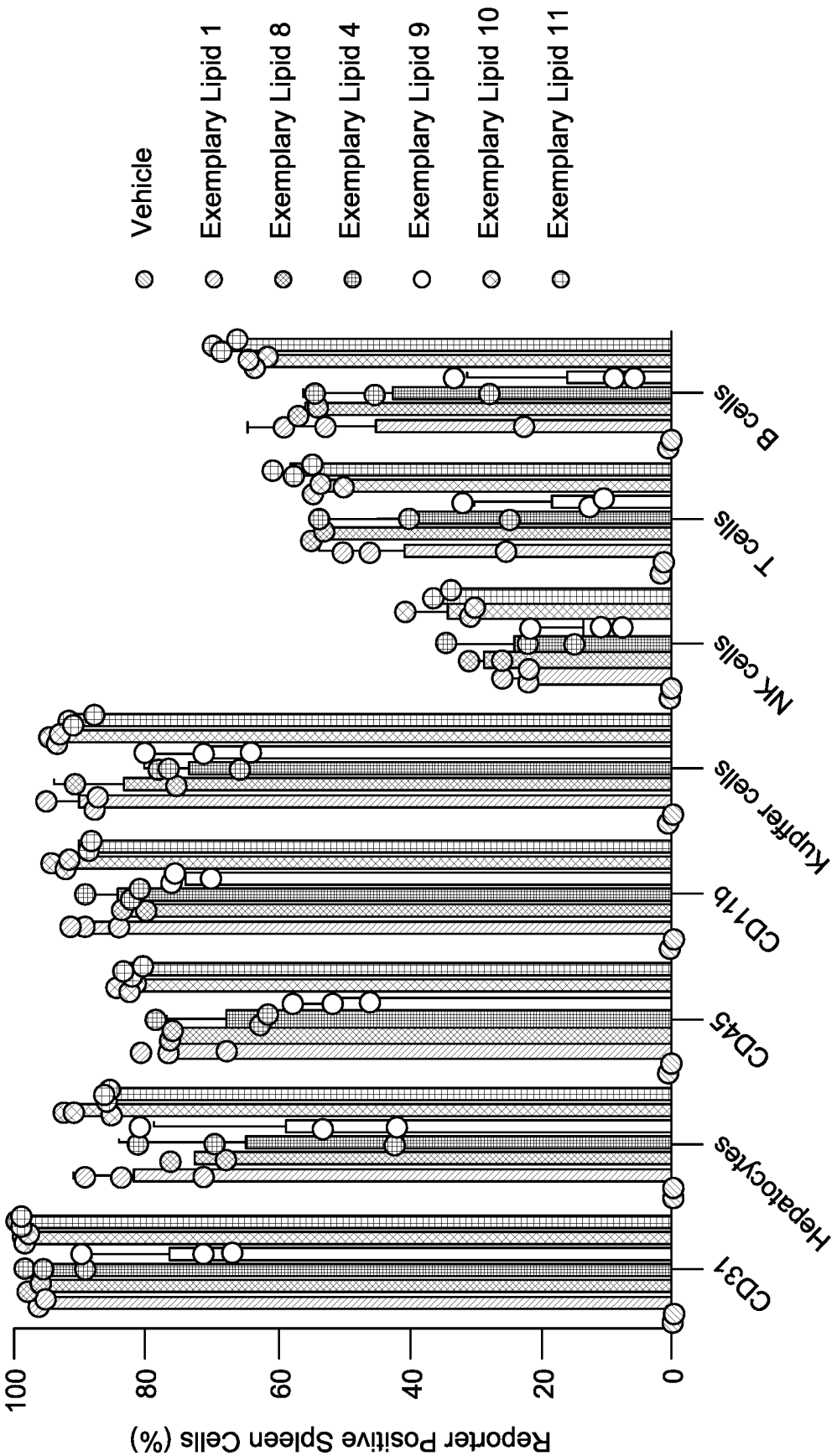
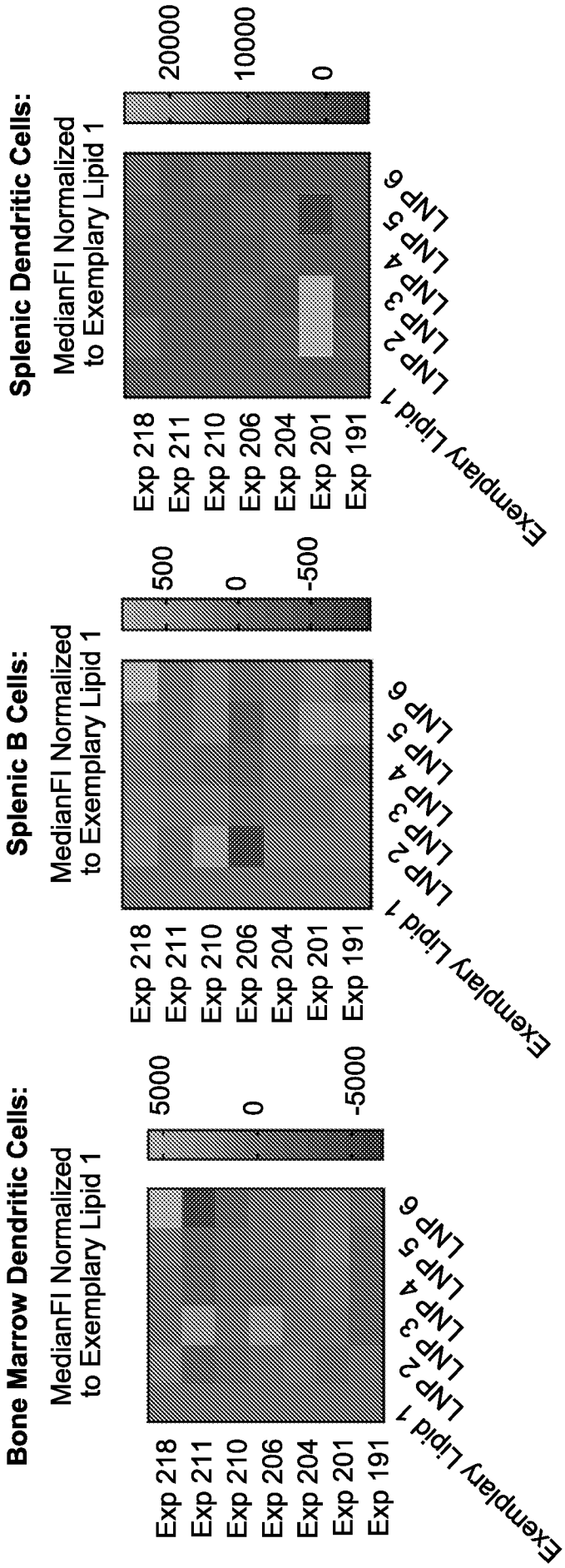

Vehicle
Exemplary Lipid 1
Exemplary Lipid 8
Exemplary Lipid 4
Exemplary Lipid 9
Exemplary Lipid 10
Exemplary Lipid 11
Reporter Positive Spleen Cells (%)
0
20
40
60
80
100
CD31
Hepatocytes
CD45
CD11b
Kupffer cells
NK cells
T cells
B cells

FIG. 13



1	8	x	x	10	11
1	x	x	x	x	x
1	x	x	x	x	x
1	x	x	x	x	x
1	x	x	x	x	x
1	15	16	x	x	x
1	x	x	x	x	x

FIG. 14

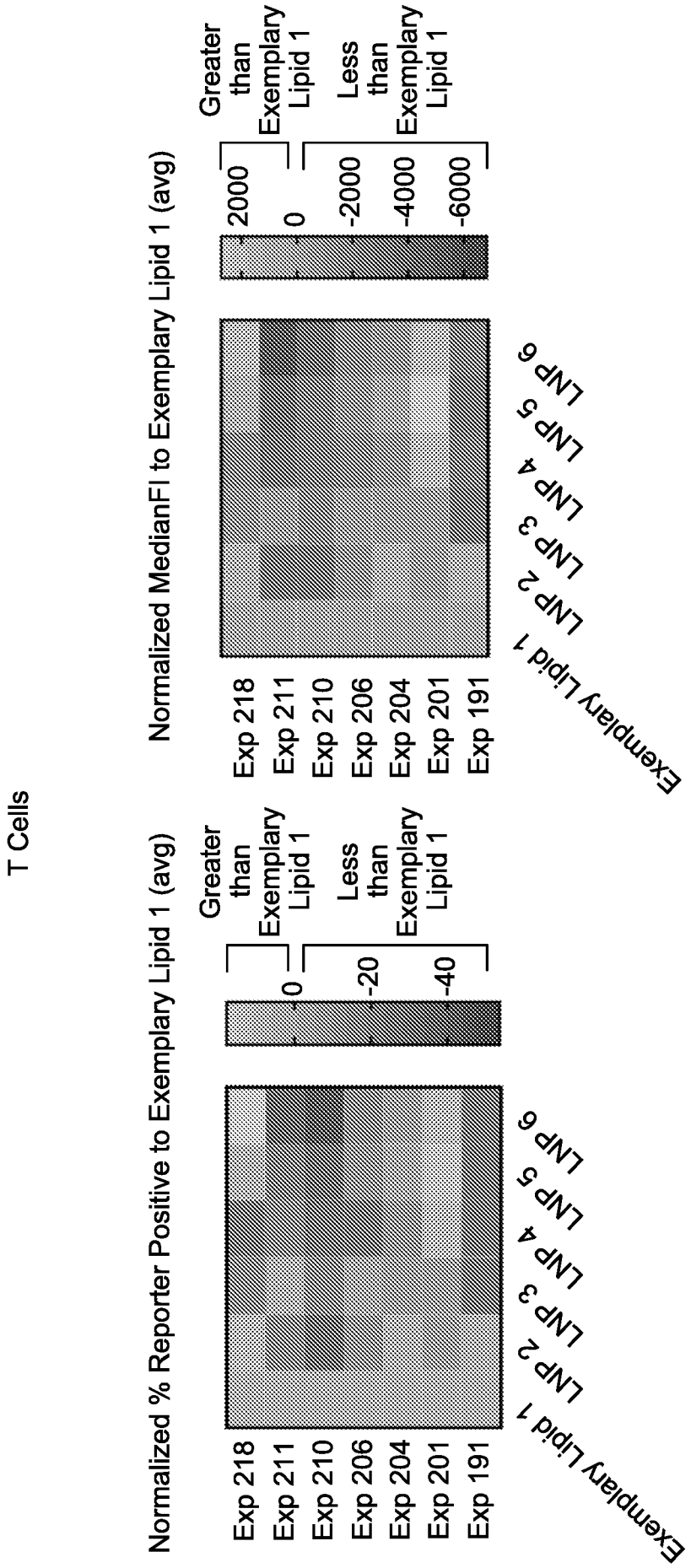

T Cells
Normalized % Reporter Positive to Exemplary Lipid 1 (avg)
Greater than Exemplary Lipid 1
Less than Exemplary Lipid 1
0
-20
-40
Exp 218
Exp 211
Exp 210
Exp 206
Exp 204
Exp 201
Exp 191
Exemplary Lipid 1
LNP 1
LNP 2
LNP 3
LNP 4
LNP 5
LNP 6
Normalized MedianFI to Exemplary Lipid 1 (avg)
Greater than Exemplary Lipid 1
Less than Exemplary Lipid 1
2000
0
-2000
-4000
-6000

FIG. 15

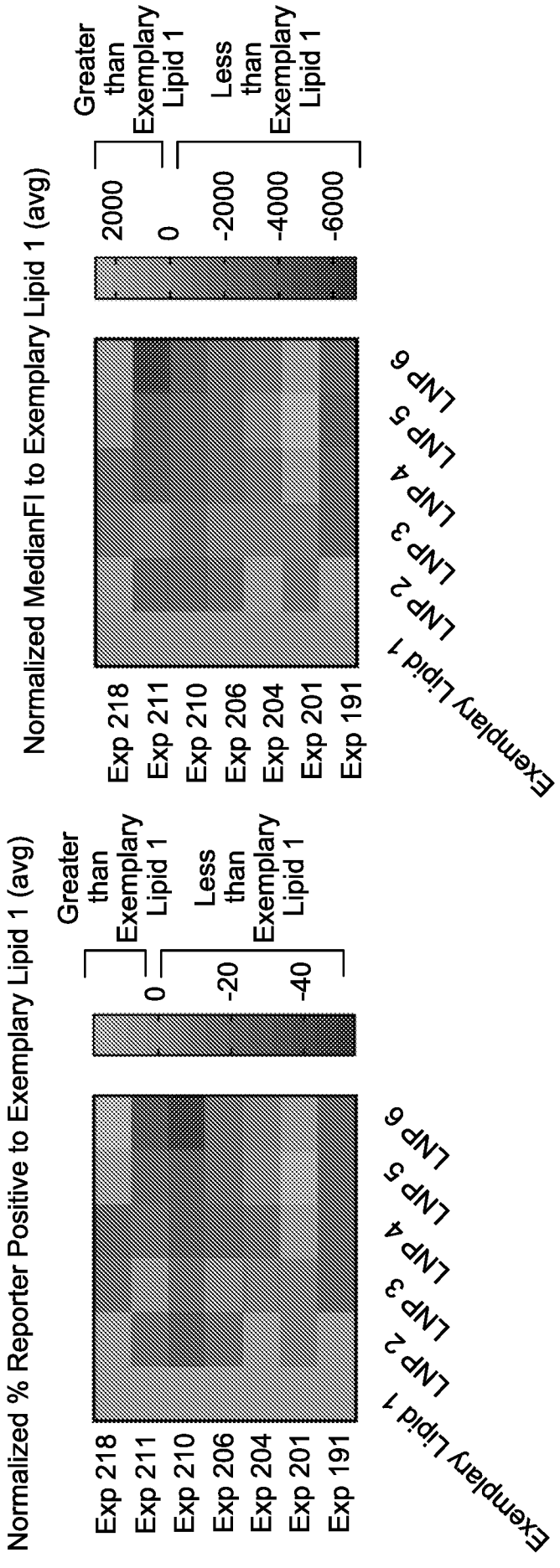

LSK (Lin-Sca-1+c-Kit+) Cells
Normalized % Reporter Positive to Exemplary Lipid 1 (avg)
Greater than Exemplary Lipid 1
Less than Exemplary Lipid 1
0
-20
-40
Exp 218
Exp 211
Exp 210
Exp 206
Exp 204
Exp 201
Exp 191
Exemplary Lipid 1
LNP 1
LNP 2
LNP 3
LNP 4
LNP 5
LNP 6
Normalized MedianFI to Exemplary Lipid 1 (avg)
Greater than Exemplary Lipid 1
Less than Exemplary Lipid 1
2000
0
-2000
-4000
-6000

FIG. 16

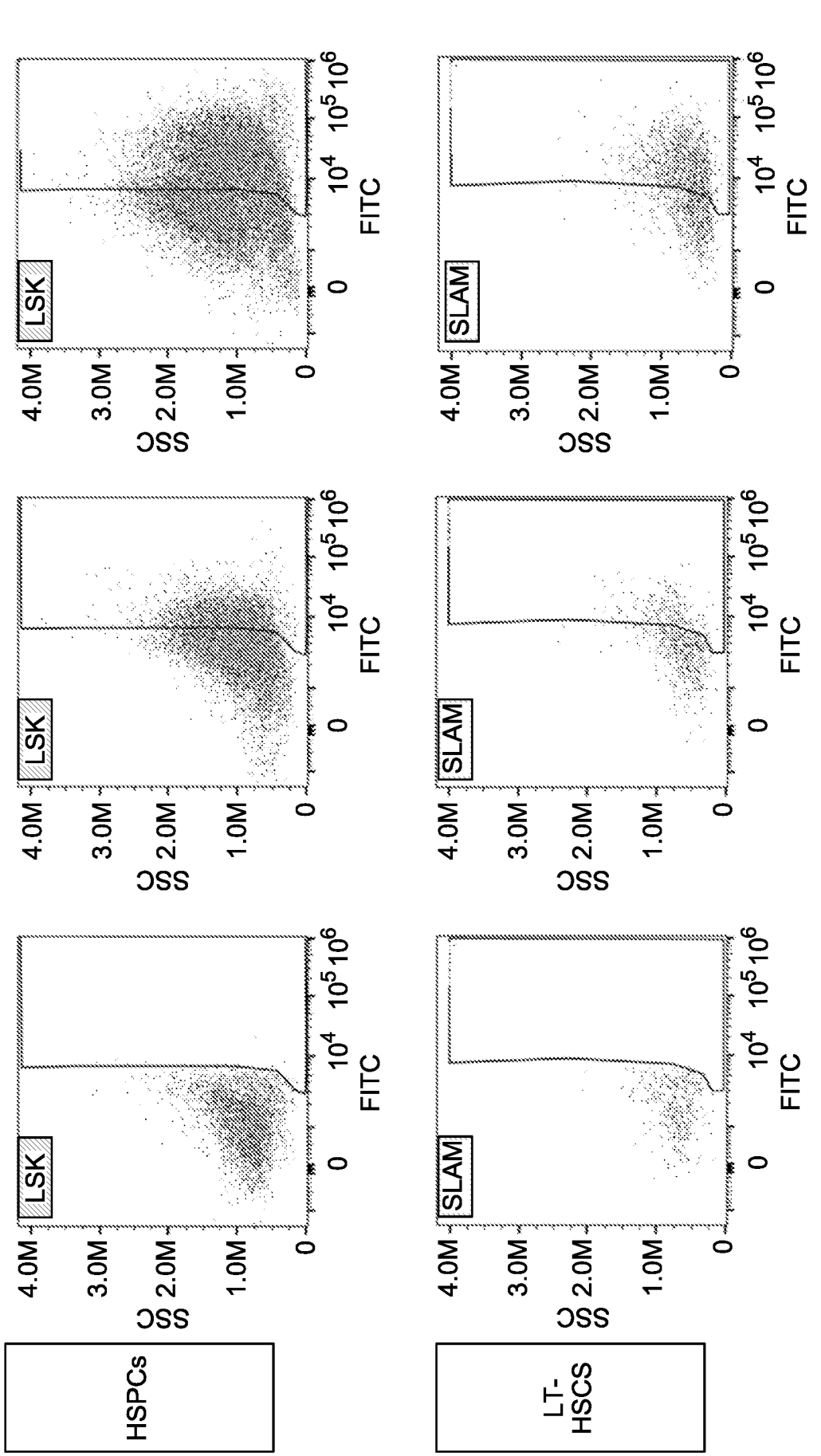

Saline Control
Exemplary Lipid 1
Exemplary Lipid 11
HSPCs
LT-HSCS
LSK
SLAM
SSC
FITC
4.0M
3.0M
2.0M
1.0M
0
10^4
10^5
10^6

FIG. 17

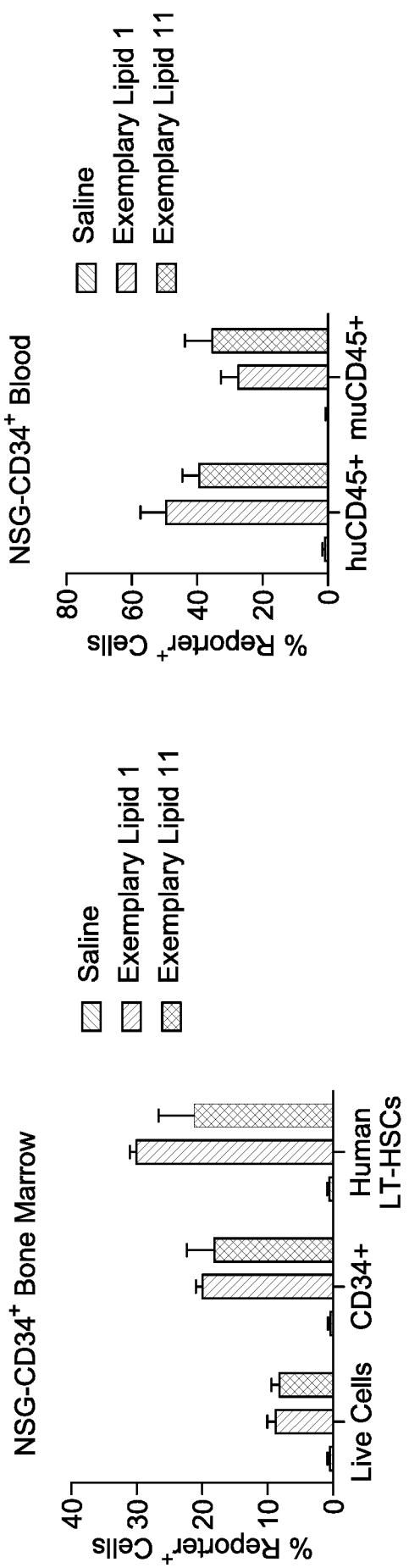

NSG-CD34+ Bone Marrow
% Reporter+ Cells
0
10
20
30
40
Live Cells
CD34+
Human LT-HSCs
Saline
Exemplary Lipid 1
Exemplary Lipid 11
NSG-CD34+ Blood
% Reporter+ Cells
0
20
40
60
80
huCD45+
muCD45+
Saline
Exemplary Lipid 1
Exemplary Lipid 11

FIG. 18

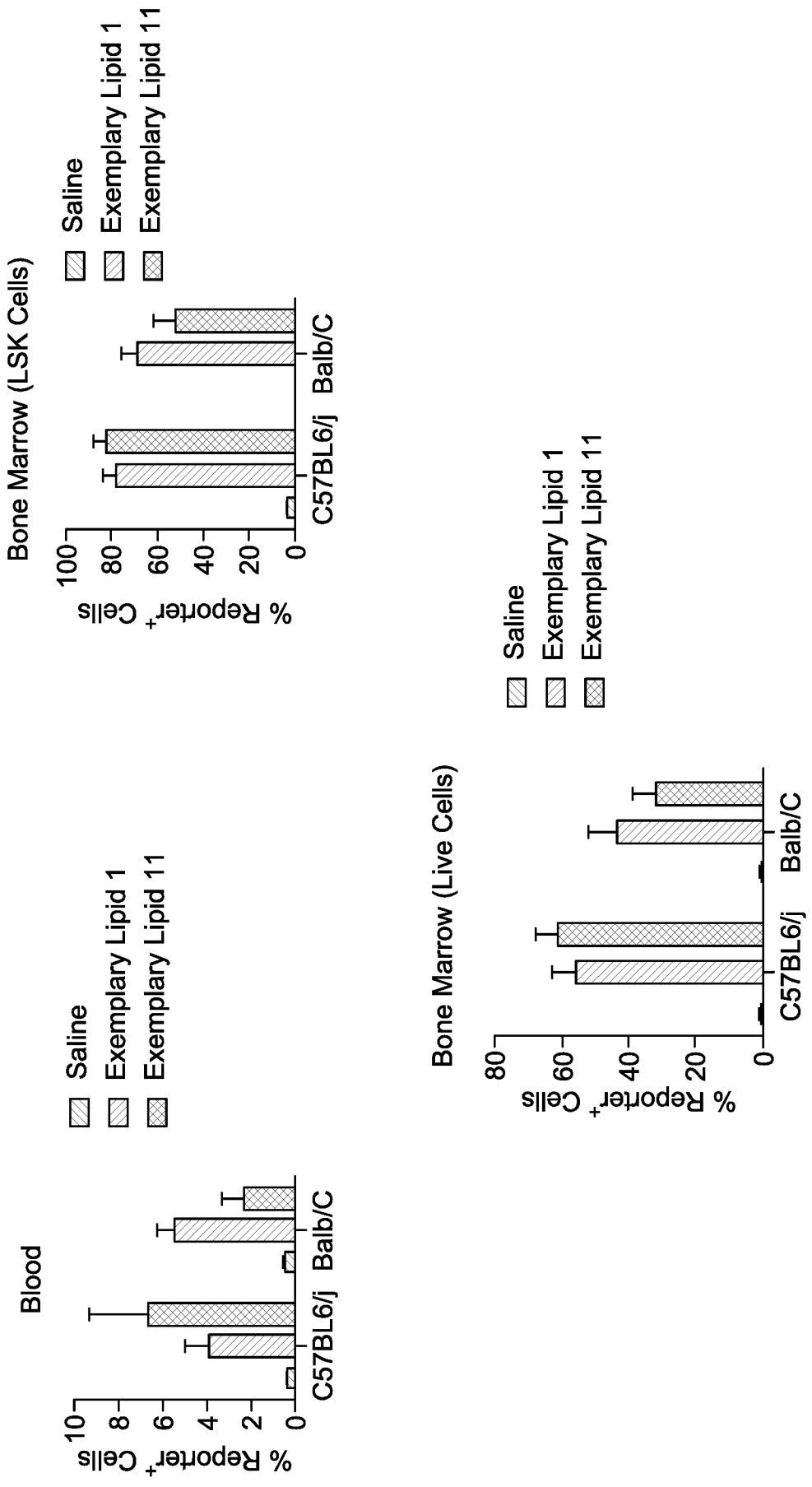

Bone Marrow (LSK Cells)
Saline
Exemplary Lipid 1
Exemplary Lipid 11
% Reporter+ Cells
100
80
60
40
20
0
C57BL6/j
Balb/C
Bone Marrow (Live Cells)
Saline
Exemplary Lipid 1
Exemplary Lipid 11
% Reporter+ Cells
80
60
40
20
0
C57BL6/j
Balb/C
Blood
Saline
Exemplary Lipid 1
Exemplary Lipid 11
% Reporter+ Cells
10
8
6
4
2
0
C57BL6/j
Balb/C

FIG. 19

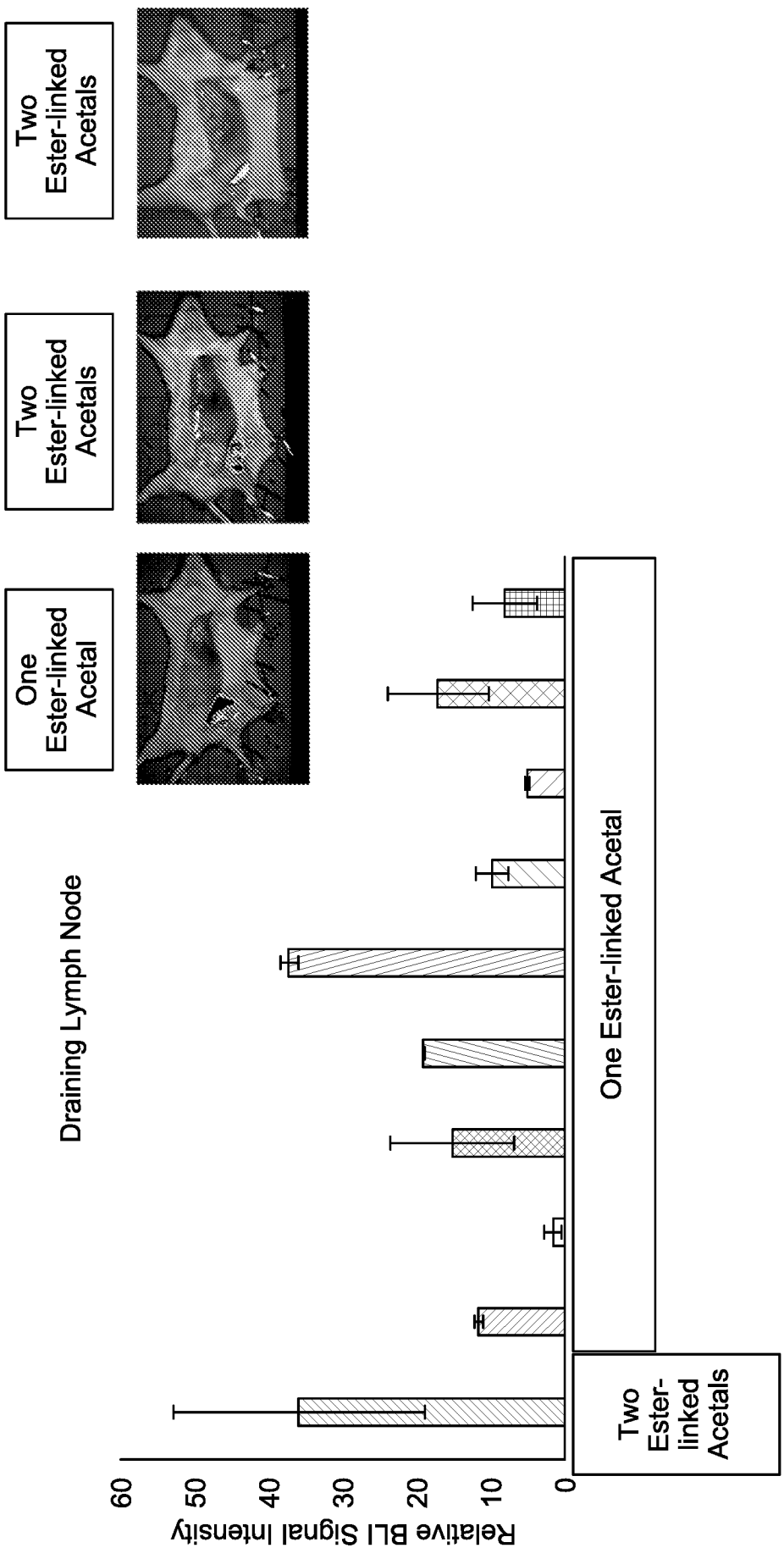

Two Ester-linked Acetals
Two Ester-linked Acetals
One Ester-linked Acetal
Draining Lymph Node
Relative BLI Signal Intensity
60
50
40
30
20
10
0
Two Ester-linked Acetals
One Ester-linked Acetal

FIG. 20

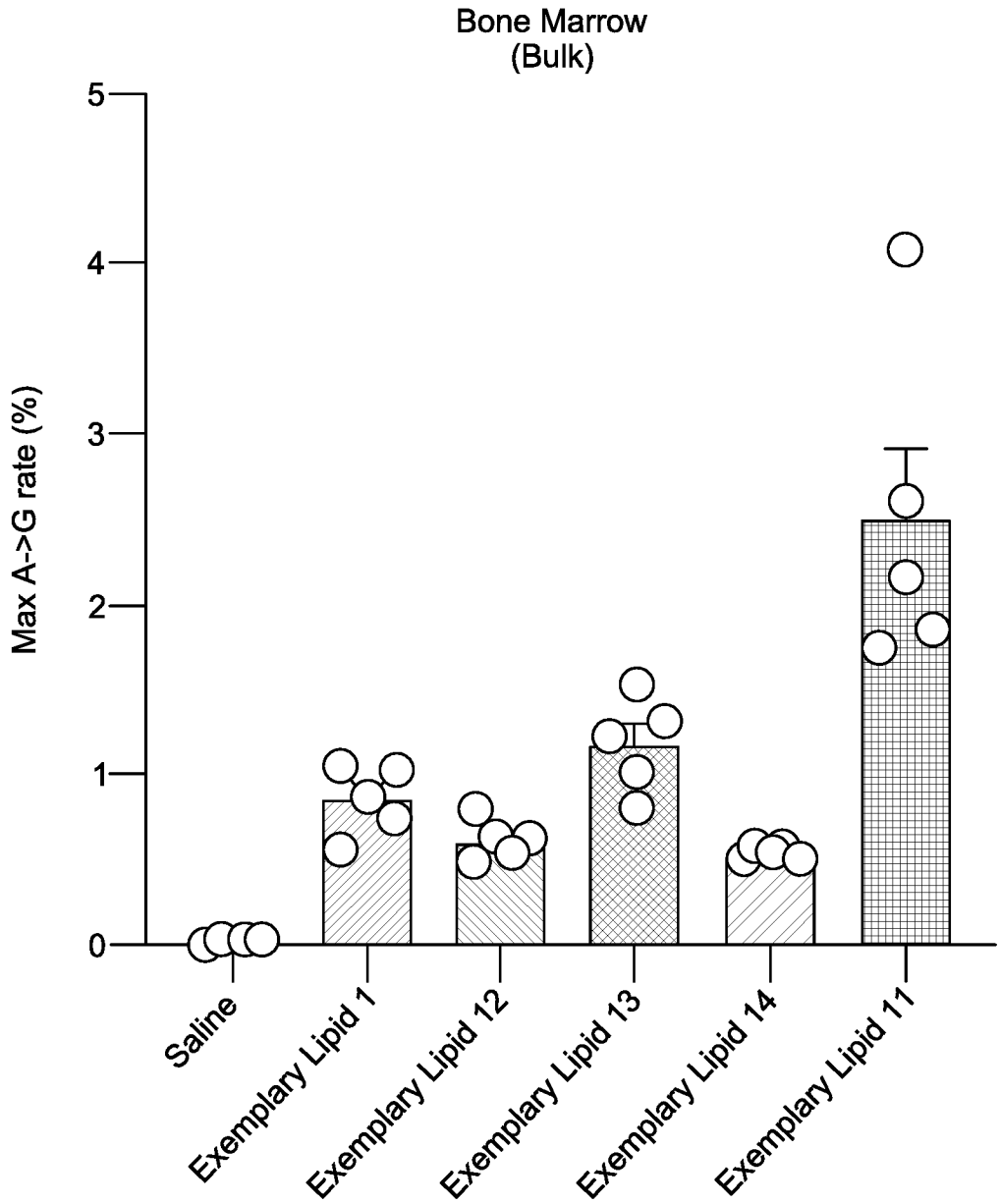

Bone Marrow
(Bulk)
Max A->G rate (%)
0
1
2
3
4
5
Saline
Exemplary Lipid 1
Exemplary Lipid 12
Exemplary Lipid 13
Exemplary Lipid 14
Exemplary Lipid 11

FIG. 21

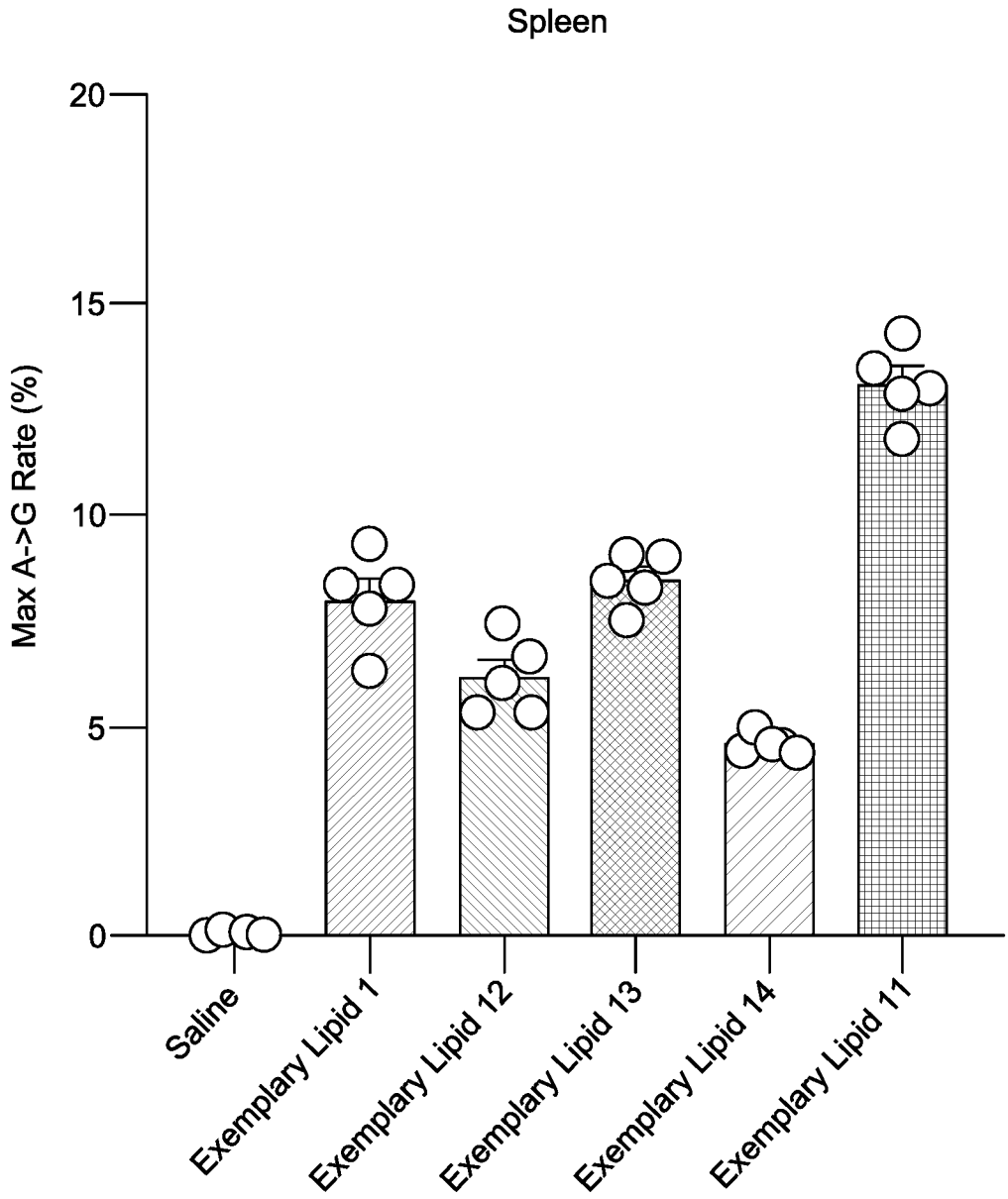

Spleen
Max A->G Rate (%)
20
15
10
5
0
Saline
Exemplary Lipid 1
Exemplary Lipid 12
Exemplary Lipid 13
Exemplary Lipid 14
Exemplary Lipid 11

FIG. 22

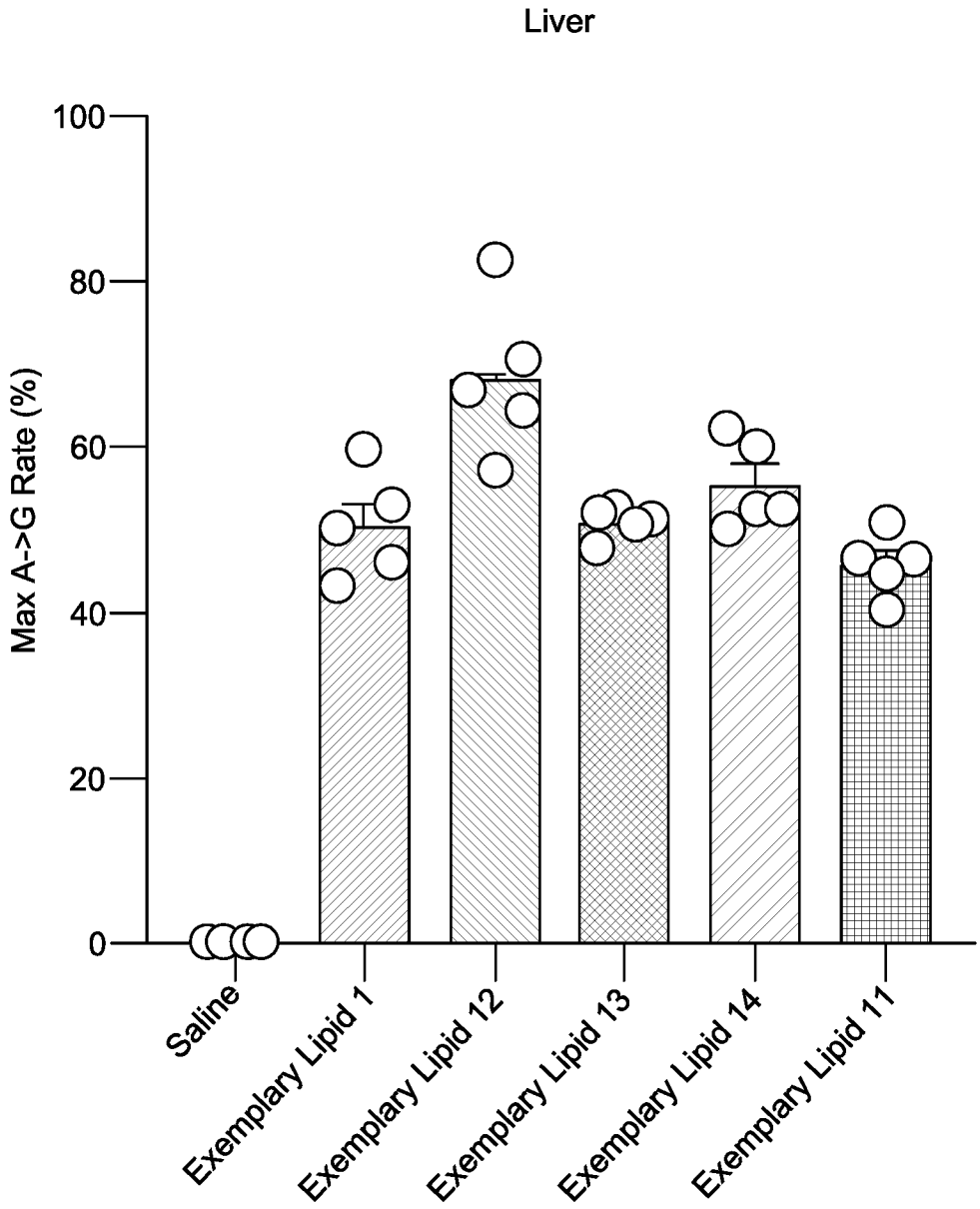

Liver
Max A->G Rate (%)
100
80
60
40
20
0
Saline
Exemplary Lipid 1
Exemplary Lipid 12
Exemplary Lipid 13
Exemplary Lipid 14
Exemplary Lipid 11

FIG. 23

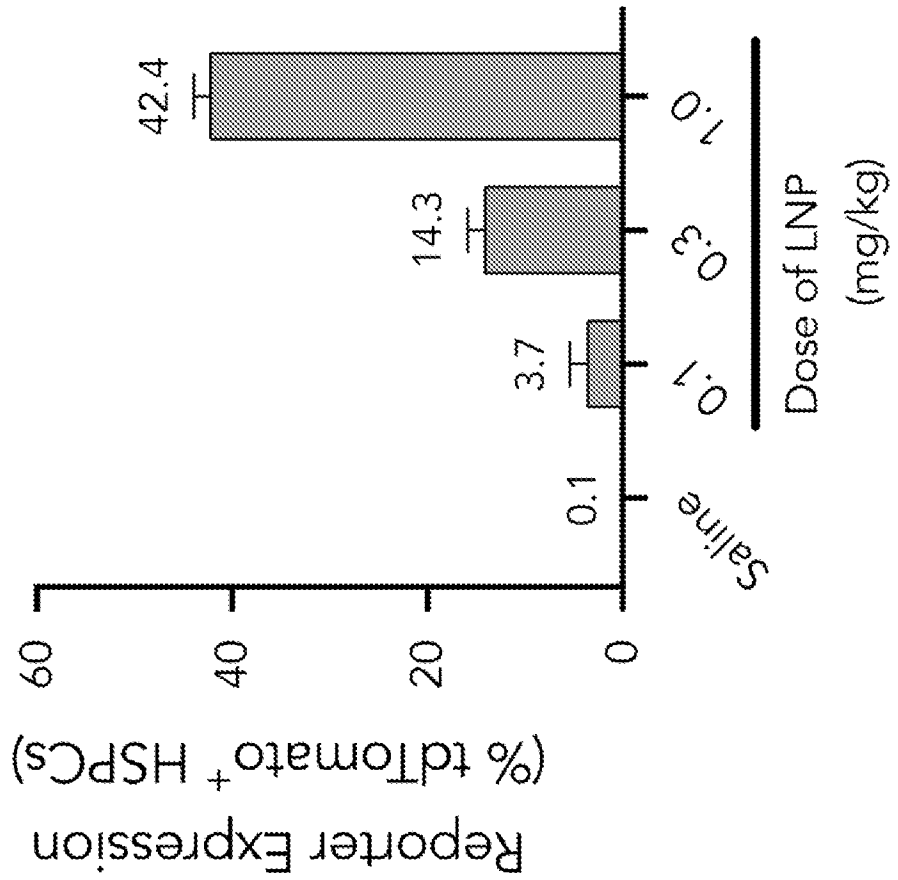

Reporter Expression
(% tdTomato+ HSPCs)
60
40
20
0
Saline
0.1
3.7
14.3
42.4
0.1
0.3
1.0
Dose of LNP
(mg/kg)

FIG. 24

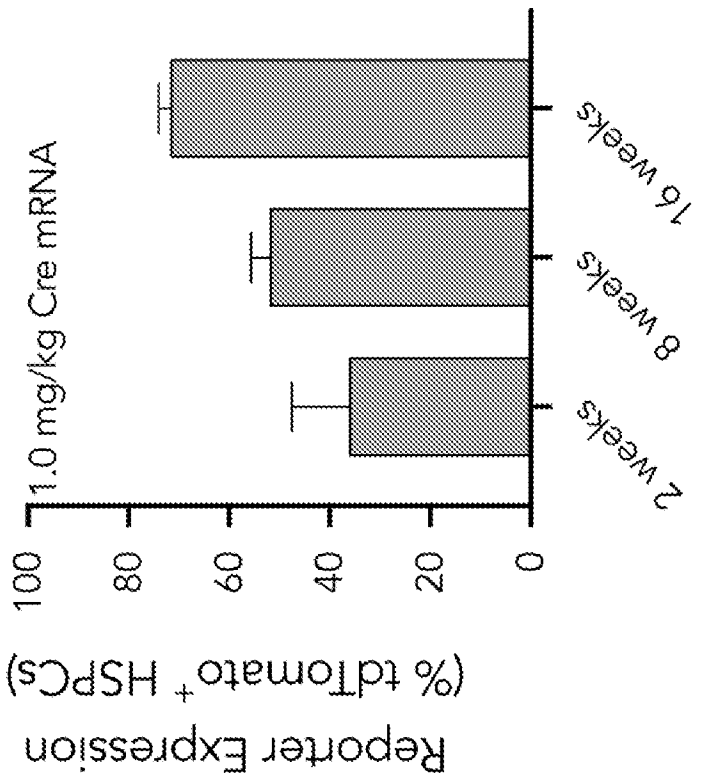


FIG. 25A

FIG. 25B

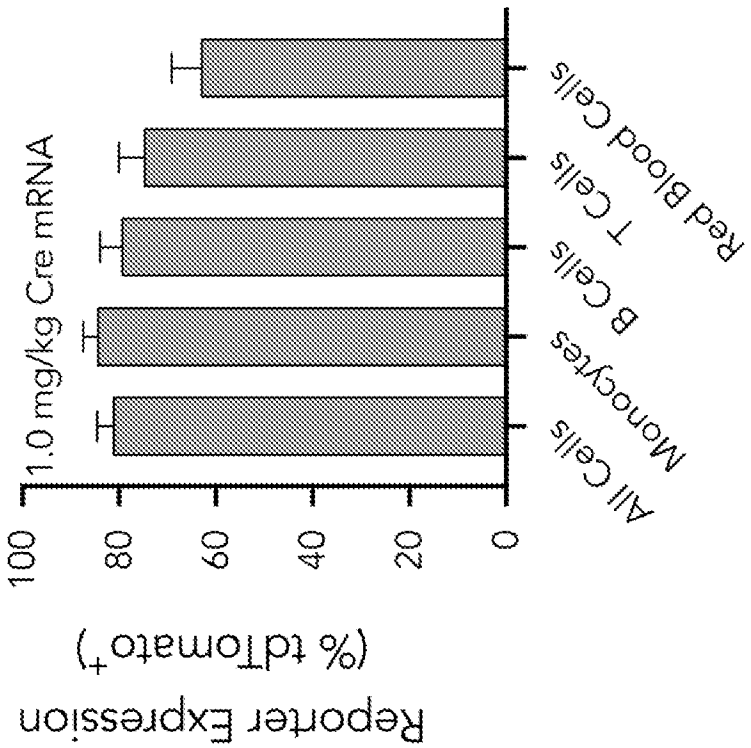


FIG. 25D

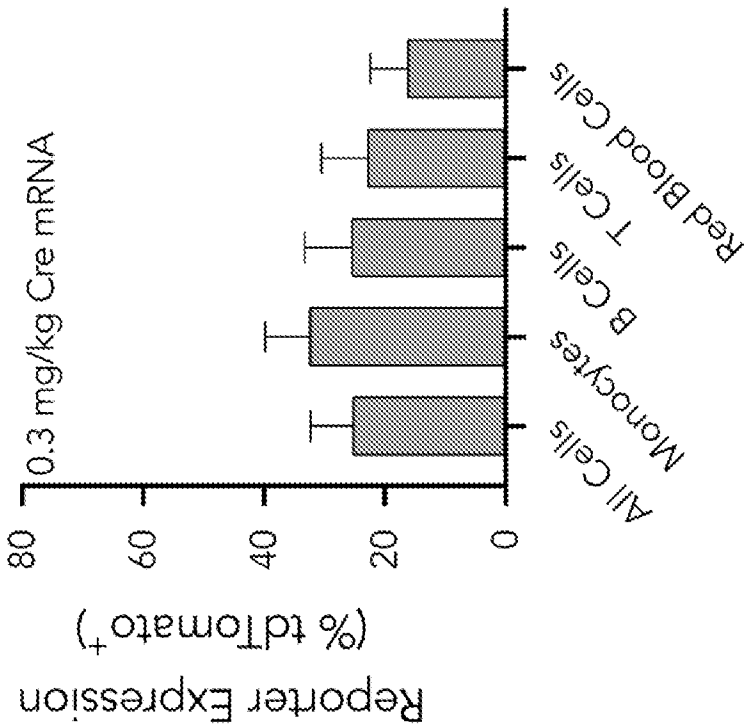


FIG. 25C

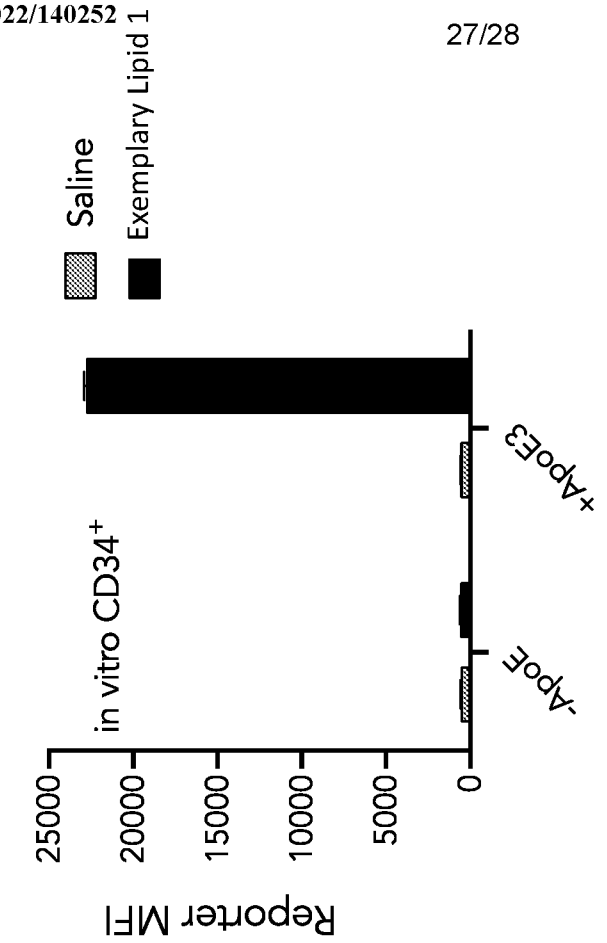


FIG. 26B

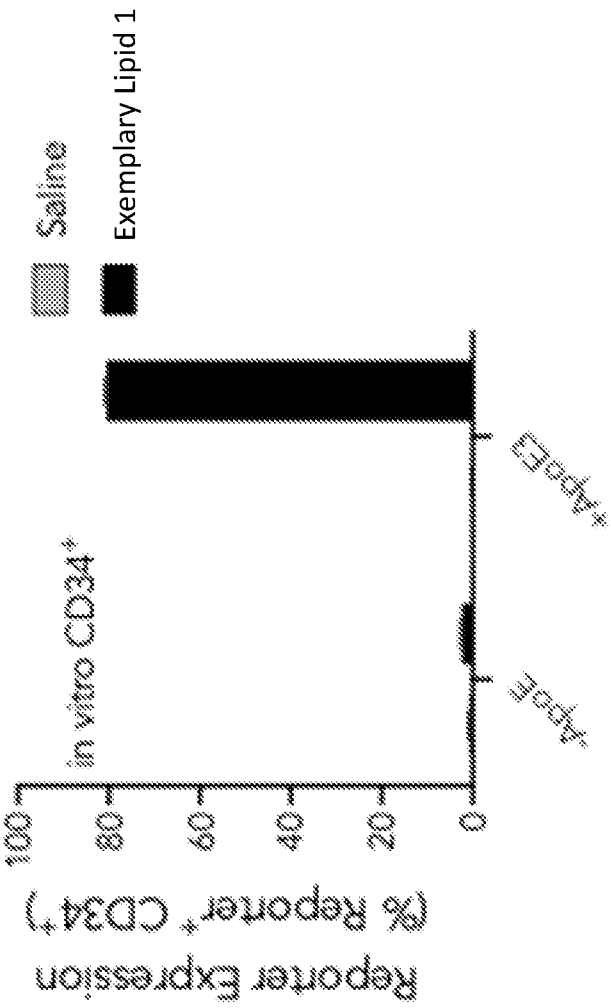


FIG. 26A

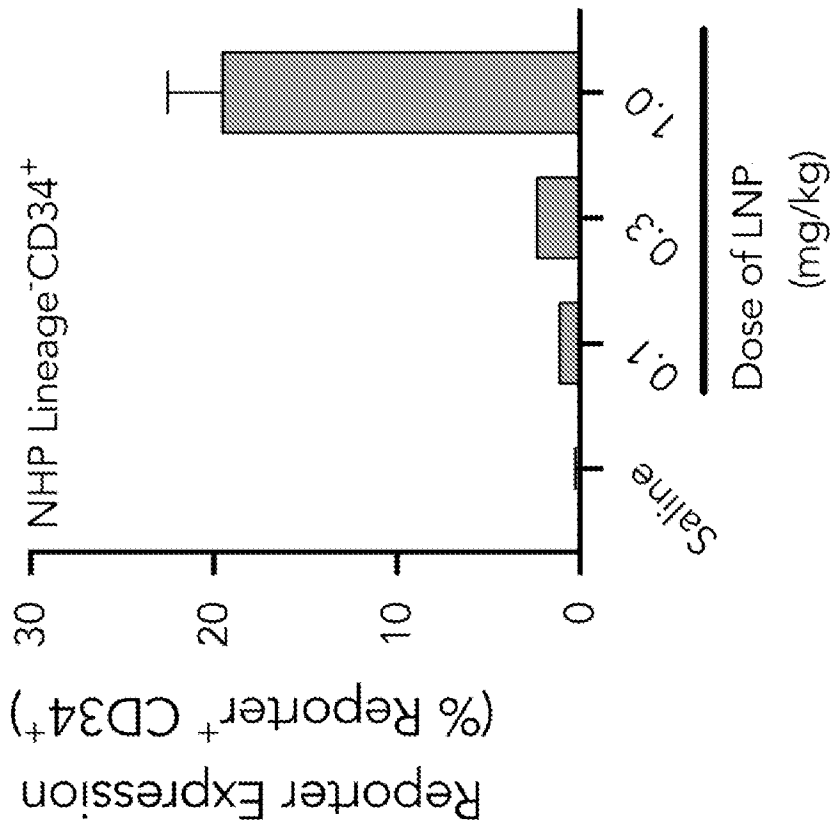

Reporter Expression
(% Reporter+ CD34+)
NHP Lineage-CD34+
30
20
10
0
Saline
0.1
0.3
1.0
Dose of LNP
(mg/kg)

FIG. 27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/64339

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/7088; A61K 31/7105; A61K 31/713 (2022.01)

CPC - A61K 31/7088; A61K 31/7105; A61K 31/713

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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/072605 A1 (INTELLIA THERAPEUTICS INC) 09 April 2020 (09.04.2020), especially: pg 5, first formula.	1-50,54,64
A	US 4,452,746 A (ISHIKURA et al.) 05 June 1984 (05.06.1984), especially: col 3, ln 1-38, N,N-bis(hydroxyethyl)-e-aminohexanoic acid.	1-50,54,64
A	PubChem-SID-149755815, Modify Date: 02 June 2019 (02.06.2019), pg 2, figure, this is a purchasable chemical.	1-50,54,64

☐ 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
"D" document cited by the applicant in the international application
"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
28 February 2022	MAR 15 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/64339

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.: 51-53, 55-63
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:

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 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.