

LIPID COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application No. 63/595,051 filed on November 01, 2023, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This application describes lipids that include novel triazole and alkyl-substituted amine compounds and intermediates used in the synthesis of the same. These triazole and alkyl-substituted amine compounds can be used, for example, in lipid nanoparticle compositions for drug delivery and cancer treatments.

BACKGROUND OF THE INVENTION

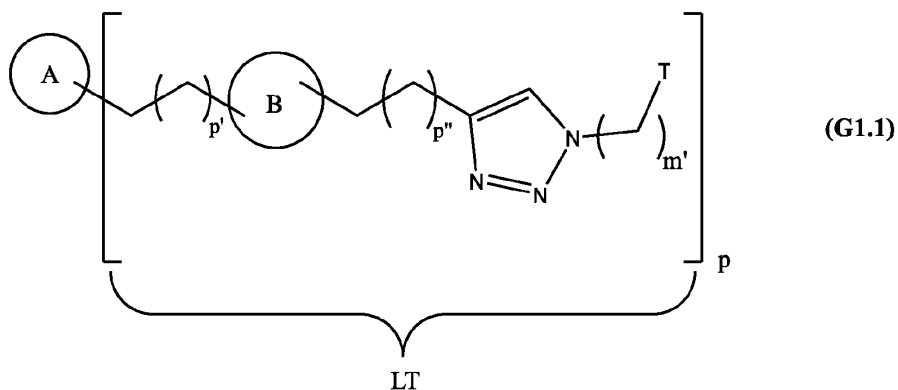
[0003] It is of great interest for therapeutics, diagnostics, reagents and for biological assays to be able to deliver a nucleic acid into a cell, such as to cause intracellular translation of the nucleic acid and production of the encoded protein. Delivery of nucleic acids has been explored extensively as a potential therapeutic option for certain disease states. In particular, nucleic acid therapy has become an increasingly important option for treatment of various diseases, including cancer treatments. Intracellular delivery of nucleic acids can stimulate the innate immune response, which can be helpful for treatment of various diseases.

[0004] Thus, there is a need to develop lipid compounds that can be useful to facilitate the delivery of nucleic acids to targeted cells or subjects in need thereof. The present invention addresses this unmet need.

BRIEF SUMMARY OF THE INVENTION

[0005] In an aspect, the present application relates to compounds represented generically by of formula (G1.1) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:

[0006] Compounds of general formula (G1.1)



wherein

moiety B in (G1.1) is C(O)O, OC(O), C(O)NH, HNC(O), or CH₂CH₂,

p = 1-6;

p' = 0-4;

p'' = 0-4;

m' = 0, 1;

moiety T is selected from

CH((CH₂)_{ll}CH₃)-CH₂)_{ll'}CH₃, ll = 2-6, ll' = 2-6

CH₃-(CH₂)_k-CH₂, k = 2-14;

(CH₃-(CH₂)_{k'})₂-CH-(CH₂)_{k''}-CH₂, k' = 0-8, k'' = 0-9;

CH₃-(CH₂)_{kk}-CH=CH-(CH₂)_{kk'}-CH₂, kk = 5-8, kk' = 5-8;

CH₃-(CH₂)_{kp}-CH=CH-(CH₂)_{kp'}-CH=CH-(CH₂)_{kp''}-CH₂, kp = 5-7, kp' = 5-7,

kp'' = 1-3;

CH₃-(CH₂)_l-O-C(O)-(CH₂)_{kk''}-CH₂, l = 2-7, kk'' = 0-4; and

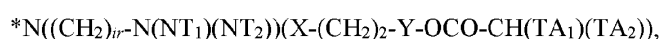
(CH₃-(CH₂)_l-CH₂)₂-CH-MS-C(O)-(CH₂)_{kk''}-CH₂, l = 2-7, kk'' = 0-5, MS is

O or NH;

and when $p > 1$, then each one of the plurality of T tails is the same or different from the remaining T tails in the same molecule,
and

the amino moiety A in (G1.1) is selected depending on the p-value as follows, wherein the term * is used to refer to a N-binding site of an LT moiety, and *(*) (or (*)*) indistinguishably is used to refer to two separate N-binding sites of two LT moieties:

$p = 1$, then A is



$ir = 2-4$,

NT_1 is H, or CH_3 ,

NT_2 is CH_3 , $(CH_2)_{r'}-OCO-(CH_2)_r-CH_3$, $(CH_2)_r-OH$, or

$(CH_2)_{r''}-CH_3$, with $r = 1-3$, $r' = 1-3$, and $r'' = 1-3$,

X is $C(O)-O$, $C(O)-CH_2$, $(CH_2)_{mm}-OCO$ with $mm = 1-3$, or

$CH_2-(CH_2)_{mm}$ with $mm = 0-3$,

Y is $S-S-(CH_2)_n$, $n = 2,3$, or $(CH_2)_q$, $q = 3-6$,

OCO is $O-C(O)$ or $C(O)-O$,

TA_1 is H or $(CH_2)_m-CH_3$, and

TA_2 is $(CH_2)_m-CH_3$,

with $m = 5-8$ and $m' = 5-8$;

$p = 2$, then A is $*(*)N-(CH_2)_t-Z$,

$t = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $N(CH_2-CH_3)_2$,

or $N(CH_3)_2$,

$p = 4$, then A is $*(*)N-(CH_2)_{w1}-E-(CH_2)_{w2}-N(*)^*$,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-

O, $O-(CH_2)_{w3}$ -(substituted or unsubstituted 1,4-

piperazinediyl)-(CH₂)_{w4}-O, substituted or unsubstituted 1,4-

piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or

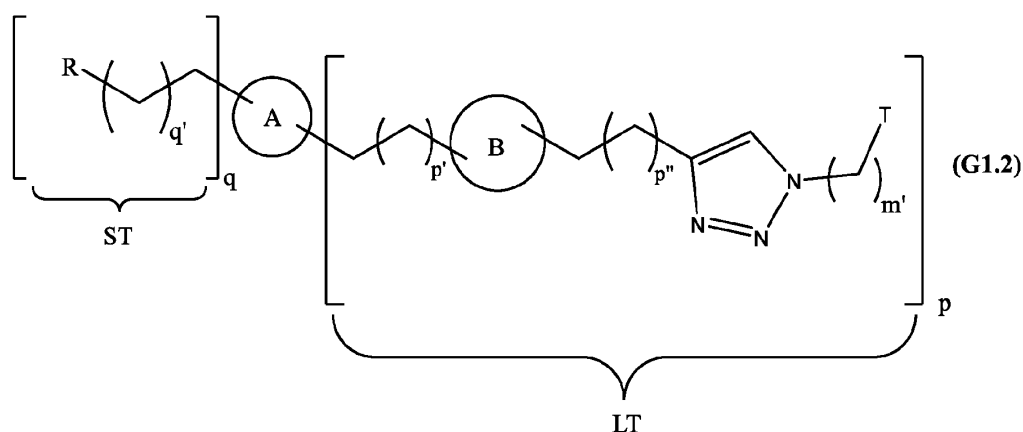
unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-cyclohexanediyl)-EE, or EE-(1,3-cyclohexanediyl)-EE, wherein $w3 = 0-4$, $w4 = 0-4$, XS is C(O)-O-(CH₂)₂, and EE is O, C(O)-O or C(O)-NH,

$p = 5$, then A is $(*)N-(CH_2)_{p1}-N^*-(CH_2)_{p2}-N(*)^*$, $p1 = 2-5$, $p2 = 2-5$, and

$p = 6$, then A is $(*)N-(CH_2)_{q1}-N((CH_2)_{q2}-N(*)^*)-(CH_2)_{q3}-N(*)^*$, wherein $q1 = 2-4$, $q2 = 2-4$, and $q3 = 2-4$.

[0007] When $p > 1$, then each one of the plurality of LT moieties may be the same or different from the remaining LT moieties in the same molecule.

[0008] In another aspect, the present application relates to compounds represented generically by formula (G1.2) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:



[0009] The amino moiety A in (G1.2) is selected when $q \geq 1$ as having its N* or N(*)* binding sites linked to at least one ST that differs from LT as indicated in general formula (G1.2).

[0010] R is OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being (CH₂)_{q'}CH₃, with $q' = 1-4$, $q'' = 1-4$,

B is as defined for formula (G1.1),

$p = 1-5$ when $q = 1-5$, and $p = 1-6$ when $q = 0-5$, with $(p + q) = 1-6$ and $p \neq 0$,

$q = 0$ leads to the compounds of general formula (G1.1) with $p = 1-6$ as defined above. All the variables concerning the amino moiety A and the moiety(ies) LT not defined for (G1.2) are as defined for (G1.1), subject to the p and q restrictions set forth above. For example, A in (G1.2) is an amino moiety, and said amino moiety A is selected depending on the $(p+q)$ -value as follows, wherein the term $*$ is used to refer to a N-binding site of an LT moiety, and $*(*)$ (or $(*)*$ indistinguishably) is used to refer to two separate N-binding sites of two LT moieties:

when $p = 1$ and $q = 0$, then such compound would be a compound of formula (G1.1);

when $p = 1$ and $q = 1$, then A is $*(*)N-(CH_2)_t-Z$,

$t = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $N(CH_2-CH_3)_2$, or $N(CH_3)_2$,

when $p+q = 4$, with $p \geq 1$ and $q \geq 1$, then A is

$*(*)N-(CH_2)_{w1}-E-(CH_2)_{w2}-N(*)*$,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-O, $O-(CH_2)_{w3}$ -(substituted or unsubstituted 1,4-piperazinediyl)- $(CH_2)_{w4}$ -O, substituted or unsubstituted 1,4-piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-cyclohexanediy)-EE, or EE-(1,3-cyclohexanediy)-EE, wherein $w3 = 0-4$, $w4 = 0-4$, XS is $C(O)-O-(CH_2)_2$, and EE is O, $C(O)-O$ or $C(O)-NH$,

when $p+q = 5$, with $p \geq 1$ and $q \geq 1$, then A is

$*(*)N-(CH_2)_{p1}-N^*-(CH_2)_{p2}-N(*)*$, $p1 = 2-5$,

$p2 = 2-5$, and

when $p+q = 6$, with $p \geq 1$ and $q \geq 1$, then A is

$*(*)N-(CH_2)_{q1}-N((CH_2)_{q2}-N(*)*)-(CH_2)_{q3}-N(*)*$,

$q1 = 2-4$, $q2 = 2-4$, and $q3 = 2-4$.

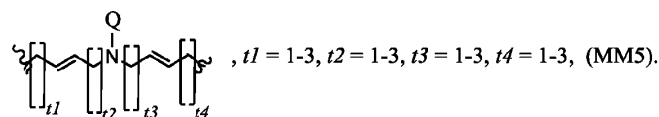
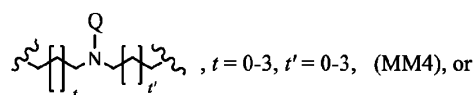
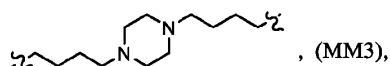
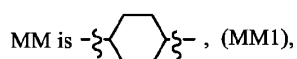
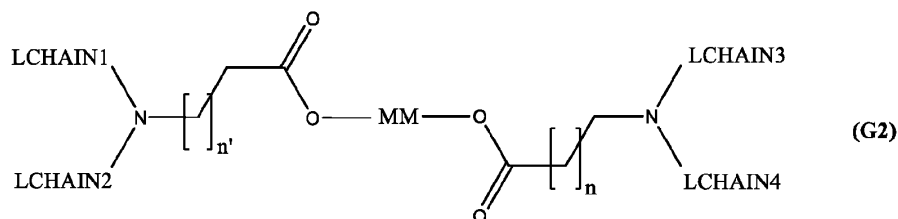
[0011] When $p > 1$, then each one of the plurality of LT moieties may be the same or different from the remaining LT moieties in the same molecule, and when $q > 1$, then each one of the plurality of ST moieties may be the same or different from the remaining ST moieties in the same molecule.

[0012] Formula (G1.2) envisages embodiments with the N^* and $N(^*)^*$ binding sites in the amino moiety A being linked to ST and/or LT according to any of the following binding embodiments for N^* : N-ST and N-LT, and according to any of the following binding embodiments for $N(^*)^*$: $N(LT)(LT)$ wherein the LT moieties are identical or different from each other, $N(ST)(LT)$ and $N(ST)(ST)$ wherein the ST moieties are identical or different from each other.

[0013] Each variable in (G1.1) and (G1.2) indicating the choice of a number of groups of substituents, or a choice of substituents, is elected independently from the choice of any other such variable, whether such variables have the same name (while referring to different groups) or not, unless explicitly indicated otherwise.

[0014] In another aspect, the present application relates to synthetic methods and intermediates used in the synthesis of triazoles (G1.1) and (G1.2) referred to above.

[0015] The present application relates in another aspect to compounds represented generically by formula (G2) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:



wherein

each occurrence of LCHAIN1 - LCHAIN4 is linear or branched C_a -alkyl, with $a = 9-15$, or $\text{CH}_2(\text{CH}_2)_v\text{CH}=\text{CH}(\text{CH}_2)_{v'}\text{CH}_3$, with $v = 8-12$, $v' = 1-4$, $v'' = 2-5$, and each occurrence of LCHAIN1 - LCHAIN4 is the same or different from each of any of the other three occurrences of LCHAIN1 - LCHAIN4,

$n = 0 - 4$,

$n' = 0 - 4$, and each occurrence of n is the same or different from each occurrence of n' ,

Q is $(\text{CH}_2)_r\text{CH}_3$ with $r = 0-2$, or $\text{CH}_2(\text{CH}_2)_{r'}\text{C}(\text{O})\text{O}(\text{CH}_2)_{r''}\text{CH}_3$ with $r' = 0-3$ and $r'' = 1-3$.

[0016] The designations (MM1), (MM2), (MM3), MM4) and (MM5) refer to the various assignments for the moiety MM in Formula (G2).

[0017] Each variable in (G2) indicating the choice of a number of groups of substituents, or a choice of substituents, is elected independently from the choice of any other such variable,

whether such variables have the same name (while referring to different groups) or not, unless explicitly indicated otherwise.

[0018] In another aspect, the present application relates to synthetic methods and intermediates used in the synthesis of compounds of any of formulae (G1.1), (G1.2) and (G2) referred to above.

[0019] In another aspect, the present application relates to a pharmaceutical composition comprising at least one compound, or combination thereof, as described herein or a stereoisomer, tautomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0020] In another aspect, the present application relates to the use of at least one compound as described herein or a stereoisomer, tautomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof, or a combination thereof for the making of lipid nanoparticle compositions, for drug delivery or cancer treatment.

[0021] Other features and advantages of the present invention are apparent from additional descriptions provided herein, including different examples. The examples provided herein illustrate different components and methodology useful in practicing the present invention. Such examples do not limit the claimed invention. Based on the present disclosure, the skilled artisan can identify and employ other components and methodology useful for practicing the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] The foregoing summary, as well as the following detailed description of preferred embodiments of the present application, will be better understood when read in conjunction with the appended drawings. It should be understood, however, that the application is not limited to the precise embodiments shown in the drawings.

[0023] FIG. 1. Tabular summary of *in vitro* screening results showing which LNPs resulted in expression of *Gaussia* luciferase from mRNA, pDNA, or both payloads.

[0024] FIG. 2A. DNA-LNP data showing circulating levels of hFIX following *in vivo* delivery of hFIX transgene expression cassette DNA with LNPs comprising lipids according to this invention, such as lipids of Formula (G1.1).

[0025] FIG. 2B. DNA-LNP data showing circulating levels of hFIX following *in vivo* delivery of hFIX transgene expression cassette DNA with LNPs comprising lipids according to this invention, such as lipids of Formula (G2).

[0026] FIG. 2C. DNA-LNP data showing circulating levels of IL-6 (representative cytokine response) following *in vivo* delivery of hFIX transgene expression cassette DNA with LNPs comprising lipids according to this invention, such as lipids of Formula (G1.1).

[0027] FIG. 2D. DNA-LNP data showing circulating levels of IL-6 (representative cytokine response) following *in vivo* delivery of hFIX transgene expression cassette DNA with LNPs comprising lipids according to this invention, such as lipids of Formula (G2).

[0028] FIG. 3A. DNA-LNP data showing *in vivo* efficacy of multiple formulation compositions of the same ionizable lipid. Tabular summary of multiple LNP formulation compositions comprising the same ionizable lipid A4L1T14, a lipid of Formula (G1.1).

[0029] FIG. 3B. DNA-LNP data showing *in vivo* efficacy of multiple LNP formulation compositions of the same ionizable lipid from FIG. 3A. The graph shows circulating levels of hFIX after delivery of hFIX transgene expression cassette DNA-LNPs with different formulation compositions with the same ionizable lipid A4L1T14, a lipid of Formula (G1.1).

[0030] FIG. 3C. DNA-LNP data showing *in vivo* efficacy of multiple LNP formulation compositions of the same ionizable lipid from FIG 3A. The graph shows circulating levels of IL-6 (representative cytokine response) after delivery of hFIX transgene expression cassette DNA-LNPs with different formulation compositions with the same ionizable lipid A4L1T14, a lipid of Formula (G1.1).

[0031] FIG. 4A. mRNA-LNP *in vivo* data showing potency of mRNA-LNPs formulated with lipids A4L1T14 and A5L1T15. hEPO expression (circulating levels of hEPO) after single IV delivery of different doses of hEPO mRNA-LNPs. hEPO levels measured from plasma 6 h after dosing.

[0032] FIG. 4B. mRNA-LNP *in vivo* data showing cytokine response following delivery of mRNA-LNPs formulated with lipids A4L1T14 and A5L1T15. Circulating MCP-1 (representative cytokine response) following single IV delivery of different doses of hEPO mRNA-LNPs. MCP-1 cytokine levels measured from plasma 6 h after dosing.

[0033] FIG. 4C. mRNA-LNP *in vivo* data showing potency of mRNA-LNPs formulated with lipids A4L1T14 and A5L1T15. Time course of circulating levels of hEPO after IV delivery of each of two doses of hEPO mRNA-LNPs formulated with lipids A4L1T14 and A5L1T15.

[0034] FIG. 5A. mRNA-LNP *in vivo* data showing that mRNA-LNPs formulated with lipids of the present invention, such as A4L1T14, can be re-dosed *in vivo*. Table of multiple LNP formulations of A4L1T14.

[0035] FIG. 5B. mRNA-LNP *in vivo* data showing that mRNA-LNPs formulated with lipids of the present invention, such as A4L1T14, can be re-dosed *in vivo*. hEPO expression (circulating hEPO levels) after multiple IV dosings in mice of hEPO mRNA-LNPs from FIG. 5A. hEPO levels measured from plasma 6 h after dosing.

[0036] FIG. 6. mRNA-LNP *in vivo* data showing potency of lipids according to this invention for mRNA delivery. Expression of hEPO using mRNA delivery by LNPs containing various ionizable lipids, including lipids according to the present invention (Formulae (G1.1) and (G2)). hEPO mRNA-LNP administered via tail vein injection to wild-type mice; hEPO expression (circulating hEPO levels) measured 6 h post-injection.

[0037] FIG. 7. mRNA-LNP *in-vivo* data showing potency of lipids according to this invention for delivery of firefly luciferase mRNA. Expression of firefly luciferase (Flux) in liver tissues after IV administration to mice of mRNA-LNPs formulated with various ionizable lipids, including lipids according to the present invention (Formula (G1.1)).

[0038] FIG. 8A. mRNA-LNP *in-vivo* data showing responses to A4L1T14-based LNP formulations. Strength of anti-OVA IgG antibody response that was induced by A4LT14-based LNP formulations when OVA mRNA-LNP was delivered intramuscularly to mice.

[0039] FIG. 8B. mRNA-LNP *in-vivo* data showing responses to A4L1T14-based LNP formulations. Strength of antigen-specific T cell (MHC-I tetramer+ CD8 cells) responses that were induced by A4L1T14-based LNP formulations following intramuscular injection of OVA mRNA-LNP.

[0040] FIG. 8C. mRNA-LNP *in-vivo* data showing responses to A4L1T14-based formulations. Strength of antigen-specific T cell (IFN- γ + CD8 cells) responses that were induced by A4L1T14-based LNP formulations following intramuscular injection of OVA mRNA-LNP.

DETAILED DESCRIPTION OF THE INVENTION

[0041] Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is for the purpose of providing context for the disclosure. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to the disclosure.

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification. All patents, published patent applications, and publications cited herein are incorporated by reference as if set forth fully herein.

[0043] It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise.

[0044] Unless otherwise indicated, the term “at least” preceding a series of elements is to be understood to refer to every element in the series. For example, the phrase “at least A, B, and C” means that each of A, B, and C is present. The term “at least one of” preceding a series of elements is to be understood to refer to a single element in the series or any combination of two or more elements in the series. For example, the phrase “at least one of A, B, and C” means that only A is present, only B is present, only C is present, both A and B are present, both A and C are present, both B and C are present, or each of A, B, and C is present. Depending on the context, “at least one of” preceding a series of elements can also encompass situations in which any one or more of the elements is present in greater than one instance, *e.g.*, “at least one of A, B, and C” can also encompass situations in which A is present in duplicate alone or further in combination with any one or more of elements B and C.

[0045] As used herein, the term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two elements are conjoined by “and/or,” a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or” as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or.”

[0046] Unless otherwise stated, any numerical value, such as a concentration or a concentration range described herein, is to be understood as being modified in all instances by the term “about” (whether written explicitly or not) and, in any case, “about” is to be construed when applied to the term that it modifies as understood by one of ordinary skill in the art, including the typical experimental uncertainties associated with the determination of the value of such term. As used herein, the use of a numerical range expressly includes all possible subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

[0047] As used herein, “subject” means any animal, such as a mammal, to whom will be or has been treated by a method described herein. The term “mammal” as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, and non-human primates (NHPs), such as monkeys or apes, humans, etc.

[0048] The phrase “pharmaceutically acceptable salt(s)” means those salts of a compound of interest that are safe and effective for topical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in the specified compounds. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, carbonate, bicarbonate, acetate, lactate, salicylate, citrate, tartrate, propionate, butyrate, pyruvate, oxalate, malonate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and

pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds used in the application can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, bismuth, and diethanolamine salts. For a review on pharmaceutically acceptable salts, *see Berge, et al.*, 66 J. Pharm. Sci. 1-19 (1977), incorporated herein by reference.

[0049] As used herein, the term “alkyl” means a saturated, monovalent, unbranched or branched hydrocarbon chain. An alkyl group can be unsubstituted or substituted with one or more suitable substituents. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl, isopropyl), butyl (*e.g.*, n-butyl, isobutyl, tert-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), etc. An alkyl group can have a specified number of carbon atoms. When numbers appear in a subscript after the symbol “C”, the subscript defines with more specificity the number of carbon atoms which that particular alkyl can contain. For example, “C₁ to C₁₀ alkyl” or “C₁₋₁₀ alkyl” is intended to include alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₈ alkyl” or “C₁₋₈ alkyl” denotes an alkyl having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

[0050] The term “cycloalkyl” refers to any stable monocyclic or polycyclic saturated hydrocarbon ring system. A cycloalkyl group can be unsubstituted or substituted with one or more suitable substituents. A cycloalkyl group can have a specified number of carbon atoms. For example, “C₃ to C₆ cycloalkyl” or “C₃₋₆ cycloalkyl” includes cycloalkyl groups having 3, 4, 5, or 6 ring carbon atoms, *i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Polycyclic cycloalkyls include bridged, fused, and spiro ring structures in which all ring atoms are carbon atoms. A “spiro ring” is a polycyclic ring system in which two rings share one carbon atom, referred to as the “spiro atom,” which is typically a quaternary carbon atom. A “fused ring” is a polycyclic ring system in which two rings share two adjacent atoms, referred to as “bridgehead atoms,” *i.e.*, the two rings share one covalent bond such that the bridgehead atoms are directly connected. A “bridged ring” is a polycyclic ring system in which two rings share three or more atoms separating the bridgehead atoms by a bridge containing at least one atom. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

[0051] As used herein, the term “alkenyl” means a linear or branched chain of hydrocarbons comprising at least one carbon to carbon double bond, optionally having the number of carbon atoms designated (*i.e.*, C₂-C₄ alkenyl or C₂₋₄alkenyl means an alkenyl having two to four carbon atoms).

[0052] As used herein, the term “alkynyl” means a linear or branched chain of hydrocarbons comprising at least one carbon to carbon triple bond, optionally having the number of carbon atoms designated (*i.e.*, C₂-C₄ alkynyl or C₂₋₄alkynyl means an alkynyl having two to four carbon atoms).

[0053] The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, phenyl, naphthyl, anthracenyl, phenanthryl, and the like. Aryl moieties are well known and described, for example, in Lewis, R. J., ed., Hawley's Condensed Chemical Dictionary, 13th Edition, John Wiley & Sons, Inc., New York (1997). An aryl group can be substituted or unsubstituted with one or more suitable substituents. An aryl group can comprise a single ring structure (*i.e.*, monocyclic) or multiple ring structures (*i.e.*, polycyclic, *e.g.*, bicyclic or tricyclic). For example, an aryl group can be a monocyclic aryl group, *e.g.*, phenyl.

[0054] The term “heterocyclyl” includes stable monocyclic and polycyclic hydrocarbons that contain at least one heteroatom ring member, such as sulfur, oxygen, or nitrogen, wherein the ring structure is saturated or partially unsaturated, provided the ring system is not fully aromatic. A heterocyclyl group can be unsubstituted, or substituted with one or more suitable substituents at any one or more of the carbon atom(s) and/or nitrogen heteroatom(s) of the heterocyclyl. A heterocyclyl can comprise a single ring structure (*i.e.*, monocyclic) or multiple ring structures (*i.e.*, polycyclic, *e.g.*, bicyclic). Polycyclic heterocyclyls include bridged, fused, and spiro ring structures in which at least one ring atom of at least one of the rings of the polycyclic ring system is a heteroatom, for instance oxygen, nitrogen, or sulfur, wherein bridged, fused, and spiro rings are as defined above. A heterocyclyl ring can be attached to the parent molecule at any suitable heteroatom (typically nitrogen) or carbon atom of the ring. The term “4- to 9-membered monocyclic or bicyclic heterocyclyl” includes any four, five, six, seven, eight, or nine membered monocyclic or bicyclic ring structure containing at least one heteroatom ring member selected from oxygen, nitrogen, and sulfur, or independently selected from oxygen and nitrogen, optionally containing one to three additional heteroatoms independently selected from oxygen,

nitrogen, and sulfur, or independently selected from oxygen and nitrogen, wherein the ring structure is saturated or partially unsaturated, provided the ring structure is not fully aromatic.

[0055] As used herein, the term “heteroaryl” includes stable monocyclic and polycyclic aromatic hydrocarbons that contain at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. A heteroaryl group can be unsubstituted or substituted with one or more suitable substituents. A heteroaryl can comprise a single ring structure (*i.e.*, monocyclic) or multiple ring structures (*i.e.*, polycyclic, *e.g.*, bicyclic or tricyclic). Each ring of a heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. Heteroaryl groups which are polycyclic, *e.g.*, bicyclic or tricyclic must include at least one fully aromatic ring, but the other fused ring or rings can be aromatic or non-aromatic. For example, for a bicyclic heteroaryl, the fused rings completing the bicyclic group can contain only carbon atoms and can be saturated, partially saturated, or unsaturated. A heteroaryl can be attached to the parent molecule at any available nitrogen or carbon atom of any ring of the heteroaryl group. In some embodiments, the term “heteroaryl” refers to 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups which have at least one heteroatom (O, S, or N) in at least one of the rings, wherein the heteroatom-containing ring typically has 1, 2, or 3 heteroatoms, such as 1 or 2 heteroatoms, selected from O, S, and/or N. A heteroaryl group can be unsubstituted, or substituted with one or more suitable substituents at any one or more of the carbon atom(s) and/or nitrogen heteroatom(s) of the heteroaryl. The nitrogen and sulfur heteroatom(s) of a heteroaryl can optionally be oxidized (*i.e.*, N→O and S(O)_r, wherein r is 0, 1 or 2).

[0056] The term “alkoxy” as used herein refers to an –O-alkyl group, wherein alkyl is as defined above. An alkoxy group is attached to the parent molecule through a bond to an oxygen atom. An alkoxy group can have a specified number of carbon atoms. For example, “C₁ to C₁₀ alkoxy” or “C₁₋₁₀ alkoxy” is intended to include alkoxy groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “C₁ to C₄ alkoxy” or “C₁₋₄ alkoxy” denotes an alkoxy having 1, 2, 3, or 4 carbon atoms. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy, isopropoxy), butoxy (*e.g.*, n-butoxy, isobutoxy, tert-butoxy), pentyloxy (*e.g.*, n-pentyloxy, isopentyloxy, neopentyloxy), etc. An alkoxy group can be

unsubstituted or substituted with one or more suitable substituents. Similarly, “alkylthio” or “thioalkoxy” represents an alkyl group as defined above attached to the parent molecule through a bond to a sulfur atom, for example, -S-methyl, -S-ethyl, etc. Representative examples of alkylthio include, but are not limited to, -SCH₃, -SCH₂CH₃, etc.

[0057] As used herein, the term “halogen” means fluorine, chlorine, bromine, or iodine. Correspondingly, the term “halo” means fluoro, chloro, bromo, and iodo.

[0058] “Haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon radicals substituted with one or more halogen atoms. “Fluorinated alkyl” or “fluoroalkyl” in particular refers to any alkyl group as defined above substituted with at least one fluoro atom, *e.g.*, one to three fluoro atoms, such as one, two, or three fluoroatoms. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Suitable examples of fluoroalkyl in particular include, but are not limited to, -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CF₂CF₃, and the like.

[0059] The terms “hydroxy” and “hydroxyl” can be used interchangeably, and refer to –OH.

[0060] The term “carboxy” refers to –COOH.

[0061] The term “ester” refers to –COOR, wherein R is alkyl as defined above.

[0062] The term “cyano” refers to –CN.

[0063] The term “oxo” refers to a double bonded oxygen group, *i.e.*, a substituent group of the formula =O.

[0064] The term “keto” refers to –C(O)R, wherein R is alkyl as defined above.

[0065] The term “amino” refers to –NH₂. One or more hydrogen atoms of an amino group can be replaced by a substituent such as an alkyl group, which is referred to as an “alkylamino.” Alkylamino groups have one or both hydrogen atoms of an amino group replaced with an alkyl group and is attached to the parent molecule through a bond to the nitrogen atom of the alkylamino group. For example, alkylamino includes methylamino (–NHCH₃), dimethylamino (–N(CH₃)₂), –NHCH₂CH₃ and the like.

[0066] The term “aminoalkyl” as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more amino groups. For example, “C₁₋₄ aminoalkyl” is intended to include alkyl groups having 1, 2, 3, or 4 carbon

atoms substituted with one or more amino groups. Aminoalkyl groups are attached to the parent molecule through a bond to a carbon atom of the alkyl moiety of the aminoalkyl group. Representative examples of aminoalkyl groups include, but are not limited to, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{NH}_2$, and $-\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_3$.

[0067] As used herein, “amido” refers to $-\text{C}(\text{O})\text{N}(\text{R})_2$, wherein each R is independently an alkyl group (including both branched and straight-chain alkyl groups) or a hydrogen atom. Examples of amido groups include, but are not limited to, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, and $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$.

[0068] The terms “hydroxyl-substituted alkyl,” “hydroxylalkyl” and “hydroxyalkyl” are used interchangeably, and refer to a branched or straight-chain aliphatic hydrocarbon group substituted with one or more hydroxyl groups. Hydroxyalkyl groups are attached to the parent molecule through a bond to a carbon atom of the alkyl moiety of the hydroxyalkyl group. A hydroxyalkyl group can have a specified number of carbon atoms. For example, “ C_1 to C_{10} hydroxyalkyl” or “ C_{1-10} hydroxyalkyl” is intended to include hydroxyalkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbon atoms. Additionally, for example, “ C_1 to C_4 hydroxylalkyl” or “ C_{1-4} hydroxyalkyl” denotes a hydroxyalkyl group having 1, 2, 3, or 4 carbon atoms. Examples of hydroxyalkyl include, but are not limited to, hydroxymethyl ($-\text{CH}_2\text{OH}$), hydroxyethyl ($-\text{CH}_2\text{CH}_2\text{OH}$), etc.

[0069] For the avoidance of doubt, when a group is “bond”, then such group is not present while the connectivity of the rest of the molecular entity or moiety is unchanged and kept as such single molecular entity or moiety. For example, E_{ex} being CH_2 or bond in the molecular entity or moiety $\text{A}_{\text{ex}}-\text{E}_{\text{ex}}-\text{B}_{\text{ex}}$, refers to the molecular entities or moieties $\text{A}_{\text{ex}}-\text{CH}_2-\text{B}_{\text{ex}}$ and $\text{A}_{\text{ex}}-\text{B}_{\text{ex}}$, the latter being the embodiment associated with the choice of E_{ex} being bond.

[0070] The assignment “OCO is O-C(O) or C(O)-O”, or an analogous assignment, means that when OCO is O-C(O), then the illustrative moiety or molecular entity $\text{Y}_{\text{ex}}-\text{OCO}-\text{V}_{\text{ex}}$ has an $\text{Y}_{\text{ex}}-\text{O}$ bond as in $\text{Y}_{\text{ex}}-\text{O}-\text{C}(\text{O})-\text{V}_{\text{ex}}$, and when OCO is C(O)-O then the illustrative moiety or molecular entity $\text{Y}_{\text{ex}}-\text{OCO}-\text{V}_{\text{ex}}$ has a $\text{V}_{\text{ex}}-\text{O}$ bond as in $\text{Y}_{\text{ex}}-\text{C}(\text{O})-\text{O}-\text{V}_{\text{ex}}$.

[0071] In accordance with convention used in the art, notations such as:

[0072] $\begin{array}{c} \text{X} \\ \vdots \\ \text{X} \end{array}$, $\begin{array}{c} \text{X} \\ \vdots \\ \text{X} \end{array}$, and -f-

[0073] are used in structural formulas herein to depict a bond that is the point of attachment of a group, moiety or substituent to the core, backbone, or parent molecule structure. An asterisk or a plurality of asterisks are used to refer to a certain binding site, or plurality of binding sites; by way of illustration, the term *N refers to one N-binding site (the binding site for an LT or ST moiety), and *(*)N refers to two separate N-binding sites in the same N member (the binding sites in the same N member for two LT moieties (identical or different from each other), two ST moieties (identical or different from each other), or one ST and one LT moieties).

[0074] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom on the ring.

[0075] The term “substituted” as used herein with respect to any organic radical (*e.g.*, alkyl, cycloalkyl, heteroaryl, aryl, heterocyclyl, etc.) means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that all normal valencies are maintained and that the substitution results in a stable compound. When a particular group is “substituted,” that group can have one or more substituents, such as from one to five substituents, one to three substituents, or one to two substituents, independently selected from the list of substituents. The term “independently” when used in reference to substituents, means that when more than one of such substituents is possible, such substituents can be the same or different from each other. Examples of suitable substituents include, but are not limited to, alkyl, halo, haloalkyl, alkoxy, amido, hydroxy, hydroxyalkyl, amino, carboxyl, ester, oxo, cyano, and the like.

[0076] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R groups, then said group can be optionally substituted with up to three R groups, and at each occurrence, R is selected independently from the definition of R.

[0077] The terms “optional” or “optionally” mean that the event or circumstance described subsequently can, but need not, occur, and such a description includes the situation in which the event or circumstance does or does not occur. For example, “optionally substituted heterocyclyl” means that a substituent group can be, but need not be, present, and such a description includes the situation of the heterocyclyl group being substituted by a suitable substituent and the heterocyclyl group not being substituted by any substituent.

[0078] One skilled in the art will recognize that in certain embodiments compounds described herein can have one or more asymmetric carbon atoms in their structure. As used herein, any chemical formulas with bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, or otherwise indicated as having a particular configuration (*e.g.*, R or S) around one or more atoms, contemplates each possible stereoisomer, or mixture of two or more stereoisomers. The term stereoisomers includes enantiomers and diastereomers. Enantiomers are stereoisomers that are non-super-imposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, *i.e.*, they are not related as mirror images, and occur when two or more stereoisomers of a compound have different configurations at one or more of the equivalent stereocenters and are not mirror images of each other. Substituent groups (*e.g.*, alkyl, heterocyclyl, etc.) can contain stereocenters in either the R or S configuration.

[0079] Certain examples can contain chemical structures that comprise (R) or (S) terminology. When (R) or (S) is used in the name of a compound or in the chemical representation of the compound, it is intended to mean that the compound is a single isomer at that stereocenter, with established absolute configuration of either (R) or (S).

[0080] Stereochemically pure isomeric forms can be obtained by techniques known in the art in view of the present disclosure. For example, diastereoisomers can be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers can be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers can also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereoselective reactions.

[0081] When compounds described herein can form tautomers, the term “tautomer” refers to compounds that are interchangeable forms of a particular compound structure and that vary in the displacement of hydrogen atoms and electrons. Tautomers are constitutional isomers of chemical compounds that readily interconvert, usually resulting in relocation of a proton (hydrogen). Thus, two structures can be in equilibrium through the movement of pi electrons and an atom (usually hydrogen). All tautomeric forms and mixtures of tautomers of the compounds described herein are included with the scope of the application.

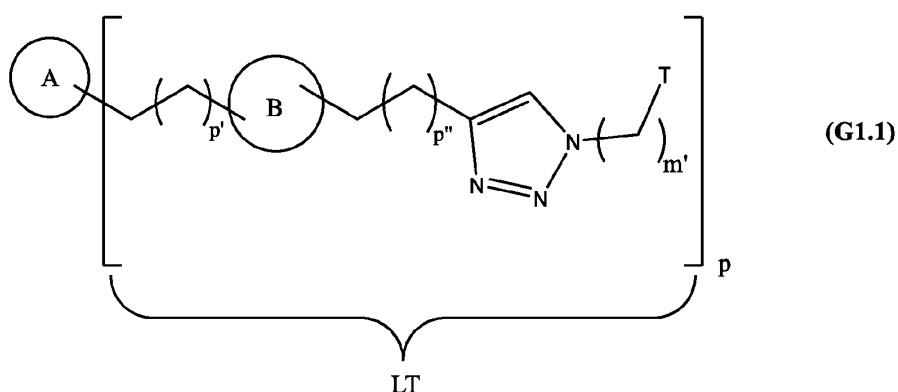
[0082] Compounds described herein can exist in solvated and unsolvated forms. The term “solvate” means a physical association, *e.g.*, by hydrogen bonding, of a compound of the application with one or more solvent molecules. The solvent molecules in the solvate can be present in a regular arrangement and/or a non-ordered arrangement. The solvate can comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. “Solvate” encompasses both solution-phase and isolable solvates. Compounds of the application can form solvates with water (*i.e.*, hydrates) or common organic solvents. Illustrative solvates include, but are not limited to, hydrates, ethanlates, methanlates, and isopropanolates. Methods of solvation are generally known in the art.

[0083] Also included within the scope of the application are all isotopes of atoms occurring in the compounds described herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C . Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0084] As used herein, the name of a compound is intended to encompass all possible existing isomeric forms, including stereoisomers (*e.g.*, enantiomers, diastereomers, racemate or racemic mixture, and any mixture thereof) and constitutional isomers, of the compound, unless indicated otherwise.

Compounds

[0085] In one general aspect, the present application relates to a compound formula (G1.1) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:



wherein

moiety B in (G1.1) is C(O)O, OC(O), C(O)NH, HNC(O), or CH₂CH₂,

p = 1-6;

p' = 0-4;

p'' = 0-4;

m' = 0, 1;

moiety T is selected from

CH(((CH₂)_{ll}CH₃)-CH₂)_{ll'}CH₃, ll = 2-6, ll' = 2-6

CH₃-(CH₂)_k-CH₂, k = 2-14;

(CH₃-(CH₂)_{k'})₂-CH-(CH₂)_{k''}-CH₂, k' = 0-8, k'' = 0-9;

CH₃-(CH₂)_{kk}-CH=CH-(CH₂)_{kk'}-CH₂, kk = 5-8, kk' = 5-8;

CH₃-(CH₂)_{k_p}-CH=CH-(CH₂)_{k_p}-CH=CH-(CH₂)_{k_p'}-CH₂, k_p = 5-7, k_p' = 5-7,

k_p' = 1-3;

CH₃-(CH₂)_l-O-C(O)-(CH₂)_{kk''}-CH₂, l = 2-7, kk'' = 0-4; and

(CH₃-(CH₂)_l-CH₂)₂-CH-MS-C(O)-(CH₂)_{kk''}-CH₂, l = 2-7, kk'' = 0-5, MS is

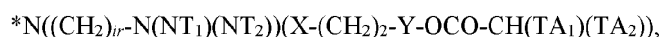
O or NH;

and when p > 1, then each one of the plurality of T tails may be the same or different from the remaining T tails in the same molecule,

and

the amino moiety A in (G1.1) is selected depending on the p-value as follows, wherein the term * is used to refer to a N-binding site of an LT moiety, and *(*) (or (*)*) indistinguishably) is used to refer to two separate N-binding sites of two LT moieties:

p = 1, then A is



$ir = 2-4$,

NT_1 is H, or CH_3 ,

NT_2 is CH_3 , $(CH_2)_r-OCO-(CH_2)_{r'}-CH_3$, $(CH_2)_r-OH$, or

$(CH_2)_{r''}-CH_3$, with $r = 1-3$, $r' = 1-3$, and $r'' = 1-3$,

X is $C(O)-O$, $C(O)-CH_2$, $(CH_2)_{mm}-OCO$ with $mm = 1-3$, or

$CH_2-(CH_2)_{mm}$ with $mm = 0-3$,

Y is $S-S-(CH_2)_n$, $n = 2,3$, or $(CH_2)_q$, $q = 3-6$,

OCO is $O-C(O)$ or $C(O)-O$,

TA_1 is H or $(CH_2)_m-CH_3$, and

TA_2 is $(CH_2)_{m'}-CH_3$,

with $m = 5-8$ and $m' = 5-8$;

p = 2, then A is $*(*)N-(CH_2)_t-Z$,

$t = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $N(CH_2-CH_3)_2$,

or $N(CH_3)_2$,

p = 4, then A is $*(*)N-(CH_2)_{w1}-E-(CH_2)_{w2}-N(*)^*$,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-

O, $O-(CH_2)_{w3}$ -(substituted or unsubstituted 1,4-

piperazinediyl)-(CH₂)_{w4}-O, substituted or unsubstituted 1,4-

piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or

unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-

cyclohexanediyl)-EE, or EE-(1,3-cyclohexanediyl)-EE,

wherein $w3 = 0-4$, $w4 = 0-4$, XS is C(O)-O-(CH₂)₂, and EE is O, C(O)-O or C(O)-NH,
 $p = 5$, then A is $^{(*)}N-(CH_2)_{p1}-N^{*}-(CH_2)_{p2}-N^{(*)}$, $p1 = 2-5$, $p2 = 2-5$, and
 $p = 6$, then A is $^{(*)}N-(CH_2)_{q1}-N((CH_2)_{q2}-N^{(*)})-(CH_2)_{q3}-N^{(*)}$, wherein
 $q1 = 2-4$, $q2 = 2-4$, and $q3 = 2-4$.

[0086] When $p > 1$, then each one of the plurality of LT moieties may be the same or different from the remaining LT moieties in the same molecule.

[0087] Each variable in (G1.1) indicating the choice of a number of groups of substituents, or a choice of substituents, is elected independently from the choice of any other such variable, whether such variables have the same name (while referring to different groups) or not, unless explicitly indicated otherwise.

[0088] In some embodiments, moiety A has one LT-substituted group indicated as $^{*}N$ in the assignment of A when $p = 1$ above.

[0089] In some embodiments, moiety A has one fully LT-substituted group indicated as $^{(*)}N$ in the assignment of A when $p = 2$ above.

[0090] In some embodiments, moiety A has two fully LT-substituted groups, each indicated as $^{(*)}N$ in the assignment of A when $p = 4$ above.

[0091] In some embodiments, moiety A has one LT-substituted group indicated as $^{*}N$ and two fully substituted groups, each indicated as $^{(*)}N$ in the assignment of A when $p = 5$ above.

[0092] In some embodiments, moiety A has three fully LT-substituted groups, each indicated as $^{(*)}N$ in the assignment of A when $p = 6$ above.

[0093] In some embodiments, $p = 1, 2, 4-6$.

[0094] When $p > 1$, all the LT moieties are identical in some embodiments of compounds of formula (G1.1), some of such LT moieties are the same whereas others are different in some other embodiments of compounds of formula (G1.1), and in still other embodiments of compounds of formula (G1.1), all the LT moieties are different.

[0095] T for each LT moiety is, in some embodiments, one of T1 – T23 in Table 2 without the azide moiety shown therein, and $m' = 0$. T for each LT moiety is, in some embodiments, one of T1 – T23 in Table 2 without the azide moiety shown therein, and $m' = 1$. The terms “moiety T” and “tail T” are used herein indistinguishably. Such T1-T23 without the corresponding azide moieties are as follows:

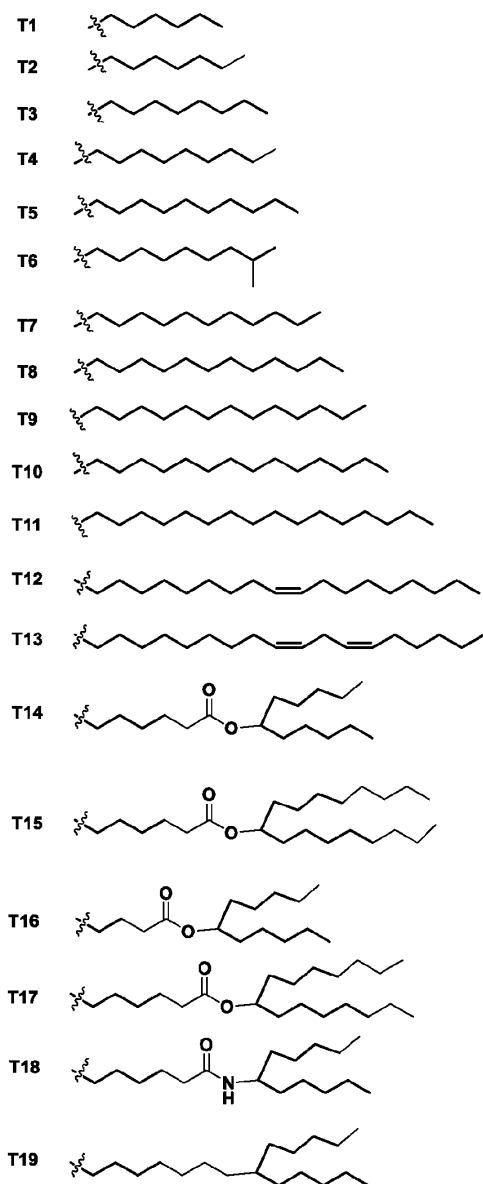


Table T2 (part 1)

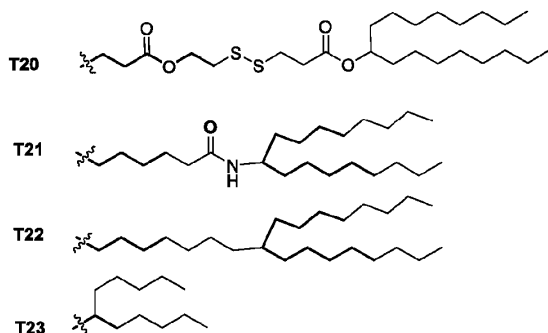


Table T2 (part 2)

[0096] In some embodiments, $p' = 1$.

[0097] In some embodiments, $p'' = 1$.

[0098] In some embodiments, $m' = 1$.

[0099] In some embodiments, $p' = p'' = 1$. In some embodiments in which $p' = p'' = 1$, B is CH_2CH_2 .

[0100] In some embodiments, B is C(O)NH or HNC(O) . In some of such embodiments where B is C(O)NH or HNC(O) , $p' = p'' = 1$.

[0101] In some embodiments, B is C(O)O or OC(O) . In some of such embodiments where B is C(O)O or OC(O) , $p' = p'' = 1$.

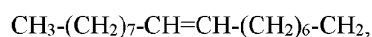
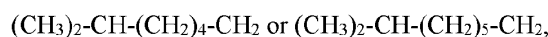
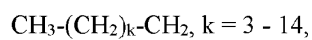
[0102] In some embodiments, $p' = p'' = m' = 1$.

[0103] In some embodiments, p is one of 1, 2, 3, 4, 5 and 6, and when p is one of 2, 3, 4, 5 and 6, then $p' = p'' = 1$ in each LT.

[0104] In some embodiments, p is one of 1, 2, 3, 4, 5 and 6, and when p is one of 2, 3, 4, 5 and 6, then $p' = p'' = 1$ in each LT and when $p = 1$ then m' is 0 or 1.

[0105] In some embodiments, p is one of 1, 2, 3, 4, 5 and 6, and when p is one of 2, 3, 4, 5 and 6, then $p' = p'' = 1$ in each LT and when p is one of 2, 3, 4, 5 and 6, then m' is 0 or 1 in each LT. In some of such embodiments, m' is the same in each LT.

[0106] In some embodiments, p is one of 1, 2, 3, 4, 5 and 6, and when p is one of 2, 3, 4, 5 and 6, then $p' = p'' = 1$ in each LT, and tail T is selected from



$\text{CH}_3-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$, and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_3-\text{CH}_2$, $l = 3$ or 6 ;
 m' is 0 or 1; and

when $p = 2, 3, 4, 5$ or 6 , then each one of the plurality of T tails is the same
 in each of said LT moieties, and each one of the plurality of m' is the same in each
 of said LT moieties.

[0107] In some embodiments, tail T is selected from

$\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 3 - 14$,
 $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_4-\text{CH}_2$ or $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_5-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$, and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_3-\text{CH}_2$, $l = 3$ or 6 ;
 and when $p > 1$, then each one of the plurality of T tails is the same as the
 remaining T tails in the same molecule.

[0108] In some embodiments, tail T is selected from

$\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 3 - 14$,
 $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_4-\text{CH}_2$ or $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_5-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$, and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_3-\text{CH}_2$, $l = 3$ or 6 ;
 and when $p > 1$, then each one of the plurality of T tails is different from
 the remaining T tails in the same molecule.

[0109] In some embodiments, $m' = 1$, and tail T is selected from

$\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 3 - 14$,
 $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_4-\text{CH}_2$ or $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_5-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$,
 $\text{CH}_3-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_6-\text{CH}_2$, and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_3-\text{CH}_2$, $l = 3$ or 6 ;
 and when $p > 1$, then each one of the plurality of T tails may be the same as
 or different from the remaining T tails in the same molecule.

[0110] In some embodiments, $p = 1$ and tail T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 3 - 14$.

[0111] In some embodiments, $p = 1$ and tail T is $(\text{CH}_3)_2\text{-CH-(CH}_2)_4\text{-CH}_2$ or $(\text{CH}_3)_2\text{-CH-(CH}_2)_5\text{-CH}_2$.

[0112] In some embodiments, $p = 1$ and tail T is $\text{CH}_3\text{-(CH}_2)_7\text{-CH=CH-(CH}_2)_6\text{-CH}_2$.

[0113] In some embodiments, $p = 1$ and tail T is $\text{CH}_3\text{-(CH}_2)_4\text{-CH=CH-CH}_2\text{-CH=CH-(CH}_2)_6\text{-CH}_2$, In some embodiments, $p = 1$ and tail T is $(\text{CH}_3\text{-(CH}_2)_l\text{-(CH}_2)_2\text{-CH-O-C(O)-(CH}_2)_3\text{-CH}_2$, $l = 3$ or 6 .

[0114] In some embodiments, $p = 1$ and A is $^*\text{N}((\text{CH}_3)_2\text{N-(CH}_2)_3)(\text{X-(CH}_2)_2\text{-Y-OCO-(CH}_2)_m\text{-CH}_3)$,

$m = 6 - 8$,

X is C(O)-O , C(O)-CH_2 or $\text{CH}_2\text{-CH}_2$,

Y is $\text{S-S-(CH}_2)_n$, wherein $n = 2, 3$, or $(\text{CH}_2)_q$, wherein $q = 3, 4$, and

OCO is O-C(O) , or C(O)-O .

[0115] When $p = 1$ and the term -OCO- in A is -O-C(O)- , it entails a Y-O bond in reference to member Y in the assignment of A. When $p = 1$ and the term -OCO- in A and is -C(O)-O- , it entails a Y-C in reference to member Y in the assignment of A.

[0116] In some embodiments with $p = 1$, the moiety $\text{A-CH}_2\text{-(CH}_2)_p\text{-B-CH}_2\text{(CH}_2)_p$ in (G1.1) is one of the following moieties in Table P1 (parts 1 and 2):

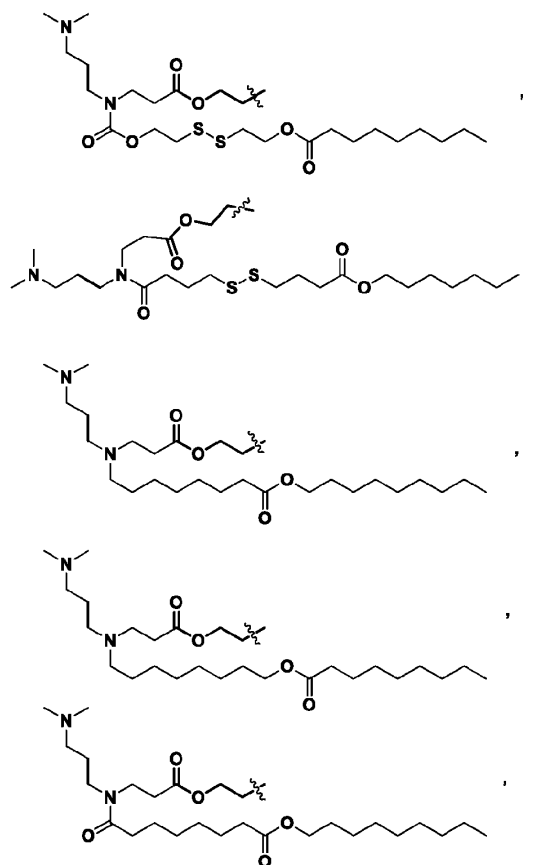


Table P1 (part 1)

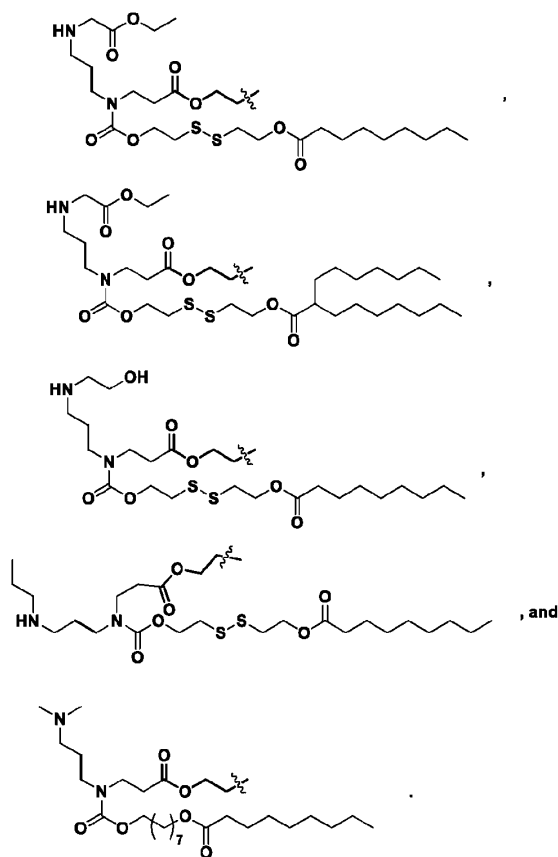


Table P1 (part 2)

wherein $p' = p'' = 1$, and B is C(O)O. The foregoing ten illustrative embodiments of moiety A-CH₂-(CH₂) _{p'} -B-CH₂(CH₂) _{p''} in (G1.1) when $p = 1$ (Table P1, parts 1 and 2) correspond, when in alkyne form, to the compounds $Ai''L1$, $i'' = 30-34$ and $38-42$ in Table 1. The N* member in each of such illustrative embodiments in the corresponding parent amine moiety A is the N member shown as a tertiary N that has the moiety CH₂-CH₂-C(O)O-CH₂-CH₂ attached to it. For each of such illustrative embodiments, the parent amine A moiety would be each of the structures shown without the moiety CH₂-CH₂-C(O)O-CH₂-CH₂.

[0117] In light of the structural and IUPAC name complexities of compounds of formula (G1.1), specific compounds of formula (G1.1) are referred to below with the notation $Ai''Lj''Tk''$, where i'' , j'' , and k'' are indices as defined below.

[0118] In some embodiments, $p = 2$ and A is $^{*}(*)N-(CH_2)_t-Z$,

$t = 2 - 6$, and

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $N(CH_2-CH_3)_2$, or $N(CH_3)_2$.

[0119] In some embodiments with $p = 2$, A is one of the following in Table P2:

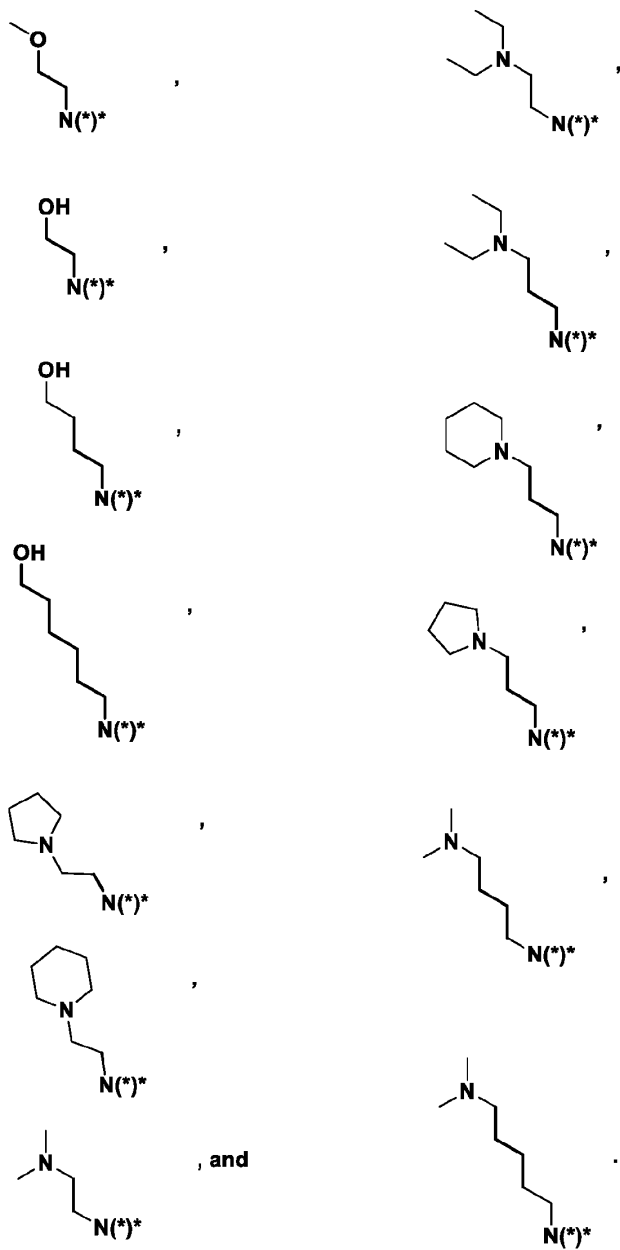


Table P2

[0120] The foregoing illustrative amine moiety A embodiments for $p = 2$ in Table P2 correspond, when in amine forms, to the amines shown in Table 1 as A17-A29.

[0121] In some embodiments, $p = 4$ and A is $^{*}(*)N-(CH_2)_{w1}-E-(CH_2)_{w2}-N^{*}(*)$,

$w1 = 2 - 6$,

$w2 = 2 - 6$,

E is bond, substituted or unsubstituted amino, O-phenylene-

O, $O-(CH_2)_{w3}$ -(substituted or unsubstituted 1,4-

piperazinediyl)- $(CH_2)_{w4}$ -O, substituted or unsubstituted 1,4-

piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or

unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-

cyclohexanediyl)-EE, or EE-(1,3-cyclohexanediyl)-EE,

wherein XS is $C(O)-O-(CH_2)_2$, and EE is O, $C(O)-O$ or

$C(O)-NH$,

$w3 = 0 - 4$, and $w4 = 0 - 4$.

[0122] In some embodiments with $p = 4$, A is one of the following in Table P4:

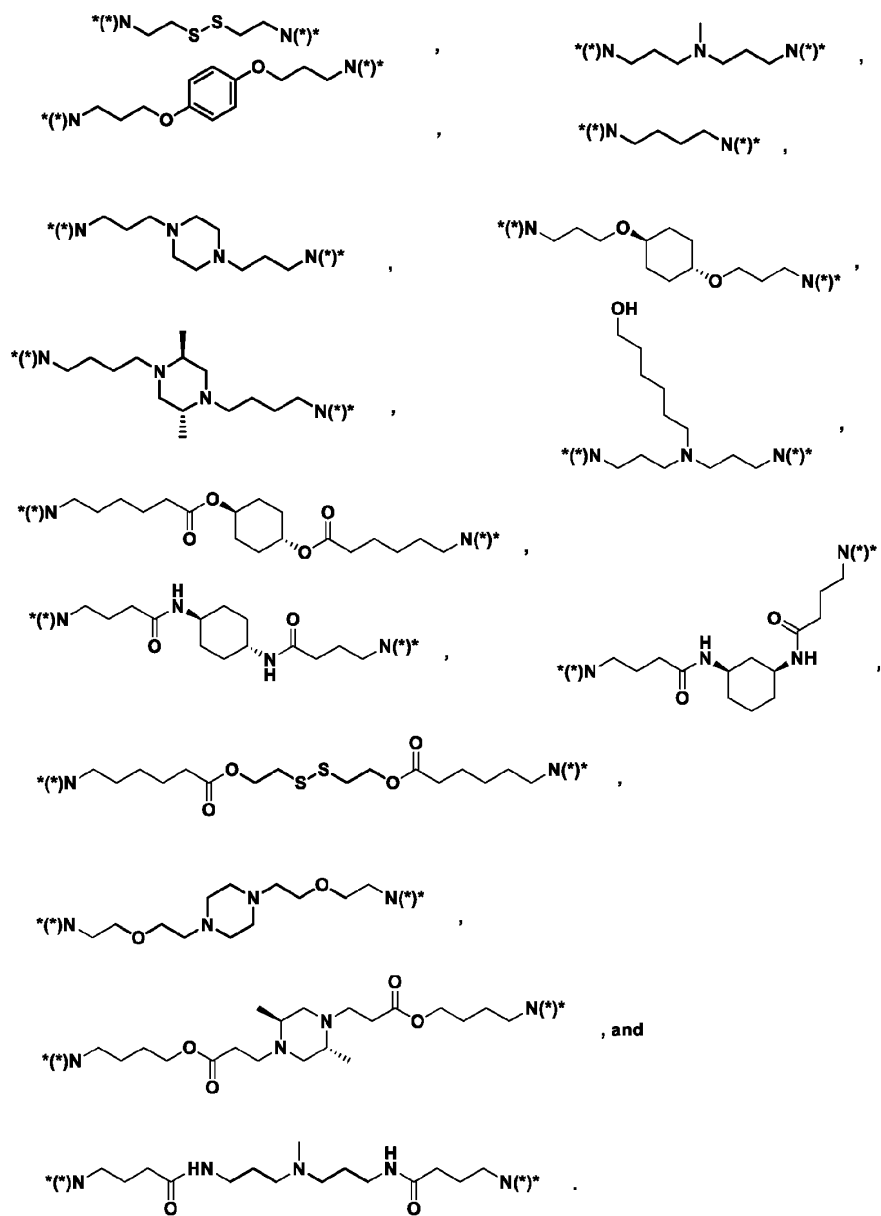
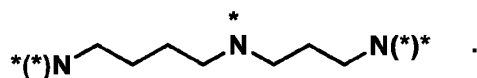


Table P4

[0123] The foregoing illustrative amine moiety A embodiments for $p = 4$ in Table P4 correspond, when in amine forms, to the amines shown in Table 1 as $A_{i''}$, with $i'' = 1-3, 5, 6, 8-12, 14, 16$, and 35-37.

[0124] In some embodiments, $p = 5$ and A is $^{*}(*)N-(CH_2)_{p1}-N^{*}-(CH_2)_{p2}-N^{*}(*)$, wherein $p1 = 2 - 4$, and $p2 = 2 - 4$.

[0125] In some embodiments with $p = 5$, A is given by the following Formula P5:

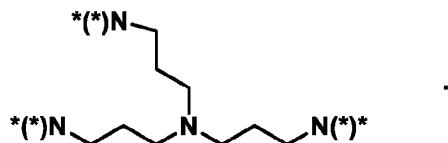


Formula P5

[0126] The foregoing illustrative amine moiety A embodiment for $p = 5$, given by Formula P5, corresponds, when in amine form, to the amine shown in Table 1 as A4.

[0127] In some embodiments, $p = 6$ and A is $^{*}(*)N-(CH_2)_{q1}-N((CH_2)_{q2}-N^{*}(*))-(CH_2)_3-N^{*}(*)$, wherein $q1 = 2 - 4$ and $q2 = 2 - 4$.

[0128] In some embodiments with $p = 6$, A is given by the following Formula P6:



Formula P6

[0129] The foregoing illustrative amine moiety A embodiment for $p = 6$ given by Formula P6 corresponds, when in amine form, to the amine shown in Table 1 as A7.

[0130] The term $*$ refers to a N-binding site of an LT moiety, and $^{*}(*)$ refers to two separate binding sites at the same N-member of two LT moieties, as also indicated above.

[0131] In some embodiments, $p = 4$, E is bond, and $w1 = w2 = 2$.

[0132] In some embodiments, $p = 4$, E is unsubstituted O-phenylen-O, $w1 = w2 = 3$, and for each LT moiety each T is $CH_3-(CH_2)_k-CH_2$ with $k = 4$ and $m' = 1$.

[0133] In some embodiments, $p = 4$, the substituted amino in E is $\begin{array}{c} | \\ \text{---} \text{N} \text{---} \\ | \end{array}$, $w1 = w2 = 3$, and for each LT moiety each T is $CH_3-(CH_2)_k-CH_2$ with $k = 5$ and $m' = 1$.

[0134] In some embodiments, $p = 4$, E is unsubstituted O-phenylen-O, $w1 = w2 = 3$, and for each LT moiety each T is $CH_3-(CH_2)_k-CH_2$ with $k = 9$, and $m' = 1$.

[0135] In some embodiments, $p = 4$, E is S-S, $w_1 = w_2 = 2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 3$, and $m' = 1$.

[0136] In some embodiments, $p = 5$, $p_1 = 3$, $p_2 = 4$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 6$, and $m' = 1$.

[0137] In some embodiments, $p = 4$, E is unsubstituted 1,4-piperazindiyl, $w_1 = w_2 = 3$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 7$, and $m' = 1$.

[0138] In some embodiments, $p = p' = p'' = 1$, $m' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ and $k = 6$.

[0139] In some embodiments, $p = p' = p'' = 1$, $m' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ and $k = 6$,

[0140] In some embodiments, $p = 2$, $t = 3$, Z is N-piperidino, $p' = 1$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 10$, and $m' = 1$.

[0141] In some embodiments, $p = 4$, E is substituted 1,4-piperazindiyl, $w_1 = w_2 = 4$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.

[0142] In some embodiments, $p = 4$, $w_1 = w_2 = 3$, E is unsubstituted $\text{C(O)-NH-(1,3-cyclohexanediy)-NH-C(O)}$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.

[0143] In some embodiments, $p = 4$, E is $\text{O-(CH}_2\text{)}_{w_3}\text{-(substituted or unsubstituted 1,4-piperazinediy)-CH}_2\text{)}_{w_4}\text{-O}$, $w_1 = w_2 = w_3 = w_4 = 2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.

[0144] In some embodiments, $p = 2$, $t = 2$, Z is $\text{N(CH}_2\text{-CH}_3\text{)}_2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_7\text{-CH=CH-(CH}_2\text{)}_6\text{-CH}_2$, $m' = 1$, and $p' = p'' = 1$.

[0145] In some embodiments, $p = 2$, $t = 2$, Z is $\text{N(CH}_2\text{-CH}_3\text{)}_2$, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 11$.

[0146] In some embodiments, $p = 2$, $t = 2$, Z is N-piperidino, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 8$.

[0147] In some embodiments, $p = 2$, $t = 3$, Z is N-pyrrolidino, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 8$.

[0148] In some embodiments, $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_4\text{-CH=CH-CH}_2\text{-CH=CH-(CH}_2\text{)}_6\text{-CH}_2$, X is C(O)-O , Y is $\text{S-S-(CH}_2\text{)}_n$ with $n = 2$, OCO is O-C(O) , and $m = 7$.

[0149] In some embodiments, $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $\text{(CH}_3\text{-(CH}_2\text{)}_l\text{-CH}_2\text{)}_2\text{-CH-O-C(O)-(CH}_2\text{)}_3\text{-CH}_2$, with $l = 3$, X is C(O)-CH_2 , Y is $\text{S-S-(CH}_2\text{)}_n$ with $n = 3$, OCO is O-C(O) , and $m = 6$.

[0150] In some embodiments, $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $(CH_3)_2-CH-(CH_2)_4-CH_2$, X is CH_2-CH_2 , Y is $(CH_2)_q$ with $q = 4$, OCO is $O-C(O)$, and $m = 7$.

[0151] In some embodiments, $p = 4$, $w_1 = w_2 = 4$, E is XS-(substituted 1,4-piperazinediyl)-XS, XS is $O-C(O)-(CH_2)_2$, and for each LT moiety $p' = p'' = 1$, $m' = 1$, T is $CH_3-(CH_2)_k-CH_2$ with $k = 4$.

[0152] In some embodiments, $p = 4$, $w_1 = w_2 = 2$, E is S-S, and for each LT moiety $p' = p'' = 1$, $m' = 1$, T is $CH_3-(CH_2)_k-CH_2$ with $k = 3$.

[0153] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 2$, Z is OH, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 5$.

[0154] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 4$, Z is OH, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 6$.

[0155] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 6$, Z is OH, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 5$.

[0156] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 2$, Z is $N(CH_3)_2$, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 9$.

[0157] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 4$, Z is $N(CH_3)_2$, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 6$.

[0158] In some embodiments, $p = 2$, $p' = p'' = 1$, $t = 5$, Z is $N(CH_3)_2$, and for each LT moiety $m' = 1$, and T is $CH_3-(CH_2)_k-CH_2$ with $k = 8$.

[0159] In some embodiments, $p = 4$, $w_1 = w_2 = 5$, E is EE-(1,4-cyclohexanediyl)-EE, EE is $C(O)-O$, and for each LT moiety $m' = 1$, $p' = p'' = 1$, T is $CH_3-(CH_2)_k-CH_2$ with $k = 7$.

[0160] In some embodiments, $p = 4$, $w_1 = w_2 = 5$, E is XS-S-S-XS, XS is $C(O)-O-(CH_2)_2$, and for each LT moiety $m' = 1$, $p' = p'' = 1$, T is $(CH_3)_2-CH-(CH_2)_5-CH_2$.

[0161] In some embodiments, $p = 1$, the amino moiety A is selected from the moieties given in Table P1, and the variables and group designators p' , p'' , B, m' and T are as set forth for general formula (G1.1).

[0162] In some embodiments, $p = 1$, the amino moiety A is selected from the moieties given in Table P1, and the variables and group designators p' , p'' , B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0163] In some embodiments, $p = 1$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for general formula (G1.1).

[0164] In some embodiments, $p = 1$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0165] In some embodiments, $p = 2$, the amino moiety A is selected from the moieties given in Table P2, and the variables and group designators p' , p'' , B, m' and T are as set forth for general formula (G1.1).

[0166] In some embodiments, $p = 2$, the amino moiety A is selected from the moieties given in Table P2, and the variables and group designators p' , p'' , B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0167] In some embodiments, $p = 2$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for general formula (G1.1).

[0168] In some embodiments, $p = 2$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0169] In some embodiments, $p = 4$, the amino moiety A is selected from the moieties given in Table P4, and the variables and group designators p' , p'' , B, m' and T are as set forth for general formula (G1.1).

[0170] In some embodiments, $p = 4$, the amino moiety A is selected from the moieties given in Table P4, and the variables and group designators p' , p'' , B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0171] In some embodiments, $p = 4$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for general formula (G1.1).

[0172] In some embodiments, $p = 4$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0173] In some embodiments, $p = 5$, the amino moiety A is according to formula P5, and the variables and group designators p' , p'' , B, m' and T are as set forth for general formula (G1.1).

[0174] In some embodiments, $p = 5$, the amino moiety A is according to formula P5, and the variables and group designators p' , p'' , B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0175] In some embodiments, $p = 5$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for general formula (G1.1).

[0176] In some embodiments, $p = 5$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

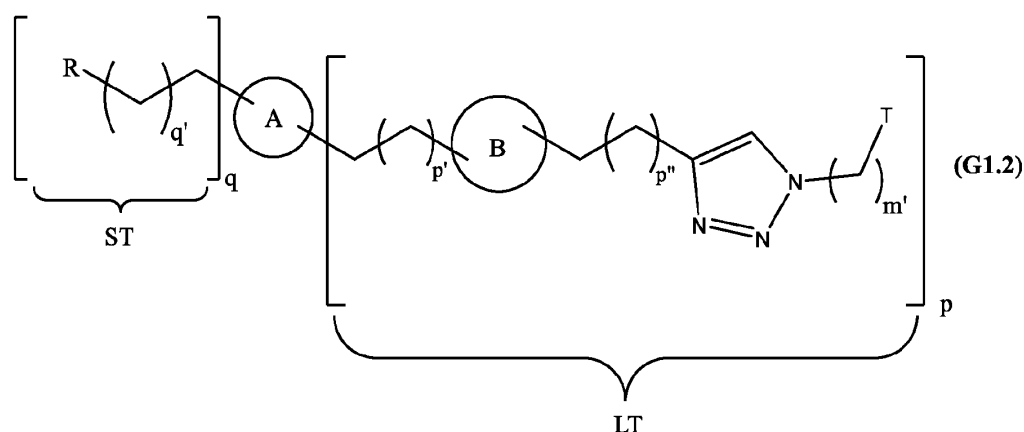
[0177] In some embodiments, $p = 6$, the amino moiety A is according to formula P6, and the variables and group designators p' , p'' , B, m' and T are as set forth for general formula (G1.1).

[0178] In some embodiments, $p = 6$, the amino moiety A is according to formula P6, and the variables and group designators p' , p'' , B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0179] In some embodiments, $p = 6$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for general formula (G1.1).

[0180] In some embodiments, $p = 6$, moiety T is selected from the moieties given in Table T2, and the variables and group designators p' , p'' , B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.1) for which such variables and group designators are specified.

[0181] In another aspect, the present application relates to compounds represented generically by of formula (G1.2) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:



[0182] The amino moiety A in (G1.2) is selected when $q \geq 1$ as having its N* or N(*)* binding sites linked to at least one ST that differs from LT as indicated in general formula (G1.2).

[0183] The illustrative embodiments of compounds of formula (G1.2) are such that, whether stated explicitly or not, p and q for the same satisfy the following characteristics (1) and (2):

- (1) $p = 1-5$ when $q = 1-5$, and $p = 1-6$ when $q = 0-5$, with $(p + q) = 1-6$ and $p \neq 0$, and
- (2) $q = 0$ leads to the compounds of general formula (G1.1) with $p = 1-6$ as defined

above.

[0184] R is OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being (CH₂)_{q'}CH₃, with $q' = 1-4$, $q'' = 1-4$, $q \geq 1$.

[0185] All the variables concerning the amino moiety A and the moiety(ies) LT not defined for (G1.2) are as defined for (G1.1), subject to the p and q restrictions set forth above. For example, A in (G1.2) is an amino moiety, and said amino moiety A is selected depending on the (p+q)-value as follows, wherein the term * is used to refer to a N-binding site of an LT

moiety, and $(*)$ (or $(*)$ indistinguishably) is used to refer to two separate N-binding sites of two LT moieties:

when $p = 1$ and $q = 0$, then such compound would be a compound of formula (G1.1);

when $p = 1$ and $q = 1$, then A is $(*)N-(CH_2)_t-Z$,

$t = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $N(CH_2-CH_3)_2$, or $N(CH_3)_2$,

when $p+q = 4$, with $p \geq 1$ and $q \geq 1$, then A is

$(*)N-(CH_2)_{w1}-E-(CH_2)_{w2}-N(*)$,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-O, $O-(CH_2)_{w3}$ -(substituted or unsubstituted 1,4-piperazinediyl)- $(CH_2)_{w4}$ -O, substituted or unsubstituted 1,4-piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-cyclohexanediy)-EE, or EE-(1,3-cyclohexanediy)-EE, wherein $w3 = 0-4$, $w4 = 0-4$, XS is $C(O)-O-(CH_2)_2$, and EE is O, $C(O)-O$ or $C(O)-NH$,

when $p+q = 5$, with $p \geq 1$ and $q \geq 1$, then A is

$(*)N-(CH_2)_{p1}-N^*-(CH_2)_{p2}-N(*)$, $p1 = 2-5$,

$p2 = 2-5$, and

when $p+q = 6$, with $p \geq 1$ and $q \geq 1$, then A is

$(*)N-(CH_2)_{q1}-N((CH_2)_{q2}-N(*))-(CH_2)_{q3}-N(*)$,

$q1 = 2-4$, $q2 = 2-4$, and $q3 = 2-4$.

[0186] Illustrative embodiments of moiety T in formula (G1.2) are given in Table T2 (parts 1 and 2; herein referred to as "Table T2") and the corresponding parent azido compounds are shown in Table 2.

[0187] To avoid repetitive recital, all the variables concerning the amino moiety A for $p \geq 2$, the moiety(ies) LT, and illustrative embodiments of the same not defined explicitly for (G1.2) are as defined for (G1.1) subject to the p- and q-assignments for (G1.2) as set forth above.

[0188] When $p > 1$, then each one of the plurality of LT moieties may be the same or different from the remaining LT moieties in the same molecule, and when $q > 1$, then each one of the plurality of ST moieties may be the same or different from the remaining ST moieties in the same molecule.

[0189] In light of the structural and IUPAC name complexities of compounds of formula (G1.2), specific compounds of formula (G1.2) are referred to below with the notation $A_i''(ST)_q(LT)_p$, where i'' being an index as defined below for compounds $A_i''L_j'''Tk''$ and p and q are as defined for p and q in reference to compounds of formula (G1.2)

[0190] Formula (G1.2) envisages embodiments with the N^* and $N(*)^*$ binding sites in the amino moiety A being linked to ST and/or LT according to any of the following binding embodiments for binding site N^* : N-ST (and $q \geq 1$) and N-LT, and according to any of the following binding embodiments for binding site $N(*)^*$: N(LT)(LT) wherein the LT moieties are identical or different from each other, N(ST)(LT) and N(ST)(ST) wherein the ST moieties are identical or different from each other.

[0191] Each variable in (G1.1) and (G1.2) indicating the choice of a number of groups of substituents, or a choice of substituents, is elected independently from the choice of any other such variable, whether such variables have the same name (while referring to different groups) or not, unless explicitly indicated otherwise.

[0192] As to illustrative embodiments of compounds of formula (G1.2), all the variable and group or moiety choices recited above for illustrative embodiments of (G1.1) are incorporated herein in reference to illustrative embodiments of (G1.2), subject to the p- and q-assignments for (G1.2) as set forth above. In addition, the following are further illustrative embodiments concerning (G1.2):

In some embodiments R is OH, with $q' = 1-4$. In other embodiments, R is OH, with $q' = 2$.

In some embodiments, $p = 2$ and $q = 3$. In other embodiments, $p = 3$, and $q = 2$.

In some embodiments, $p + q = 5$, and A is $*(*)N-(CH_2)_{p1}-N^*-(CH_2)_{p2}-N(*)^*$, $p1 = 2-5$, $p2 = 2-5$. In some embodiments with $p + q = 5$, A is $*(*)N-(CH_2)_4-N^*-(CH_2)_3-N(*)^*$.

In some embodiments, $p + q = 5$, $p = 3$ and $q = 2$. In other embodiments, $p + q = 5$, $p = 2$ and $q = 3$.

In some embodiments with $q \geq 2$, all the ST moieties are the same.

In some embodiments with $p \geq 2$, all the LT moieties are the same.

In some embodiments with $p \geq 2$ and $q \geq 2$, all the ST moieties are the same and all the LT moieties are the same.

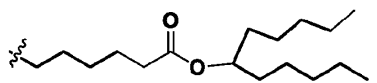
[0193] In some embodiments of compounds of formula (G1.2) with $p + q = 2$, $p = 1$ and $q = 1$, such compound embodiments have formulae $A_i''(ST)_1(LT)_1$, (or simply $A_i''(ST)(LT)$), $i'' = 17-29$, wherein amine moiety A is one of amine moieties shown in Table P2, as described in illustrations for compounds of formula (G1.1) with $p = 2$. Embodiments of moiety T are given in Table T2. ST and LT moieties are illustratively embodied by any of the foregoing definitions given for the same.

[0194] In some embodiments of compounds of formula (G1.2) with $p + q = 4$, such compound embodiments have formulae $A_i''(ST)_1(LT)_3$, $A_i''(ST)_2(LT)_2$, or $A_i''(ST)_3(LT)_1$, $i'' = 1-3, 5, 6, 8-12, 14, 16$, and $35-37$, wherein amine moiety A is one of amine moieties shown in Table P4, as described in illustrations for compounds of formula (G1.1) with $p = 4$. ST and LT moieties are illustratively embodied by any of the foregoing definitions given for the same. Embodiments of moiety T are given in Table T2. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments.

[0195] In some embodiments of compounds of formula (G1.2) with $p + q = 5$, such compound embodiments have formulae $A_i''(ST)_1(LT)_4$, $A_i''(ST)_2(LT)_3$, $A_i''(ST)_3(LT)_2$, or $A_i''(ST)_4(LT)_1$, $i'' = 4$, wherein amine moiety A is the amine moiety shown in Formula P5, as described in illustrations for compounds of formula (G1.1) with $p = 5$. ST and LT moieties are illustratively embodied by any of the foregoing definitions given for the same. Embodiments of moiety T are given in Table T2. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments.

[0196] In some embodiments of compounds of formula (G1.2) with $p + q = 5$, B is C(O)O. In some of such embodiments, all the LT moieties are the same, all the ST moieties are the same.

[0197] In some embodiments of compounds of formula (G1.2) with $p + q = 5$, with B being C(O)O, all the LT moieties being the same, and all the ST moieties are the same, each ST is CH₂CH₂CH₂OH, and [$p = 3$ and $q = 2$] or [$p = 2$ and $q = 3$]. In some of such embodiments, T is



[0198] In some embodiments of compounds of formula (G1.2) with $p + q = 6$, such compound embodiments have formulae $A_{i''}(\text{ST})_1(\text{LT})_5$, $A_{i''}(\text{ST})_2(\text{LT})_4$, $A_{i''}(\text{ST})_3(\text{LT})_3$, $A_{i''}(\text{ST})_4(\text{LT})_2$, or $A_{i''}(\text{ST})_5(\text{LT})_1$, $i'' = 7$, wherein amine moiety A is amine moiety shown as Formula P6, as described in illustrations for compounds of formula (G1.1) with $p = 6$. ST and LT moieties are illustratively embodied by any of the foregoing definitions given for the same. Embodiments of moiety T are given in Table T2. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments.

[0199] Further illustrative embodiments of compounds of formula (G1.2) include, but are not limited to, the following compounds:

[0200] Compounds of formula $A_{i''}(\text{ST})_1(\text{LT})_1$, (or simply $A_{i''}(\text{ST})(\text{LT})$), $i'' = 17-29$, wherein amine moiety A is one of amine moieties shown in Table P2, as described in illustrations for compounds of formula (G1.1) with $p = 2$. ST is $(\text{CH}_2)_q\text{-R}$, with R selected from OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being $(\text{CH}_2)_q\text{-CH}_3$, with $q' = 1-4$, $q'' = 1-4$; and LT is one of $\text{L}_{j''}\text{-T}_{k''}$, $j'' = 1-3$, $k'' = 1-23$. In some of such embodiments of compounds of formula $A_{i''}(\text{ST})_1(\text{LT})_1$, ST is CH₂CH₂CH₂OH;

compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_3$, $A_{i''}(\text{ST})_2(\text{LT})_2$, or $A_{i''}(\text{ST})_3(\text{LT})_1$, $i'' = 1-3, 5, 6, 8-12, 14, 16$, and 35-37, wherein amine moiety A is one of amine moieties shown in Table P4, as described in illustrations for compounds of formula (G1.1) with $p = 4$. ST is at least one of $(\text{CH}_2)_q\text{-R}$, with R selected from OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being $(\text{CH}_2)_q\text{-CH}_3$, with $q' = 1-4$, $q'' = 1-4$; and LT is at least one of $\text{L}_{j''}\text{-T}_{k''}$, $j'' = 1-3$, $k'' = 1-$

23. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. In some of such embodiments of compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_3$, $A_{i''}(\text{ST})_2(\text{LT})_2$, or $A_{i''}(\text{ST})_3(\text{LT})_1$, ST is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$;

compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_4$, $A_{i''}(\text{ST})_2(\text{LT})_3$, $A_{i''}(\text{ST})_3(\text{LT})_2$, or $A_{i''}(\text{ST})_4(\text{LT})_1$, $i'' = 4$, wherein amine moiety A is the amine moiety shown in Formula P5, as described in illustrations for compounds of formula (G1.1) with $p = 5$. ST is at least one of $(\text{CH}_2)_q\text{-R}$, with R selected from OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being $(\text{CH}_2)_{q'}\text{-CH}_3$, with $q' = 1-4$, $q'' = 1-4$; and LT is at least one of $\text{L}_{j''}\text{T}_{k''}$, $j'' = 1-3$, $k'' = 1-23$. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. In some of such embodiments of compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_4$, $A_{i''}(\text{ST})_2(\text{LT})_3$, $A_{i''}(\text{ST})_3(\text{LT})_2$, or $A_{i''}(\text{ST})_4(\text{LT})_1$, ST is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$;

compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_5$, $A_{i''}(\text{ST})_2(\text{LT})_4$, $A_{i''}(\text{ST})_3(\text{LT})_3$, $A_{i''}(\text{ST})_4(\text{LT})_2$, or $A_{i''}(\text{ST})_5(\text{LT})_1$, $i'' = 7$, wherein amine moiety A is amine moiety shown as Formula P6, as described in illustrations for compounds of formula (G1.1) with $p = 6$. ST is at least one of $(\text{CH}_2)_q\text{-R}$, with R selected from OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being $(\text{CH}_2)_{q'}\text{-CH}_3$, with $q' = 1-4$, $q'' = 1-4$; and LT is at least one of $\text{L}_{j''}\text{T}_{k''}$, $j'' = 1-3$, $k'' = 1-23$.

23. When there is more than one ST moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. When there is more than one LT moiety, all are identical in some embodiments, whereas there is at least one different in other embodiments. In some of such embodiments of compounds of formulae $A_{i''}(\text{ST})_1(\text{LT})_5$, $A_{i''}(\text{ST})_2(\text{LT})_4$, $A_{i''}(\text{ST})_3(\text{LT})_3$, $A_{i''}(\text{ST})_4(\text{LT})_2$, or $A_{i''}(\text{ST})_5(\text{LT})_1$, ST is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$.

[0201] The foregoing illustratively formulae of type $A_{i''}(\text{ST})_{st}(\text{LT})_{lt}$, with indices i'' , st and lt as defined above do not indicate the specific binding site of each of such ST and LT moieties to N* and N(*)* sites, so they are meant to represent embodiments in which each of the ST and each of the LT moieties may be bound to any N* or N(*)* binding site in amine moiety A. Notation to specify such binding sites for specific ST and LT moieties is set forth below.

[0202] In some embodiments, $p+q = 2$, the amino moiety A is selected from the moieties given in Table P2, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for general formula (G1.2).

[0203] In some embodiments, $p+q = 2$, the amino moiety A is selected from the moieties given in Table P2, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0204] In some embodiments, $p+q = 2$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for general formula (G1.2).

[0205] In some embodiments, $p+q = 2$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0206] In some embodiments, $p+q = 4$, the amino moiety A is selected from the moieties given in Table P4, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for general formula (G1.2).

[0207] In some embodiments, $p+q = 4$, the amino moiety A is selected from the moieties given in Table P4, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0208] In some embodiments, $p+q = 4$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for general formula (G1.2).

[0209] In some embodiments, $p+q = 4$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0210] In some embodiments, $p+q = 5$, the amino moiety A is according to formula P5, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for general formula (G1.2).

[0211] In some embodiments, $p+q = 5$, the amino moiety A is according to formula P5, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0212] In some embodiments, $p+q = 5$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for general formula (G1.2).

[0213] In some embodiments, $p+q = 5$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0214] In some embodiments, $p+q = 6$, the amino moiety A is according to formula P6, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for general formula (G1.2).

[0215] In some embodiments, $p+q = 6$, the amino moiety A is according to formula P6, and the variables and group designators R, q, q', p', p'', B, m' and T are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0216] In some embodiments, $p+q = 6$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for general formula (G1.2).

[0217] In some embodiments, $p+q = 6$, moiety T is selected from the moieties given in Table T2, and the variables and group designators R, q, q', p', p'', B, m' and A are as set forth for any one of the foregoing illustrative embodiments of compounds of formula (G1.2) for which such variables and group designators are specified.

[0218] In some of the foregoing illustrative embodiments of compounds of formula (G1.2), ST is selected from the moieties given in Table 2.1. In other of the foregoing embodiments of compounds of formula (G1.2), St is ST1, which is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$.

[0219] Further illustrative embodiments of compounds of formula (G1.1), wherein $p = 1$, include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A30L1T1, A30L1T2, A30L1T3, A30L1T4, A30L1T5, A30L1T6, A30L1T7, A30L1T8, A30L1T9, A30L1T10, A30L1T11, A30L1T12, A30L1T13, A30L1T14, A30L1T15, A31L1T1, A31L1T2, A31L1T3, A31L1T4, A31L1T5, A31L1T6, A31L1T7, A31L1T8, A31L1T9, A31L1T10, A31L1T11, A31L1T12, A31L1T13, A31L1T14, A31L1T15, A32L1T1, A32L1T2, A32L1T3, A32L1T4, A32L1T5, A32L1T6, A32L1T7, A32L1T8, A32L1T9, A32L1T10, A32L1T11, A32L1T12, A32L1T13, A32L1T14, A32L1T15, A33L1T1, A33L1T2, A33L1T3, A33L1T4, A33L1T5, A33L1T6, A33L1T7, A33L1T8, A33L1T9, A33L1T10, A33L1T11, A33L1T12, A33L1T13, A33L1T14, A33L1T15, A34L1T1, A34L1T2, A34L1T3, A34L1T4, A34L1T5, A34L1T6, A34L1T7, A34L1T8, A34L1T9, A34L1T10, A34L1T11, A34L1T12, A34L1T13, A34L1T14, A34L1T15, A40L1T15, A41L1T15, A38L1T15, A39L1T15, and A42L1T20.

[0220] Further illustrative embodiments of compounds of formula (G1.1), wherein $p = 2$, include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A17L1T1, A17L1T2, A17L1T3, A17L1T4, A17L1T5, A17L1T6, A17L1T7, A17L1T8, A17L1T9, A17L1T10, A17L1T11, A17L1T12, A17L1T13, A17L1T14, A17L1T15, A18L1T1, A18L1T2, A18L1T3, A18L1T4, A18L1T5, A18L1T6, A18L1T7, A18L1T8, A18L1T9, A18L1T10, A18L1T11, A18L1T12, A18L1T13, A18L1T14, A18L1T15, A19L1, A19L1T1, A19L1T2, A19L1T3, A19L1T4, A19L1T5, A19L1T6, A19L1T7, A19L1T8, A19L1T9, A19L1T10, A19L1T11, A19L1T12, A19L1T13, A19L1T14, A19L1T15, A20L1T1, A20L1T2, A20L1T3, A20L1T4, A20L1T5, A20L1T6, A20L1T7, A20L1T8, A20L1T9, A20L1T10, A20L1T11, A20L1T12, A20L1T13, A20L1T14, A20L1T15, A21L1T1, A21L1T2, A21L1T3, A21L1T4, A21L1T5, A21L1T6, A21L1T7, A21L1T8, A21L1T9, A21L1T10, A21L1T11, A21L1T12, A21L1T13, A21L1T14, A21L1T15, A22L1T1, A22L1T2, A22L1T3, A22L1T4, A22L1T5, A22L1T6, A22L1T7, A22L1T8, A22L1T9, A22L1T10, A22L1T11, A22L1T12, A22L1T13, A22L1T14, A22L1T15, A23L1T1, A23L1T2, A23L1T3, A23L1T4, A23L1T5, A23L1T6, A23L1T7, A23L1T8, A23L1T9, A23L1T10, A23L1T11, A23L1T12, A23L1T13, A23L1T14, A23L1T15, A24L1T1, A24L1T2, A24L1T3, A24L1T4, A24L1T5, A24L1T6, A24L1T7, A24L1T8, A24L1T9, A24L1T10, A24L1T11, A24L1T12, A24L1T13, A24L1T14, A24L1T15,

A25L1T1, A25L1T2, A25L1T3, A25L1T4, A25L1T5, A25L1T6, A25L1T7, A25L1T8, A25L1T9, A25L1T10, A25L1T11, A25L1T12, A25L1T13, A25L1T14, A25L1T15, A26L1T1, A26L1T2, A26L1T3, A26L1T4, A26L1T5, A26L1T6, A26L1T7, A26L1T8, A26L1T9, A26L1T10, A26L1T11, A26L1T12, A26L1T13, A26L1T14, A26L1T15, A27L1T1, A27L1T2, A27L1T3, A27L1T4, A27L1T5, A27L1T6, A27L1T7, A27L1T8, A27L1T9, A27L1T10, A27L1T11, A27L1T12, A27L1T13, A27L1T14, A27L1T15, A28L1T1, A28L1T2, A28L1T3, A28L1T4, A28L1T5, A28L1T6, A28L1T7, A28L1T8, A28L1T9, A28L1T10, A28L1T11, A28L1T12, A28L1T13, A28L1T14, A28L1T15, A29L1T1, A29L1T2, A29L1T3, A29L1T4, A29L1T5, A29L1T6, A29L1T7, A29L1T8, A29L1T9, A29L1T10, A29L1T11, A29L1T12, A29L1T13, A29L1T14, and A29L1T15.

[0221] Further illustrative embodiments of compounds of formula (G1.1), wherein $p = 4$, include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A1L1T1, A1L1T2, A1L1T3, A1L1T4, A1L1T5, A1L1T6, A1L1T7, A1L1T8, A1L1T9, A1L1T10, A1L1T11, A1L1T12, A1L1T13, A1L1T14, A1L1T15, A2L1T1, A2L1T2, A2L1T3, A2L1T4, A2L1T5, A2L1T6, A2L1T7, A2L1T8, A2L1T9, A2L1T10, A2L1T11, A2L1T12, A2L1T13, A2L1T14, A2L1T15, A3L1T1, A3L1T2, A3L1T3, A3L1T4, A3L1T5, A3L1T6, A3L1T7, A3L1T8, A3L1T9, A3L1T10, A3L1T11, A3L1T12, A3L1T13, A3L1T14, A3L1T15, A5L1T1, A5L1T2, A5L1T3, A5L1T4, A5L1T5, A5L1T6, A5L1T7, A5L1T8, A5L1T9, A5L1T10, A5L1T11, A5L1T12, A5L1T13, A5L1T14, A5L1T15, A6L1T1, A6L1T2, A6L1T3, A6L1T4, A6L1T5, A6L1T6, A6L1T7, A6L1T8, A6L1T9, A6L1T10, A6L1T11, A6L1T12, A6L1T13, A6L1T14, A6L1T15, A8L1T1, A8L1T2, A8L1T3, A8L1T4, A8L1T5, A8L1T6, A8L1T7, A8L1T8, A8L1T9, A8L1T10, A8L1T11, A8L1T12, A8L1T13, A8L1T14, A8L1T15, A9L1T1, A9L1T2, A9L1T3, A9L1T4, A9L1T5, A9L1T6, A9L1T7, A9L1T8, A9L1T9, A9L1T10, A9L1T11, A9L1T12, A9L1T13, A9L1T14, A9L1T15, A11L1T1, A11L1T2, A11L1T3, A11L1T4, A11L1T5, A11L1T6, A11L1T7, A11L1T8, A11L1T9, A11L1T10, A11L1T11, A11L1T12, A11L1T13, A11L1T14, A11L1T15, A12L1T1, A12L1T2, A12L1T3, A12L1T4, A12L1T5, A12L1T6, A12L1T7, A12L1T8, A12L1T9, A12L1T10, A12L1T11, A12L1T12, A12L1T13, A12L1T14, A12L1T15,

A14L1T1, A14L1T2, A14L1T3, A14L1T4, A14L1T5, A14L1T6, A14L1T7, A14L1T8, A14L1T9, A14L1T10, A14L1T11, A14L1T12, A14L1T13, A14L1T14, A14L1T15, A16L1T1, A16L1T2, A16L1T3, A16L1T4, A16L1T5, A16L1T6, A16L1T7, A16L1T8, A16L1T9, A16L1T10, A16L1T11, A16L1T12, A16L1T13, A16L1T14, A16L1T15, A35L1T1, A35L1T2, A35L1T3, A35L1T4, A35L1T5, A35L1T6, A35L1T7, A35L1T8, A35L1T9, A35L1T10, A35L1T11, A35L1T12, A35L1T13, A35L1T14, A35L1T15, A36L1T1, A36L1T2, A36L1T3, A36L1T4, A36L1T5, A36L1T6, A36L1T7, A36L1T8, A36L1T9, A36L1T10, A36L1T11, A36L1T12, A36L1T13, A36L1T14, A36L1T15, A37L1T1, A37L1T2, A37L1T3, A37L1T4, A37L1T5, A37L1T6, A37L1T7, A37L1T8, A37L1T9, A37L1T10, A37L1T11, A37L1T12, A37L1T13, A37L1T14, A37L1T15, A5L2T21, A5L3T22, A6L2T18, A6L3T19, and A10L1T19.

[0222] Further illustrative embodiments of compounds of formula (G1.1), wherein $p = 5$, include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A4L1T1, A4L1T2, A4L1T3, A4L1T4, A4L1T5, A4L1T6, A4L1T7, A4L1T8, A4L1T9, A4L1T10, A4L1T11, A4L1T12, A4L1T13, A4L1T14, A4L1T15, A4L1T16, A4L1T17, A4L1T19, A4L2T18, A4L2T14, A4L3T19, and A4L3T14.

[0223] Further illustrative embodiments of compounds of formula (G1.1), wherein $p = 6$, include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A7L1T1, A7L1T2, A7L1T3, A7L1T4, A7L1T5, A7L1T6, A7L1T7, A7L1T8, A7L1T9, A7L1T10, A7L1T11, A7L1T12, A7L1T13, A7L1T14, and A7L1T15.

[0224] Illustrative embodiments of compounds of formula (G1.1) include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A1L1T1, A1L1T2, A1L1T3, A1L1T4, A1L1T5, A1L1T6, A1L1T7, A1L1T8, A1L1T9, A1L1T10, A1L1T11, A1L1T12, A1L1T13, A1L1T14, A1L1T15, A2L1T1, A2L1T2, A2L1T3, A2L1T4, A2L1T5, A2L1T6, A2L1T7, A2L1T8, A2L1T9, A2L1T10, A2L1T11, A2L1T12, A2L1T13, A2L1T14, A2L1T15, A3L1T1, A3L1T2, A3L1T3, A3L1T4, A3L1T5, A3L1T6, A3L1T7, A3L1T8, A3L1T9, A3L1T10, A3L1T11, A3L1T12, A3L1T13, A3L1T14, A3L1T15,

A4L1T1, A4L1T2, A4L1T3, A4L1T4, A4L1T5, A4L1T6, A4L1T7, A4L1T8, A4L1T9,
A4L1T10, A4L1T11, A4L1T12, A4L1T13, A4L1T14, A4L1T15, A4L1T16, A4L1T17 A4L1T19,
A4L2T18, A4L2T14, A4L3T19, A4L3T14,
A5L1T1, A5L1T2, A5L1T3, A5L1T4, A5L1T5, A5L1T6, A5L1T7, A5L1T8, A5L1T9,
A5L1T10, A5L1T11, A5L1T12, A5L1T13, A5L1T14, A5L1T15, A5L2T21, A5L3T22,
A6L1T1, A6L1T2, A6L1T3, A6L1T4, A6L1T5, A6L1T6, A6L1T7, A6L1T8, A6L1T9,
A6L1T10, A6L1T11, A6L1T12, A6L1T13, A6L1T14, A6L1T15, A6L2T18, A6L3T19,
A7L1T1, A7L1T2, A7L1T3, A7L1T4, A7L1T5, A7L1T6, A7L1T7, A7L1T8, A7L1T9,
A7L1T10, A7L1T11, A7L1T12, A7L1T13, A7L1T14, A7L1T15,
A8L1T1, A8L1T2, A8L1T3, A8L1T4, A8L1T5, A8L1T6, A8L1T7, A8L1T8, A8L1T9,
A8L1T10, A8L1T11, A8L1T12, A8L1T13, A8L1T14, A8L1T15,
A9L1T1, A9L1T2, A9L1T3, A9L1T4, A9L1T5, A9L1T6, A9L1T7, A9L1T8, A9L1T9,
A9L1T10, A9L1T11, A9L1T12, A9L1T13, A9L1T14, A9L1T15,
A10L1T19,
A11L1T1, A11L1T2, A11L1T3, A11L1T4, A11L1T5, A11L1T6, A11L1T7, A11L1T8,
A11L1T9, A11L1T10, A11L1T11, A11L1T12, A11L1T13, A11L1T14, A11L1T15,
A12L1T1, A12L1T2, A12L1T3, A12L1T4, A12L1T5, A12L1T6, A12L1T7, A12L1T8,
A12L1T9, A12L1T10, A12L1T11, A12L1T12, A12L1T13, A12L1T14, A12L1T15,
A14L1T1, A14L1T2, A14L1T3, A14L1T4, A14L1T5, A14L1T6, A14L1T7, A14L1T8,
A14L1T9, A14L1T10, A14L1T11, A14L1T12, A14L1T13, A14L1T14, A14L1T15,
A16L1T1, A16L1T2, A16L1T3, A16L1T4, A16L1T5, A16L1T6, A16L1T7, A16L1T8,
A16L1T9, A16L1T10, A16L1T11, A16L1T12, A16L1T13, A16L1T14, A16L1T15,
A17L1T1, A17L1T2, A17L1T3, A17L1T4, A17L1T5, A17L1T6, A17L1T7, A17L1T8,
A17L1T9, A17L1T10, A17L1T11, A17L1T12, A17L1T13, A17L1T14, A17L1T15,
A18L1T1, A18L1T2, A18L1T3, A18L1T4, A18L1T5, A18L1T6, A18L1T7, A18L1T8,
A18L1T9, A18L1T10, A18L1T11, A18L1T12, A18L1T13, A18L1T14, A18L1T15,
A19L1, A19L1T1, A19L1T2, A19L1T3, A19L1T4, A19L1T5, A19L1T6, A19L1T7, A19L1T8,
A19L1T9, A19L1T10, A19L1T11, A19L1T12, A19L1T13, A19L1T14, A19L1T15,
A20L1T1, A20L1T2, A20L1T3, A20L1T4, A20L1T5, A20L1T6, A20L1T7, A20L1T8,
A20L1T9, A20L1T10, A20L1T11, A20L1T12, A20L1T13, A20L1T14, A20L1T15,

A21L1T1, A21L1T2, A21L1T3, A21L1T4, A21L1T5, A21L1T6, A21L1T7, A21L1T8,
A21L1T9, A21L1T10, A21L1T11, A21L1T12, A21L1T13, A21L1T14, A21L1T15,
A22L1T1, A22L1T2, A22L1T3, A22L1T4, A22L1T5, A22L1T6, A22L1T7, A22L1T8,
A22L1T9, A22L1T10, A22L1T11, A22L1T12, A22L1T13, A22L1T14, A22L1T15,
A23L1T1, A23L1T2, A23L1T3, A23L1T4, A23L1T5, A23L1T6, A23L1T7, A23L1T8,
A23L1T9, A23L1T10, A23L1T11, A23L1T12, A23L1T13, A23L1T14, A23L1T15,
A24L1T1, A24L1T2, A24L1T3, A24L1T4, A24L1T5, A24L1T6, A24L1T7, A24L1T8,
A24L1T9, A24L1T10, A24L1T11, A24L1T12, A24L1T13, A24L1T14, A24L1T15,
A25L1T1, A25L1T2, A25L1T3, A25L1T4, A25L1T5, A25L1T6, A25L1T7, A25L1T8,
A25L1T9, A25L1T10, A25L1T11, A25L1T12, A25L1T13, A25L1T14, A25L1T15,
A26L1T1, A26L1T2, A26L1T3, A26L1T4, A26L1T5, A26L1T6, A26L1T7, A26L1T8,
A26L1T9, A26L1T10, A26L1T11, A26L1T12, A26L1T13, A26L1T14, A26L1T15,
A27L1T1, A27L1T2, A27L1T3, A27L1T4, A27L1T5, A27L1T6, A27L1T7, A27L1T8,
A27L1T9, A27L1T10, A27L1T11, A27L1T12, A27L1T13, A27L1T14, A27L1T15,
A28L1T1, A28L1T2, A28L1T3, A28L1T4, A28L1T5, A28L1T6, A28L1T7, A28L1T8,
A28L1T9, A28L1T10, A28L1T11, A28L1T12, A28L1T13, A28L1T14, A28L1T15,
A29L1T1, A29L1T2, A29L1T3, A29L1T4, A29L1T5, A29L1T6, A29L1T7, A29L1T8,
A29L1T9, A29L1T10, A29L1T11, A29L1T12, A29L1T13, A29L1T14, A29L1T15,
A30L1T1, A30L1T2, A30L1T3, A30L1T4, A30L1T5, A30L1T6, A30L1T7, A30L1T8,
A30L1T9, A30L1T10, A30L1T11, A30L1T12, A30L1T13, A30L1T14, A30L1T15,
A31L1T1, A31L1T2, A31L1T3, A31L1T4, A31L1T5, A31L1T6, A31L1T7, A31L1T8,
A31L1T9, A31L1T10, A31L1T11, A31L1T12, A31L1T13, A31L1T14, A31L1T15,
A32L1T1, A32L1T2, A32L1T3, A32L1T4, A32L1T5, A32L1T6, A32L1T7, A32L1T8,
A32L1T9, A32L1T10, A32L1T11, A32L1T12, A32L1T13, A32L1T14, A32L1T15,
A33L1T1, A33L1T2, A33L1T3, A33L1T4, A33L1T5, A33L1T6, A33L1T7, A33L1T8,
A33L1T9, A33L1T10, A33L1T11, A33L1T12, A33L1T13, A33L1T14, A33L1T15,
A34L1T1, A34L1T2, A34L1T3, A34L1T4, A34L1T5, A34L1T6, A34L1T7, A34L1T8,
A34L1T9, A34L1T10, A34L1T11, A34L1T12, A34L1T13, A34L1T14, A34L1T15,
A35L1T1, A35L1T2, A35L1T3, A35L1T4, A35L1T5, A35L1T6, A35L1T7, A35L1T8,
A35L1T9, A35L1T10, A35L1T11, A35L1T12, A35L1T13, A35L1T14, A35L1T15,

A36L1T1, A36L1T2, A36L1T3, A36L1T4, A36L1T5, A36L1T6, A36L1T7, A36L1T8, A36L1T9, A36L1T10, A36L1T11, A36L1T12, A36L1T13, A36L1T14, A36L1T15, A37L1T1, A37L1T2, A37L1T3, A37L1T4, A37L1T5, A37L1T6, A37L1T7, A37L1T8, A37L1T9, A37L1T10, A37L1T11, A37L1T12, A37L1T13, A37L1T14, A37L1T15, A38L1T15, A39L1T15, A40L1T15, A41L1T15, and A42L1T20.

[0225] See also Table C1 (parts 1 and 2) regarding some of the compounds listed above.

[0226] Illustrative compounds of formula (G1.1) include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A2L1T2, A3L1T3, A8L1T8, A1L1T1, A4L1T4, A5L1T5, A5L1T15, A34L1T4, A11L1T11, A26L1T9, A6L1T2, A12L1T2, A14L1T2, A21L1T13, A24L1T12, A25L1T10, A22L1T7, A27L1T7, A30L1T13, A30L1T15, A31L1T14, A33L1T6, A37L1T2, A4L1T4, A18L1T3, A19L1T4, A20L1T3, A23L1T8, A28L1T4, A29L1T7, A35L1T5, A36L1T6, A4L1T16, A4L1T17, A4L1T19, A4L2T18, A4L2T14, A4L3T19, A4L3T14, A40L1T15, A41L1T15, A5L2T21, A5L3T22, A6L2T18, A6L3T19, A10L1T19, A38L1T15, A39L1T15, and A42L1T20.

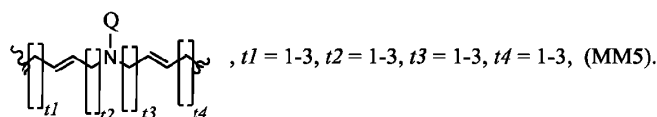
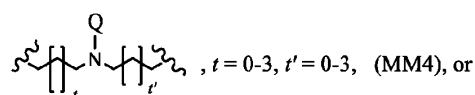
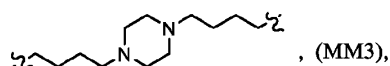
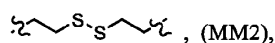
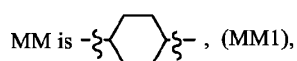
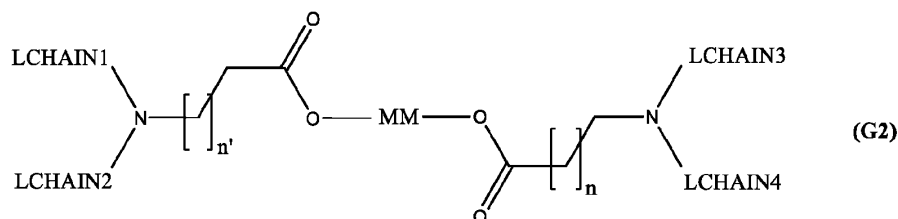
[0227] Variables that are not specified for the foregoing illustrative embodiments are defined as the same variables are defined in formula (G1.1).

[0228] The foregoing illustrative lists of $A_i''L_j''T_k''$ lipids, with $j'' = 1-3$, $k'' = 1-23$, and i'' as given therein for each formula designation, are not limiting as to restricting their interpretation only to the collections of compounds whose formulae designations are expressly recited in such lists. Any subgroup of lipids recited in any of such lists, reciting any number of such lipids, represents a set of illustrative compounds of formula (G1.1) that include, but are not limited to, any such listed compound(s), and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof.

[0229] Illustrative compounds of compounds of formula (G1.2) include, but are not limited to, the following compounds, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

A4(L1T14)₃(ST1)₂, and A4(L1T14)₂(ST1)₃;
A4(L1T14)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎, A4(L1T14)₁₋₁(ST1)₂₋₄(L1T14)₂₋₃₍₁₎,
A4(L1T14)₂₋₄(ST1)₁₋₁(L1T14)₁₋₃₍₁₎(ST1)₁₋₃₍₁₎,
A4(L1T14)₁₋₄(ST1)₁₋₄(ST1)₁₋₁(L1T14)₂₋₃₍₁₎, A4(L1T14)₁₋₃₍₁₎(ST1)₁₋₃₍₁₎(ST1)₁₋₁(L1T14)₂₋₄,
and A4(L1T14)₁₋₁(ST1)₁₋₁(ST1)₁₋₁(L1T14)₂₋₃₍₁₎;
A4(ST1)₁₋₁(ST1)₂₋₄(L1T14)₂₋₃₍₁₎, A4(ST1)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎,
A4(ST1)₂₋₄(L1T14)₁₋₁(ST1)₁₋₃₍₁₎(L1T14)₁₋₃₍₁₎,
A4(ST1)₁₋₄(L1T14)₁₋₄(L1T14)₁₋₁(ST1)₂₋₃₍₁₎, A4(ST1)₁₋₃₍₁₎(L1T14)₁₋₃₍₁₎(L1T14)₁₋₁(ST1)₂₋₄,
and A4(ST1)₁₋₁(L1T14)₁₋₁(L1T14)₁₋₁(ST1)₂₋₃₍₁₎.

[0230] The present application relates in another aspect to a compound represented generically by formula (G2) and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof:



wherein

each occurrence of LCHAIN1 - LCHAIN4 is linear or branched C_a-alkyl, with *a* = 9-15, or CH₂(CH₂)_νCH=CH(CH₂)_{ν'}CH₃, with *ν*' = 1-4, *ν*'' = 2-5, and each occurrence of LCHAIN1 - LCHAIN4 is the same or different from each of any of the other three occurrences of LCHAIN1 - LCHAIN4,

n = 0 - 4,

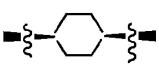
n' = 0 - 4, and each occurrence of *n* is the same or different from each occurrence of *n*' ,

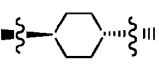
Q is (CH₂)_rCH₃ with *r* = 0-2, or CH₂(CH₂)_rC(O)O(CH₂)_{r'}CH₃ with *r*' = 0-3 and *r*'' = 1-3.

[0231] Each variable in (G2) indicating the choice of a number of groups of substituents, or a choice of substituents, is elected independently from the choice of any other such variable, whether such variables have the same name (while referring to different groups) or not, unless explicitly indicated otherwise.

[0232] The designations (MM1), (MM2), (MM3), and MM4) refer to the various assignments for the moiety MM in Formula (G2).

[0233] In some embodiments MM is MM1.

[0234] In some embodiments MM1 is  (MM1.1).

[0235] In some embodiments MM1 is  (MM1.2).

[0236] In some embodiments, each of LCHAIN1 – LCHAIN4 is a linear alkyl.

[0237] In some embodiments, at least one of LCHAIN1 – LCHAIN4 is a branched alkyl.

[0238] In some embodiments, LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 = linear alkyl.

[0239] In some embodiments, LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 = mono-unsaturated linear alkyl.

[0240] In some embodiments, LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.

[0241] In some embodiments, LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₂(CH₂)_{v'}CH=CH(CH₂)_{v''}CH₃, with v' = 2, v'' = 4.

[0242] In some embodiments, n = n'.

[0243] In some embodiments, n = n' = 1.

[0244] In some embodiments, n = 1 and n' = 4.

[0245] In some embodiments, n = 4 and n' = 1.

[0246] In some embodiments, n = 1 and n' = 4, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.

[0247] In some embodiments, MM1 is MM1.1, n = n' = 1, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.

[0248] In some embodiments, MM1 is MM1.2, n = n' = 1, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.

[0249] In some embodiments, MM is MM2.

[0250] In some embodiments, MM is MM3.

[0251] In some embodiments, MM is MM4.

[0252] In some embodiments, MM is MM4, and Q is $(\text{CH}_2)_r\text{CH}_3$ with $r = 0-1$, or $\text{CH}_2(\text{CH}_2)_{r'}\text{C}(\text{O})\text{O}(\text{CH}_2)_{r''}\text{CH}_3$ with $r' = 1-2$ and $r'' = 1-3$.

[0253] In some embodiments, MM is MM4, and Q is CH_3 , or $\text{CH}_2(\text{CH}_2)_{r'}\text{C}(\text{O})\text{O}(\text{CH}_2)_{r''}\text{CH}_3$ with $r' = 1$ and $r'' = 1$.

[0254] In some embodiments, MM is MM4, and Q is CH_3 , or $\text{CH}_2(\text{CH}_2)_{r'}\text{C}(\text{O})\text{O}(\text{CH}_2)_{r''}\text{CH}_3$ with $r' = r'' = 1$, and $t = t' = 1, 2$.

[0255] In some embodiments, MM is MM4, $t = 1, 2$ and $t' = 1, 2$.

[0256] In some embodiments, MM is MM4, $t = t' = 1, 2$.

[0257] In some embodiments, MM is MM5, $t1 = 1, 2$, $t2 = 1, 2$, $t3 = 1, 2$, $t4 = 1, 2$.

[0258] In some embodiments, MM is MM5, $t1 = t2 = t3 = t4 = 1, 2$.

[0259] In some embodiments, MM is MM5, $t1 = t2 = t3 = t4 = 1$.

[0260] In some embodiments, MM is MM5, $t1 = t2 = t3 = t4 = 1$, Q is CH_3 .

[0261] In some embodiments, MM is MM2, $n = n' = 1$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0262] In some embodiments, MM is MM2, $n = 1$, $n' = 4$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0263] In some embodiments, MM is MM3, $n = n' = 1$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0264] In some embodiments, MM is MM3, $n = 1$, $n' = 4$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0265] In some embodiments, MM is MM4, $n = n' = 1$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0266] In some embodiments, MM is MM4, $n = 1$, $n' = 4$, and $\text{LCHAIN1} = \text{LCHAIN2} = \text{LCHAIN3} = \text{LCHAIN4}$ is $\text{CH}_3-(\text{CH}_2)_8-\text{CH}_2$, $\text{CH}_3-(\text{CH}_2)_{10}-\text{CH}_2$, or $\text{CH}_3-(\text{CH}_2)_{12}-\text{CH}_2$.

[0267] In some embodiments, MM is one of MM1, MM2 and MM3, and n, n' , LCHAIN1 , LCHAIN2 , LCHAIN3 and LCHAIN4 are defined as in any of the foregoing embodiments defining such indices and group designations.

[0268] In some embodiments, MM is MM4, and n, n' , LCHAIN1 , LCHAIN2 , LCHAIN3 , LCHAIN4 , Q, t , and t' are defined as in any of the foregoing embodiments defining such indices and group designations. In some embodiments, MM is MM4, and n, n' , LCHAIN1 , LCHAIN2 ,

LCHAIN3, LCHAIN4, are defined as in any of the foregoing embodiments defining such indices and group designations, and Q, *t*, and *t'* are defined as they are for formula (G2).

[0269] In some embodiments, MM is MM5, and n, n', LCHAIN1, LCHAIN2, LCHAIN3, LCHAIN4, Q, *t1*, *t2*, *t3*, and *t4* are defined as in any of the foregoing embodiments defining such indices and group designations. In some embodiments, MM is MM5, and n, n', LCHAIN1, LCHAIN2, LCHAIN3, LCHAIN4, are defined as in any of the foregoing embodiments defining such indices and group designations, and Q, *t1*, *t2*, *t3*, and *t4* are defined as they are for formula (G2).

[0270] Illustrative compounds of formula (G2) include, but are not limited to, compounds with the following formula, and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof:

[0271] A101T101, A101T102, A101T103, A102T101, A102T102, A102T103, A103T101, A103T102, A103T103, A104T101, A104T102, A104T103, A105T101, A105T102, A105T103, A106T101, A106T102, A106T103, A107T101, A107T102, A107T103, A109T101, A107T104, A110T101, and A108T101.

[0272] The foregoing list of *Aii''Tkk''* lipids, with *ii''* = 101 - 110 and *kk''* = 101 - 104, is not limiting as to restricting its interpretation only to the collection of compounds whose formulae designations are expressly recited in such list. Any subgroup of lipids recited in any of such list, reciting any number of such lipids, represents a set of illustrative compounds of formula (G2) that include, but are not limited to, any such listed compound(s), and any tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof.

Methods of Preparation

[0273] Compounds described herein can be prepared by any number of processes as described generally below and more specifically illustrated by the illustrative compounds which follow in the Examples section herein.

[0274] By way of illustration, but not as a limitation, compounds of formulae (G1) and (G2) described herein can be prepared according to the following procedures shown in the following Examples as well as the examples shown in this application. One of ordinary skill in the art will recognize that, to obtain various compounds of formulae (G1) or (G2) as described

herein, starting materials can be suitably selected so that the ultimately desired substituent groups will be carried through (*i.e.*, be stable over the course of the synthesis) the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in place of the ultimately desired substituent, a suitable group that may be carried through (*i.e.*, be stable over the course of the synthesis) the reaction scheme and replaced as appropriate with the desired substituent.

[0275] Unless otherwise specified, the variables in the following Examples and procedures are as defined above in reference to the various embodiments of compounds of formulae (G1) or (G2). If no temperature or temperature range is stated, it is to be understood that the reaction is to be conducted at room temperature.

EXAMPLES

[0276] The following examples of the application are to further illustrate the nature of the application. It should be understood that the following examples do not limit the application and the scope of the application is to be determined by the appended claims.

[0277] Unless indicated otherwise, the abbreviations for chemical reagents and synthesis conditions have their ordinary meaning known in the art as follows:

“ACN” refers to acetonitrile;

“BnNH₂” refers to benzylamine;

“Boc” refers to *tert*-butoxycarbonyl;

“BuBr” refers to 1-bromobutane (n-butyl bromide);

“CAD” refers to charged aerosol detector;

“DCC” refers to N,N'-dicyclohexylcarbodiimide;

“DCM” refers to dichloromethane;

“DEAD” refers to diethyl azodicarboxylate;

“DHP” refers to dihydropyran;

“DIEA” or “DIPEA” refers to N,N-diisopropylethylamine;

“DLin-MC3-DMA” refers to 4-(dimethylamino)-butanoic acid, (10Z,13Z)-1-(9Z,12Z)-9,12-octadecadien-1-yl-10,13-nonadecadien-1-yl ester (CAS # 1224606-06-7);

“DMAP” refers to 4-dimethylaminopyridine;

“DMF” refers to dimethylformamide;

“DMSO” refers to dimethylsulfoxide;
“DNA” refers to deoxyribonucleic acid;
“DOPE” refers to 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine;
“DPPF” refers to 1,1'-Bis(diphenylphosphino)ferrocene;
“DSPC” refers to 1,2-distearoyl-sn-glycero-3-phosphocholine;
“EA” refers to ethyl acetate;
“EDCI” refers to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;
“EDTA” refers to ethylenediaminetetraacetic acid;
“ELSD” refers to evaporative light-scattering detector;
“EtOH” refers to ethanol;
“FIX” refers to factor IX;
“GalNAc” refers to N-acetylgalactosamine;
“h”, “hr” or “hrs” refers to hours;
“HATU” refers to hexafluorophosphate azabenzotriazole tetramethyl uronium (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate);
“hEPO” refers to human erythropoietin;
“Hex” refers to hexanes;
“hFIX” refers to human factor IX;
“HOBT” or “HOBt” refers to hydroxybenzotriazole (1H-1,2,3-Benzotriazol-1-ol);
“IFN-γ” refers to interferon-gamma;
“IgG” refers to immunoglobulin G;
“IL-6” refers to interleukin-6;
“i-PrOH” refers to isopropanol;
“IV” refers to intravenous;
“LAH” refers to lithium aluminum hydride;
“LCMS” refers to liquid chromatography-mass spectrometry;
“LDA” refers to lithium diisopropyl amide;
“LLOQ” refers to the lower limit of quantification of an assay;
“LNP” refers to lipid nanoparticles;
“LP-01” refers to 9Z,12Z-octadecadienoic acid, 3-[4,4-bis(octyloxy)-1-oxobutoxy]-2-

[[[3-(diethylamino)propoxy]carbonyl]oxy]methyl]propyl ester (CAS # 1799316-64-5);

“MC3” see DLin-MC3-DMA;

“MCP-1” refers to monocyte chemoattractant protein-1;

“m-CPBA” refers to meta-chloroperoxybenzoic acid;

“MHC-I tetramer” refers to class I major histocompatibility complex (MHC) tetramer;

“MeOH” refers to methanol;

“MTBE” refers to methyl tert-butyl ether;

“min” refers to minutes;

“mRNA” refers to messenger RNA;

“NaHMDS” refers to sodium bis(trimethylsilyl)amide;

“NaVC” refers to refers to L(+) sodium ascorbate, CAS # 134-03-2;

“OTBDPS” refers to TBDPS ether;

“OVA” refers to ovalbumin;

“Pd/C” refers to palladium on carbon;

“pDNA” refers to plasmid DNA;

“PDI” refers to the polydispersity index, as a measure of the width of nanoparticle size distribution.

“PE” refers to petroleum ether;

“PEG” refers to polyethylene glycol;

“PPh3” refers to triphenylphosphine;

“Prep-HPLC” refers to preparative high performance liquid chromatography;

“Prep-TLC” refers to preparatory thin layer chromatography;

“Py” refers to pyridine;

“RNA” refers to ribonucleic acid;

“r.t.” and “rt” refer to room temperature;

“RT” or “Rt” refers to retention time;

“SM-102” refers to 8-[(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino]-octanoic acid, 1-octylnonyl ester (CAS # 2089251-47-6);

“TBAB” refers to tetrabutylammonium bromide;

“TBAF” refers to tetrabutylammonium fluoride;

“TBDPS” refers to *tert*-butyldiphenylsilyl;

“TBDPSO” refers to TBDPS ether;

“TBS” refers to *tert*-butyldimethylsilyl;

“TBSO” refers to TBS ether”

“t-BuOH” refers to *tert*-butyl alcohol;

“TEA” refers to triethyl amine;

“TFA” refers to trifluoroacetic acid;

“THF” refers to tetrahydrofuran;

“TLC” refers to thin layer chromatography;

“TMSI” or “TMS-I” refers to trimethylsilyl iodide;

“Tol” refers to toluene;

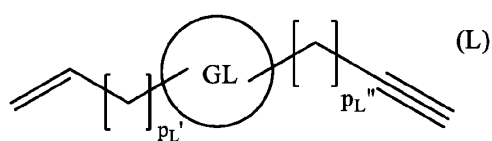
“TsOH” refers to *p*-toluenesulfonic acid;

“ULOQ” refers to the upper limit of quantification of an assay; and

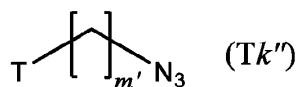
“VcNa”, “VCNa” or “VcONa” refers to L(+) sodium ascorbate, CAS # 134-03-2.

[0278] Compound designations, whether letters, numbers, or combinations of letters and numbers, may be typed in bold-face font or not, and this difference in font is not meant to confer any substantive difference to the compound designations. For the named compounds below, chemical names have been generated with the structure-to-name conversion tool of the software ChemDraw[®] (see furthermore note on chiral compound naming after Table 1).

[0279] Some embodiments of compounds of formulae (G1) are prepared by hydroamination of the alkene group(s) in one or more compound(s) of general formula (L)

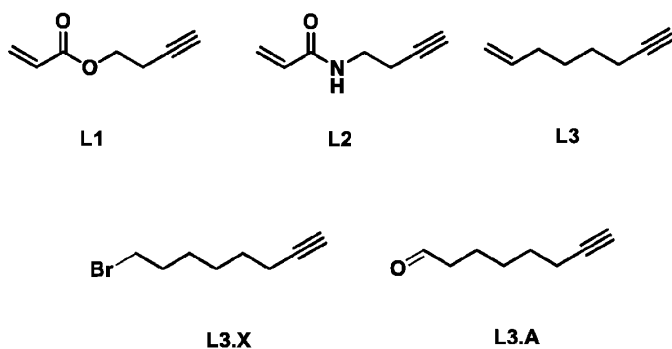


where GL is OCO (which is either C(O)-O or O-C(O)), OCNH (which is either C(O)NH or HN-C(O)), or CH₂CH₂, with the parent compound of a moiety A to yield a hydroaminated alkyne derivative whose alkyne moiety further undergoes cycloaddition with an azide (*Tk''*), wherein *k''* has the value determined by *m'* and T, as more extensively described in the following Examples,



to yield a triazole derivative within the scope of general formulae (G1). Other embodiments of compounds of formulae (G1) are prepared by cycloaddition with an azide (Tk''), wherein k'' has the value determined by m' and T, with an alkyne moiety AL as more extensively described in the following Examples. The values of p_L' in (L) and p' in formulae (G1) are related in the form $p' = p_L' + 1$, for $p' \geq 1$, so that when $p' = 1, 2, 3, 4$, then $p_L' = 0, 1, 2, 3$, respectively. The values of p_L'' in (L) and p'' in formulae (G1) are related in the form $p_L'' - 1 = p''$, so that when $p'' = 0, 1, 2, 3, 4$, then $p_L'' = 1, 2, 3, 4, 5$, respectively. The natural number m' is as defined for general formulae (G1).

[0280] Illustrative embodiments of compounds of general formula (G1.1) in the following examples are referred to with terms $\text{Ai}''\text{Lj}''\text{Tk}''$, where i'' , j'' , and k'' are labelling natural numbers. Sometimes reference is made to “compound $\text{Ai}''\text{Lj}''\text{Tk}''$ ” and sometimes reference is made to “lipid $\text{Ai}''\text{Lj}''\text{Tk}''$ ”, terms that are considered herein interchangeable and with the same meaning. In compound L, the variables p' and p'' (or p_L' and p_L'') are judiciously chosen as to introduce the desired number of units between the alkene group and the moiety GL (in the case of p' or p_L'), and the desired number of units between the moiety GL and the alkyne group (in the case of p'' or p_L''). For example, when $p' = 1$ and $p'' = 1$ (or $p_L' = 0$ and $p_L'' = 2$), then compound L is selected from compounds L1, L2 and L3 in the following examples.



[0281] In some embodiments, the alkyne moiety is introduced by an alkene, such as L1 or L2, in which case the generated hydroaminated compounds are noted as $\text{Ai}''\text{L1Tk}''$ or $\text{Ai}''\text{L2Tk}''$, respectively. In other embodiments, the alkyne moiety is introduced by a halide-derivative such

as L3.X. In other embodiments, the alkyne moiety is introduced by an aldehyde-derivative such as L3.A. Whether such moiety is introduced by L3, L3.A or L3.X, the compounds where the moiety corresponding to GL is CH_2CH_2 are herein named with the term L3 appearing in them because the alkene (L3), aldehyde (L3.A) or halo (L3.X) intermediate does not change the structure of such final compounds $A_i''\text{L}_3\text{T}_k''$, only the reaction performed in one of the synthetic steps to obtain them. As explained below, i'' and k'' are labelling natural numbers. Note that the appropriate choice of the length of the chain in embodiments such as L3.X and L3.A may lead to embodiments of formulae G1 where $p' = 0$, such as by choosing a $(\text{CH}_2)_5$ instead of a $(\text{CH}_2)_6$ chain in alkyne L3.X or a $(\text{CH}_2)_4\text{CHO}$ instead of a $(\text{CH}_2)_5\text{CHO}$ chain in alkyne L3.A.

[0282] Embodiments that introduce moiety L with an aldehyde derivative such as L3.A rely on a reductive amination by reacting an aldehyde such as L3.A, with a starting amine to produce an alkylated amine that has a higher degree of substitution than the starting amine. Embodiments that introduce moiety L with a halide such as L3.X rely on an amine alkylation by reacting a halide, such as L3.X, with a starting amine to produce an alkylated amine that has a higher degree of substitution than the starting amine. As illustrated by the Examples of synthesis of compounds of formula (G1.2), this generation of alkyne derivatives is also applicable to the LT moiety(ies) in compounds of formula (G1.2).

[0283] Upon hydroamination/reductive amination/amine alkylation of L with a parent compound of an amino moiety A, the resulting aminated alkyne derivative is referred to as $A_i''\text{L}_j''$ in the following examples, with i'' and j'' being labelling natural numbers. In compound T_k'' , the variable m' is judiciously chosen as to introduce the desired number of units between the azido group and the moiety T. Table 2 (parts 1 and 2) lists illustrative embodiments of such azides. Only "Table 2" is recited, with the same meaning, to refer to "Table 2, parts 1 and 2").

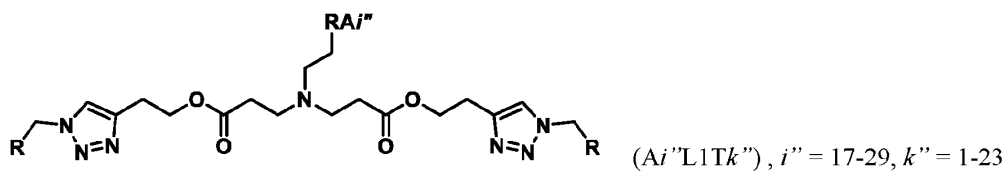
[0284] The term $A_i''\text{L}_j''$ is used herein to refer to such compound or moiety regardless of its preparation method. For example, as further described and illustrated in the Examples below, in some embodiments, $A_i''\text{L}_j''$ is prepared through alkene hydroamination, aldehyde reductive amination or amine alkylation of an amine (comprising at least one primary and/or secondary amino group) with linkers that comprise each an alkene group, as indicated above, and in some other embodiments it is prepared as to generate directly compound $A_i''\text{L}_j''$ without resorting to an alkene hydroamination, as shown for the preparation of compounds A30L1, A31L1, A32L1, A33L1, A34L1, A38L1, A39L1, A40L1, A41L1 and A42L1 whose structures are given in Table

1, as described in the corresponding examples below. No matter how $Ai''Lj''$ is generated, embodiments of compounds of formula (G1.1) are prepared through azide-alkyne cycloaddition of the alkyne group in moiety $Ai''Lj''$ with an azide Tk'' to yield compounds $Ai''Lj''Tk''$. As illustrated by the Examples of synthesis of compounds of formula (G1.2), azide-alkyne cycloadditions analogous to the ones for compounds of formula (G1.1) are also applicable to the LT moiety(ies) in compounds of formula (G1.2).

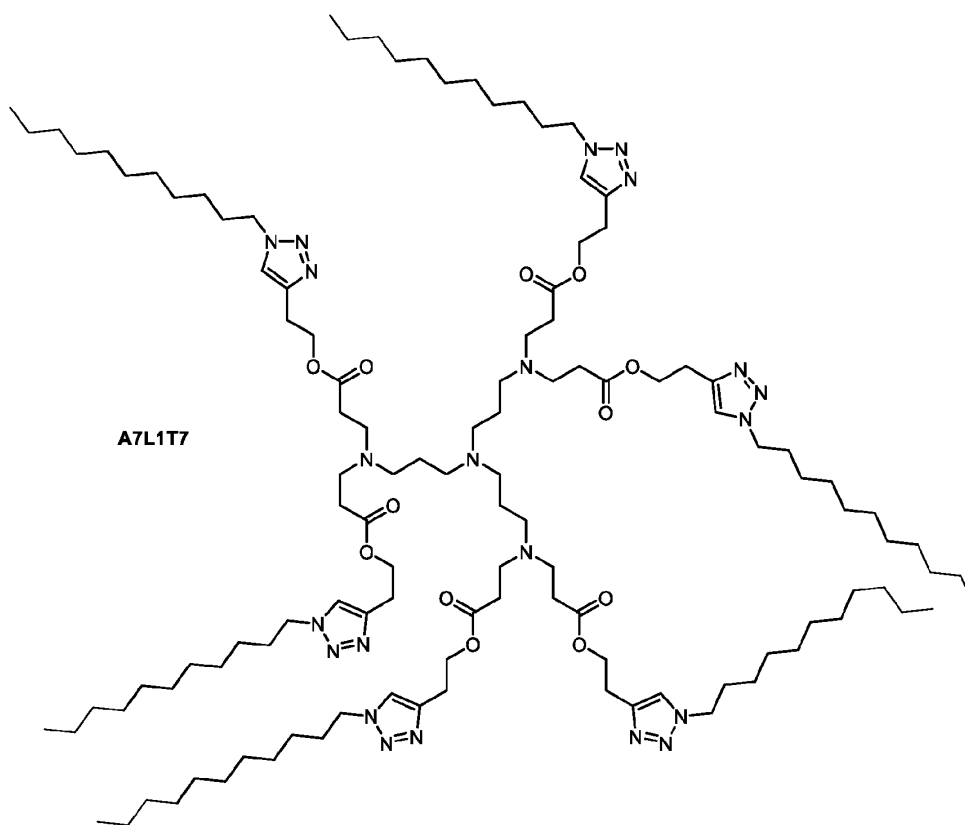
[0285] By way of illustration, compounds A30L1, A31L1, A32L1, A33L1, A34L1, A38L1, A39L1, A40L1, A41L1, and A42L1 illustrate compounds $Ai''Lj''$, with $i'' = 30-34$ and $38-42$, and $j'' = 1$, with only one alkyne group available for cycloaddition with an azide, as illustratively shown in Table 1. Although not synthesized through the alkene hydroamination of an isolated secondary amine, the fact that each of such compounds comprises only one L moiety with one alkyne group makes them subject to the terminology that they have one *N moiety each as far as nomenclature is concerned.

[0286] Each $-NH_2$ group in amines Ai'' , $i'' = 17-29$, illustratively shown in Table 1, undergoes two hydroaminations with two linker compounds of formula (L), each one with the alkene group of each of such two compounds (L), for example, compound L1. Each of such $-NH_2$ groups is an example of a *(*)N member. In this illustration, the final compound will thus comprise two linker-derived moieties, each with a moiety containing a triazole group and a tail attached to it (LT moiety). This is illustrated by compounds of formula $Ai''L1Tk''$ with $k'' = 1-23$ and $i'' = 17-29$. Compounds of formula $Ai''L2Tk''$ with $k'' = 14, 18, 21$ and $i'' = 4-6$, illustrate compounds obtained through hydroaminations with L2. Compounds of formula $Ai''L3Tk''$ with $k'' = 14, 19, 22$ and $i'' = 4-6$, illustrate compounds obtained through reductive aminations with L3.O or through amine alkylations with L3.X.

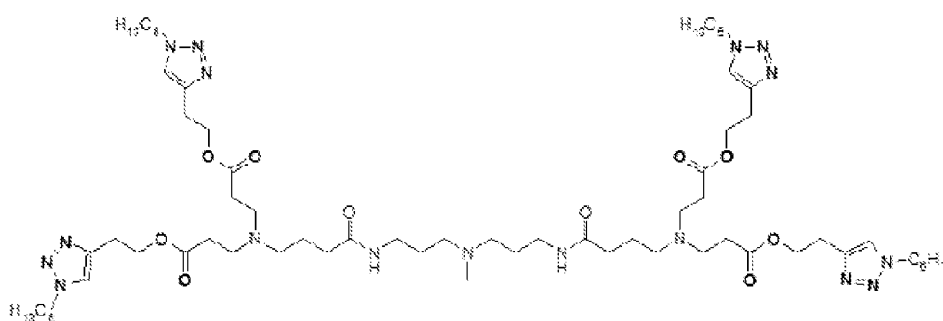
[0287] In another illustration, compound of formula $Ai''L1Tk''$ shown below, is an illustrative generic formula for compounds derived from a primary amine that could be, for example, any amine Ai'' , $i'' = 17-29$ shown in Table 1, and Tk'' , $k'' = 1-23$, could be any azide among those illustratively shown in Table 2. The group " RAi'' " is implicitly defined based on the formulae Ai'' , $i'' = 17-29$, given in Table 1, wherein RAi'' is the moiety in each of such Ai'' , $i'' = 17-29$, that is attached to the terminus $CH_2-CH_2-NH_2$ in each of such Ai'' , $i'' = 17-29$. This compound is an illustration of an embodiment with $p = 2$ as defined for formula (G1.1), and the primary amino group is a *(*)N center.



[0288] In another illustration, compound of formula Ai''L1Tk'', with $i'' = 7$ and $k'' = 7$ shown below, is the formula for a compound derived from amine A7, shown in Table 1, that has three primary amino groups, each being a $^{(*)}N$ member, and two linkers L1 attached to each of such primary amino groups, and in turn azide T7, shown in Table 2, attaches to each alkyno group of each of such L1 linkers, thus leading to compound A7L1T7, which was synthesized as described in the corresponding example given below. This compound is an illustration of an embodiment with $p = 6$ as defined for formula (G1.1):



[0289] In another illustration, compound of formula $Ai''L1Tk''$ with $i'' = 16$ and $k'' = 1$ shown below, is the formula for a compound derived from amine A16, shown in Table 1, that has two terminal primary amino groups, each being a $*(*)N$ member. Two linkers L1 attach to each of such primary amino groups and in turn azide T1, shown in Table 2, attaches to each alkyno group of each of such L1 linkers, thus leading to compound A16L1T1, which was synthesized as described in the corresponding example given below. This compound is an illustration of an embodiment with $p = 4$ as defined for formula (G1). Structural formula for A16L1T1:

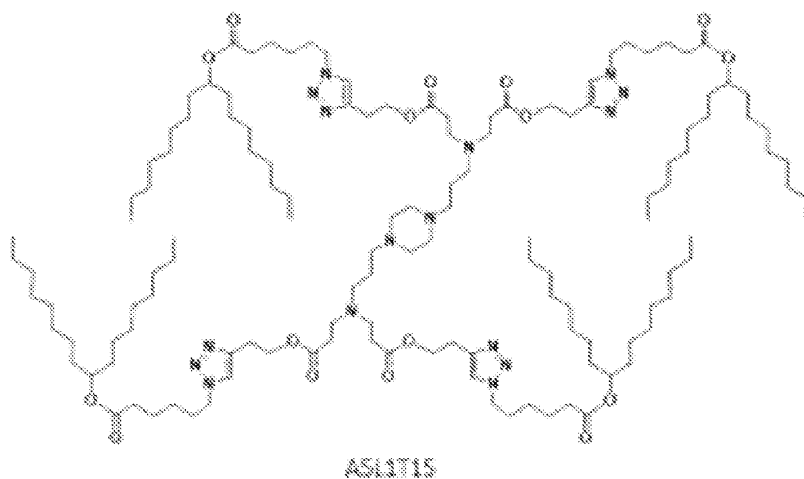


(A16L1T1)

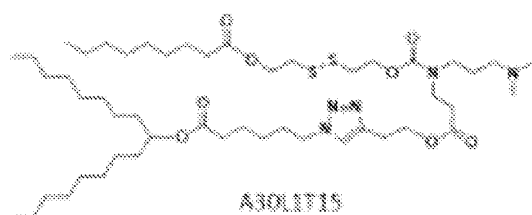
[0290] Other illustrative embodiments of compounds with $p = 4$ as defined for formula (G1.1) are compounds A11L1T11, A12L1T2, A10L1T19 and A16L1T1.

[0291] A4L1T4 is an illustrative embodiment that has linkers L1 attached to all the $*(*)N$ (here primary amino) and also $*N$ (here secondary amino) members in amine A4 and where the notation $*N$ refers here to the N member in the $-NH-$ moiety in A4.

[0292] In another illustration, compound of formula $Ai''L1Tk''$ with $i'' = 5$ and $k'' = 15$ shown below, is the formula for a compound derived from amine A5, shown in Table 1, that has two terminal primary amino groups. Each of such groups is a $*(*)N$ member in this compound. Two linkers L1 attach to each of such primary amino groups and in turn azide T15, shown in Table 2, attaches to each alkyno group of each of such L1 linkers, thus leading to compound A5L1T15, which was synthesized according to Example A5L1T15 given below, and whose full structural formula is given below. This compound is an illustration of an embodiment with $p = 4$ as defined for formula (G1.1):



[0293] In another illustration, compound of formula $Ai''L1Tk''$ with $i'' = 30$ and $k'' = 15$ shown below, is the formula for a compound derived from parent compound A30L1, shown in Table 1. One linker L1 is attached to the *N member in such compound A30L1 and in turn azide T15, shown in Table 2, attaches to the alkyno group of such L1 linker, thus leading to compound A30L1T15, which was synthesized according to Example A30L1T15 given below, and whose full structural formula is given below. This compound is an illustration of an embodiment with $p = 1$ as defined for formula (G1.1).



[0294] In light of the large space that would be taken by the full structural formulae for compounds $Ai''Lj''Tk''$, such as those referred to in Table C1 (parts 1 and 2), nomenclature is provided herein to refer to them concisely, and to ascertain the structural formula of any such lipid given as an $Ai''Lj''Tk''$ formula or, *vice versa*, to name any of such structural formulae in

the $Ai''Lj''Tk''$ notation. This is accomplished by relying on the formulae given in Tables 1-2 and the criteria provided throughout this application. The examples for the syntheses of the various moieties in $Ai''Lj''Tk''$ lipids and the full $Ai''Lj''Tk''$ compounds given below illustrate how to prepare such $Ai''Lj''Tk''$ lipids. $Ai''Lj''Tk''$ lipids for which no express synthesis narrative is provided are synthesized in reference to the synthetic examples given in this application. Such examples, together with those given explicitly for compounds of formula (G1.2), illustrate by analogy synthetic steps for moieties LT in compounds of formula (G1.2) whose syntheses are not explicitly given below. Known azide-alkyne chemistry may be used to supplement the synthetic methods illustratively described herein, to design alternative synthetic schemes, or to use in the synthesis of lipids for which no express synthesis is described herein, such as chemistry disclosed in references that include the following: N. Zuin Fantoni, *et al.*, Chem. Rev. **121**, 7122-54 (2021) "A Hitchhiker's Guide to Click-Chemistry with Nucleic Acids"; Y. Zhao, *et al.*, Molecules **28**(3), 1400 (2023) "Overview of 1,5-Selective Click Reaction of Azides with Alkynes or Their Synthetic Equivalents"; P.K. Avti, *et al.*, Molecules **18**(8), 9531-49 (2013) "Alkyne-Azide 'Click' Chemistry in Designing Nanocarriers for Applications in Biology"; and "Click Chemistry Azide-Alkyne Cycloaddition" in Organic Chemistry Portal, at <<https://www.organic-chemistry.org/namedreactions/click-chemistry.shtml>>.

[0295] According to the nomenclature for $Ai''Lj''Tk''$ lipids used in Table C1 (parts 1 and 2), Tables 1-2 and in examples below, Lj'' refers to the linker compound that comprises an alkene group and an alkyne group as shown for compound of formula (L). For some illustrative embodiments, such as those referred to in Table C1 (parts 1 and 2), $j'' = 1$, so Lj'' for such illustrative embodiments is L1. The following narrative description concerning L1 is analogously applicable to L2 and L3, for which it is not repeated. There are two L1-derived linker moieties that are attached to each $*(*)N$ member of an Ai'' moiety ($i'' = 1-12, 14, 16-29, 35-37$), and there is one L1-derived linker moiety to each $*N$ member of an Ai'' moiety ($i'' = 4$) or to the $*N$ member of moieties $Ai''L1$ ($i'' = 30-34, 38-42$) as indicated above. When amine Ai'' has $*N$ and $*(*)N$ members (such as when $i'' = 4$), such amine Ai'' - linker L1 attachments take place at both the $*N$ and $*(*)N$ sites of the Ai'' moiety. Because the alkyne group of each L1-derived linker moiety undergoes an azide-alkyne cycloaddition, generating a triazole with the rest (tail T as defined by general formula (Tk'')) of the azide reactant, the final compound will have as many triazole-T moieties derived from such azide-alkyne cycloaddition as linker moieties L1 are

attached to the amine Ai'' , $i'' = 1-12, 14, 16-29, 35-37$, moiety or to the one L1 moiety of $Ai''L1$, $i'' = 30-34$ and $38-42$, moiety. Examples of such parent amines Ai'' for such Ai'' , $i'' = 1-12, 14, 16-29, 35-37$, moieties, and examples of parent $Ai''Lj''$, $i'' = 30-34$ and $38-42$, compounds for such $Ai''Lj''$, $i'' = 30-34$ and $38-42$, moieties are shown in Table 1. Examples of azides comprising an azido group and a tail T are shown in Table 2. Examples of such tails T as incorporated in compounds of formulae (G1.1) and (G1.2), without the azido group, are shown in Table T2. Any one of Tables 2 and T2 may indistinguishably be referred to concerning any particular tail, or moiety, T in any compound of formulae (G1.1) and (G1.2). Examples of such amino moieties A as incorporated in compounds of formulae (G1.1) and (G1.2), are shown in Tables P1, P2, P4 and formulae P5 and P6. Any one of Tables 1 and Tables P1, P2, P4 and formulae P5 and P6 may indistinguishably be referred to concerning any particular amino moiety A in any compound of formulae (G1.1) and (G1.2). The examples below also provide illustrations of compounds designated according to such $Ai''Lj''Tk''$ terminology. The structural formula of any $Ai''Lj''Tk''$ referred to in these examples of compound of formula (G1.1) is determined by (a) identifying the amino moiety Ai'' , $i'' = 1-12, 14, 16-29, 35-37$, or intermediate $Ai''L1$, $i'' = 30-34$ and $38-42$, moiety as per the illustrations in Table 1; (b) when the relevant moiety is Ai'' , $i'' = 1-12, 14, 16-29, 35-37$ (rather than $Ai''L1$, $i'' = 30-34$ and $38-42$), identifying the number of *N and *(*)N members in such amine Ai'' , and attaching two L1 moieties by the alkene terminus of each of such L1 moiety as described above to each *(*)N member, and in some embodiments one L1 moiety to each *N member when present, to form moieties $Ai''(L1)_p$, $p = 1-6$, and $i'' = 1-12, 14, 16-29, 35-37$; and (c) attaching to each alkyne end of each moiety $Ai''(L1)_p$, $p = 1-6$ and $i'' = 1-12, 14, 16-37$ the azido moiety of a tail Tk'' as the result of an azide-alkyne cycloaddition with the formation of a triazole-tail moiety for each such L1 moiety. The number of *N and *(*)N members in each of the examples of Ai'' , $i'' = 1-12, 14, 16-29, 35-37$, and $Ai''L1$, $i'' = 30-34$ and $38-42$, is given below. The foregoing nomenclature criteria are provided for $Ai''Lj''Tk''$ nomenclature purposes, and to convert (through the use of such nomenclature and the examples, express formulae, and moiety information provided herein) any compound designation in the form $Ai''Lj''Tk''$, with specified values for i'' , j'' , and k'' , to its corresponding chemical structure, or *vice versa*. As noted above, the foregoing narrative description concerning L1 is analogously applicable to L2 and L3 regarding compounds $Ai''Lj''Tk''$, $j'' = 1-3$. Although only amines of type $Ai''L1$, $i'' = 30-34$ and $38-42$, are explicitly given in Table 1, the corresponding amines

$Ai''L2$ and $Ai''L3$, $i'' = 30-34$ and $38-42$, are readily envisaged when the alkyne moiety in them as shown in Table 1 is changed to the corresponding alkyne moiety that formally corresponds with $L2$ and $L3$, respectively.

[0296] Various Tk'' in some embodiments of lipids $Ai''Lj''Tk''$ correspond to identical tails Tk'' in $Ai''Lj''Tk''$ derived from the same parent azide Tk'' , whereas in other embodiments tails Tk'' may be different. This feature equally applies to LT moieties in compounds of formula (G1.2). Unless indicated otherwise, the notation $Ai''Lj''Tk''$ is to be interpreted herein as referring to a lipid embodiment in which the various Tk'' are identical when more than one is present, as determined according to the criteria given above. Analogously, and unless indicated otherwise, the notation $Ai''Lj''Tk''$ is to be interpreted herein as referring to a lipid embodiment in which the various Lj'' , when a plurality of Lj'' exist, are identical.

[0297] Table 1 (parts 1-4; herein referred to only as "Table 1") shows illustrative embodiments of amines Ai'' , $i'' = 1-12, 14, 16-29$, and $35-37$, that generate the corresponding Ai'' moiety in compounds designated with the terminology $Ai''Lj''Tk''$, when $i'' = 1-12, 14, 16-29$, and $35-37$. The same Ai'' designation is used for the parent amine and for the corresponding moiety in the $Ai''Lj''Tk''$ compound. Table 1 also shows illustrative embodiments of compounds $Ai''Lj''$, $i'' = 30-34$ and $38-42$, and $j'' = 1$, that generate the corresponding $Ai''L1$ moiety in compounds designated with the terminology $Ai''L1Tk''$, when $i'' = 30-34$ and $38-42$. As with the amines and the corresponding amine moieties, the same $Ai''L1$ designation is used for the parent compound shown in Table 1 and for the corresponding moiety in the $Ai''Lj''Tk''$ compound. The examples below provide further illustrations of such compounds and moieties. A first set of illustrative embodiments of $Ai''Lj''$, $j'' = 1$, moieties include $A1L1$, $A2L1$, $A3L1$, $A4L1$, $A5L1$, $A6L1$, $A7L1$, $A8L1$, $A9L1$, $A10L1$, $A11L1$, $A12L1$, $A14L1$, $A16L1$, $A17L1$, $A18L1$, $A19L1$, $A20L1$, $A21L1$, $A22L1$, $A23L1$, $A24L1$, $A25L1$, $A26L1$, $A27L1$, $A28L1$, $A29L1$, $A30L1$, $A31L1$, $A32L1$, $A33L1$, $A34L1$, $A35L1$, $A36L1$, and $A37L1$. Analogous moieties to those given in the foregoing first set with the corresponding i'' values, and with $j'' = 2, 3$ instead of $j'' = 1$, illustrate moieties $Ai''L2$ and $Ai''L3$, respectively. A second set of illustrative embodiments of $Ai''Lj''$, $j'' = 1$, moieties include $A30L1$, $A31L1$, $A32L1$, $A33L1$, $A34L1$, $A38L1$, $A39L1$, $A40L1$, $A41L1$ and $A42L1$. Analogous moieties to those given in the foregoing second set with the corresponding i'' values, and with $j'' = 2, 3$ instead of $j'' = 1$, illustrate moieties $Ai''L2$ and

Ai''L3, respectively, when the moiety L1 is replaced by an L2 or L3 moiety (such as L3.X, L3.A, or a moiety analogous to L3.X or L3.A that has a shorter chain, as indicated above).

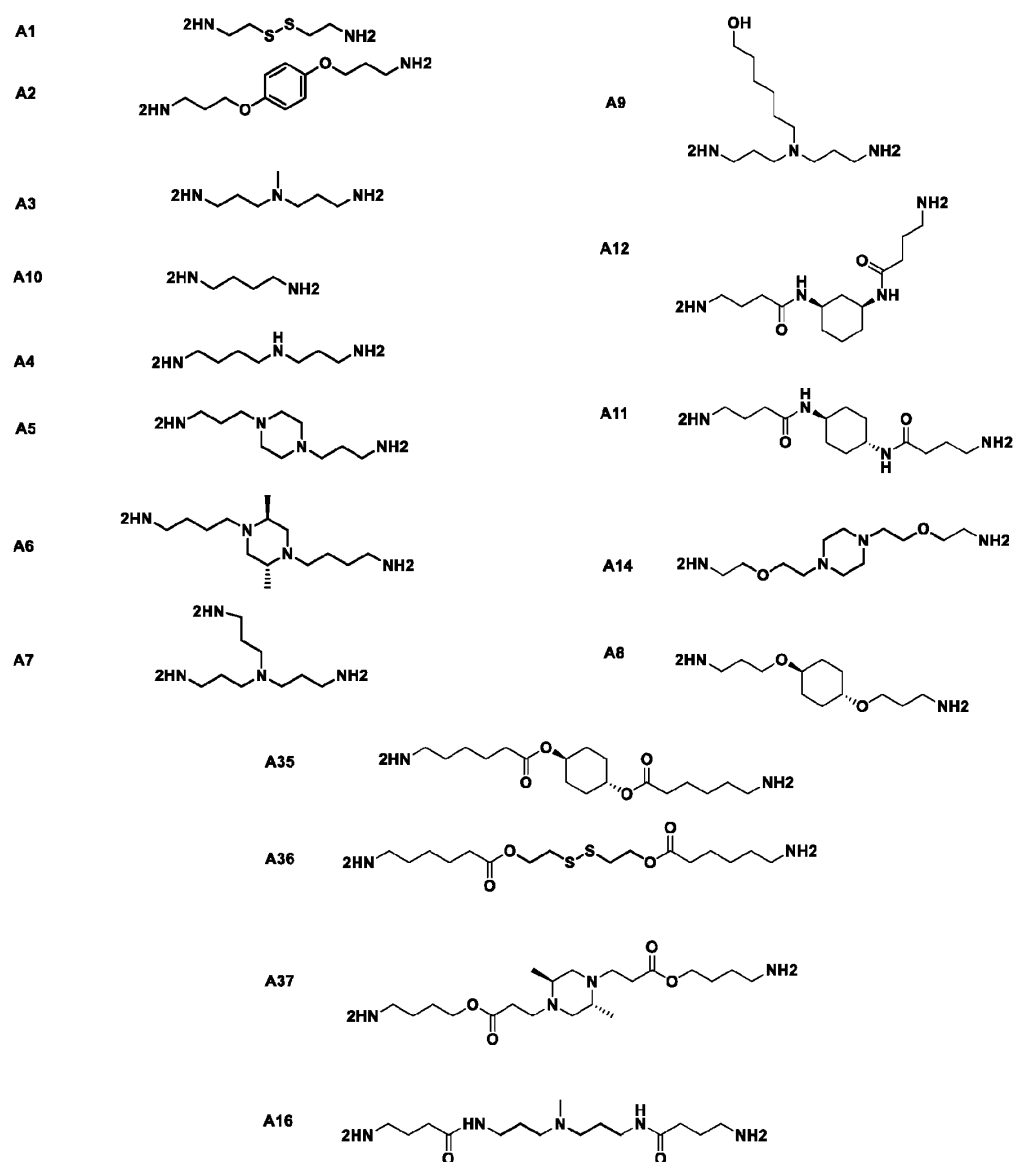


Table 1 (part 1)

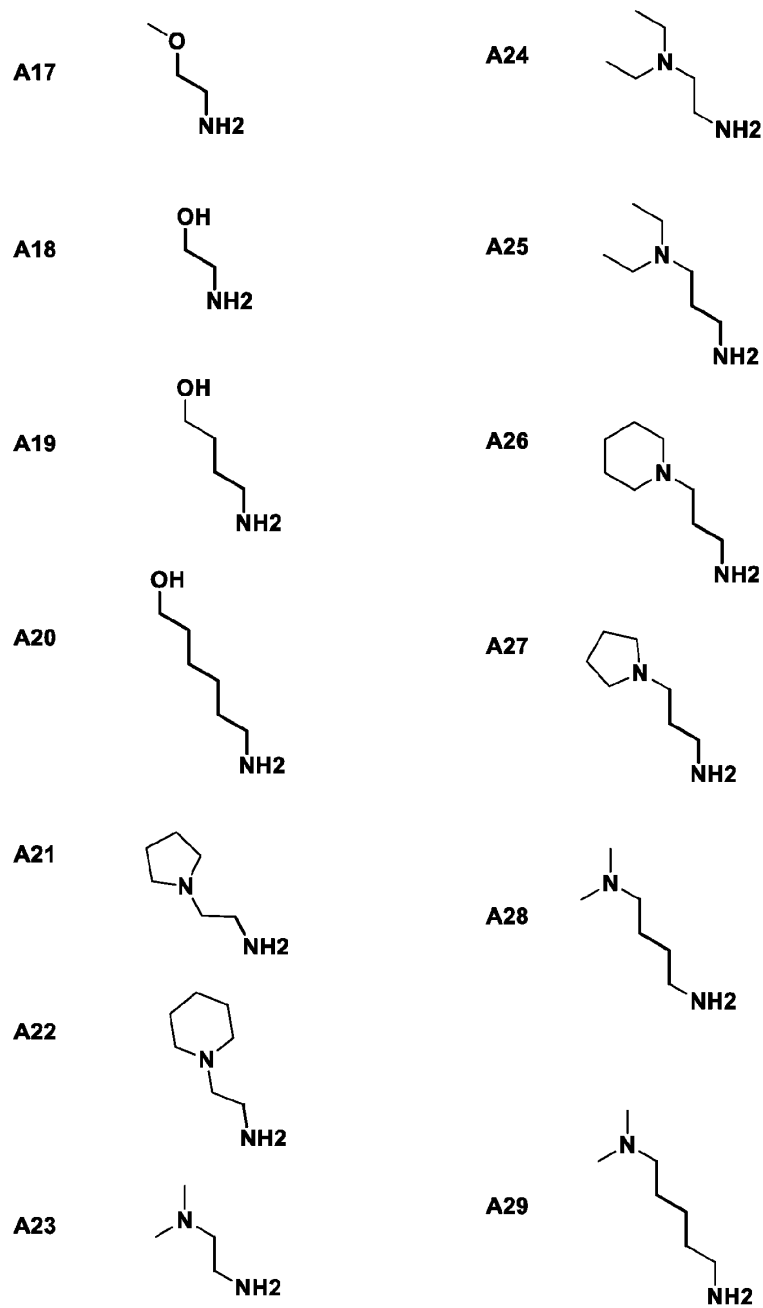
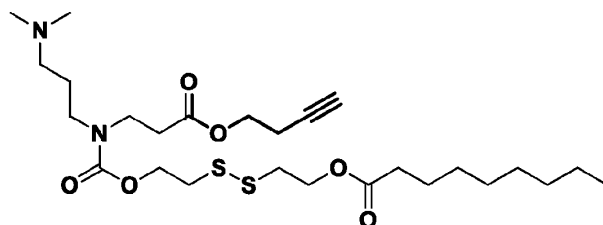
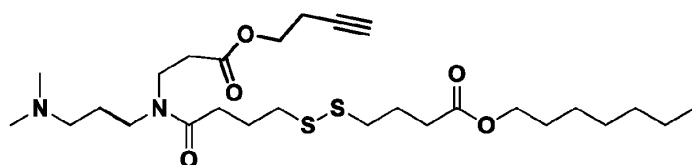


Table 1 (part 2)

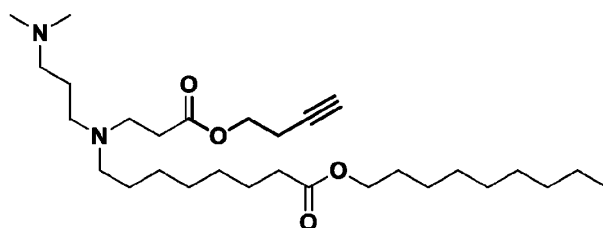
A30L1



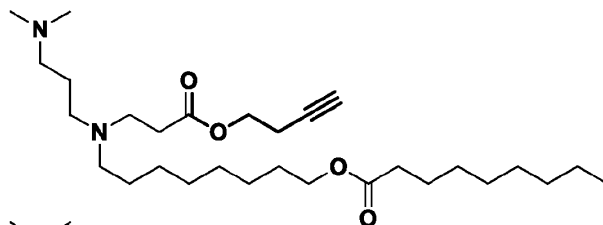
A31L1



A32L1



A33L1



A34L1

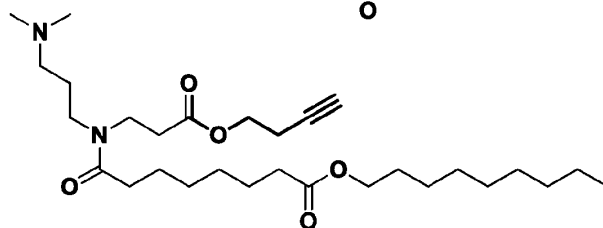


Table 1 (part 3)

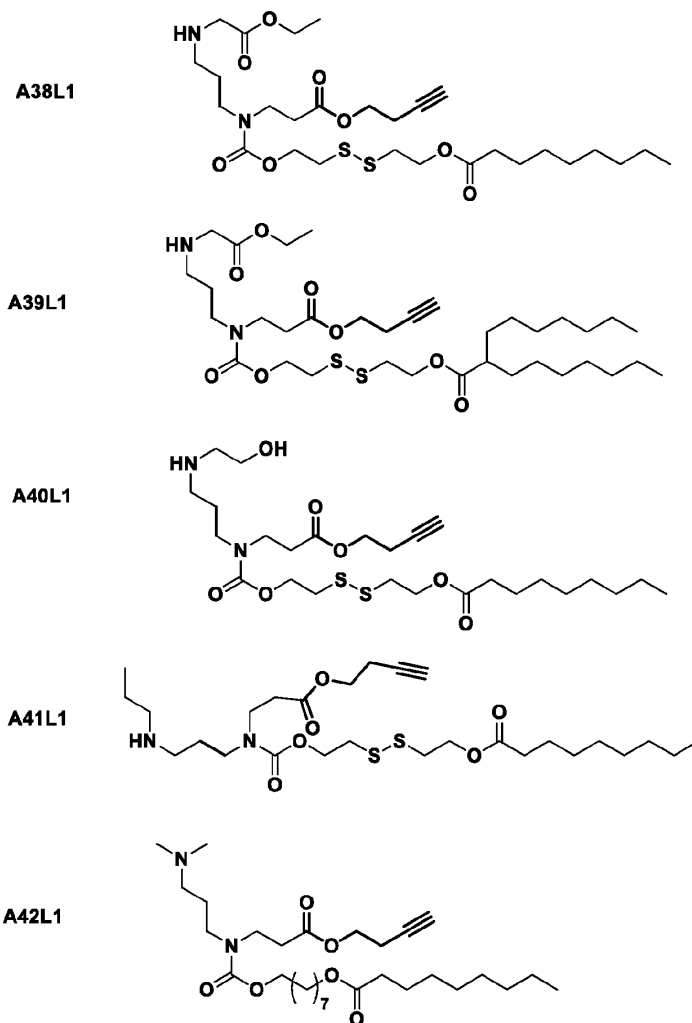


Table 1 (part 4)

[0298] The group that is displayed in Table 1 as “NH₂” refers to the amino group “NH₂”.

[0299] Chiral compounds that comprise one of the following amino moieties: A6, A8, A11, A12, A35, A37, A101 and A102, can present themselves in pure enantiomeric and racemate forms. The corresponding ChemDraw[®]-generated names have been edited to recite the terms trans/cis instead of the absolute stereocenter configurations R/S, even when the described synthesis procedures (see Example A12L1, as an illustration) and/or other disclosure provided in

the specification permit the identification of any such absolute stereocenter configuration. In addition to the compound forms explicitly, or by implication, identified in the specification, and no matter how they are named, the racemates thereof and the corresponding enantiomers are all envisaged within the scope of this invention.

[0300] The parent compounds $Ai''L1$, with $i'' = 30 - 34$ and $38 - 42$, illustrate embodiments in which $p = 1$ (one $*N$ member) in formula (G1.1) when any of such $Ai''L1$, with $i'' = 30 - 34$ and $38 - 42$, is a moiety in a compound of formula (G1.1). The parent amines Ai'' , with $i'' = 17 - 29$, illustrate embodiments in which $p = 2$ (one $*(*)N$ member (in these cases such $*(*)N$ member being a primary amino group)) in formula (G1.1) when any of such Ai'' , with $i'' = 17 - 29$, is a moiety in a compound of formula (G1.1). The parent amines Ai'' , with $i'' = 1-3, 5, 6, 8-10, 14, 35, 36$ and 37 , illustrate embodiments in which $p = 4$ (two $*(*)N$ members (in these cases each of such $*(*)N$ members being a primary amino group)) in formula (G1.1) when any of such Ai'' , with $i'' = 1-3, 5, 6, 8-10, 14, 35, 36$ and 37 , is a moiety in a compound of formula (G1.1). The parent amines Ai'' , with $i'' = 11, 12$ and 16 , illustrate further embodiments in which $p = 4$ (two $*(*)N$ members (in these cases each of such $*(*)N$ members being a primary amino group)) in formula (G1.1), when any of such Ai'' , with $i'' = 11, 12$, and 16 , is a moiety in a compound of formula (G1.1). In reference to parent amines Ai'' with $i'' = 11, 12$ and 16 , the NH group that is part of an amido moiety is not a $*N$ member. The parent amine Ai'' , with $i'' = 7$, illustrates an embodiment in which $p = 6$ (three $*(*)N$ members (in these cases each of such $*(*)N$ members being a primary amino group)) in formula (G1.1) when such Ai'' , with $i'' = 7$, is a moiety in a compound of formula (G1.1). The parent amine Ai'' , with $i'' = 4$, illustrates an embodiment in which $p = 5$ (two $*(*)N$ members and one $*N$ member (in this case each of such $*(*)N$ members being a primary amino group and such $*N$ member being a secondary amino group)) in formula (G1.1) when such Ai'' , with $i'' = 4$, is a moiety in a compound of formula (G1.1). In reference to parent amine Ai'' with $i'' = 4$, the NH group is not part of an amido moiety, and it is in this case a $*N$ member. As noted above, the foregoing narrative description concerning L1 in parent compounds $Ai''L1$ is analogously applicable to L2 and L3 regarding compounds $Ai''Lj''Tk''$, $j'' = 1-3$. Although only amines of type $Ai''L1$, $i'' = 30-34$ and $38-42$, are explicitly given in Table 1, the corresponding amines $Ai''L2$ and $Ai''L3$, $i'' = 30-34$ and $38-42$, are readily envisaged when the alkyne moiety in them as shown in Table 1 is changed to the

corresponding alkyne moiety that formally corresponds with L2 and L3 (such as L3.X, L3.A, or a moiety analogous to L3.X or L3.A that has a shorter chain, as indicated above), respectively.

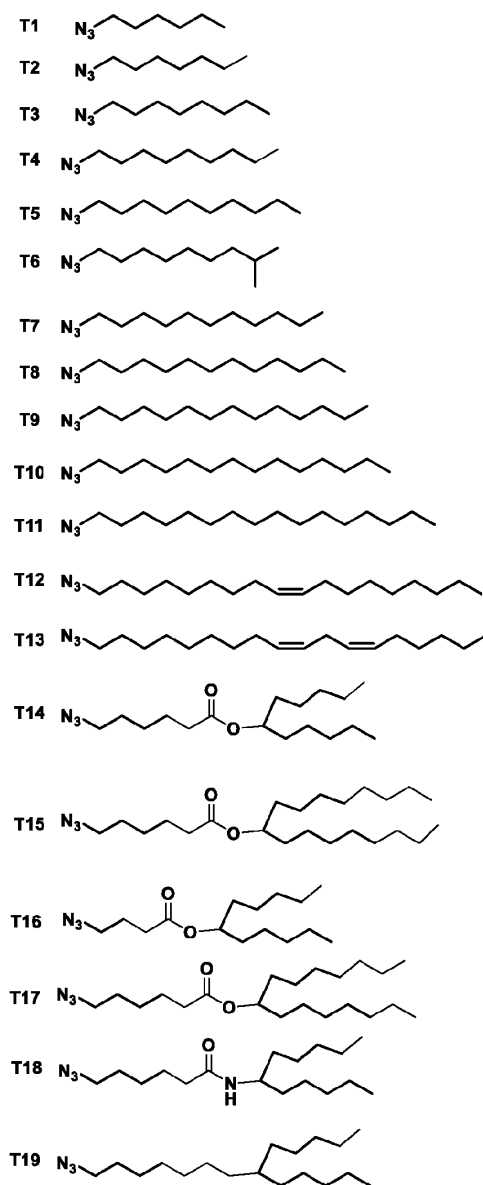


Table 2 (part 1)

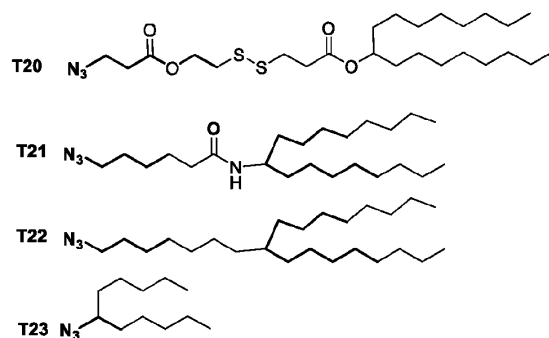
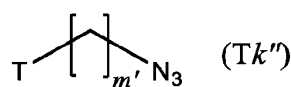


Table 2 (part 2)

[0301] Table 2 shows illustrative embodiments of azides that generate the moiety that

corresponds with the $\left(\begin{array}{c} \text{T} \\ \text{---} \end{array} \right)_{m'}$ moiety in Formula (G1.1) and in moieties LT in compounds of formula (G1.2). By way of illustration of the use of the terminology in such moiety and also in the azide notation



T1 is generated by the choice $m' = 0$ and $T = (\text{CH}_2)_5\text{CH}_3$, or by the choice $m' = 1$ and $T = (\text{CH}_2)_4\text{CH}_3$; T15 is generated by the choice $m' = 0$ and $T = (\text{CH}_2)_5\text{C}(\text{O})\text{OCH}((\text{CH}_2)_7\text{CH}_3)(\text{CH}_2)_7\text{CH}_3$ or $m' = 1$ and $T = (\text{CH}_2)_4\text{C}(\text{O})\text{OCH}((\text{CH}_2)_7\text{CH}_3)(\text{CH}_2)_7\text{CH}_3$; T23 is generated only by the choice $m' = 0$ and $T = \text{CH}((\text{CH}_2)_4\text{CH}_3)(\text{CH}_2)_4\text{CH}_3$.

[0302] The same Tk'' designation is used for the parent azide in Table 2 and for the corresponding moiety in the Ai''Lj''Tk'' compound for lipid embodiments in which the various Tk'' in lipid Ai''Lj''Tk'' are identical, which is as the notation Ai''Lj''Tk'' is to be interpreted herein, unless indicated otherwise. The same Tk'' designation is used for the parent azide in Table 2 and for the corresponding moiety in the LT moieties in compounds of formula (G1.2) for lipid embodiments in which the various Tk'' in LT moieties in compounds of formula (G1.2) are identical, which is as the corresponding notation in LT moieties in compounds of formula (G1.2) is to be interpreted herein, unless indicated otherwise.

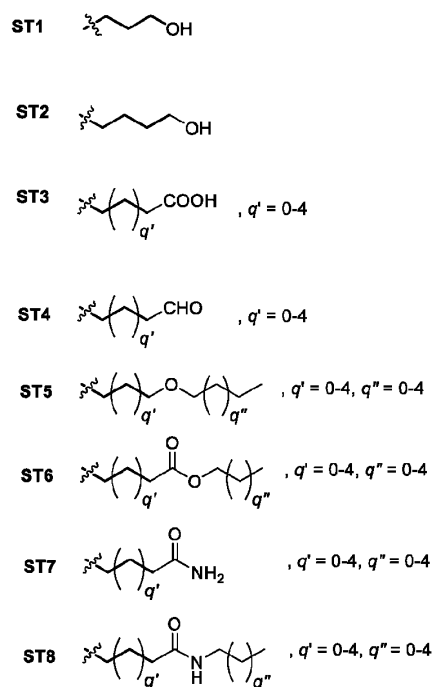


Table 2.1

[0303] Table 2.1 shows illustrative embodiments of moiety ST in Formula (G1.2). The notation  in reference to moieties listed in Table 2.1 means -CH₂. For example, ST1 is -CH₂CH₂CH₂OH; ST3 when $q' = 0$ is -CH₂-CH₂-COOH, and the same convention applies to ST1-ST8 in Table 2.1.

[0304] The tabular summary shown in Table C1 (parts 1 and 2) refers to compounds of formulae $A_i''L_j''Tk''$ with $k'' = 1-15$, $j'' = 1$, and i'' as indicated therein, as illustrative embodiments of compounds of formula (G1.1).

Table C1

[0305] This table (parts 1 and 2) shows in a tabular arrangement 510 compound designations that correspond to compounds $A_i''L_j''Tk''$ with $k'' = 1-15$, $j'' = 1$, and i'' as indicated therein, made as illustrative embodiments of compounds of formula (G1.1).

Table C1 (part 1)

	T1	T2	T3	T4	T5	T6	T7
A1L1	A1L1T1	A1L1T2	A1L1T3	A1L1T4	A1L1T5	A1L1T6	A1L1T7
A2L1	A2L1T1	A2L1T2	A2L1T3	A2L1T4	A2L1T5	A2L1T6	A2L1T7
A3L1	A3L1T1	A3L1T2	A3L1T3	A3L1T4	A3L1T5	A3L1T6	A3L1T7
A4L1	A4L1T1	A4L1T2	A4L1T3	A4L1T4	A4L1T5	A4L1T6	A4L1T7
A5L1	A5L1T1	A5L1T2	A5L1T3	A5L1T4	A5L1T5	A5L1T6	A5L1T7
A6L1	A6L1T1	A6L1T2	A6L1T3	A6L1T4	A6L1T5	A6L1T6	A6L1T7
A7L1	A7L1T1	A7L1T2	A7L1T3	A7L1T4	A7L1T5	A7L1T6	A7L1T7
A8L1	A8L1T1	A8L1T2	A8L1T3	A8L1T4	A8L1T5	A8L1T6	A8L1T7
A9L1	A9L1T1	A9L1T2	A9L1T3	A9L1T4	A9L1T5	A9L1T6	A9L1T7
A11L1	A11L1T1	A11L1T2	A11L1T3	A11L1T4	A11L1T5	A11L1T6	A11L1T7
A12L1	A12L1T1	A12L1T2	A12L1T3	A12L1T4	A12L1T5	A12L1T6	A12L1T7
A14L1	A14L1T1	A14L1T2	A14L1T3	A14L1T4	A14L1T5	A14L1T6	A14L1T7
A16L1	A16L1T1	A16L1T2	A16L1T3	A16L1T4	A16L1T5	A16L1T6	A16L1T7
A17L1	A17L1T1	A17L1T2	A17L1T3	A17L1T4	A17L1T5	A17L1T6	A17L1T7
A18L1	A18L1T1	A18L1T2	A18L1T3	A18L1T4	A18L1T5	A18L1T6	A18L1T7
A19L1	A19L1T1	A19L1T2	A19L1T3	A19L1T4	A19L1T5	A19L1T6	A19L1T7
A20L1	A20L1T1	A20L1T2	A20L1T3	A20L1T4	A20L1T5	A20L1T6	A20L1T7
A21L1	A21L1T1	A21L1T2	A21L1T3	A21L1T4	A21L1T5	A21L1T6	A21L1T7
A22L1	A22L1T1	A22L1T2	A22L1T3	A22L1T4	A22L1T5	A22L1T6	A22L1T7
A23L1	A23L1T1	A23L1T2	A23L1T3	A23L1T4	A23L1T5	A23L1T6	A23L1T7
A24L1	A24L1T1	A24L1T2	A24L1T3	A24L1T4	A24L1T5	A24L1T6	A24L1T7
A25L1	A25L1T1	A25L1T2	A25L1T3	A25L1T4	A25L1T5	A25L1T6	A25L1T7
A26L1	A26L1T1	A26L1T2	A26L1T3	A26L1T4	A26L1T5	A26L1T6	A26L1T7
A27L1	A27L1T1	A27L1T2	A27L1T3	A27L1T4	A27L1T5	A27L1T6	A27L1T7
A28L1	A28L1T1	A28L1T2	A28L1T3	A28L1T4	A28L1T5	A28L1T6	A28L1T7
A29L1	A29L1T1	A29L1T2	A29L1T3	A29L1T4	A29L1T5	A29L1T6	A29L1T7
A30L1	A30L1T1	A30L1T2	A30L1T3	A30L1T4	A30L1T5	A30L1T6	A30L1T7
A31L1	A31L1T1	A31L1T2	A31L1T3	A31L1T4	A31L1T5	A31L1T6	A31L1T7
A32L1	A32L1T1	A32L1T2	A32L1T3	A32L1T4	A32L1T5	A32L1T6	A32L1T7
A33L1	A33L1T1	A33L1T2	A33L1T3	A33L1T4	A33L1T5	A33L1T6	A33L1T7
A34L1	A34L1T1	A34L1T2	A34L1T3	A34L1T4	A34L1T5	A34L1T6	A34L1T7
A35L1	A35L1T1	A35L1T2	A35L1T3	A35L1T4	A35L1T5	A35L1T6	A35L1T7
A36L1	A36L1T1	A36L1T2	A36L1T3	A36L1T4	A36L1T5	A36L1T6	A36L1T7
A37L1	A37L1T1	A37L1T2	A37L1T3	A37L1T4	A37L1T5	A37L1T6	A37L1T7

Table C1 (part 2)

	T8	T9	T10	T11	T12	T13	T14	T15
A1L1	A1L1T8	A1L1T9	A1L1T10	A1L1T11	A1L1T12	A1L1T13	A1L1T14	A1L1T15
A2L1	A2L1T8	A2L1T9	A2L1T10	A2L1T11	A2L1T12	A2L1T13	A2L1T14	A2L1T15
A3L1	A3L1T8	A3L1T9	A3L1T10	A3L1T11	A3L1T12	A3L1T13	A3L1T14	A3L1T15
A4L1	A4L1T8	A4L1T9	A4L1T10	A4L1T11	A4L1T12	A4L1T13	A4L1T14	A4L1T15
A5L1	A5L1T8	A5L1T9	A5L1T10	A5L1T11	A5L1T12	A5L1T13	A5L1T14	A5L1T15
A6L1	A6L1T8	A6L1T9	A6L1T10	A6L1T11	A6L1T12	A6L1T13	A6L1T14	A6L1T15
A7L1	A7L1T8	A7L1T9	A7L1T10	A7L1T11	A7L1T12	A7L1T13	A7L1T14	A7L1T15
A8L1	A8L1T8	A8L1T9	A8L1T10	A8L1T11	A8L1T12	A8L1T13	A8L1T14	A8L1T15
A9L1	A9L1T8	A9L1T9	A9L1T10	A9L1T11	A9L1T12	A9L1T13	A9L1T14	A9L1T15
A11L1	A11L1T8	A11L1T9	A11L1T10	A11L1T11	A11L1T12	A11L1T13	A11L1T14	A11L1T15
A12L1	A12L1T8	A12L1T9	A12L1T10	A12L1T11	A12L1T12	A12L1T13	A12L1T14	A12L1T15
A14L1	A14L1T8	A14L1T9	A14L1T10	A14L1T11	A14L1T12	A14L1T13	A14L1T14	A14L1T15
A16L1	A16L1T8	A16L1T9	A16L1T10	A16L1T11	A16L1T12	A16L1T13	A16L1T14	A16L1T15
A17L1	A17L1T8	A17L1T9	A17L1T10	A17L1T11	A17L1T12	A17L1T13	A17L1T14	A17L1T15
A18L1	A18L1T8	A18L1T9	A18L1T10	A18L1T11	A18L1T12	A18L1T13	A18L1T14	A18L1T15
A19L1	A19L1T8	A19L1T9	A19L1T10	A19L1T11	A19L1T12	A19L1T13	A19L1T14	A19L1T15
A20L1	A20L1T8	A20L1T9	A20L1T10	A20L1T11	A20L1T12	A20L1T13	A20L1T14	A20L1T15
A21L1	A21L1T8	A21L1T9	A21L1T10	A21L1T11	A21L1T12	A21L1T13	A21L1T14	A21L1T15
A22L1	A22L1T8	A22L1T9	A22L1T10	A22L1T11	A22L1T12	A22L1T13	A22L1T14	A22L1T15
A23L1	A23L1T8	A23L1T9	A23L1T10	A23L1T11	A23L1T12	A23L1T13	A23L1T14	A23L1T15
A24L1	A24L1T8	A24L1T9	A24L1T10	A24L1T11	A24L1T12	A24L1T13	A24L1T14	A24L1T15
A25L1	A25L1T8	A25L1T9	A25L1T10	A25L1T11	A25L1T12	A25L1T13	A25L1T14	A25L1T15
A26L1	A26L1T8	A26L1T9	A26L1T10	A26L1T11	A26L1T12	A26L1T13	A26L1T14	A26L1T15
A27L1	A27L1T8	A27L1T9	A27L1T10	A27L1T11	A27L1T12	A27L1T13	A27L1T14	A27L1T15
A28L1	A28L1T8	A28L1T9	A28L1T10	A28L1T11	A28L1T12	A28L1T13	A28L1T14	A28L1T15
A29L1	A29L1T8	A29L1T9	A29L1T10	A29L1T11	A29L1T12	A29L1T13	A29L1T14	A29L1T15
A30L1	A30L1T8	A30L1T9	A30L1T10	A30L1T11	A30L1T12	A30L1T13	A30L1T14	A30L1T15
A31L1	A31L1T8	A31L1T9	A31L1T10	A31L1T11	A31L1T12	A31L1T13	A31L1T14	A31L1T15
A32L1	A32L1T8	A32L1T9	A32L1T10	A32L1T11	A32L1T12	A32L1T13	A32L1T14	A32L1T15
A33L1	A33L1T8	A33L1T9	A33L1T10	A33L1T11	A33L1T12	A33L1T13	A33L1T14	A33L1T15
A34L1	A34L1T8	A34L1T9	A34L1T10	A34L1T11	A34L1T12	A34L1T13	A34L1T14	A34L1T15
A35L1	A35L1T8	A35L1T9	A35L1T10	A35L1T11	A35L1T12	A35L1T13	A35L1T14	A35L1T15
A36L1	A36L1T8	A36L1T9	A36L1T10	A36L1T11	A36L1T12	A36L1T13	A36L1T14	A36L1T15
A37L1	A37L1T8	A37L1T9	A37L1T10	A37L1T11	A37L1T12	A37L1T13	A37L1T14	A37L1T15

[0306] Compounds of formulae (G1) may present multiple constitutional isomers because of any one, or a combination of, a plurality of molecular features.

[0307] In one of such instances constitutional isomers of formula (G1.1) are generated, for example, when $p > 1$, not all of the LT moieties are identical and the amino moiety A presents a molecular asymmetry (such as A4, that has four methylene units linearly disposed on one side of the central group NH (an N* site) and three methylene units linearly disposed on the other side of such NH group). In another illustrative instance, constitutional isomers of formula (G1.1) are generated, for example, when $p > 1$, the amino moiety A does not present a molecular asymmetry,

but different LT moieties may be bonded in different arrangements to the $N(*)^*$ and/or N^* sites in the amino moiety A. For example, when two identical LT moieties (say, LT' each) and other two identical moieties (say, LT'' each), with LT' being different from LT'' , bind to all the available sites of, for example A5, then two constitutional isomers may be generated even though A5 does not present a molecular asymmetry (one constitutional isomers having both LT' moieties bound to one terminal $N(*)^*$ center and both LT'' moieties bound to the other terminal $N(*)^*$ center, and the other constitutional isomer having one LT' and one LT'' moieties bound to one terminal $N(*)^*$ center and one LT' and one LT'' moieties bound to the other terminal $N(*)^*$ center).

[0308] As indicated above, specific compounds of formula (G1.2) are referred to with the notation $A_{i''}(ST)_q(LT)_p$, where $i'' = 1-12, 14, 16-29, 35-37$, and $(p + q)$ being equal to the number of binding sites in $A_{i''}$ (one for each N^* member and two for each $N(*)^*$ member in $A_{i''}$), with p and q being subject to the restrictions given above for compounds of formula (G1.2).

[0309] In another instance, constitutional isomers of formula (G1.2) are generated when $p \geq 1, q \geq 1$ in (G1.2) and the amino moiety A presents a molecular asymmetry (as illustratively indicated above in reference to A4) or not (as illustratively indicated above in reference to A5), with all the ST moieties ($q > 1$) being the same or different and/or all the LT moieties ($p > 1$) being the same or different. For example, a compound (G1.2) of formula $A4(L1T14)_3(ST1)_2$, with amino moiety A4, three L1T14 moieties, and two ST1 moieties, presents several constitutional isomers, such as

$A4(L1T14)_{1-1}(L1T14)_{2-4}(ST1)_{2-3(1)}$ (whose full structure is shown below),

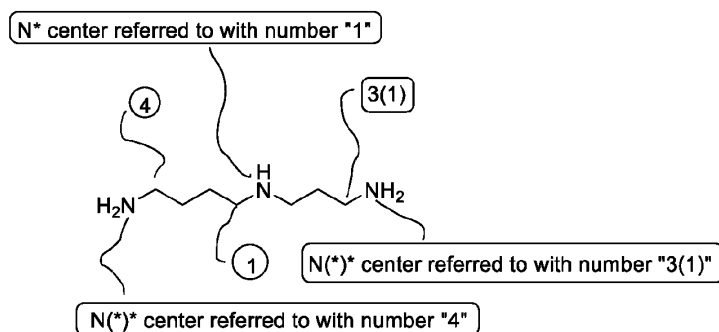
$A4(L1T14)_{1-1}(ST1)_{2-4}(L1T14)_{2-3(1)}$ (whose full structure is shown below),

$A4(ST1)_{1-1}(ST1)_{1-4}(L1T14)_{1-4}(L1T14)_{2-3(1)}$, and

$A4(L1T14)_{1-1}(ST1)_{1-4}(L1T14)_{1-4}(ST1)_{1-3(1)}(L1T14)_{1-3(1)}$.

[0310] In the foregoing $A4(L1T14)_3(ST1)_2$ constitutional isomers, each ST and LT moiety within parenthesis has an index with two parts, each part being separated by a hyphen. The number on the left of the hyphen indicates the number of such ST or LT moieties at the binding site specified by the part of the index on the right-hand side of the hyphen. Such part of the index on the right-hand side of the hyphen refers to the number of the C-member in the amine moiety (A4 in this example) when it is named according to the IUPAC convention. A single digit on the right-hand side of the hyphen refers to the number of a C-member in the parent chain in the

IUPAC nomenclature of A4 (and such number is assigned to the N(*)* or N* center bound to it), and a numerical term that has digit followed by another within parenthesis on the right-hand side of the hyphen refers to the number (digit preceding the parenthesis) of a C-member in a chain that is a substituent at the C-member in the parent chain indicated by the number within parenthesis (and such numerical term is assigned to the N(*)* or N* center bound to it). Accordingly, the name of A4 is N¹-(3-aminopropyl)butane-1,4-diamine, and the N(*)* and N* centers in it are assigned the numbers according to the foregoing convention as shown in the illustrative structure below:



A4 is N¹-(3-aminopropyl)butane-1,4-diamine

[0311] The 1-4 chain in the preceding figure is the parent chain according to IUPAC nomenclature, starting at methylene carbon 1 and ending at methylene carbon 4.

[0312] This nomenclature permits the listing of the LT and ST moieties in any order, while the named structure is definite. For example, the formulae

A4(L1T14)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎,

A4 (L1T14)₂₋₄(L1T14)₁₋₁(ST1)₂₋₃₍₁₎, and

A4(ST1)₂₋₃₍₁₎(L1T14)₁₋₁(L1T14)₂₋₄,

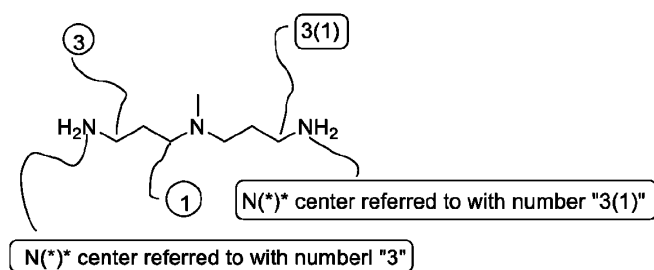
all refer to the same structure that has two ST1 moieties at the N(*)* center 3(1), one L1T14 moiety at the N* center 1, and two L1T14 moieties at the N(*)* center 4.

[0313] The indices generated according to the foregoing convention are thus the ones used in illustrative compounds A4(L1T14)_p(ST1)_q, with p and q defined as in formula (G1.2). Because the IUPAC nomenclature is of general knowledge and acceptance, one of ordinary skill in the art would be able to name any other of the constitutional isomers within the scope of (G1.2). The

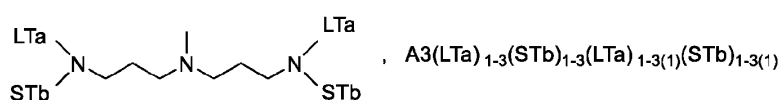
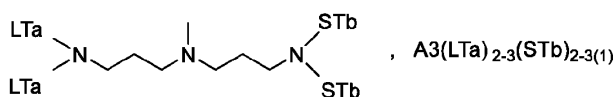
foregoing nomenclature convention presents the advantageous feature of being able to distinguish between identical terminal moieties in structurally symmetric amines. For example, even though A3 is symmetric with respect to the central tertiary amino moiety, the foregoing nomenclature permits distinguishing between the following (G1.2) constitutional isomers (each having (in this illustrative embodiment) two identical LTa moieties and two identical STb moieties, each chosen as indicated for LT and ST, respectively, in (G1.2))

A3(LTa)₂₋₃(STb)₂₋₃₍₁₎ and

A3(LTa)₁₋₃(STb)₁₋₃(LTa)₁₋₃₍₁₎(STb)₁₋₃₍₁₎, as shown in the illustrative structures below (where LTa represents an LT moiety and STb represents an ST moiety:



A3 is N¹-(3-aminopropyl)propane-1,3-diamine



Because the nomenclature defined above for (G1.2) constitutional isomers focuses on features of the amino moiety A, such nomenclature is analogously applicable to designate specific (G1.1) constitutional isomers and for compounds of formula (G1.1) that have a plurality of different LT moieties and each of such LT is to be specified the N* or N(*)* member to which it is bound.

[0314] As indicated above and as exemplified by the synthesis described below for illustrative embodiments of compounds of formula (G1.2), the synthesis part concerning the amino A and LT moieties in compounds of formula (G1.2) is analogous to that for compounds of formula (G1.1). As to the ST moieties in compounds of formula (G1.2), the synthesis proceeds through an initial amino moiety, or the preparation of the same. This initial amino moiety may correspond to the amino moiety A_i of the final compound $A_i(ST)_q(LT)_p$, or be part of it that is to be bound to ST moieties. In the latter case, once the ST moieties are substituting the desired positions, suitably protected when needed, the amino moiety that is substituted with such ST moieties (or ST precursors) that are suitably protected, is used to form the final amino moiety (through processes such as amine alkylation) while leaving N^* and/or $N(^*)^*$ members in it available for the desired reactions with linkers such as L1, L2, L3.A and L3.X, and subsequently with T_k azides to form therein the LT moiety(ies) as in the synthesis of (G1.1) compounds, following with a deprotection of the ST moieties at the end of the process or at a convenient intermediate step.

[0315] Checked embodiments of compounds of formula (G1.1) in salt-free form exhibited purity above 85% by HPLC, and it was determined by ELSD, LCMS to be in the range of 86% to 100% with an average purity of $94\% \pm 5\%$. Illustrative embodiments of such purity determinations are provided in Table 3.

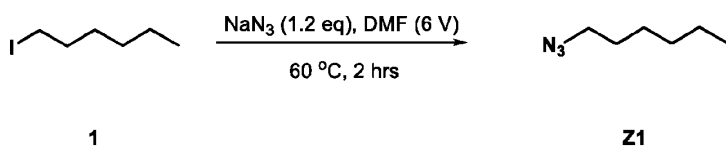
Compound ID	Purity (ELSD, LCMS)	Net Weight	Salt Type	Physical Property
A6L1T2	97%	200 mg	free	Yellow oil
A12L1T2	100%	200 mg	free	yellow oil
A14L1T2	87%	200 mg	free	Yellow oil
A22L1T7	100%	200 mg	free	yellow solid
A11L1T11	100%	200 mg	Free	Off-white solid
A23L1T8	88%	200 mg	free	Yellow solid
A24L1T12	95%	200 mg	free	Yellow solid
A26L1T9	100%	200 mg	free	Yellow oil
A28L1T4	87%	200 mg	free	Yellow solid
A29L1T7	100%	200 mg	free	Yellow solid
A35L1T5	98.36%	200 mg	Free	Brown solid
A36L1T6	86.71%	200 mg	Free	Brown solid
A2L1T2	100%	200 mg	free	Yellow oil
A3L1T3	95.7%	200 mg	free	Yellow oil

A8L1T8	92.2%	200 mg	free	Brown solid
A7L1T7	96.9%	210 mg	free	Brown solid
A16L1T1	94.3%	210 mg	free	Brown solid
A18L1T3	96.69%	200 mg	free	Yellow oil
A19L1T4	92.13%	200 mg	free	Yellow oil
A20L1T3	86.01%	200 mg	free	Yellow oil
A30L1T13	87.9%	200 mg	free	Yellow oil
A31L1T14	91.9%	200 mg	free	Yellow oil
A33L1T6	95.9%	200 mg	free	Yellow oil

Table 3

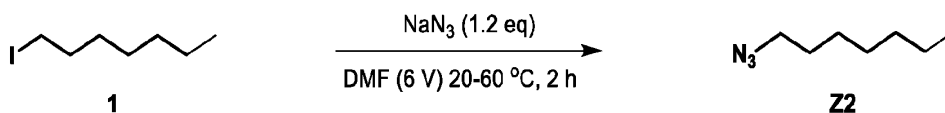
[0316] By way of illustration, but not as limitation, examples below with preparation information illustrate the syntheses of the parent compounds and their derived moieties in a variety of $A_i''L_j''Tk''$ and $A_i''(ST)_q(LT)_p$ compounds that exemplify compounds of formulae (G1). Most of the lipids referred to in the tabular summary shown in Table C1 (parts 1 and 2) and elsewhere in the specification and drawings, with the designation described above and whose preparation is not described herein, were prepared according to synthesis methods analogous to those described below. Some of them have not yet actually been prepared, although synthesis schemes have been designed. Note that the full recitation of the synthesis of such compounds of formulae (G1) would be analogous to the synthesis recitations and schemes provided below for illustrative compounds of formulae (G1). Such cumulative information that may be generated with the teachings disclosed herein and the ordinary skill in the art is not provided here. Compounds that were synthesized, but whose syntheses are not presented herein explicitly, include compounds named in parts of this specification and drawings where physical, chemical and/or biochemical characteristics of such compounds are disclosed, either because they have been employed in standard experiments or tests referred to herein or because they have been used in tests or assays herein described (for example, compounds used to generate *in vivo* mRNA delivery test data presented below and in the drawings). See also general references on azide-alkyne click chemistry cited above, chemical reactions referred to above, and reactions explicitly set forth in the following Examples.

Example AZ1



[0317] Azide Z1 is designated as azide T1 in Table 2. To a solution of compound 1 in this Example AZ1 (25 g, 117.89 mmol, 17.42 mL, 1 eq) in DMF (150 mL) was slowly added NaN₃ (9.20 g, 141.46 mmol, 1.2 eq) in batches. The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f=0.58) showed reactant was used up. The reaction mixture was quenched by addition H₂O 1000 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. Added 100 ml t-BuOH and concentrated in vacuum at 30 °C. Compound Z1 (46.4 g, 94.12 mmol, 79.84% yield, 25.8% purity) was obtained as colorless oil. 12.0 g in a solution of t-BuOH (60 ml). ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.26 (t, *J* = 7.0 Hz, 2H), 1.60 (quin, *J* = 7.2 Hz, 2H), 1.34 - 1.28 (m, 6H), 0.93 - 0.86 (m, 3H).

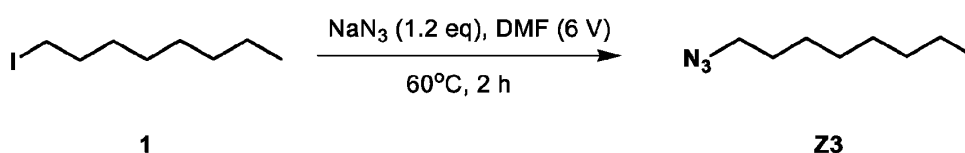
Example AZ2



[0318] Azide Z2 is designated as azide T2 in Table 2. To a solution of compound 1 in this Example AZ2 (20 g, 88.46 mmol, 1 eq) in DMF (120 mL) was added NaN₃ (6.90 g, 106.15 mmol, 1.2 eq). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether/Ethyl acetate = 1/0, product R_f = 0.55) showed compound 1 was used up. The reaction mixture was quenched by addition H₂O 400 mL at 20 °C, and extracted with n-hexane 300 mL. The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue and added t-BuOH (5V) to the residue. The extracted water was prepared into dilute aqueous solution with a ratio of more than 1:50 (aqueous phase: water). After cooling in ice bath, saturated sodium hypochlorite (NaClO) solution was slowly

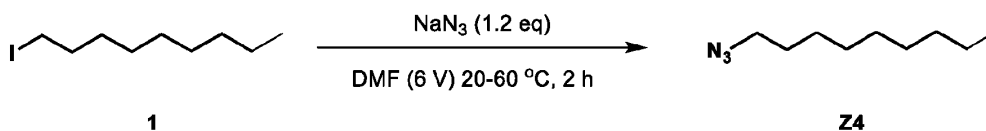
dropped into the solution under stirring. About 20 mL NaClO solution was needed to quench 1 g sodium azide, and the solution was left to stand overnight after stirring. The crude product was purified by silica gel chromatography eluted with PE/EtOAc = 1/0 to give product. Compound Z2 (45 g, 84.92 mmol, 83.48% yield, 26.65% purity) was obtained as colorless oil. 12.0 g in a solution of t-BuOH (58 mL). ¹H NMR: (400 MHz CDCl₃) δ ppm 3.24 (t, *J* = 7.0 Hz, 2H), 1.64 - 1.55 (m, 2H), 1.52 (s, 7H), 1.26 (s, 47H), 0.93 - 0.83 (m, 3H).

Example AZ3



[0319] Azide Z3 is designated as azide T3 in Table 2. To a solution of compound 1 in this Example AZ3 (21.6 g, 89.95 mmol, 1 eq) in DMF (130 mL) was added NaN₃ (7.02 g, 107.94 mmol, 1.2 eq). The mixture was stirred at 60°C for 2 h. TLC(Petroleum ether : Ethyl acetate=20:1, *R_f*-sm=0.83, *R_f*-product = 0.5) showed reactant was used up. The reaction mixture was quenched by addition H₂O 500 mL at 20 °C, and extracted with n-hexane 100*2 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered under reduced pressure to give crude reaction mixture. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. Compound Z3 (62.2 g, crude) (in t-BuOH) was obtained as colorless oil. The converted mass is about 11.3 g. ¹H NMR: (400 MHz CDCl₃) δ ppm 3.21 (t, *J* = 6.9 Hz, 2H), 1.55 (quin, *J* = 7.1 Hz, 2H), 1.36 - 1.25 (m, 8H), 0.84 (t, *J* = 6.5 Hz, 5H).

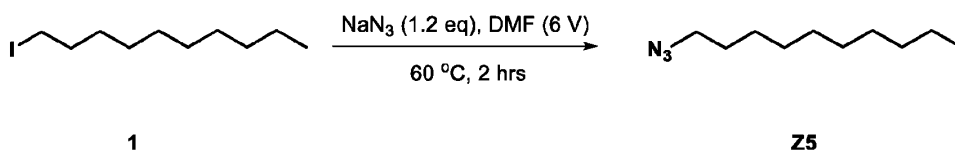
Example AZ4



[0320] Azide Z4 is designated as azide T4 in Table 2. To a solution of compound 1 in this Example AZ4 (20 g, 78.69 mmol, 1 eq) in DMF (120 mL) was added NaN₃ (6.14 g, 94.43 mmol,

1.2 eq). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether: Ethyl acetate=1:0, product R_f =0.45) indicated compound **1** was consumed completely. The reaction mixture was quenched by addition H₂O 1000 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The reaction mixture was extracted by adding t-BuOH (115 mL), reducing pressure and concentrating to get the product. Compound **Z4** (50.1 g, 69.44 mmol, 76.73% yield, 23.46% purity). 12.2 g in a solution of t-BuOH (64 mL) was obtained as a Brown oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 3.25 (br t, J = 6.5 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.34 (br s, 6H), 0.97 - 0.78 (m, 3H).

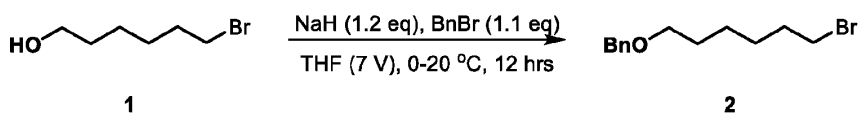
Example AZ5



[0321] Azide **Z5** is designated as azide **T5** in Table 2. To a solution of compound **1** in this Example AZ5 (20 g, 74.58 mmol, 1 eq) in DMF (120 mL) was slowly added NaN₃ (5.82 g, 89.49 mmol, 1.2 eq) in batches. The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f =0.58) showed reactant was used up. The reaction mixture was quenched by addition H₂O 300 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound **Z5** (14.4 g, 78.56 mmol, 91.60% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.26 (t, J = 7.0 Hz, 2H), 1.67 - 1.56 (m, 2H), 1.44 - 1.21 (m, 14H), 0.89 (t, J = 6.8 Hz, 3H).

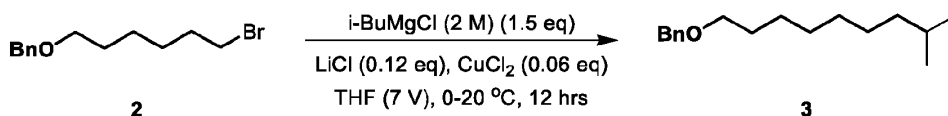
Example AZ6

Example AZ6.1



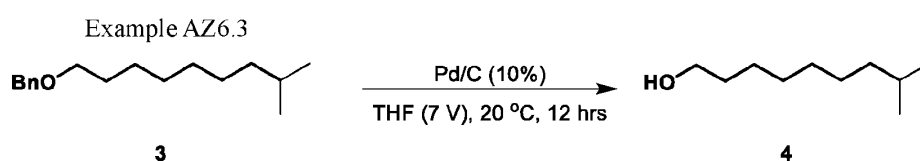
[0322] To a solution of compound 1 in this Example AZ6 (54 g, 298.23 mmol, 39.02 mL, 1 eq) in THF (378 mL). The solution was then cooled to 0 °C, and NaH (14.31 g, 357.87 mmol, 60% purity, 1.2 eq) was added followed by BnBr (56.11 g, 328.05 mmol, 38.96 mL, 1.1 eq). The mixture was stirred at 20 °C for 12 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f=0.5) showed reactant was used up. The reaction mixture was quenched by addition H₂O 400 mL at 20 °C, and extracted with EtOAc 400 mL. The combined organic layers were washed with brine 50 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0~200/1). Compound 2 (54 g, 199.12 mmol, 66.77% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 7.37 - 7.33 (m, 4H), 7.32 - 7.27 (m, 1H), 4.52 (s, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 1.88 (quin, *J* = 6.9 Hz, 2H), 1.69 - 1.60 (m, 2H), 1.51 - 1.38 (m, 4H).

Example AZ6.2

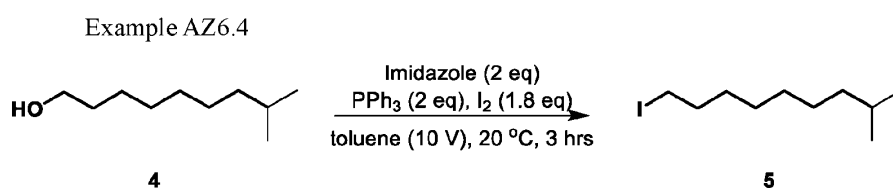


[0323] Compound 2 (66 g, 243.37 mmol, 1 eq) was dissolved in THF (462 mL). The solution was then cooled to 0 °C and a solution of [prepared from LiCl (1.24 g, 29.20 mmol, 598.69 μL, 0.12 eq) and CuCl₂ (1.96 g, 14.60 mmol, 0.06 eq) in THF (30 mL) was added followed by dropwise addition of bromo(isobutyl) magnesium (0.6 M, 608.42 mL, 1.5 eq). The solution was stirred at 0 °C for 1 h and then stirred at 20 °C for 11 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f=0.41) showed reactant was used up. The reaction mixture was quenched by addition NH₄Cl 600 mL at 20 °C, and extracted with EtOAc 600 mL. The combined organic layers were washed with brine 500 mL, dried over Na₂SO₄, filtered and concentrated

under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0~100/1). Compound **3** (57 g, 229.47 mmol, 72.53% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 7.26 (d, J = 4.4 Hz, 4H), 7.21 - 7.14 (m, 1H), 4.42 (s, 2H), 3.42 - 3.35 (m, 2H), 1.58 - 1.49 (m, 2H), 1.43 (br dd, J = 6.7, 13.4 Hz, 1H), 1.33 - 1.25 (m, 2H), 1.25 - 1.12 (m, 6H), 1.12 - 1.03 (m, 2H), 0.79 (d, J = 6.6 Hz, 6H).



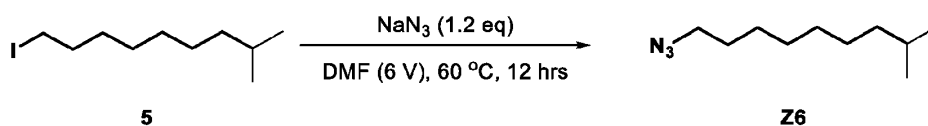
[0324] Compound **3** (57 g, 229.47 mmol, 1 eq) was dissolved in EtOH (500 mL). The solution was added Pd/C (5.70 g, 5.36 mmol, 10% purity, 2.33e-2 eq). The solution was stirred under 50 Psi at 25 °C for 12 h. TLC (Petroleum ether : Ethyl acetate=5:1, product R_f=0.25) showed reactant was used up. Reaction liquid filtration. The filter liquor was concentrated in vacuo. The filter cake is recycled to the corresponding recycling bucket. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0~200/1~50/1). Compound **4** (31 g, 195.86 mmol, 85.35% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.70 - 3.60 (m, 2H), 1.63 - 1.47 (m, 3H), 1.40 - 1.22 (m, 9H), 1.20 - 1.11 (m, 2H), 0.87 (d, J = 6.7 Hz, 6H).



[0325] Compound **4** (30 g, 189.54 mmol, 1 eq) were dissolved in Tol. (300 mL) and imidazole (25.81 g, 379.07 mmol, 2 eq), molecular iodine (86.59 g, 341.17 mmol, 68.72 mL, 1.8 eq) and triphenylphosphane (99.43 g, 379.07 mmol, 2 eq) were slowly added to the solution. The reaction mixture was stirred for 12 h at 20 °C. TLC (Petroleum ether : Ethyl acetate=20:1, product

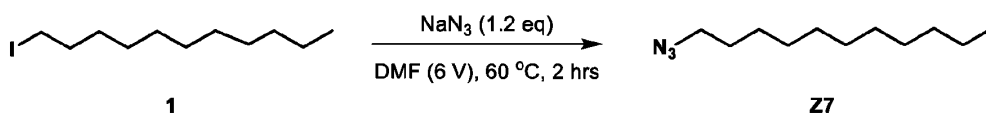
R_f=0.78) showed reactant was used up. The reaction mixture was quenched by addition Na₂S₂O₃ 500 mL at 20 °C, and extracted with EtOAc 500 mL. The combined organic layers were washed with brine 500 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound **5** (31 g, 115.60 mmol, 60.99% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.20 (t, J = 7.1 Hz, 2H), 1.83 (quin, J = 7.2 Hz, 2H), 1.59 - 1.46 (m, 1H), 1.44 - 1.35 (m, 2H), 1.34 - 1.23 (m, 6H), 1.16 (q, J = 6.7 Hz, 2H), 0.87 (d, J = 6.6 Hz, 6H).

Example AZ6.5



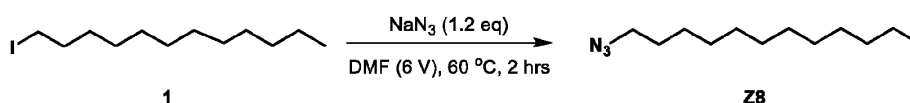
[0326] Azide Z6 is designated as azide T6 in Table 2. To a solution of compound **5** (28 g, 104.41 mmol, 1 eq) in DMF (168 mL) was slowly added NaN₃ (8.15 g, 125.29 mmol, 1.2 eq) in batches. The mixture was stirred at 60 °C for 1 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f=0.60) showed reactant was used up. The reaction mixture was quenched by addition H₂O 1000 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound Z6 (16 g, 87.29 mmol, 76.01% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.27 (t, J = 7.0 Hz, 2H), 1.67 - 1.46 (m, 3H), 1.42 - 1.24 (m, 8H), 1.16 (q, J = 6.7 Hz, 2H), 0.87 (d, J = 6.6 Hz, 6H).

Example AZ7



[0327] Azide Z7 is designated as azide T7 in Table 2. To a solution of compound 1 in this Example AZ7 (20 g, 70.87 mmol, 1 *eq*) in DMF (120 mL) was added NaN₃ (5.53 g, 85.05 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether/Ethyl acetate = 20/1, product R_f = 0.48) showed reactant was used up. The reaction mixture was quenched by addition H₂O 400 mL at 20 °C, and extracted with n-hexane 300 mL. The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The extracted water was prepared into dilute aqueous solution with a ratio of more than 1:50 (aqueous phase: water). After cooling in ice bath, saturated sodium hypochlorite (NaClO) solution was slowly dropped into the solution under stirring. About 200 mL NaClO solution was needed to quench 1 g sodium azide, and the solution was left to stand overnight after stirring. The crude product was purified by silica gel chromatography eluted with PE/EtOAc = 1/0. Compound Z7 (13.70 g, 69.43 mmol, 97.97% yield) was obtained as colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 3.26 (t, *J* = 7.0 Hz, 2H), 1.42 - 1.20 (m, 18H), 0.89 (t, *J* = 6.8 Hz, 3H).

Scheme AZ8

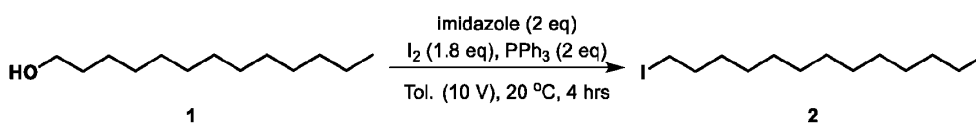


[0328] Azide Z8 is designated as azide T8 in Table 2. To a solution of compound 1 in this Example AZ8 (20 g, 67.52 mmol, 1 *eq*) in DMF (120 mL) was added NaN₃ (5.27 g, 81.02 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether/Ethyl acetate = 1/0, product R_f = 0.64) showed reactant was used up. The reaction mixture was quenched by addition H₂O 400 mL at 20 °C, and extracted with n-hexane 300 mL. The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The extracted water was prepared into dilute aqueous solution with a ratio of more than 1:50 (aqueous phase: water). After cooling in ice bath, saturated sodium hypochlorite (NaClO) solution was slowly dropped into the solution under stirring. About 200 mL NaClO solution was needed to quench 1 g sodium azide, and the solution was left to stand overnight after stirring. The crude product was purified by silica gel chromatography eluted with PE/EtOAc = 1/0 to give product. Compound Z8 (14.1 g, 66.72 mmol, 85.93% yield) was obtained as colorless oil.

^1H NMR: (400 MHz CDCl_3) δ ppm 3.32 - 3.20 (m, 2H), 1.67 - 1.51 (m, 2H), 1.41 - 1.22 (m, 18H), 0.95 - 0.83 (m, 3H).

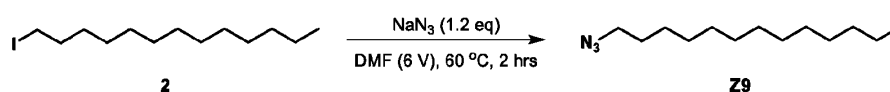
Example AZ9

Example AZ9.1



[0329] To a solution of compound 1 in this Example AZ9.1 (23 g, 114.79 mmol, 1 eq) in toluene (230 mL), imidazole (8.61 g, 126.50 mmol, 1.10 eq), I_2 (52.44 g, 206.63 mmol, 41.62 mL, 1.8 eq), PPh_3 (60.22 g, 229.59 mmol, 2 eq) were slowly added to the solution. The reaction mixture was stirred for 3 h at 20 °C. TLC (Petroleum ether/Ethyl acetate = 20/1, PMA, product R_f = 0.70) showed reactant was used up. The reaction mixture was diluted with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (400 mL) and ethyl acetate (400 mL $\times$ 3), the organic phases were extracted and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (column height: 500 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/0 to 10/1). Compound 2 (37 g, 119.26 mmol, 95.57% yield) as colorless oil. ^1H NMR: (400 MHz, CDCl_3) δ ppm 3.20 (t, $J=7.09$ Hz, 2 H) 1.83 (quin, $J=7.15$ Hz, 2 H) 1.36 - 1.45 (m, 2 H) 1.17 - 1.32 (m, 18 H) 0.89 (t, $J=6.72$ Hz, 3 H).

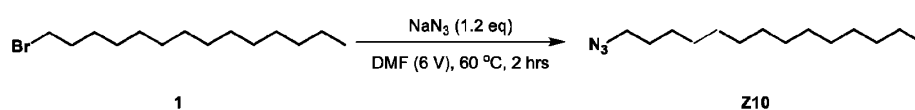
Example AZ9.2



[0330] Azide Z9 is designated as azide T9 in Table 2. To a solution of compound 2 in this Example AZ9.2 (34 g, 109.59 mmol, 1 eq) in DMF (204 mL) was slowly added NaN_3 (8.55 g, 131.50 mmol, 1.2 eq) in batches. The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f =0.50) showed reactant was used up. The reaction mixture was quenched by addition H_2O 1000 mL at 20 °C and extracted with n-hexane 100 $\times$ 2 mL. The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4 , filtered and

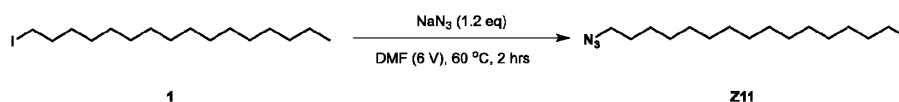
concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound Z9 (22 g, 97.62 mmol, 81.72% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 3.26 (t, *J* = 7.0 Hz, 2H), 1.66 - 1.55 (m, 2H), 1.27 (s, 20H), 0.89 (t, *J* = 6.7 Hz, 3H).

Example AZ10



[0331] Azide Z10 is designated as azide T10 in Table 2. To a solution of compound 1 in this Example AZ10 (20 g, 72.13 mmol, 21.51 mL, 1 *eq*) in DMF (120 mL) was added NaN₃ (5.63 g, 86.55 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether: Ethyl acetate=1:0, product R_f=0.45) indicated compound **1** was consumed completely. The reaction mixture was quenched by addition H₂O 1000 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound Z10 (13.74 g, 57.39 mmol, 79.57% yield) was obtained as a colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 3.18 (t, *J* = 7.0 Hz, 2H), 1.53 (quin, *J* = 7.2 Hz, 2H), 1.31 - 1.17 (m, 22H), 0.87 - 0.74 (m, 3H).

Example AZ11

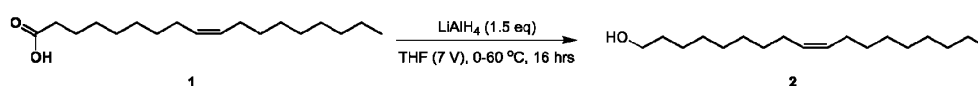


[0332] Azide Z11 is designated as azide T11 in Table 2. To a solution of compound 1 in this Example AZ11 (20 g, 56.76 mmol, 1 *eq*) in DMF (120 mL) was added NaN₃ (4.43 g, 68.12 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether:

Ethyl acetate=1:0, product $R_f=0.45$) indicated compound **1** was consumed completely. The reaction mixture was quenched by addition H_2O 1000 mL at 20 °C and extracted with *n*-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1/0). Compound **Z11** (13.8 g, 51.64 mmol, 79.10% yield) was obtained as a colorless oil. 1H NMR: (400 MHz $CDCl_3$) δ ppm 3.33 - 3.21 (m, 2H), 1.72 - 1.53 (m, 2H), 1.29 (br s, 26H), 1.00 - 0.83 (m, 3H).

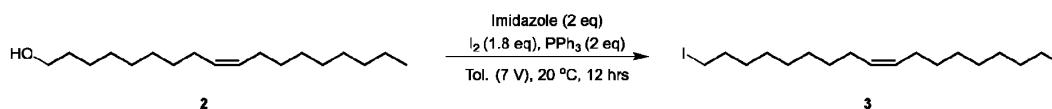
Example AZ12

Example AZ12.1



[0333] Compound **1** in this Example AZ12.1 (20 g, 70.81 mmol, 20.00 mL, 1 eq) were dissolved in THF (140 mL) and added dropwise to a cooled suspension (0 °C) of $LiAlH_4$ (38.39 g, 106.21 mmol, 38.4 mL, 10.5% purity, 1.5 eq). The mixture was refluxed (60 °C) for 1 h and then stirred 16 h at 25 °C. TLC (Petroleum ether/Ethyl acetate = 5/1, product $R_f = 0.51$) showed reactant was used up. Dilute with appropriate amount of THF and cool to 0 °C, slowly add 4 mL water, add 4 mL sodium hydroxide solution of 15%, then add 12 mL water, heat up to room temperature and stir for 15 minutes, add some anhydrous $MgSO_4$, stir for 15 minutes, filter and remove salt. The crude product was purified by silica gel chromatography eluted with PE: EtOAc=5:1 to give product as colorless oil. Compound **2** in this Example AZ12.1 (25 g, crude) was obtained as colorless oil. 1H NMR: (400 MHz $CDCl_3$) δ ppm 5.46 - 5.23 (m, 2H), 3.64 (t, $J = 6.6$ Hz, 2H), 2.12 - 1.95 (m, 4H), 1.64 - 1.49 (m, 2H), 1.46 - 1.07 (m, 22H), 0.98 - 0.79 (m, 3H).

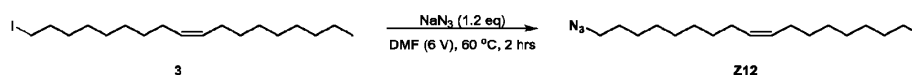
Example AZ12.2



[0334] Compound **2** in this Example AZ12.2 (25 g, 93.12 mmol, 1 eq) were dissolved in Tol. (175 mL) and imidazole (12.68 g, 186.24 mmol, 2 eq), I_2 (42.54 g, 167.61 mmol, 33.76 mL,

1.8 *eq*) and PPh₃ (48.85 g, 186.24 mmol, 2 *eq*) were slowly added to the solution. The reaction mixture was stirred for 2 hours at 20°C. TLC (Petroleum ether: Ethyl acetate = 5:1, product R_f = 0.9) showed reactant was used up. After addition of saturated Na₂S₂O₃ solution (500 mL) and ethyl acetate (200 mL*3), the organic phases were extracted and washed with brine (300 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EtOAc = 1:0 to give product as colorless oil. Compound 3 in this Example AZ12.2 (17 g, 44.93 mmol, 44.27% yield) was obtained as colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 5.36 (td, *J* = 2.9, 5.9 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.02 (br d, *J* = 6.0 Hz, 4H), 1.83 (s, 2H), 1.29 (br d, *J* = 11.3 Hz, 22H), 0.89 (s, 3H).

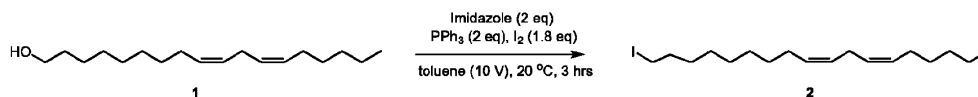
Example AZ12.3



[0335] Azide Z12 is designated as azide T12 in Table 2. To a solution of compound 3 in this Example AZ12.3 (13 g, 34.36 mmol, 1 *eq*) in DMF (78 mL) was added NaN₃ (2.68 g, 41.23 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether: Ethyl acetate = 1:0, product R_f = 0.24) showed a new signal point is generated and a small amount of reactant is left. The reaction mixture was quenched by addition H₂O 400 mL at 20 °C, and extracted with n-hexane 300 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The extracted water was prepared into dilute aqueous solution with a ratio of more than 1:50 (aqueous phase: water). After cooling in ice bath, saturated sodium hypochlorite (NaClO) solution was slowly dropped into the solution under stirring. About 20 mL NaClO solution was needed to quench 1 g sodium azide, and the solution was left to stand overnight after stirring. The crude product was purified by silica gel chromatography eluted with PE: EtOAc=1:0 to give product as colorless oil. Compound Z12 (10 g, 34.07 mmol, 99.17% yield) was obtained as colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 5.36 (ddd, *J* = 2.6, 3.3, 5.8 Hz, 2H), 3.26 (t, *J* = 7.0 Hz, 2H), 2.12 - 1.94 (m, 4H), 1.67 - 1.54 (m, 2H), 1.30 (br d, *J* = 13.6 Hz, 22H), 0.93 - 0.85 (m, 3H).

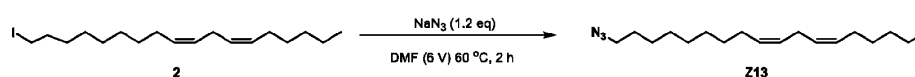
Example AZ13

Example AZ13.1



[0336] To a solution of compound 1 in this Example AZ13.1 (25 g, 93.82 mmol, 1 eq) were dissolved in toluene (250 mL) and imidazole (12.77 g, 187.65 mmol, 2 eq), I₂ (42.86 g, 168.88 mmol, 34.02 mL, 1.8 eq) and PPh₃ (49.22 g, 187.65 mmol, 2 eq) were slowly added to the solution. The reaction mixture was stirred for 3 h at 20 °C. TLC (Petroleum ether/Ethyl acetate=1/0, phosphomolybdic acid, product R_f=0.55) showed product formation and reactant was used up. TLC showed that the reaction was over. After addition of saturated Na₂S₂O₃ solution, the aqueous phase was extracted with EA (250 mL*3). The combined organic phase was washed with brine (250 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 500 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=1/0 to 1/1). Compound 2 in this Example AZ13.1 (31 g, 82.37 mmol, 87.79% yield) was obtained as colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 5.44 - 5.30 (m, 4H), 3.20 (t, J = 7.0 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.06 (q, J = 7.0 Hz, 4H), 1.88 - 1.79 (m, 2H), 1.39 - 1.26 (m, 16H), 0.90 (t, J = 6.8 Hz, 3H).

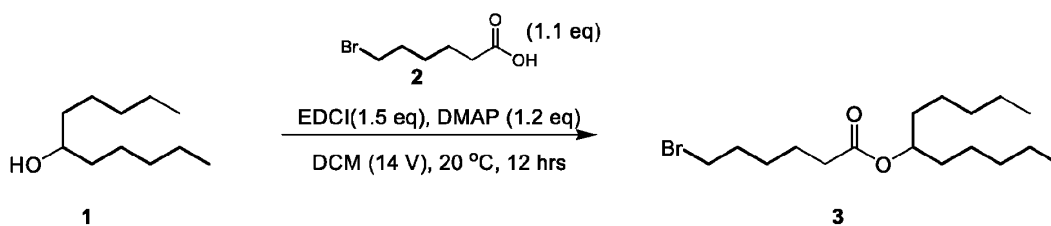
Example AZ13.2



[0337] Azide Z13 is designated as azide T13 in Table 2. To a solution of compound 2 in this Example AZ13.2 (27 g, 71.74 mmol, 1 eq) in DMF (162 mL) was added NaN₃ (5.60 g, 86.09 mmol, 1.2 eq). The mixture was stirred at 60°C for 2 h. TLC (Petroleum ether: Ethyl acetate=1:0, product R_f=0.45) indicated compound 2 was consumed completely. The reaction mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound Z13 (15.77 g, 54.10 mmol, 67.94% yield), was obtained as a colorless oil ¹H NMR: (400 MHz CDCl₃) δ ppm 5.42 - 5.19 (m, 4H), 3.19 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 6.4 Hz, 2H), 1.98 (q, J = 6.7 Hz, 4H), 1.58 - 1.45 (m, 2H), 1.33 - 1.19 (m, 16H), 0.82 (t, J = 6.7 Hz, 3H).

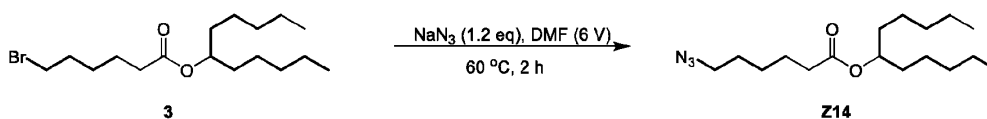
Example AZ14

Example AZ14.1



[0338] To a solution of compound 1 in this Example AZ14.1 (20 g, 116.07 mmol, 1 *eq*) in DCM (280 mL) was added EDCI (26.70 g, 139.29 mmol, 1.2 *eq*), DMAP (21.27 g, 174.11 mmol, 1.5 *eq*) and compound 2 (24.90 g, 127.68 mmol, 1.1 *eq*) were added in batches and stirred at 20 °C for 16 h. TLC (Petroleum ether/Ethyl acetate =20/1, DNP, product: R_f = 0.49) indicated compound 1 was consumed completely. The reaction mixture was diluted with water (275 mL), acidified with 2M hydrochloric acid (125 mL) and extracted with DCM (400 mL). The organic phase was extracted and washed with brine and dried over Na_2SO_4 . The organic phase was concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel chromatography (column height: 250 mm, diameter: 60 mm, 100 - 200 mesh silica gel, Petroleum ether/Ethyl acetate = 200/1 to 50/1). Compound 3 in this AZ14.1 (33.7 g, 96.47 mmol, 66.49% yield) as colorless oil. ^1H NMR: (400 MHz CDCl_3) δ ppm 0.87 - 0.98 (m, 6 H) 1.15 - 1.33 (m, 12 H) 1.44 - 1.54 (m, 6 H) 1.67 (quin, $J=7.57$ Hz, 2 H) 1.74 - 2.06 (m, 2 H) 2.32 (t, $J=7.38$ Hz, 2 H) 3.29 - 3.62 (m, 2 H) 4.88 (quin, $J=6.25$ Hz, 1 H).

Example AZ14.2

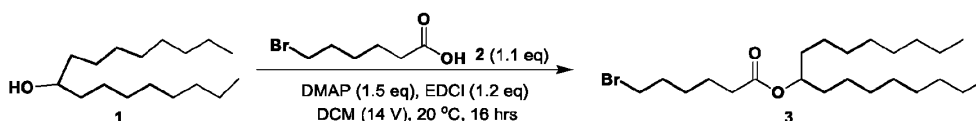


[0339] Azide Z14 is designated as azide T14 in Table 2. To a solution of compound 3 in this Example AZ14.2 (28.5 g, 81.58 mmol, 1 *eq*) in DMF (170 mL) was added NaN_3 (6.36 g, 97.90 mmol, 1.2 *eq*). The mixture was stirred at 60 °C for 16 h. TLC (Petroleum ether : Ethyl acetate =20:1, $R_{f\text{-sm}}$ =0.5, $R_{f\text{-product}}$ = 0.44) showed reactant was used up. The reaction mixture was

quenched by addition H₂O 500 mL at 20 °C, and extracted with n-hexane 100*2 mL. The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:0-100:1). Compound Z14 (26.1 g, 83.80 mmol, 92.54% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 4.87 (quin, J = 6.3 Hz, 1H), 3.27 (t, J = 6.9 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 1.71 - 1.58 (m, 4H), 1.56 - 1.47 (m, 4H), 1.46 - 1.37 (m, 2H), 1.34 - 1.23 (m, 12H), 0.90 - 0.86 (m, 6H).

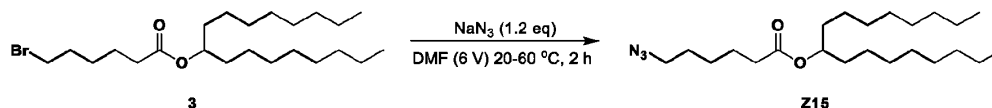
Example AZ15

Example AZ15.1



[0340] Compound 1 in this Example AZ15.1 (20 g, 77.98 mmol, 1 eq) was dissolved in DCM (280 mL), stirred at 20 °C, and EDCI (17.94 g, 93.58 mmol, 1.2 eq), DMAP (14.29 g, 116.97 mmol, 1.5 eq) and Compound 2 in this Example AZ15.1 (16.73 g, 85.78 mmol, 1.1 eq) were added to the reaction system in batches and stirred at 20 °C for 12h. TLC (Petroleum ether/Ethyl acetate=20/1, phosphomolybdic acid, product R_f = 0.4) showed product formation and a small amount of reactants remaining. TLC showed that the reaction was over, acidified with 2M hydrochloric (75 mL 2M hydrochloric and 425 mL H₂O) acid, The aqueous phase was extracted with DCM (280 mL*2). The combined organic phase was washed with brine (280 mL*2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 500 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=200/1 to 40/1). Compound 3 in this Example AZ15.1 (30 g, 69.20 mmol, 88.74% yield) was obtained as colorless oil. ¹H NMR: (400 MHz CDCl₃) δ ppm 4.87 (t, J = 6.2 Hz, 1H), 3.41 (t, J = 6.8 Hz, 2H), 2.34 - 2.28 (m, 2H), 1.88 (s, 2H), 1.70 - 1.62 (m, 2H), 1.53 - 1.47 (m, 5H), 1.34 - 1.19 (m, 27H), 0.88 (s, 4H).

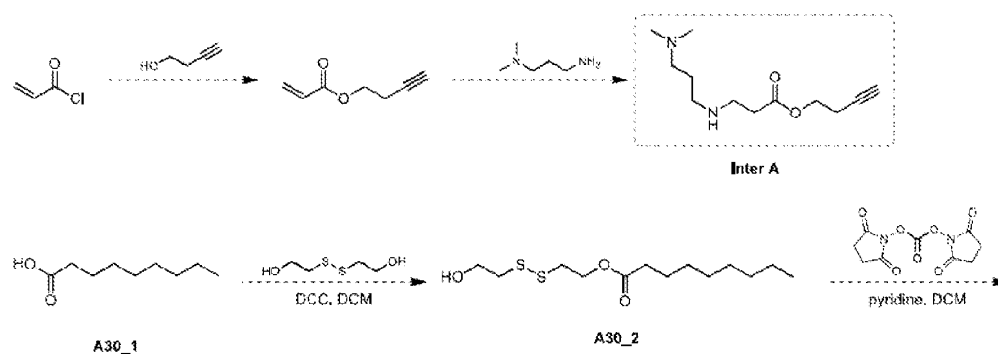
Example AZ15.2

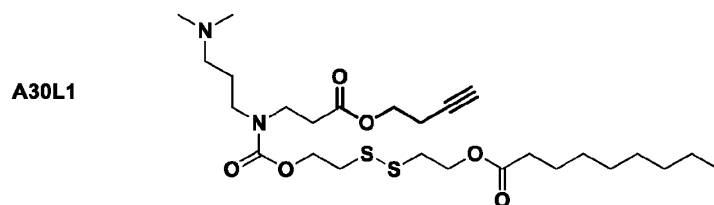
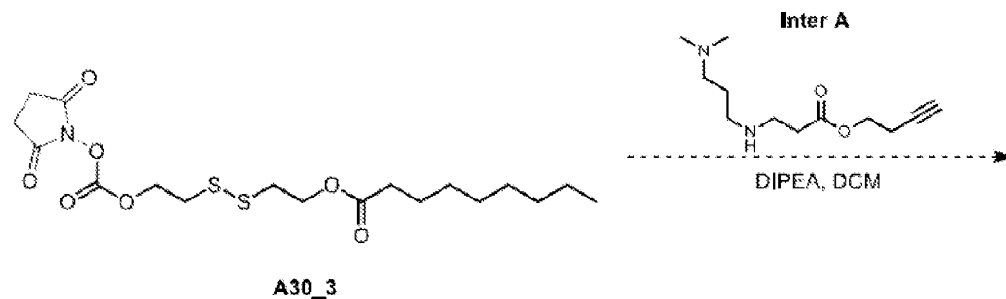


[0341] Azide Z15 is designated as azide T15 in Table 2. To a solution of compound 3 in this Example AZ15.2 (28 g, 64.59 mmol, 1 eq) in DMF (198 mL) was slowly added NaN₃ (5.04 g, 77.51 mmol, 1.2 eq) in batches. The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether : Ethyl acetate=20:1, product R_f=0.49) showed reactant was used up. The reaction mixture was quenched by addition H₂O 1000 mL at 20 °C and extracted with n-hexane 200 mL. The combined organic layers were washed with brine 300 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0). Compound Z15 (26.9 g, 67.99 mmol, 81.95% yield) was obtained as colorless oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 10.03 (s, 1 H), 8.58 (br d, *J* = 7.60 Hz, 1 H), 7.46 (br d, *J* = 8.40 Hz, 1 H), 7.23 - 7.35 (m, 4 H), 7.05 - 7.20 (m, 5 H), 6.85 (br d, *J* = 8.00 Hz, 1 H), 6.12 (dd, *J* = 10.0, 1.69 Hz, 1 H), 5.88 (s, 1 H), 5.37 (s, 1 H), 4.90 (br s, 1 H), 4.62 (br d, *J* = 3.20 Hz, 2 H), 4.29 - 4.40 (m, 1 H), 4.23 (br s, 1 H), 4.10 (s, 2 H), 3.84 (s, 2 H), 2.18 - 2.33 (m, 4 H), 1.77 - 2.16 (m, 5 H), 1.55 - 1.75 (m, 6 H), 1.39 (s, 3 H), 0.88 (s, 4 H).

Example A30L1

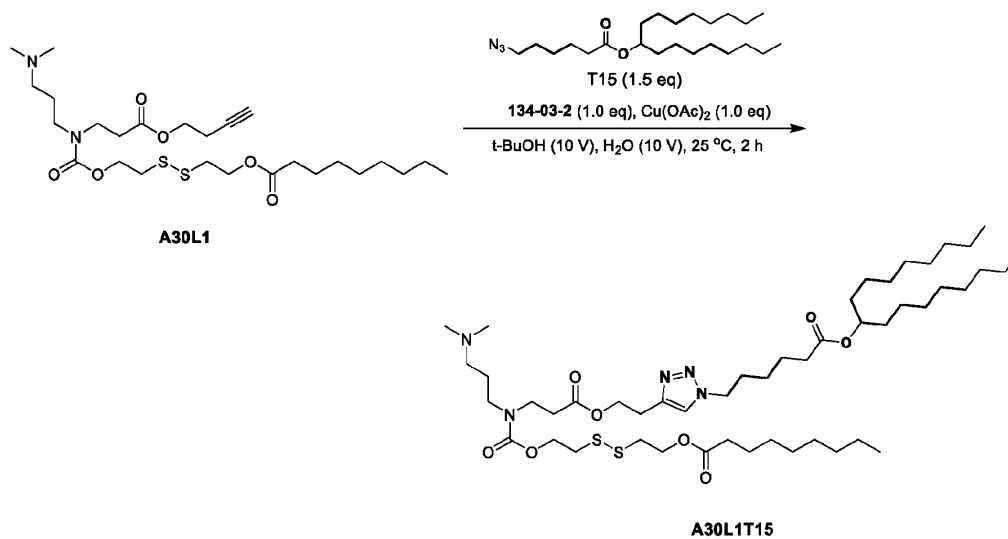
[0342] This compound (A30L1: 9-(3-(dimethylamino)propyl)-8,12-dioxo-7,13-dioxo-3,4-dithia-9-azaheptadec-16-yn-1-yl nonanoate) was prepared according to the following scheme:





Compound "Inter A" was also used in the synthesis of compounds A31L1, A32L1, A33L1 and A34L1.

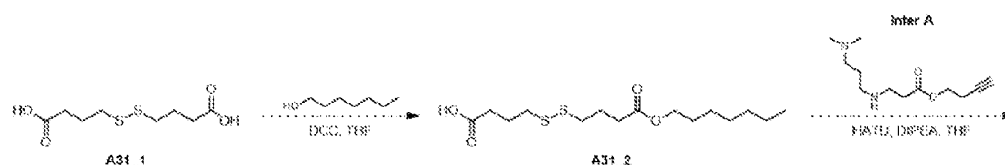
Example A30L1T15

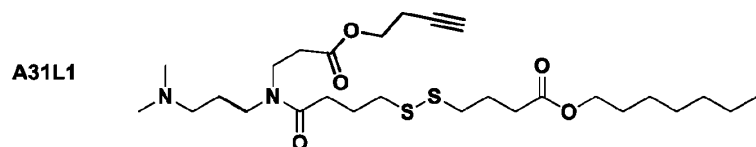


[0343] To a solution of A30L1 (2.35 g, 4.30 mmol, 1.00 eq) in t-BuOH (20 mL) and H₂O (20 mL) was added Cu(OAc)₂ (780 mg, 4.30 mmol, 1.0 eq) and L(+) sodium ascorbate (CAS: 134-03-2 mg, 852 mg, 4.30 mmol, 1.00 eq), T15 (2.55 g, 6.45 mmol, 1.50 eq) was added into the mixture and stirred at 25°C for 2 hrs. TLC (DCM : MeOH = 10 : 1, product: R_f = 0.4) showed the starting material was consumed completely. The suspension was filtered and the filtrate was diluted with H₂O (100 mL) and extracted with ethyl acetate (100 mL*3). The combined organic layers were washed with brine (30 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate to DCM: MeOH = 3:1 to 10:1). Then crude product was purified by semi-preparative reverse phase HPLC (column: C1 250×80mm, 10μm; mobile phase: [water (TFA)-ACN]; gradient: 65%-95% B over 25 min). The collected fraction was concentrated to remove acetonitrile, and extracted with ethyl acetate (50 mL*3). The combined organic layers were washed with brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated to give product. A30L1T15 (9-(3-(dimethylamino)propyl)-15-(1-(6-(heptadecan-9-yloxy)-6-oxohexyl)-1H-1,2,3-triazol-4-yl)-8,12-dioxo-7,13-dioxo-3,4-dithia-9-azapentadecyl nonanoate, 600 mg, 636.67 μmol, 14.81% yield) was obtained as a yellow oil. ¹H NMR (400 MHz CDCl₃): δ 7.39 (br s, 1H), 4.86 (t, *J* = 6.4 Hz, 1H), 4.39 - 4.30 (m, 8H), 3.56 - 3.49 (m, 2H), 3.29 (br s, 2H), 3.07 (t, *J* = 6.4 Hz, 2H), 2.98 - 2.88 (m, 4H), 2.61 (m, 2H), 2.37 - 2.25 (m, 12H), 1.93 (m, 3H), 1.76 (m, 2H), 1.65 (dt, *J* = 7.2, 14.8 Hz, 4H), 1.50 (br d, *J* = 5.6 Hz, 4H), 1.44 - 1.35 (m, 3H), 1.26 (br s, 32H), 0.88 (t, *J* = 6.8 Hz, 9H).

Example A31L1

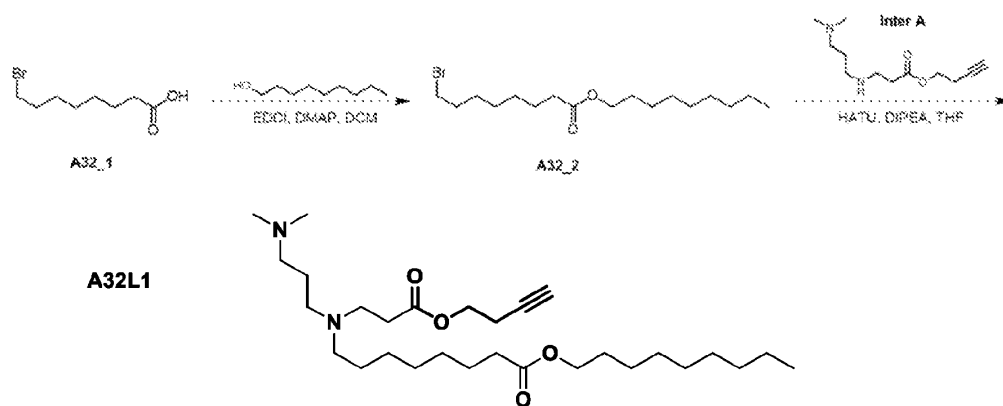
[0344] This compound (A31L1: heptyl 4-((4-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)-4-oxobutyl)disulfaneyl)butanoate) was prepared according to the following scheme:





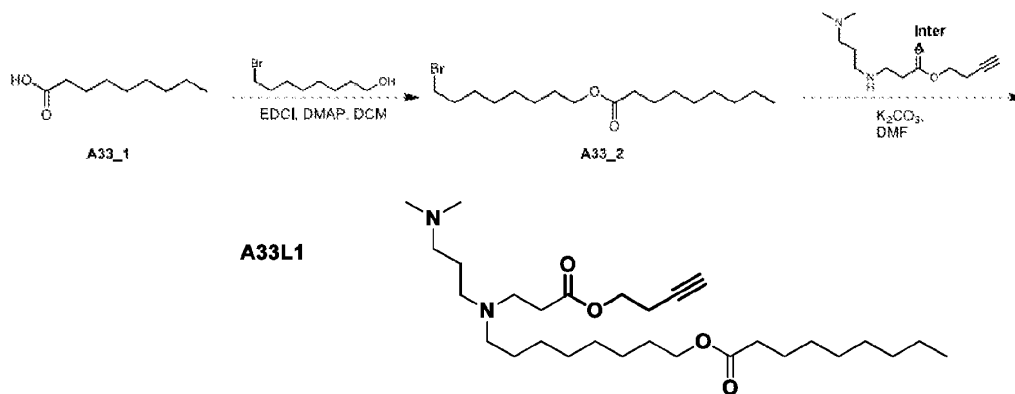
Example A32L1

[0345] This compound (A32L1: nonyl 8-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)octanoate) was prepared according to the following scheme:

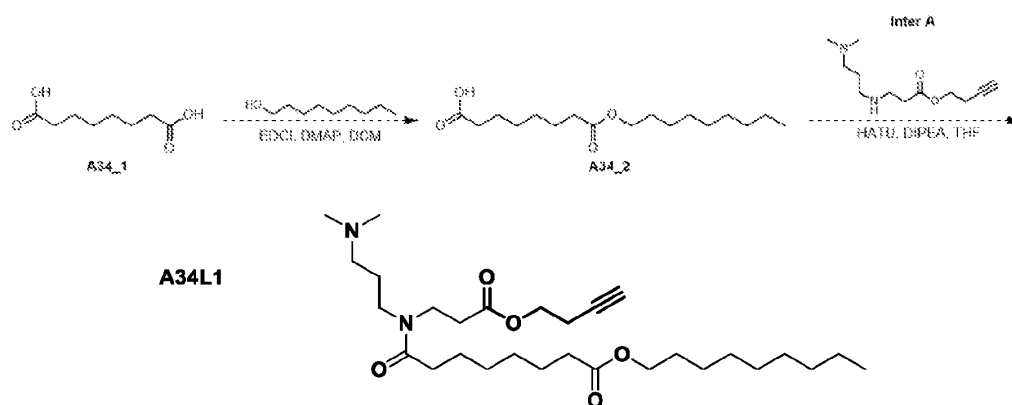


Example A33L1

[0346] This compound (A33L1: 8-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)octyl nonanoate) was prepared according to the following scheme:

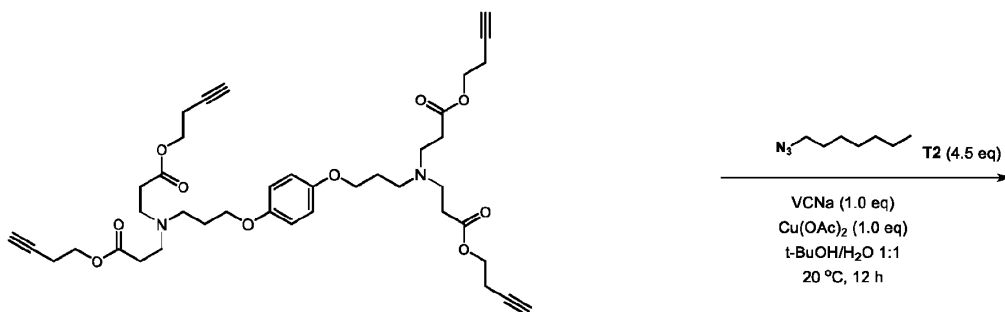
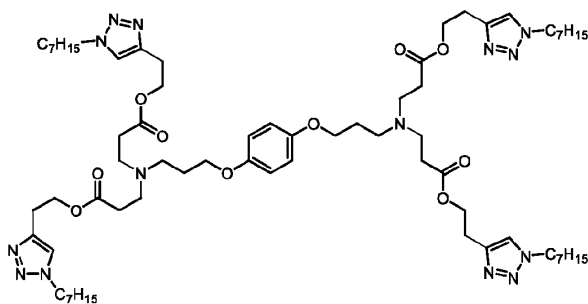


Example A34L1



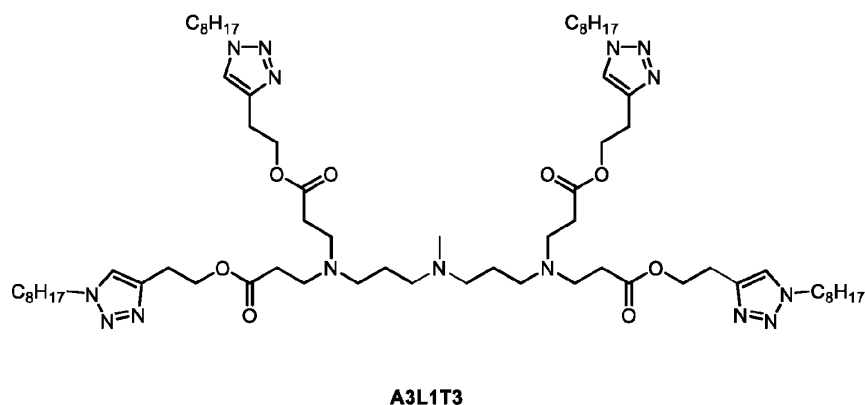
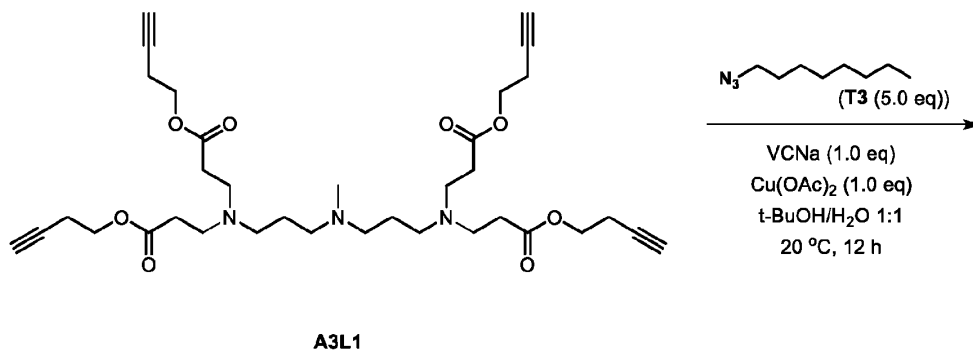
A34L1: nonyl 8-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)-8-oxooctanoate

Example A2L1T2

**A2L1****A2L1T2**

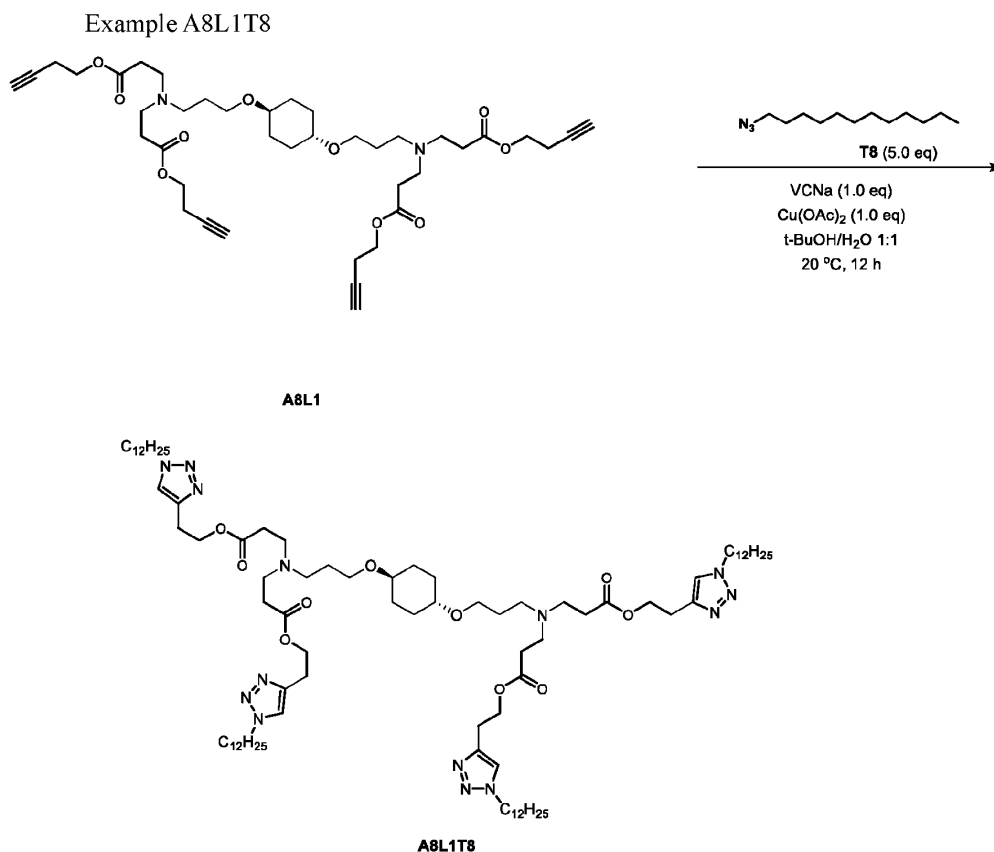
[0347] To a solution of compound T2 (220 mg, 1.56 mmol, 4.5 eq) in t-BuOH (2.0 mL), H₂O (2.0 mL) was added VCNa (68.7 mg, 347 μ mol, 1.0 eq) and Cu(OAc)₂ (63.0 mg, 347 μ mol, 1.0 eq), compound A2L1 (0.25 g, 347 μ mol, 1.0 eq). The mixture was stirred at 20 °C for 12h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.43) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (50 mL), the organic phase was washed with (15, 5.0 mL) (0.1M EDTA, CH₃COONa, pH = 5). The organic phase was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. Compound A2L1T2 (tetrakis(2-(1-heptyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-(((1,4-phenylenebis(oxy))bis(propane-3,1-diyl))bis(azanetriyl))tetracarbonate, 0.2 g, 156 μ mol, 44.9% yield) was obtained as yellow oil.

Example A3L1T3



tetrakis(2-(1-octyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-(((methyazanediyl)bis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate

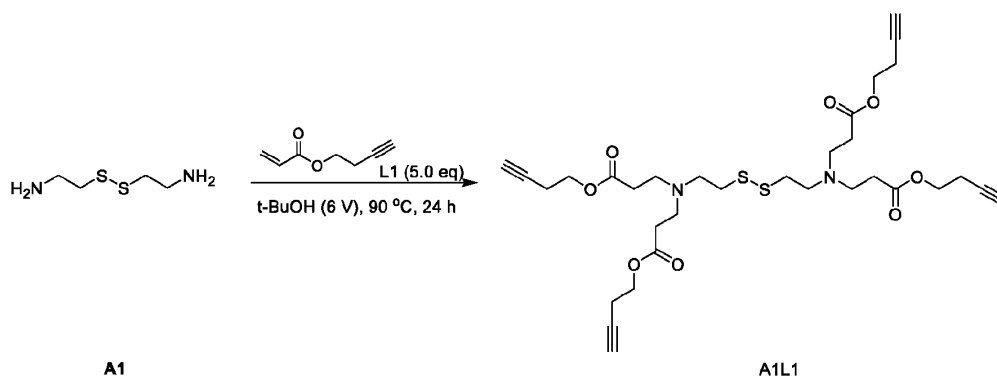
[0348] To a solution of compound A3L1 (0.25 g, 390 μ mol, 1.0 eq) in t-BuOH (2 mL), H₂O (2 mL) was added VCNa (77.2 mg, 390 μ mol, 1.0 eq) and Cu(OAc)₂ (70.8 mg, 390 μ mol, 1.0 eq), compound **T3** (302 mg, 1.95 mmol, 5.0 eq). The mixture was stirred at 20 °C for 12h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.43) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (50 mL), the organic phase was washed with (15, 5 mL)(0.1M EDTA, CH₃COONa, pH = 5) and then washed with saturated NaHCO₃(10 mL). The organic phase was separated,dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. Compound A3L1T3 (0.2 g, 158 μ mol, 40.7% yield) was obtained as yellow oil.



[0349] To a solution of compound A8L1 (0.2 g, 275 μmol , 1.0 eq) in t-BuOH (2.0 mL), H₂O (2.0 mL) was added VCNa (54.5 mg, 275 μmol , 1.0 eq) and Cu(OAc)₂ (50.0 mg, 275 μmol , 1.0 eq), compound T8 (291 mg, 1.38 mmol, 5.0 eq). The mixture was stirred at 20 °C for 12h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.43) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (50 mL), the organic phase was washed with (15, 5.0 mL) (0.1M EDTA, CH₃COONa, pH = 5) and then washed with saturated NaHCO₃ (10 mL). The organic phase was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. Compound A8L1T8 (tetrakis(2-(1-dodecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(oxy))bis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 0.2 g, 127

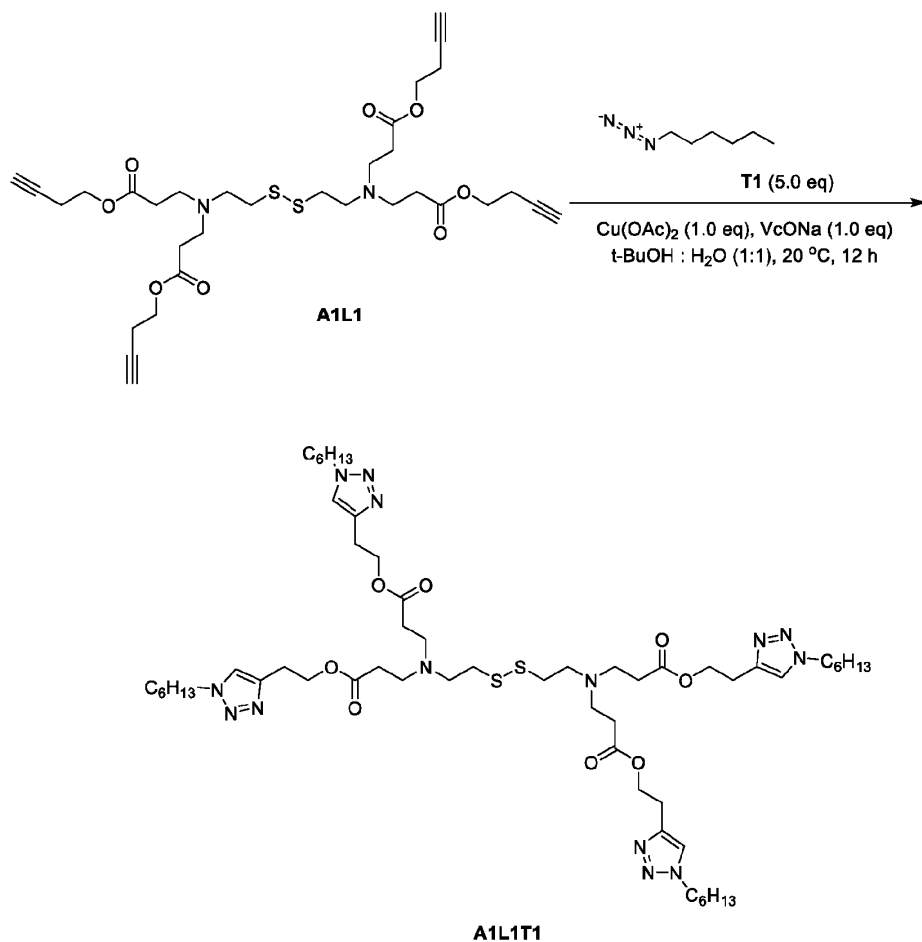
μmol, 46.2% yield) was obtained as a brown solid.

Example A1L1



[0350] To a solution of A1 (3 g, 19.70 mmol, 1 *eq*) in t-BuOH (18 mL) was added L1 (15.90 g, 128.05 mmol, 6.5 *eq*). The mixture was stirred at 90 °C for 24 h. TLC(Dichloromethane : Methanol=10:1, product R_f =0.64) showed the raw material response to complete. The mixture was evaporated to dryness. The residue was purified by column chromatography (product R_f = 0.61) (SiO₂, Dichloromethane: Methanol=100/1 to 10/1). A1L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-(((disulfanediy)bis(ethane-2,1-diyl))bis(azanetriyl))tetrapropionate, 4.5 g, 6.94 mmol, 35.21% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.19 (t, J = 6.8 Hz, 8H), 2.71 - 2.88 (m, 16H), 2.44 - 2.59 (m, 16H), 2.03 (t, J = 2.6 Hz, 4H).

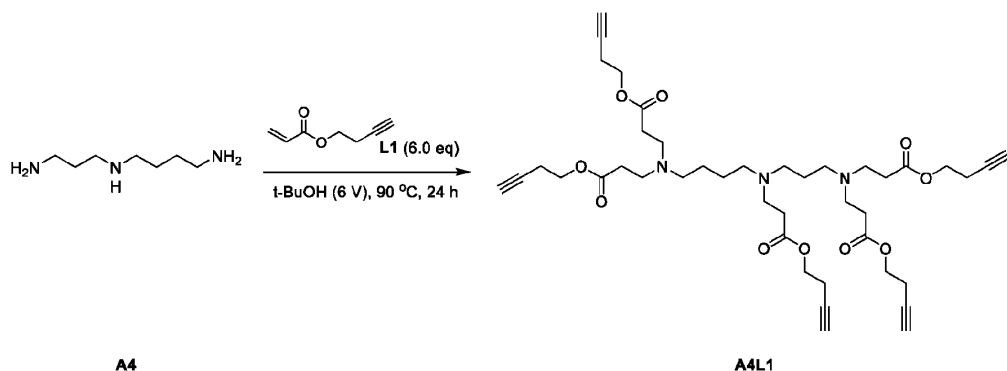
Example A1L1T1



[0351] To a solution of A1L1 (300 mg, 462.37 μmol , 1 *eq*) in t-BuOH (2 mL), H₂O (2 mL) was added VcONa (91.60 mg, 462.37 μmol , 1 *eq*), Cu(OAc)₂ (83.98 mg, 462.37 μmol , 1 *eq*) and T1 (294.04 mg, 2.31 mmol, 5 *eq*). The mixture was stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.43) showed the raw material response to complete. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), then 20 mL (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 20 °C for 10 min. The organic phase was separated, washed with NaHCO₃

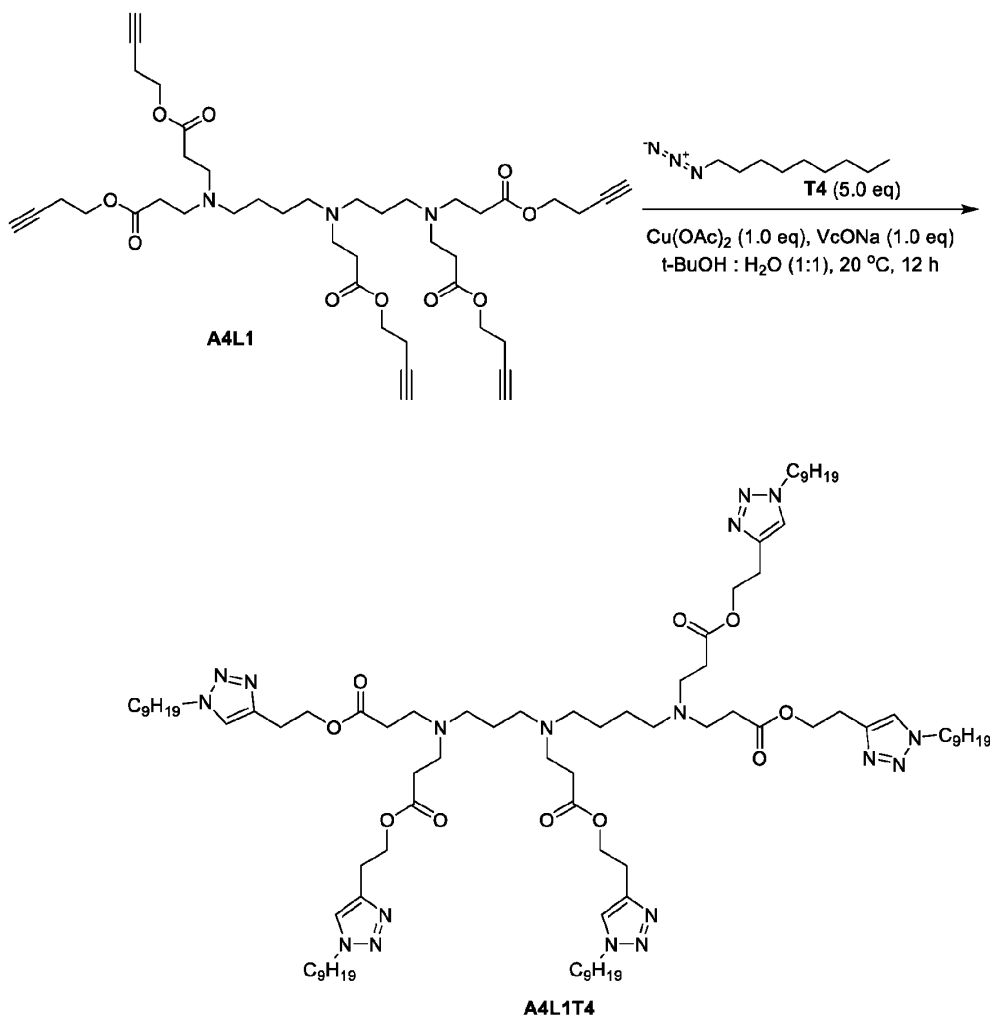
20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. A1L1T1 (tetrakis(2-(1-hexyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-(((disulfanediyl)bis(ethane-2,1-diyl))bis(azanetriyl))tetrapropionate, 220 mg, 190.05 μ mol, 41.10% yield, 100% purity) was obtained as yellow oil.

Example A4L1



[0352] To a solution of A4 (3 g, 20.65 mmol, 1 *eq*) in t-BuOH (15 mL) was added **L1** (16.67 g, 134.26 mmol, 6.5 *eq*). The mixture was stirred at 90 °C for 24 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.48) showed the raw material response to complete. The mixture was evaporated to dryness. The residue was purified by column chromatography (product R_f = 0.48) (SiO₂, Dichloromethane: Methanol=100/1 to 10/1). A4L1 (di(but-3-yn-1-yl) 3,3'-((3-((4-(bis(3-(but-3-yn-1-yloxy)-3-oxopropyl)amino)butyl)(3-(but-3-yn-1-yloxy)-3-oxopropyl)amino)propyl)azanediyl)dipropionate, 4.5 g, 5.88 mmol, 28.44% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.18 (t, *J* = 6.8 Hz, 10H), 2.77 (t, *J* = 7.2 Hz, 10H), 2.34 - 2.59 (m, 28H), 2.02 (t, *J* = 2.6 Hz, 5H), 1.55 (quin, *J* = 7.1 Hz, 2H), 1.33 - 1.44 (m, 4H).

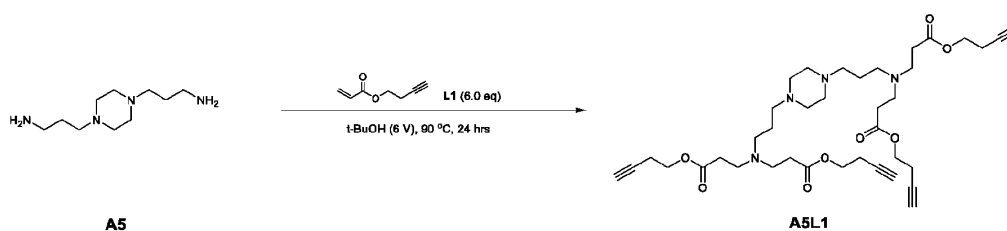
Example A4L1T4



[0353] To a solution of A4L1 (300 mg, 391.68 μmol , 1 eq) in t-BuOH (2 mL), H₂O (2 mL) was added VcONa (77.59 mg, 391.68 μmol , 1 eq), Cu(OAc)₂ (71.14 mg, 391.68 μmol , 1 eq) and T4 (397.79 mg, 2.35 mmol, 6 eq). The mixture was stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.43) showed the raw material response to complete. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL. The organic phase was separated then 20 mL (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 20 °C for 20 min. The organic phase was separated, washed with NaHCO₃ 20 mL, dried

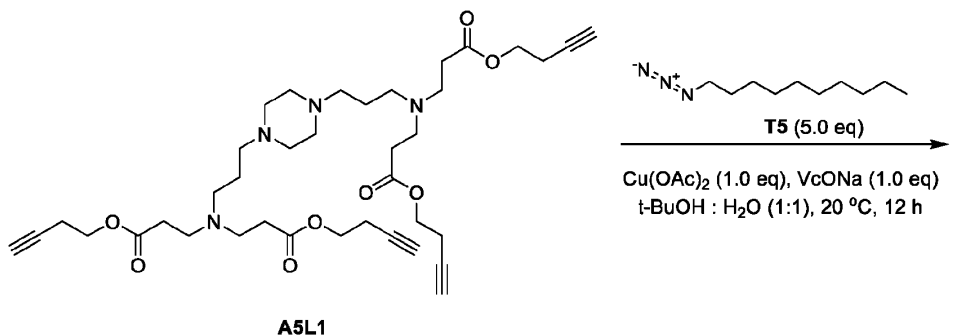
over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. A4L1T4 (bis(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((3-((4-(bis(3-(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)amino)butyl)(3-(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)amino)propyl)azanediyl)dipropionate, 0.22 g, 136.45 μmol, 34.84% yield, 100% purity) was obtained as a brown solid.

Example A5L1



[0354] To a solution of compound A5 (3.00 g, 14.98 mmol, 1.00 eq) in t-BuOH (18 mL) was added compound L1 (11.1 g, 89.85 mmol, 6.00 eq). The mixture was stirred at 90 °C for 24 hours. LCMS showed the reactant A5 was consumed and one main peak was detected. The reaction mixture was concentrated under reduced pressure to give residue. The residue was purified by flash silica gel column chromatography (5 - 10% methanol in dichloromethane) to give the product. Compound A5L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((piperazine-1,4-diylbis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 7.5 g, 10.76 mmol, 71.87% yield) was obtained as a yellow oil. LCMS: Rt = 0.266, mas spectrum M + H = 349.5, 100%.

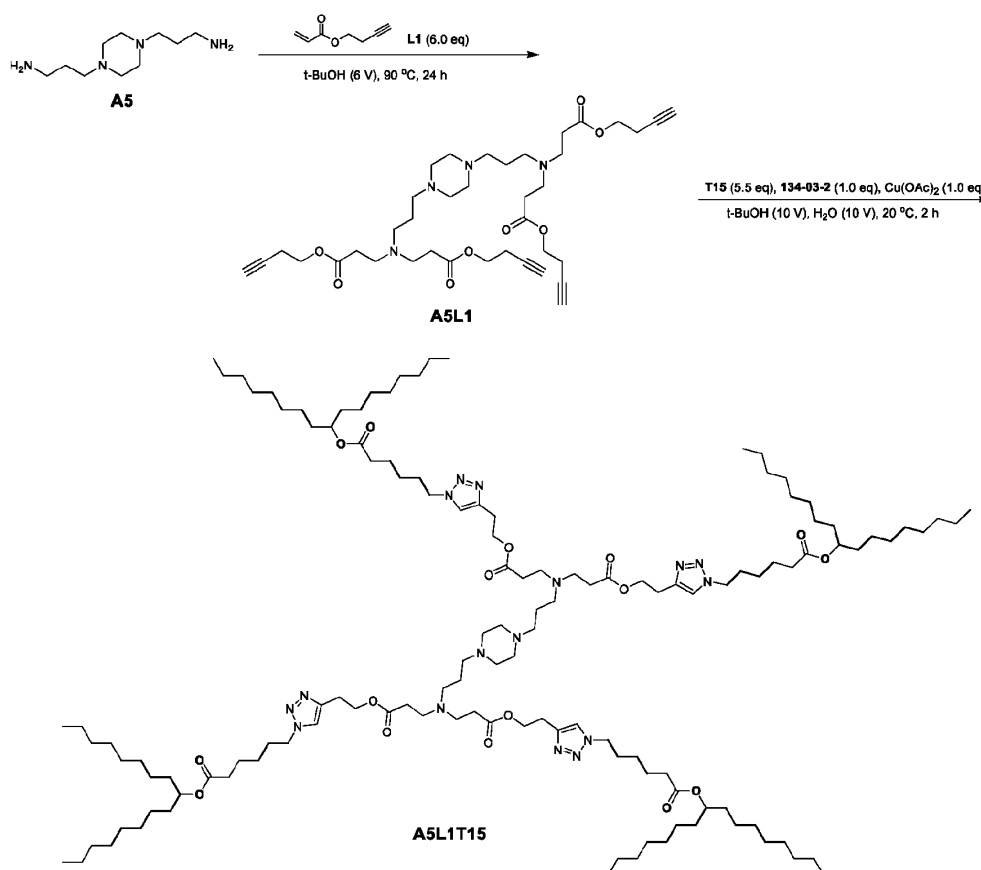
Example A5L1T5



[0355] To a solution of A5L1 (300 mg, 430.50 μmol , 1 *eq*) in t-BuOH (3 mL), H₂O (3 mL) was added VcONa (85.28 mg, 430.50 μmol , 1 *eq*), Cu(OAc)₂ (78.19 mg, 430.50 μmol , 1 *eq*) and **T5** (394.53 mg, 2.15 mmol, 5 *eq*). The mixture was stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.43) showed the raw material response to complete. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL. The organic phase was separated then 20 mL (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 20 °C for 20 min. The organic phase was separated, washed with NaHCO₃ 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without

purification. A5L1T5 (tetrakis(2-(1-decyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-((piperazine-1,4-diylbis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 0.22 g, 126.15 μ mol, 29.30% yield, 82% purity) was obtained as a yellow solid.

Example A5L1T15



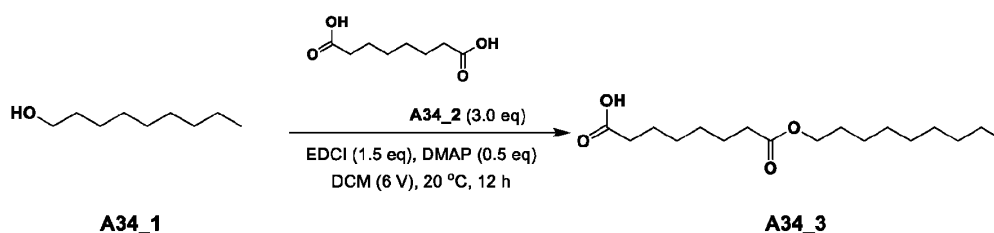
[0356] To a solution of A5L1 (3.00 g, 4.30 mmol, 1.00 eq), compound T15 (9.37 g, 23.6 mmol, 5.50 eq) in t-BuOH (30 mL), H₂O (30 mL) was added L (+) sodium ascorbate (CAS: 134-03-2, 852 mg, 4.30 mmol, 1.00 eq) and Cu(OAc)₂ (781 mg, 4.30 mmol, 1.0 eq) at 25 °C. The mixture was stirred at 25 °C for 12 hours. LCMS showed the reactant A5L1 was consumed and one main peak was detected. The reaction mixture was diluted with water (100 mL) and was extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed by brine and

dried over sodium sulfate. Then the mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel column chromatography (5 - 7% methanol in dichloromethane) to give the product (Dichloro methane: Methanol = 10:1, R_f = 0.4).

Compound A5L1T15 (3.2 g, 1.30 mmol, 30.20% yield, 92.6% purity) was obtained as a yellow oil. LCMS: R_t = 0.585, $1/3(M + H)$ = 760.8, 92% purity. ^1H NMR: (400 MHz,

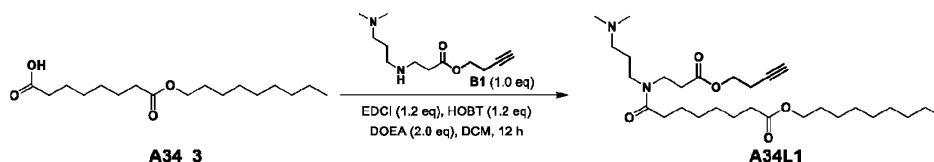
CHLOROFORM- d) δ : 7.39 (s, 4H), 4.96 - 4.80 (m, 4H), 4.42 - 4.27 (m, 16H), 3.06 (t, J = 6.6 Hz, 8H), 2.75 (t, J = 6.6 Hz, 8H), 2.44 (d, J = 5.6 Hz, 16H), 2.30 (t, J = 7.2 Hz, 12H), 1.93 (t, J = 7.6 Hz, 8H), 1.73 - 1.63 (m, 12H), 1.51 (d, J = 4.8 Hz, 16H), 1.42 - 1.36 (m, 8H), 1.26 (s, 100H), 0.96 - 0.80 (m, 24H).

Example A34_3



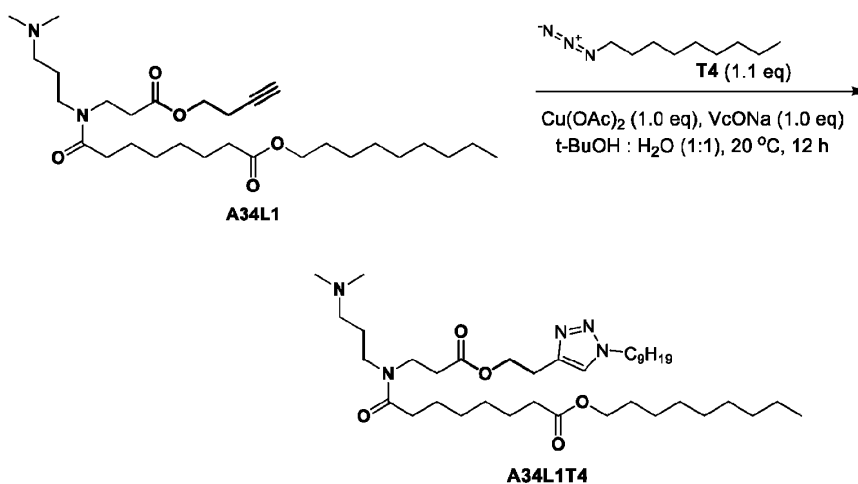
[0357] To a solution of A34_1 (5 g, 34.6 mmol, 1 *eq*) and A34_2 (18.1 g, 103 mmol, 3 *eq*) in DCM (30 mL) was added EDCI (9.97 g, 51.9 mmol, 1.5 *eq*) and DMAP (2.12 g, 17.3 mmol, 0.5 *eq*). The mixture was stirred at 20 °C for 12h. TLC (Petroleum ether: Ethyl acetate = 5:1, product R_f = 0.43) showed the raw material response to complete. The residue was diluted with H₂O 100 mL and extracted with DCM 200 mL. Dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 20/1. A34_3 (8 g, 26.63 mmol, 76.82% yield) was obtained as a white solid.

Example A34L1



[0358] To a solution of A34_3 (5.84 g, 19.44 mmol, 1.1 *eq*) in DCM (24 mL) was added EDCI (4.07 g, 21.21 mmol, 1.2 *eq*) and HOBT (2.87 g, 21.21 mmol, 1.2 *eq*) and DIEA (4.57 g, 35.35 mmol, 6.16 mL, 2 *eq*). The mixture was stirred for 10 min. B1 (4 g, 17.67 mmol, 1 *eq*) was added to the mixture and the mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.33) showed the raw material response to complete. The residue was diluted with H₂O 100 mL and extracted with DCM 250 mL. The combined organic layers were washed with NaHCO₃ 100 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Dichloromethane: Methanol=100/1 to 20/1). A34L1 (nonyl 8-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)-8-oxooctanoate, 5.0 g, 8.89 mmol, 50.32% yield, 90.5% purity) was obtained as yellow oil.

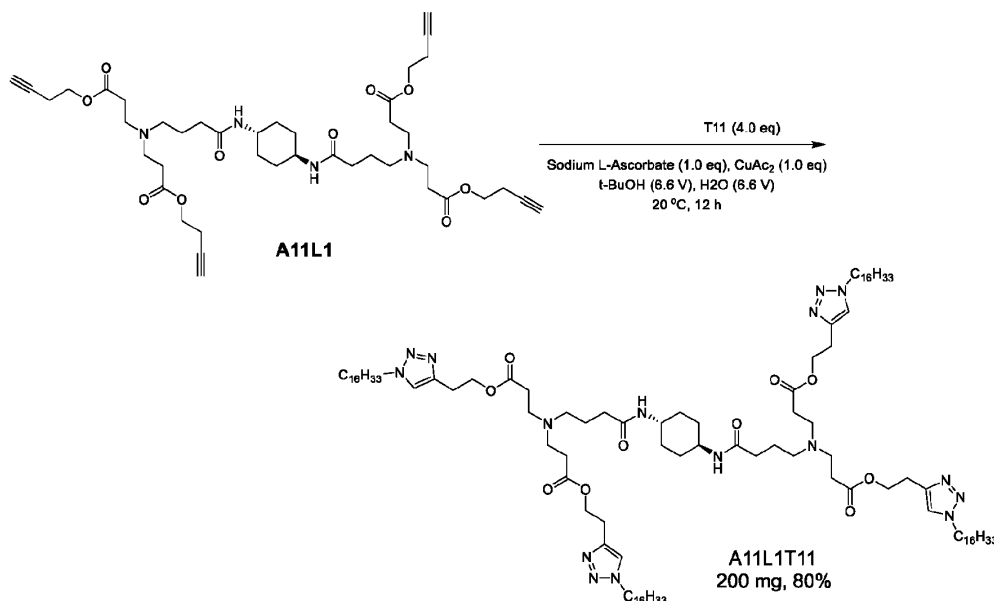
Example A34L1T4



[0359] A 40 mL glass bottle equipped with magnetic stirrer, to a solution of A34L1 (0.35 g, 619.19 μmol, 1 *eq*) in t-BuOH (1.7 mL) and H₂O (1.7 mL) was added VcONa (122.66 mg,

619.19 μmol , 1 *eq*), $\text{Cu}(\text{OAc})_2$ (112.46 mg, 619.19 μmol , 1 *eq*) and T4 (480.37 mg, 681.11 μmol , 1.1 *eq*). The resulting mixture was stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, $R_f=0.02$) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 10 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. 0.1 M EDTA : 2.92 g EDTA dissolved in 100 mL water and added about 3.25 g sodium acetate to adjust pH=5. The crude product was dissolved in EtOAc (5 mL), then 0.1M EDTA (10 mL) was added, the mixture was stirred at 20 °C for 5 min. The organic phase was separated, repeat the above steps three times, until the water phase becomes colorless, washed with NaHCO_3 solution (10 mL $\times$ 2). The organic phase dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give product. A34L1T4 (nonyl 8-((3-(dimethylamino)propyl)(3-(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)amino)-8-oxooctanoate, 200 mg, 294.99 μmol , 47.64% yield) as brown oil.

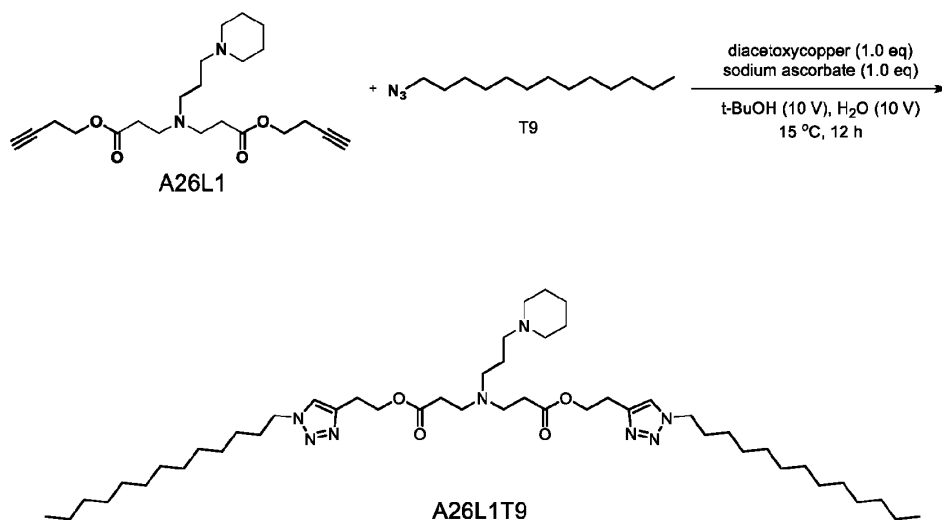
Example A11L1T11



[0360] To a solution of compound A11L1 (0.15 g, 192 μmol , 1.0 *eq*) in t-BuOH (1.00 mL) and H_2O (1.00 mL) was added compound T11 (205 mg, 768 μmol , 4.0 *eq*) Sodium L-

Ascorbate (38.0 mg, 192 μmol , 1.0 eq) and CuAc_2 (34.8 mg, 192 μmol , 1.0 eq) at 20 $^\circ\text{C}$. The solution was stirred at 25 $^\circ\text{C}$ for 12 h. TLC (dichloromethane : methanol = 10 : 1, the starting material: R_f = 0.50, product: R_f = 0.48) showed the reaction was completed. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15.0 mL). The organic phase was separated, washed with brine 5.00 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10.0 mL), THF (2.00 mL), then 20.0 mL (0.1M EDTA, AcONa, pH = 5) was added, the mixture was stirred at 25 $^\circ\text{C}$ for 30 min. The organic phase was separated, washed with brine 5.00 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the A11L1T11 (tetrakis(2-(1-hexadecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(azanediyl))bis(4-oxobutane-4,1-diyl))bis(azanetriyl))tetrapropionate, 108 μmol , 56.2% yield, 100% purity) as a off-white solid.

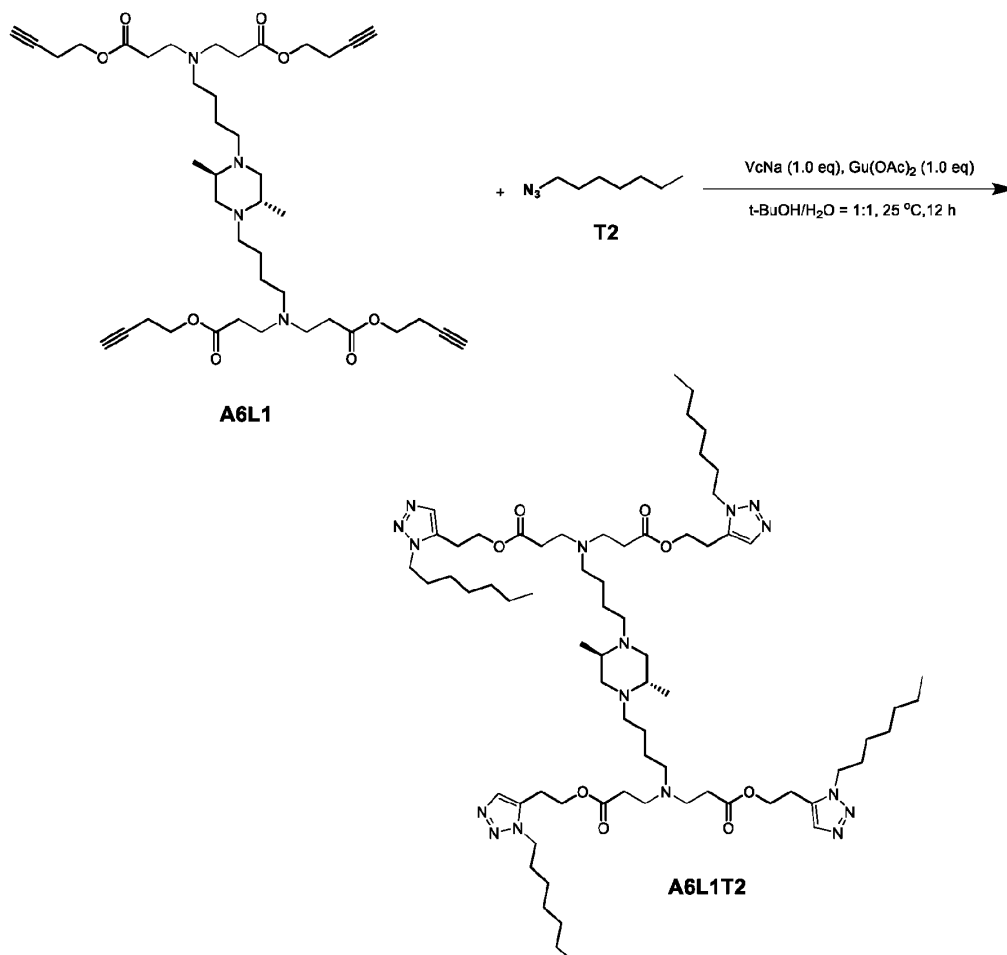
Example A26L1T9



[0361] To a solution of A26L1 (0.15 g, 384 μ mol, 1.0 eq) in t-BuOH (1.5 mL) H₂O (1.5 mL) was added sodium ascorbate (76.0 mg, 384 μ mol, 1.0 eq), diacetoxycopper (69.7 mg, 384 μ mol, 1.0 eq) and T9 (176 mg, 960 μ mol, 2.5 eq) at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, Product/R_f = 0.5, material/R_f = 0.3) showed the

reaction was completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The crude product was dissolved in EtOAc (10 mL) and THF (2 mL), then 20 mL (0.1M EDTA, CH_3COONa , pH=5) was added to the mixture, the mixture was stirred at 25 °C for 30 min. The mixture was washed with NaHCO_3 (5 mL). The organic phase was separated, washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give A26L1T9 (bis(2-(1-tridecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((3-(piperidin-1-yl)propyl)azanediyl)dipropionate, 0.2 g, 264 μmol , 68.8% yield) as yellow oil.

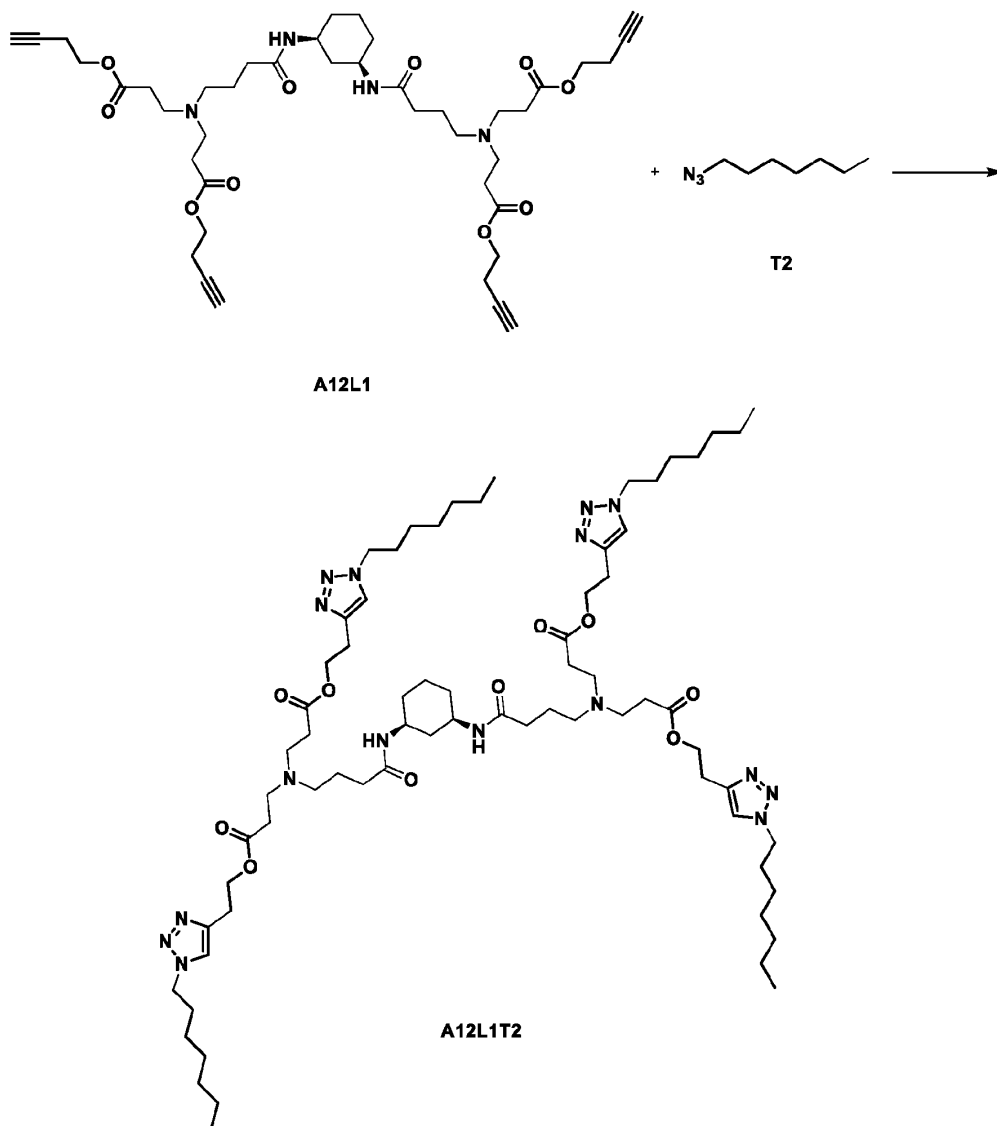
Example A6L1T2



[0362] To a solution of compound A6L1 (0.2 g, 265 μmol , 1.0 eq) in H_2O (1 ml), $t\text{-BuOH}$ (1 ml) was added VcNa (52.62 mg, 265.61 μmol , 1.0 eq), $\text{Cu}(\text{OAc})_2$ (48.2 mg, 265.6 μmol , 1.0 eq) and compound T2 (225 mg, 1.59 mmol, 6.0 eq). The mixture was stirred at 25°C for 12 h. TLC (Dichloromethane/Methanol = 10/1, R_f = 0.31) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 ml). The organic phase was separated, washed with brine 5 ml, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 ml), THF (2 ml), then 20 ml (0.1 M EDTA, CH_3COONa , pH=5) was added, the mixture was stirred at 25°C for 30 min. The organic phase was separated, washed with

NaHCO₃ .aq 10 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound A6L1T2 (tetrakis(2-(1-heptyl-1H-1,2,3-triazol-5-yl)ethyl) 3,3',3'',3'''-((((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(butane-4,1-diyl))bis(azanetriyl))tetrapropionate, 0.2 g, 151 μmol, 57.1% yield) was obtained as a yellow solid.

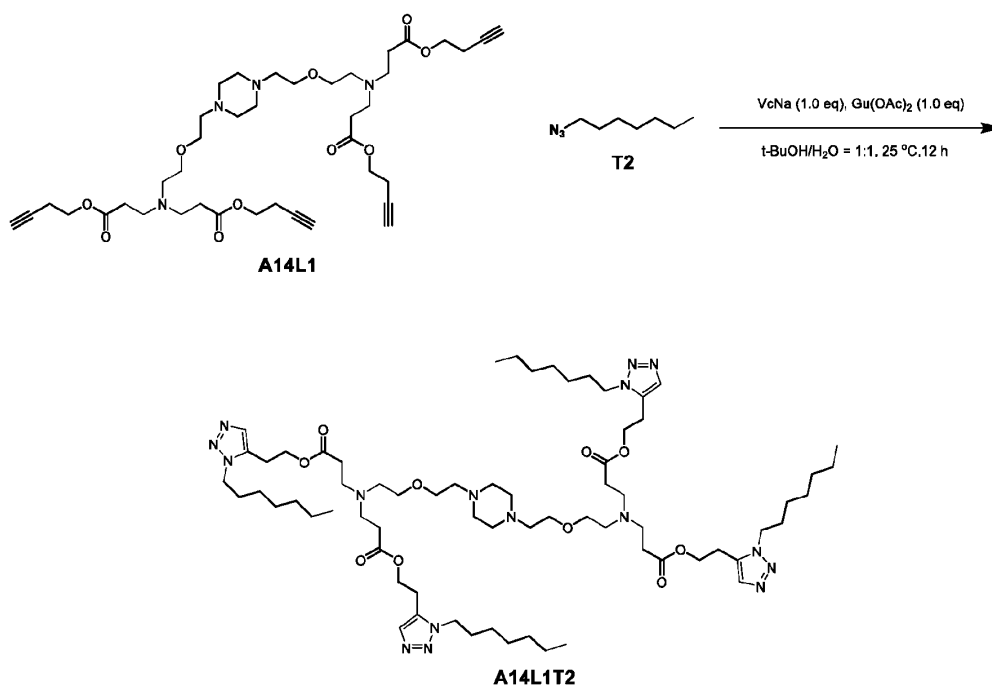
Example A12L1T2



[0363] To a solution of A12L1 (0.3 g, 384 μmol , 1.0 eq) in t-BuOH (1.5 mL) H₂O (1.5 mL) was added sodium ascorbate (76.0 mg, 384 μmol , 1.0 eq), diacetoxycopper (69.7 mg, 384 μmol , 1.0 eq) and **T2** (244 mg, 1.7 mmol, 4.5 eq) at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, Product/ R_f = 0.5, material/ R_f = 0.3) showed the

reaction was completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue. The crude product was dissolved in EtOAc (10 mL) and THF (2 mL), then 20 mL (0.1M EDTA, CH_3COONa , pH=5) was added to the mixture, the mixture was stirred at 25 °C for 30 min. The mixture was washed with NaHCO_3 (5 ml). The organic phase was separated, washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum to give A12L1T2 (tetrakis(2-(1-heptyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-((((cis)-cyclohexane-1,3-diyl)bis(azanediyl))bis(4-oxobutane-4,1-diyl))bis(azanetriyl))tetrapropionate, 0.2 g, 127 μmol , 33% yield) as yellow oil.

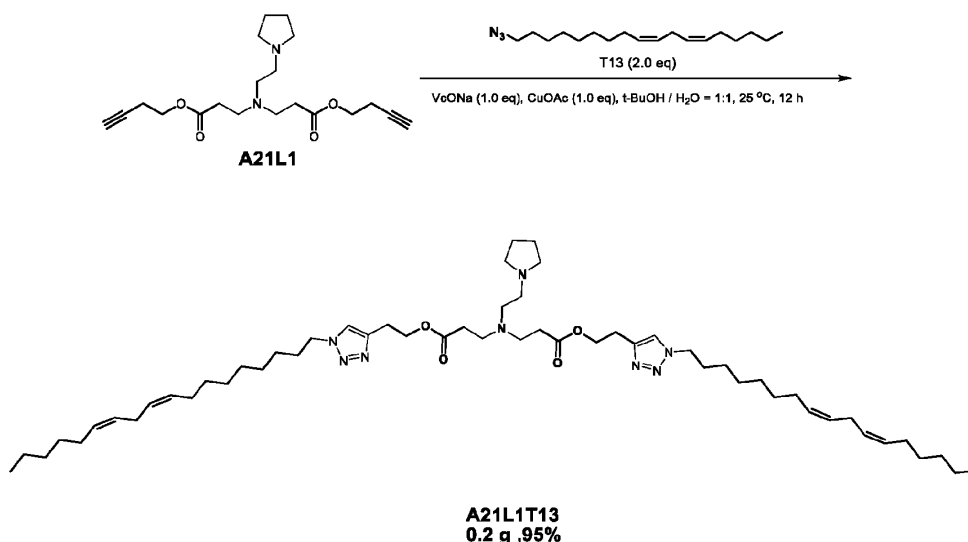
Example A14L1T2



[0364] To a solution of compound A14L1 (0.2 g, 264 μmol , 1.0 eq) in H_2O (1 ml), t-BuOH (1 ml) was added VcNa (52.3 mg, 264 μmol , 1.0 eq), $\text{Cu}(\text{OAc})_2$ (47.9 mg, 264 μmol , 1.0 eq) and compound T2 (223 mg, 1.59 mmol, 6.0 eq). The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, R_f = 0.31) showed reaction was used up. The

suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 ml). The organic phase was separated, washed with brine 5 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 ml), THF (2 ml), then 20 ml (0.1 M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO₃ aq 10 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound A14L1T2 (tetrakis(2-(1-heptyl-1H-1,2,3-triazol-5-yl)ethyl) 3,3',3'',3'''-(((piperazine-1,4-diyl)bis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(azanetriyl))tetrapropionate, 0.2 g, 151 μmol, 57.2% yield) was obtained as a yellow solid.

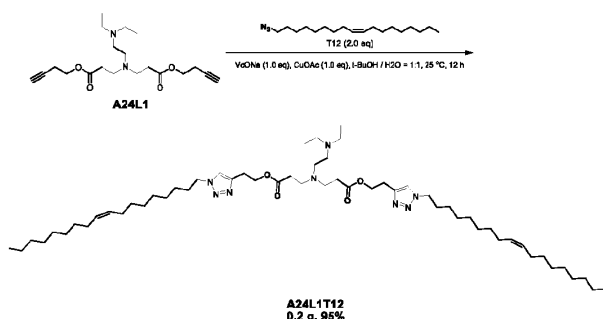
Example A21L1T13



[0365] To a solution of compound A21L1 in t-BuOH (2 mL) and H₂O (2 mL) was added VcONa (109 mg, 551 μmol, 1 eq) and CuOAc (100 mg, 551 μmol, 1 eq) and compound T13 (321 mg, 1.10 mmol, 2 eq). The mixture was stirred at 25 °C for 12h. LCMS (product: RT = 2.424 min; M + H / 2 = 473.5) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (5 mL), filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in

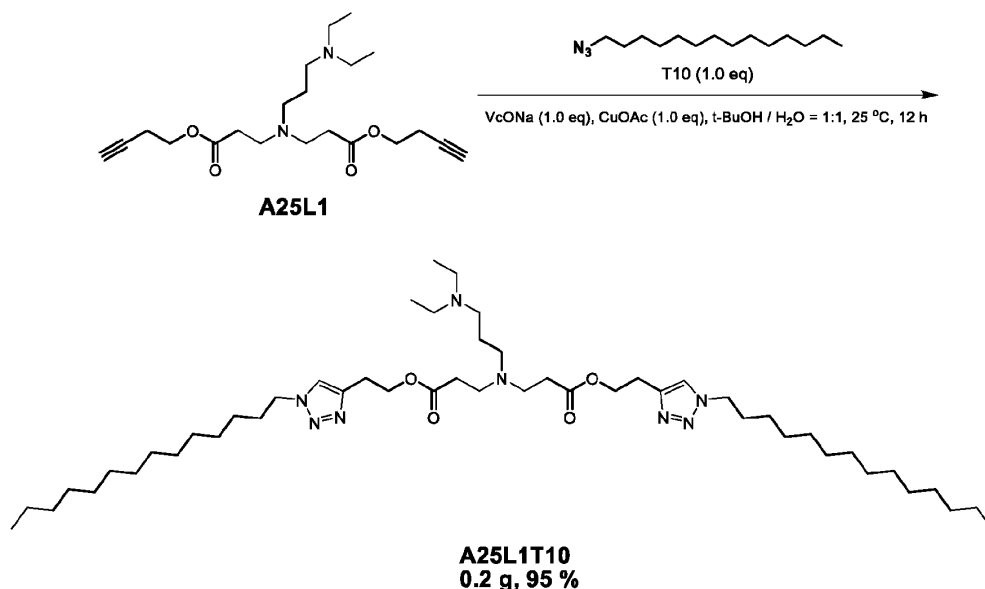
EtOAc (5 mL), then 15 mL (0.1M EDTA, CH₃COONa, pH=5) was added the mixture was stirred at 25 °C for 10 min, and extracted with EtOAc (5 mL × 2). The combined organic layers were washed with NaHCO₃ 10mL. Then concentrated under reduced pressure to give a residue. Without purification. Compound A21L1T13 (2-(1-((8Z,11Z)-heptadeca-8,11-dien-1-yl)-1H-1,2,3-triazol-4-yl)ethyl 3-((3-(2-(1-((9Z,12Z)-octadeca-9,12-dien-1-yl)-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)(2-(pyrrolidin-1-yl)ethyl)amino)propanoate, 0.2 g, 211 μmol, 38.3% yield) was obtained as a yellow oil. LCMS R_t = 2.855, M + H = 945.7, 91%.

Example A24L1T12



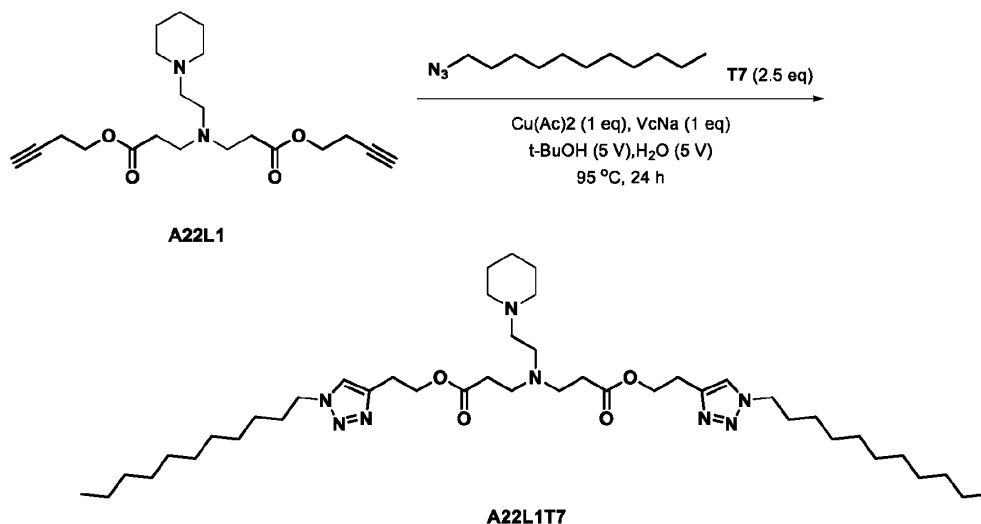
[0366] To a solution of compound **A24L1** (0.2 g, 548 μmol, 1 eq) in t-BuOH (2 mL) and H₂O (2 mL) was added VcONa (108 mg, 548 μmol, 1 eq) and CuOAc (99.6 mg, 548 μmol, 1 eq) and compound T12 (322 mg, 1.10 mmol, 2 eq). The mixture was stirred at 25 °C for 12h. LCMS (product: RT = 2.558 min; M + H / 2 = 476) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (5 mL), filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (5 mL), then 15 mL (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 25 °C for 10 min, and extracted with EtOAc (5 mL × 2). The combined organic layers were washed with NaHCO₃ 10mL. Then concentrated under reduced pressure to give a residue. Without purification. Compound A24L1T12 (bis(2-(1-((Z)-octadec-9-en-1-yl)-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((2-(diethylamino)ethyl)azanediyl)dipropionate, 0.2 g, 210 μmol, 38.3% yield) was obtained as a yellow solid. LCMS: R_t = 2.140, M + H = 951.8, 95.6%.

Example A25L1T10



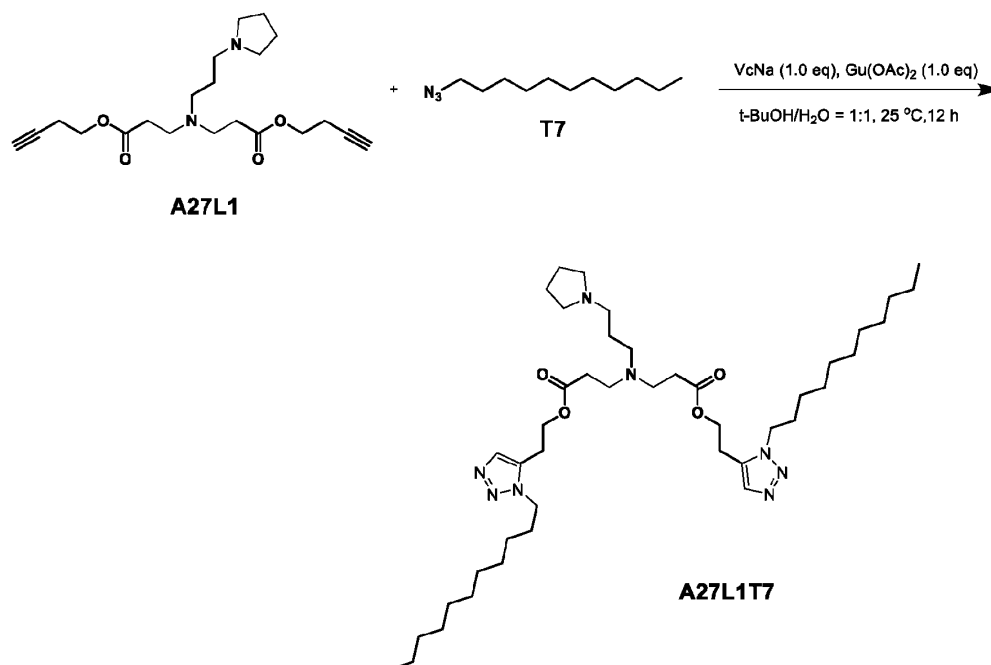
[0367] To a solution of compound A25L1 (0.25 g, 660 μmol , 1 eq) in t-BuOH (2 mL) and H₂O (2 mL) was added VcONa (130 mg, 660 μmol , 1 eq) and CuOAc (119 mg, 660 μmol , 1 eq) and compound T10 (316 mg, 1.32 mmol, 2 eq). The mixture was stirred at 25 °C for 12h. LCMS (product: RT = 2.040 min; M + H / 2 = 429) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (5 mL), filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (5 mL), then 15 mL (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 25 °C for 10 min, and extracted with EtOAc (5 mL $\times$ 2). The combined organic layers were washed with NaHCO₃ 10mL. Then concentrated under reduced pressure to give a residue. Without purification. Compound A25L1T10 (bis(2-(1-tetradecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((3-(diethylamino)propyl)azanediyl)dipropionate, 0.2 g, 233 μmol , 35.3% yield) was obtained as a yellow solid. LCMS: R_t = 2.065, M + H = 857.8, 95%.

Example A22L1T7



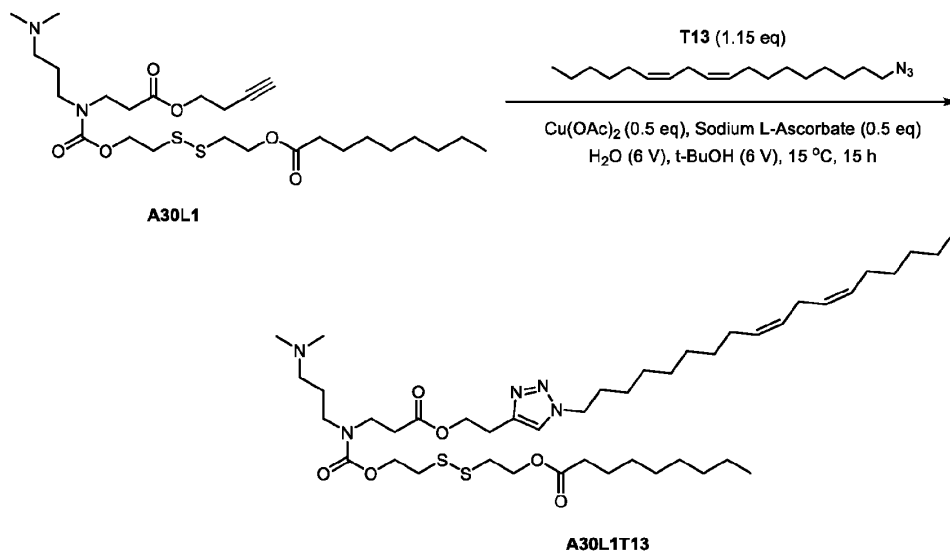
[0368] To a solution of A22L1 (200 mg, 531 μmol , 1.0 eq) in 2-methylpropan-2-ol (1 mL) and H_2O (1 mL) was added T7 (262 mg, 1.33 mmol, 2.5 eq) sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (105 mg, 531 μmol , 1.0 eq) and diacetylcopper (96.5 mg, 531 μmol , 1.0 eq) at 20 $^\circ\text{C}$. The mixture was stirred 12 h at 20 $^\circ\text{C}$. TLC (Dichloromethane/Methanol = 10/1, Product/ R_f = 0.4) showed the reaction was completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), THF (2 mL), then 20 mL (0.1M EDTA, CH_3COONa , pH = 5) was added, the mixture was stirred at 25 $^\circ\text{C}$ for 30 min. The organic phase was separated, washed with sat. NaHCO_3 (5 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. Without purification. Obtained A22L1T7 (bis(2-(1-undecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((2-(piperidin-1-yl)ethyl)azanediyl)dipropionate, 200 mg, 259 μmol , 48.8% yield) as yellow solid. LCMS: m/z = 386.3 ($\text{M}/2+\text{H}$) $^+$, R_t = 0.901 min.

Example A27L1T7



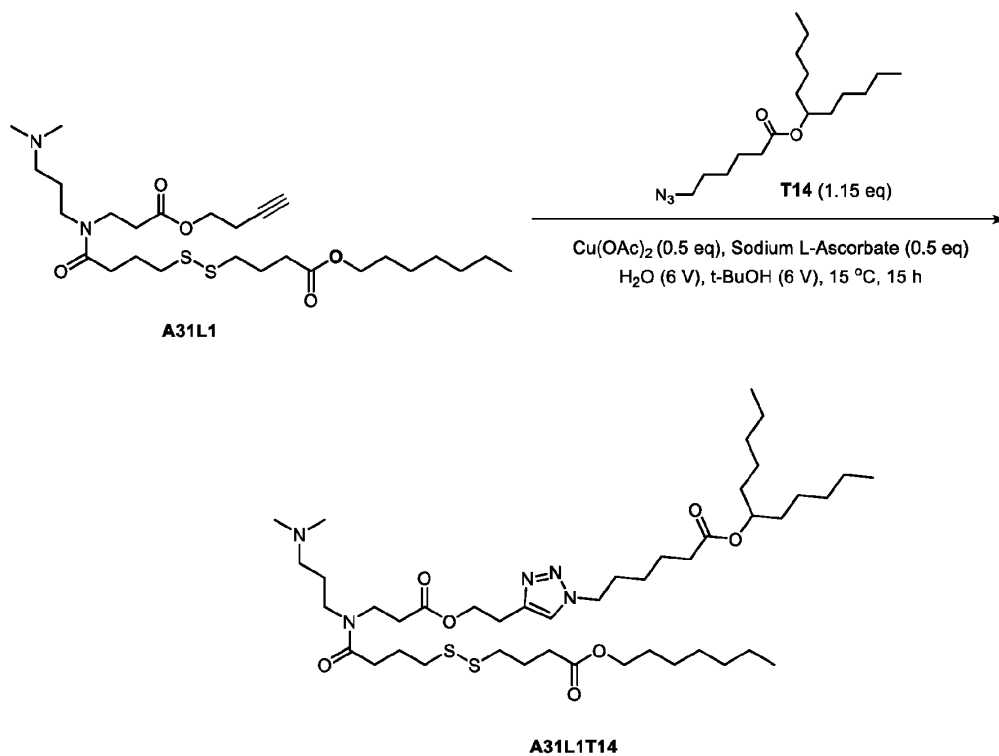
[0369] To a solution of compound A27L1 (0.2 g, 531 μmol , 1.0 eq) in t-BuOH (2 ml), H₂O (2 ml) was added VcNa (105 mg, 531 μmol , 1.0 eq) and Cu(OAc)₂ (96.4 mg, 531 μmol , 1.0 eq) and compound T7 (262 mg, 1.33 mmol, 2.5 eq). The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 10/1, product/R_f = 0.4; start material/R_f = 0.6) indicated compound A27L1 was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 ml). The organic phase was separated, washed with brine 5 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 ml), THF (2ml), then 5 ml (0.1M EDTA, CH₃COONa, pH=5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with sat. NaHCO₃ 5 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound A27L1T7 (bis(2-(1-undecyl-1H-1,2,3-triazol-5-yl)ethyl) 3,3'-((3-(pyrrolidin-1-yl)propyl)azanediyl)dipropionate, 0.2 g, 259 μmol , 48.8% yield) was obtained as yellow solid.

Example A30L1T13



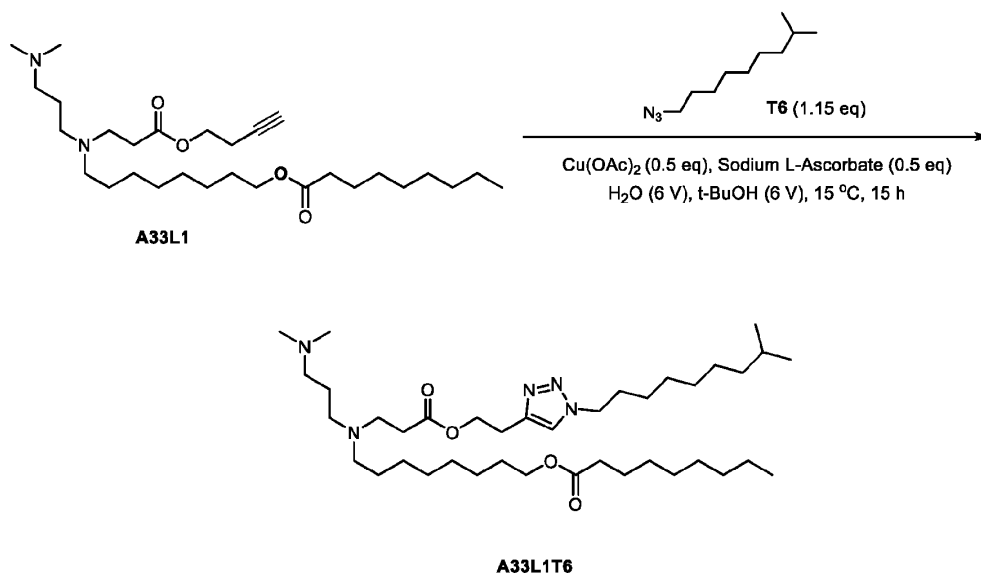
[0370] To a solution of compound A30L1 (300 mg, 549 μmol , 1.0 eq) in H_2O (2 mL) and $t\text{-BuOH}$ (2 mL) was added $\text{Cu}(\text{OAc})_2$ (50 mg, 274 μmol , 0.5 eq) and sodium L-ascorbate (54 mg, 274 μmol , 0.5 eq) and compound T13 (184 mg, 631 μmol , 1.15 eq). The mixture was stirred at 15 °C for 15h. TLC (dichloromethane/ methanol = 10/1, R_f = 0.3) indicated compound A30L1 was consumed completely and one new spot formed. The reaction was clean according to TLC. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite and the filter cake was washed with EtOAc (5 mL). The mixture was separated, washed with brine (5 mL). To the organic layer was added 20 mL (0.1M EDTA, AcONa, pH=5) and stirred at 25 °C for 30 min. The mixture was separated, washed with NaHCO_3 (15 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound A30L1T13 (9-(3-(dimethylamino)propyl)-15-(1-((9Z,12Z)-octadeca-9,12-dien-1-yl)-1H-1,2,3-triazol-4-yl)-8,12-dioxo-7,13-dioxo-3,4-dithia-9-azapentadecyl nonanoate, 200 mg, 239 μmol , 43.5% yield) was obtained as a yellow oil.

Example A31L1T14



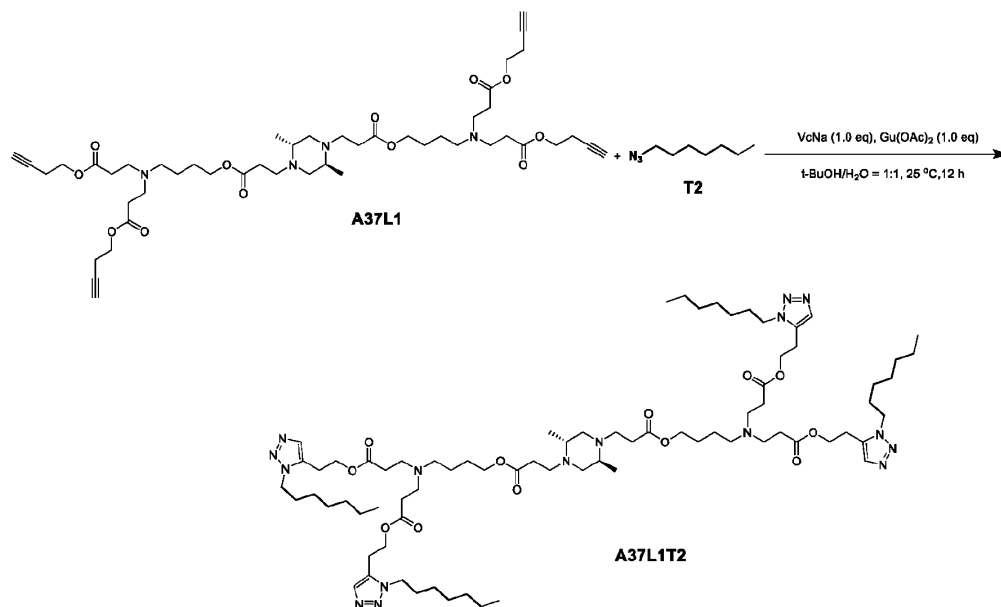
[0371] To a solution of compound A31L1 (250 mg, 459 μ mol, 1.0 eq) in H₂O (2 mL) and t-BuOH (2 mL) was added Cu(OAc)₂ (42 mg, 229 μ mol, 0.5 eq) and sodium L-ascorbate (45 mg, 229 μ mol, 0.5 eq) and compound T14 (164 mg, 528 μ mol, 1.15 eq). The mixture was stirred at 15 °C for 15h. TLC (dichloromethane/ methanol = 10/1, R_f = 0.3) indicated compound **A31L1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite and the filter cake was washed with EtOAc (5 mL). The mixture was separated, washed with brine (5 mL). To the organic layer was added 20 mL (0.1M EDTA, AcONa, pH=5) and stirred at 25 °C for 30 min. The mixture was separated, washed with NaHCO₃ (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound A31L1T14 (undecan-6-yl 6-(4-(7-(3-(dimethylamino)propyl)-4,8,17-trioxo-3,18-dioxo-12,13-dithia-7-azapentacosyl)-1H-1,2,3-triazol-1-yl)hexanoate, 220 mg, 257 μ mol, 56.0% yield) was obtained as a yellow oil.

Example A33L1T6



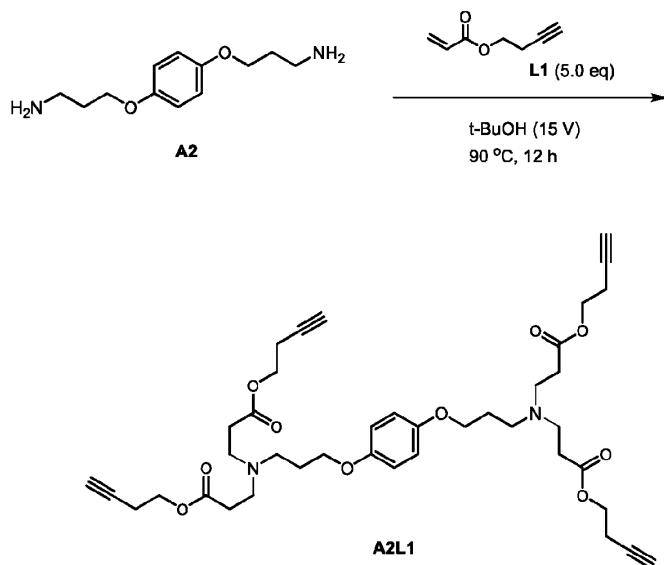
[0372] To a solution of compound A33L1 (350 mg, 707 μmol , 1.0 eq) in H_2O (2 mL) and $t\text{-BuOH}$ (2 mL) was added $\text{Cu}(\text{OAc})_2$ (64 mg, 354 μmol , 0.5 eq) and sodium L-ascorbate (70 mg, 354 μmol , 0.5 eq) and compound T6 (149 mg, 814 μmol , 1.15 eq). The mixture was stirred at 15 °C for 15h. TLC (dichloromethane/ methanol = 10/1, R_f = 0.3) indicated compound A33L1 was consumed completely and one new spot formed. The reaction was clean according to TLC. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of Celite and the filter cake was washed with EtOAc (5 mL). The mixture was separated, washed with brine (5 mL). To the organic layer was added 20 mL (0.1M EDTA, AcONa, pH=5) and stirred at 25 °C for 30 min. The mixture was separated, washed with NaHCO_3 (15 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was used into the next step without further purification. Compound A33L1T6 (8-((3-(dimethylamino)propyl)(3-(2-(1-(8-methylnonyl)-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)amino)octyl nonanoate, 200 mg, 295 μmol , 41.7% yield) was obtained as a yellow oil.

Example A37L1T2



[0373] To a solution of compound A37L1 (0.25 g, 278 μmol , 1.0 eq) in t-BuOH (2 ml), H₂O (2 ml) was added VcNa (55.2 mg, 278 μmol , 1.0 eq) and Cu(OAc)₂ (50.6 mg, 278 μmol , 1.0 eq), compound T2 (157 mg, 1.11 mmol, 4.0 eq). The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 10:1, product/*R_f* = 0.4; start material/*R_f* = 0.6) indicated compound A37L1 was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 ml). The organic phase was separated, washed with brine 5 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 ml), THF (2ml), then 5 ml (0.1 M EDTA, CH₃COONa, pH=5) was added the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with sat. NaHCO₃ 5 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound A37L1T2 (tetrakis(2-(1-heptyl-1H-1,2,3-triazol-5-yl)ethyl) 3,3',3'',3'''-((((3,3'-((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(propanoyl))bis(oxy))bis(butane-4,1-diyl))bis(azanetriyl))tetrapropionate, 0.2 g, 136 μmol , 49.0% yield) was obtained as brown oil.

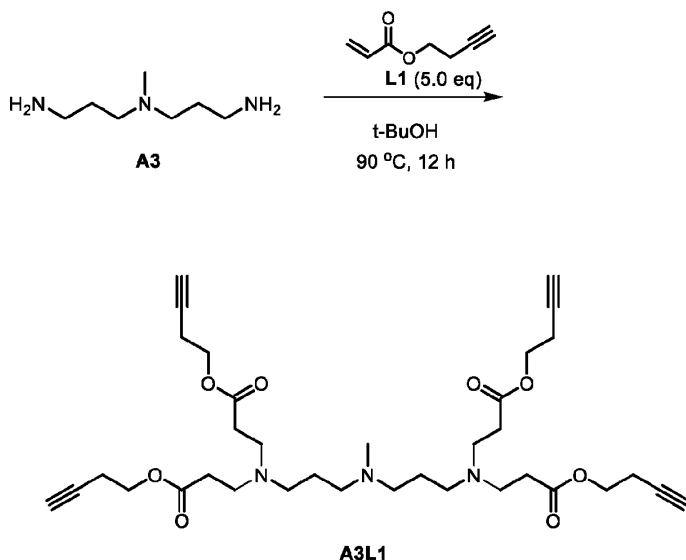
Example A2L1



[0374] To a solution of compound A2 (3.00 g, 13.4 mmol, 1.0 eq) in t-BuOH (30 mL) was added compound L1 (8.30 g, 66.9 mmol, 5.0 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.2) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (30 mL). The residue was diluted with H₂O (10mL) and extracted with DCM (100mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to Ethyl acetate/THF 20/1). Compound A2L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-(((1,4-phenylenebis(oxy))bis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 4.00 g, 5.55 mmol, 41.5% yield) was obtained as yellow oil.

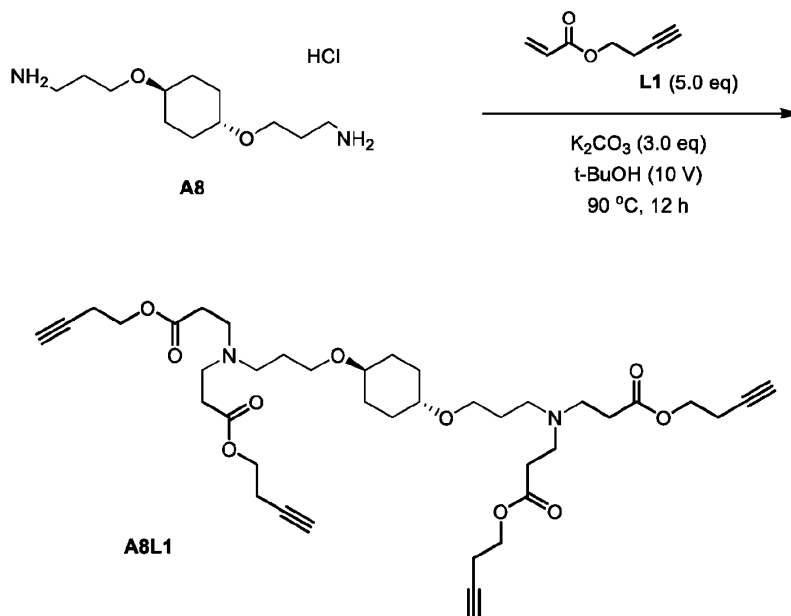
¹H NMR: 400 MHz CDCl₃ δ ppm 6.82 (s, 4 H), 4.17 (t, J = 6.82 Hz, 8 H), 3.92 (t, J = 6.07 Hz, 4 H), 2.80 (t, J = 7.00 Hz, 8 H), 2.61 (t, J = 6.82 Hz, 4 H), 2.44 - 2.56 (m, 16 H), 2.01 (t, J = 2.63 Hz, 3 H), 1.85-1.91 (m, 4 H), 1.56 (s, 2 H).

Example A3L1



[0375] To a solution of compound A3 (2.00 g, 13.8 mmol, 1.0 eq) in t-BuOH (30 mL) was added compound L1 (8.55 g, 68.9 mmol, 5.0 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.2) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (30 mL). The residue was diluted with H₂O (10 mL) and extracted with DCM (100 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to Ethyl acetate/MeOH 20/1). Compound A3L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-(((methylazanediyl)bis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 6.00 g, 9.35 mmol, 67.9% yield) was obtained as Light yellow oil. ¹H NMR: 400 MHz CDCl₃ δ ppm 4.19 (t, J = 6.82 Hz, 8 H), 2.78 (t, J = 7.13 Hz, 8 H), 2.54 (td, J = 6.82, 2.63 Hz, 8 H), 2.40 - 2.51 (m, 12 H), 2.31 (s, 4 H), 2.20 (s, 3 H), 2.02 (t, J = 2.63 Hz, 3 H), 1.60 (s, 4 H).

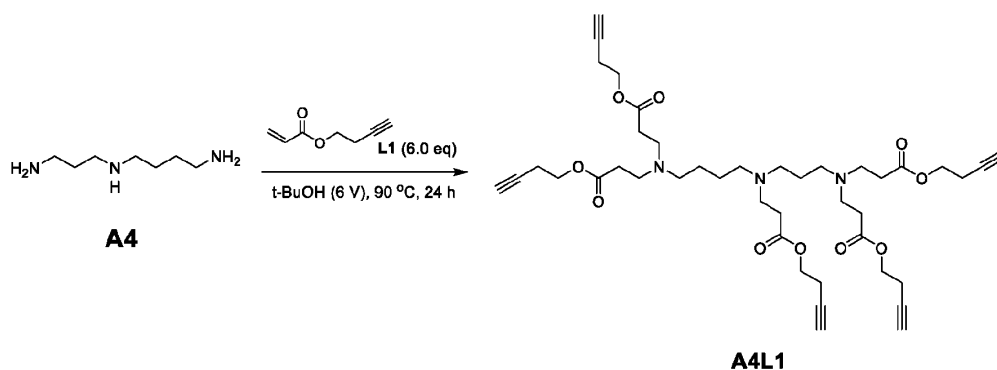
Example A8L1



[0376] To a solution of compound A8 (3.00 g, 9.89 mmol, 1.0 eq, 2HCl) in t-BuOH (30 mL) was added K_2CO_3 (4.10 g, 29.7 mmol, 3.0 eq) and compound L1 (6.14 g, 49.5 mmol, 5.0 eq). The mixture was stirred at 90°C for 12 h. TLC (Dichloromethane: Methanol = 10: 1, product R_f = 0.18) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (30 mL). The residue was diluted with H_2O (10mL) and extracted with DCM (100mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 100/1 to Ethyl acetate/THF 20/1). Compound A8L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(oxy))bis(propane-3,1-diyl))bis(azanetriyl))tetrapropionate, 3.00 g, 4.12 mmol, 41.7% yield, 99.9% purity) was obtained as yellow oil.

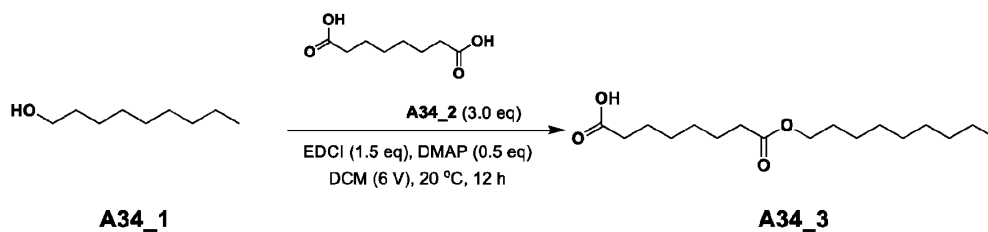
^1H NMR: 400 MHz CDCl_3 δ ppm 4.19 (t, J = 6.82 Hz, 8 H), 3.43 (t, J = 6.25 Hz, 4 H), 3.22 (s, 2 H), 2.77 (t, J = 7.13 Hz, 8 H), 2.41 - 2.61 (m, 20 H), 1.93 - 2.06 (m, 8 H), 1.63 - 1.72 (m, 4 H), 1.52 - 1.60 (m, 2 H), 1.22 - 1.33 (m, 4 H).

Example A4L1



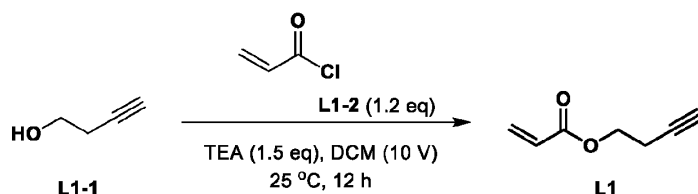
[0377] To a solution of A4 (3 g, 20.65 mmol, 1 eq) in t-BuOH (15 mL) was added L1 (16.67 g, 134.26 mmol, 6.5 eq). The mixture was stirred at 90 °C for 24 h. TLC (Dichloromethane: Methanol = 10:1, product R_f = 0.48) showed the raw material response to complete. The mixture was evaporated to dryness. The residue was purified by column chromatography (product R_f = 0.48) (SiO₂, Dichloromethane: Methanol=100/1 to 10/1). A4L1 (di(but-3-yn-1-yl) 3,3'-((3-((4-(bis(3-(but-3-yn-1-yloxy)-3-oxopropyl)amino)butyl)(3-(but-3-yn-1-yloxy)-3-oxopropyl)amino)propyl)azanediyl)dipropionate, 4.5 g, 5.88 mmol, 28.44% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.18 (t, J = 6.8 Hz, 10H), 2.77 (t, J = 7.2 Hz, 10H), 2.34 - 2.59 (m, 28H), 2.02 (t, J = 2.6 Hz, 5H), 1.55 (quin, J = 7.1 Hz, 2H), 1.33 - 1.44 (m, 4H).

Example A34_3



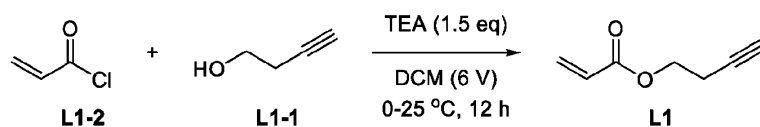
[0378] To a solution of A34_1 (5 g, 34.6 mmol, 1 *eq*) and A34_2 (18.1 g, 103 mmol, 3 *eq*) in DCM (30 mL) was added EDCI (9.97 g, 51.9 mmol, 1.5 *eq*) and DMAP (2.12 g, 17.3 mmol, 0.5 *eq*). The mixture was stirred at 20 °C for 12h. TLC (Petroleum ether: Ethyl acetate = 5:1, product R_f = 0.43) showed the raw material response to complete. The residue was diluted with H₂O 100 mL and extracted with DCM 200 mL. Dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 20/1. A34_3 (8 g, 26.63 mmol, 76.82% yield) was obtained as a white solid.

Example L1



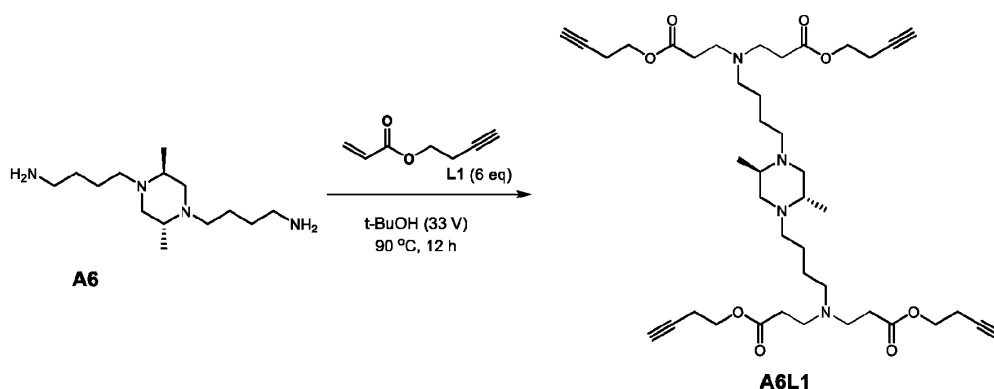
[0379] To a solution of compound L1-1 (200 g, 2.85 mol, 216 mL, 1 *eq*) in DCM (2 L) was added TEA (433 g, 4.28 mol, 596 mL, 1.5 *eq*) and compound L1-2 (310 g, 3.42 mol, 278 mL, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether : Ethyl acetate = 5:1, R_f = 0.45) showed reactant was used up. The reaction mixture was added H₂O (1 L). The organic phase was separated, washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Dichloromethane = 100/1 to 1/1). Compound L1 (but-3-yn-1-yl acrylate, 500 g, 4.03 mol, 70.6% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ ppm 6.44 (dd, J = 17.2, 1.41 Hz, 1 H), 6.08 - 6.20 (m, 1 H), 5.86 (dd, J = 10.4, 1.34 Hz, 1 H), 4.27 (t, J = 6.8 Hz, 2 H), 2.58 (td, J = 6.8, 2.8 Hz, 2 H), 2.02 (t, J = 2.8 Hz, 1 H).

In another illustrative embodiment, L1 was synthesized as follows:



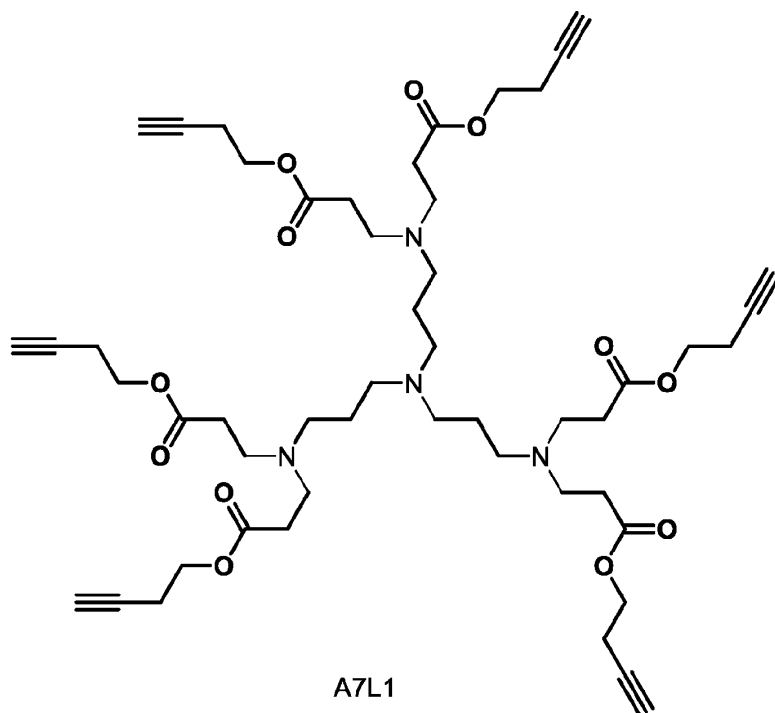
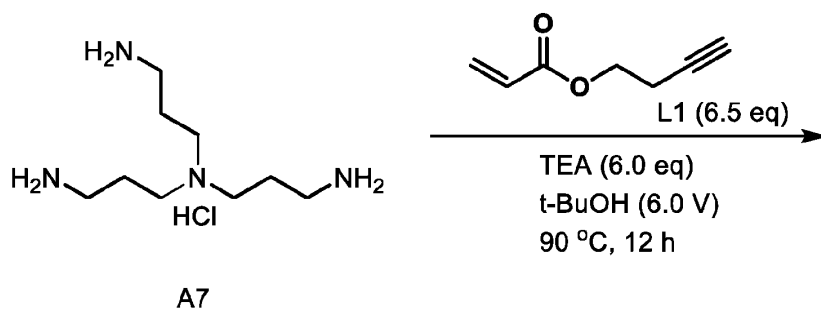
[0380] To a solution of compound L1-1 (20 g, 285.3 mmol, 21.6 mL, 1.0 eq) in DCM (120 mL) was added TEA (43.3 g, 428.0 mmol, 59.5 mL, 1.5 eq) and compound L1-2 (30.99 g, 342.4 mmol, 27.8 mL, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 2/1, R_f (compound L1-1) = 0.24, R_f (L1) = 0.77) indicated the reaction was complete. The reaction was pour into 50 mL H₂O, and extracted with DCM (50 mL × 2), the combined organic phase was concentrated. The residue was purified by flash silica gel chromatography (ISCO®, 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). L1 (25 g, 201.3 mmol, 70.5% yield) was obtained as colorless oil.

Example A6L1



[0381] To a solution of compound A6 (3 g, 11.7 mmol, 1 eq) in t-BuOH (100 mL) was added compound L1 (8.71 g, 70.2 mmol, 6 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Dichloromethane/Methanol = 100/1 to 1/1). Compound A6L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(butane-4,1-diyl))bis(azanetriyl))tetrapropionate, 4 g, 5.31 mmol, 45.4% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ ppm 4.19 (t, J = 6.8 Hz, 8 H), 2.78 (t, J = 7.2 Hz, 12 H), 2.29 - 2.61 (m, 23 H), 2.13 - 2.27 (m, 3 H), 1.93 - 2.08 (m, 6 H), 1.30 - 1.52 (m, 8 H), 1.05 (br d, J = 6.0 Hz, 6 H).

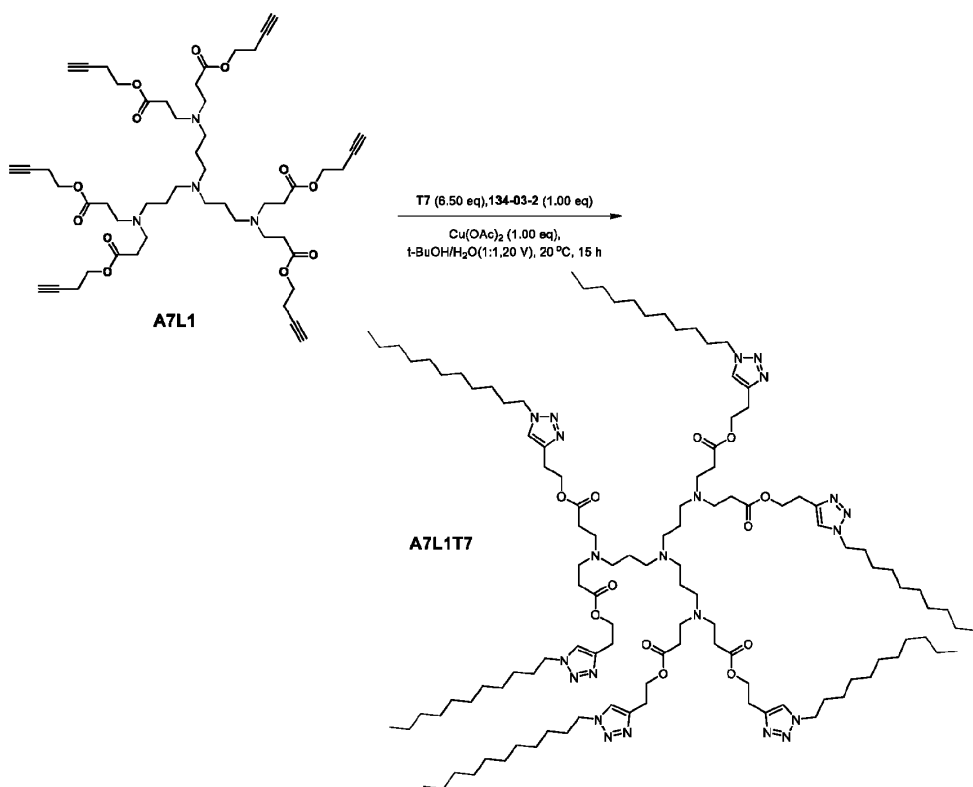
Example A7L1



[0382] To a solution of compound A7 (5.00 g, 22.2 mmol, 1.00 *eq*, HCl) in t-BuOH (30.0 mL) was added TEA (13.5 g, 133.5 mmol, 18.6 mL, 6.00 *eq*) and compound L1 (17.9 g, 144.6 mmol, 6.5 *eq*). The mixture was stirred at 90 °C for 12 h. LC-MS showed of compound A7

consumed completely and 100% of desired compound was detected. TLC (Dichloromethane: Methanol = 10:1, R_f (product) = 0.43) indicated compound A7 was consumed completely and two new spots formed. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (30.0 mL). The residue was purified by column chromatography (SiO₂, DCM: MeOH = 100/1 to 10/1). Compound A7L1 (hexa(but-3-yn-1-yl) 3,3',3'',3''',3''',3''''-(nitrilotris(propane-3,1-diyl))tris(azanetriyl))hexapropionate, 4.00 g, 4.29 mmol, 19.3% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.17-4.20 (m, 12H), 3.05 (s, 1H), 2.70-2.87 (m, 12H), 2.31-2.63 (m, 35H), 2.03 (s, 6H), 1.55-1.62 (m, 4H).

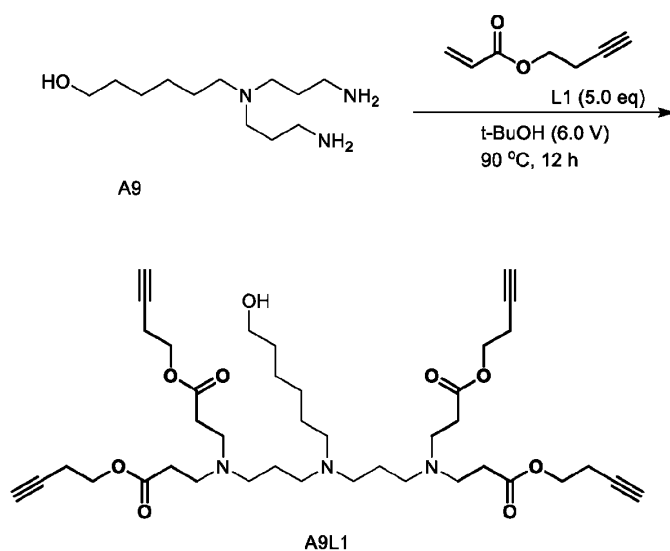
Example A7L1T7



[0383] To a solution of A7L1 (200 mg, 214 μmol, 1.00 eq) in t-BuOH (2.0 mL) and H₂O (2.0 mL) was added L(+) sodium ascorbate (CAS # 134-03-2, 42.5 mg, 214 μmol, 1.00 eq) and Cu(OAc)₂ (38.9 mg, 214 μmol, 1.00 eq) and compound T7 (274 mg, 1.39 mmol,

6.50 eq). The mixture was stirred at 15 °C for 12 hrs. TLC (Dichloromethane: Methanol = 10:1, R_f (Product) = 0.43) indicated reactant 1 was consumed completely and two new spots formed. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated and 20 mL (0.1M EDTA, CH_3COONa , pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with sat. NaHCO_3 (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. Compound A7L1T7 (hexakis(2-(1-undecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3''',3''',3''''-(((nitrilotris(propene-3,1-diyl))tris(azanetriyl)))hexapropionate, 200 mg, 91.5 μmol , 42.7% yield, 96.9% purity) was obtained as a brown solid. LC-MS RT (product) = 2.334 min) showed desired compound was detected.

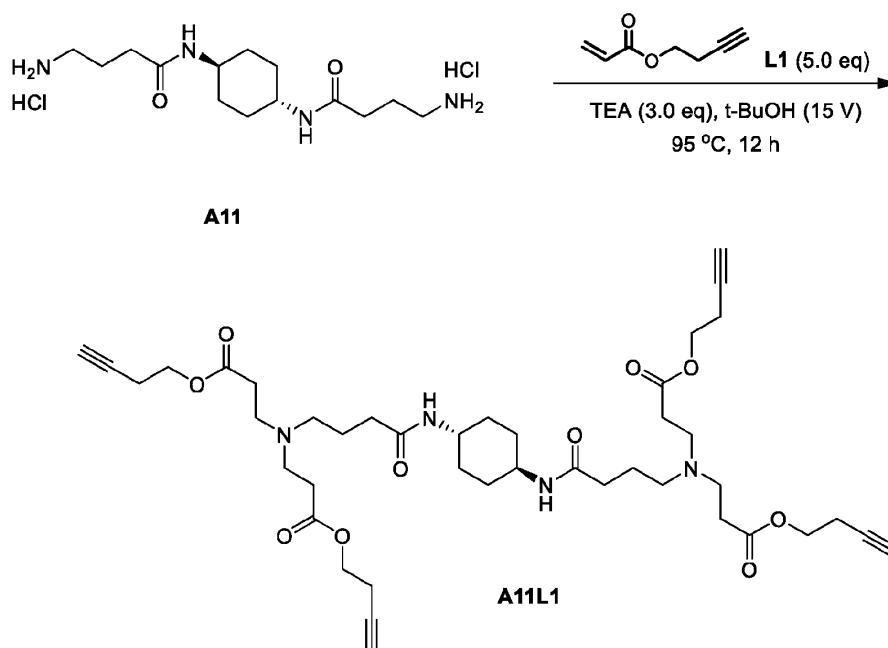
Example A9L1



[0384] To a solution of compound A9 (2.40 g, 10.4 mmol, 1.00 eq) in *t*-BuOH (15.0 mL) was added compound L1 (6.44 g, 51.9 mmol, 5.00 eq). The mixture was stirred at 95 °C for 12h. LC-MS showed of compound A9 consumed completely and 94% of desired compound was detected. The reaction mixture was allowed to cold to room temperature. The combined filtrates were concentrated to dryness. The residue was purified by column chromatography (SiO_2 , Petroleum ether/THF = 100/1 to 1/1). A9L1 (tetra(but-3-yn-1-yl) 3,3',3'',3''',3''',3''''-(((6-hydroxyhexyl)azanediyl)bis(propene-3,1-diyl))bis(azanetriyl))tetrapropionate, 4.0 g, 5.50 mmol,

26.49% yield) was obtained as yellow oil. ^1H NMR: 400 MHz CDCl_3 , δ 4.17-4.26 (m, 8H), 3.60-3.66 (m, 2H), 2.76-2.80 (m, 8H), 2.52-2.56 (m, 8H), 2.35-2.46 (m, 18H), 2.01-2.05 (m, 4H), 1.52-1.61 (m, 6H), 1.26-1.46 (m, 7H).

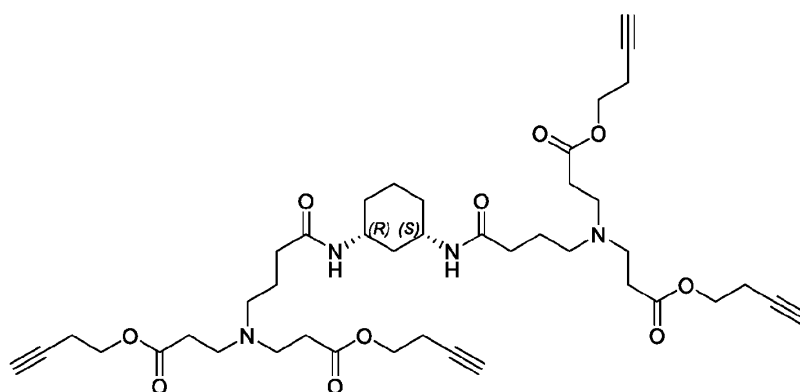
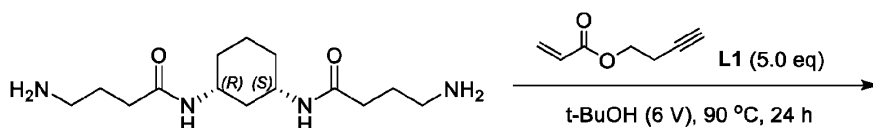
Example A11L1



[0385] To a solution of compound A11 (3.00 g, 10.5 mmol, 1.0 eq) in t-BuOH (45.0 mL) was added TEA (3.20 g, 31.6 mmol, 4.40 mL, 3.0 eq) and compound L1 (6.55 g, 52.7 mmol, 5.0 eq). The solution was stirred at 95 °C for 12 h. TLC (DCM : MeOH = 10 : 1, R_f = 0.60) and LCMS (product: RT = 0.934 min) showed the starting material was consumed completely. After filtration via filter paper, the mother liquid was concentrated under reduced pressure to dryness to provide a white solid. The crude product was purified by column chromatography on silica gel eluted with petroleum EtOAc : THF : MeOH = 1 : 0 : 0 to 0 : 0 : 1. A11L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(azanediyl))bis(4-oxobutane-4,1-diyl))bis(azanetriyl))tetrapropionate, 3.60 g, 4.61 mmol, 43.7% yield) was obtained as a white solid. ^1H NMR: (400 MHz, CDCl_3) δ : 6.27 - 6.25 (br d, J = 8.0 Hz, 2 H), 4.21 - 4.17 (t, J = 13.6 Hz, 8 H), 3.77 - 3.76 (d, J = 6.4 Hz, 2 H), 2.73 - 2.72 (t, J = 6.4 Hz, 8 H), 2.56 - 2.53 (m, 8 H),

2.46 (m, 8 H), 2.44 - 2.43 (m, 8 H), 2.13 (m, 4 H), 2.04 - 2.03 (t, $J = 2.4$ Hz, 4 H), 1.77 - 1.74 (t, $J = 12.4$ Hz, 4 H), 1.32 - 1.31 (m, 4 H), 1.28 (m, 4 H).

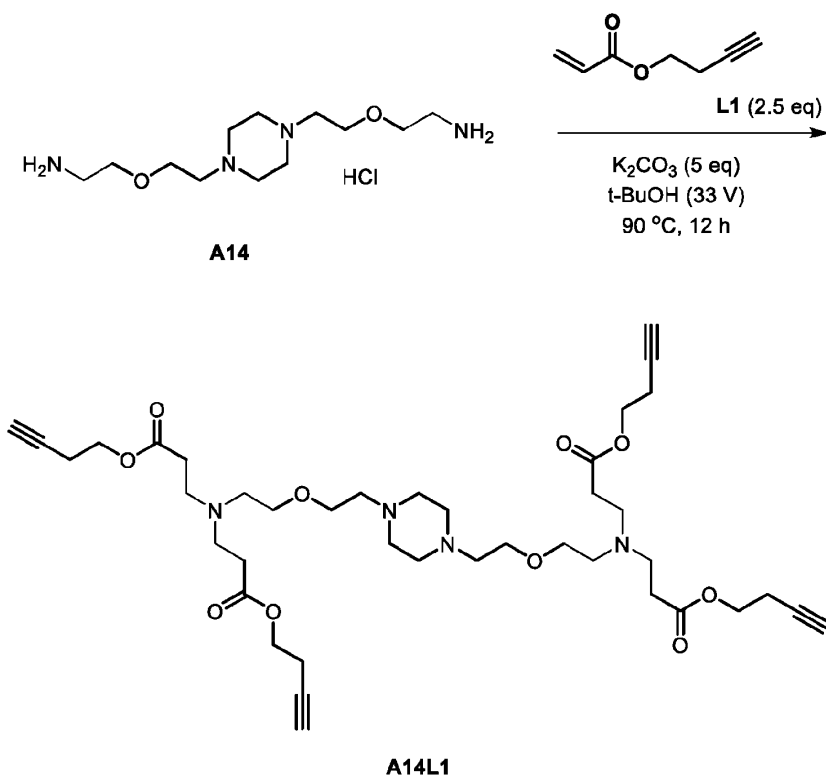
Example A12L1



[0386] To a solution of A12 (5 g, 15.58 mmol, 1 *eq*, HCl) in t-BuOH (20 mL) was added TEA (4.73 g, 46.75 mmol, 6.51 mL, 3 *eq*) and L1 (11.61 g, 93.50 mmol, 6 *eq*). The mixture was stirred at 90 °C for 24h. LCMS showed the starting material was consumed completely. The mixture was evaporated to dryness. The residue was purified by column chromatography (product $R_f=0.52$) (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1). A12L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((1R,3S)-cyclohexane-1,3-diyl)bis(azanediyl))bis(4-oxobutane-4,1-diyl))bis(azanetriyl))tetrapropionate, 6 g, 7.68 mmol, 49.30% yield) was obtained as yellow oil.

¹H NMR: 400 MHz CDCl₃ δ 6.17 (br d, $J = 7.9$ Hz, 2H), 4.19 (t, $J = 6.8$ Hz, 8H), 3.85 (dtd, $J = 4.2, 7.8, 11.7$ Hz, 2H), 2.65 - 2.83 (m, 8H), 2.55 (dt, $J = 2.6, 6.8$ Hz, 8H), 2.45 (t, $J = 6.6$ Hz, 8H), 2.38 (br t, $J = 6.0$ Hz, 4H), 2.19 - 2.27 (m, 1H), 2.12 (t, $J = 7.0$ Hz, 4H), 2.04 (t, $J = 2.6$ Hz, 4H), 2.02 - 1.94 (m, 2H), 1.68 - 1.86 (m, 5H), 1.62 (br s, 1H), 1.39 - 1.53 (m, 1H), 0.98 - 1.19 (m, 3H).

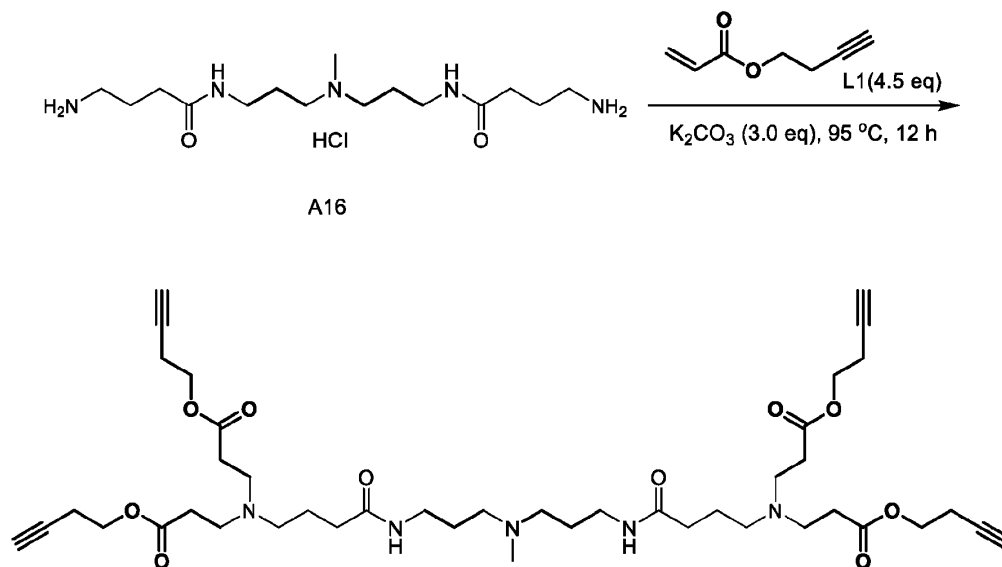
Example A14L1



[0387] To a solution of compound A14 (3 g, 7.39 mmol, 1 *eq*, 4HCl) in t-BuOH (100 mL) was added K₂CO₃ (5.10 g, 36.9 mmol, 5 *eq*) and compound L1 (5.50 g, 44.3 mmol, 6 *eq*). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to yield a residue. The residue was purified by column chromatography (SiO₂, Dichloromethane/Methanol = 100/1 to 1/1). Compound A14L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((piperazine-1,4-diylbis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(azanetriyl))tetrapropionate, 3.9 g, 5.15 mmol, 69.8% yield) was obtained as a yellow oil.

¹H NMR: 400 MHz CDCl₃ δ ppm 4.18 (t, *J* = 6.8 Hz, 8 H), 3.56 (t, *J* = 5.6 Hz, 4 H), 3.48 (t, *J* = 6.0 Hz, 4 H), 2.84 (t, *J* = 7.2 Hz, 8 H), 2.66 (t, *J* = 6.0 Hz, 5 H), 2.02 (t, *J* = 2.4 Hz, 4 H).

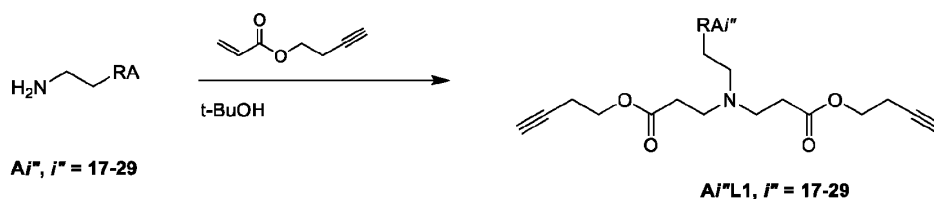
Example A16L1



[0388] To a solution of compound A16 (4.30 g, 12.2 mmol, 1.00 *eq*, HCl) in *t*-BuOH (30.0 mL) was added K₂CO₃ (5.07 g, 36.7 mmol, 3.00 *eq*) and compound L1 (6.83 g, 55.0 mmol, 4.50 *eq*). The mixture was stirred at 90 °C for 12h. LC-MS (RT = 1.803) showed of compound A16 consumed completely and 100% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove *t*-BuOH (30 mL). The residue was purified by column chromatography (SiO₂, DCM: MeOH = 100/1 to 10/1). Compound A16L1 (di(but-3-yn-1-yl) 4,22-bis(3-(but-3-yn-1-yloxy)-3-oxopropyl)-13-methyl-8,18-dioxo-4,9,13,17,22-pentaazapentacosanedioate, 4.00 g, 4.93 mmol, 40.3% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 8.84-8.87 (t, *J* = 8 Hz, 2H), 4.17-4.21 (t, *J* = 8 Hz, 8H), 3.29-3.33 (m, 4H), 2.74-2.78 (t, *J* = 8 Hz, 8H), 2.53-2.57 (m, 8H), 2.41-2.47 (m, 16H), 2.22 (s, 3H), 2.15-2.18 (t, *J* = 8 Hz, 4H), 2.03-2.04 (t, *J* = 4 Hz, 4H), 1.68-1.79 (m, 8H).

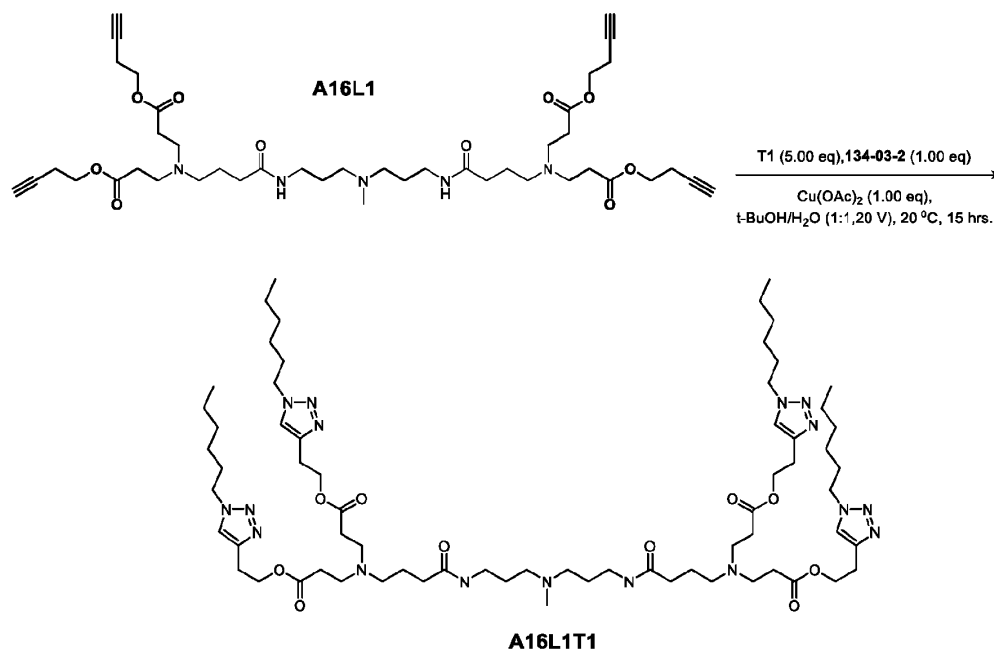
Example A1''L1, *i*'' = 17 - 29

[0389] Compounds $Ai''L1$, $i'' = 17-29$ can be prepared as schematically shown below, where the group “ RAi'' ” is implicitly defined based on the formulae Ai'' , $i'' = 17-29$, given in Table 1, as indicated above.



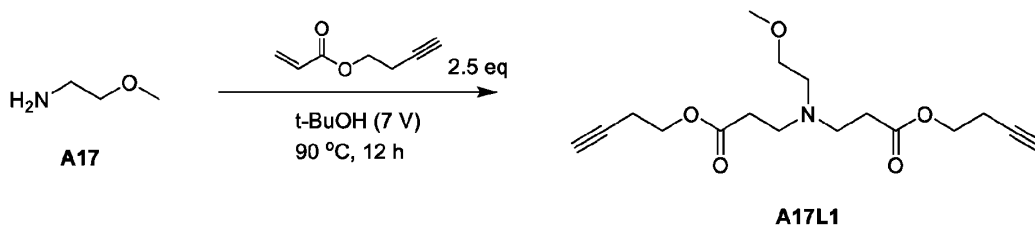
[0390] $L1$ is added to a solution of amine Ai'' , $i'' = 17-29$ in a solvent such as $t-BuOH$. The mixture is stirred, at for example $90^\circ C$ for a certain time, such as 12 h. The reaction is followed by, for example TLC (for example with dichloromethane/methanol = 10/1), where the respective $R_{f(Ai'')}$ and $R_{f(Ai''L1)}$ are used as indicators of reaction completion. The reaction medium is treated to obtain a final residue that eventually is purified, such as by column chromatography purification (for example SiO_2 , petroleum ether/ethyl acetate = 100/1 to 0/1). Such reaction medium treatment may involve steps such as concentrated under vacuum yielding a first residue that is then subject to extraction, such as for example by diluting it with H_2O and extracting with DCM, with the combined organic layer then dried over, for example, Na_2SO_4 , filtered and concentrated under reduced pressure to give a final residue. Such preparation process yields compound $Ai''L1$, $i'' = 17-29$ with yields that in embodiments of this invention ranged from 34% to over 90%.

Example A16L1T1



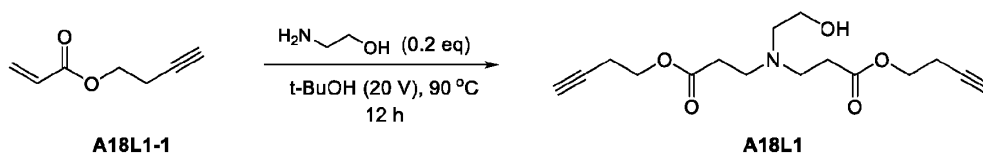
[0391] To a solution of compound A16L1 (400 mg, 493 μ mol, 1.00 eq) in t-BuOH (4.0 mL) and H₂O (4.0 mL) was added L(+) sodium ascorbate (CAS # 134-03-2, 97.6 mg, 493 μ mol, 1.00 eq) and Cu(OAc)₂ (89.5 mg, 493 μ mol, 1.00 eq) and compound T1 (313 mg, 2.46 mmol, 5.00 eq). The mixture was stirred at 15 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f (product) = 0.43) indicated reactant 1 was consumed completely and two new spots formed. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated and 20 mL (0.1M EDTA, CH₃COONa, pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with sat. NaHCO₃ (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound A16L1T1 (bis(2-(1-hexyl-1H-1,2,3-triazol-4-yl)ethyl) 4,22-bis(3-(2-(1-hexyl-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)-13-methyl-8,18-dioxo-4,9,13,17,22-pentaazapentacosanedioate, 200 mg, 143 μ mol, 29.0% yield, 94.3% purity) was obtained as yellow oil. LC-MS RT (product) = 1.402 min showed desired compound was detected.

Example A17L1



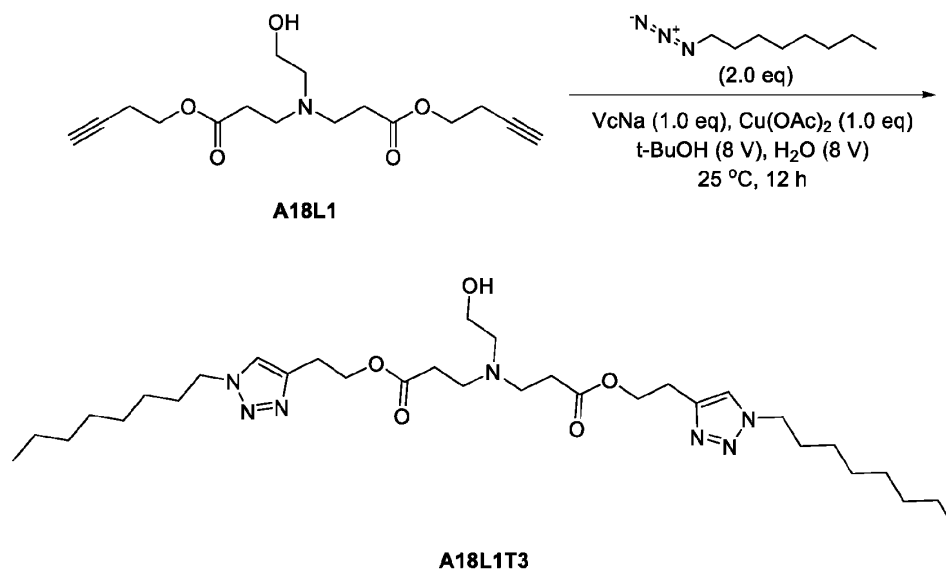
[0392] To a solution of A17 (1 g, 13.3 mmol, 1.16 mL, 1.0 eq) in t-BuOH (10 mL) was added but-3-ynyl prop-2-enoate (4.13 g, 33.2 mmol, 2.5 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, $R_{f(A17)} = 0.06$, $R_{f(A17L1)} = 0.35$) indicated the reaction was complete. The reaction was concentrated under vacuum, the residue was diluted with H₂O (10 mL) and extracted with DCM (10 mL $\times$ 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 0/1). A17L1 (di(but-3-yn-1-yl) 3,3'-((2-methoxyethyl)azanediyl)dipropionate, 4.0 g, 12.3 mmol, 92.9% yield) was obtained as light yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.19 (t, $J = 6.80$ Hz, 4 H), 3.44 (t, $J = 6.00$ Hz, 2 H), 3.34 (s, 3 H), 2.86 (t, $J = 7.20$ Hz, 4 H), 2.67 (t, $J = 6.00$ Hz, 2 H), 2.46 - 2.59 (m, 8 H), 2.01 (t, $J = 2.40$ Hz, 2 H).

Example A18L1



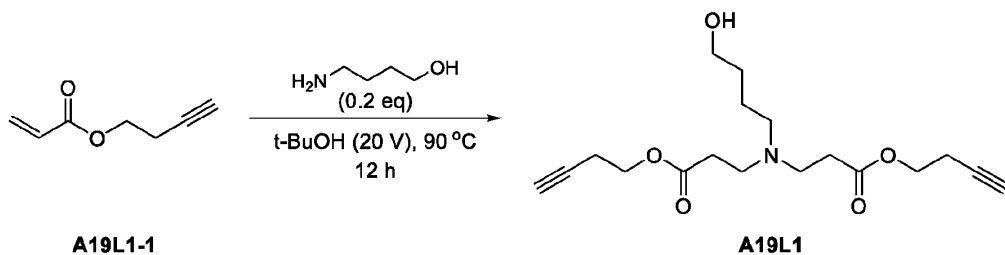
[0393] To a solution of Compound A18L1-1 (1.00 g, 16.4 mmol, 988 μ L, 1.00 eq) in t-BuOH (20 mL) was added but-3-ynyl prop-2-enoate (5.08 g, 40.9 mmol, 2.50 eq). The mixture was stirred at 90 °C for 12 h. LC-MS (Product Rt = 1.934, MS+1 = 310) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate to DCM: MeOH = 50:1 to 0:1) Compound A18L1 (di(but-3-yn-1-yl) 3,3'-((2-hydroxyethyl)azanediyl)dipropionate, 3.80 g, 12.3 mmol, 75.0% yield) as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.19 (t, $J = 6.8$ Hz, 4H), 3.58 (t, $J = 4.8$ Hz, 2H), 2.81 (t, $J = 6.8$ Hz, 4H), 2.47 - 2.61 (m, 10H), 2.01 (t, $J = 2.8$ Hz, 2H).

Example A18L1T3



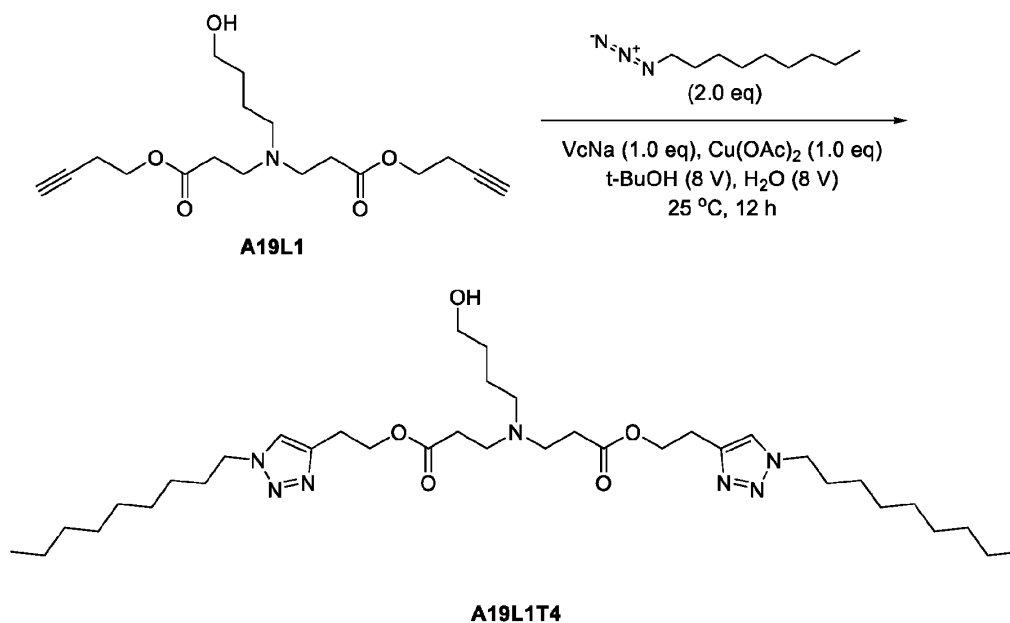
[0394] To a solution of Compound A18L1 (0.20 g, 647 μ mol, 1.00 *eq*) in H₂O (2 mL) and t-BuOH (2 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (128 mg, 647 μ mol, 1.00 *eq*), diacetoxycopper (117 mg, 647 μ mol, 1 *eq*) and 1-azido-octane (1.12 g, 1.29 mmol, 2.00 *eq*). The mixture was stirred at 25 °C for 12 h. LC-MS (Product Rt = 1.065, MS+1 = 620.5) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 mL). The organic phase was separated, washed with brine 5 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), then 20 mL (0.1M EDTA, CH₃COONa, Ph = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO₃ 15 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a A18L1T3 (bis(2-(1-octyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((2-hydroxyethyl)azanediyl)dipropionate, 0.20 g, 323 μ mol, 49.9% yield) as a yellow oil.

Example A19L1



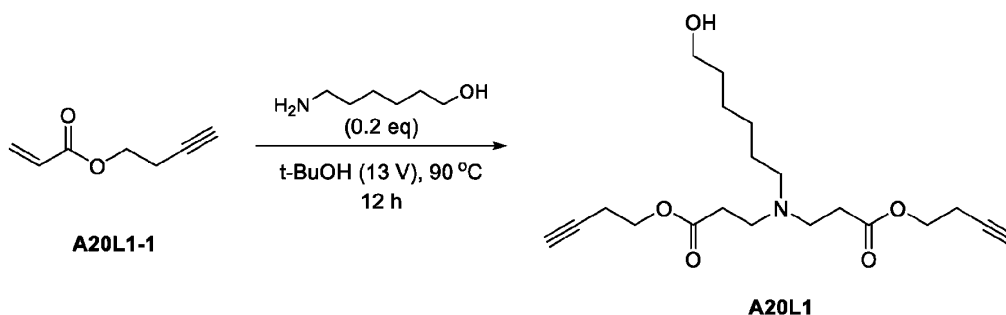
[0395] To a solution of A19L1-1 (1.00 g, 11.2 mmol, 1.04 mL, 1.00 eq) in t-BuOH (20 mL) was added but-3-ynyl prop-2-enoate (3.48 g, 28.0 mmol, 2.50 eq). The mixture was stirred at 90 °C for 12 h. LC-MS (Product Rt=2.03, MS+1=338) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate to DCM: MeOH = 50:1 to 0:1) to give a compound A19L1 (di(but-3-yn-1-yl) 3,3'-((4-hydroxybutyl)azanediyl)dipropionate, 3.30 g, 9.78 mmol, 87.1% yield) as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.19 (t, *J* = 6.8 Hz, 4H), 3.83 (s, 1H), 3.57 (t, *J* = 5.6 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 4H), 2.45 - 2.55 (m, 10H), 2.01 (t, *J* = 2.8 Hz, 2H), 1.60 (t, *J* = 5.6 Hz, 4H).

Example A19L1T4



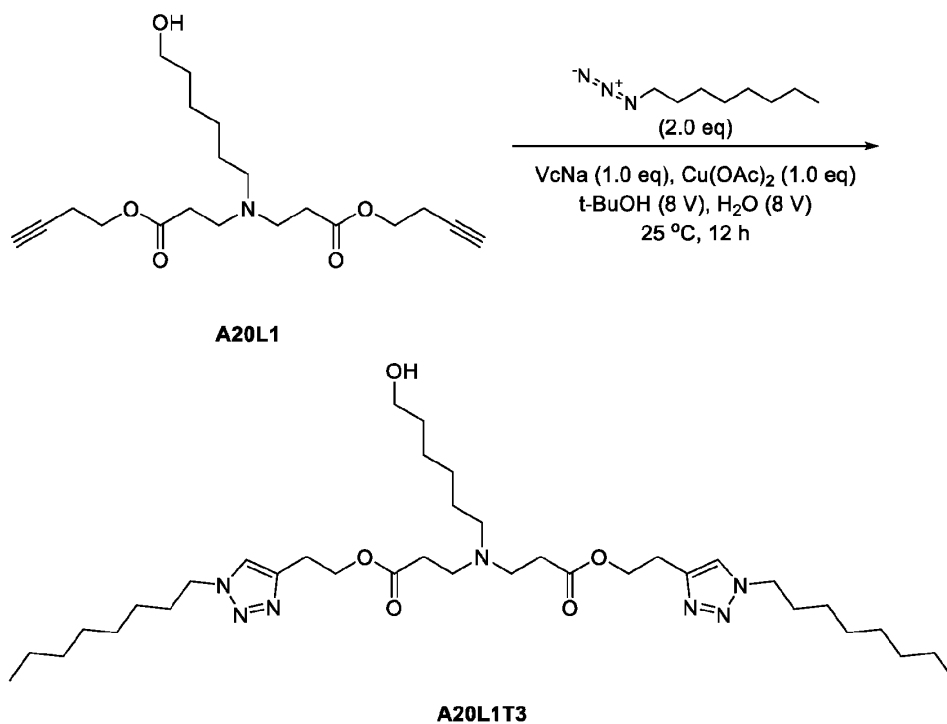
[0396] To a solution of Compound A19L1 (0.20 g, 593 μmol , 1.00 *eq*) in H_2O (2 mL) and *t*-BuOH (2 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (117 mg, 593 μmol , 1.00 *eq*), diacetoxycopper (108 mg, 593 μmol , 1.00 *eq*) and 1-azidononane (826 mg, 1.19 mmol, 2.00 *eq*). The mixture was stirred at 25 °C for 12 h. LC-MS (Product R_t = 1.348, $\text{MS}+1$ = 676.5) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 mL), the organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), then 20 mL (0.1M EDTA, CH_3COONa , pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO_3 15 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a Compound A19L1T4 (bis(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((4-hydroxybutyl)azanediyl)dipropionate, 0.20 g, 296 μmol , 49.9% yield) as a yellow oil.

Example A20L1



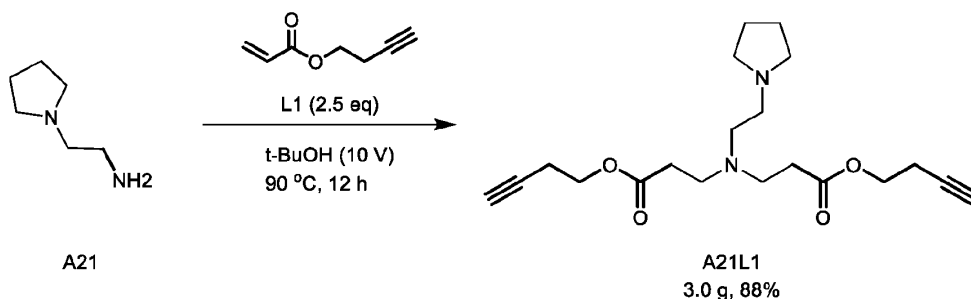
[0397] To a solution of Compound A20L1-1 (1.50 g, 12.8 mmol, 1.00 *eq*) in t-BuOH (20 mL) was added but-3-ynyl prop-2-enoate (3.97 g, 32.00 mmol, 2.5 *eq*). The mixture was stirred at 90 °C for 12 h. LC-MS (Product Rt = 2.21, MS+1 = 366) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate to DCM: MeOH = 50:1 to 0:1) to give a compound A20L1 (di(but-3-yn-1-yl) 3,3'-((6-hydroxyhexyl)azanediyl)dipropionate, 3.60 g, 9.85 mmol, 76.9% yield) as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.18 (t, *J* = 6.8 Hz, 4H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 4H), 2.41 - 2.55 (m, 10H), 2.01 (t, *J* = 2.4 Hz, 2H), 1.46 - 1.60 (m, 2 H), 1.28 - 1.37 (m, 7H).

Example A20L1T3



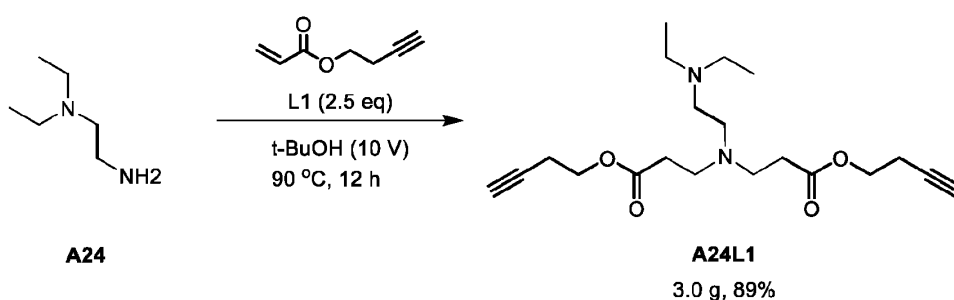
[0398] To a solution of A20L1 (0.25 g, 684.06 μmol , 1.00 *eq*) in H_2O (2 mL) and *t*-BuOH (2 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (136 mg, 684 μmol , 1 *eq*), diacetoxycopper (124 mg, 684 μmol , 1.00 *eq*) and 1-azidooctane (1.18 g, 1.37 mmol, 2.00 *eq*). The mixture was stirred at 25 °C for 12 h. LC-MS (Product Rt = 1.152, MS+1 = 676.5) showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 mL), the organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), then 20 mL (0.1M EDTA CH_3COONa , pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO_3 15 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a Compound A20L1T3 (bis(2-(1-octyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((6-hydroxyhexyl)azanediyl)dipropionate, 0.20 g, 296 μmol , 43.2% yield) as a yellow oil.

Example A21L1



[0399] To a solution of compound A21 (2.0 g, 17.5 mmol, 1 eq) in *t*-BuOH (20 mL) was added compound L1 (5.44 g, 43.7 mmol, 2.5 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane/Methanol = 10:1, compound A21 R_f = 0.02, compound L1 R_f = 0.55, compound A21L1 R_f = 0.20) indicated compound A21 was consumed completely. The reaction mixture was poured into H₂O (30 mL), and extracted with DCM (20 mL × 3). Then the organic phase was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~6% DCM/MeOH ethergradient @ 40 mL/min). Compound A21L1 (di(but-3-yn-1-yl) 3,3'-(2-(pyrrolidin-1-yl)ethyl)azanediyl)dipropionate, 4.4 g, 12.1 mmol, 69.3% yield) was obtained as a yellow oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 4.18 (t, J = 6.80 Hz, 4 H), 2.81 (t, J = 6.80 Hz, 4 H), 2.58 - 2.61 (m, 2 H), 2.46 - 2.56 (m, 14 H), 2.01 (t, J = 2.40 Hz, 2 H), 1.77 (dt, J = 6.40, 3.20 Hz, 4 H) LCMS: R_t = 1.901, $M + H$ = 363, 88%.

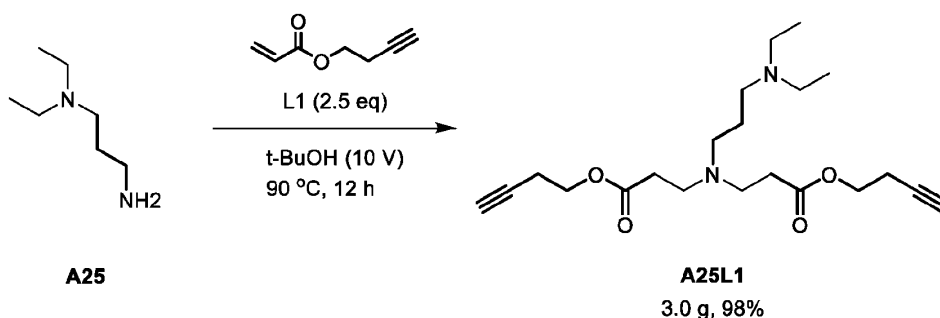
Example A24L1



[0400] To a solution of compound A24 (3 g, 25.8 mmol, 3.63 mL, 1 eq) in *t*-BuOH (30 mL) was added compound L1 (8.01 g, 64.5 mmol, 2.5 eq). The mixture was stirred at 90 °C for

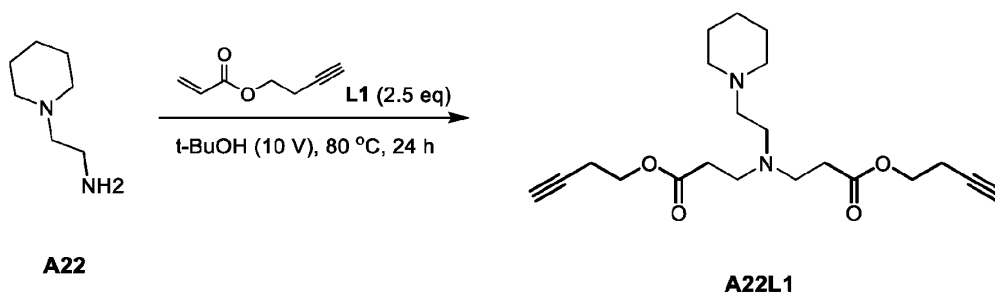
12h. TLC (Dichloromethane/Methanol = 10/1, compound A24 R_f = 0.10, compound A24L1 R_f = 0.15) indicated compound A24 was consumed completely. The reaction mixture was poured into H₂O (30 mL), and extracted with EtOAc (30 mL $\times$ 3). Then the organic phase was concentrated under vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 0/1). Compound A24L1 (di(but-3-yn-1-yl) 3,3'-((2-(diethylamino)ethyl)azanediyl)dipropionate, 7.0 g, 19.2 mmol, 74.3% yield) was obtained as a yellow oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 4.19 (t, J = 6.80 Hz, 4 H), 2.81 (t, J = 7.20 Hz, 4 H), 2.48 - 2.56 (m, 16 H), 2.01 (t, J = 2.40 Hz, 2 H), 1.03 (t, J = 7.20 Hz, 6 H). LCMS: R_t = 1.936, $M + H$ = 365, 89%.

Example A25L1



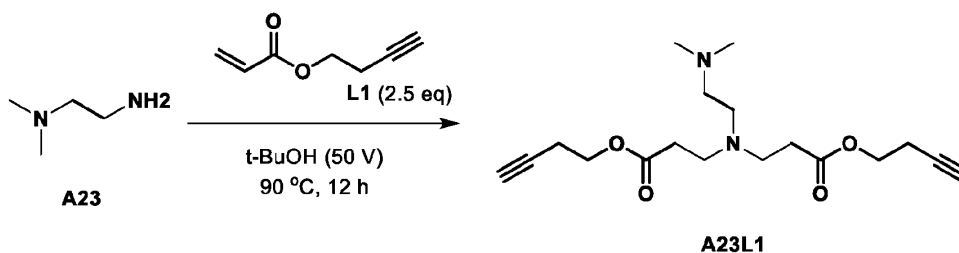
[0401] To a solution of compound A25 (3 g, 23.0 mmol, 1 eq) in t-BuOH (30 mL) was added compound L1 (7.15 g, 57.5 mmol, 2.5 eq). The mixture was stirred at 90 °C for 12h. TLC (Dichloromethane/Methanol = 10/1, compound A25 R_f = 0.05, compound A25L1 R_f = 0.12) indicated compound A25 was consumed completely. The reaction mixture was poured into H₂O (30 mL), and extracted with EtOAc (30 mL $\times$ 3). Then the organic phase was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO[®]; 80 g SepaFlash[®] Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether, gradient @ 40 mL/min). Compound A25L1 (di(but-3-yn-1-yl) 3,3'-((3-((diethylamino)propyl)azanediyl)dipropionate, 5.5 g, 14.3 mmol, 62.2% yield, 98.7% purity) was obtained as a yellow oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 4.19 (t, J = 7.20 Hz, 4 H), 2.78 (t, J = 7.20 Hz, 4 H), 2.40 - 2.55 (m, 16 H), 2.01 (t, J = 2.40 Hz, 2 H), 1.58 (quin, J = 7.60 Hz, 2 H), 1.02 (t, J = 7.20 Hz, 6 H). LCMS: R_t = 1.572, $M + H$ = 379, 98%.

Example A22L1



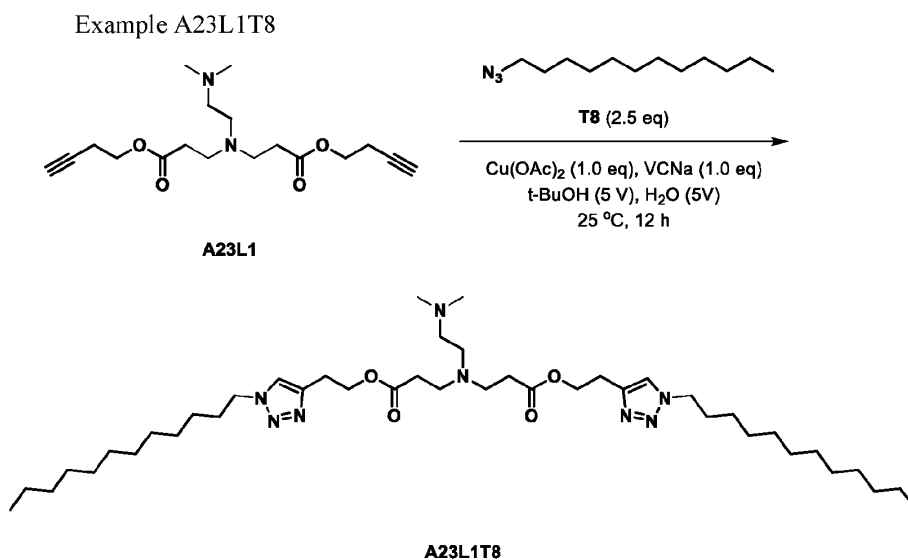
[0402] To a solution of A22 (3.0 g, 23.4 mmol, 3.34 mL, 1.0 eq) in t-BuOH (50 mL) was added L1 (7.26 g, 58.5 mmol, 2.5 eq) at 25 °C. The mixture was stirred 12 h at 80 °C. TLC (Dichloromethane/Methanol = 10/1, Product/ R_f = 0.5) showed the reaction was completely. The reaction mixture was quenched by addition H₂O (100 mL) and then extracted with DCM (50 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to Ethyl acetate/Methanol 40/1). Obtain A22L1 (di(but-3-yn-1-yl) 3,3'-((2-(piperidin-1-yl)ethyl)azanediyl)dipropionate, 3.0 g, 7.97 mmol, 34.0% yield) as yellow oil. ¹H NMR: (400 MHz, CDCl₃) δ ppm 4.11-4.20 (m, 4H), 2.39-2.82 (m, 20H), 2.01-2.04 (d, J = 13.6 Hz, 2H), 1.26-1.58 (m, 6H). LCMS: m/z = 377.2 (M^+H^+), R_t = 0.868 min.

Example A23L1



[0403] To a solution of compound A23 (3 g, 34.0 mmol, 3.72 mL, 1 eq) in t-BuOH (150 mL) was added compound L1 (10.6 g, 85.1 mmol, 2.5 eq). The mixture was stirred at

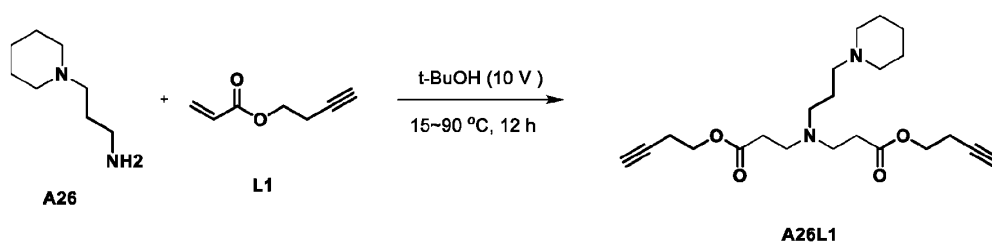
90 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to yield a residue. The residue was purified by column chromatography (SiO₂, Dichloromethane/Methanol = 100/1 to 1/1). Compound A23L1 (di(but-3-yn-1-yl) 3,3'-((2-(dimethylamino)ethyl)azanediyl)dipropionate, 4 g, 11.89 mmol, 34.9% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ ppm 4.19 (t, J = 6.8 Hz, 4 H), 2.82 (t, J = 7.2 Hz, 4 H), 2.44 - 2.62 (m, 10 H), 2.33 - 2.42 (m, 2 H), 2.25 (s, 6 H), 2.01 (t, J = 2.8 Hz, 2 H).



[0404] To a solution of compound A23L1 (0.2 g, 594 μ mol, 1 *eq*) in t-BuOH (1 mL) H₂O (1 mL) was added VCNa (117 mg, 594 μ mol, 1 *eq*), Cu(OAc)₂ (108 mg, 594 μ mol, 1 *eq*) and compound T8 (314 mg, 1.49 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL), the organic phase was separated, washed with brine 5 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), THF (2mL), then 20 mL (0.1M EDTA, CH₃COONa, pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO₃ (aq) 10 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue.

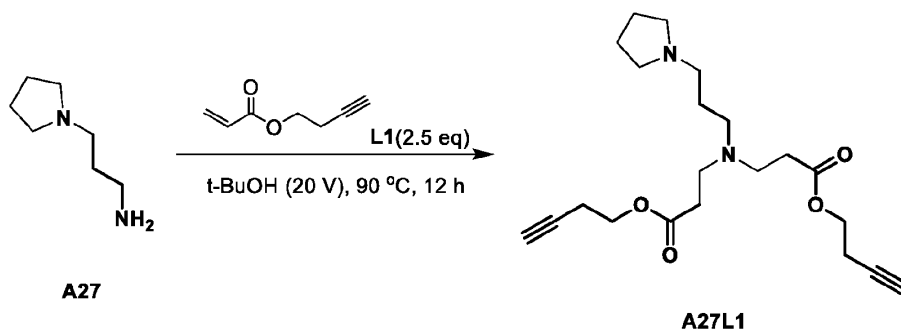
Without purification. Compound A23L1T8 (bis(2-(1-dodecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((2-(dimethylamino)ethyl)azanediyl)dipropionate, 0.2 g, 263 μ mol, 44.3% yield) was obtained as a yellow solid.

Example A26L1



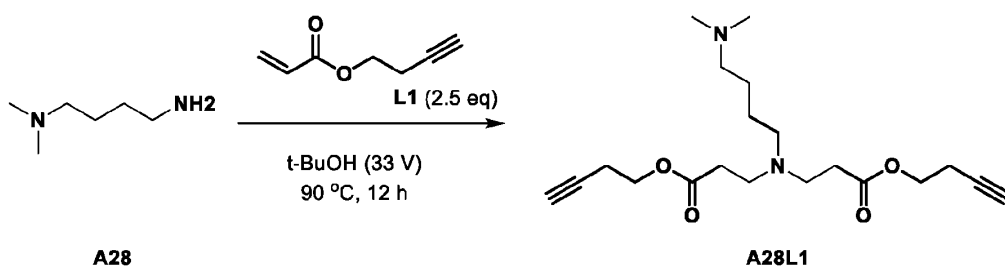
[0405] To a solution of A26 (3.0 g, 21.1 mmol, 1.0 eq) in t-BuOH (30 mL) was added L1 (6.55 g, 52.7 mmol, 2.5 eq) at 15 °C. The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane/Methanol=10/1, product/ R_f = 0.55) showed reactant was completely. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (15 mL). The residue was diluted with H₂O (10 mL) and extracted with DCM 100 (mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=0/1 to give A26L1 (di(3-butyn-1-yl) 3,3'-((3-(piperidin-1-yl)propyl)azanediyl)dipropionate, 3.2 g, 8.19 mmol, 38.8% yield) as yellow oil. ¹H NMR: (400 MHz CDCl₃) δ 4.18 (t, J = 6.0 Hz, 4H), 2.77 (t, J = 8.8 Hz, 4H), 2.53-2.54 (m, 4H), 2.52-2.53 (m, 7H), 2.48 (s, 3H), 2.45-2.46 (m, 2H), 2.01 (t, J = 2.8 Hz, 2H), 1.56-1.61 (m, 6H), 1.42 (s, 2H). LCMS: ($M/2 + H^+$) = 391.2.

Example A27L1



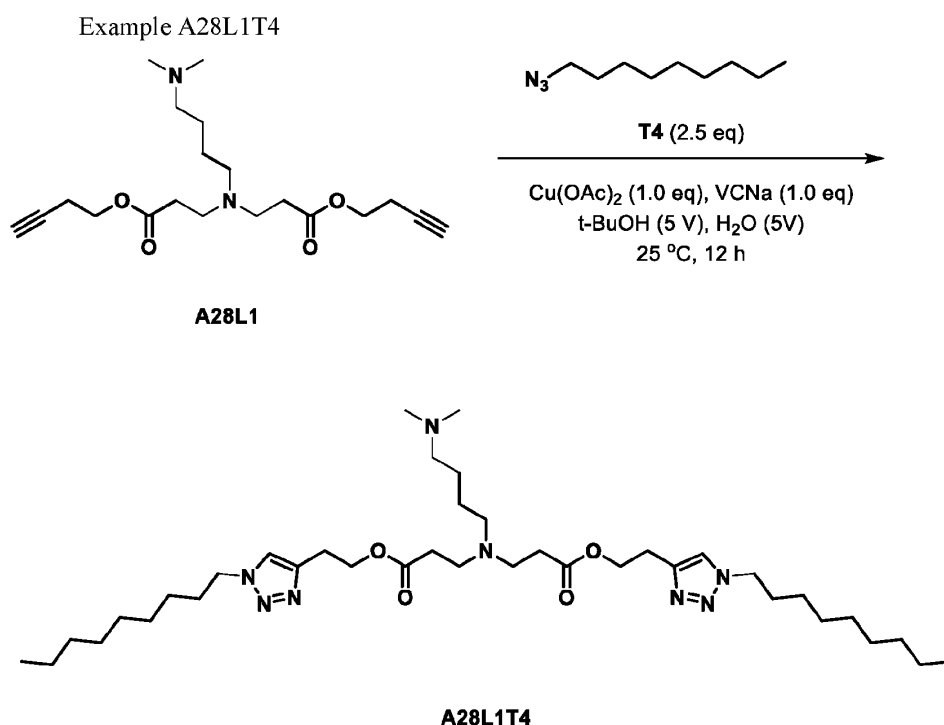
[0406] To a solution of compound A27 (4.0 g, 31.2 mmol, 1.0 eq) in t-BuOH (80 ml) was added compound L1 (9.68 g, 77.9 mmol, 2.5 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane/Methanol = 10:1, product/ R_f = 0.7; start material/ R_f = 0.2) indicated compound A27 was consumed completely. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (50 ml). The residue was diluted with H₂O 50 ml and extracted with DCM 50 ml. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/1). Compound A27L1 (di(but-3-yn-1-yl) 3,3'-((3-(pyrrolidin-1-yl)propyl)azanediyl)dipropionate, 6.0 g, 15.9 mmol, 51.0% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.16-4.19 (t, J = 6.8 Hz, 4H), 2.76-2.79 (t, J = 7.2 Hz, 4H), 2.39-2.54 (m, 16H), 2.00-2.01 (t, J = 2.8 Hz, 2H), 1.77-1.81 (m, 4H), 1.72-1.77 (m, 2H). LCMS : (M+H⁺ = 377).

Example A28L1



[0407] To a solution of compound A28 (3 g, 25.8 mmol, 1 eq) in t-BuOH (100 mL) was added compound L1 (8.01 g, 64.5 mmol, 2.5 eq). The mixture was stirred at 90 °C for 12 h. TLC

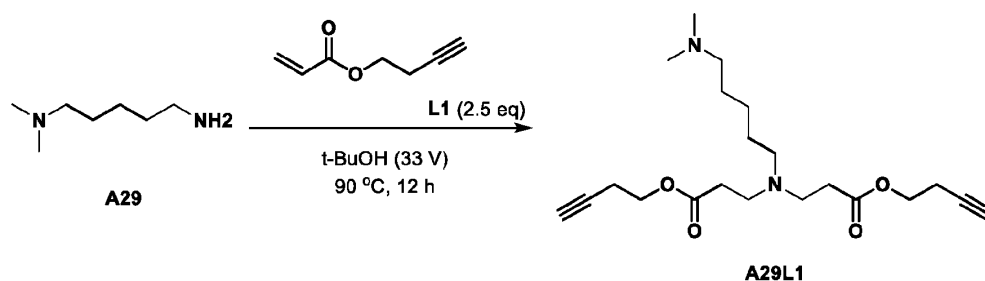
(Dichloromethane : Methanol = 10:1, R_f = 0.14) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Dichloromethane/Methanol = 100/1 to 1/1). Compound A28L1 (di(but-3-yn-1-yl) 3,3'-((4-(dimethylamino)butyl)azanediyl)dipropionate, 4 g, 11.0 mmol, 42.5% yield) was obtained as a yellow oil. ^1H NMR: 400 MHz CDCl_3 δ ppm 4.18 (t, J = 6.8 Hz, 4 H), 2.77 (t, J = 7.2 Hz, 4 H), 2.53 (br d, J = 2.8 Hz, 4 H), 2.46 (br t, J = 7.2 Hz, 6 H), 2.22 (s, 8 H), 1.98 - 2.07 (m, 2 H), 1.43 (br t, J = 3.6 Hz, 4 H).



[0408] To a solution of compound A28L1 (0.2 g, 549 μmol , 1 *eq*) in H_2O (1 mL), t-BuOH (1 mL) was added VCNa (109 mg, 549 μmol , 1 *eq*), $\text{Cu}(\text{OAc})_2$ (100 mg, 549 μmol , 1 *eq*) and T4 (232 mg, 1.37 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and

concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), THF (2mL), then 20 mL (0.1M EDTA, CH₃COONa, pH = 5) was added the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO₃ (aq) 10 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Without purification. Compound A28L1T4 (bis(2-(1-nonyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((4-(dimethylamino)butyl)azanediyl)dipropionate, 0.2 g, 284 μmol, 51.8% yield) was obtained as a yellow solid.

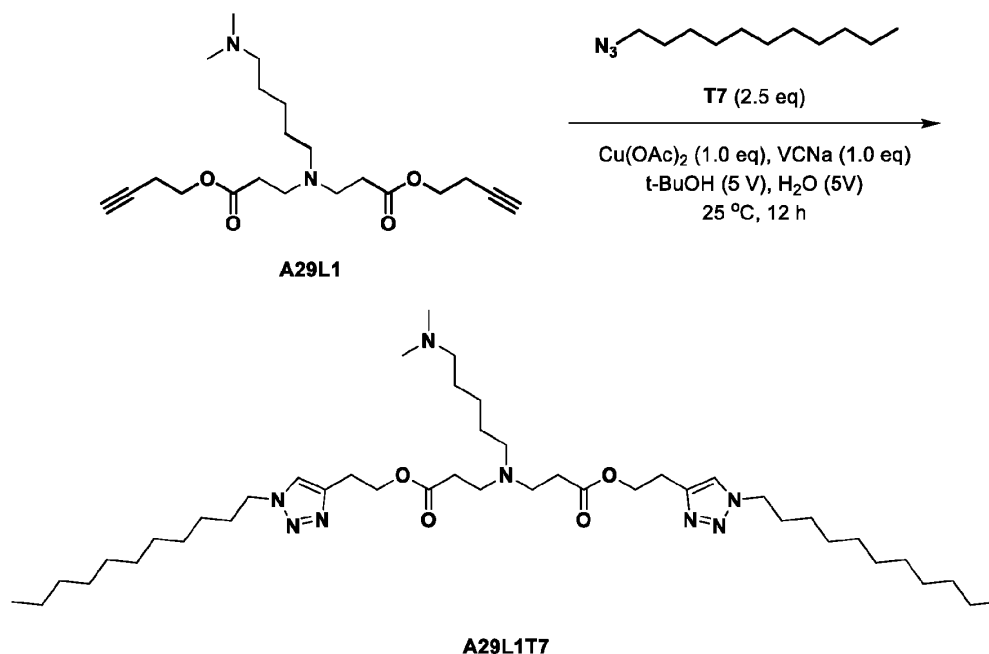
Example A29L1



[0409]

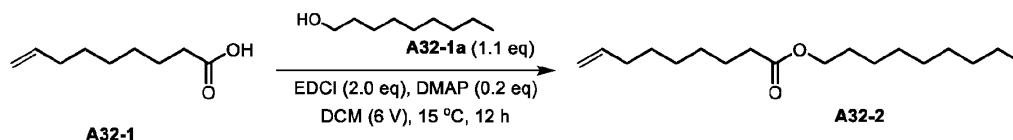
To a solution of compound A29 (3 g, 23.0 mmol, 1 *eq*) in t-BuOH (100 mL) was added compound L1 (7.15 g, 57.6 mmol, 2.5 *eq*). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, *R_f* = 0.31) showed reactant was used up. The reaction mixture was concentrated under reduced pressure to yield a residue. The residue was purified by column chromatography (SiO₂, Dichloromethane/Methanol = 100/1 to 1/1). Compound A29L1 (di(but-3-yn-1-yl) 3,3'-((5-(dimethylamino)pentyl)azanediyl)dipropionate, 4 g, 10.6 mmol, 45.9% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ ppm 4.18 (t, *J* = 6.8 Hz, 4 H), 2.77 (t, *J* = 7.2 Hz, 4 H), 2.53 (td, *J* = 6.8, 2.8 Hz, 4 H), 2.36 – 2.50 (m, 6 H), 2.18 – 2.28 (m, 8 H), 2.01 (t, *J* = 2.4 Hz, 2 H), 1.37 – 1.52 (m, 4 H), 1.27 (br d, *J* = 7.2 Hz, 2 H).

Example A29L1T7



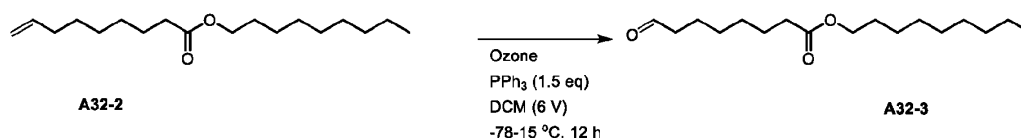
[0410] To a solution of compound A29L1 (0.2 g, 528 μmol , 1 *eq*) in H_2O (1.5 mL), *t*-BuOH (1.5 mL) was added VCNa (105 mg, 528 μmol , 1 *eq*), $\text{Cu}(\text{Oac})_2$ (96.0 mg, 528 μmol , 1 *eq*) and T7 (261 mg, 1.32 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.31) showed reactant was used up. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (15 mL). The organic phase was separated, washed with brine 5 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was dissolved in EtOAc (10 mL), THF (2mL), then 20 mL (0.1M EDTA, CH_3COONa , pH= 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with NaHCO_3 (aq) 10 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. Without purification. Compound A29L1T7 (bis(2-(1-undecyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((5-(dimethylamino)pentyl)azanediyl)dipropionate, 0.2 g, 259 μmol , 48.9% yield) was obtained as a yellow solid.

Example A32-2



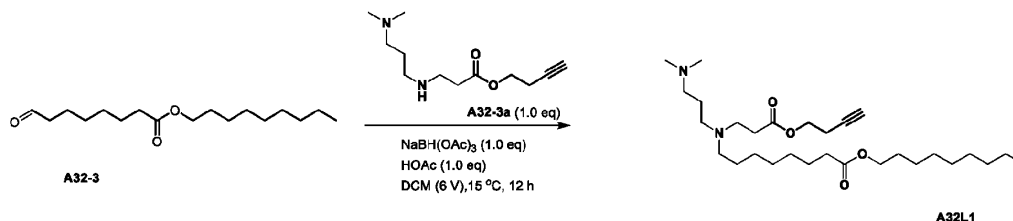
[0411] To a solution of compound A32-1 (3.00 g, 19.2 mmol, 1.00 *eq*) in DCM (18.0 mL) was added EDCI (7.36 g, 38.4 mmol, 2.00 *eq*) and DMAP (469.2 mg, 3.84 mmol, 0.20 *eq*) and compound A32-1a (3.05 g, 21.1 mmol, 1.10 *eq*). The mixture was stirred at 15 °C for 12h. TLC (Petroleum ether: Ethyl acetate = 15:1, R_f (product) = 0.58) indicated compound A32-1 was consumed completely and two new spots formed. The reaction mixture was concentrated under reduced pressure to remove DCM (18.0 mL). The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1). Compound A32-2 (3.80 g, 13.5 mmol, 70.1% yield) was obtained as white oil. ¹H NMR: 400 MHz CDCl₃ δ 5.77-5.84 (m, 1H), 4.92-5.02 (m, 2H), 4.04-4.08 (m, 2H), 2.28-2.32 (m, 2H), 2.02-2.05 (m, 2H), 1.58-1.62 (m, 4H), 1.28-1.39 (m, 18H), 0.87-0.90 (m, 3H).

Example A32-3



[0412] Ozone was bubbled into a solution of compound A32-2 (3.80 g, 13.5 mmol, 1.00 *eq*) in DCM (24.0 mL) at -78 °C for 10 minutes. After excess O₃ was purged by O₂, PPh₃ (5.29 g, 20.2 mmol, 1.50 *eq*) was added at -78 °C, the mixture was stirred at 20 °C for 12h. TLC (Petroleum ether: Ethyl acetate = 8:1, R_f (product) = 0.43) indicated compound A32-2 was consumed completely. The reaction mixture was concentrated under reduced pressure to remove DCM (30 mL). The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 10/1). Compound A32-3 (2.80 g, 9.84 mmol, 73.2% yield) was obtained as white oil. ¹H NMR: 400 MHz CDCl₃ δ 9.76-9.77 (t, *J* = 4.0 Hz, 1H), 4.05-4.08 (t, *J* = 8.0 Hz, 2H), 2.41-2.45 (m, 2H), 2.28-2.32 (t, *J* = 8.0 Hz 2H), 1.62-1.64 (m, 6H), 1.28-1.39 (m, 16H), 0.87-0.90 (m, 3H).

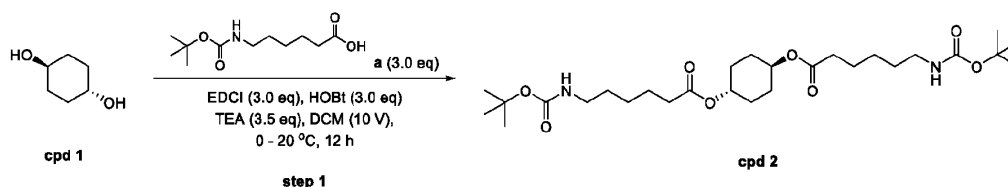
Example A32L1



[0413] To a solution of compound A32-3 (2.80 g, 9.84 mmol, 1.20 *eq*) in DCM (18.0 mL) was added compound A32-3a (1.86 g, 8.20 mmol, 1.00 *eq*) and HOAc (492.6 mg, 8.20 mmol, 469.6 μL , 1.00 *eq*) for 0.5 h and added NaBH(OAc)_3 (1.74 g, 8.20 mmol, 1.00 *eq*). The mixture was stirred at 15 °C for 11.5 h. LC-MS showed of compound A32-3 consumed completely and 98% of desired compound was detected. The reaction mixture was concentrated to dryness. The residue was purified by column chromatography (SiO_2 , DCM: MeOH = 100/1 to 10/1).

Compound A32L1 (nonyl 8-((3-(but-3-yn-1-yloxy)-3-oxopropyl)(3-(dimethylamino)propyl)amino)octanoate, 3.00 g, 6.06 mmol, 73.9% yield) was obtained as white oil. ^1H NMR: 400 MHz CDCl_3 δ 4.17-4.20 (t, $J = 4.0$ Hz, 2H), 4.04-4.07 (t, $J = 4.0$ Hz, 2H), 2.68-2.81 (m, 4H), 2.52-2.56 (m, 8H), 2.45-2.49 (m, 4H), 2.37-2.41 (m, 2H), 2.27-2.31 (t, $J = 8.0$ Hz, 2H), 2.02-2.03 (m, 5H), 1.74-1.81 (m, 2H), 1.58-1.65 (m, 4H), 1.28-1.42 (m, 19H), 0.87-0.90 (m, 3H).

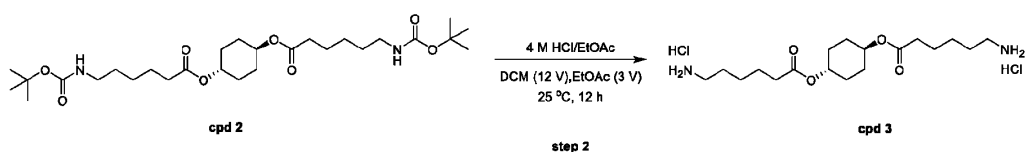
Example cpd 2



[0414] To a solution of cpd 1 in DCM (40.0 mL) was added compound a (23.8 g, 103 mmol, 3.0 *eq*), HOBT (13.9 g, 103 mmol, 3.0 *eq*), TEA (12.2 g, 120 mmol, 16.7 mL, 3.5 *eq*) and EDCI (19.8 g, 103 mmol, 3.0 *eq*) at 0 °C. The reaction solution was stirred at 20 °C for 3 h. TLC (petroleum ether : ethyl acetate = 1 : 1, product: $R_f = 0.6$) showed the starting material was consumed completely. After filtration via filter paper or Celite pad, the organic layer was concentrated under reduced pressure to dryness to provide a white solid. The crude product was purified by column chromatography on silica gel eluted with petroleum ether : ethyl acetate = 1 : 0 to 0 : 1. Compound cpd 2 (11.5 g, 21.1 mmol, 61.5% yield) was obtained as a white solid. ^1H

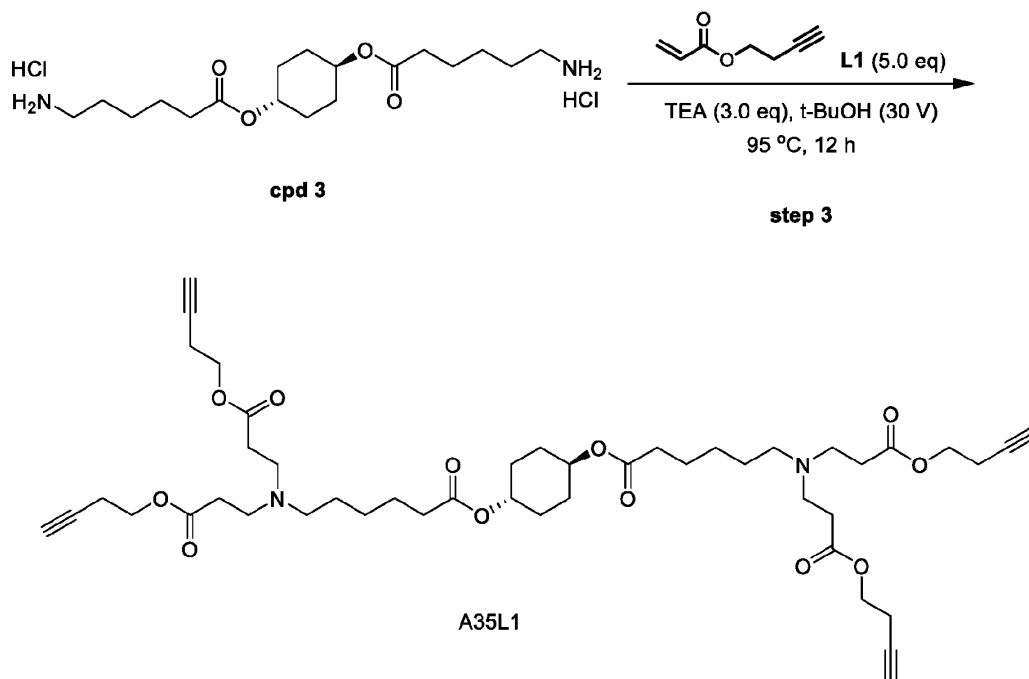
NMR: (400 MHz, CD₃OD) δ : 4.80 (br s, 2 H), 3.04 - 3.01 (t, J = 14.0 Hz, 4 H), 2.33 - 2.29 (m, 4 H), 1.97 - 1.95 (d, J = 7.2 Hz, 4 H), 1.64 - 1.60 (m, 4 H), 1.56 - 1.54 (m, 4 H), 1.47 - 1.45 (m, 6 H), 1.43 (s, 18 H), 1.35 - 1.33 (m, 5 H).

Example cpd 3

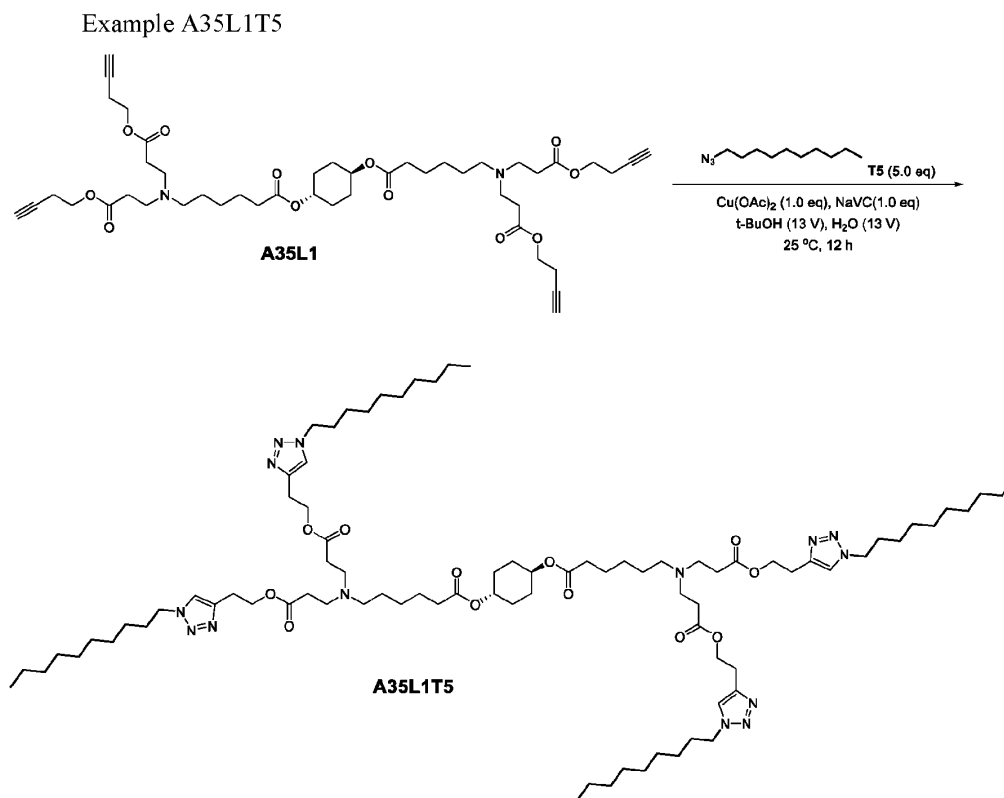


[0415] To a solution of cpd 2 in EtOAc (31.5 mL) and DCM (126 mL) was added 4 M HCl/EtOAc (4 M, 116 mL, 24.0 eq). The solution was stirred at 25 °C for 12 h. TLC (petroleum ether : ethyl acetate = 1 : 1, product: R_f = 0.60) showed the starting material was consumed completely. Filtered the white solid of cpd 3 (7.26 g, 17.4 mmol, 90.3% yield, 2 HCl) with suction and wash with 25.0 mL of DCM. Compound cpd 3 (7.26 g, 17.4 mmol, 90.3% yield, 2 HCl) was obtained as a white solid. ¹H NMR: (400 MHz, CD₃OD) δ : 4.79 (s, 2 H), 2.94 - 2.90 (t, J = 15.2 Hz, 4 H), 2.37 - 2.33 (t, J = 14.8 Hz, 4 H), 1.97 - 1.96 (m, 4 H), 1.70 - 1.64 (m, 8 H), 1.55 (m, 4 H), 1.42 (m, 4 H).

Example A35L1

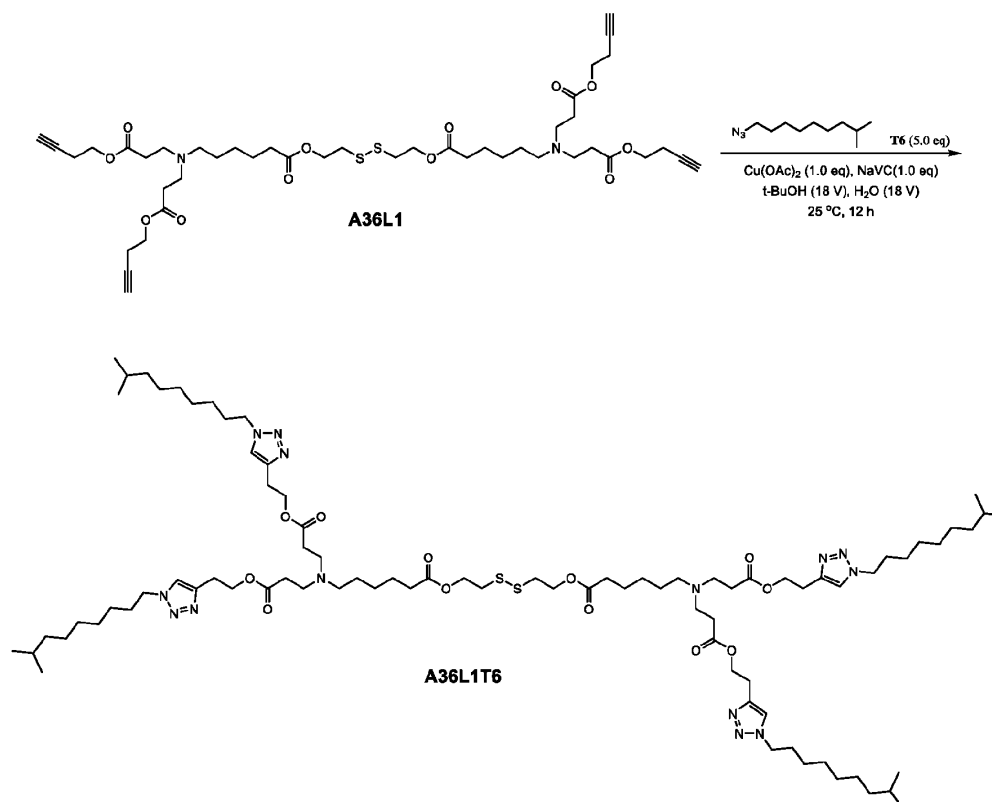


[0416] To a solution of cpd 3 (4.00 g, 9.63 mmol, 1.0 eq, 2 HCl) in t-BuOH (120 mL) was added TEA (2.92 g, 28.8 mmol, 4.02 mL, 3.0 eq) and compound L1 (5.98 g, 48.1 mmol, 5.0 eq). The solution was stirred at 95 °C for 12 h. LCMS (product: RT = 0.509 min) and TLC (dichloromethane : methanol = 10 : 1, product: R_f = 0.6) showed the starting material was consumed completely. After filtration via filter paper or Celite pad, the organic layer was concentrated under reduced pressure to dryness. The crude product was purified by column chromatography on silica gel eluted with petroleum dichloromethane : ethyl acetate = 1 : 0 to 0 : 1. A35L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(oxy))bis(6-oxohexane-6,1-diyl))bis(azanetriyl))tetrapropionate, 5.50 g, 6.56 mmol, 68.0% yield) was obtained as a brown oil. ^1H NMR: (400 MHz, CDCl_3) δ : 4.80 (s, 2 H), 4.20 - 4.17 (t, J = 13.6 Hz, 8 H), 2.79 - 2.75 (t, J = 14.8 Hz, 8 H), 2.55 - 2.52 (t, J = 16 Hz, 8 H), 2.47 - 2.46 (t, J = 14.0 Hz, 8 H), 2.42 - 2.38 (t, J = 14.4 Hz, 4 H), 2.28 (t, J = 15.2 Hz, 4 H), 2.02 - 2.01 (m, 4 H), 2.02 - 2.01 (m, 4 H), 1.99 - 1.93 (m, 4 H), 1.66 - 1.52 (m, 10 H), 1.47 - 1.40 (m, 4 H), 1.32 - 1.26 (m, 4 H).



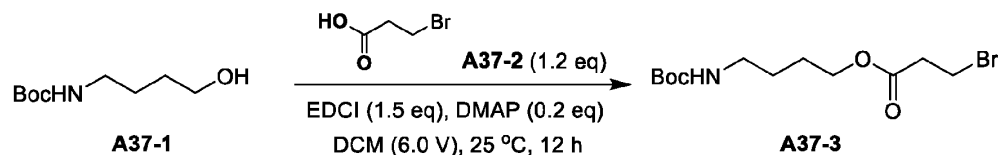
[0417] To a solution of A35L1 (220 mg, 262 μmol , 1.0 eq) in t-BuOH (3.00 mL), H_2O (3.00 mL) was added NaVC (51.9 mg, 262 μmol , 1.0 eq), Cu(OAc)_2 (47.6 mg, 262 μmol , 1.0 eq) and T5 (240 mg, 1.31 mmol, 5.0 eq). The solution was stirred at 25 °C for 12 h. TLC (DCM : MeOH = 10 : 1, product: R_f = 0.56) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10 mL). The organic phase was separated, washed with brine 5.00 mL, dried over Na_2SO_4 and filtered. Then 15.0 mL of solution (0.1 M EDTA, CH_3COONa , pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with brine 5.00 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. A35L1T5 (tetrakis(2-(1-decyl-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-((((trans)-cyclohexane-1,4-diyl)bis(oxy))bis(6-oxohexane-6,1-diyl))bis(azanetriyl))tetrapropionate, 200 mg, 139 μmol , 53.3% yield) was obtained as a brown solid.

Example A36L1T6



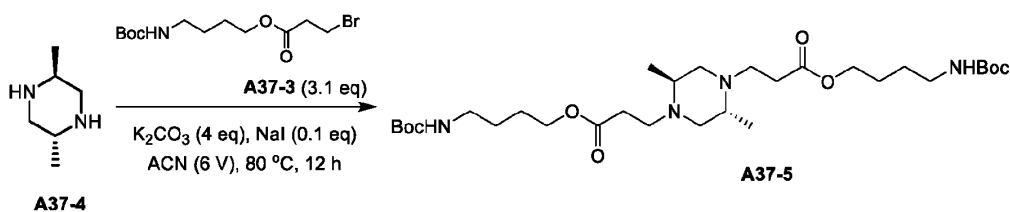
[0418] To a solution of A36L1 (220 mg, 250 μ mol, 1.0 eq) in t-BuOH (4.00 mL) and H₂O (4.00 mL) was added NaVC (49.6 mg, 250 μ mol, 1.0 eq), Cu(OAc)₂ (45.5 mg, 250 μ mol, 1 eq) and L1 (229 mg, 1.25 mmol, 5.0 eq). The solution was stirred at 25 °C for 12 h. TLC (DCM : MeOH = 10 : 1, product: R_f = 0.56) showed the starting material was consumed completely. The suspension was filtered through a pad of Celite and the filter cake was washed with DCM (10.0 mL). The organic phase was separated, washed with brine 5.00 mL, dried over Na₂SO₄ and filtered. Then 15.0 mL of solution (0.1 M EDTA, CH₃COONa, pH = 5) was added, the mixture was stirred at 25 °C for 30 min. The organic phase was separated, washed with brine 5.00 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. A36L1T6 (tetrakis(2-(1-(8-methylnonyl)-1H-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-(((disulfanediy)bis(ethane-2,1-diyl))bis(oxy))bis(6-oxohexane-6,1-diyl))bis(azanetriyl))tetrapropionate, 200 mg, 136 μ mol, 54.4% yield) was obtained as a brown solid.

Example A37-3



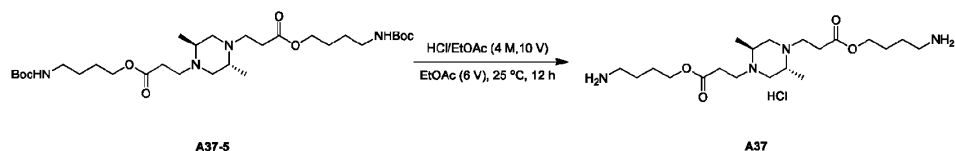
[0419] To a solution of compound A37-1 (40.0 g, 211 mmol, 1.0 eq) in DCM (250 ml) was added EDCI (60.7 g, 317 mmol, 1.5 eq) and DMAP (5.16 g, 42.2 mmol, 0.2 eq) compound A37-2 (38.8 g, 253 mmol, 26.2 ml, 1.2 eq). The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 2/1, product/*R_f* = 0.5; start material/*R_f* = 0.3) showed the raw material response to complete. The residue was diluted with H₂O 15 ml and extracted with DCM 20 ml. The combined organic layers were washed with brine 15 ml, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/1). Compound A37-3 (10.0 g, 30.8 mmol, 14.5% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.58 (s, 1H), 3.73-3.78 (m, 1H), 3.56-3.59 (d, *J* = 6.4, 2H), 3.14-3.16 (m, 2H), 2.81-2.85 (m, 2H), 2.77-2.80 (m, 1H), 1.64-1.71 (m, 2H), 1.52-1.61 (m, 2H), 1.44 (s, 9H).

Example A37-5



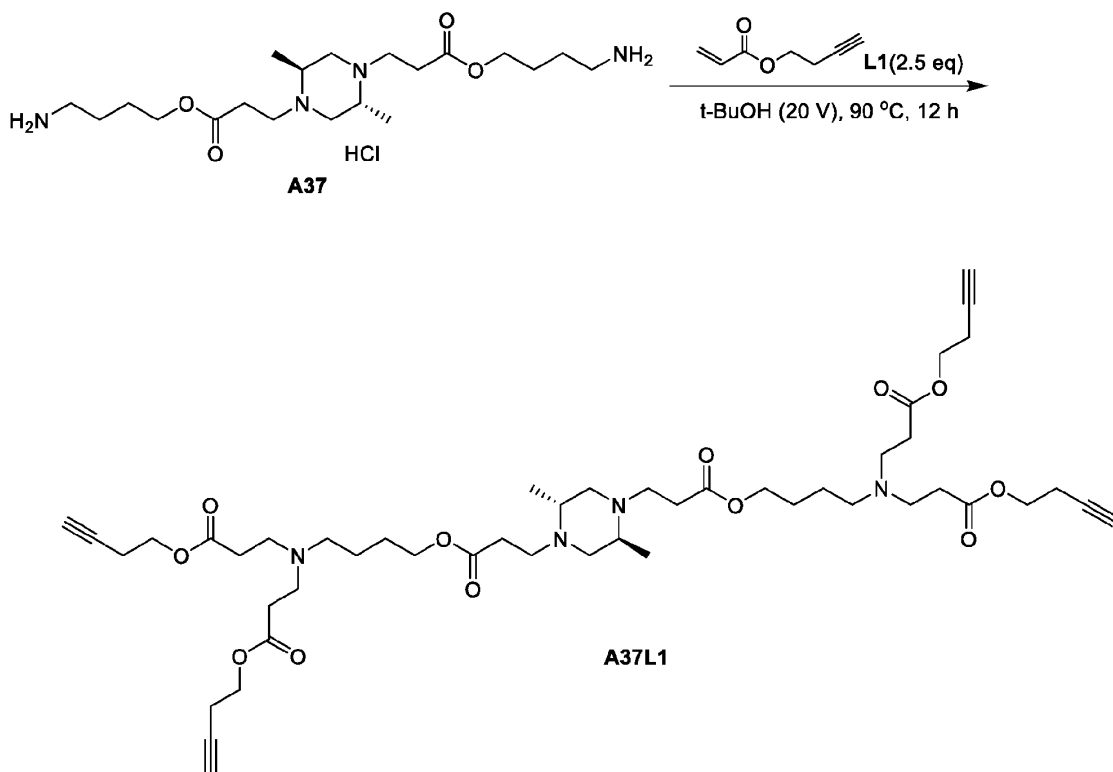
[0420] To a solution of compound A37-4 (1.0 g, 8.76 mmol, 1.0 eq) in ACN (60 ml) was added K₂CO₃ (4.84 g, 35.0 mmol, 4.0 eq) and NaI (131 mg, 875 μmol, 0.1 eq) compound A37-3 (8.80 g, 27.1 mmol, 3.1 eq). The mixture was stirred at 80 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, product/*R_f* = 0.6; start material/*R_f* = 0.2) showed the raw material response to complete. The mixture was evaporated to dryness. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/1). Compound A37-5 (5.0 g, 8.32 mmol, 95.0% yield) was obtained as a white solid.

Example A37



[0421] To a solution of compound A37-5 (5.0 g, 8.32 mmol, 1.0 eq) in EtOAc (25 ml) was added HCl/EtOAc (4 M, 50 ml, 24.0 eq). The mixture was stirred at 15 °C for 12 h. TLC (Dichloromethane/Methanol = 10/1, product/ R_f = 0; start material/ R_f = 0.5) showed the raw material response to complete. Evaporate the solution on a water bath under reduced pressure using a rotary evaporator. Compound A37 (bis(4-aminobutyl) 3,3'-((2R,5S)-2,5-dimethylpiperazine-1,4-diyl)dipropionate, 3.5 g, 8.01 mmol, 96.2% yield, HCl) was obtained as a white solid. ^1H NMR: 400 MHz D_2O δ 4.15-4.17 (m, 4H), 3.82-3.96 (m, 6H), 3.35-3.45 (m, 4H), 2.91-3.00 (m, 8H), 1.68-1.73 (m, 5H), 1.48-1.50 (t, J = 6.0, 6H).

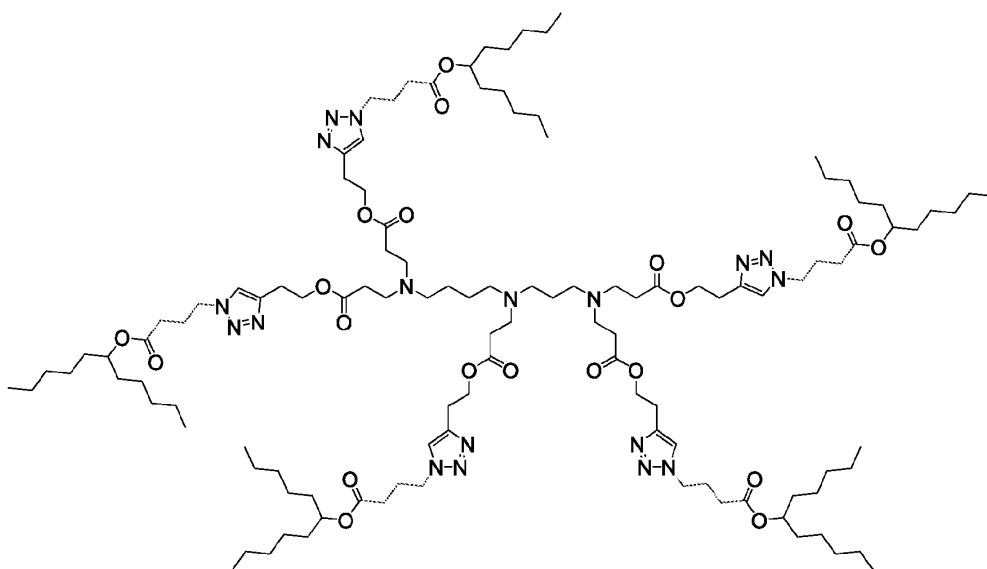
Example A37L1



[0422] To a solution of compound A37 (3.0 g, 6.86 mmol, 1.0 eq, HCl) in t-BuOH (60 ml) was added NaOAc (1.69 g, 20.5 mmol, 3.0 eq) and compound L1 (4.26 g, 34.3 mmol, 5.0 eq). The mixture was stirred at 90 °C for 12 h. TLC (Dichloromethane/Methanol= 10/1, product/ R_f = 0.6; start material/ R_f = 0) indicated compound A37 was consumed completely. The reaction mixture was concentrated under reduced pressure to remove t-BuOH (50 ml). The residue was diluted with H₂O 50 (ml) and extracted with DCM (50 ml). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give are residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 1/1). Compound A37L1 (tetra(but-3-yn-1-yl) 3,3',3'',3'''-((((3,3'-((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(propanoyl))bis(oxy))bis(butane-4,1-diyl))bis(azanetriyl))tetrapropionate, 4.0 g, 4.46 mmol, 64.9% yield) was obtained as yellow oil. ¹H NMR: 400 MHz CDCl₃ δ 4.16-4.20 (m, 8H), 4.04-4.07 (d, *J* = 6.4 Hz, 4H), 3.04-3.13 (m, 2H), 2.73-2.80 (m, 10H), 2.53-2.70 (m, 2H), 2.50-2.52 (m, 8H), 2.32-2.47 (m, 18H), 1.99-2.06 (m, 6H), 1.56-1.63 (m, 4H), 1.43-1.50 (m, 4H),

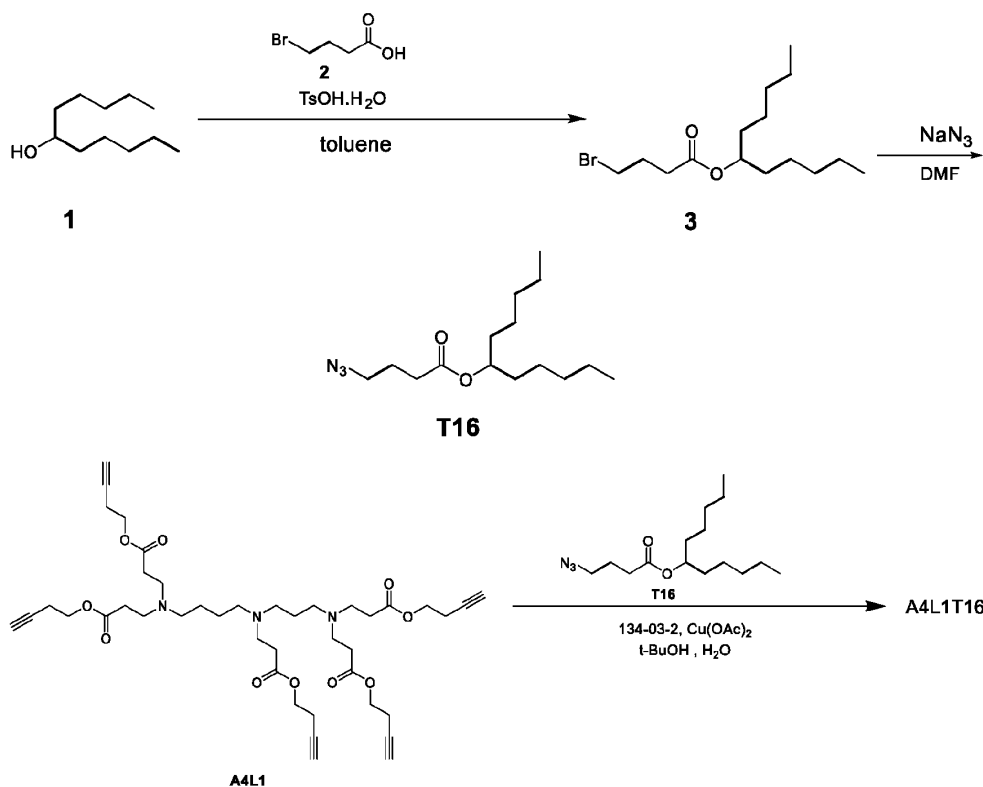
1.03-1.05 (t, $J = 6.4$ Hz, 6H). LCMS : ($M/2 + H^+ = 449$).

Example A4L1T16



1-pentylhexyl 4-[4-[2-[3-[4-[bis[3-oxo-3-[2-[1-[4-oxo-4-(1-pentylhexoxy)butyl]triazol-4-yl]ethoxy]propyl]amino]butyl-[3-[bis[3-oxo-3-[2-[1-[4-oxo-4-(1-pentylhexoxy)butyl]triazol-4-yl]ethoxy]propyl]amino]propyl]amino]propanoyloxy]ethyl]triazol-1-yl]butanoate

[0423] This compound has the chemical formula $C_{117}H_{204}N_{18}O_{20}$, with a molecular weight of 2183.03 g/mol, an exact mass of 2181.55 g/mol, and pKa values 8.168, 5.363 and 6.308. The compound preparation, and that of intermediates used in the same, were made as follows:



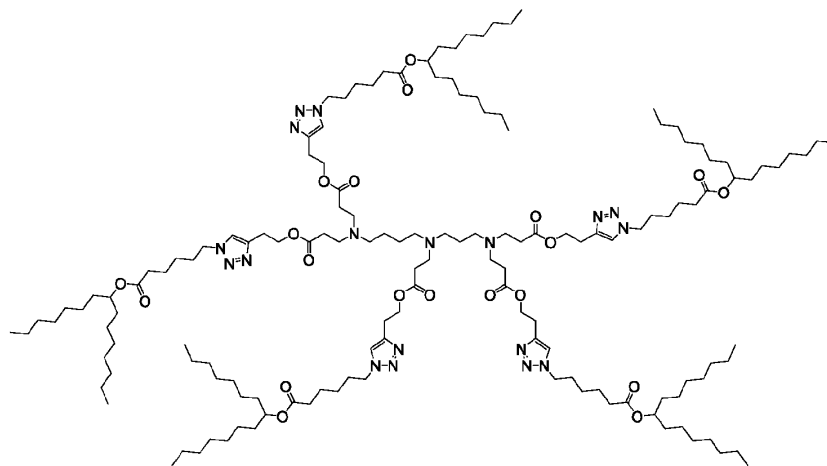
[0424] To a solution of compound **1** (500 mg, 2.90 mmol, 1.0 *eq*) in toluene (30 mL) was added TsOH.H₂O (55.2 mg, 290 μ mol, 0.1 *eq*) and compound **2** (1.45 g, 8.71 mmol, 3.0 *eq*). The reaction was stirred at 130 °C for 2 hrs. TLC (PE: EA = 10:1) showed the reactant (R_f = 0.40) was consumed completely and one new major spot (R_f = 0.50) was detected. The mixture was concentrated in vacuum to give residue. The crude product was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~1% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). The product compound **3** (720 mg, 2.12 mmol, 73.2% yield, 94.8% purity) was obtained as a colorless oil which was confirmed by HNMR. ¹H NMR: NMR (400 MHz, CHLOROFORM-d): δ = 4.90 (q, J = 6.4 Hz, 1H), 3.48 (t, J = 6.4 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 2.18 (q, J = 6.8 Hz, 2H), 1.55 - 1.49 (m, 4H), 1.28 (br s, 12H), 0.91 - 0.87 (m, 6H).

[0425] To a solution of compound **3** (700 mg, 2.18 mmol, 1.0 *eq*) in DMF (5 mL) was added NaN₃ (250 mg, 3.85 mmol, 1.77 *eq*). The mixture was stirred at 60 °C for 2 hrs. TLC

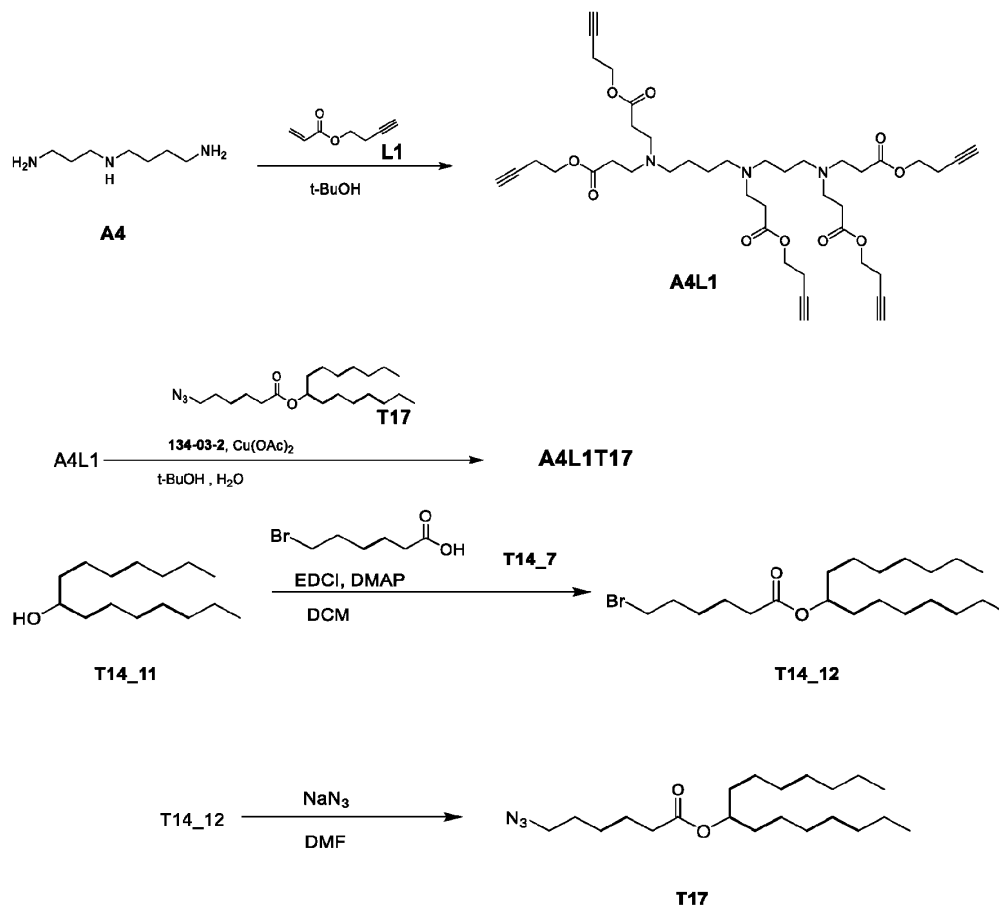
(PE: EA = 20: 1) showed the reactant ($R_f = 0.50$) was consumed completely and one new major spot ($R_f = 0.53$) was detected. The reaction was quenched by saturated NaHCO_3 (30 mL) to adjust to pH = 9 at 20 °C and extracted with PE (30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The product T16 (500 mg, 1.71 mmol, 78.7% yield, 97.2% purity) was obtained as yellow oil which was confirmed by HNMR and used for next step directly without purification. ^1H NMR: (400 MHz, CHCl_3 -d): $\delta = 4.89$ (q, $J = 6.4$ Hz, 1H), 3.36 (t, $J = 6.8$ Hz, 2H), 2.41 (t, $J = 7.3$ Hz, 2H), 1.92 (q, $J = 7.2$ Hz, 2H), 1.55 - 1.49 (m, 4H), 1.28 (br d, $J = 2.8$ Hz, 12H), 0.89 (br t, $J = 6.4$ Hz, 6H).

[0426] To a solution of compound T16 (300 mg, 392 μmol , 1.0 *eq*) in *t*-BuOH (3 mL) and H_2O (3 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (77.6 mg, 392 μmol , 1.0 *eq*), $\text{Cu}(\text{OAc})_2$ (71.1 mg, 392 μmol , 1.0 *eq*) and compound A4L1 (666 mg, 2.35 mmol, 6.0 *eq*). The mixture was stirred at 20 °C for 1 h. LCMS showed the product ($t_p=0.471$ min, $[\text{M}+1]^+=728.7$) was the main peak. The mixture was diluted with water (30 mL) and extracted with dichloromethane (30 mL x 2). The combined organic phase was washed with brine (30 mL x 2), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The crude product was purified by flash silica gel chromatography (ISCO[®]; 80.0 g SepaFlash[®] Silica Flash Column, Eluent of 5~8% Dichloromethane / Methanol ether gradient @ 70 mL/min). The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μm ; mobile phase: [water (TFA)-ACN]; gradient: 50%-80% B over 15 min). The product A4L1T16 (600 mg, 273 μmol , 69.6% yield, 99.2% purity) was obtained as a white solid which was confirmed by CAD: product: RT = 11.983 min., LCMS product: RT = 0.471 min., ^1H NMR (400 MHz, CHCl_3 -d): $\delta = 7.44$ (s, 5H), 4.92 - 4.85 (m, 5H), 4.41 (t, $J = 6.8$ Hz, 10H), 4.34 (t, $J = 6.9$ Hz, 10H), 3.06 (t, $J = 6.9$ Hz, 10H), 2.75 (br t, $J = 7.2$ Hz, 10H), 2.45 - 2.32 (m, 28H), 2.25 - 2.18 (m, 10H), 1.67 (br s, 12H), 1.51 - 1.48 (m, 10H), 1.38 (br s, 4H), 1.27 (br s, 60H), 0.88 (br t, $J = 6.4$ Hz, 30H).

Example A4L1T17



[0427] This compound has the chemical formula $C_{147}H_{264}N_{18}O_{20}$, with a molecular weight of 2603.84 g/mol, an exact mass of 2602.02 g/mol, and pKa values 8.168, 5.363 and 6.308. The compound preparation, and that of some intermediates used in the same, were made as follows:



[0428] A mixture of compound **T14_7** (564 mg, 2.89 mmol, 1.1 *eq*), compound **T14_11** (0.60 g, 2.63 mmol, 1.0 *eq*), EDCI (755 mg, 3.94 mmol, 1.5 *eq*) and DMAP (385 mg, 3.15 mmol, 1.2 *eq*) in DCM (30 mL) was stirred at 20 °C for 12 h. TLC (dichloromethane: methanol=10:1) showed the reactant ($R_f = 0.46$) was consumed completely and one new major spot ($R_f = 0.88$) was detected. The mixture was concentrated in vacuum to give residue. The crude product was by flash silica gel chromatography (petroleum ether: ethyl acetate = 0~2%). The product compound **T14_12** (2.50 g, 6.17 mmol, 46.9% yield) was obtained as colourless oil. ¹H NMR (400 MHz, CDCl₃): δ = 4.99 - 4.82 (m, 1H), 3.66 - 3.34 (m, 2H), 2.45 - 2.20 (m, 2H), 1.93 - 1.75 (m, 2H), 1.70 - 1.63 (m, 2H), 1.57 - 1.46 (m, 6H), 1.27 (br s, 20H), 1.01 - 0.83 (m, 6H).

[0429] A mixture of compound **T14_12** (2.80 g, 6.91 mmol, 1.0 *eq*) in DMF (28 mL) was

added NaN_3 (670 mg, 10.3 mmol, 1.49 eq) and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. LCMS did not detected the desired MS. TLC (petroleum ether: ethyl acetate = 20:1) showed the reactant (R_f = 0.37) was consumed completely and one new major spot (R_f = 0.35) was detected. The reaction was quenched by saturated NaHCO_3 (28 mL) to adjust to pH = 9 at 20 °C and extracted with PE (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The product compound **T17** (2.40 g, 6.53 mmol, 94.55% yield) was obtained as colourless oil and used for next step directly without purification. ^1H NMR (400 MHz, CDCl_3): δ = 4.93 - 4.83 (m, 1H), 3.31 - 3.25 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.72 - 1.59 (m, 4H), 1.52 (br d, J = 5.6 Hz, 4H), 1.46 - 1.38 (m, 2H), 1.27 (br s, 20H), 0.89 (t, J = 6.8 Hz, 6H).

[0430] A mixture of compound **L1** (1.54 g, 12.4 mmol, 6.0 eq) and compound **A4** (0.30 g, 2.07 mmol, 1.0 eq) in t-BuOH (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 12 hrs under N_2 atmosphere. LCMS showed the starting material was consumed completely. The mixture was concentrated in vacuum to give residue. The crude product was by flash silica gel chromatography (petroleum ether: ethyl acetate = 0~100%). The crude product was by flash silica gel chromatography (dichloromethane: methanol = 0-1%). The product **A4L1** (4.80 g, 6.26 mmol, 60.6% yield, 99.8% purity) was obtained as yellow oil. LCMS product: RT = 0.295 min. ^1H NMR (400 MHz, CDCl_3):

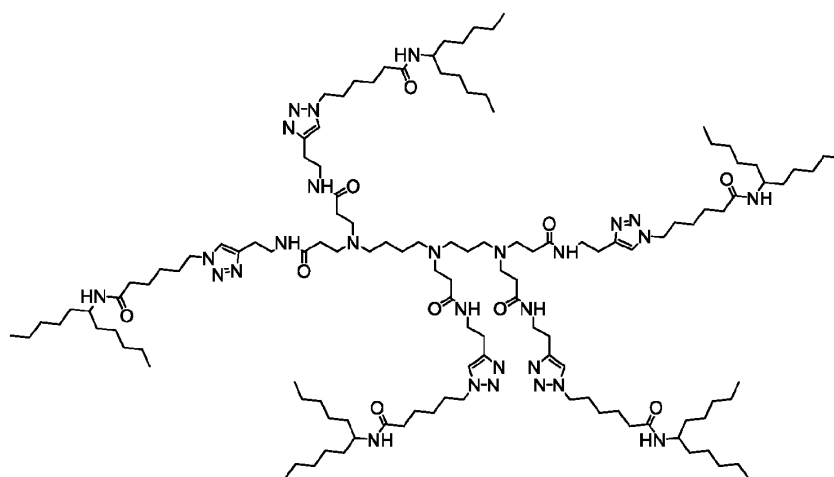
[0431] δ = 4.19 (t, J = 6.8 Hz, 10H), 2.83 - 2.71 (m, 10H), 2.54 (dt, J = 2.6, 6.8 Hz, 10H), 2.49 - 2.37 (m, 17H), 2.03 (t, J = 2.6 Hz, 4H), 1.68 (br s, 2H), 1.55 (q, J = 6.8 Hz, 2H), 1.39 (br s, 4H).

[0432] To a solution of compound **A4L1** (500 mg, 653 μmol , 1.0 eq) in H_2O (5 mL) and t-BuOH (5 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (129 mg, 653 μmol , 1.0 eq), $\text{Cu}(\text{OAc})_2$ (118 mg, 653 μmol , 1.0 eq) and compound **T17** (1.44 g, 3.92 mmol, 6.0 eq). The mixture was stirred at 20 °C for 2 h. LCMS showed the starting material was consumed completely. The mixture was diluted with water (30 mL) and extracted with dichloromethane (30 mL x 2). The combined organic phase was washed with brine (30 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product

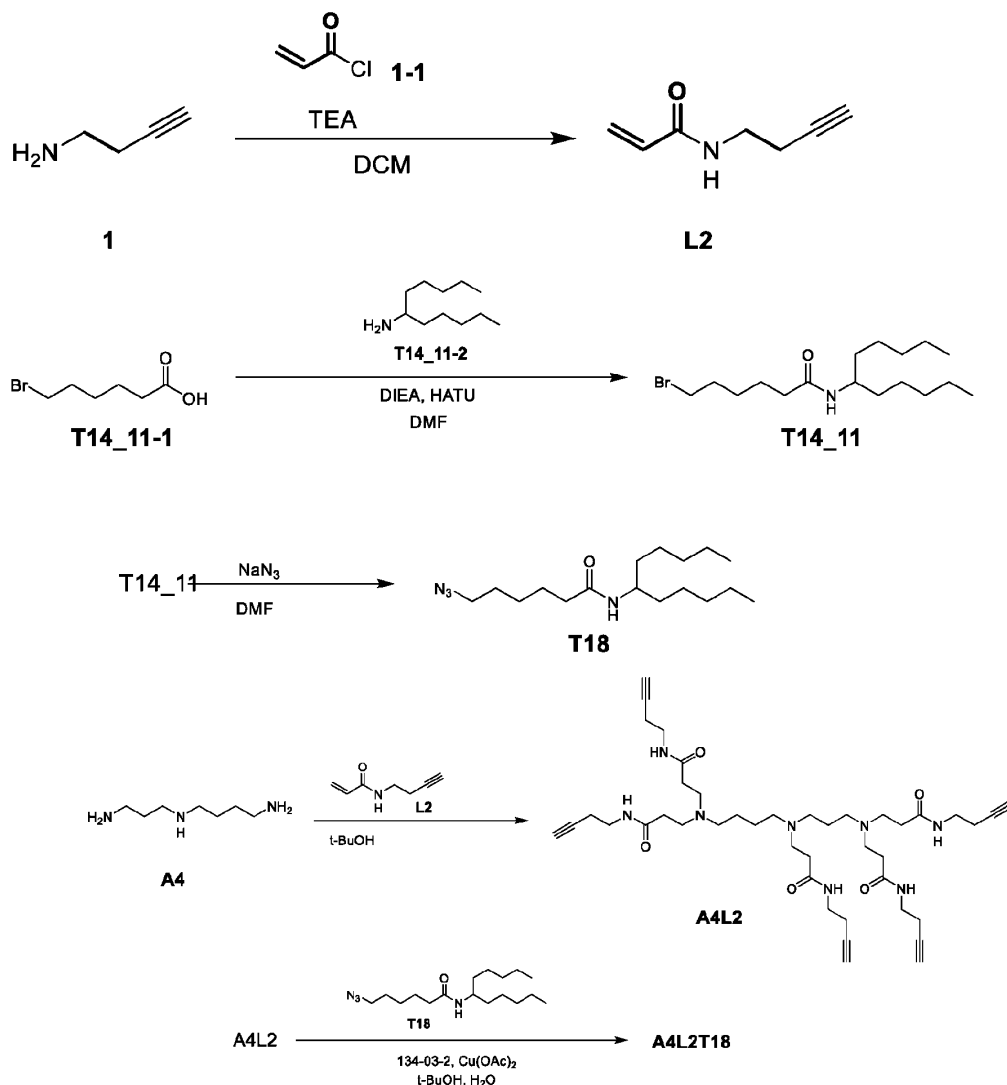
was by flash silica gel chromatography (dichloromethane: methanol = 0~10%). The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μ m; mobile phase: [water (TFA)-(ACN-THF2/1)]; gradient: 68%-98% B over 15 min) and lyophilized to give the product. The residue was purified by prep-HPLC (column: PHS-Phenyl-Hexyl 250 * 50 mm * 7 μ m; mobile phase: [water (HCl) - ACN]; gradient: 68%-98% B over 15 min) and lyophilized to give the product. The product A4L1T17 (400 mg, 140 μ mol, 21.5% yield, 91.374% purity) was obtained as yellow oil. LCMS product: RT = 0.588 min. CAD product: RT = 9.556 min.

[0433] ^1H NMR (400 MHz, CDCl_3): δ = 7.41 (s, 5H), 4.89 (br s, 5H), 4.33 (br t, J = 6.8 Hz, 18H), 3.06 (t, J = 7.0 Hz, 10H), 2.78 - 2.72 (m, 8H), 2.47 - 2.35 (m, 16H), 2.30 (t, J = 7.4 Hz, 10H), 1.93 (q, J = 7.6 Hz, 10H), 1.72 - 1.59 (m, 26H), 1.51 (br d, J = 5.6 Hz, 20H), 1.41 - 1.36 (m, 12H), 1.26 (br s, 94H), 0.88 (t, J = 6.8 Hz, 30H).

Example A4L2T18



[0434] This compound has the chemical formula $\text{C}_{127}\text{H}_{234}\text{N}_{28}\text{O}_{10}$, with a molecular weight of 2313.46 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:



[0435] To a solution of compound **1** (1.00 g, 14.5 mmol, 1.0 *eq*) in DCM (40 mL) was added TEA (1.76 g, 17.4 mmol, 2.42 mL, 1.2 *eq*) and DMAP (88.4 mg, 724 μmol , 0.05 *eq*) and compound **1-1** (1.57 g, 17.4 mmol, 1.41 mL, 1.2 *eq*) in DCM (60 mL) at 0 °C. The mixture was stirred at 25 °C for 12 hrs. TLC (Petroleum ether: Ethyl acetate = 1:1, R_f = 0.51) indicated Reactant **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The residue was diluted with water (30 mL) and extracted with

dichloromethane (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 12.0 g SepaFlash[®] Silica Flash Column, Eluent of 0~30% Ethylacetate/Petroleum ethergradient @ 50 mL/min). Compound **L2** (4.80 g, 38.9 mmol, 67.3% yield) was obtained as yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.33 - 6.26 (m, 1H), 6.18 - 6.08 (m, 1H), 6.03 (br s, 1H), 5.66 (dd, J = 1.2, 10.3 Hz, 1H), 3.50 (q, J = 6.4 Hz, 2H), 2.45 (dt, J = 2.4, 6.4 Hz, 2H), 2.02 (t, J = 2.8 Hz, 1H).

[0436] To a solution of compound **T14-11-1** (1.14 g, 5.84 mmol, 1.0 *eq*) in DCM (10 mL) was added DIEA (1.51 g, 11.7 mmol, 2.03 mL, 2.0 *eq*) and EDCI (1.34 g, 7.00 mmol, 1.2 *eq*) and DMAP (143 mg, 1.17 mmol, 0.2 *eq*). The mixture was stirred at 25 °C for 0.5 h. Then, compound **T14-11-2** (1.00 g, 5.84 mmol, 1.0 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. TLC (Petroleum ether: Ethyl acetate=3:1, R_f = 0.52) indicated that the reactant was consumed completely and many new spots formed. The reaction was not optimal according to TLC. The residue was diluted with water (30 mL) and extracted with dichloromethane (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 12.0 g SepaFlash[®] Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ethergradient @ 60 mL/min). Compound **T14-11** (700 mg, 2.01 mmol, 34.4% yield) was obtained as a light yellow solid. ¹H NMR (400 MHz, CDCl₃):

[0437] δ = 5.09 (br d, J = 8.8 Hz, 1H), 3.98 - 3.84 (m, 1H), 3.56 - 3.36 (m, 2H), 2.18 (t, J = 7.2 Hz, 2H), 1.94 - 1.76 (m, 2H), 1.73 - 1.62 (m, 3H), 1.52 - 1.44 (m, 4H), 1.38 - 1.31 (m, 4H), 0.93 - 0.78 (m, 6H).

[0438] To a solution of compound **T14-11** (2.56 g, 7.35 mmol, 1.0 *eq*) in DMF (15 mL) was added NaN₃ (0.52 g, 8.00 mmol, 1.09 *eq*). The mixture was stirred at 60 °C for 2 h under N₂ atmosphere. LC-MS showed the reactant was consumed completely and the desired mass was detected. The reaction mixture was adjusted to a pH of more than 9 with saturated sodium carbonate (50 mL) and was diluted with water (50 mL) was extracted with hexane (50 mL x 2). Then the combined organic layers were dried over anhydrous sodium sulfate and were concentrated. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The crude product was used into the next step without further

purification. Compound **T18** (2.18 g, 7.02 mmol, 95.5% yield) was obtained as yellow oil.

[0439] LCMS product: RT = 0.541 min. ¹H NMR (400 MHz, CDCl₃): δ = 5.07 (br d, *J* = 8.9 Hz, 1H), 4.00 - 3.84 (m, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.18 (t, *J* = 7.4 Hz, 2H), 1.68 - 1.60 (m, 4H), 1.52 - 1.39 (m, 4H), 1.30 (br d, *J* = 5.6 Hz, 14H), 0.88 (br t, *J* = 6.1 Hz, 6H).

[0440] To a solution of compound **A4** (500 mg, 3.44 mmol, 1.0 *eq*) in *t*-BuOH (10 mL) was added **L2** (2.54 g, 20.6 mmol, 6.0 *eq*). The mixture was stirred at 90 °C for 12 h. LC-MS showed the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated. The residue was purified by flash silica gel chromatography (ISCO®, 12.0 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). Compound **A4L2** (1.20 g, 1.58 mmol, 45.8% yield) was obtained as yellow oil.

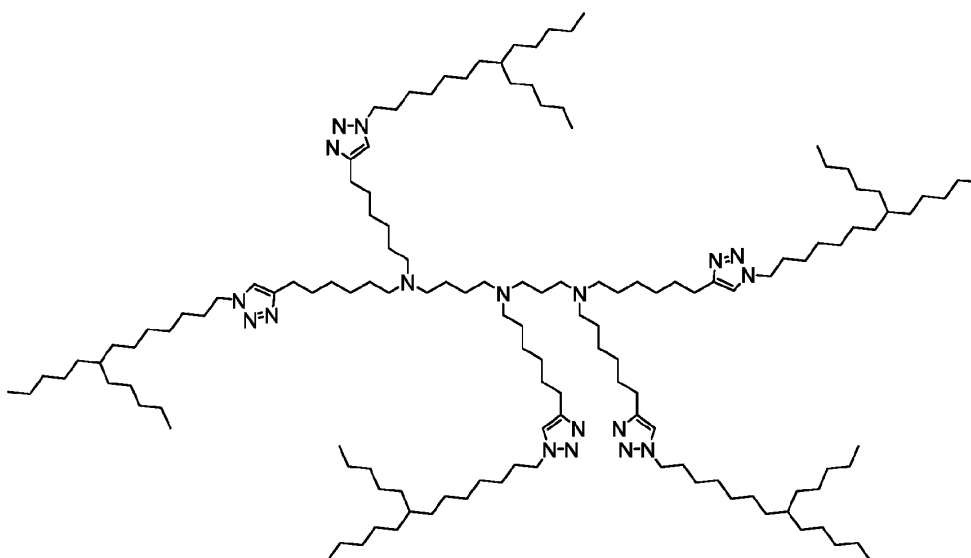
[0441] LCMS product: RT = 0.238 min. ¹H NMR (400 MHz, CDCl₃): δ = 3.45 - 3.35 (m, 10H), 2.92 - 2.69 (m, 10H), 2.65 - 2.52 (m, 4H), 2.50 - 2.35 (m, 24H), 2.05 (t, *J* = 2.4 Hz, 5H), 1.94 (br dd, *J* = 3.6, 5.6 Hz, 5H), 1.68 (br s, 2H), 1.48 (br d, *J* = 7.6 Hz, 4H).

[0442] To a solution of compound **A4L2** (350 mg, 460 μmol, 1.0 *eq*) in *t*-BuOH (3.5 mL) and H₂O (3.5 mL) was added sodium (2R)-2-[(1S)-1,2-dihydroxyethyl]-3-hydroxy-5-oxo-2H-furan-4-olate (91.1 mg, 460 μmol, 1.0 *eq*) (CAS: 134-03-2) and Cu(OAc)₂ (83.5 mg, 460 μmol, 1.0 *eq*) and compound **T18** (857 mg, 2.76 mmol, 6.0 *eq*). The mixture was stirred at 25 °C for 2 h. LC-MS showed the reactant was consumed completely and one main peak with desired *m/z* or desired mass was detected. The residue was diluted with water (30 mL) and extracted with dichloromethane (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μm; mobile phase: [water (TFA)-(ACN-THF2/1)]; gradient: 42%-72% B over 15 min). Compound **A4L2T18** (190 mg, 81.3 μmol, 17.6% yield, 99.0% purity) was obtained as light yellow oil. LCMS product: RT = 0.571 min. CAD product: RT = 7.701 min.

[0443] ¹H NMR: (400 MHz, CDCl₃): δ = 7.93 - 7.82 (m, 4H), 7.59 - 7.45 (m, 5H), 5.71 (br s, 5H), 4.31 (br t, *J* = 7.2 Hz, 10H), 3.93 - 3.83 (m, 5H), 3.53 (br s, 10H), 2.92 (br t, *J* = 6.4 Hz, 10H), 2.64 (br d, *J* = 6.0 Hz, 8H), 2.33 (br d, *J* = 6.0 Hz, 12H), 2.16 (t, *J* = 7.2 Hz, 10H), 1.94 - 1.87 (m, 10H), 1.77 - 1.65 (m, 32H), 1.51 - 1.42 (m, 12H), 1.32 - 1.23 (m, 70H), 0.87 (br t, *J* =

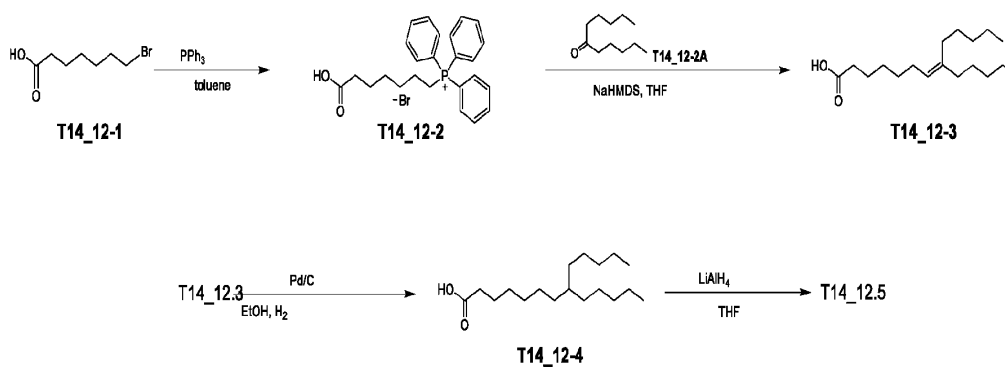
6.4 Hz, 30H).

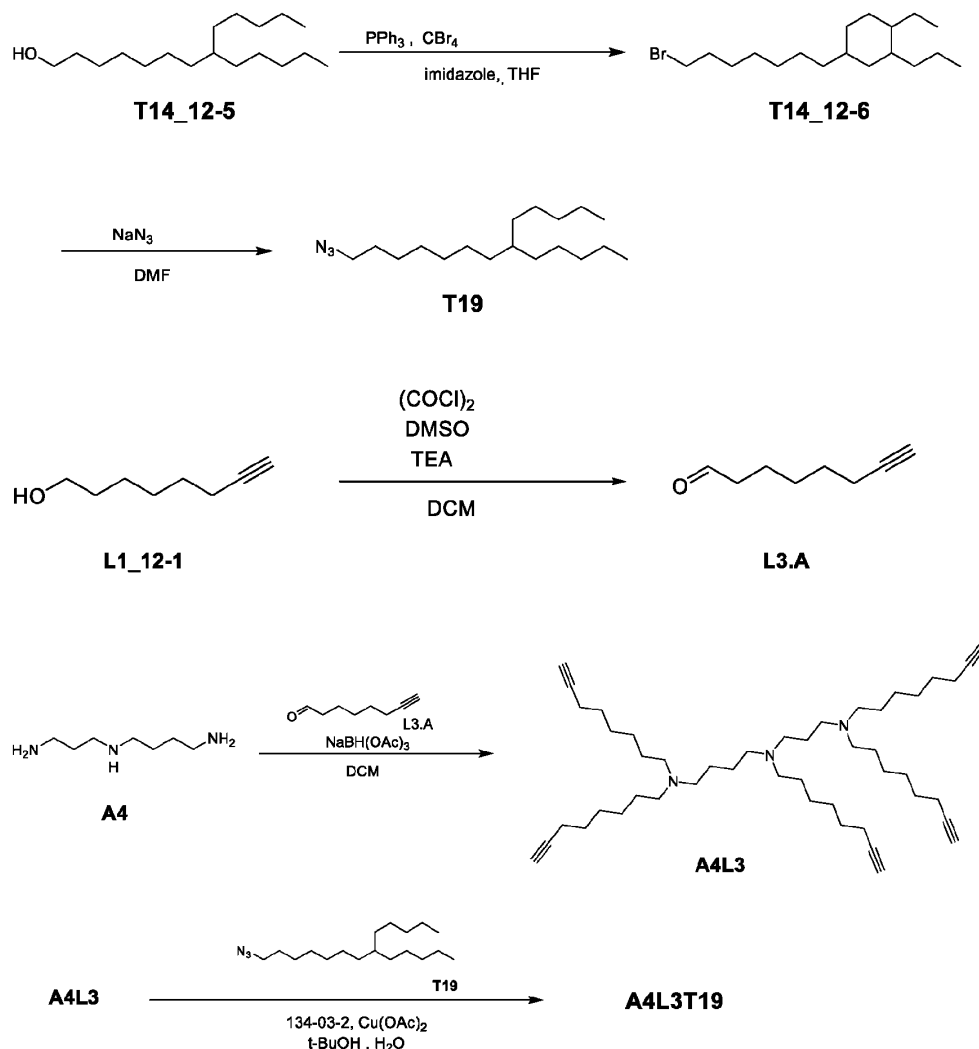
Example A4L3T19



N¹-(3-(bis(6-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)hexyl)amino)propyl)-N¹,N⁴,N⁴-tris(6-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)hexyl)butane-1,4-diamine

[0444] This compound has the chemical formula C₁₃₇H₂₆₄N₁₈, with a molecular weight of 2163.75 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:



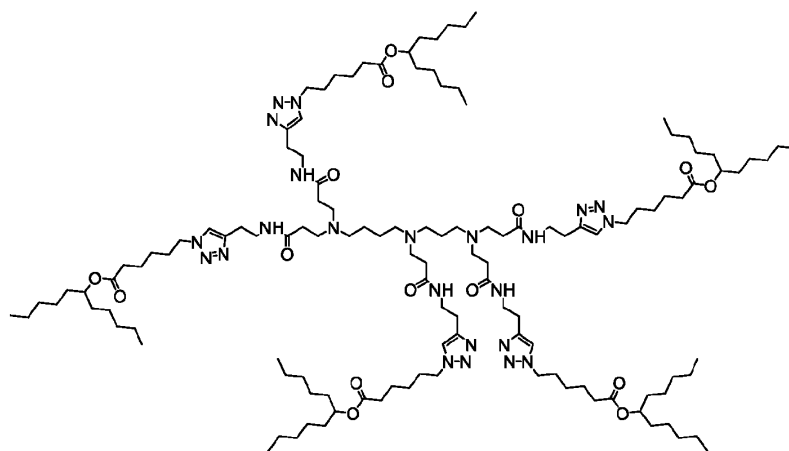


[0445] To a solution of **A4L3** (250 mg, 364.35 μmol , 1 eq) in t-BuOH (3 mL) and H_2O (3 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (72.18 mg, 364.35 μmol , 1 eq), diacetoxycopper (66.18 mg, 364.35 μmol , 1 eq) and **T19** (646.01 mg, 2.19 mmol, 6 eq). The mixture was stirred at 20 °C for 1h. A new peak was detected by LCMS. The residue was diluted with water 30 mL and extracted with dichloromethane 10 mL (10 mL * 3). The combined organic layers were washed with brine (10 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue

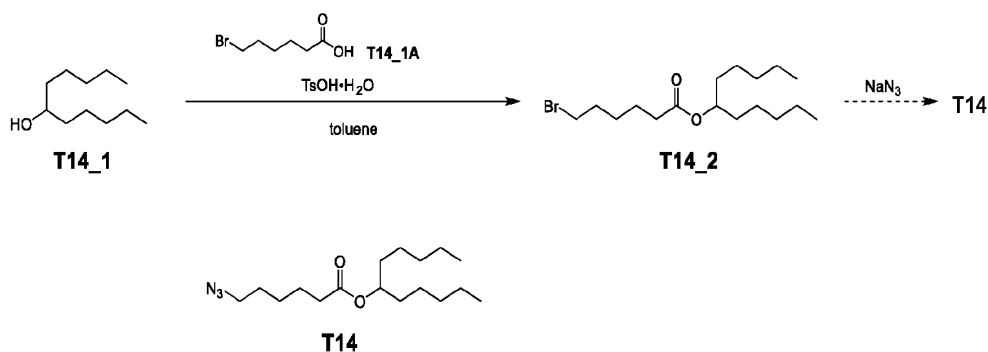
was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μm ; mobile phase: [water(HCl)-ACN]; gradient: 68%-98% B over 15 min). Compound **A4L3T19** (60 mg, 27.73 μmol , 7.61% yield) obtained as a light yellow oil. CAD: $(\text{M}/2 + \text{H}^+) = 1082.7$.

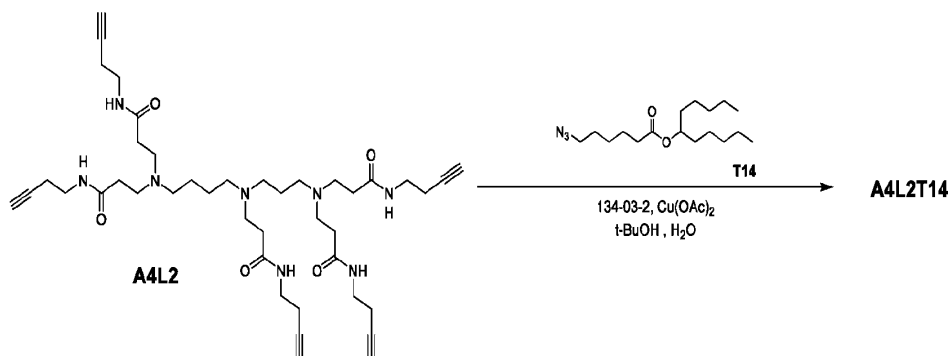
[0446] ^1H NMR (400 MHz, CHLOROFORM-*d*): $\delta = 7.28 - 7.27$ (m, 5H), 4.32 – 4.28 (m, 10H), 2.72 – 2.42 (m, 24H), 1.86 - 1.23 (m, , 195 H), 0.90 – 0.87 (m, 30H).

Example A4L2T14



[0447] This compound has the chemical formula $\text{C}_{127}\text{H}_{229}\text{N}_{23}\text{O}_{15}$, with a molecular weight of 2318.38 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:

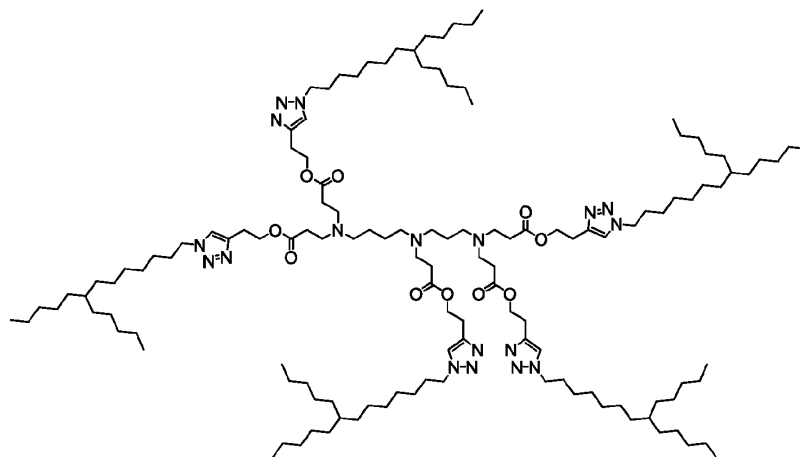




[0448] To a solution of compound **A4L2** (350 mg, 460 μmol , 1.0 *eq*) in t-BuOH (3.5 mL) and H₂O (3.5 mL) was added sodium,(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (91.1 mg, 460 μmol , 1.0 *eq*) and Cu(OAc)₂ (83.5 mg, 460 μmol , 1.0 *eq*) and compound **T14** (859 mg, 2.76 mmol, 6.0 *eq*). The mixture was stirred at 20 °C for 2 h. LC-MS showed Reactant **A4L2** was consumed completely and the desired mass was detected. The residue was diluted with water (30 mL) and extracted with dichloromethane (30 mL * 3). The combined organic layers were washed with brine (30 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μm ; mobile phase: [water (TFA) - (CAN - THF 2/1)]; gradient: 58%-88% B over 15 min).

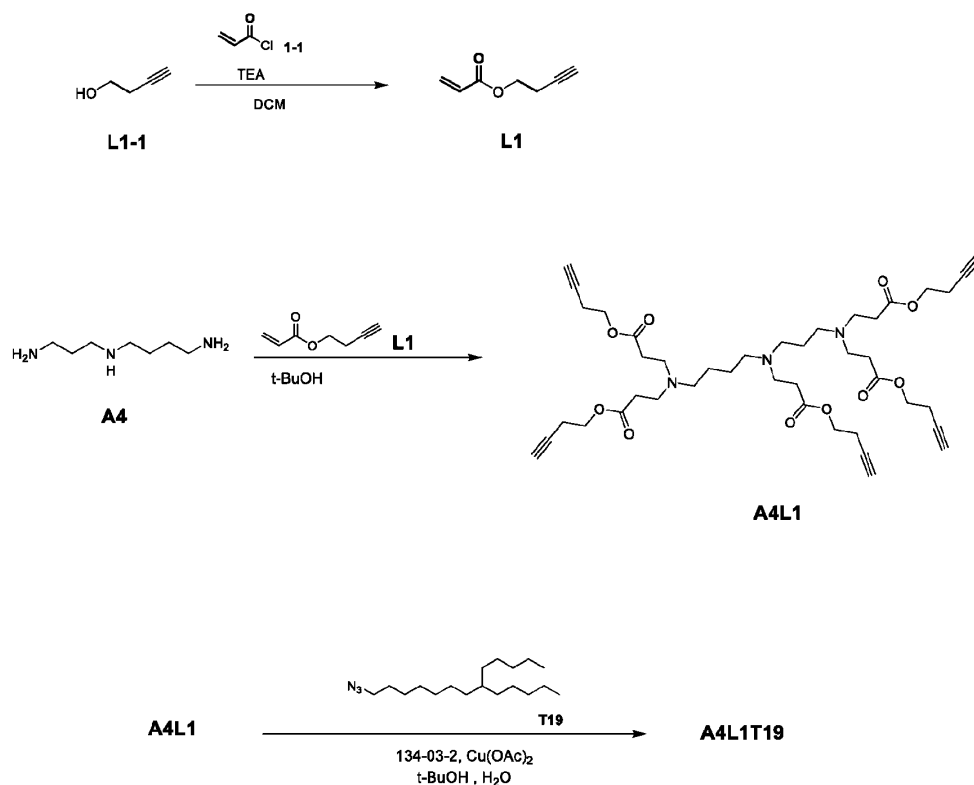
Compound **A4L2T14** (200 mg, 85.1 μmol , 18.5% yield, 98.6% purity) was obtained as yellow oil. LCMS product: RT = 0.679 min. CAD product: RT = 12.391 min. ¹H NMR (400 MHz, CDCl₃): δ = 7.79 (br d, *J* = 6.0 Hz, 4H), 7.58 - 7.43 (m, 5H), 4.86 - 4.86 (m, 1H), 4.86 (q, *J* = 6.4 Hz, 4H), 4.32 (br t, *J* = 7.2 Hz, 10H), 3.59 - 3.48 (m, 10H), 2.93 (br t, *J* = 6.8 Hz, 10H), 2.65 (br d, *J* = 5.6 Hz, 8H), 2.29 (br t, *J* = 7.6 Hz, 16H), 1.96 - 1.88 (m, 12H), 1.78 (br d, *J* = 15.6 Hz, 14H), 1.67 (td, *J* = 7.6, 15.2 Hz, 12H), 1.55 - 1.45 (m, 22H), 1.37 - 1.20 (m, 70H), 0.93 - 0.84 (m, 30H).

Example A4L1T19



bis(2-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)ethyl) 3,3'-((3-((4-(bis(3-oxo-3-(2-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)ethoxy)propyl)amino)butyl)(3-oxo-3-(2-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)ethoxy)propyl)azanediyl)dipropionate

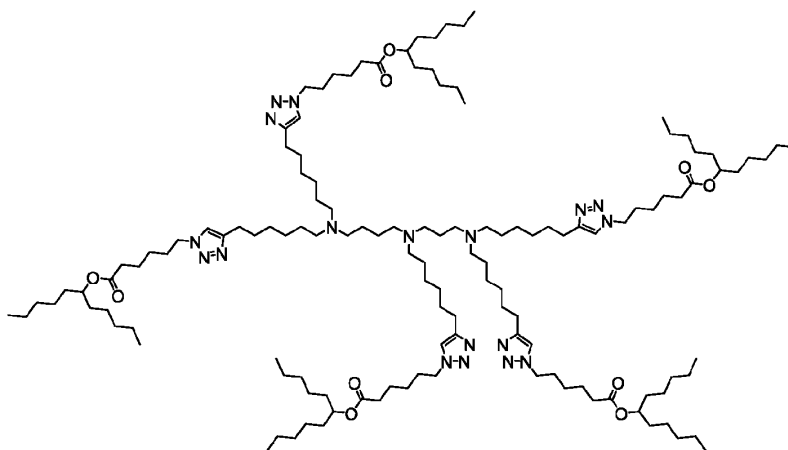
[0449] This compound has the chemical formula $C_{132}H_{244}N_{18}O_{10}$, with a molecular weight of 2243.52 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:



[0450] To a solution of **A4L1** (280 mg, 366 μ mol, 1.0 eq) in H₂O (2 mL) and *t*-BuOH (2 mL) was added Cu(OAc)₂ (66.4 mg, 366 μ mol, 1.0 eq), sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (72.4 mg, 366 μ mol, 1.0 eq) and compound **T19** (648 mg, 2.19 mmol, 6.0 eq). The mixture was stirred at 20 °C for 2 h. LCMS showed the starting material was consumed completely. The mixture was diluted with water (30 mL) and extracted with dichloromethane (30 mL x 2). The combined organic phase was washed with brine (30 mL x 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μ m; mobile phase: [water (TFA) - (CAN - THF 2/1)]; gradient: 68%-98% B over 15 min) and lyophilized to give the product. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150 * 25 * 10 μ m; mobile phase: [water (TFA) - (CAN - THF 2/1)]; gradient: 68%-98% B over 10 min) and lyophilized to give the product. The product **A4L1T19** (170 mg, 73.3 μ mol, 20.0% yield, 96.6% purity) was obtained as yellow oil. LCMS product: RT

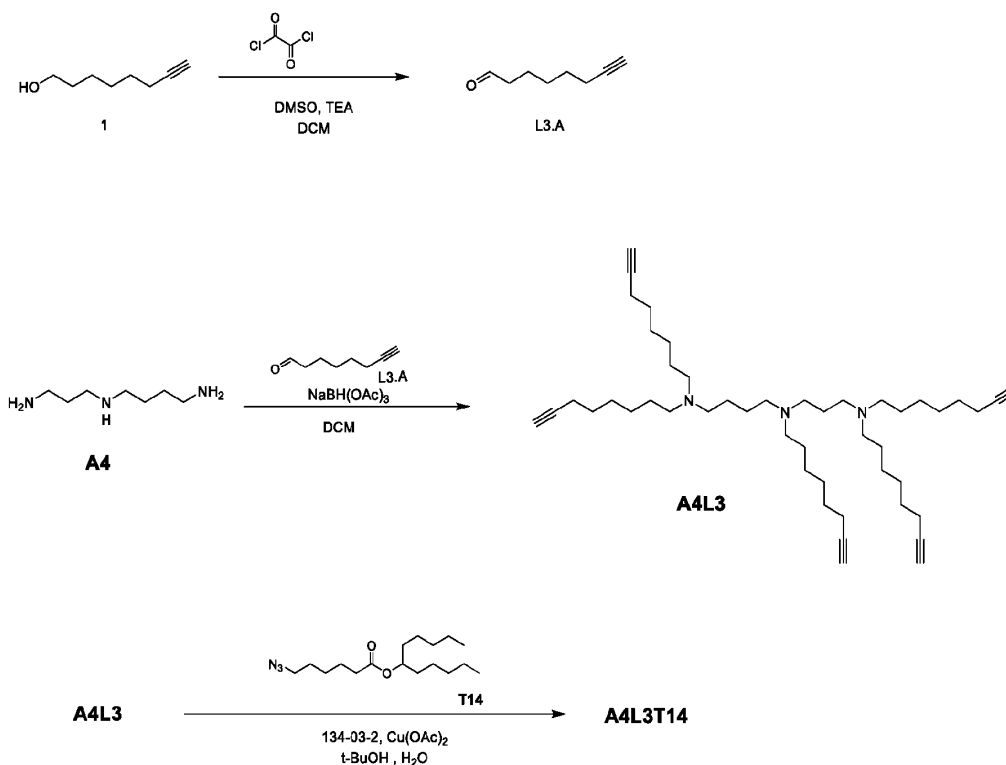
= 3.547 min. CAD product: RT = 11.557 min. ^1H NMR (400 MHz, CDCl_3): δ = 7.60 - 7.35 (m, 5H), 4.33 (q, J = 6.8 Hz, 18H), 3.06 (br t, J = 6.9 Hz, 8H), 2.78 - 2.69 (m, 8H), 2.43 (br t, J = 7.0 Hz, 10H), 1.92 - 1.86 (m, 8H), 1.59 (br s, 22H), 1.36 - 1.28 (m, 39H), 1.23 (br s, 96H), 0.89 (t, J = 7.0 Hz, 30H).

Example A4L3T14



di(undecan-6-yl) 6,6'-((((3-((4-(bis(6-(1-(6-oxo-6-(undecan-6-yloxy)hexyl)-1H-1,2,3-triazol-4-yl)hexyl)amino)butyl)(6-(1-(6-oxo-6-(undecan-6-yloxy)hexyl)-1H-1,2,3-triazol-4-yl)hexyl)amino)propyl)azanediyl)bis(hexane-6,1-diyl))bis(1H-1,2,3-triazole-4,1-diyl))dihexanoate

[0451] This compound has the chemical formula $\text{C}_{132}\text{H}_{244}\text{N}_{18}\text{O}_{10}$, with a molecular weight of 2243.52 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:

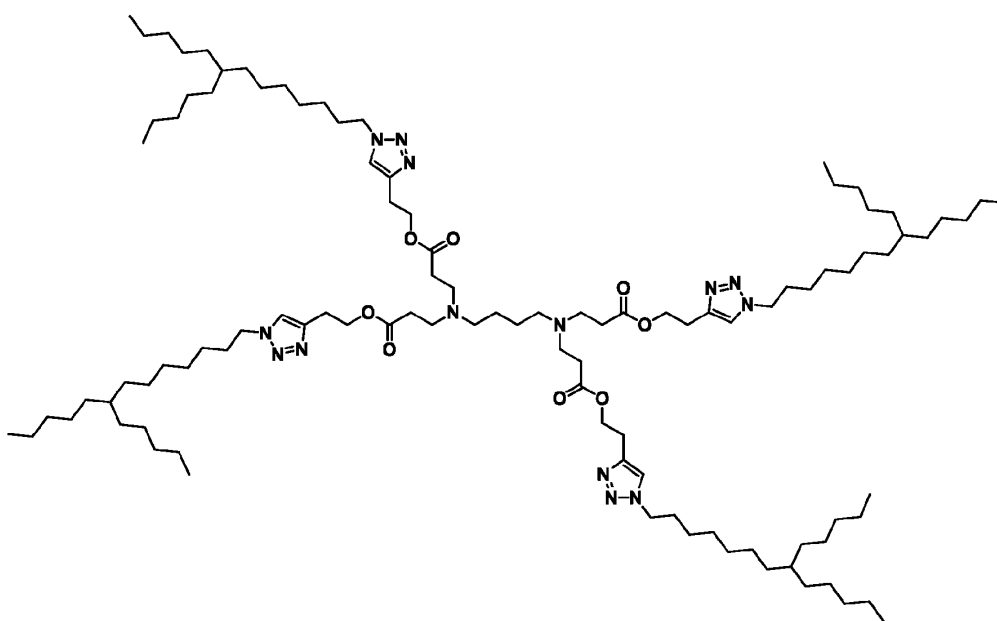


[0452] To a solution of **A4L3** (350 mg, 510.09 μmol , 1 eq) in t-BuOH (3 mL) and H_2O (3 mL) was added $\text{Cu}(\text{OAc})_2$ (92.65 mg, 510.09 μmol , 1 eq), sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (101.05 mg, 510.09 μmol , 1 eq) and **T14** (794.37 mg, 2.55 mmol, 5 eq). The mixture was stirred at 25 °C for 1h. LCMS showed the starting material was consumed completely. The mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL $\times$ 2). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μm ; mobile phase: [water (TFA)-ACN]; gradient:55%-85% B over 15 min) and lyophilized to give the product. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μm ; mobile phase: [water (HCl)-ACN]; gradient:60%-80% B over 10 min) and lyophilized to give the product. Compound of **A4L3T14** (100 mg, 43.87 μmol , 8.60% yield, 98.421% purity) was obtained as a yellow oil. LCMS product: RT = 0.522 min. CAD product:

RT = 13.559 min.

[0453] ^1H NMR (400 MHz, CDCl_3): δ = 7.29 - 7.27 (m, 5H), 4.92 - 4.82 (m, 5H), 4.31 (t, J = 7.2 Hz, 10H), 2.70 (t, J = 7.6 Hz, 10H), 2.47 - 2.35 (m, 12H), 2.30 (t, J = 7.2 Hz, 10H), 1.92 (, J = 7.2 Hz, 12H), 1.68 (d, J = 7.2, 15.1 Hz, 28H), 1.53 - 1.47 (m, 22H), 1.40 - 1.25 (m, 100H), 0.88 (t, J = 6.6 Hz, 30H).

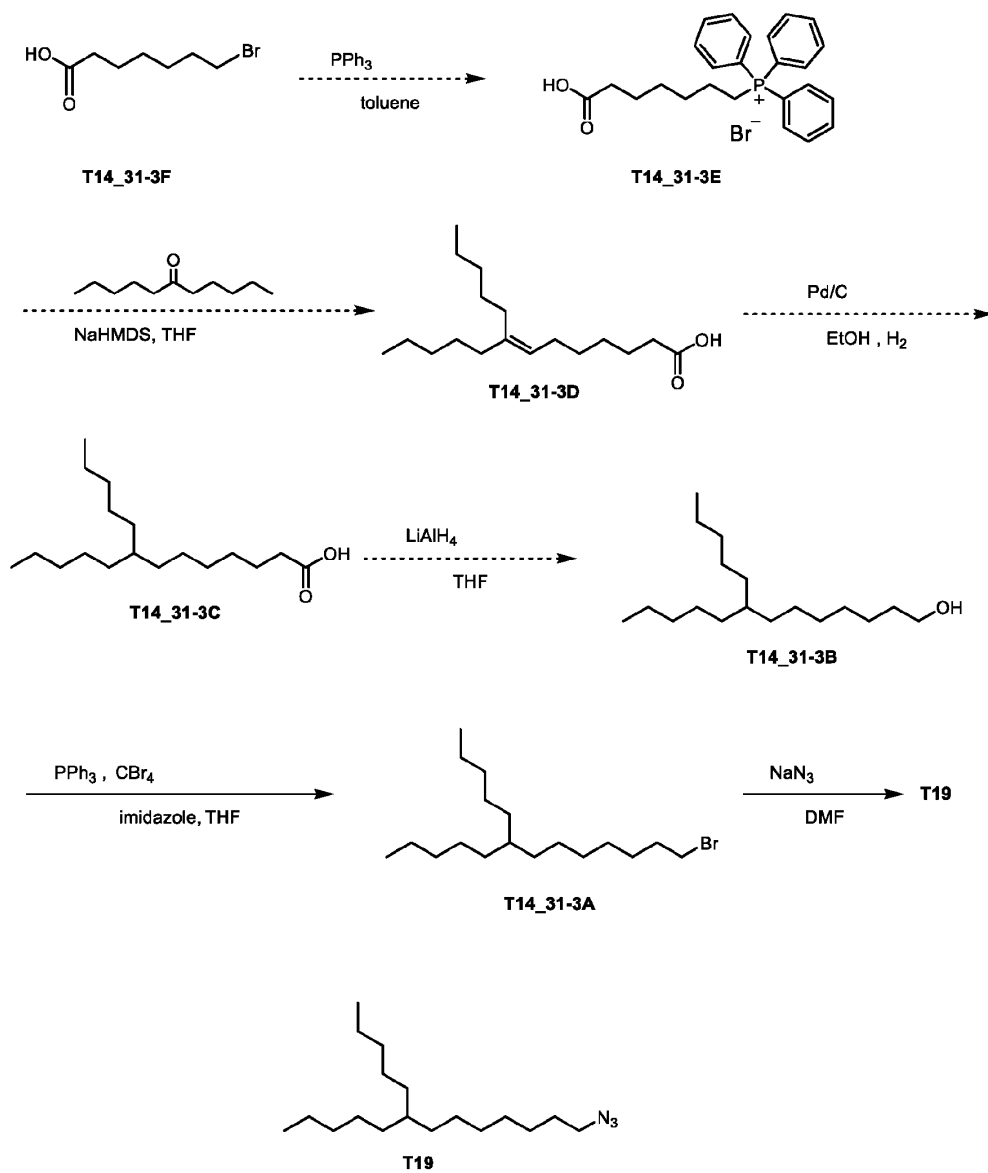
Example A10L1T19

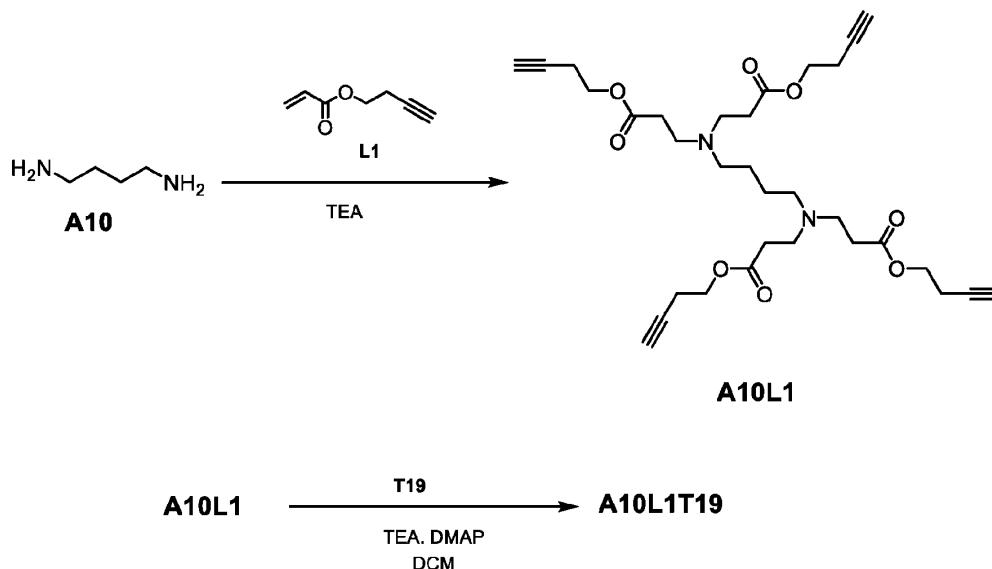


A10L1T19

tetrakis(2-(1-(8-pentyltridecyl)-1*H*-1,2,3-triazol-4-yl)ethyl) 3,3',3'',3'''-(butane-1,4-diylbis(azanetriyl))tetrapropionate

[0454] The compound preparation, and that of some intermediates used in the same, were made as follows:





[0455] A mixture of **T14_31-3B** (0.57 g, 2.11 mmol, 1 eq), triphenylphosphane (1.38 g, 5.27 mmol, 2.5 eq), carbon tetrabromide (1.40 g, 4.21 mmol, 2 eq) and imidazole (573.83 mg, 8.43 mmol, 4 eq) in THF (10 mL) was stirred at 25 °C for 12 h under N₂ atmosphere. TLC (Petroleum ether: Ethyl acetate = 1:0, R_f = 0.99) indicated that **T14_31-3B** was consumed completely and one new spot formed. The reaction mixture was quenched by adding water (10 mL), and then extracted with ethyl acetate 40 mL (20 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®, 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound **T14_31-3A** (1.3 g, 3.90 mmol, 92.52% yield) was obtained as a colourless oil. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 3.42 (t, J = 6.8 Hz, 2H), 1.87 (q, J = 7.2 Hz, 2H), 1.47 - 1.40 (m, 2H), 1.35 - 1.20 (m, 25H), 0.89 (t, J = 7.2 Hz, 6H).

[0456] To a solution of **T14_31-3A** (1.3 g, 3.90 mmol, 1 eq) in DMF (10 mL) was slowly added NaN₃ (320 mg, 4.92 mmol, 1.26 eq). The mixture was stirred at 60 °C for 2 h. TLC (Petroleum ether : Ethyl acetate = 1:0, R_f = 0.9) indicated that **T14_31-3A** was consumed completely and one new spot formed. The reaction was quenched by saturated Na₂CO₃ (10 mL) to adjust to pH = 9 at 20 °C and extracted with PE (20 mL). The combined organic layers were

washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The product was used into the next step without further purification. Compound **T19** (0.8 g, 2.71 mmol, 69.43% yield) was obtained as a light yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 3.27 (t, J = 7.2 Hz, 2H), 1.64 - 1.59 (m, 2H), 1.40 - 1.21 (m, 27H), 0.89 (t, J = 7.2 Hz, 6H).

[0457] A mixture of **A10** (0.3 g, 3.40 mmol, 342.08 μ L, 1 eq), TEA (1.03 g, 10.21 mmol, 1.42 mL, 3 eq) and but-3-yn-1-yl acrylate (2.53 g, 20.42 mmol, 6 eq) was stirred at 100 °C for 12h. The desired mass was detected by LCMS. The reaction was quenched by adding water (10 mL), and then extracted with DCM 40 mL (20 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% MeOH/DCM ethergradient @ 50 mL/min). Compound **A10L1** (1.6 g, 2.71 mmol, 79.60% yield, 99% purity) was obtained as a light yellow oil. LCMS: (M + H⁺) = 585.0.

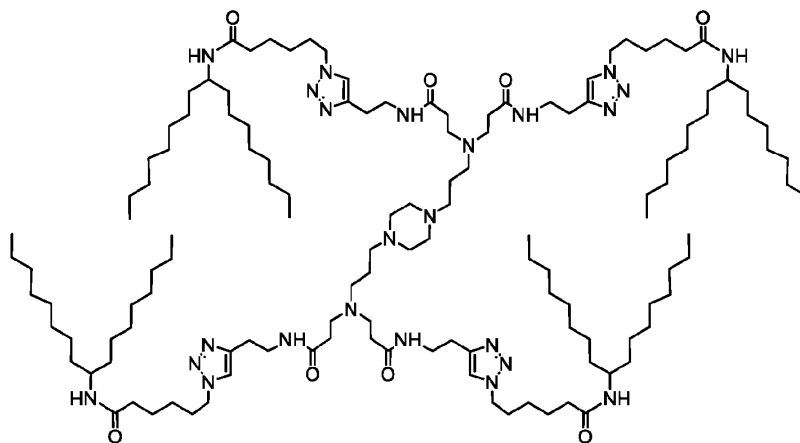
[0458] ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 4.19 (t, J = 6.8 Hz, 8H), 2.78 (t, J = 7.2 Hz, 8H), 2.56 - 2.52 (m, 8H), 2.47 (t, J = 7.2 Hz, 8H), 2.42 (s, 4H), 2.02 (t, J = 2.4 Hz, 4H), 1.40 (s, 4H).

[0459] To a solution of **A10L1** (350 mg, 598.60 μ mol, 1 eq) in t-BuOH (5 mL) and water (5 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (118.59 mg, 598.60 μ mol, 1 eq), diacetoxycopper (108.73 mg, 598.60 μ mol, 1 eq) and 1-azido-8-pentyltridecane (**T19**, 796.00 mg, 2.69 mmol, 4.5 eq). The mixture was stirred at 25 °C for 2 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0.9) indicated **A10L1** was consumed completely and one new spot formed. The reaction mixture was quenched by adding water (10 mL), and then extracted with DCM 50 mL (25 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 4 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% MeOH/DCM ethergradient @ 30 mL/min). The residue was purified by prep-HPLC (column: CD12-WePure Biotech Phenyl-Hexyl 150*25mm*7 μ m; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 65%-95% B over 15.0 min). Compound **A10L1T19** (200 mg, 0.11 mmol, 18.47% yield, 97.69% purity) was obtained as a light yellow oil. CAD: (M/2 + H⁺) = 884.0.

[0460] ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 7.40 (s, 4H), 4.33 (q, J = 7.2 Hz,

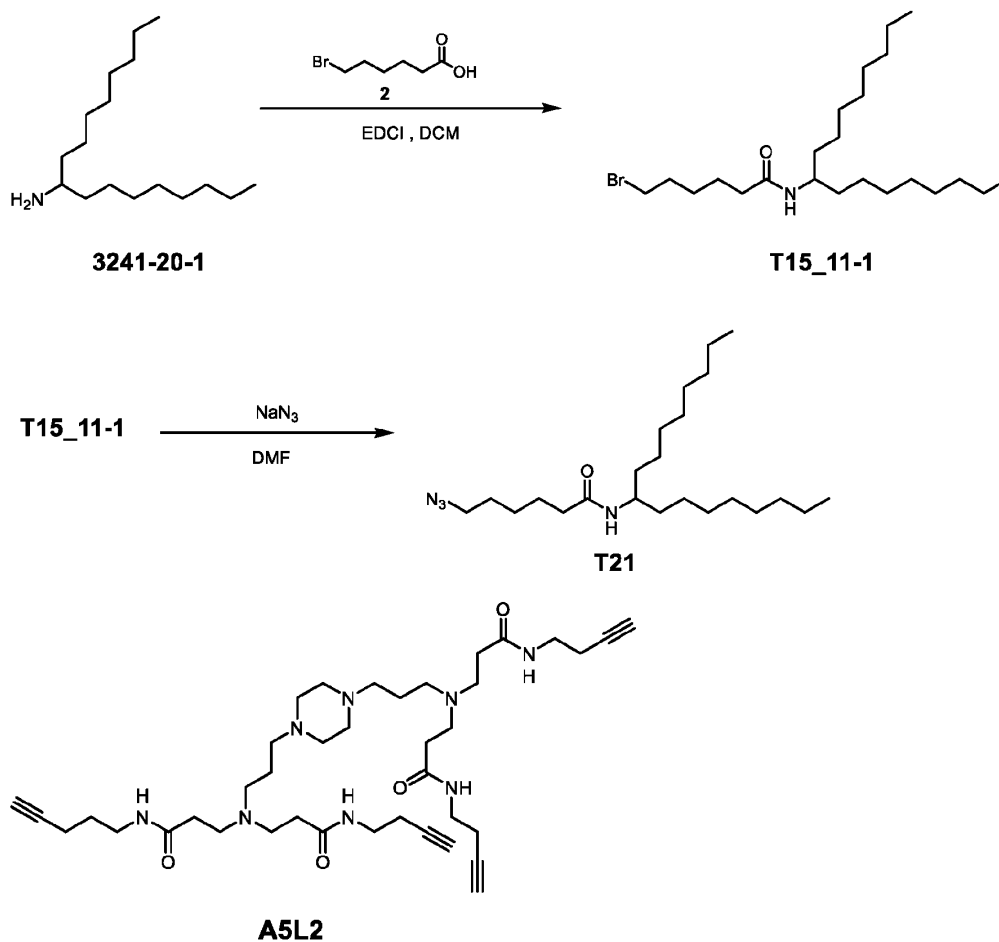
16H), 3.06 (t, J = 6.8 Hz, 8H), 2.74 (t, J = 6.8 Hz, 8H), 2.43 (t, J = 6.8 Hz, 12H), 1.89 (t, J = 6.8 Hz, 8H), 1.37 - 1.29 (m, 32H), 1.27 - 1.17 (m, 80H), 0.89 (t, J = 7.1 Hz, 24H).

Example A5L2T21



6,6',6'',6'''-((((3,3',3'',3'''-((piperazine-1,4-diylbis(propane-3,1-diyl))bis(azanetriyl))tetrakis(propanoyl))tetrakis(azanediy))tetrakis(ethane-2,1-diyl))tetrakis(1H-1,2,3-triazole-4,1-diyl))tetrakis(N-(heptadecan-9-yl)hexanamide)

[0461] This compound has the chemical formula $C_{130}H_{244}N_{24}O_8$, with a molecular weight of 2271.54 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:



[0462] To a solution of compound **2** (500 mg, 2.56 mmol, 1 eq) was dissolved in DCM (25 mL), and EDCI (540 mg, 2.82 mmol, 1.1 eq) was added in portions at 0 °C, after stirring for 30 min, compound **3241-20-1** (720 mg, 2.82 mmol, 1.1 eq) was added dropwise to the reaction solution. After the dropwise addition, the mixture was stirred at 20 °C for 12 h. LCMS showed the product (RT = 0.680 min, [M+1]⁺=432.2) was the main peak. The mixture was concentrated in vacuum to give residue. The crude product was purified by flash silica gel chromatography (ISCO[®]; 4 g SepaFlash[®] Silica Flash Column, Eluent of 5~8% Ethylacetate/Petroleum ether gradient @ 40 mL/min). Compound **T15_11-1** (800 mg, 1.85 mmol, 72.1% yield, 100% purity) was obtained as a white solid which was confirmed by HNMR. LCMS product: RT =

0.680 min.

[0463] ^1H NMR (400 MHz, CHLOROFORM- d): δ = 5.10 (br d, J = 8.8 Hz, 1H), 3.98 - 3.82 (m, 1H), 3.41 (t, J = 6.8 Hz, 2H), 2.18 (t, J = 7.6 Hz, 2H), 1.89 (quin, J = 7.2 Hz, 2H), 1.70 - 1.64 (m, 2H), 1.52 - 1.43 (m, 4H), 1.35 - 1.23 (m, 26H), 0.88 (t, J = 6.8 Hz, 6H).

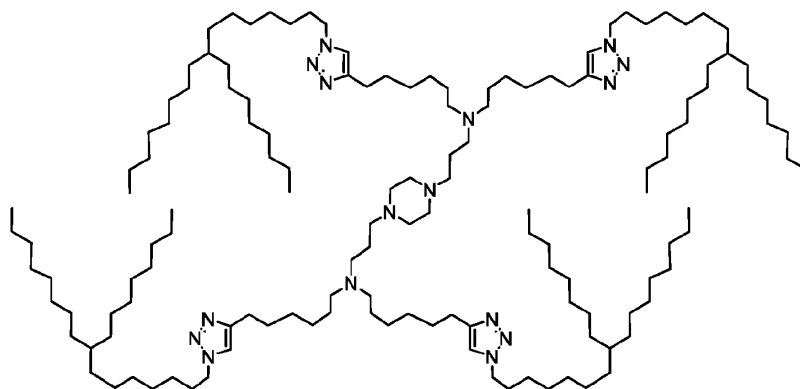
[0464] To a solution of compound **T15_11-1** (4.6 g, 10.6 mmol, 1.0 eq) in DMF (40 mL) was added NaN_3 (650 mg, 10.0 mmol, 0.94 eq). The mixture was stirred at 60 °C for 2h. LCMS showed the product (RT = 0.690 min, $[\text{M}+1]^+ = 395.4$) was the main peak. The reaction was quenched by saturated NaHCO_3 (9 mL) to adjust to pH = 9 at 20 °C and extracted with PE 30 mL. The combined organic layers were washed with brine 40 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The crude product was used for next step directly without purification. Compound **T21** (4.1 g, 10.3 mmol, 97.5% yield, 99.9% purity) was obtained as a yellow solid which was confirmed by HNMR. LCMS product: RT = 0.690 min. ^1H NMR (400 MHz, CHLOROFORM- d): δ = 5.10 (br d, J = 9.2 Hz, 1H), 3.97 - 3.82 (m, 1H), 3.27 (t, J = 6.8 Hz, 2H), 2.17 (t, J = 7.6 Hz, 2H), 1.75 - 1.56 (m, 5H), 1.53 - 1.36 (m, 5H), 1.35 - 1.19 (m, 28H), 0.88 (t, J = 6.8 Hz, 6H).

[0465] To a solution of compound **A5** (200 mg, 998 μmol , 1.0 eq) was added compound **L2** (737 mg, 5.99 mmol, 6.0 eq). The mixture was stirred at 100 °C for 12h. LCMS showed the product (RT = 0.336 min, $[\text{M}+1]^+ = 693.4$) was the main peak. The mixture was concentrated in vacuum to give residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 μm); mobile phase: [water(TFA)-ACN]; gradient: 0%-30% B over 25 min) and lyophilized to give the product. The compound **A5L2** (600 mg, 865 μmol , 86.7% yield) was obtained as a yellow oil. LCMS product: RT = 0.336 min.

[0466] To a solution of compound **A5L2** (300 mg, 432 μmol , 1.0 eq) in H_2O (4 mL) and t -BuOH (4 mL) t -BuOH (4 mL) was added sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (85.7 mg, 432 μmol , 1.0 eq), $\text{Cu}(\text{OAc})_2$ (78.6 mg, 432 μmol , 1.0 eq) and compound **T21** (854 mg, 2.16 mmol, 5.0 eq). The mixture was stirred at 20 °C for 1 h. LCMS showed the product (tp = 0.528 min, $[\text{M}/3]^+ = 758.2$) was the main peak. The mixture was diluted with water (30 mL) and extracted with dichloromethane (30 mL $\times$ 2). The combined organic phase was washed with brine (30 mL $\times$ 2), dried with anhydrous Na_2SO_4 , filtered and concentrated in

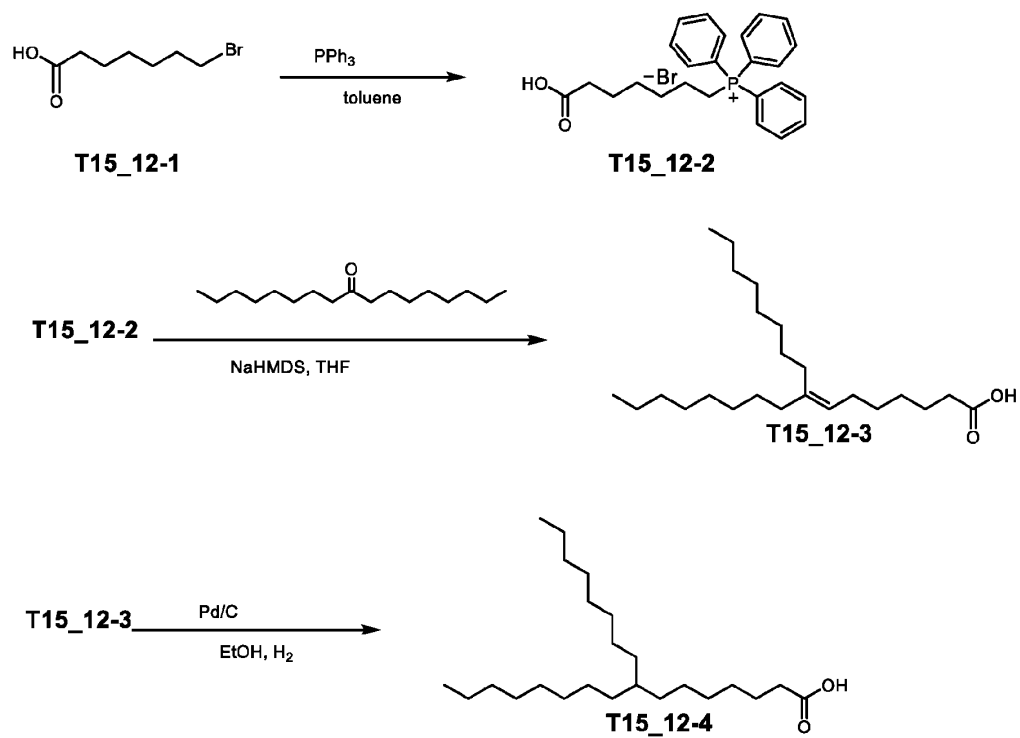
vacuum. The residue was purified by prep-HPLC (column: CD27-PHS XP phenyl-Hexyl 150*25*7um; mobile phase: [water(TFA)-ACN]; gradient: 55%-85% B over 15 min). The compound **A5L2T21** (120 mg, 47.81 μ mol, 11.0% yield, 90.5% purity) was obtained as a white solid which was confirmed by HNMR. LCMS product: RT = 0.528 min. CAD product: RT = 13.727 min. ^1H NMR (400 MHz, CHLOROFORM- d): δ = 7.77 - 7.71 (m, 4H), 7.46 (s, 4H), 5.58 (br d, J = 9.2 Hz, 4H), 4.34 - 4.29 (m, 8H), 3.91 - 3.83 (m, 4H), 3.56 (q, J = 6.4 Hz, 8H), 2.92 (br t, J = 6.8 Hz, 8H), 2.65 (br t, J = 6.1 Hz, 8H), 2.43 (br t, J = 6.8 Hz, 10H), 2.34 - 2.27 (m, 12H), 2.16 (t, J = 7.2 Hz, 8H), 1.91 (td, J = 7.3, 14.8 Hz, 12H), 1.80 (br s, 22H), 1.67 (br s, 6H), 1.59 (br d, J = 6.4 Hz, 4H), 1.45 (br dd, J = 5.6, 10.7 Hz, 10H), 1.25 (br s, 88H), 0.88 (t, J = 6.8 Hz, 24H).

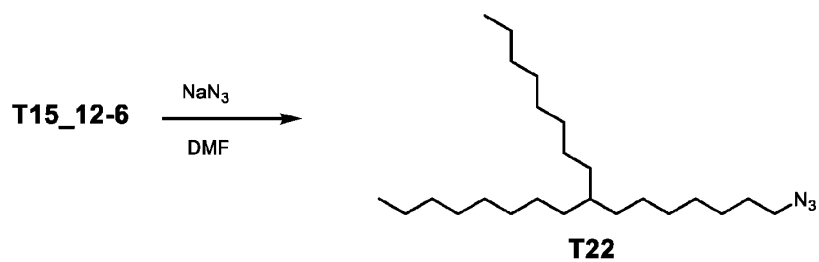
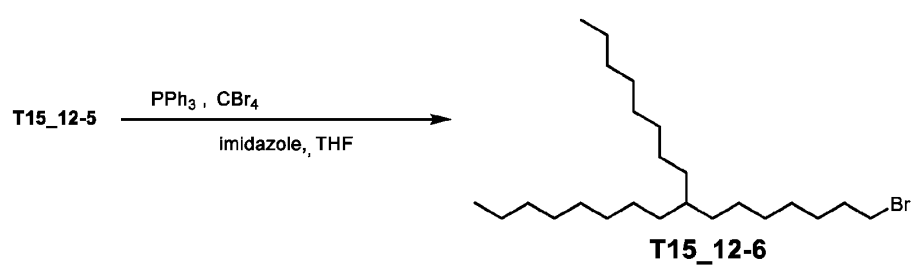
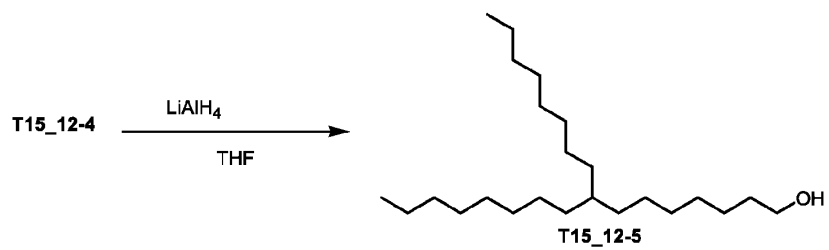
Example A5L3T22

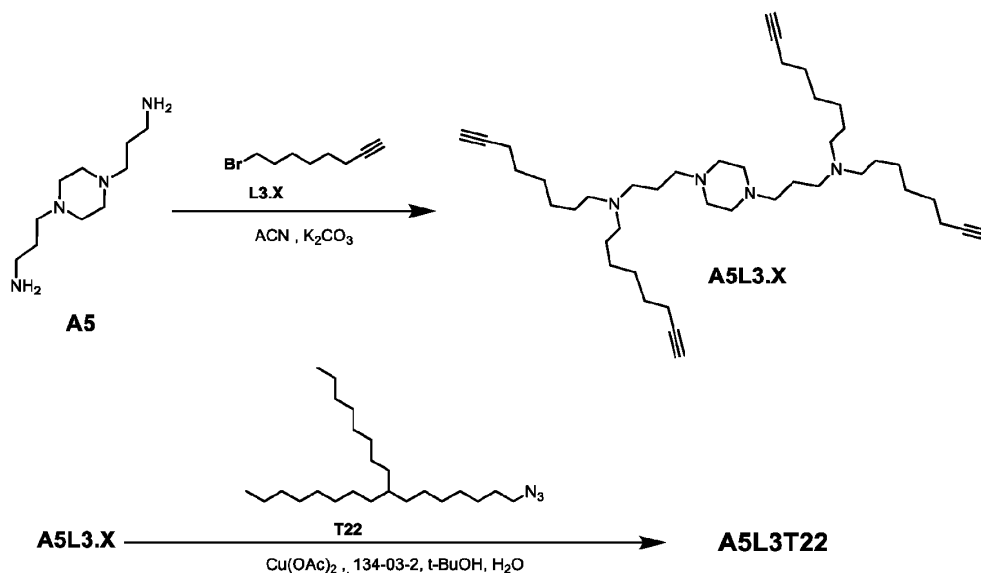


N,N' -(piperazine-1,4-diylbis(propane-3,1-diyl))bis(6-(1-(8-octylhexadecyl)-1H-1,2,3-triazol-4-yl)-N-(6-(1-(8-octylhexadecyl)-1H-1,2,3-triazol-4-yl)hexyl)hexan-1-amine)

[0467] This compound has the chemical formula $\text{C}_{138}\text{H}_{268}\text{N}_{16}$, with a molecular weight of 2151.77 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:

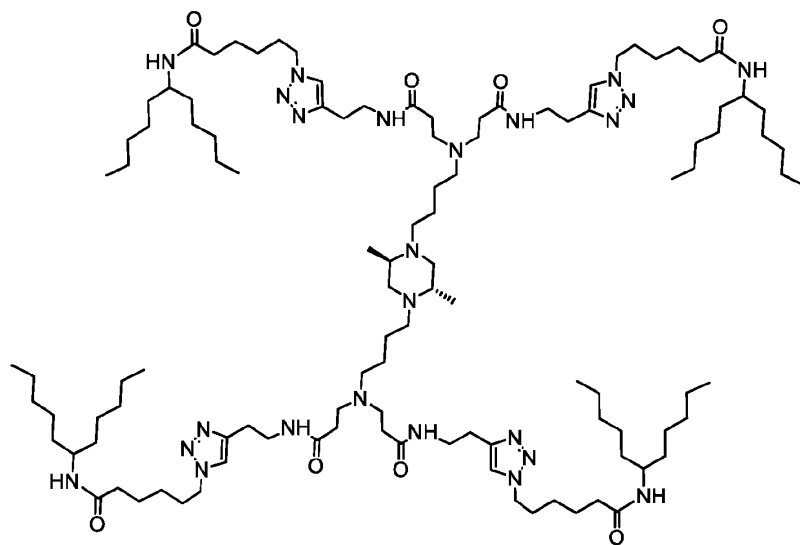






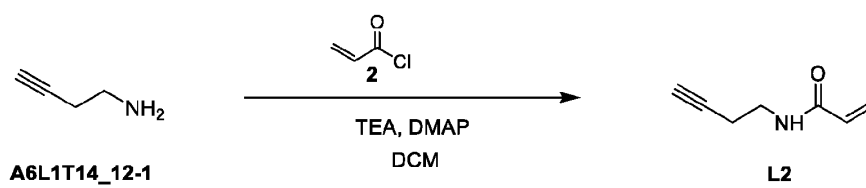
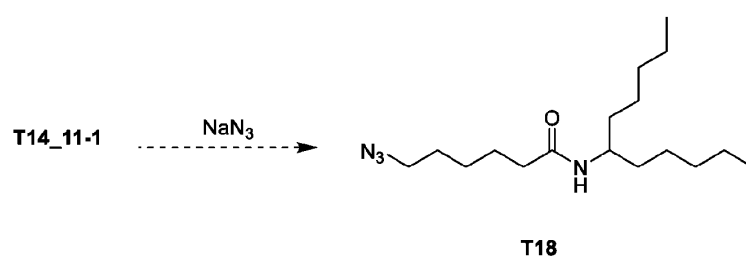
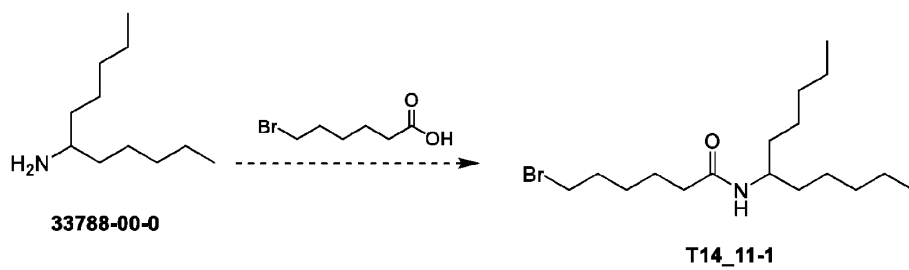
[0468] To a solution of **A5L3.X** (100 mg, 157.97 μ mol, 1 *eq*) in H_2O (1 mL) and *t*-BuOH (1 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (31.29 mg, 157.97 μ mol, 1 *eq*), diacetylcopper (28.69 mg, 157.97 μ mol, 1 *eq*) and **T22** (299.87 mg, 789.83 μ mol, 5 *eq*). The mixture was stirred at 25 °C for 1 h. LC-MS showed **A5L3.X** was consumed completely and one main peak with desired *m/z*. The reaction mixture was quenched by adding H_2O (10 mL) at 25 °C, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (20 mL *2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD30-WePure Biotech Phenyl-Hexyl 250*50mm*7 μ m; mobile phase: [H_2O (0.1%TFA)-ACN:THF=2:1]; gradient: 70%-100% B over 15.0 min). Compound **A5L3T22** (130 mg, 60.42 μ mol, 38.25% yield) was obtained as a white solid. LCMS: ($M/3 + H^+$) = 718.1. CAD: ($M/3 + H^+$) = 718.3. 1H NMR (400 MHz, $CHLOROFORM-d$): δ : 7.28 (s, 4H), 4.31 (t, J = 7.4 Hz, 8H), 3.20 - 3.08 (m, 4H), 3.07 - 3.06 (m, 1H), 3.07 - 2.94 (m, 12H), 2.90 - 2.80 (m, 4H), 2.71 (t, J = 7.5 Hz, 7H), 2.17 - 2.05 (m, 4H), 1.93 - 1.86 (m, 11H), 1.70 (br d, J = 7.0 Hz, 18H), 1.43 - 1.37 (m, 14H), 1.32 (br d, J = 8.1 Hz, 22H), 1.27 (br s, 75H), 1.22 (br s, 60H), 0.92 - 0.85 (m, 24H).

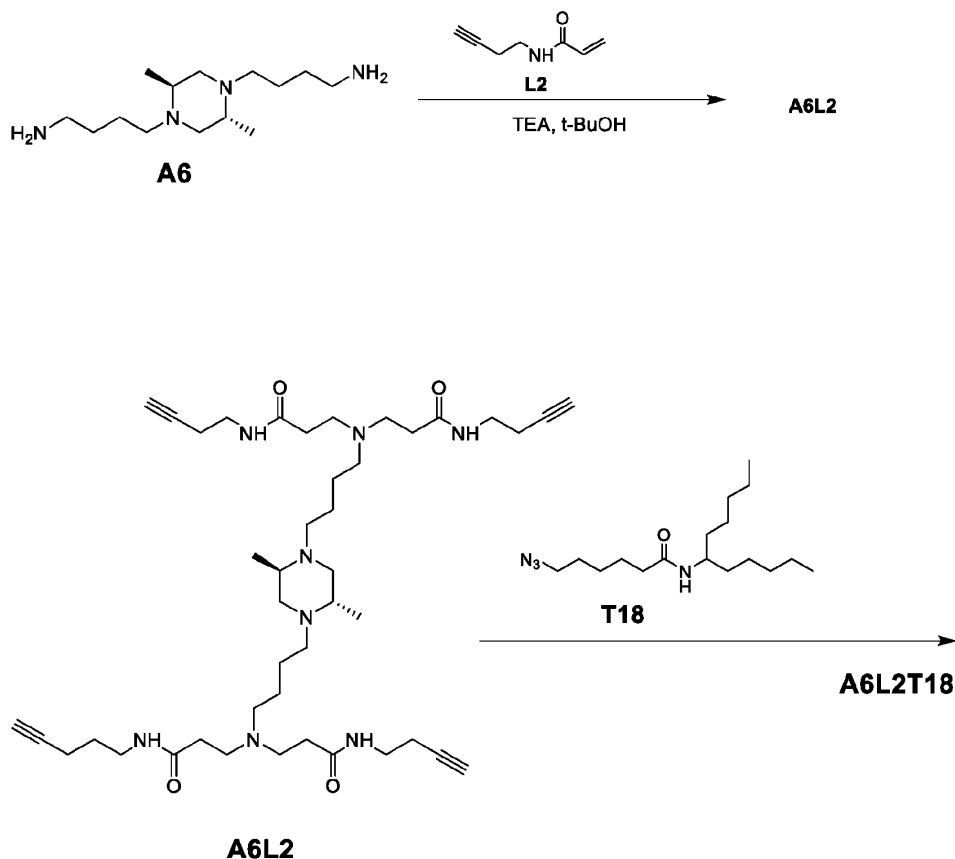
Example A6L2T18



6,6',6'',6'''-((((3,3',3'',3'''-((((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(butane-4,1-diyl))bis(azanetriyl))tetrakis(propanoyl))tetrakis(azanediy))tetrakis(ethane-2,1-diyl))tetrakis(1*H*-1,2,3-triazole-4,1-diyl))tetrakis(*N*-(undecan-6-yl)hexanamide)

[0469] This compound has the chemical formula $C_{110}H_{204}N_{24}O_8$, with a molecular weight of 1991.00 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:





[0470] To a solution of compound **A6L1T14_12-1** (1.00 g, 9.47 mmol, 1.0 *eq*, HCl) in DCM (10 mL) was added TEA (2.88 g, 28.4 mmol, 3.96 mL, 3.0 *eq*) and DMAP (57.8 mg, 473 μmol, 0.05 *eq*) and compound **2** (1.03 g, 11.3 mmol, 923 μL, 1.2 *eq*) in DCM (10 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h. TLC (Petroleum ether: Ethyl acetate=1:1, R_f = 0.47) indicated compound **A6L1T14_12-1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The residue was diluted with water 30 mL and extracted with dichloromethane 50 mL (50 mL * 3). The combined organic layers were washed with brine 50 mL (50 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound **L2** (4.15 g, 33.7 mmol, 71.1% yield) was obtained as a white solid.

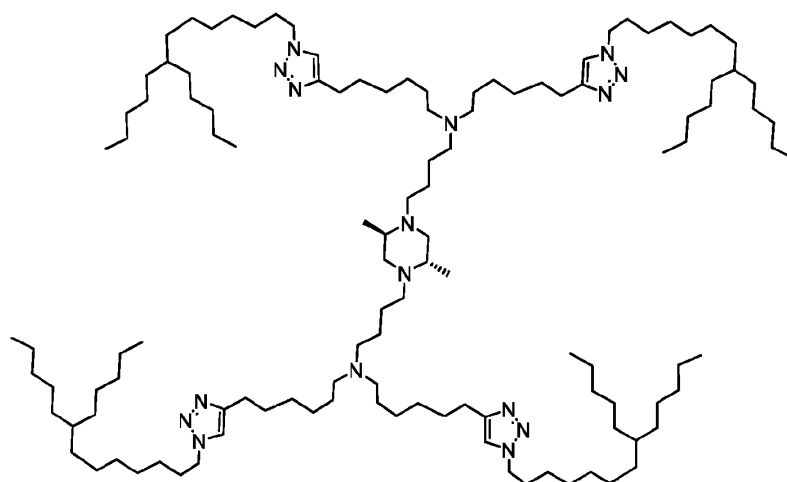
[0471] ^1H NMR (400 MHz, CDCl_3): δ = 6.36 - 6.24 (m, 1H), 6.17 - 6.07 (m, 1H), 6.04 - 5.81 (m, 1H), 5.67 (dd, J = 1.4, 10.3 Hz, 1H), 3.51 (q, J = 6.3 Hz, 2H), 2.46 (dt, J = 2.6, 6.4 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H).

[0472] To a solution of compound **A6** (500 mg, 1.71 mmol, 1.0 eq, HCl) in t-BuOH (10 mL) was added TEA (1.21 g, 11.9 mmol, 1.66 mL, 7.0 eq) and compound **L2** (1.68 g, 13.6 mmol, 8.0 eq). The mixture was stirred at 100 °C for 12h. LC-MS showed that compound **A6** was consumed completely and the desired mass was detected. The reaction mixture concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 μm); mobile phase: [water(TFA)-ACN]; gradient: 0%-30% B over 25 min). Compound **A6L2** (300 mg, 400 μmol , 23.4% yield) was obtained as a light yellow oil. LCMS product: RT = 0.216 min.

[0473] ^1H NMR (400 MHz, DEUTERIUM OXIDE): δ = 3.79 - 3.68 (m, 2H), 3.55 - 3.41 (m, 12H), 3.38 - 3.23 (m, 14H), 3.09 (br d, J = 10.4 Hz, 4H), 2.78 (br t, J = 6.1 Hz, 8H), 2.47 - 2.33 (m, 12H), 1.86 (br s, 6H), 1.79 - 1.68 (m, 2H), 1.40 (br d, J = 5.4 Hz, 6H).

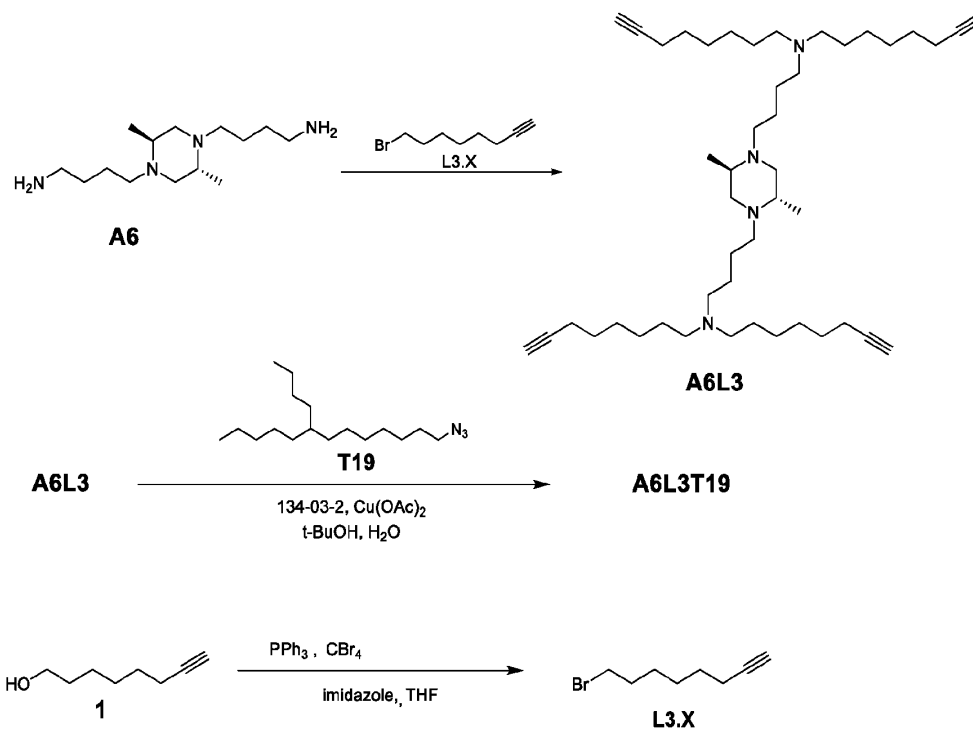
[0474] To a solution of compound **A6L2** (250 mg, 333 μmol , 1.0 eq) in t-BuOH (3 mL) and H_2O (3 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (66.1 mg, 333 μmol , 1.0 eq), $\text{Cu}(\text{OAc})_2$ (60.6 mg, 333 μmol , 1.0 eq) and compound **T18** (518.13 mg, 1.67 mmol, 5 eq). The mixture was stirred at 20 °C for 2h. LC-MS showed compound **T18** was consumed completely and one main peak with the desired mass was detected. The residue was diluted with water 30 mL and extracted with dichloromethane 20 mL (20 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD27-PHS XP phenyl-Hexyl 150*25*7 μm ; mobile phase: [water(TFA)-ACN]; gradient: 35%-65% B over 10 min). Compound **A6L2T18** (80 mg, 37.2 μmol , 11.1% yield, 92.6% purity) was obtained as a light yellow oil. LCMS product: RT = 0.508 min. CAD product: RT = 12.763 min. ^1H NMR (400 MHz, CDCl_3): δ = 7.82 (br t, J = 5.6 Hz, 4H), 7.48 (s, 4H), 5.57 (br d, J = 9.2 Hz, 4H), 4.31 (t, J = 7.2 Hz, 8H), 3.94 - 3.83 (m, 4H), 3.55 (q, J = 6.8 Hz, 8H), 2.93 (t, J = 6.8 Hz, 8H), 2.81 - 2.58 (m, 12H), 2.40 (br s, 4H), 2.32 (br t, J = 6.4 Hz, 8H), 2.16 (t, J = 7.4 Hz, 8H), 1.94 - 1.87 (m, 8H), 1.70 - 1.64 (m, 10H), 1.50 - 1.43 (m, 8H), 1.39 - 1.21 (m, 76H), 0.97 (br s, 6H), 0.91 - 0.84 (m, 24H).

Example A6L3T19



N,N'-(((trans)-2,5-dimethylpiperazine-1,4-diyl)bis(butane-4,1-diyl))bis(6-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)-N-(6-(1-(8-pentyltridecyl)-1H-1,2,3-triazol-4-yl)hexyl)hexan-1-amine)

[0475] This compound has the chemical formula $C_{118}H_{228}N_{16}$, with a molecular weight of 1871.23 g/mol. The compound preparation, and that of some intermediates used in the same, were made as follows:



[0476] To a solution of compound **1** (5.00 g, 39.6 mmol, 1.0 *eq*) in THF (50 mL) was added CBr_4 (26.2 g, 79.2 mmol, 2.0 *eq*) and PPh_3 (26.0 g, 99.0 mmol, 2.5 *eq*) and imidazole (2.70 g, 39.6 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 12h. TLC (Ethyl acetate: Petroleum ether=0:1, R_f = 0.42) indicated compound **1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO[®], 80 g SepaFlash[®] Silica Flash Column, Eluent of 0%Ethylacetate/Petroleum ethergradient @ 50 mL/min). Compound **L3.X** (4.0 g, 21.15 mmol, 53.3% yield) was obtained as a colorless oil.

[0477] ^1H NMR (400 MHz, CDCl_3): δ = 3.42 (t, J = 6.8 Hz, 2H), 2.21 (br t, J = 6.8 Hz, 2H), 1.95 (br s, 1H), 1.93 - 1.83 (m, 2H), 1.56 (s, 2H), 1.46 (br s, 4H).

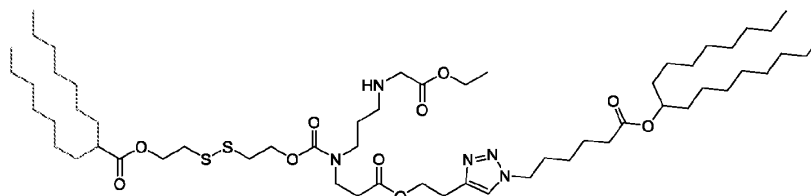
[0478] To a solution of compound **A6** (1.00 g, 3.41 mmol, 1.0 *eq*, HCl) in MeCN (10 mL) and H_2O (3 mL) was added K_2CO_3 (1.42 g, 10.24 mmol, 3.0 *eq*) and compound **L3.X** (2.91 g, 15.3 mmol, 4.5 *eq*). The mixture was stirred at 60 °C for 4h. LC-MS showed compound **A6** was consumed completely and desired mass was detected. The residue was diluted with water 20 mL

and extracted with ethyl acetate 20 mL (20 mL * 3). The combined organic layers were washed with brine 20 mL (20 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 μ m); mobile phase: [water(TFA)-ACN]; gradient: 15%-45% B over 25 min). Compound **A6L3** was obtained as a white solid. LCMS product: RT = 0.351 min. ^1H NMR (400 MHz, METHANOL- d_4): δ = 3.67 - 3.54 (m, 2H), 3.54 - 3.42 (m, 2H), 3.33 (br s, 2H), 3.27 - 3.10 (m, 12H), 3.10 - 2.91 (m, 4H), 2.24 - 2.16 (m, 11H), 1.89 - 1.67 (m, 16H), 1.60 - 1.47 (m, 16H), 1.46 - 1.34 (m, 14H).

[0479] To a solution of compound **A6L3** (350 mg, 507 μ mol, 1.0 *eq*) in H_2O (3 mL) and *t*-BuOH (3 mL) was added sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (100 mg, 507 μ mol, 1.0 *eq*, CAS: 134-03-2) and $\text{Cu}(\text{OAc})_2$ (92.2 mg, 507 μ mol, 1.0 *eq*) and compound **T19** (750 mg, 2.54 mmol, 5.0 *eq*). The mixture was stirred at 20 $^\circ\text{C}$ for 2h. LC-MS showed compound **A6L3** was consumed completely and the desired mass was detected. The residue was diluted with water 20 mL and extracted with dichloromethane 20 mL (20 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD27-PHS XP phenyl-Hexyl 150*25*7 μ m; mobile phase: [water(TFA)-ACN]; gradient: 60%-90% B over 15 min). Compound **A6L3T19** (190 mg, 99.7 μ mol, 19.6% yield, 98.2% purity) was obtained as a yellow oil. LCMS product: RT = 0.563 min. CAD product: RT = 16.097 min. ^1H NMR (400 MHz, CDCl_3):

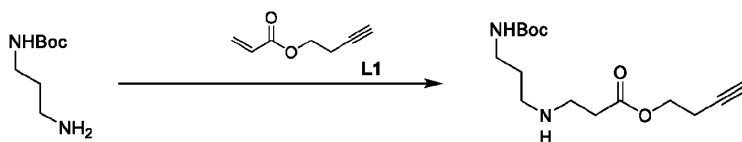
[0480] δ = 7.26 (s, 4H), 4.30 (t, J = 7.2 Hz, 8H), 2.79 (br s, 1H), 2.77 (br d, J = 1.6 Hz, 1H), 2.71 (t, J = 7.6 Hz, 10H), 2.51 - 2.32 (m, 12H), 2.23 (br dd, J = 2.4, 10.2 Hz, 2H), 2.06 - 1.97 (m, 2H), 1.92 - 1.85 (m, 8H), 1.67 (td, J = 7.6, 14.6 Hz, 32H), 1.51 - 1.36 (m, 24H), 1.30 (br s, 14H), 1.23 (br s, 80H), 1.04 (d, J = 6.0 Hz, 6H), 0.89 (t, J = 7.2 Hz, 24H).

Example A39L1T15



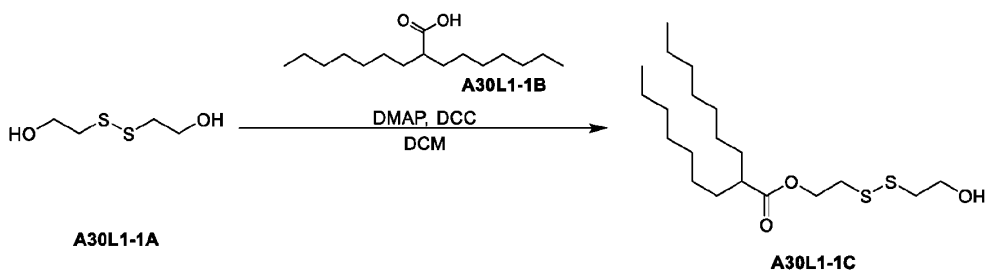
ethyl 9-(3-(2-(1-(6-(heptadecan-9-yloxy)-6-oxohexyl)-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)-1-((2-heptylnonanoyl)oxy)-8-oxo-7-oxa-3,4-dithia-9,13-diazapentadecan-15-oate

[0481] This compound has the chemical formula $C_{58}H_{107}N_5O_{10}S_2$, with a molecular weight of 1098.64 g/mol, and a $pK_a = 6.366$. The compound preparation, and that of some intermediates used in the same, were made as follows:



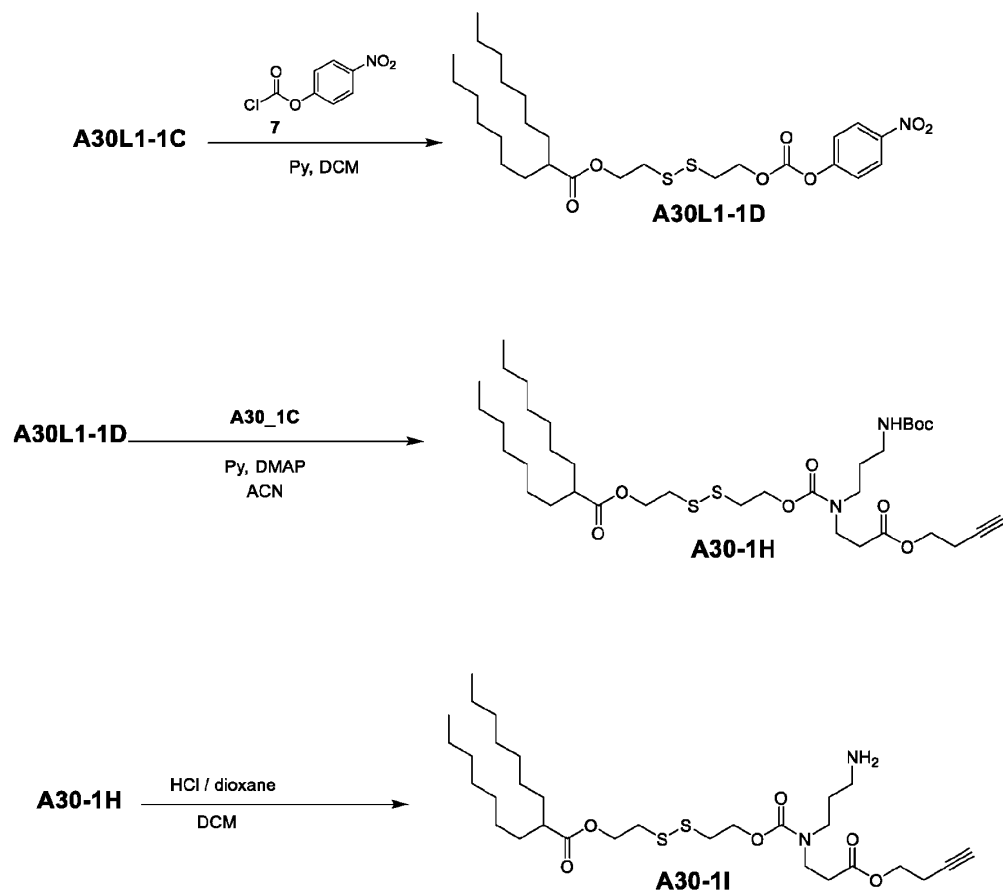
A30-1A

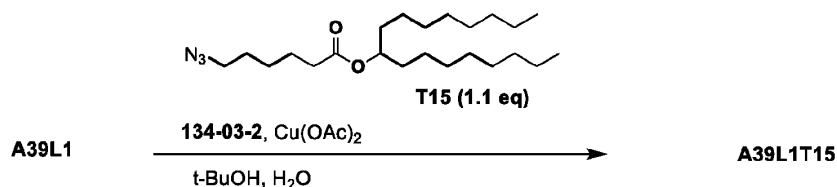
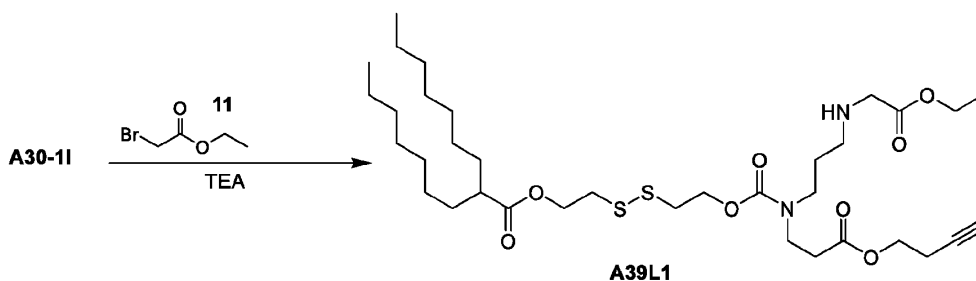
A30-1C



A30L1-1A

A30L1-1C





[0482] To a solution of compound **A30-1A** (1.00 g, 5.74 mmol, 1.00 mL, 1.0 eq) in compound **L1** (570 mg, 4.59 mmol, 0.8 eq) was added to a 3-neck round bottom flask at 25 °C. The mixture was stirred at 100 °C for 5 hrs. LCMS showed desired mass was detected. The mixture was concentrated in vacuum to give residue. The crude product was purified by flash silica gel chromatography (ISCO[®], 12 g SepaFlash[®] Silica Flash Column, Eluent of 20~30% Ethylacetate/Petroleum ether gradient @ 50 mL/min). The compound **A30-1C** (800 mg, 2.58 mmol, 44% yield, 96.1% purity) was obtained as a yellow oil which was confirmed by HNMR. LCMS product: RT = 0.215 min. ¹H NMR (400 MHz, CDCl₃):

[0483] δ = 5.04 (br s, 1H), 4.18 - 4.23 (m, 2H), 3.19 - 3.21 (m, 2H), 2.90 (t, J = 6.4 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.54 - 2.57 (m, 4H), 2.01 - 2.02 (m, 1H), 1.68 (s, 1H), 1.66 (quin, J = 6.4 Hz, 2H), 1.64 (s, 9H).

[0484] To a solution of compound **A30L1-1A** (1.00 g, 3.90 mmol, 1.0 eq) in DCM (8 mL) was added DMAP (571 mg, 4.68 mmol, 1.2 eq), DCC (885 mg, 4.29 mmol, 867 μ L, 1.1 eq) and compound **A30L1-1B** (1.80 g, 11.7 mmol, 3.0 eq). The mixture was stirred at 20 °C for 12 h. TLC (PE: EA = 3:1) showed the reactant (R_f = 0.13) was consumed completely and one new

major spot ($R_f = 0.41$) was detected. The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was purified by flash silica gel chromatography (ISCO[®]; 40 g SepaFlash[®] Silica Flash Column, Eluent of 10~20% Ethylacetate/Petroleum ether gradient @ 50 mL/min). The compound **A30L1-1C** (3.70 g, 9.42 mmol, 80.5% yield) was obtained as a colorless oil which was confirmed by HNMR.

[0485] ¹H NMR (400 MHz, CDCl₃): δ = 4.31 - 4.41 (m, 2H), 3.83 - 3.96 (m, 2H), 2.83 - 3.00 (m, 4H), 2.28 - 2.40 (m, 1H), 2.03 - 2.20 (m, 1H), 1.55 - 1.65 (m, 2H), 1.44 (br dd, $J = 6.0$, 13.5 Hz, 2H), 1.26 - 1.29 (m, 20H), 0.99 - 0.78 (m, 6H).

[0486] To a solution of compound **A30L1-1C** (1.00 g, 2.55 mmol, 1.0 eq) in DCM (25 mL) was added Py (402 mg, 5.09 mmol, 411 μ L, 2.0 eq) and compound **7** (770 mg, 3.82 mmol, 1.5 eq). The mixture was stirred at 0 °C for 30 min. TLC (PE : EA=3:1) showed the compound **A30L1-1C** ($R_f = 0.40$) was consumed completely and one new major spot ($R_f = 0.62$) was detected. Petroleum ether is poured into the reaction solution, filtered and concentrated in vacuum to afford the product. Compound **A30L1-1D** (1.40 g, 2.51 mmol, 98.5% yield) was obtained as a colorless oil which was confirmed by HNMR. ¹H NMR (400 MHz, CDCl₃):

[0487] δ = 8.26 - 8.34 (m, 2H), 7.38 - 7.42 (m, 2H), 4.56 (t, $J = 6.8$ Hz, 2H), 4.37 (t, $J = 6.8$ Hz, 2H), 3.03 - 3.08 (m, 2H), 2.97 (t, $J = 6.4$ Hz, 2H), 2.30 - 2.40 (m, 1H), 1.57 - 1.64 (m, 2H), 1.41 - 1.49 (m, 2H), 1.26 - 1.31 (m, 20H), 0.86 - 0.91 (m, 6H).

[0488] To a solution of compound **A30L1-1D** (1.40 g, 2.51 mmol, 1.0 eq) in ACN (40 mL) was added Py (397 mg, 5.02 mmol, 405 μ L, 2.0 eq) DMAP (153 mg, 1.26 mmol, 0.5 eq) and compound **A30-1C** (898 mg, 3.01 mmol, 1.2 eq). The mixture was stirred at 25 °C for 12 h. LCMS showed the product ($R_t = 0.635$ min, $[M+1]^+ = 717.4$) was the main peak. The mixture was concentrated in vacuum to give residue. The crude product was purified by flash silica gel chromatography (ISCO[®]; 4 g SepaFlash[®] Silica Flash Column, Eluent of 10~20% Ethylacetate/Petroleum ether gradient @ 50 mL/min). Compound **A30-1H** (1.74 g, 2.42 mmol, 96.4% yield, 99.7% purity) was obtained as a colorless oil which was confirmed by HNMR. LCMS product: $R_t = 0.635$ min. ¹H NMR (400 MHz, CDCl₃):

[0489] δ = 4.31 - 4.40 (m, 4H), 4.20 (t, $J = 6.8$ Hz, 2H), 3.47 - 3.59 (m, 2H), 3.27 - 3.40 (m, 2H), 3.12 (br d, $J = 4.1$ Hz, 2H), 2.94 (td, $J = 6.5$, 9.9 Hz, 4H), 2.64 (t, $J = 7.1$ Hz, 2H), 2.54 (dt, $J = 2.4$, 6.7 Hz, 2H), 2.34 (tt, $J = 5.3$, 8.8 Hz, 1H), 2.02 (br s, 1H), 1.53 - 1.79 (m, 5H), 1.46

(s, 10H), 1.21 - 1.32 (m, 20H), 0.79 - 0.95 (m, 6H).

[0490] To a solution of compound **A30-1H** (850 mg, 1.19 mmol, 1.0 eq) in DCM (5 mL) was added HCl/dioxane (2 M, 11.85 mL, 20 eq). The mixture was stirred at 20 °C for 12h. LCMS showed the product ($R_t = 0.491$ min, $[M+1]^+ = 617.5$) was the main peak. The mixture was concentrated in vacuum to give residue. The product compound **A30-1I** (1.55 g, 2.35 mmol, 98.9% yield, 98.9% purity, HCl) was obtained as a colorless oil. LCMS product: $R_t = 0.491$ min.

[0491] To a solution of compound **A30-1I** (800 mg, 1.22 mmol, 1.0 eq, HCl) in DCM (15 mL) was added TEA (185 mg, 1.84 mmol, 255 μ L, 1.5 eq) then compound **11** (204 mg, 1.22 mmol, 135 μ L, 1.0 eq) in DCM (5 mL) dropwise into the mixture. The mixture was stirred at 20 °C for 4 hrs. LCMS showed the product ($R_t = 3.626$ min, $[M+1]^+ = 703.5$) was the main peak. The mixture was concentrated in vacuum to give residue. The crude product was purified by flash silica gel chromatography (ISCO[®], 20 g SepaFlash[®] Silica Flash Column, Eluent of 4~5% Dichloromethane / Methanol ether gradient @ 20 mL/min). The product compound **A39L1** (750 mg, 1.06 mmol, 43.4% yield, 99.8% purity) was obtained as a yellow oil which was confirmed by HNMR. LCMS product: $R_t = 3.626$ min. ¹H NMR (400 MHz, CHLOROFORM-d):

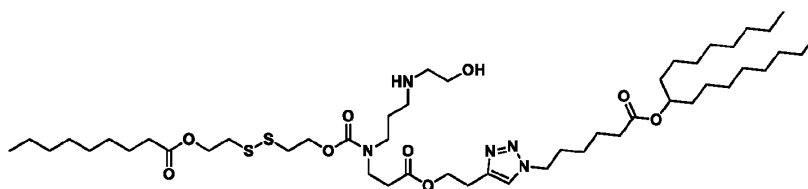
[0492] $\delta = 4.34$ (br t, $J = 6.4$ Hz, 4H), 4.16 - 4.24 (m, 4H), 3.48 - 3.59 (m, 2H), 3.29 - 3.44 (m, 4H), 2.89 - 2.98 (m, 4H), 2.60 - 2.69 (m, 4H), 2.54 (dt, $J = 2.5, 6.7$ Hz, 2H), 2.28 - 2.40 (m, 1H), 2.02 (br s, 1H), 1.76 (br d, $J = 4.8$ Hz, 2H), 1.53 - 1.67 (m, 2H), 1.44 (br dd, $J = 5.6, 14.1$ Hz, 2H), 1.18 - 1.33 (m, 23H), 0.88 (t, $J = 6.8$ Hz, 6H).

[0493] To a solution of compound **A39L1** (750 mg, 1.07 mmol, 1.0 eq) in t-BuOH (8.0 mL) and H₂O (8 mL) was added compound sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-3-hydroxy-5-oxo-2H-furan-4-olate (211 mg, 1.07 mmol, 1.0 eq) (CAS: 134-03-0), Cu(OAc)₂ (193 mg, 1.07 mmol, 1.0 eq) and compound **T15** (633 mg, 1.60 mmol, 1.5 eq). The mixture was stirred at 20 °C for 1 h. LCMS showed the product ($R_t = 0.662$ min, $[M/2+1]^+ = 550.2$) was the main peak. The mixture was diluted with water (20 mL) and extracted with dichloromethane (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by flash silica gel chromatography (ISCO[®], 12 g SepaFlash[®] Silica Flash Column, Eluent of 5~8% Dichloromethane / Methanol ether gradient @ 30 mL/min). The residue was further purified by semi-preparative reverse phase HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μ m;

mobile phase: [water (TFA)-ACN]; gradient: 62%-92% B over 10 min). Compound **A39L1T15** (380 mg, 314 μ mol, 29.47% yield, 90.9% purity) was obtained as a yellow oil which was confirmed by HNMR. LCMS product: RT = 0.662 min. CAD product: RT = 14.670 min.

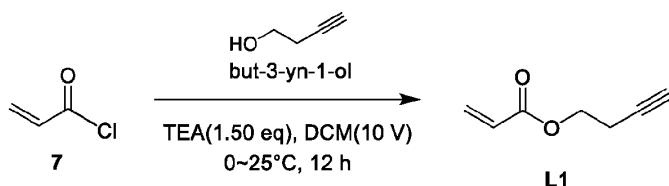
[0494] ^1H NMR (400 MHz, CHLOROFORM- d): δ = 7.38 (br d, J = 6.8 Hz, 1H), 4.86 (t, J = 6.2 Hz, 1H), 4.31 - 4.39 (m, 8H), 4.06 - 4.26 (m, 2H), 3.52 (br d, J = 3.4 Hz, 2H), 3.39 (s, 2H), 3.33 (br d, J = 5.3 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.90 - 2.97 (m, 4H), 2.53 - 2.69 (m, 4H), 2.32 - 2.38 (m, 1H), 2.30 (t, J = 7.2 Hz, 2H), 1.91 - 1.96 (m, 2H), 1.65 - 1.77 (m, 6H), 1.57 - 1.61 (m, 2H), 1.51 (br d, J = 6.0 Hz, 3H), 1.39 (br dd, J = 8.0, 15.5 Hz, 4H), 1.24 - 1.30 (m, 46H), 0.88 (t, J = 6.8 Hz, 12H).

Example A40L1T15



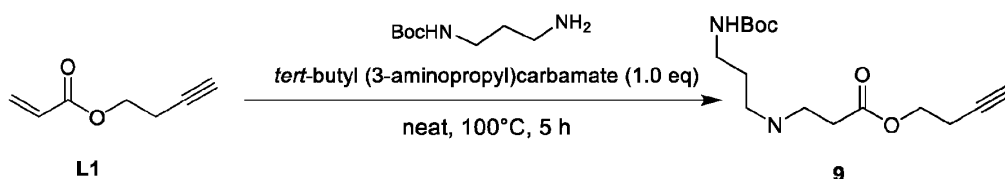
15-(1-(6-(heptadecan-9-yloxy)-6-oxohexyl)-1H-1,2,3-triazol-4-yl)-9-(3-((2-hydroxyethyl)amino)propyl)-8,12-dioxo-7,13-dioxo-3,4-dithia-9-azapentadecyl nonanoate

[0495] This compound preparation, and that of some intermediates used in the same, were made as follows:

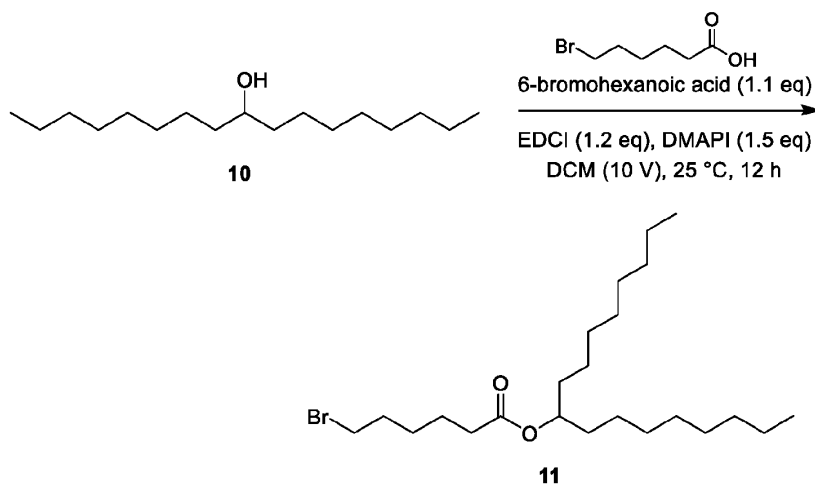


[0496] To a solution of but-3-yn-1-ol (14 g, 199.74 mmol, 15.12 mL, 1 eq), DMAP (1.22 g, 9.99 mmol, 0.05 eq) and TEA (30.32 g, 299.62 mmol, 41.70 mL, 1.5 eq) in DCM (300 mL), was added compound **7** (21.69 g, 239.69 mmol, 19.47 mL, 1.2 eq) 0 °C. The mixture was then stirred at 25 °C for 12 h. TLC (PE: EA=5:1) indicated two new spots (R_f = 0.70). The reaction mixture was quenched by adding H₂O 500 mL, and extracted with DCM 300 mL. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under

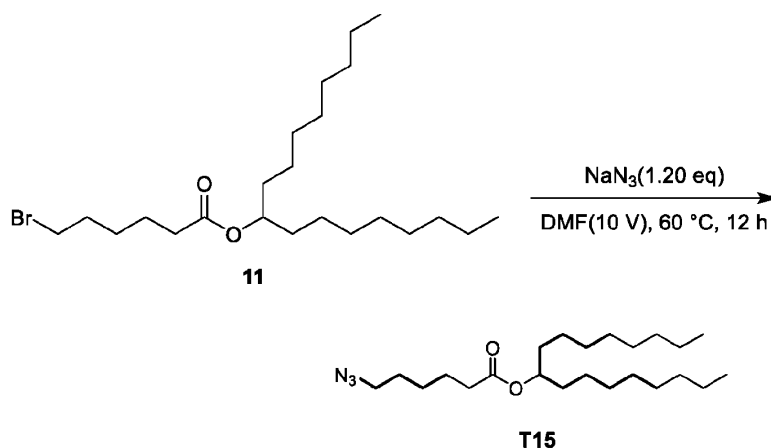
reduced pressure to give a residue. The crude product was distilled in vacuum (60 °C, 0.2 MPa pressure/oil pump). Compound **L1** (75 g, 604.17 mmol, 60.49% yield) was obtained as a light yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.45 (dd, *J* = 1.2, 17.2 Hz, 1H), 6.15 (dd, *J* = 10.4, 17.2 Hz, 1H), 5.86 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 2H), 2.58 (dt, *J* = 2.4, 6.8 Hz, 2H), 2.02 (t, *J* = 2.8 Hz, 1H).



[0497] A mixture of compound **L1** (1.00 g, 5.74 mmol, 1.00 mL, 1.0 eq) and tert-butyl (3-aminopropyl)carbamate (570 mg, 4.59 mmol, 0.8 eq) was stirred at 100 °C for 5 h. LCMS showed that the desired mass was detected. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 20~30% Ethylacetate/Petroleum ether gradient @ 50 mL/min). Compound **9** (800 mg, 2.58 mmol, 44% yield, 96.1% purity) was obtained as a yellow oil which was confirmed by HNMR. LCMS product: RT = 0.215 min. ¹H NMR (400 MHz, CDCl₃): δ = 5.04 (s, 1H), 4.18 - 4.23 (m, 2H), 3.19 - 3.21 (m, 2H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.54 - 2.57 (m, 4H), 2.01 - 2.02 (m, 1H), 1.68 (s, 1H), 1.66 (quin, *J* = 6.4 Hz, 2H), 1.64 (s, 9H).

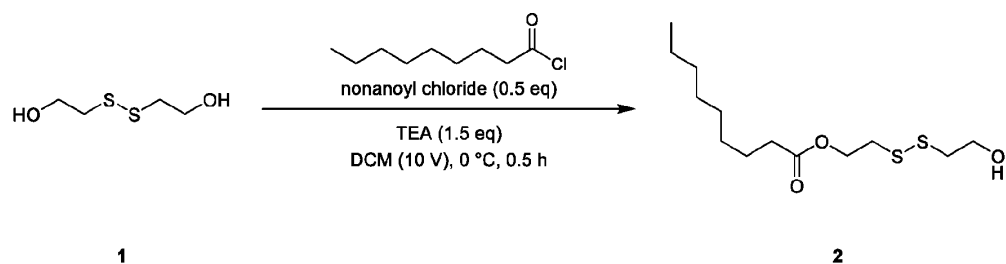


[0498] To a solution of 6-bromohexanoic acid (16.73 g, 85.78 mmol, 1.1 eq) and heptadecan-9-ol (20 g, 77.98 mmol, 1 eq) in DCM (2000 mL) was added DMAP (14.29 g, 116.97 mmol, 1.5 eq) and EDCI (17.94 g, 93.58 mmol, 1.2 eq). The mixture was stirred at 25 °C for 12 h. TLC (PE: EA=20:1) indicated two new spots (R_f = 0.77). 1000 mL water were added to the reaction mixture, and the aqueous phase was extracted with DCM (500 mL $\times$ 3). The combined organic phase was washed with brine (200 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1 to 20/1). Compound **11** (55 g, 126.87 mmol, 32.54% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 4.87 (m, 1H), 3.54-3.39 (m, 1H), 2.33-2.29 (m, 2H), 1.9-1.26 (m, 34H), 0.90-0.86 (t, J = 6.4 Hz, 6H).



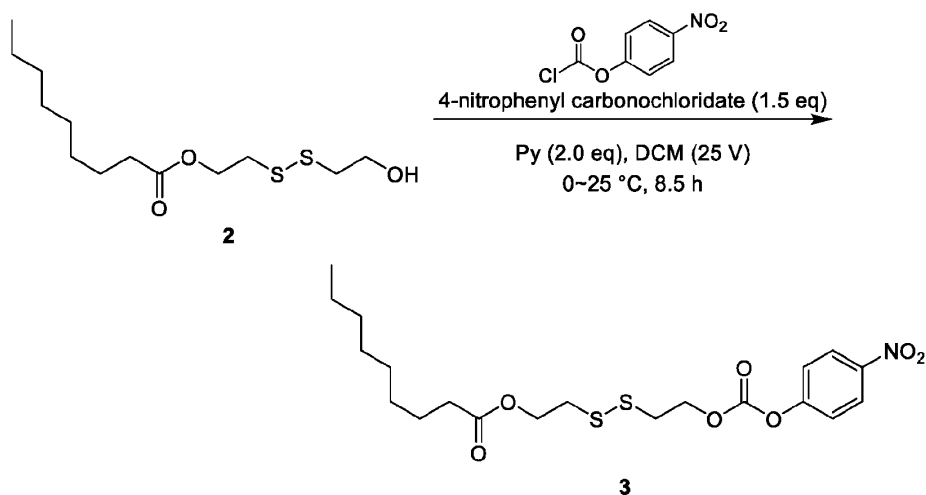
[0499] To a solution of **11** (55 g, 126.87 mmol, 1 eq) in DMF (550 mL) was added NaN₃ (9.95 g, 153.05 mmol, 1.21 eq). The mixture was stirred at 60 °C for 12hr. TLC(PE:EA=20:1) indicated one new spot was detected (R_f = 0.76). The reaction mixture was quenched by H₂O 1000 mL at 20 °C and extracted with PE 1000 mL. The combined organic layers were washed with brine 500 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The aqueous phase was diluted 50 times, quenched with sodium hypochlorite, and left overnight, then discarded. The product was used into the next step without further purification. Compound **T15** (45 g, 113.75 mmol, 89.65% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃):

δ = 4.89-4.86 (m, 1H), 3.22 (m, 2H), 2.30 (m, 2H), 1.66-1.26 (m, 34H), 0.89-0.86 (t, J = 6.0 Hz, 6H).

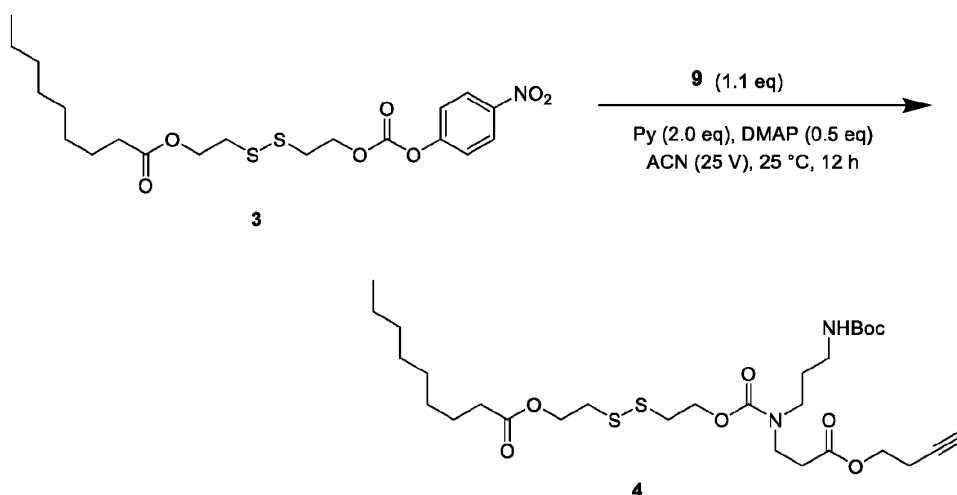


[0500] To a solution of **1** (2.5 g, 16.21 mmol, 1 *eq*) in DCM (25 mL) was added TEA (2.46 g, 24.31 mmol, 3.38 mL, 1.5 *eq*) and nonanoyl chloride (1.43 g, 8.10 mmol, 1.52 mL, 0.5 *eq*) in DCM (15 mL). The mixture was stirred at 0°C for 0.5hr. LC-MS showed that compound **1** was consumed completely and the desired mass was detected. The reaction mixture was quenched with 50 mL water and the aqueous phase was extracted with DCM (50 mL $\times$ 3). The combined organic phases were washed with brine (20 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 10/1). Compound **2** (5.8 g, 19.70 mmol, 30.38% yield) was obtained as a colorless oil. LCMS: m/z = 317.1 ($M+\text{Na}$)⁺, R_t = 3.13 min.

¹H NMR (400 MHz, CDCl₃): δ = 4.36 (t, J = 6.8 Hz, 2H), 3.90 (t, J = 5.6 Hz, 2H), 3.06 - 2.79 (m, 4H), 2.33 (t, J = 7.6 Hz, 2H), 1.67 - 1.60 (m, 2H), 1.35 - 1.24 (m, 11H), 0.97 - 0.77 (m, 3H).

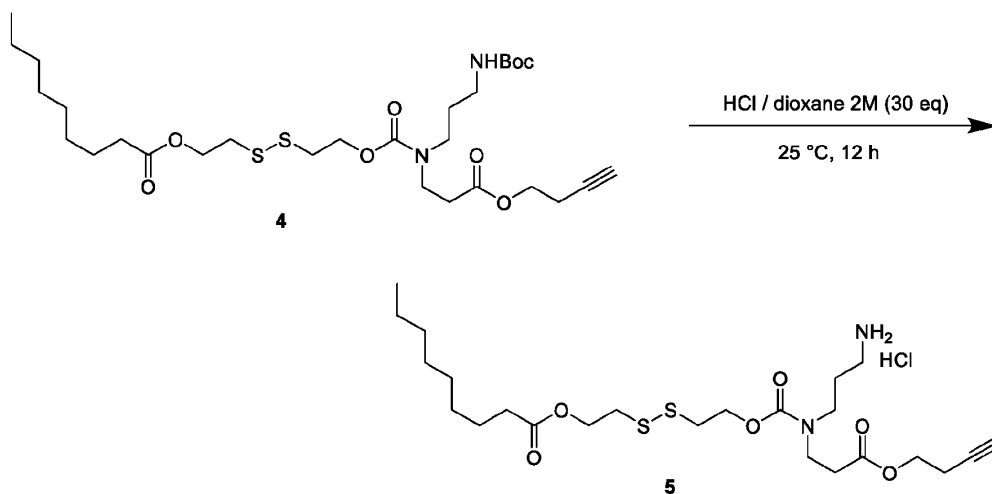


[0501] To a solution of **2** (5 g, 16.98 mmol, 1 *eq*) in DCM (80 mL) was added Py (2.69 g, 33.96 mmol, 2.74 mL, 2 *eq*) and 4-nitrophenyl carbonochloridate (3.76 g, 18.68 mmol, 1.1 *eq*). The mixture was stirred at 0 °C for 30 min. The mixture was stirred at 25 °C for 8 h. TLC (PE:EA=10:1) indicated three new spots were detected ($R_f = 0.51$). The reaction mixture was quenched with 40 mL water. The aqueous phase was extracted with DCM (30.0 mL $\times$ 3). The reaction mixture was filtered and the filtrate was concentrated to remove the water under reduced pressure to give product. Crude compound **3** (4.5 g, 9.79 mmol, 57.67% yield) was obtained as a colorless oil.



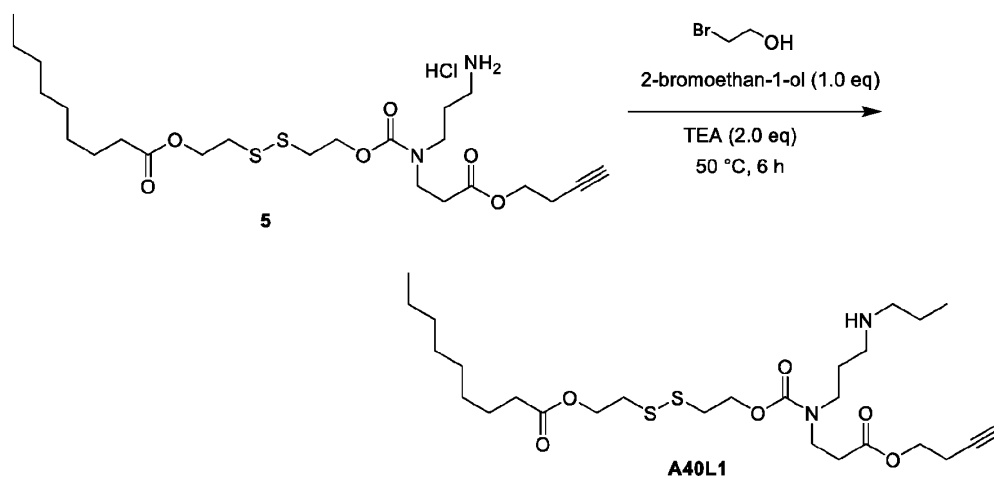
[0502] To a solution of compound **3** (4.5 g, 9.79 mmol, 1 *eq*) in MeCN (70 mL) was added Py (1.55 g, 19.58 mmol, 1.58 mL, 2 *eq*), DMAP (598.11 mg, 4.90 mmol, 0.5 *eq*) and compound **9** (3.21 g, 10.77 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 12h. LC-MS showed that compound **3** was consumed completely and the desired mass was detected. The reaction mixture was quenched with 100 mL water, the aqueous phase was extracted with ethyl acetate (100 mL ×3). The combined organic phases were washed with brine (50 mL ×3), dried with anhydrous sodiumsulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, DCM: MeOH=10:1). Compound **4** (2.3 g, 3.72 mmol, 37.96% yield) was obtained as a colorless oil. LCMS: $m/z = 519.3$ (M-100)⁺, $R_t = 0.591$ min.

[0503] ¹H NMR (400 MHz, CDCl₃): $\delta = 4.43 - 4.30$ (m, 4H), 4.20 (t, $J = 6.8$ Hz, 2H), 3.52 (d, $J = 6.4$ Hz, 2H), 3.42 - 3.24 (m, 2H), 3.11 (d, $J = 4.8$ Hz, 2H), 2.94 (d, $J = 6.4$, 8.4 Hz, 4H), 2.64 (t, $J = 7.2$ Hz, 2H), 2.54 (t, $J = 2.4$, 6.8 Hz, 2H), 2.32 (t, $J = 7.6$ Hz, 2H), 2.08 - 2.01 (m, 2H), 1.70 (d, $J = 6.0$ Hz, 2H), 1.65 - 1.59 (m, 2H), 1.45 (s, 9H), 1.33 - 1.25 (m, 10H), 0.88 (t, $J = 6.8$ Hz, 3H).

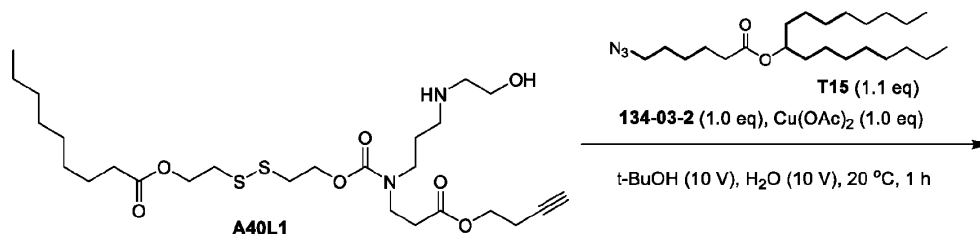


[0504] A mixture of compound **4** (2 g, 3.23 mmol, 1 *eq*) and HCl/dioxane (2 M, 47.62 mL, 29.47 *eq*) was stirred at 20 °C for 12hr. LC-MS showed that compound **4** was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give residue. Compound **5** (1.1 g, 2.12 mmol, 65.62% yield) was obtained as a colorless oil. LCMS: $m/z = 519.3$ (M+1)⁺, $R_t = 0.44$ min.

[0505] ^1H NMR (400 MHz, CDCl_3): δ = 4.41 - 4.30 (m, 4H), 4.20 (t, J = 6.8 Hz, 2H), 3.53 (t, J = 6.4 Hz, 2H), 3.48 (s, 2H), 3.06 (t, J = 6.4 Hz, 2H), 2.94 (q, J = 6.4 Hz, 4H), 2.65 (t, J = 6.8 Hz, 2H), 2.55 (t, J = 2.4, 6.8 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 2.12 - 2.02 (m, 3H), 1.62 (d, J = 7.2 Hz, 2H), 1.28 (d, J = 7.2 Hz, 10H), 0.93 - 0.82 (m, 3H).

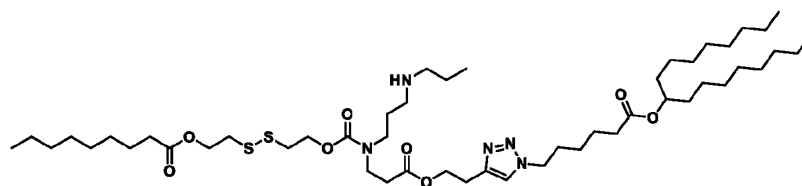


[0506] To a solution of compound **5** (550 mg, 929.60 μmol , 1 eq, 2HCl) in DCM (8 mL) was added TEA (188.13 mg, 1.86 mmol, 258.78 μL , 2 eq) and 2-bromoethan-1-ol (116.17 mg, 929.60 μmol , 65.89 μL , 1 eq). The mixture was stirred at 50 $^\circ\text{C}$ for 6 h. LC-MS showed the desired mass was detected. The reaction mixture was quenched with 20 mL water and the aqueous phase was extracted with DCM (20 mL $\times$ 3). The combined organic phases were washed with brine (20 mL $\times$ 3), dried with anhydrous sodiumsulfate, filtered and concentrated in vacuum. Compound **6** (200 mg, 355.38 μmol , 38.23% yield) was obtained as a colorless oil. LCMS: m/z = 563.4 ($\text{M}+1$) $^+$, R_t = 0.436 min.

**A40L1T15**

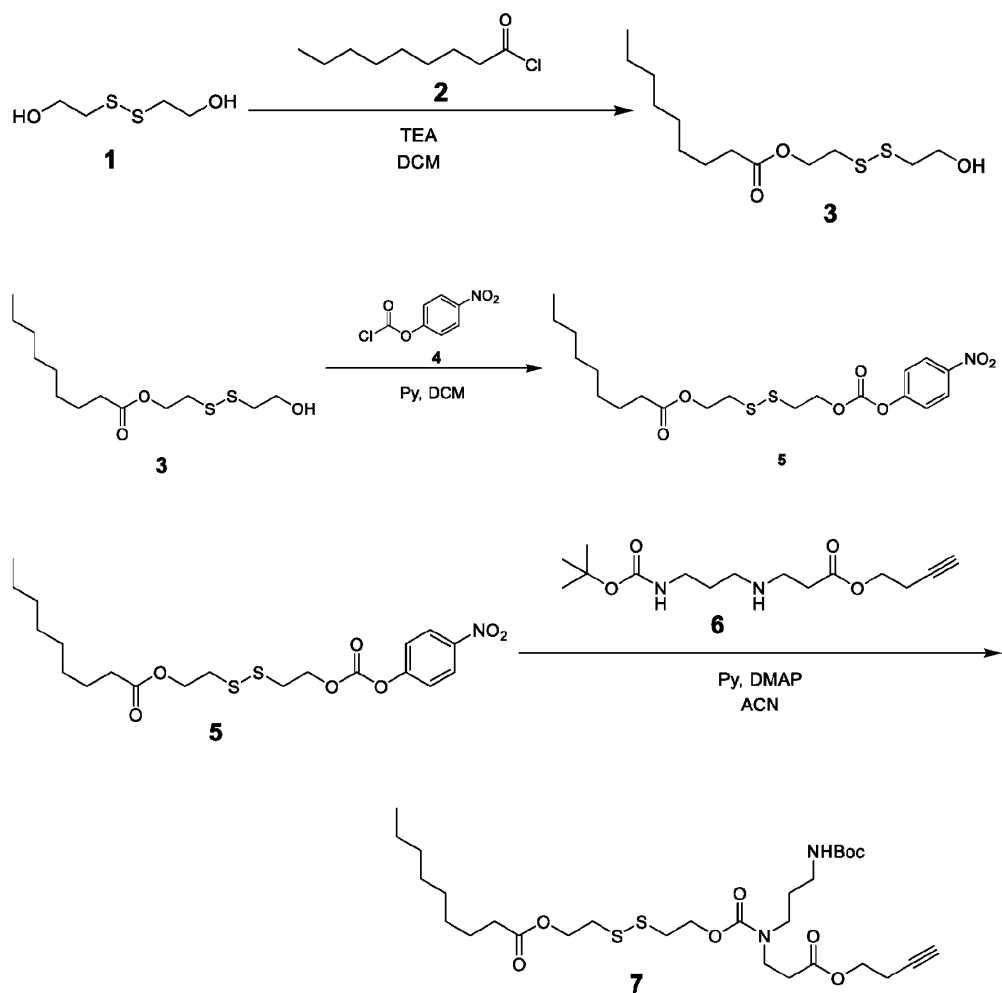
[0507] To a solution of compound **6** (200 mg, 355.38 μ mol, 1 eq) and compound **12** (154.65 mg, 390.92 μ mol, 1.1 eq) in t-BuOH (2 mL) and H₂O (2 mL) was added sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (70.40 mg, 355.38 μ mol, 1 eq, CAS: 134-03-2) and Cu(OAc)₂ (64.55 mg, 355.38 μ mol, 1 eq). The mixture was stirred at 25 °C for 2h. LC-MS showed that the desired mass was detected. 10 mL water were added to the reaction mixture. The aqueous phase was extracted with DCM (10 mL $\times$ 3). The combined organic phases were washed with brine (10 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μ m; mobile phase: [water(TFA)-ACN]; gradient: 50%-80% B over 15 min). Compound **A40L1T15** (70 mg, 73.04 μ mol, 41% purity, 20.55% yield) was obtained as a brown oil. LCMS product: RT = 0.636 min. CAD product: RT = 11.678 min.

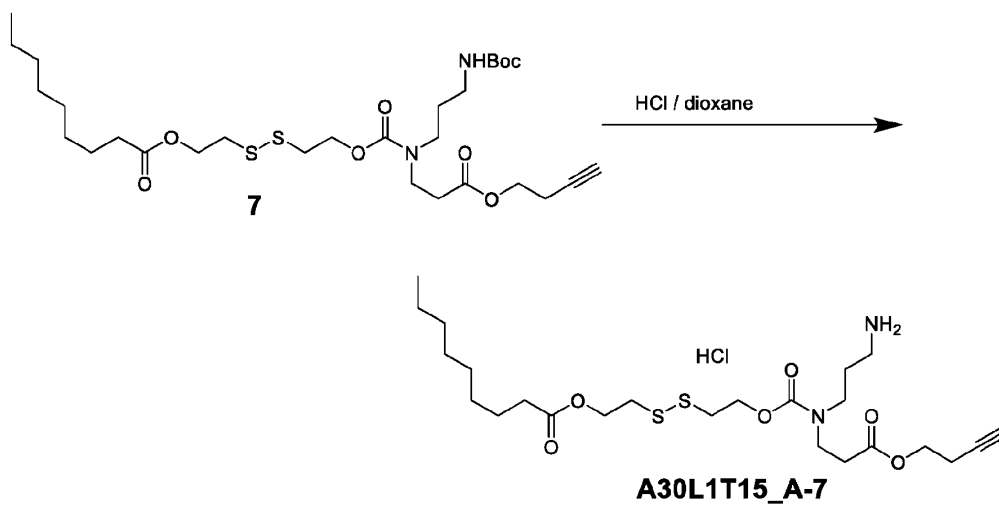
Example A41L1T15

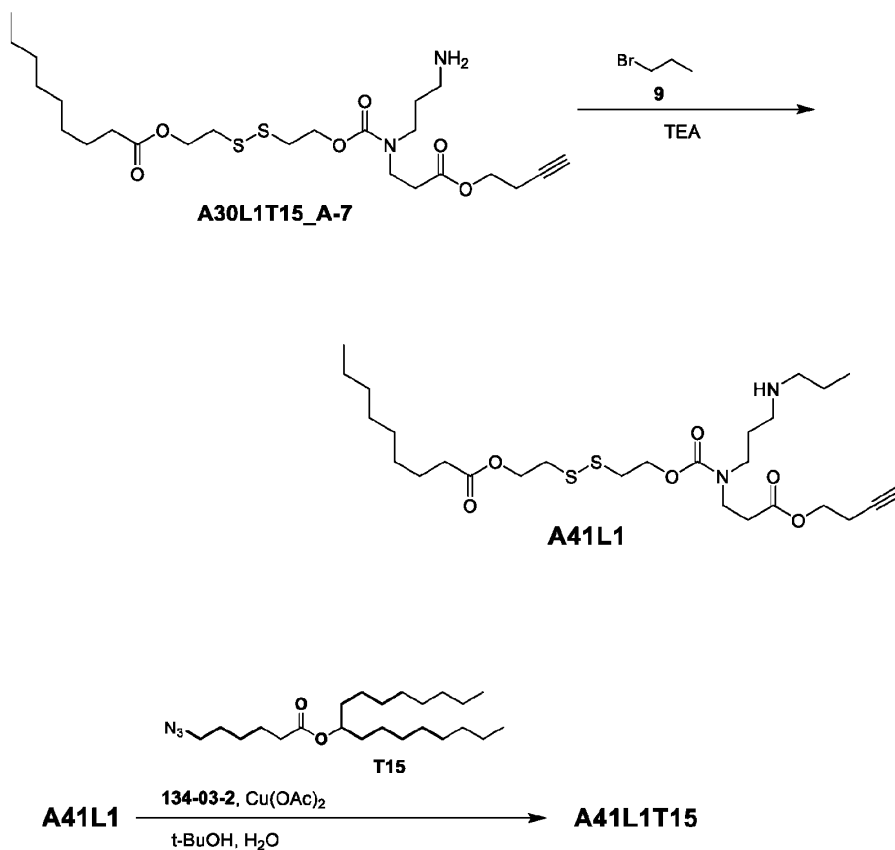


9-(3-(2-(1-(6-(heptadecan-9-yloxy)-6-oxohexyl)-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)-8-oxo-7-oxa-3,4-dithia-9,13-diazahexadecyl nonanoate

[0508] This compound preparation, and that of some intermediates used in the same, were made as follows:







Two reactions were carried out in parallel.

[0509] To a solution of **1** (2.5 g, 16.2 mmol, 1.0 *eq*) in DCM (25 mL) was added TEA (2.46 g, 24.3 mmol, 3.38 mL, 1.5 *eq*) and **2** (1.43 g, 8.10 mmol, 1.52 mL, 0.5 *eq*) in DCM (15 mL). The mixture was stirred at 0 °C for 0.5 h. LC-MS showed Reactant 1 was consumed completely and the desired mass was detected. Combined two reactions for work up. The reaction mixture was poured into 50 mL water, the aqueous phase was extracted with DCM (50 mL $\times$ 3). The combined organic phase was washed with brine (20 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 10/1). Compound **3** (5.8 g, 19.70 mmol, 30.38% yield) was obtained as a colorless oil, which was confirmed by HNMR. LCMS: m/z = 317.1 (M+Na)⁺, R_t = 3.13 min. ¹H NMR (400 MHz, CDCl₃): δ = 4.36 (t, J = 6.7 Hz, 2H), 3.90 (t, J =

5.8 Hz, 2H), 3.06 - 2.79 (m, 4H), 2.33 (t, $J = 7.5$ Hz, 2H), 1.67 - 1.60 (m, 2H), 1.35 - 1.24 (m, 11H), 0.97 - 0.77 (m, 3H).

[0510] To a solution of **3** (5 g, 16.9 mmol, 1.0 *eq*) in DCM (80 mL) was added Py (2.69 g, 33.9 mmol, 2.74 mL, 2.0 *eq*) and **4** (3.76 g, 18.6 mmol, 1.1 *eq*). The mixture was stirred at 0 °C for 30 mins. The mixture was stirred at 25 °C for 8 hrs. TLC (Petroleum ether: Ethyl acetate = 10:1, indicated 0% of Reactant 1 remained, and three new spot was detected. The reaction mixture was poured into 40.0 mL water, the aqueous phase was extracted with DCM (30.0 mL $\times 3$). The reaction mixture was filtered and filtrate was co-evaporated to remove the water under reduced pressure to give product. Compound **5** (4.5 g, 9.79 mmol, 57.67% yield) was obtained as a colorless oil.

[0511] To a solution of **5** (4.5 g, 9.79 mmol, 1.0 *eq*) in MeCN (70 mL) was added Py (1.55 g, 19.5 mmol, 1.58 mL, 2.0 *eq*), DMAP (598 mg, 4.90 mmol, 0.5 *eq*) and **6** (3.21 g, 10.77 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 12 hr. LC-MS showed the reactant was consumed completely and desired mass was detected. The reaction mixture was added 100 mL water, the aqueous phase was extracted with ethyl acetate (100 mL $\times 3$). The combined organic phase was washed with brine (50 mL $\times 3$), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 5/1). The residue was purified by column chromatography (SiO₂, DCM: MeOH=10:1). Compound **7** (2.3 g, 3.72 mmol, 37.9% yield) was obtained as a colorless oil, which was confirmed by HNMR. LCMS: $m/z = 519.3$ (M-100), RT = 0.591 min.

[0512] ¹H NMR (400 MHz, CDCl₃): δ = 4.43 - 4.30 (m, 4H), 4.20 (t, $J = 6.8$ Hz, 2H), 3.52 (br d, $J = 6.5$ Hz, 2H), 3.42 - 3.24 (m, 2H), 3.11 (br d, $J = 4.9$ Hz, 2H), 2.94 (td, $J = 6.6, 8.3$ Hz, 4H), 2.64 (br t, $J = 7.0$ Hz, 2H), 2.54 (dt, $J = 2.5, 6.7$ Hz, 2H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.08 - 2.01 (m, 2H), 1.70 (br d, $J = 5.9$ Hz, 2H), 1.65 - 1.59 (m, 2H), 1.45 (s, 9H), 1.33 - 1.25 (m, 10H), 0.88 (t, $J = 6.8$ Hz, 3H).

[0513] To a solution of **7** (2.0 g, 3.23 mmol, 1.0 *eq*) was added HCl/dioxane (2 M, 47.6 mL, 29.4 *eq*). The mixture was stirred at 20 °C for 12 h. LC-MS showed the reactant was consumed completely and desired mass was detected. The reaction mixture was co-evaporated under reduced pressure to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 5/1). The residue was purified by column

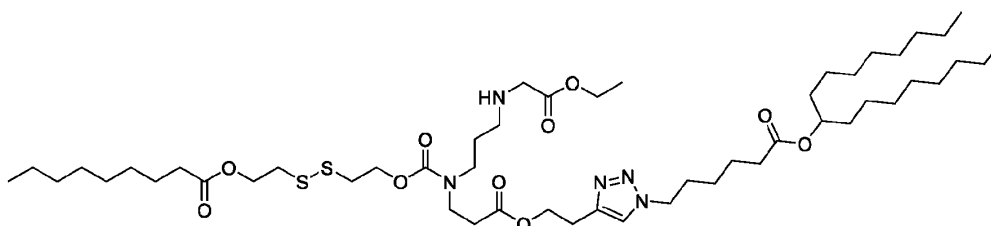
chromatography (SiO₂, DCM: MeOH=10:1). Compound **A30L1T15_A-7** (1.1 g, 2.12 mmol, 65.6% yield) was obtained as a colorless oil, which was confirmed by ¹HNMR. LCMS: *m/z* = 519.3 (M+1)⁺, *R*_t = 0.44 min. ¹H NMR (400 MHz, CDCl₃): δ = 4.41 - 4.30 (m, 4H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.53 (br t, *J* = 6.4 Hz, 2H), 3.48 (br s, 2H), 3.06 (br t, *J* = 6.4 Hz, 2H), 2.94 (q, *J* = 6.4 Hz, 4H), 2.65 (br t, *J* = 6.9 Hz, 2H), 2.55 (dt, *J* = 2.6, 6.7 Hz, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.12 - 2.02 (m, 3H), 1.62 (br d, *J* = 7.4 Hz, 2H), 1.28 (br d, *J* = 7.1 Hz, 10H), 0.93 - 0.82 (m, 3H).

[0514] To a solution of **A30L1T15_A-7** (550 mg, 929 μmol, 1.0 *eq*, 2HCl) and **9** (114 mg, 929 μmol, 84.5 μL, 1.0 *eq*) in DCM (8 mL) was added TEA (188 mg, 1.86 mmol, 258 μL, 2.0 *eq*) and K₂CO₃ (385 mg, 2.79 mmol, 3.0 *eq*). The mixture was stirred at 50 °C for 6 h. LC-MS showed that the reactant was not consumed completely and the desired mass was detected. The reaction mixture was added 20 mL water, the aqueous phase was extracted with DCM (20 mL × 3). The combined organic phase was washed with brine (20 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. Compound **A41L1** (120 mg, 213 μmol, 23.0% yield) was obtained as a colorless oil. LCMS: *m/z* = 561.3 (M+1)⁺, *R*_t = 2.682 min.

[0515] To a solution of **T15** (93.12 mg, 235.37 μmol, 1.1 *eq*) and **A41L1** (120 mg, 213 μmol, 1.0 *eq*) in *t*-BuOH (2 mL) and H₂O (2 mL) was added sodium; (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (42.4 mg, 213 μmol, 1.0 *eq*) and Cu(OAc)₂ (38.8 mg, 213 μmol, 1.0 *eq*). The mixture was stirred at 25 °C for 2 h. LC-MS showed that the reactant was consumed completely, and desired mass was detected. The reaction mixture was added 10 mL water, the aqueous phase was extracted with DCM (10 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10um; mobile phase: [water(TFA)-ACN]; gradient: 50%-80% B over 15 min). CAD showed the compound purity was 94.7%. Compound **A41L1T15** (60 mg, 62.7 μmol, 29.32% yield) was obtained as a brown oil, which was confirmed by HNMR. LCMS product: *RT* = 0.644 min. CAD product: *RT* = 12.286 min. ¹H NMR (400 MHz, CDCl₃): δ = 7.40 (s, 1H), 4.86 (t, *J* = 6.3 Hz, 1H), 4.35 (td, *J* = 6.1, 10.3 Hz, 8H), 3.53 (br t, *J* = 6.9 Hz, 2H), 3.43 - 3.33 (m, 2H), 3.08 (t, *J* = 6.7 Hz, 2H), 2.97 - 2.91 (m, 4H), 2.66 - 2.58 (m, 2H), 2.36 - 2.27 (m, 4H), 2.00 - 1.87

(m, 4H), 1.69 - 1.62 (m, 8H), 1.51 (br d, $J = 6.1$ Hz, 4H), 1.41 - 1.37 (m, 2H), 1.26 (br s, 36H), 1.01 - 0.85 (m, 12H).

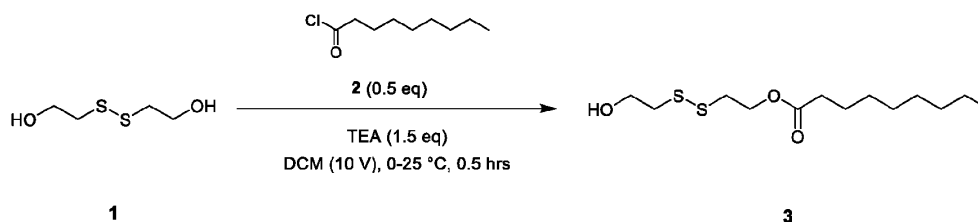
Example A38L1T15



A38L1T15

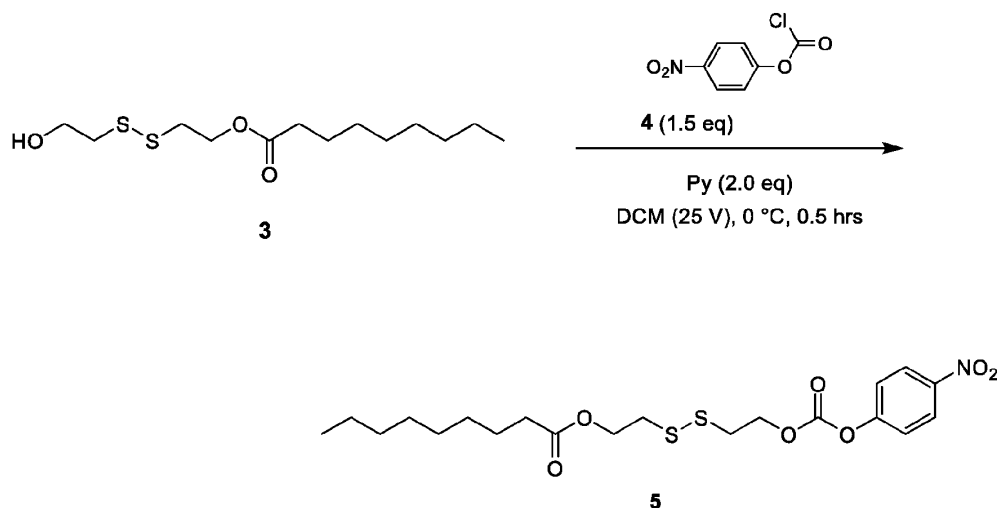
ethyl 9-(3-(2-(1-(6-(heptadecan-9-yloxy)-6-oxohexyl)-1*H*-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)-1-(nonanoyloxy)-8-oxo-7-oxa-3,4-dithia-9,13-diazapentadecan-15-oate

[0516] This compound has the chemical formula $C_{51}H_{93}N_5O_{10}S_2$, with a molecular weight of 1000.45 g/mol, and a $pK_a = 6.366$. This compound preparation, and that of some intermediates used in the same, were made as follows:

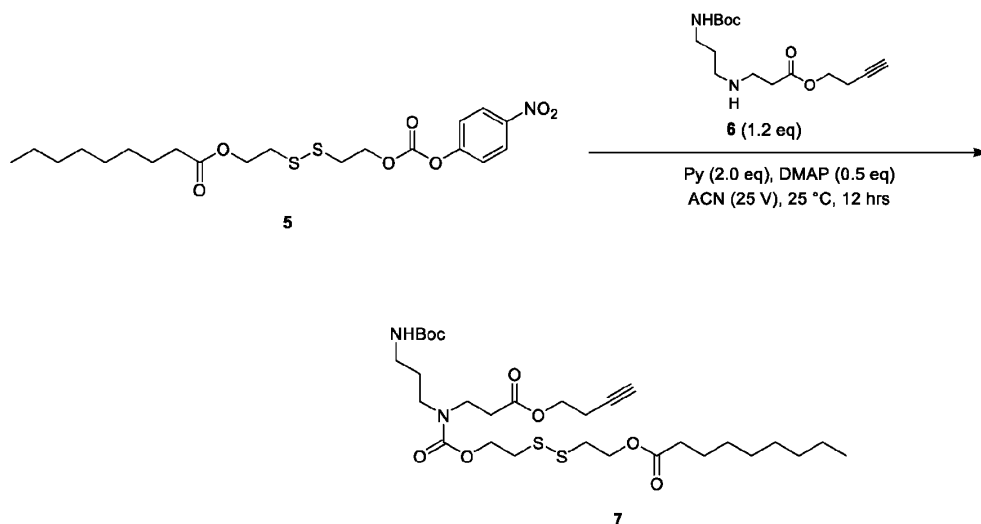


[0517] To a solution of compound **1** (1.00 g, 6.48 mmol, 1.0 eq) in DCM (100 mL) was added TEA (984 mg, 9.72 mmol, 1.35 mL, 1.5 eq) and compound **2** (572 mg, 3.24 mmol, 609 μL , 0.5 eq) in DCM (60 mL). The mixture was stirred at 0 $^\circ\text{C}$ for 0.5 hrs. LCMS showed the starting material was consumed completely. The mixture was diluted with water (60 mL) and extracted with dichloromethane (30 mL $\times$ 2). The combined organic phase was washed with brine (30 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was by flash silica gel chromatography (petroleum ether: ethylacetate= 0~40%). Compound of **3** (6.50 g, 22.0 mmol, 34% yield, 99.8% purity) was obtained as a yellow oil. LCMS product: RT = 0.481 min. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.35$ (t, $J = 6.8$ Hz, 2H), 3.89 (t, $J = 5.8$ Hz, 2H), 2.87 - 2.94 (m, 4H), 2.32 (t, $J = 7.6$ Hz, 2H),

2.04 - 2.06 (m, 1H), 1.63 (quin, $J = 7.2$ Hz, 2H), 1.28 (br d, $J = 7.0$ Hz, 10H), 0.88 (t, $J = 6.8$ Hz, 3H).

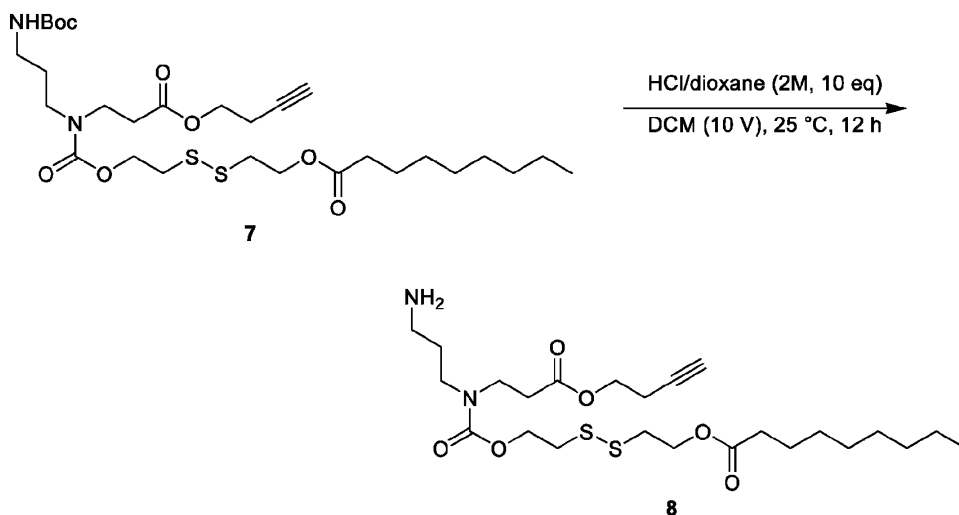


[0518] To a solution of **3** (0.75 g, 2.55 mmol, 1.0 eq) in DCM (25 mL) was added Py (402 mg, 5.09 mmol, 411 μ L, 2.0 eq) and **4** (770 mg, 3.82 mmol, 1.5 eq). The mixture was stirred at 0 °C for 30min. TLC (petroleum ether:ethylacetate = 10:1) showed the reactant ($R_f = 0.38$) was consumed completely and one new major spot ($R_f = 0.61$) was detected. The mixture was diluted with PE (10 mL). Solids are precipitated and filtered. The mixture was concentrated in vacuum to give residue. The crude product was used to next step directly without purification. Compound of **5** (2.3 g, 5.00 mmol, 98.2 % yield) was obtained as a colourless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 8.32 - 8.27$ (m, 2H), 7.43 - 7.38 (m, 2H), 4.56 (t, $J = 6.6$ Hz, 2H), 4.36 (t, $J = 6.6$ Hz, 2H), 3.05 (t, $J = 6.6$ Hz, 2H), 2.97 (t, $J = 6.6$ Hz, 2H), 2.33 (t, $J = 7.6$ Hz, 2H), 1.67 - 1.59 (m, 2H), 1.28 (br d, $J = 7.0$ Hz, 10H), 0.88 (t, $J = 6.8$ Hz, 3H).



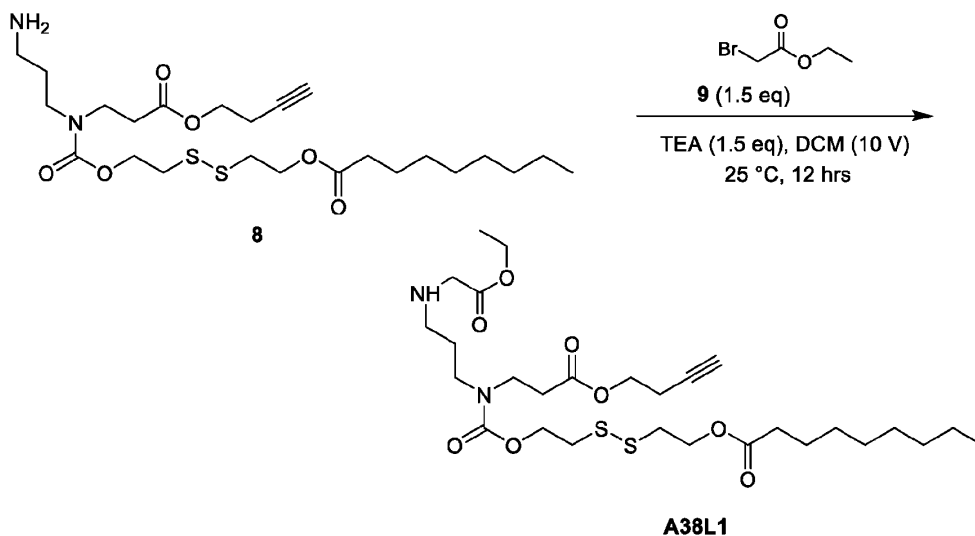
[0519] To a solution of compound **5** (1.00 g, 2.18 mmol, 1.0 eq) in MeCN (10 mL) was added Py (344 mg, 4.35 mmol, 351 μ L, 2.0 eq), DMAP (133 mg, 1.09 mmol, 0.5 eq) and compound **6** (779 mg, 2.61 mmol, 1.2 eq). The mixture was stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely. The mixture was concentrated in vacuum to give residue. The crude product was by flash silica gel chromatography (petroleum ether: ethylacetate=0~20%). Compound of **7** (1.2 g, 1.94 mmol, 89.1% yield, 100% purity) was obtained as a colourless oil. LCMS product: RT = 0.523 min. ^1H NMR (400 MHz, CDCl_3):

[0520] δ = 4.34 (q, J = 7.0 Hz, 4H), 4.20 (t, J = 6.8 Hz, 2H), 3.56 - 3.47 (m, 2H), 3.38 - 3.28 (m, 2H), 3.11 (br d, J = 5.2 Hz, 2H), 2.97 - 2.90 (m, 4H), 2.64 (t, J = 7.0 Hz, 2H), 2.54 (dt, J = 2.4, 6.7 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 2.04 - 2.00 (m, 1H), 1.70 (br d, J = 6.0 Hz, 2H), 1.65 - 1.58 (m, 2H), 1.45 (s, 9H), 1.28 (br d, J = 7.0 Hz, 10H), 0.88 (t, J = 6.8 Hz, 3H).

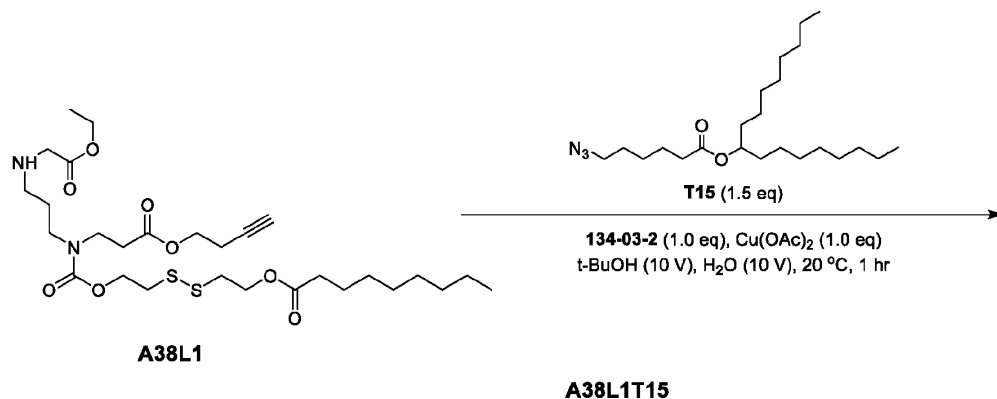


[0521] To a solution of compound **7** (600 mg, 969 μmol , 1.0 eq) in DCM (2 mL) was added HCl/dioxane (2 M, 4.85 mL, 10 eq). The mixture was stirred at 25 $^{\circ}\text{C}$ for 12h. LCMS showed the starting material was consumed completely. The mixture was concentrated in vacuum to give residue. The crude product was used to next step directly without purification. Compound **8** (9-(3-aminopropyl)-8,12-dioxo-7,13-dioxo-3,4-dithia-9-azaheptadec-16-yn-1-yl nonanoate, 1.00 g, 1.64 mmol, 84.7% yield, 97.2% purity, 2HCl) was obtained as a colourless oil. LCMS product: RT = 0.424 min. ^1H NMR (400 MHz, CDCl_3):

[0522] δ = 8.41 (br s, 2H), 4.29 - 4.42 (m, 4H), 4.20 (t, J = 6.8 Hz, 2H), 3.71 (s, 2H), 3.41 - 3.59 (m, 4H), 3.07 (br s, 2H), 2.98 - 3.00 (m, 4H), 2.65 (br t, J = 6.6 Hz, 2H), 2.55 (dt, J = 2.6, 6.7 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 2.03 - 2.14 (m, 3H), 1.57 - 1.69 (m, 2H), 1.29 (br d, J = 7.0 Hz, 10H), 0.82 - 0.95 (m, 3H).

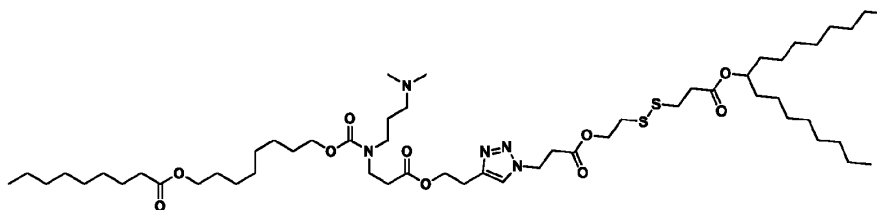


[0523] To a solution of compound **8** (1.00 g, 1.69 mmol, 1.0 eq, 2HCl) in DCM (15 mL) was added dropwise TEA (256 mg, 2.54 mmol, 352 μ L, 1.5 eq). And then compound **9** (282 mg, 1.69 mmol, 187 μ L, 1.0 eq) in DCM (5 mL) was added dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely. The mixture was concentrated in vacuum to give residue. The crude product was by flash silica gel chromatography (dichloromethane: methanol = 0–6%). Compound A38L1 (ethyl 9-(3-(but-3-yn-1-yloxy)-3-oxopropyl)-1-(nonanoyloxy)-8-oxo-7-oxa-3,4-dithia-9,13-diazapentadecan-15-oate, 468 mg, 758 μ mol, 44.8% yield, 98% purity) was obtained as a yellow oil. LCMS product: RT = 0.430 min. ^1H NMR (400 MHz, CDCl_3): δ = 4.38 - 4.31 (m, 4H), 4.24 - 4.15 (m, 4H), 3.54 (br s, 2H), 3.46 - 3.30 (m, 4H), 2.94 (q, J = 6.8 Hz, 4H), 2.64 (br t, J = 7.0 Hz, 4H), 2.54 (dt, J = 2.3, 6.8 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 2.02 (br s, 1H), 1.93 - 1.85 (m, 1H), 1.76 (br d, J = 1.0 Hz, 2H), 1.63 (quin, J = 7.2 Hz, 2H), 1.37 - 1.23 (m, 13H), 0.89 (t, J = 6.8 Hz, 3H).



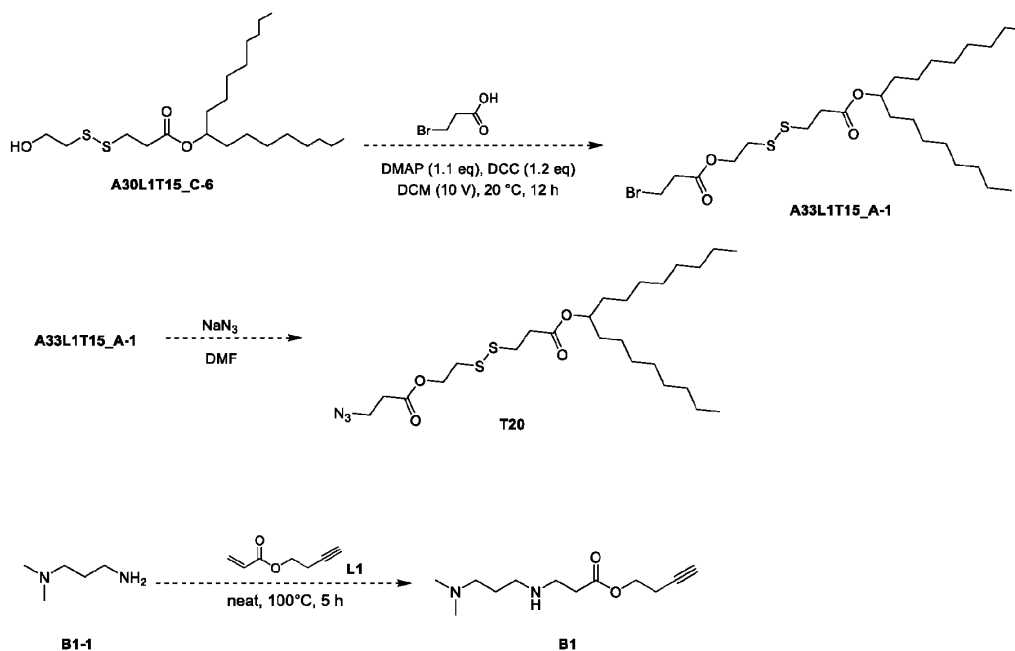
[0524] To a solution of compound **A38L1** (468 mg, 773 μ mol, 1.0 eq) in t-BuOH (3 mL) and H₂O (3 mL) was added compound sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-3-hydroxy-5-oxo-2H-furan-4-olate (153 mg, 773 μ mol, 1.0 eq) (CAS: 134-03-2), Cu(OAc)₂ (140 mg, 773 μ mol, 1.0 eq) and compound **T15** (459 mg, 1.16 mmol, 1.5 eq). The mixture was stirred at 25 °C for 1 h. LCMS showed the starting material was consumed completely. The mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL $\times$ 2). The combined organic phase was washed with brine (10 mL $\times$ 2), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was by flash silica gel chromatography (dichloromethane: methanol = 0~10%). The compound **A38L1T15** (200 mg, 199 μ mol, 25.8% yield) was obtained as a yellow oil. LCMS product: RT = 0.604 min. CAD product: RT = 12.435 min. ¹H NMR (400 MHz, CDCl₃): δ = 7.46 - 7.31 (m, 1H), 4.92 - 4.80 (m, 1H), 4.40 - 4.30 (m, 8H), 4.20 (q, J = 7.2 Hz, 2H), 3.52 (br s, 2H), 3.46 - 3.37 (m, 2H), 3.36 - 3.32 (m, 1H), 3.07 (t, J = 6.8 Hz, 2H), 2.99 - 2.88 (m, 4H), 2.70 - 2.54 (m, 4H), 2.31 (q, J = 7.8 Hz, 4H), 1.96 - 1.91 (m, 2H), 1.79 - 1.71 (m, 4H), 1.67 (br d, J = 7.8 Hz, 2H), 1.63 (br d, J = 7.0 Hz, 2H), 1.51 (br d, J = 5.8 Hz, 3H), 1.45 - 1.35 (m, 4H), 1.30 - 1.25 (m, 36H), 0.88 (br t, J = 6.6 Hz, 9H).

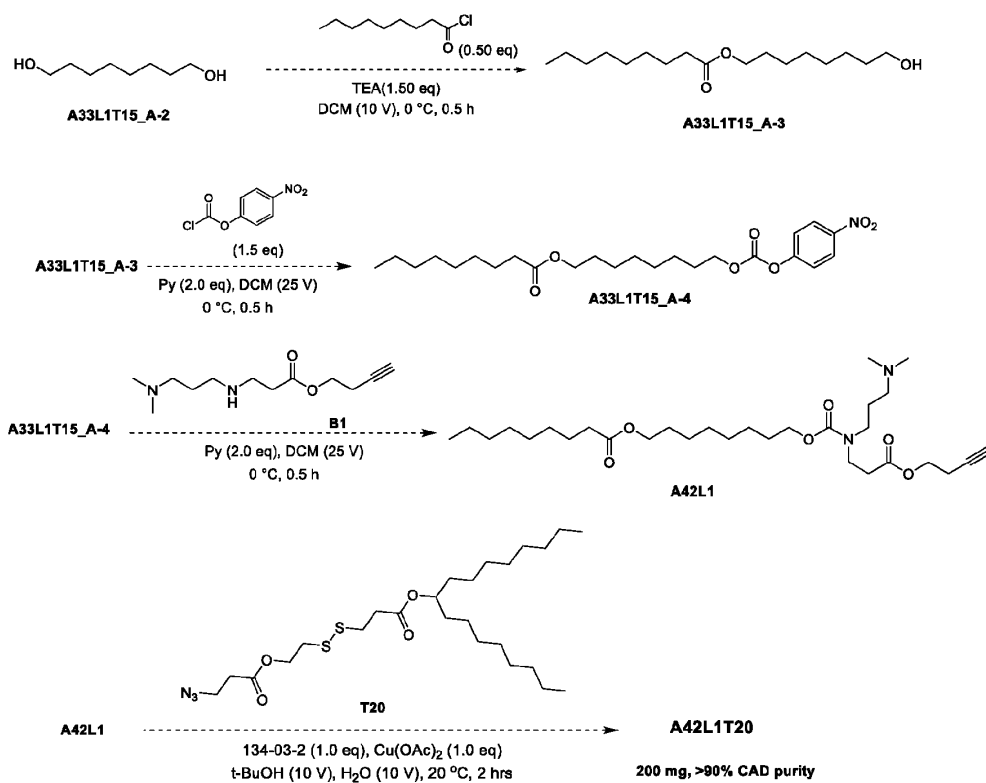
Example A42L1T20



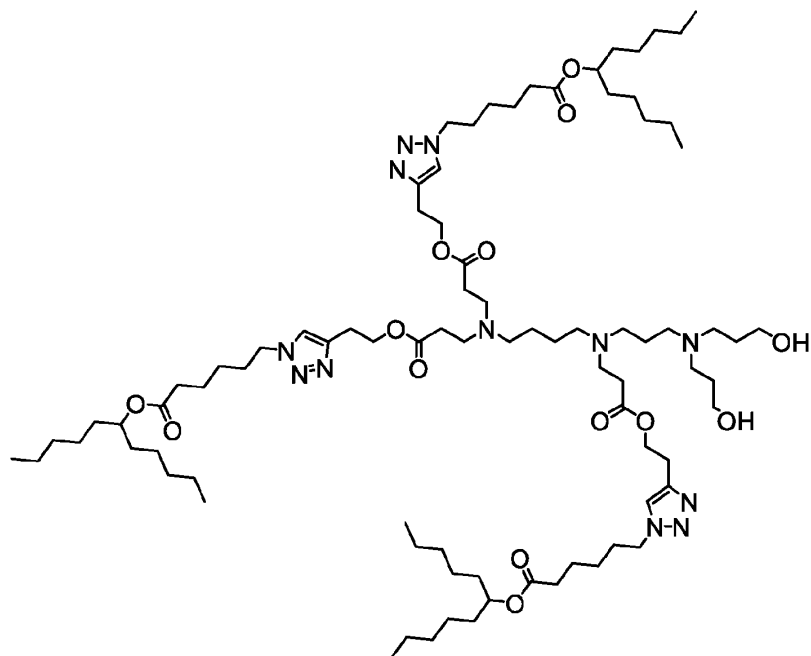
8-(((3-(dimethylamino)propyl)(3-(2-(1-(3-(2-((3-(heptadecan-9-yloxy)-3-oxopropyl)disulfaneyl)ethoxy)-3-oxopropyl)-1H-1,2,3-triazol-4-yl)ethoxy)-3-oxopropyl)carbamoyl)oxy)octyl nonanoate

[0525] This compound is synthesized, for example, according to the following synthetic path:

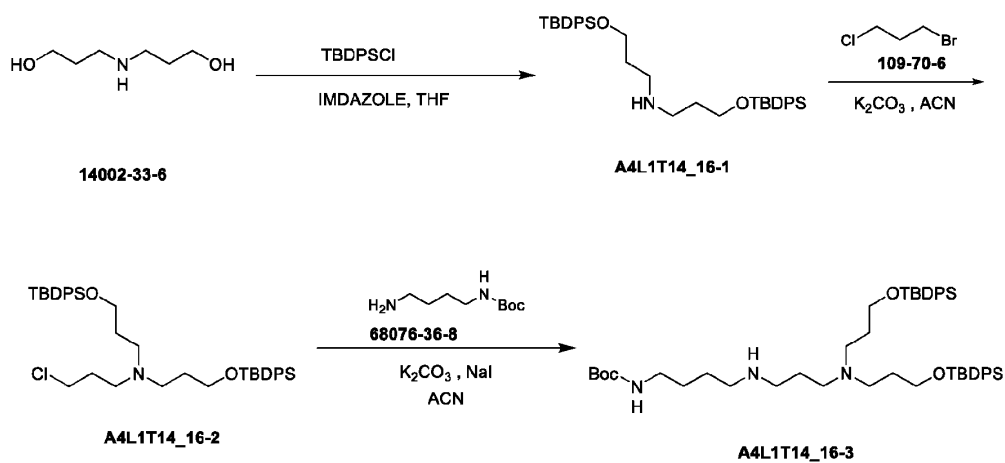


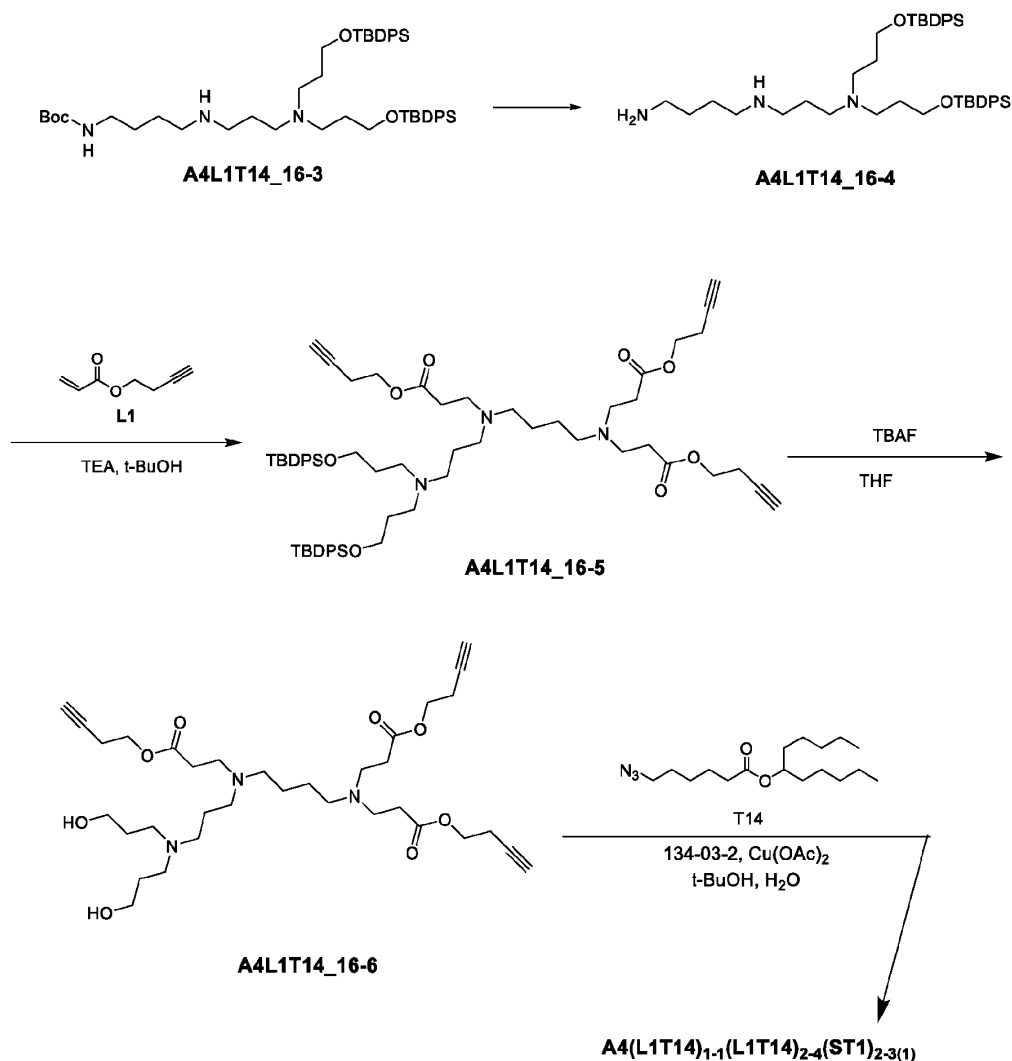


Example A4(L1T14)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎



[0526] This compound has the chemical formula $C_{85}H_{154}N_{12}O_{14}$, with a molecular weight of 1568.24 g/mol. This compound preparation, and that of some intermediates used in the same, were made as follows:





[0527] To a solution of compound **14002-33-6** (5 g, 37.54 mmol, 1 eq) in THF (300 mL) was added imidazole (5.62 g, 82.59 mmol, 2.2 eq) and tert-butyl-chloro-diphenyl-silane (25.80 g, 93.85 mmol, 24.02 mL, 2.5 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. LC-MS showed compound **14002-33-6** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by adding H₂O (10 mL) at 25 °C, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by flash silica gel chromatography (ISCO®; 1 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 45 mL/min). Compound **A4L1T14_16-1** (10 g, 16.39 mmol, 43.67% yield) was obtained as a yellow oil. LCMS: (M + H⁺) = 610.4.

[0528] To a solution of compound **A4L1T14_16-1** (10 g, 16.39 mmol, 1.0 eq) in ACN (90 mL) was added K₂CO₃ (4.53 g, 32.79 mmol, 2.0 eq) and compound **109-70-6** (6.45 g, 40.98 mmol, 4.04 mL, 2.5 eq). The mixture was stirred at 45 °C for 16 h. LC-MS showed compound **A4L1T14_16-1** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®, 40g SepaFlash® Silica Flash Column, Eluent of 5~8% Dichloromethane: Methanol ether gradient @ 60 mL/min). Compound **A4L1T14_16-2** (7 g, 10.20 mmol, 62.20% yield) was obtained as a yellow oil. LCMS: (M + H⁺) = 686.5.

[0529] To a solution of compound **A4L1T14_16-2** (6 g, 8.74 mmol, 1.0 eq) in ACN (60 mL) was added NaI (655.01 mg, 4.37 mmol, 0.5 eq), K₂CO₃ (2.42 g, 17.48 mmol, 2 eq) and compound **68076-36-8** (4.11 g, 21.85 mmol, 2.5 eq). The mixture was stirred at 60 °C for 12 h. LC-MS showed compound **A4L1T14_16-2** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by adding H₂O (50 mL) at 25 °C, and extracted with DCM (20 mL *3). The combined organic layers were washed with brine (20 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®, 10 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethylacetate/Petroleum ether gradient @ 45 mL/min). Compound **A4L1T14_16-3** (7 g, 7.35 mmol, 84.08% yield, 88% purity) was obtained as a yellow oil.

[0530] LCMS: (M + H⁺) = 838.7.

[0531] To a solution of compound **A4L1T14_16-3** (3.5 g, 4.18 mmol, 1 eq) in DCM (35 mL) was added iodo(trimethyl)silane (1.25 g, 6.26 mmol, 852.44 µL, 1.5 eq) at -78 °C. The mixture was stirred at 25 °C for 12 h. LC-MS showed that compound **A4L1T14_16-3** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound **A4L1T14_16-4** (3 g, 4.06 mmol, 97.34% yield) was obtained as a yellow oil. The product was used directly for next step.

[0532] LCMS: (M + H⁺) = 738.6.

[0533] To a solution of compound **A4L1T14_16-4** (3 g, 4.06 mmol, 1.0 eq) in t-BuOH

(30 mL) was added TEA (822.45 mg, 8.13 mmol, 1.13 mL, 2.0 *eq*) and compound **L1** (2.02 g, 16.26 mmol, 4.0 *eq*). The mixture was stirred at 90 °C for 12 h. LC-MS showed compound **A4L1T14_16-4** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove solvent.

Compound **A4L1T14_16-5** (4 g, crude) was obtained as a yellow oil. The product was used directly for next step. LCMS: (M + H⁺) = 556.1.

[0534] To a solution of compound **A4L1T14_16-5** (2 g, 1.80 mmol, 1.0 *eq*) in THF (20 mL) was added TBAF (1 M, 2.70 mL, 1.5 *eq*) at -78 °C. The mixture was stirred at 25 °C for 12 h. LC-MS showed that compound **A4L1T14_16-5** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by adding H₂O (10 mL) at 25 °C, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®], 3 g SepaFlash[®] Silica Flash Column, Eluent of 5% Dichloromethane:Methanolethergradient @ 45 mL/min). Compound **A4L1T14_16-6** (400 mg, 631.10 μmol, 35.05% yield) was obtained as a yellow oil.

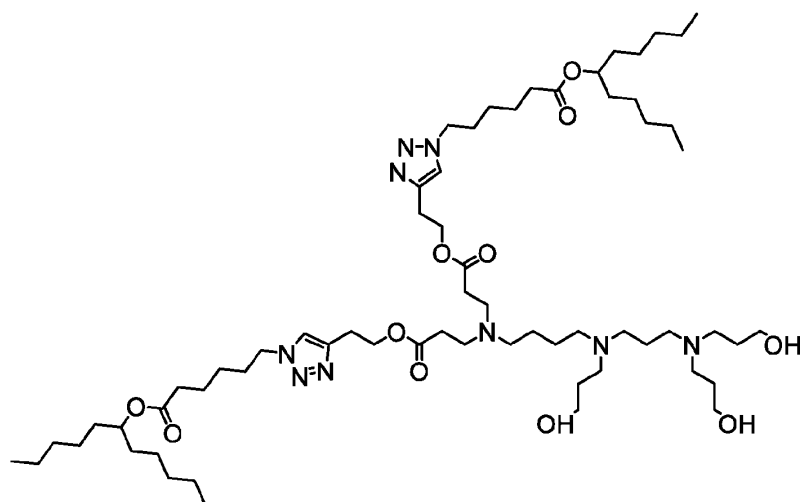
[0535] LCMS: (M + H⁺) = 634.5.

[0536] To a solution of compound **A4L1T14_16-6** (400 mg, 631.10 μmol, 1.0 *eq*) in t-BuOH (2 mL) and H₂O (2 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (125.02 mg, 631.10 μmol, 1.0 *eq*, CAS: 134-03-2), diacetylcopper (114.63 mg, 631.10 μmol, 1.0 *eq*) and compound **T14** (982.82 mg, 3.16 mmol, 5.0 *eq*). The mixture was stirred at 25 °C for 1 h. LC-MS showed that compound **A4L1T14_16-6** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by addition H₂O (10 mL) at 25 °C, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: CD27-PHS XP phenyl-Hexyl 150*25*7um; mobile phase: [water (TFA)-ACN]; gradient:42%-72% B over 15 min). Compound **A4(L1T14)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎** (300 mg, 191.30 μmol, 30.31% yield) obtained as a yellow oil. LCMS: (M/2 + H⁺) = 785.2. CAD: (M/2 + H⁺) = 784.8.

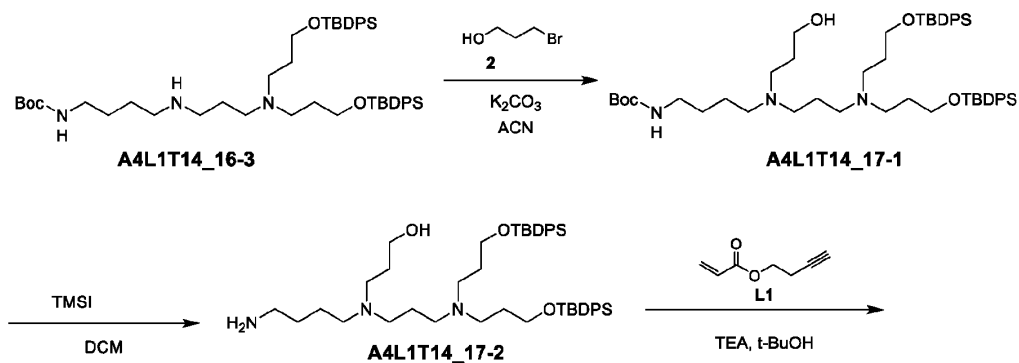
[0537] ¹H NMR (400 MHz, CHLOROFORM-d): δ: 7.41 (s, 3H), 4.87 (quin, J = 6.4 Hz,

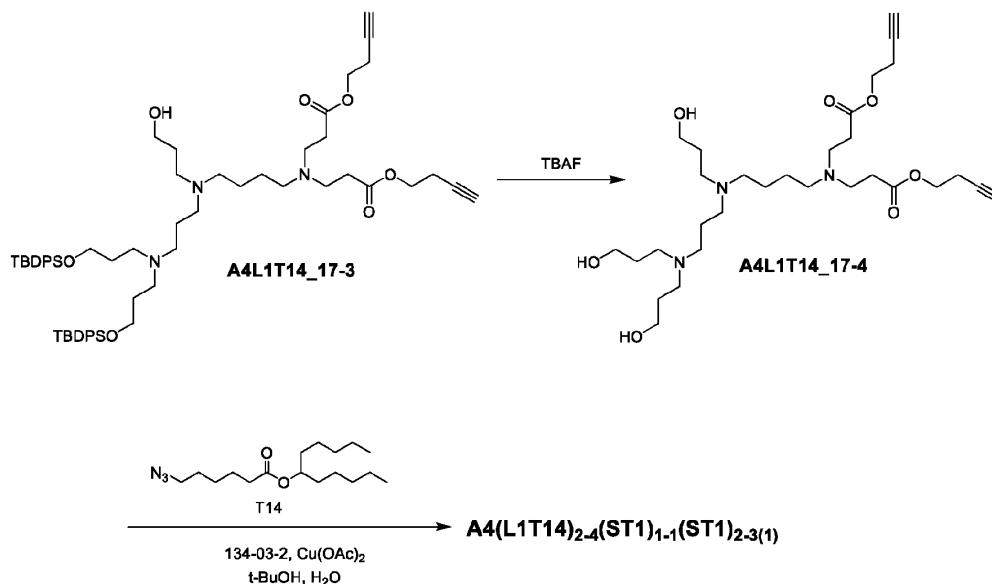
3H), 4.39 - 4.28 (m, 12H), 3.74 (m, $J = 5.6$ Hz, 4H), 3.06 (m, $J = 6.8$ Hz, 6H), 2.75 (t, $J = 7.2$ Hz, 6H), 2.67 (s, 3H), 2.47 - 2.35 (m, 12H), 2.30 (m, $J = 7.2$ Hz, 6H), 1.93 ($J = 7.2$ Hz, 6H), 1.74 (dd, $J = 5.6, 11.6$ Hz, 6H), 1.71 - 1.60 (m, 15H), 1.52 (s, 5H), 1.49 (d, $J = 1.6$ Hz, 2H), 1.43 - 1.35 (m, 10H), 1.34 - 1.21 (m, 37H), 0.95 - 0.81 (m, 18H).

Example A4(L1T14)₂₋₄(ST1)₁₋₁(ST1)₂₋₃₍₁₎



[0538] This compound has the chemical formula $C_{64}H_{119}N_9O_{11}$, with a molecular weight of 1190.71 g/mol. This compound preparation, and that of some intermediates used in the same, were made as follows:





[0539] To a solution of compound **A4L1T14_16-3** (1 g, 1.19 mmol, 1 *eq*) in MeCN (10 mL) was added K₂CO₃ (329.72 mg, 2.39 mmol, 2 *eq*) and compound **2** (663.19 mg, 4.77 mmol, 431.48 μ L, 4 *eq*). The mixture was stirred at 25 °C for 12 h. LC-MS showed compound **A4L1T14_16-3** was consumed completely and one main peak with desired *m/z* was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound **A4L1T14_17-1** (650 mg, 725.13 μ mol, 60.79% yield) was obtained as a yellow oil. The product was used directly for next step. LCMS: (*M* + *H*⁺) = 896.5.

[0540] To a solution of compound **A4L1T14_17-1** (650 mg, 725.13 μ mol, 1 *eq*) in DCM (6 mL) was added iodo(trimethyl)silane (217.64 mg, 1.09 mmol, 148.05 μ L, 1.5 *eq*) at -78 °C. The mixture was stirred at 25 °C for 12 h. LC-MS showed that compound **A4L1T14_17-1** was consumed completely and one main peak with desired *m/z* was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound **A4L1T14_17-2** (500 mg, 627.92 μ mol, 86.59% yield) was obtained as a yellow oil. The product used directly for next step.

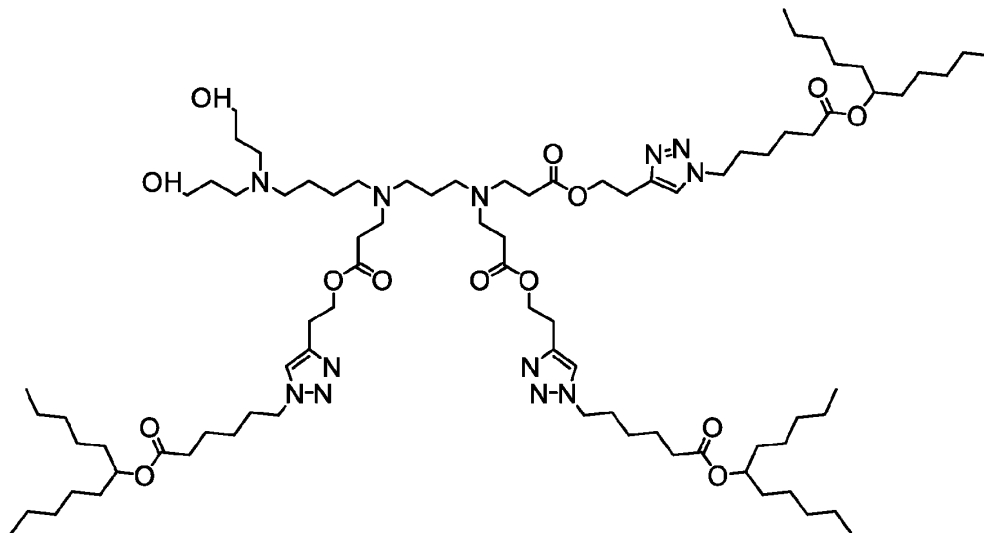
[0541] LCMS: (*M* + *H*⁺) = 796.6.

[0542] To a solution of compound **A4L1T14_17-2** (500 mg, 627.92 μ mol, 1 *eq*) in t-BuOH (5 mL) was added TEA (127.08 mg, 1.26 mmol, 174.80 μ L, 2 *eq*) and compound **L1** (233.84 mg, 1.88 mmol, 3 *eq*). The mixture was stirred at 90 °C for 2 h. LC-MS showed

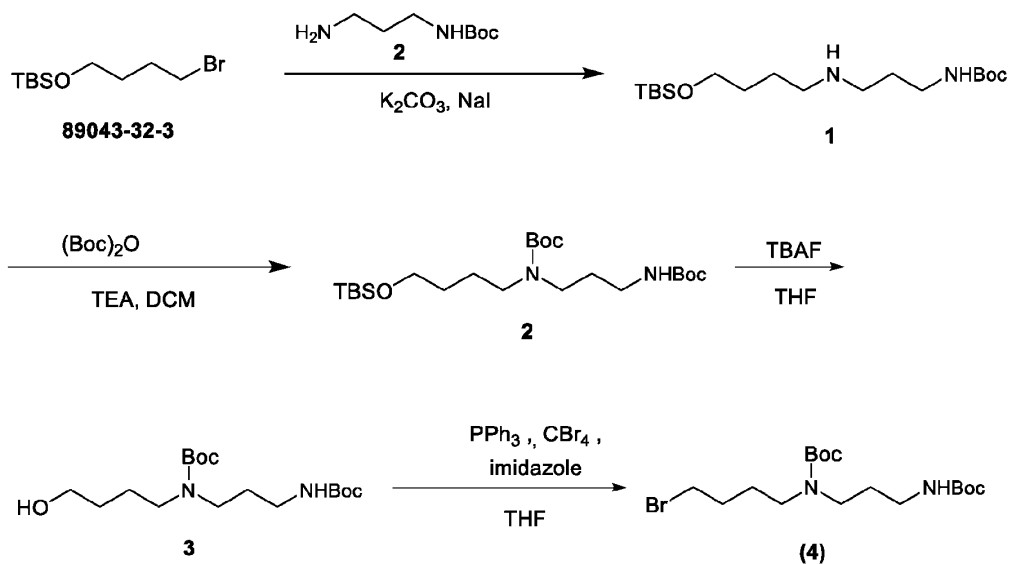
compound **A4L1T14_17-2** was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by adding H_2O (10 mL) at $25^\circ C$, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 1 g SepaFlash® Silica Flash Column, Eluent of 5%Dichloromethane : Methanolethergradient @ 45 mL/min). Compound **A4L1T14_17-3** (327 mg, 313.05 μmol , 49.86% yield) was obtained as a yellow oil. LCMS: $(M/2 + H^+) = 523.2$.

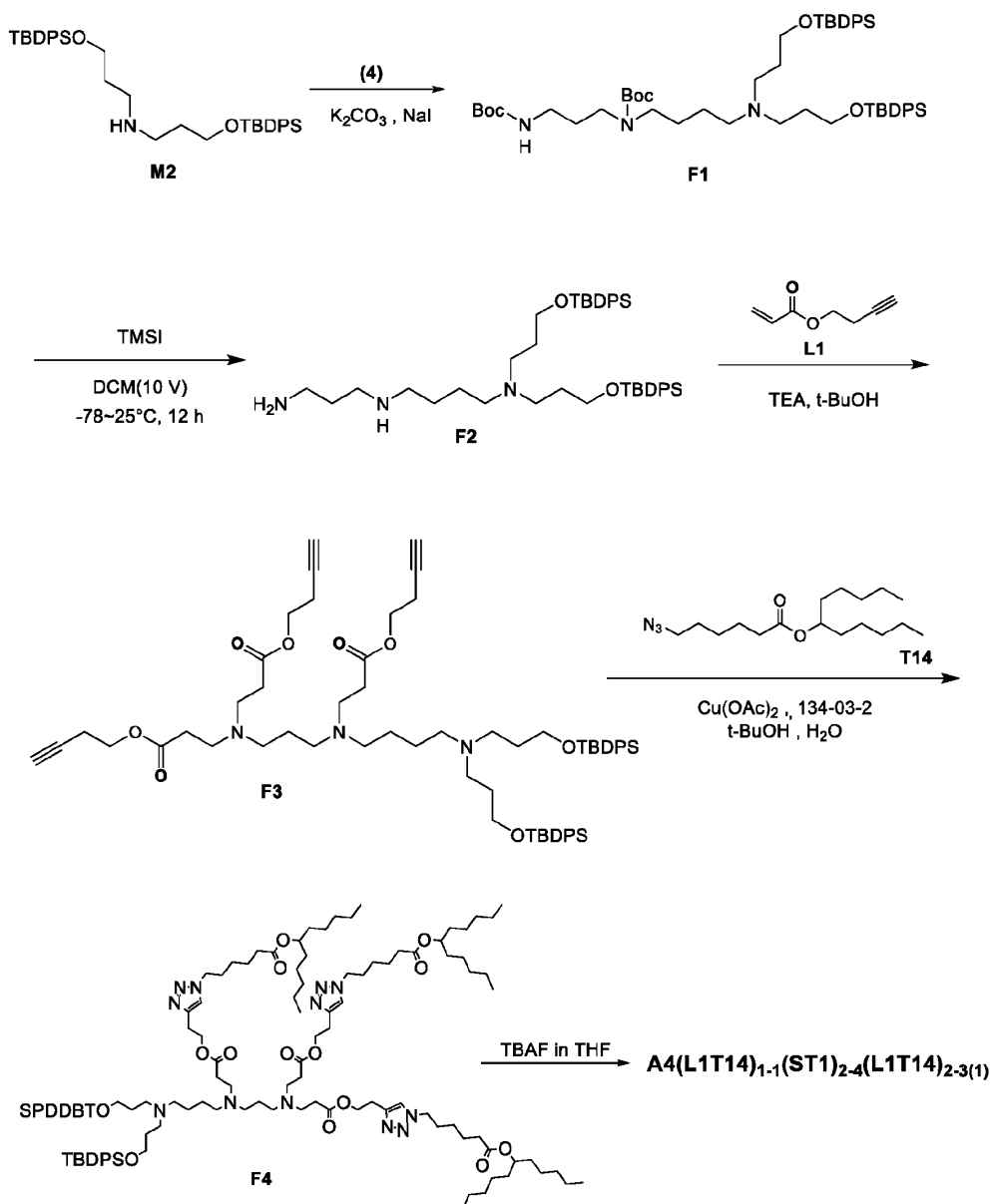
[0543] To a solution of compound **A4L1T14_17-3** (327 mg, 313.05 μmol , 1 *eq*) in THF (3 mL) was added tetrabutylammonium;fluoride;trihydrate (1 M, 469.58 μL , 1.5 *eq*). The mixture was stirred at $25^\circ C$ for 12h. TLC (Dichloromethane: Methanol= 10:1) indicated that compound **A4L1T14_17-3** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was quenched by adding H_2O (20mL) at $25^\circ C$, and extracted with DCM (10 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. Compound **A4L1T14_17-4** (177 mg, 311.75 μmol , 99.59% yield) was obtained as a yellow oil. The product used directly for next step.

[0544] To a solution of compound **A4L1T14_17-4** (177 mg, 311.75 μmol , 1 *eq*) in *t*-BuOH (1 mL) and H_2O (1 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (61.76 mg, 311.75 μmol , 1 *eq*, CAS: 134-03-2), diacetoxy copper (56.62 mg, 311.75 μmol , 1 *eq*) and compound **T14** (388.40 mg, 1.25 mmol, 4 *eq*). The mixture was stirred at $25^\circ C$ for 1h. TLC indicated compound **A4L1T14_17-4** was consumed completely and one new spot formed. Desired mass was detected by CAD-MS. The mixture was filtered. The residue was purified by flash silica gel chromatography (ISCO®, 1g SepaFlash® Silica Flash Column, Eluent of 0~6% Ethylacetate/Petroleum ether gradient @ 60 mL/min). Compound **A4(L1T14)₂₋₄(ST1)₁₋₁(ST1)₂₋₃₍₁₎** (70 mg, 58.79 μmol , 18.86% yield) was obtained as a colourless oil. CAD-MS: $(M/2 + H^+) = 596.2$. 1H NMR (400 MHz, CHLOROFORM-*d*): δ : 7.46 (s, 2H), 4.90 - 4.82 (m, 2H), 4.42 - 4.29 (m, 7H), 3.85 - 3.69 (m, 6H), 3.45 - 3.13 (m, 17H), 3.05 (t, $J = 6.4$ Hz, 4H), 2.92 - 2.84 (m, 4H), 2.45 - 2.37 (m, 3H), 2.30 (t, $J = 7.2$ Hz, 6H), 2.03 - 1.82 (m, 19H), 1.67 (td, $J = 7.6, 15.3$ Hz, 5H), 1.55 - 1.45 (m, 8H), 1.42 - 1.34 (m, 4H), 1.33 - 1.21 (m, 23H), 0.88 (t, $J = 6.8$ Hz, 12H).

Example A4(ST1)₂₋₄(L1T14)₁₋₁(L1T14)₂₋₃₍₁₎

[0545] This compound has the chemical formula $C_{85}H_{154}N_{12}O_{14}$, with a molecular weight of 1568.24 g/mol. This compound preparation, and that of some intermediates used in the same, were made as follows:





[0546] To a solution of 89043-32-3 (10 g, 37.41 mmol, 1 eq) and 2 (6.52 g, 37.41 mmol, 6.53 mL, 1 eq) in MeCN (100 mL) was added K_2CO_3 (10.34 g, 74.83 mmol, 2 eq) and NaI (2.80 g, 18.71 mmol, 0.5 eq). The mixture was stirred at 60°C for 12h. The desired mass was detected

by LCMS: $R_t = 0.525$ min. The reaction mixture was filtered and concentrated under reduced pressure to remove MeCN. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) and Eluent of 0~10% MeOH/DCM ether gradient @ 60 mL/min). **3** (3.7 g, 10.16 mmol, 27.15% yield) was obtained as a colorless oil. LCMS: $(M + H^+) = 361.3$.

[0547] To a solution of **1** (3.7 g, 10.26 mmol, 1 eq) in DCM (37 mL) was added (Boc)₂O (3.36 g, 15.39 mmol, 3.54 mL, 1.5 eq) and TEA (3.11 g, 30.78 mmol, 4.28 mL, 3 eq). The mixture was stirred at 25 °C for 12h. The desired mass was detected by LCMS ($R_t = 0.688$ min). The reaction mixture was quenched by adding water (30 mL) and extracted with DCM (25 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 12 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). **4** (3.7 g, 8.03 mmol, 78.27% yield) was obtained as a colorless oil.

[0548] LCMS: $(M + H^+) = 461.3$. ¹H NMR (400 MHz, CHLOROFORM-*d*) :

[0549] $\delta = 3.62$ (t, $J = 6.0$ Hz, 2H), 3.29 - 3.08 (m, 6H), 1.65 (d, $J = 4.4$ Hz, 2H), 1.59 - 1.49 (m, 4H), 1.45 (d, $J = 7.6$ Hz, 18H), 0.90 (s, 9H), 0.05 (s, 6H).

[0550] A mixture of **2** (3.7 g, 8.03 mmol, 1 eq) and TBAF (1 M, 12.05 mL, 1.5 eq) in THF (37 mL) was stirred at 25 °C for 12h. The desired mass was detected by LCMS ($R_t = 0.453$ min). The reaction mixture was quenched by adding water (10 mL), and then extracted with DCM (10 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 4 g SepaFlash[®] Silica Flash Column, Eluent of 0~20% MeOH/DCM ether gradient @ 20 mL/min). Compound **3** (2.78 g, 8.02 mmol, 100.00% yield) was obtained as a colorless oil. LCMS: $(M + H^+) = 347.0$. ¹H NMR (400 MHz, CHLOROFORM-*d*): $\delta = 3.68$ (t, $J = 6.0$ Hz, 2H), 3.29 - 3.09 (m, 6H), 1.71 - 1.65 (m, 3H), 1.61 (d, $J = 6.4$ Hz, 2H), 1.57 - 1.53 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H).

[0551] A mixture of **3** (1.39 g, 4.01 mmol, 1 eq), PPh₃ (2.63 g, 10.03 mmol, 2.5 eq), CBr₄ (2.66 g, 8.02 mmol, 2 eq) and IMIDAZOLE (1.09 g, 16.05 mmol, 4 eq) in THF (14 mL) was stirred at 25 °C for 12h under N₂ atmosphere. The desired mass was detected by LCMS ($R_t = 0.541$ min). The reaction mixture was quenched by adding water (20 mL), and then extracted with EA (20 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated

under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 12 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). **6** (1.7 g, 4.15 mmol, 51.76% yield) was obtained as a colorless oil. LCMS: (M + H⁺) = 430.9. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 3.43 (t, J = 6.4 Hz, 2H), 3.30 - 3.07 (m, 6H), 1.89 - 1.81 (m, 2H), 1.68 (d, J = 7.2, 14.8 Hz, 4H), 1.47 (s, 9H), 1.45 (s, 9H).

[0552] A mixture of **M2** (1.7 g, 4.15 mmol, 1 eq), **4** (2.79 g, 4.57 mmol, 1.1 eq), K₂CO₃ (1.15 g, 8.31 mmol, 2 eq) and NaI (311.24 mg, 2.08 mmol, 0.5 eq) in MeCN (17 mL) was stirred at 60 °C for 12h. The desired mass was detected by LCMS. The reaction mixture was filtered and concentrated under reduced pressure to remove MeCN. The residue was purified by flash silica gel chromatography (ISCO[®]; 12 g SepaFlash[®] Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound **F1** (3.6 g, 3.18 mmol, 76.67% yield, 83% purity) was obtained as a colorless oil. LCMS: (M + H⁺) = 938.5.

[0553] ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 7.66 (dd, J = 1.6, 7.6 Hz, 8H), 7.43 - 7.35 (m, 13H), 3.68 (t, J = 6.0 Hz, 4H), 3.29 - 3.19 (m, 2H), 3.09 (d, J = 5.2 Hz, 4H), 2.52 (s, 4H), 2.38 (br d, J = 1.6 Hz, 2H), 1.73 - 1.60 (m, 8H), 1.44 (s, 18H), 1.06 - 1.04 (m, 18H).

[0554] To a solution of **F1** (1.8 g, 1.92 mmol, 1 eq) in DCM (15 mL) was added TMSI (767.59 mg, 3.84 mmol, 522.17 μ L, 2 eq) at -78°C. The mixture was stirred at 25°C for 12h. The desired mass was detected by LCMS (Rt = 0.491 min). The reaction mixture was concentrated under reduced pressure to remove DCM. Compound **F2** (1.4 g, 1.63 mmol, 85.03% yield, 86% purity) was obtained as a brown oil and was used into the next step without further purification.

[0555] LCMS: (M + H⁺) = 738.5.

[0556] To a solution of **F2** (1.4 g, 1.90 mmol, 1 eq), **L1** (1.18 g, 9.48 mmol, 5 eq) in *t*-BuOH (6 mL) was added TEA (959.53 mg, 9.48 mmol, 1.32 mL, 5 eq). The mixture was stirred at 100 °C for 12h. The desired mass was detected by LCMS (Rt = 1.659 min). The mixture was diluted with water 10 mL and extracted with DCM 20 mL (10 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO[®]; 20 g SepaFlash[®] Silica Flash Column, Eluent of 0~10% MeOH/DCM ether gradient @ 30 mL/min). Compound **F3** (1.1 g, 869.61 μ mol, 45.85% yield, 87.8% purity) was obtained as a light yellow oil. LCMS: (M/2 + H⁺) = 556.2. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 7.66 (d, J = 7.2 Hz, 8H), 7.46 - 7.31

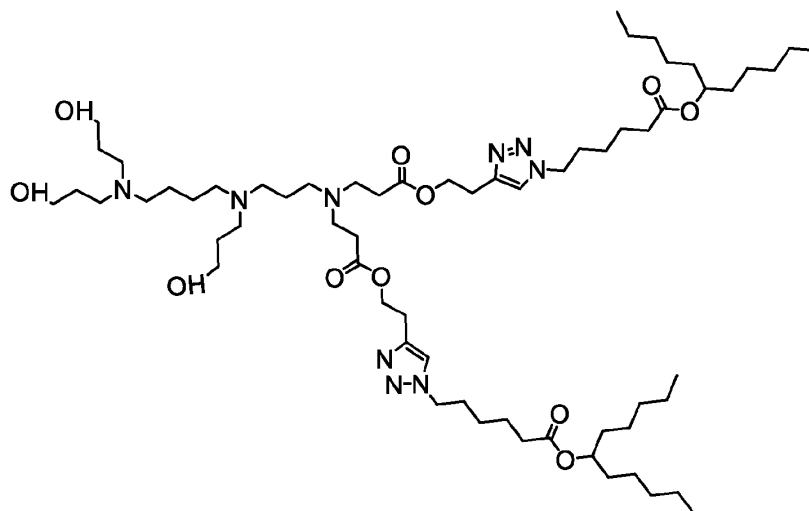
(m, 12H), 4.22 - 4.13 (m, 6H), 3.68 (t, J = 6.0 Hz, 4H), 2.76 (t, J = 7.2 Hz, 6H), 2.57 - 2.49 (m, 10H), 2.48 - 2.34 (m, 14H), 2.02 - 1.99 (m, 2H), 1.67 (d, J = 4.4 Hz, 4H), 1.57 - 1.52 (m, 3H), 1.38 (br s, 4H), 1.05 (s, 18H).

[0557] To a solution of **F3** (1.1 g, 990.45 μ mol, 1 eq) in t-BuOH (10 mL) and water (10 mL) was added sodium;(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (196.21 mg, 990.45 μ mol, 1 eq, CAS: 134-03-2), diacetoxycopper (179.90 mg, 990.45 μ mol, 1 eq) and **T14** (1.08 g, 3.47 mmol, 3.5 eq). The mixture was stirred at 25 °C for 2 h. The desired mass was detected by LCMS (R_t = 0.766 min). The residue was diluted with water 10 mL and extracted with DCM (15 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM ether gradient @ 30 mL/min). The residue was purified by prep-HPLC (column: CD30-WePure Biotech Phenyl-Hexyl 250*50mm*7 μ m; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 45%-75% B over 25.0 min). Compound **F4** (600 mg, 283.07 μ mol, 28.58% yield, 96.48% purity) was obtained as a light yellow oil. LCMS: ($M/3 + H^+$) = 682.2.

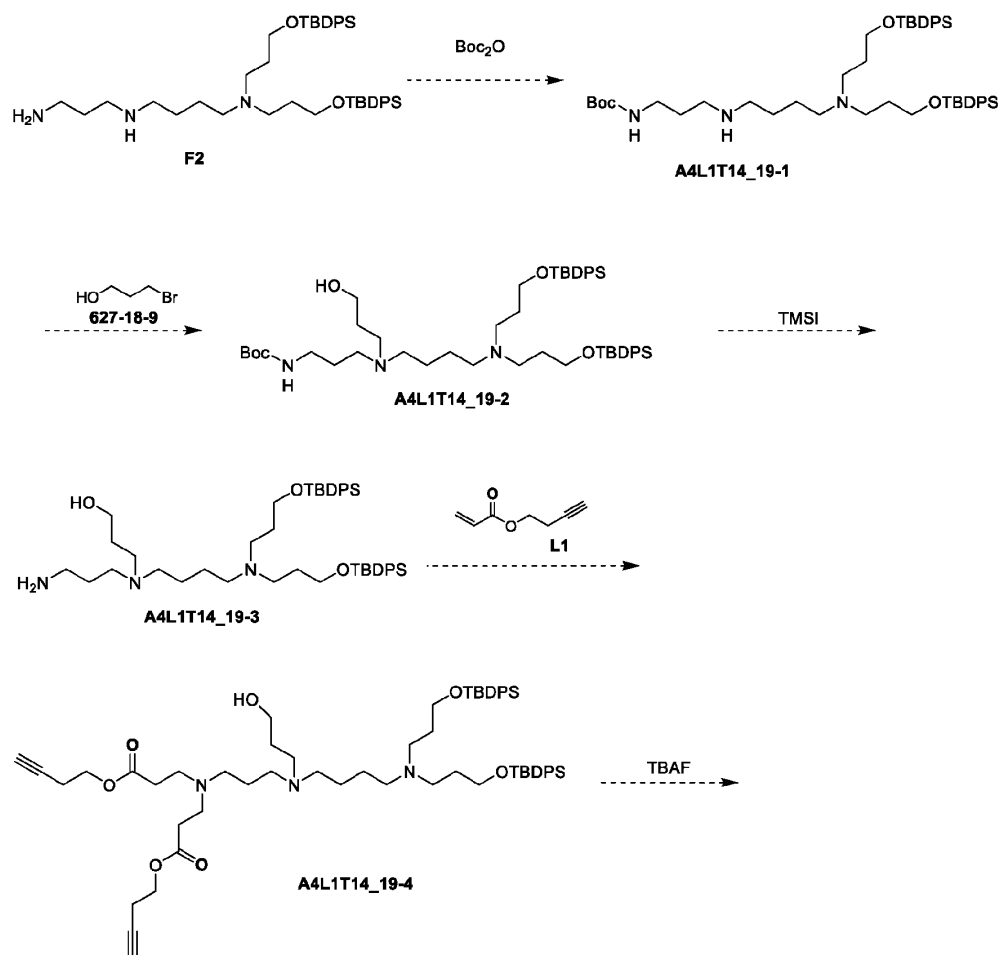
[0558] To a solution of **F4** (500 mg, 244.50 μ mol, 1 eq) in THF (5 mL) was added TBAF (1 M, 366.75 μ L, 1.5 eq). The mixture was stirred at 25 °C for 12h. The desired mass was detected by LCMS (R_t = 2.44 min). The reaction mixture was concentrated under reduced pressure to remove THF. The residue was purified by prep-HPLC (column: CD12-WePure Biotech Phenyl-Hexyl 150*25mm*7 μ m; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient:38%-68% B over 15.0 min). **A4(L1T14)₁₋₁(ST1)₂₋₄(L1T14)₂₋₃₍₁₎** (100 mg, 59.90 μ mol, 24.50% yield, 93.94% purity) was obtained as a colorless oil. LCMS: ($M/2 + H^+$) = 784.7. CAD: ($M/2 + H^+$) = 785.0.

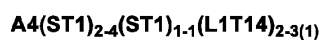
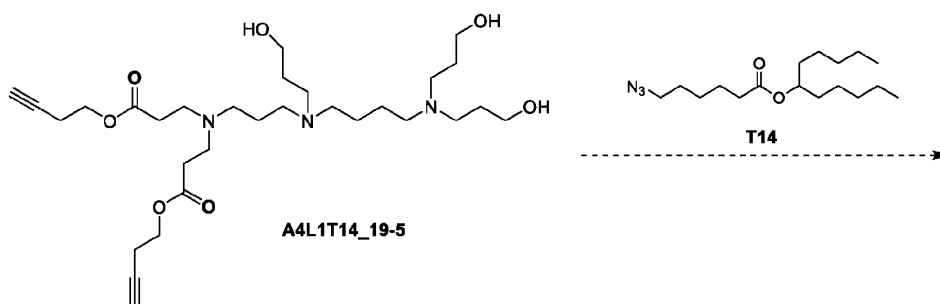
[0559] ¹H NMR (400 MHz, CHLOROFORM-*d*) : δ = 7.52 - 7.45 (m, 3H), 4.86 (quin, J = 6.4 Hz, 3H), 4.42 - 4.30 (m, 12H), 3.84 (s, 4H), 3.44 (d, J = 5.6 Hz, 6H), 3.36 - 3.16 (m, 16H), 3.06 (t, J = 6.0 Hz, 8H), 2.90 (d, J = 4.8 Hz, 8H), 2.30 (t, J = 7.6 Hz, 6H), 1.98 - 1.89 (m, 10H), 1.67 (quin, J = 7.6 Hz, 6H), 1.55 - 1.46 (m, 12H), 1.37 (t, J = 7.6 Hz, 6H), 1.27 (d, J = 2.0 Hz, 36H), 0.88 (t, J = 6.8 Hz, 18H).

Example A4(ST1)₂₋₄(ST1)₁₋₁(L1T14)₂₋₃₍₁₎



[0560] This compound has the chemical formula $C_{64}H_{119}N_9O_{11}$, with a molecular weight of 1190.71 g/mol. This compound is prepared, for example, according to the following synthetic path:

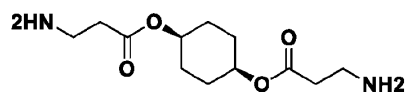




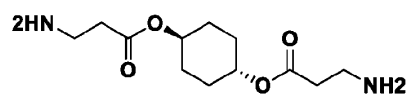
[0561] All possible combinations of the above-indicated embodiments of compounds of formula (G1) and their tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates are considered to be embraced within the scope of this application.

[0562] In reference to the terms *Aii''Tkk''*, where *ii''* and *kk''* are labelling natural numbers greater than 100 for embodiments of compounds of formula (G2), *Aii''* refers to an amine, such as those illustrated by amines *Aii''*, *ii''* = 101-110 in Table 4 (parts 1 and 2), and *Tkk''* refers to an alkyl aldehyde, such as those illustrated by the corresponding aldehydes *Tkk''*, *kk''* = 101-104 in Table 5. Embodiments of alkylated amines *Aii''Tkk''* were obtained through reductive amination (also known as reductive alkylation) as described below. As with the notation for illustrative embodiments of compounds of formula (G1) in the notation *Ai''Lj''Tk''*, when the terms *Aii''* and *Tkk''* are part of the notation *Aii''Tkk''*, they refer respectively to the moieties derived from *Aii''* and *Tkk''* after amine alkylation (regardless of the method to accomplish it, such as reductive alkylation or any other alkylation method), just as each of the terms *Ai''*, *Lj''*, and *Tk''* in *Ai''Lj''Tk''* refer respectively to moieties in *Ai''Lj''Tk''* that derive from the corresponding amine *Ai''*, *i''* = 1-12, 14, 16-29, 35-37, linker *Lj''*, or *Ai''L1* with *i''* = 30-34 and 38-42 compounds, and azide *Tk''* after they have undergone the reactions referred to above to form compounds *Ai''Lj''Tk''*.

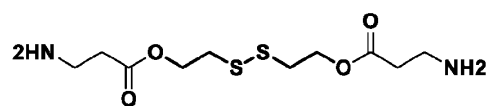
A101



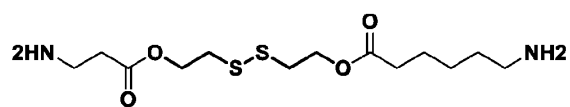
A102



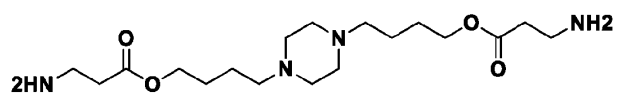
A103



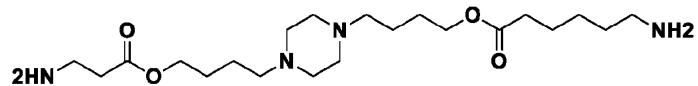
A104



A105



A106



A107

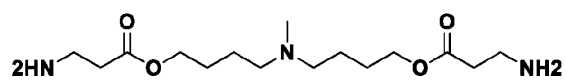


Table 4 (part 1)

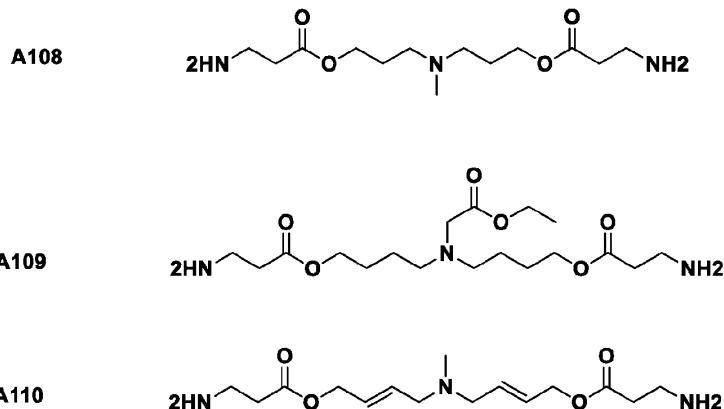


Table 4 (part 2)

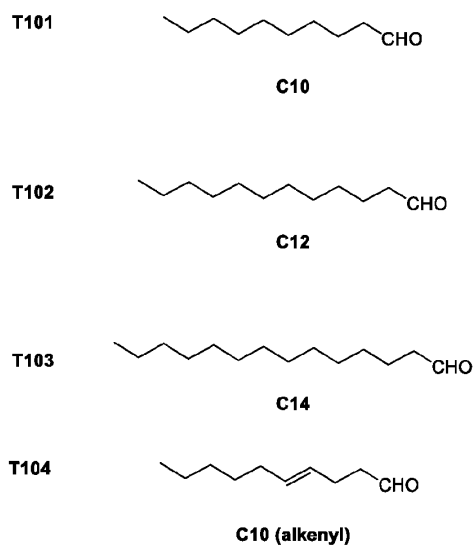
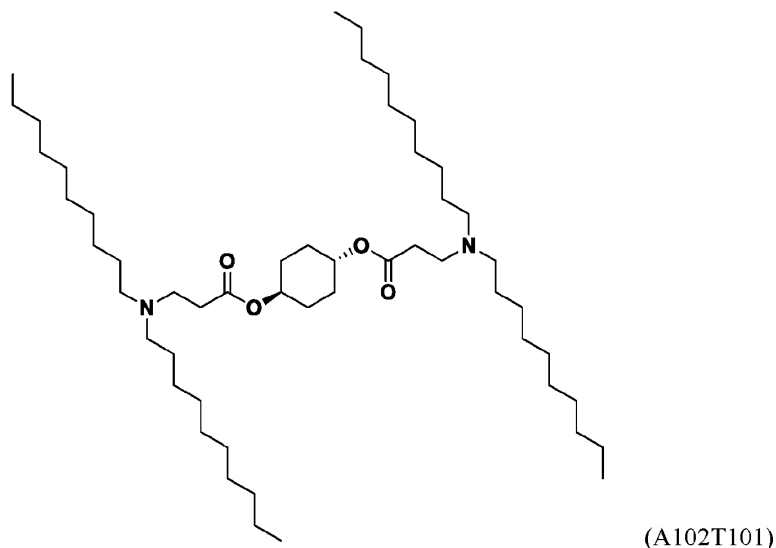
Table 4 showing amines *Aii''*, *ii''* = 101-110The group shown in Table 4 as "NH₂" represents the amino group NH₂.

Table 5

Table 5 showing alkyl and alkenyl aldehydes used to make *Aii''Tk''* compounds. CXX, with XX = 10, 12, 14, refer to the chain length that each such alkyl or alkenyl aldehyde introduces upon reductive alkylation.

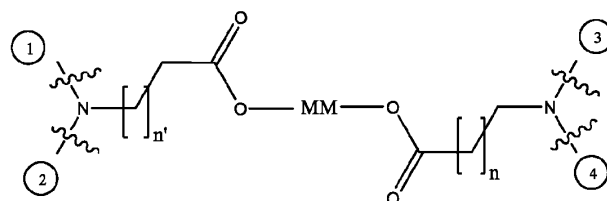
For example, lipid A102T101, $ii'' = 102$, and $kk'' = 101$, is compound of formula



[0563] The example A102T101 shows a lipid in which amine alkylation has proceeded to yield full alkyl substitutions of each primary amino group in A102. In embodiments of lipids according to this invention, primary amino groups in compounds Aii'' are fully alkyl-substituted through the corresponding amine alkylation reactions. When there is more than one alkylation of an amino group, the various Tkk'' are the same in some embodiments whereas they are different in other embodiments. Unless indicated otherwise, the notation $Aii''Tkk''$ refers to lipids in which the amino groups in the corresponding parent amine Aii'' have been fully alkylated by the same parent Tkk'' . When amine Aii'' has been alkylated by a plurality of parent Tkk'' moieties, with at least one of such Tkk'' moieties being different from the others, then the nomenclature of such lipids is given as $Aii''(Tkk'')_{\alpha}(Tkk'')_{\beta}(Tkk'')_{\gamma}(Tkk'')_{\delta}$, with each of α , β , γ , and δ indicating

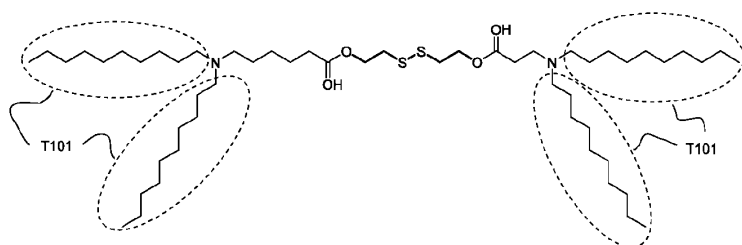
how many of each Tkk'' moieties are at each molecular site $\textcircled{1}$, $\textcircled{2}$, $\textcircled{3}$, and $\textcircled{4}$ (see structure below displaying such circled reference numbers), respectively, and each of such α , β , γ , and δ indices is 1, although it may be 2 when two Tkk'' moieties on the same molecular structure side are the same. See, for example, the structures given below for $A104(T101)_1(T102)_1(T101)_2$ and $A104(T101)_2(T101)_1(T102)_1$.

Amines Aii" in Table 4 are illustrative embodiments of parent amines of the moiety

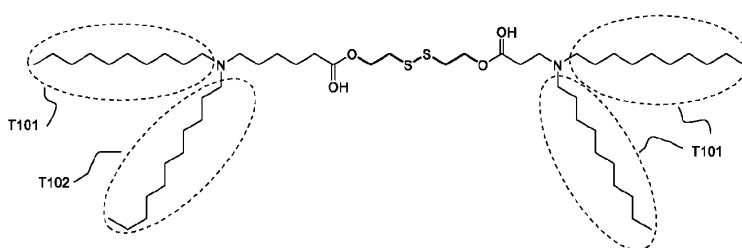
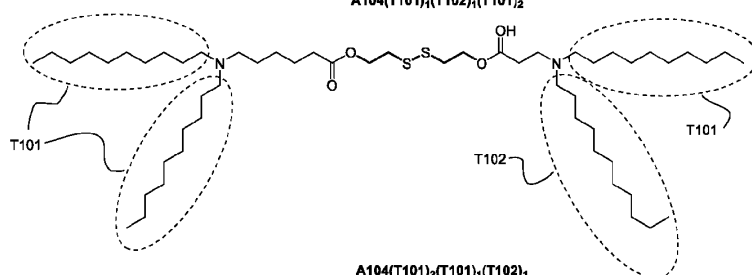


in formula (G2), with the applicable choices of MM, n and n' . Numbers 1-4 within circles in this moiety are reference numbers for the respective molecular sites. As illustrations of this terminology, the case where $n = n' = 1$, and MM is $(\text{CH}_2)_4\text{N}(\text{CH}_3)(\text{CH}_2)_4$ refers to A107; the case where $n = n' = 1$, and MM is $(\text{CH}_2)_4\text{N}(\text{CH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_3)(\text{CH}_2)_4$ refers to A109; and the case where $n' = 1$, $n = 4$, and MM is $(\text{CH}_2)_2\text{-S-S-(CH}_2)_2$ refers to A104.

[0564] Even though only one choice of the pair (n, n') when $n \neq n'$ may be explicitly named or exemplified with an illustrative compound, the compound(s) corresponding to the other choices of (n, n') with the same $(n + n')$ value are also envisaged as illustrative embodiments when different choices of moieties LCHAIN1 - LCHAIN4, and/or of the indices t and t' -when applicable as per general formula (G2), make of all such compounds different chemical entities because, although they all have the same molecular formula, they are in different isomeric forms. Furthermore, even though only one choice of the pair (t, t') when $t \neq t'$ may be explicitly named or exemplified with an illustrative compound, the compound(s) corresponding to the other choices of (t, t') with the same $(t + t')$ value are also envisaged as illustrative embodiments when different choices of moieties LCHAIN1 - LCHAIN4, and/or of the indices n and n' , make of all such compounds different chemical entities because, although they all have the same molecular formula, they are in different isomeric forms. By way of illustration, the example A104T101 (structure shown below), in which all four LCHAIN moieties are the same (T101 each, in this case) does not entail different chemical entities even though $n' = 1$ and $n = 4$ for A104. However, the same A104 leads to the different chemical entities $\text{A104(T101)}_1(\text{T102})_1(\text{T101})_2$ and $\text{A104(T101)}_2(\text{T101})_1(\text{T102})_1$ (structures also shown below), because both have three LCHAIN moieties that are the same (T101 each, in this case) and one different LCHAIN moiety (T102 in this case), and $n \neq n'$ in this case.



A104T101

A104(T101)₁(T102)₁(T101)₂A104(T101)₂(T101)₁(T102)₁

[0565] These examples illustrate a type of isomerism that some of (G2) embodiments of this invention present, just as illustrated above for (G1.1) and (G1.2) isomers. Depending on the source of terminology definitions, these isomers may be named as constitutional isomers or, more narrowly, chain -or skeletal- isomers. The term constitutional isomer or constitutional isomerism will be used herein to refer to them, as done above for (G1.1) and (G1.2) constitutional isomers.

[0566] In some embodiments, constitutional isomerism is presented by compounds with $n \neq n'$ and at least one LCHAIN moiety being different from the other LCHAIN moieties. In other embodiments, constitutional isomerism is presented by compounds with $t \neq t'$ and at least one LCHAIN moiety being different from the other LCHAIN moieties. In other embodiments constitutional isomerism is presented by compounds with $t \neq t'$ and $n \neq n'$ while all four

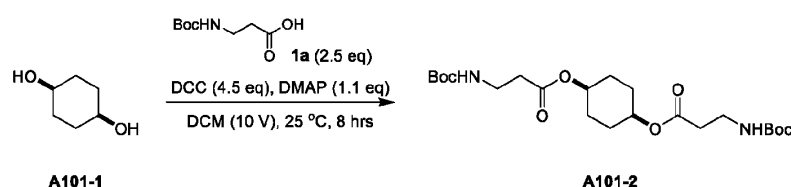
LCHAIN moieties are the same. In other embodiments constitutional isomerism is presented by compounds with $t \neq t'$ and $n \neq n'$ with at least one LCHAIN moiety being different from the other LCHAIN moieties. Embodiments of compounds according to this invention are envisaged to encompass any of such constitutional isomers within the scope of formula (G2).

[0567] Alkyl bromides Tkk'' in Table 5 are illustrative embodiments of parent alkyl moieties LCHAIN1 - LCHAIN4, with the applicable choices for the same, in formula (G2).

The examples below provide further illustrations of amine/moieties Aii'' and tails Tkk'' .

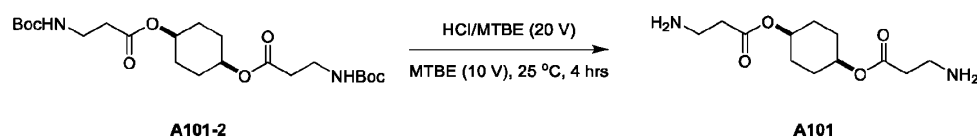
Example A101

Example A101.1



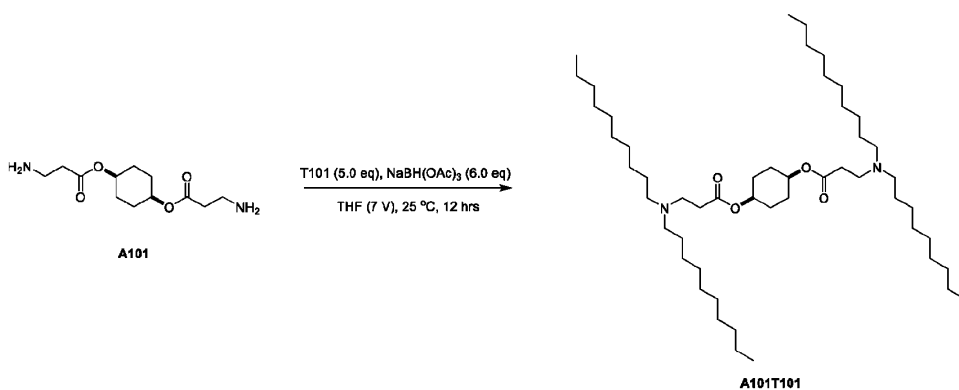
[0568] Charged compound A101-1 (1.00 g, 8.61 mmol, 1.00 eq) in DCM (18.0 mL). Added compound 1a (4.07 g, 21.5 mmol, 2.50 eq), DCC (7.99 g, 38.7 mmol, 7.84 mL, 4.50 eq) and DMAP (1.16 g, 9.47 mmol, 1.10 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 5 h. TLC indicated compound A101-1 (Petroleum ether: Ethyl acetate = 2: 1, R_f = 0.25, Product = 0.40) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was partitioned between H₂O (20.0 mL) and DCM (20.0mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 0/1). Compound **A101-2** (3.90 g, 8.51 mmol, 98.7% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 6.86 (t, J = 5.2 Hz, 2H), 4.75 (s, 1H), 3.16 (m, J = 4.0 Hz, 4H), 2.41 (t, J = 6.8 Hz, 4H).

Example A101.2



[0569] Charged compound **A101-2** (2.90 g, 6.32 mmol, 1.00 eq) in MTBE (40.0 mL). Added HCl/MTBE (4.00 M, 58.0 mL, 36.7 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 4 h. TLC (Petroleum ether: Ethyl acetate = 1: 1, R_f = 0.53, Product = 0.06) indicated compound A101-2 was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Without further purification. Compound A101 (0.60 g, 1.81 mmol, 83.0% yield, 2 HCl) was obtained as a white solid. ^1H NMR: 400 MHz, CDCl_3 δ 8.03 (s, 4H), 4.81 (s, 2H), 3.01 (s, 4H), 2.69 (t, J = 7.2 Hz, 4H), 1.71 (d, 8H), 1.59 (s, 1H).

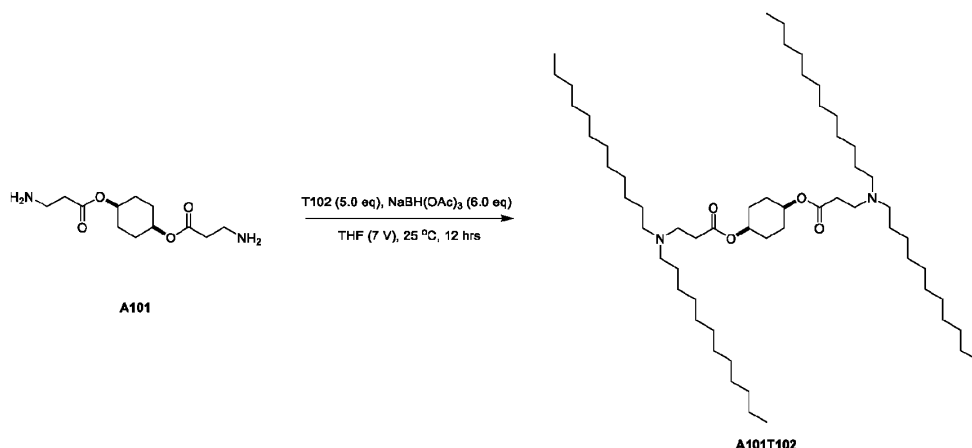
Example A101T101



[0570] Charged compound A101 (0.60 g, 1.81 mmol, 1.00 eq, 2 HCl) in THF (30.0 mL). Added compound T101 (1.42 g, 9.06 mmol, 1.71 mL, 5.00 eq) to the mixture. The mixture was stirred at 25 °C for 1 h. Added $\text{NaBH}(\text{OAc})_3$ (2.30 g, 10.9 mmol, 6.00 eq) to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether: Ethyl acetate = 1: 1, R_f = 0.53, Product = 0.06) indicated compound A101 was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO_3 (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=90/1 to 0/1). A101T101 ((cis)-cyclohexane-1,4-diyl bis(3-(dodecylamino)propanoate), 0.87 g, 1.06 mmol, 58.6% yield) was obtained as a white solid. ^1H NMR: 400 MHz, CDCl_3 δ 4.87 (br s, 2H),

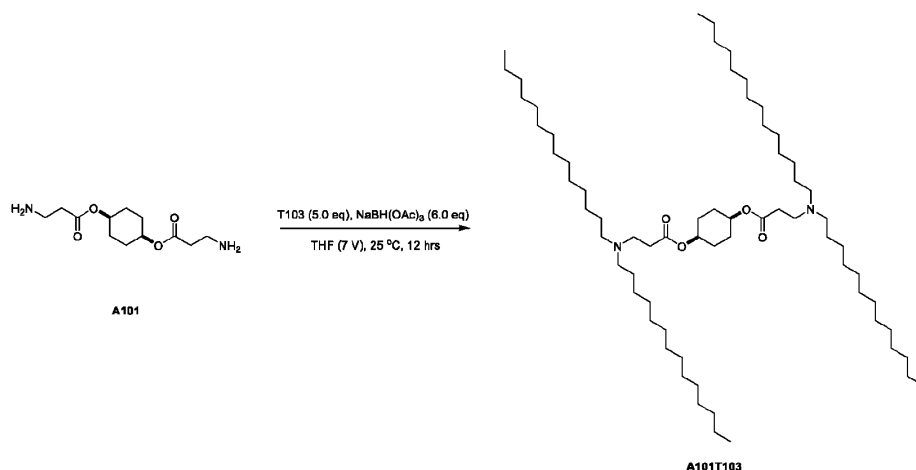
2.79 (br t, $J = 6.8$ Hz, 4H), 2.36 - 2.47 (m, 10 H), 1.78 - 1.91 (m, 4H), 1.56 - 1.76 (m, 6 H), 1.42 (br s, 8H), 1.19-1.36 (m, 56H), 0.89 (t, $J = 7.2$ Hz, 12H).

Example A101T102



[0571] Charged compound A101 (0.70 g, 2.11 mmol, 1.00 eq, 2 HCl) in THF (50.0 mL). Added compound T102 (1.95 g, 10.5 mmol, 5.00 eq) to the mixture. The mixture was stirred at 25 °C for 1 h. Added NaBH(OAc)₃ (2.69 g, 12.6 mmol, 6.00 eq) to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, Product = 0.13) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 90/1 to 0/1). A101T102 ((cis)-cyclohexane-1,4-diyl bis(3-(didodecylamino)propanoate), 0.95 g, 1.02 mmol, 48.2% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 4.87 (br s, 2H), 2.79 (br s, 3H), 2.33 - 2.48 (m, 10H), 1.76-1.88 (m, 4H), 1.66 - 1.75 (m, 4H), 1.57 (s, 3H), 1.42 (br s, 7H), 1.27 (s, 73H), 0.89 (t, $J = 7.2$ Hz, 12H)

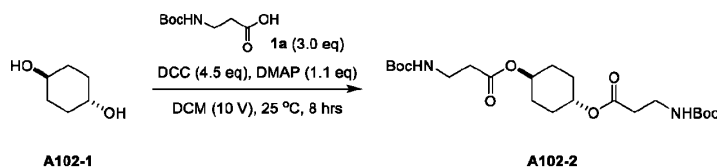
Example A101T103



[0572] Charged compound A101 (0.70 g, 2.11 mmol, 1.00 eq, 2 HCl) in THF (50.0 mL). Added compound T103 (2.24 g, 10.6 mmol, 5.00 eq) to the mixture. The mixture was stirred at 25 °C for 1 h. Added NaBH(OAc)₃ (2.69 g, 12.7 mmol, 6.00 eq) to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated compound A101 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, Product = 0.19) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 90/1 to 0/1). A101T103 ((cis)-cyclohexane-1,4-diyl bis(3-(ditetradecylamino)propanoate), 0.84 g, 804 μmol, 38.0% yield) was obtained as a colorless oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.87 (br s, 2H), 2.79 (br s, 3H), 2.40 (br d, *J* = 5.6 Hz, 10H), 1.77 - 1.85 (m, 4H), 1.67-1.75 (m, 4H), 1.57 (br s, 4H), 1.42 (br s, 9H), 1.27 (s, 86H), 0.89 (br t, *J* = 6.4 Hz, 12H).

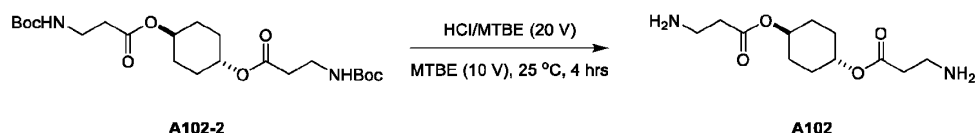
Example A102

Example A102.1



[0573] Charged compound A102-1 (9.00 g, 77.4 mmol, 1.00 eq) in DCM (180 mL). Added compound 1a (36.6 g, 193 mmol, 2.50 eq), DCC (71.9 g, 348 mmol, 70.5 mL, 4.50 eq) and DMAP (10.4 g, 85.2 mmol, 1.10 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 5 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 2: 1, R_f = 0.25, product = 0.43) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was partitioned between H₂O (80.0 mL) and DCM (80.0 mL). The organic phase was separated, washed with brine (50.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 0/1). Compound **A102-2** (30.0 g, 65.4 mmol, 84.4% yield) was obtained as a white oil. ¹H NMR: 400 MHz, DMSO δ 4.30 - 4.37 (m, 4H), 3.89 (t, J = 5.8 Hz, 1H), 2.88 - 2.96 (m, 5H), 2.79 (br t, J = 7.6 Hz, 3H), 2.31 - 2.51 (m, 14H), 1.37-1.47 (m, 13H), 1.27 (s, 74H), 0.89 (t, J = 6.8 Hz, 12H).

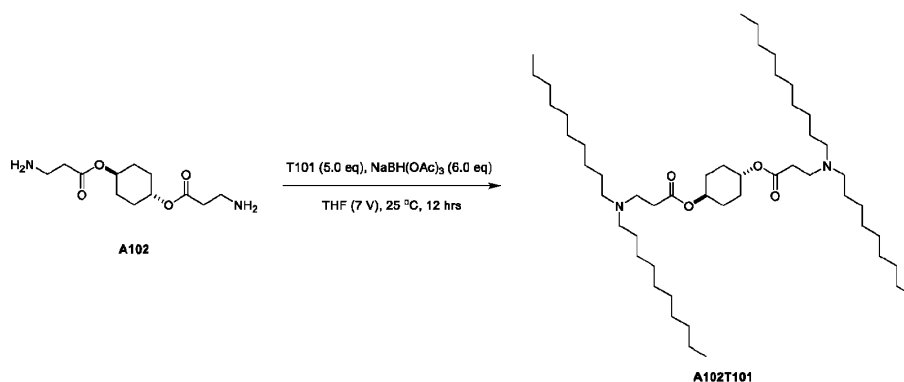
Example A102.2



[0574] Charged compound A102-2 (8.00 g, 17.4 mmol, 1.00 eq) in MTBE (80.0 mL). HCl/MTBE (4.00 M, 160 mL, 36.6 eq) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 4 h. TLC (Petroleum ether: Ethyl acetate = 1: 1, R_f = 0.53, product = 0.06) indicated compound A102-2 was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Without further purification. Compound **A102** (4.50 g, 17.4 mmol, 99.8% yield) was obtained as a white solid. ¹H NMR: 400 MHz, DMSO δ 8.06 (br s, 5H),

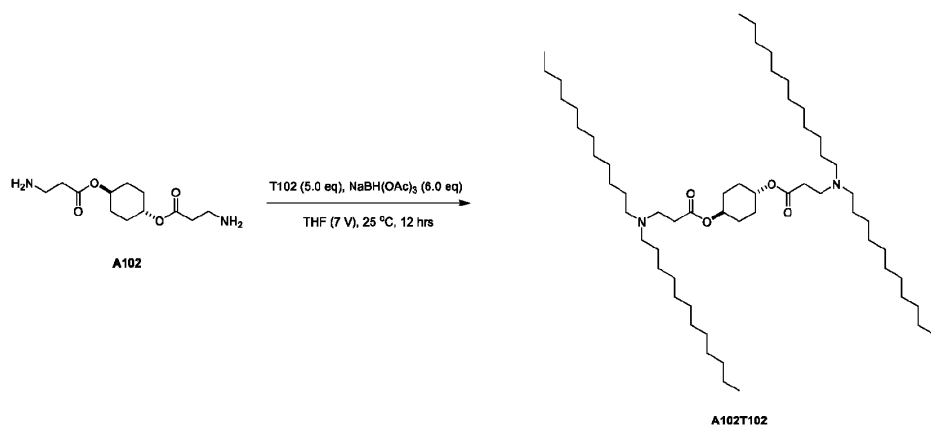
4.76 (br s, 2H), 2.99 (br s, 4H), 2.68 (t, $J = 7.2$ Hz, 4H), 1.90 (br d, $J = 6.8$ Hz, 4H), 1.47-1.61 (m, 4H).

Example A102T101



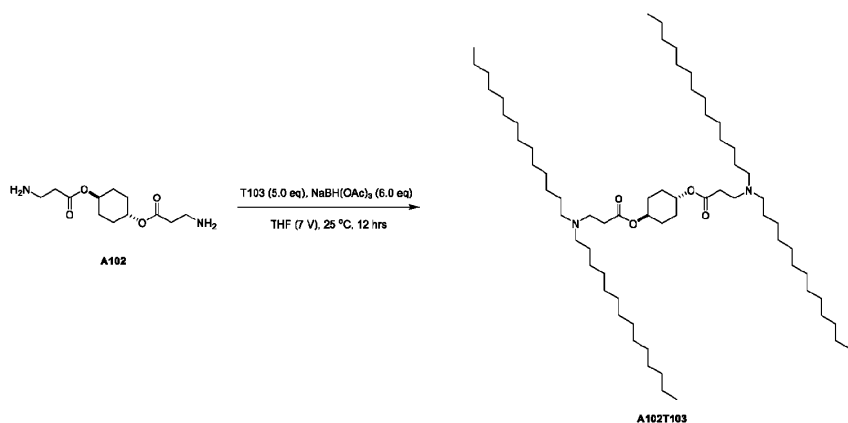
[0575] Charged compound A102 (1.00 g, 3.87 mmol, 1.00 eq) in THF (50.0 mL). Compound T101 (3.02 g, 19.3 mmol, 3.60 mL, 5.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. NaBH(OAc)₃ (4.92 g, 23.2 mmol, 6.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 2: 1, $R_f = 0.05$, product = 0.17) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 0/1). A102T101 ((trans)-cyclohexane-1,4-diyl bis(3-(didecylamino)propanoate), 1.00 g, 1.22 mmol, 31.5% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 4.81 (br s, 2H), 2.77 (br s, 4H), 2.39 (br d, $J = 5.0$ Hz, 11H), 1.97 (br d, $J = 7.6$ Hz, 4H), 1.47 - 1.65 (m, 6H), 1.41 (br s, 8H), 1.18 - 1.35 (m, 59H), 0.82 - 0.95 (m, 12H).

Example A102T102



[0576] Charged compound A102 (1.00 g, 3.87 mmol, 1.00 eq) in THF (50.0 mL). Compound T102 (3.57 g, 19.3 mmol, 5.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 1 h. NaBH(OAc)₃ (4.92 g, 23.2 mmol, 6.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, product = 0.17) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 90/1 to 0/1). A102T102 ((trans)-cyclohexane-1,4-diyl bis(3-(didodecylamino)propanoate), 0.55 g, 590 μmol, 15.2% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 4.81 (br s, 2H), 2.77 (br t, *J* = 7.2 Hz, 4H), 2.35 - 2.45 (m, 10H), 1.93 - 2.01 (m, 4H), 1.50 - 1.74 (m, 7H), 1.37-1.47 (m, 9H), 1.27 (s, 68H), 0.89 (m, 12H).

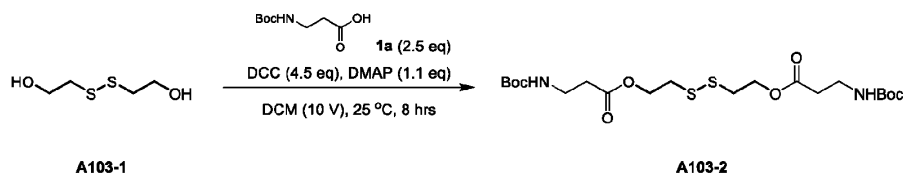
Example A102T103



[0577] Charged compound A102 (0.60 g, 2.32 mmol, 1.00 eq) in THF (40.0 mL). Compound T103 (2.47 g, 11.6 mmol, 5.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 1 h. NaBH(OAc)₃ (2.95 g, 13.9 mmol, 6.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, product = 0.17) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 90/1 to 0/1). The residue was purified by column chromatography (column: X-Select CSH Phenyl-Hexyl 100*30 5u; mobile phase: [H₂O(0.04% HCl)-THF:ACN=1:3]; gradient: 40%-85% B over 10.0 min). A102T103 ((trans)-cyclohexane-1,4-diyl bis(3-(ditetradecylamino)propanoate), 0.67 g, 641 μmol, 63.2% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 4.81 (br s, 2H), 2.78 (br s, 4H), 2.39 (br s, 10H), 1.93-2.01 (m, 4H), 1.54 (br t, *J* = 6.4 Hz, 5H), 1.43 (br d, *J* = 8.8 Hz, 9H), 1.26 (s, 94H), 0.89 (m, 12H).

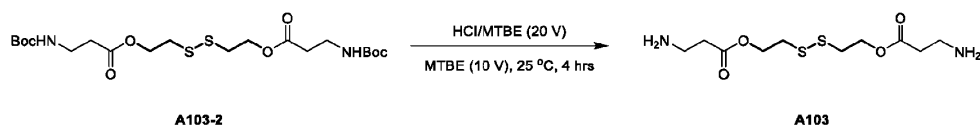
Example A103

Example A103.1



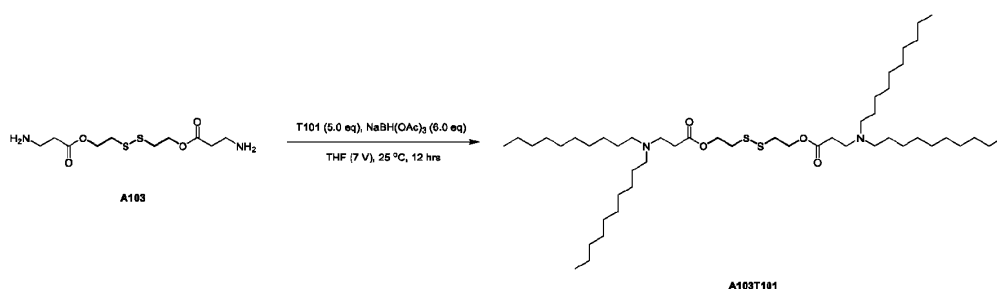
[0578] Charged compound **A103-1** (4.00 g, 25.9 mmol, 1.00 eq) in DCM (80.0 mL). Compound **1a** (12.2 g, 64.8 mmol, 2.50 eq), DCC (24.0 g, 116 mmol, 23.6 mL, 4.50 eq) and DMAP (3.48 g, 28.5 mmol, 1.10 eq) were added to the mixture at 0 °C. The mixture was stirred at 25 °C for 5 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 1: 1, R_f = 0.20, product = 0.41) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was partitioned between H₂O (50.0 mL) and DCM (50.0 mL). The organic phase was separated, washed with brine (30.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 0/1). Compound **A103-2** (11.2 g, 22.5 mmol, 86.9% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 5.06 (br s, 2H), 4.37 (br t, J = 6.4 Hz, 3H), 3.41 (br d, J = 5.6 Hz, 4H), 2.93 (br t, J = 6.4 Hz, 4H), 2.50 - 2.67 (m, 4H), 1.44 (br s, 18H).

Example A103.2



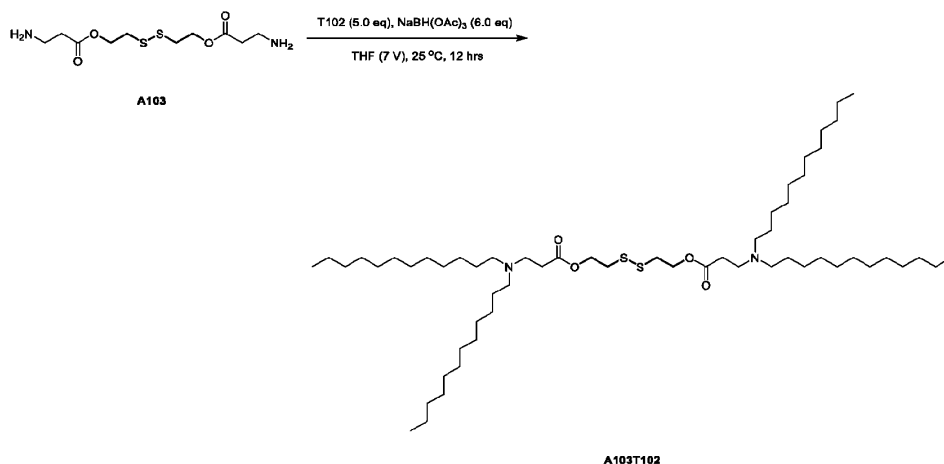
[0579] Charged compound **A103-2** (6.00 g, 12.0 mmol, 1.00 eq) in MTBE (60.0 mL). HCl/MTBE (4.00 M, 120 mL, 39.7 eq) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 4 h. TLC indicated compound **A103-2** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Without further purification. Compound **A103** (4.00 g, 9.61 mmol, 79.5% yield, 80% purity, HCl) was obtained as a white solid. ¹H NMR: 400 MHz, DMSO δ 8.17 (br s, 6H), 4.30 (t, J = 6.0 Hz, 4H), 3.01 (br t, J = 6.0 Hz, 8H), 2.71 - 2.77 (m, 4H).

Example A103T101



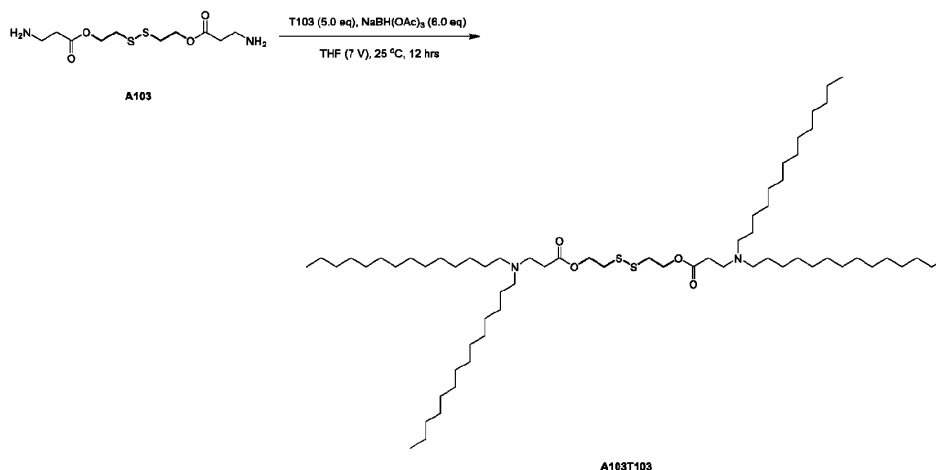
[0580] Charged compound **A103** (0.50 g, 1.50 mmol, 1.00 eq, HCl) in THF (50.0 mL). Compound **T101** (1.17 g, 7.51 mmol, 1.42 mL, 5.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 1 h. NaBH(OAc)₃ (1.91 g, 9.01 mmol, 6.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, product = 0.17) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (30.0 mL) and DCM (30.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 80/1 to 0/1). The residue was purified by column chromatography (column: Phenomenex Titank C18 Bulk 250*70mm 10u; mobile phase: [H₂O (0.05% HCl)-ACN: THF = 1:1]; gradient: 30%-60% B over 20.0 min). **A103T101** (disulfanediybis(ethane-2,1-diyl) bis(3-(didecylamino)propanoate), 1.00 g, 1.17 mmol, 50.0% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.8 Hz, 4H), 2.93 (t, *J* = 6.8 Hz, 4H), 2.79 (br s, 4H), 2.34 - 2.52 (m, 12H), 1.42 (br s, 8H), 1.27 (s, 52H), 0.89 (t, *J* = 6.4 Hz, 12H).

Example A103T102



[0581] Charged compound **A102** (1.00 g, 3.00 mmol, 1.00 eq, HCl) in THF (50.0 mL). Compound **T102** (2.77 g, 15.0 mmol, 5.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 1 h. NaBH(OAc)₃ (3.82 g, 18.0 mmol, 6.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated compound **A102** (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, product = 0.17) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO₃ (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 90/1 to 0/1). The residue was purified by column chromatography (column: Welch Xtimate C1 100*30mm*5um; mobile phase: [H₂O (0.04% HCl)-ACN: THF = 1:1]; gradient: 35%-75% B over 20.0 min). **A103T102** (disulfanediybis(ethane-2,1-diyl) bis(3-(didodecylamino)propanoate), 1.00 g, 1.03 mmol, 40.0% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 2.80 (br s, 4H), 2.35 - 2.67 (m, 13H), 1.43 (br s, 9H), 1.27 (s, 61H), 0.89 (t, *J* = 6.8 Hz, 13H).

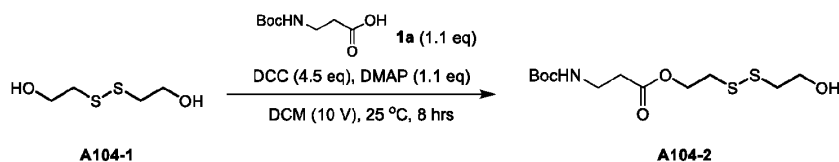
Example A103T103



[0582] Charged compound **A103** (1.00 g, 3.00 mmol, 1.00 eq, HCl) in THF (50.0 mL). Compound **T103** (3.19 g, 15.0 mmol, 5.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 1 h. $\text{NaBH}(\text{OAc})_3$ (3.82 g, 18.0 mmol, 6.00 eq) was added to the mixture at 25 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.04, product = 0.25) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the reaction mixture was partitioned between NaHCO_3 (15.0 mL) and DCM (15.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 90/1 to 0/1). **A103T103** (disulfanediyldis(ethane-2,1-diyl) bis(3-(ditetradecylamino)propanoate), 0.85 g, 785 μmol , 26.1% yield) was obtained as a white solid. ^1H NMR: 400 MHz, CDCl_3 δ 4.34 (t, J = 6.6 Hz, 4H), 2.93 (t, J = 6.6 Hz, 4H), 2.80 (br s, 4H), 2.34 - 2.56 (m, 12H), 1.43 (br s, 14H), 1.27 (s, 93H), 0.89 (t, J = 6.8 Hz, 15H).

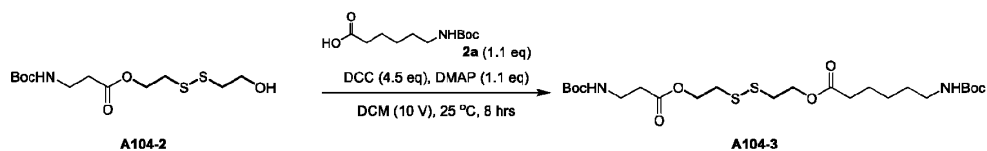
Example A104

Example A104.1



[0583] Charged compound **A104-1** (1.00 g, 6.48 mmol, 1.00 eq) in DCM (20.0 mL). Compound **1a** (1.35 g, 7.13 mmol, 1.10 eq), DCC (6.02 g, 29.1 mmol, 5.90 mL, 4.50 eq) and DMAP (871 mg, 7.13 mmol, 1.10 eq) were added to the mixture at 0 °C. The mixture was stirred at 25 °C for 6 h. TLC indicated compound **A104-1** (Petroleum ether: Ethyl acetate = 2: 1, R_f = 0.21, product = 0.37) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was partitioned between H₂O (20.0 mL) and DCM (20.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 0/1). Compound **A104-2** (2.00 g, 4.92 mmol, 75.8% yield, 80.0% purity) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 5.04 (br s, 1H), 4.39 (br t, J = 6.4 Hz, 2H), 3.90 (br t, J = 4.8 Hz, 2H), 3.41 (br d, J = 5.2 Hz, 2H), 2.79 - 3.04 (m, 4H), 2.56 (br t, J = 5.6 Hz, 2H), 2.19 (br s, 1H), 1.45 (br s, 9H).

Example A104.2

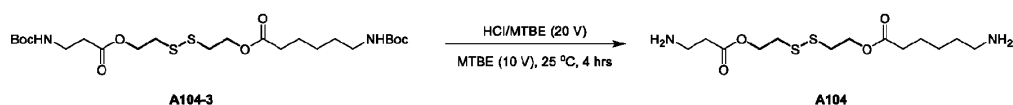


[0584] Charged compound **A104-2** (2.00 g, 6.15 mmol, 1.00 eq) in DCM (40.0 mL). Added DCC (5.71 g, 27.6 mmol, 5.59 mL, 4.50 eq), compound **2a** (1.56 g, 6.76 mmol, 1.10 eq) and DMAP (825 mg, 6.76 mmol, 1.10 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 6 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 2: 1, R_f = 0.21, product = 0.37) was consumed completely and many new spots formed. The reaction was messy according to TLC. The reaction mixture was partitioned between H₂O (20.0 mL) and DCM (20.0 mL). The organic phase was separated, washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 0/1).

Compound **A104-3** (3.00 g, 5.57 mmol, 90.6% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 5.08 (br s, 1H), 4.52 - 4.66 (m, 1H), 4.25 - 4.42 (m, 4H), 3.40 (q, *J* = 5.8 Hz, 2H), 3.11 (q, *J* = 6.4 Hz, 2H), 2.92 (td, *J* = 6.4, 2.4 Hz, 4H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.61 - 1.67 (m, 2H), 1.48 (br d, *J* = 7.6 Hz, 2H), 1.43 (s, 18H), 1.35 (br d, *J* = 7.0 Hz, 2H).

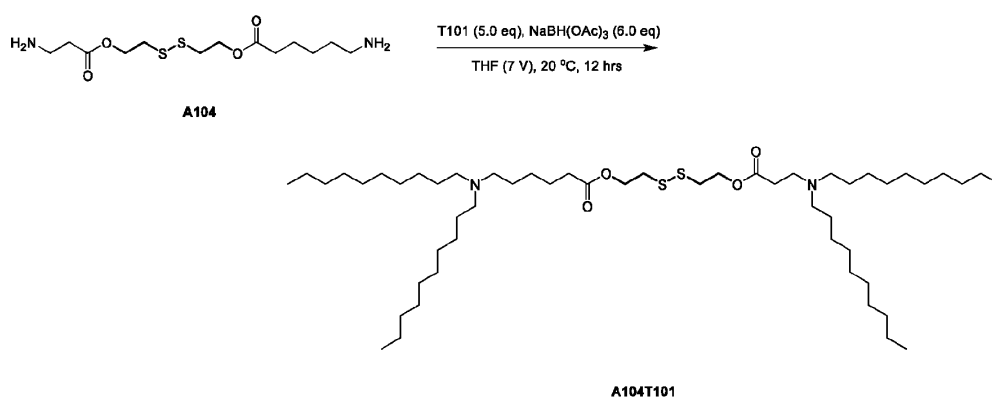
Example A104.3



[0585] Charged compound **A104-3** (3.00 g, 5.57 mmol, 1.00 eq) in MTBE (40.0 mL).

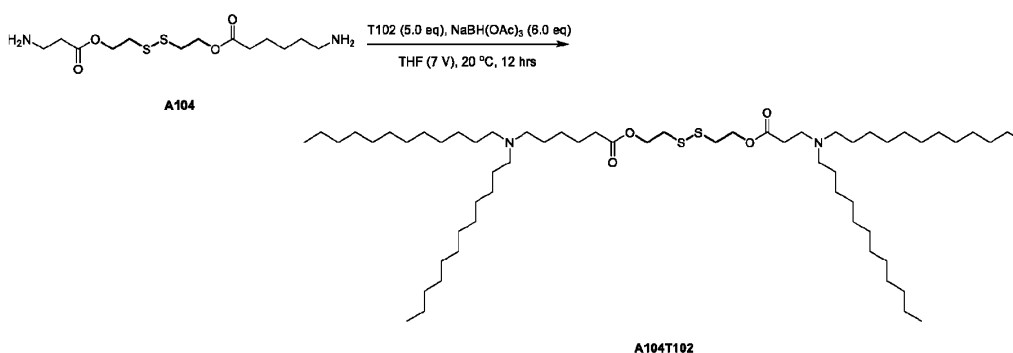
Added HCl/MTBE (4.00 M, 51.0 mL, 36.6 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 4 h. TLC (Petroleum ether: Ethyl acetate = 1: 1, *R_f* = 0.53, product = 0.06) indicated compound **A104-3** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE (50.0 mL) at 25 °C for 30 min. Compound **A104** (2.60 g, 5.37 mmol, 100% yield, 4 HCl) was obtained as a white solid. ¹H NMR: 400 MHz, DMSO δ 7.86 - 8.29 (m, 6H), 4.24 - 4.33 (m, 4H), 2.99 (q, *J* = 6.4 Hz, 6H), 2.73 (br t, *J* = 7.0 Hz, 4H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.51 - 1.58 (m, 4H), 1.26 - 1.36 (m, 2H).

Example A104T101



[0586] Charged compound **A104** (800 mg, 1.65 mmol, 1.00 eq, 2 HCl) in THF (10.0 mL). Added compound **T101** (1.29 g, 8.26 mmol, 1.56 mL, 5.00 eq) to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. Added NaBH(OAc)₃ (2.10 g, 9.91 mmol, 6.00 eq) to the mixture at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated Reactant 1 (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.08, product = 0.26) was consumed completely and many new spots formed. The reaction was messy according to TLC. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator. The residue was purified by prep-HPLC (column: X-Select CSH Phenyl-Hexyl 100*30 5u; mobile phase: [H₂O (0.04% HCl)-THF: ACN=1:3]; gradient: 30%-65% B over 10.0 min). **A104T101** (2-((2-((3-(didecylamino)propanoyl)oxy)ethyl)disulfaneyl)ethyl 6-(didecylamino)hexanoate, 816 mg, 907 μmol, 45.3% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.30 - 2.49 (m, 14H), 1.65 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.42 (br d, *J* = 5.8 Hz, 8H), 1.27 (s, 55H), 0.89 (t, *J* = 6.8 Hz, 12H).

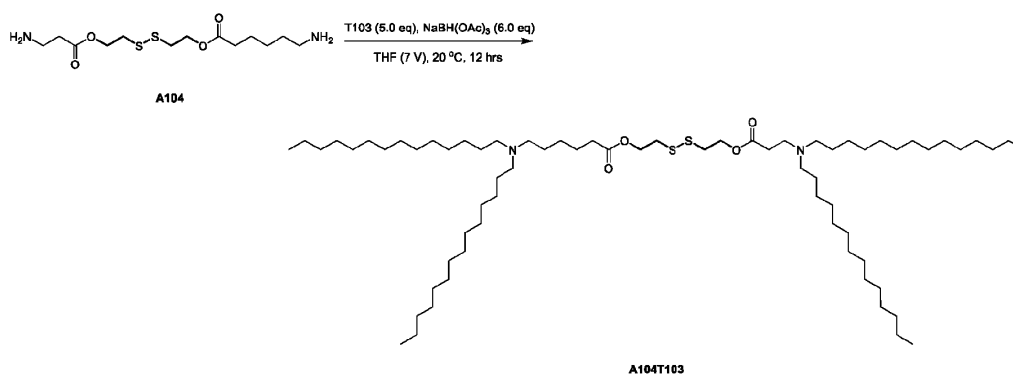
Example A104T102



[0587] Charged compound **A104** (800 mg, 1.65 mmol, 1.00 eq, 2 HCl) in THF (10.0 mL). Compound **T102** (1.52 g, 8.26 mmol, 5.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. NaBH(OAc)₃ (2.10 g, 9.91 mmol, 6.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC indicated compound **A104** (Petroleum ether: Ethyl acetate = 0: 1, R_f = 0.05, product = 0.27) was consumed completely and many new spots formed. The reaction was messy according to TLC. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator. The residue was purified by prep-HPLC (column: X-

Select CSH Phenyl-Hexyl 100*30 5u; mobile phase: [H₂O(0.04%HCl)-THF:ACN=1:3];gradient:35%-75% B over 10.0 min). **A104T102** (2-((2-((3-(didodecylamino)propanoyl)oxy)ethyl)disulfaneyl)ethyl 6-(didodecylamino)hexanoate, 600 mg, 593 μ mol, 75.0% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 2.79 (br t, *J* = 7.2 Hz, 2H), 2.28-2.51 (m, 13H), 1.61 - 1.71 (m, 3H), 1.43 (br d, *J* = 5.4 Hz, 8H), 1.22 - 1.35 (m, 76H), 0.89 (t, *J* = 6.8 Hz, 12H).

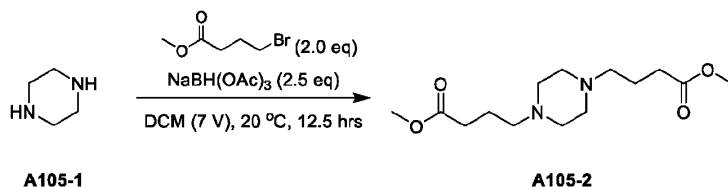
Example A104T103



[0588] Charged compound **A104** (0.80 g, 1.65 mmol, 1.00 eq, 2 HCl) in THF (11.0 mL). Compound **T103** (1.75 g, 8.26 mmol, 5.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. NaBH(OAc)₃ (2.10 g, 9.91 mmol, 6.00 eq) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC (Petroleum ether: Ethyl acetate= 3: 1, *R_f*= 0.08, Product = 0.57) indicated compound **A104** was consumed completely and many new spots formed. The reaction was messy according to TLC. Evaporated the solution on a water bath under reduced pressure using a rotary evaporator. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: [H₂O (0.05%HCl)-THF: ACN=1:3]; gradient: 38%-88% B over 20.0 min). **A104T103** (2-((2-((3-(ditetradecylamino)propanoyl)oxy)ethyl)disulfaneyl)ethyl 6-(ditetradecylamino)hexanoate, 590 mg, 524 μ mol, 36.8% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.30 - 2.51 (m, 13H), 1.65 (dt, *J* = 15.2, 7.6 Hz, 3H), 1.42 (br d, *J* = 5.6 Hz, 10H), 1.27 (s, 90H), 0.89 (t, *J* = 6.8 Hz, 12H).

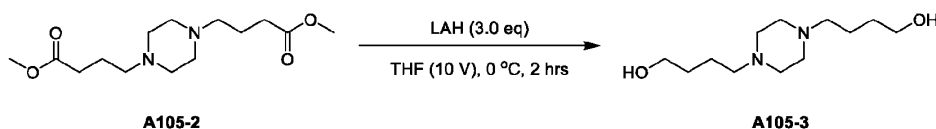
Example A105

Example A105.1



[0589] Charged compound **A105-1** (7.50 g, 87.0 mmol, 1.00 eq) in DCM (200 mL). Added methyl 4-oxobutanoate (20.2 g, 174 mmol, 2.00 eq) into the mixture. Stirred at 20 °C for 30 min. Added NaBH(OAc)_3 (46.1 g, 217 mmol, 2.50 eq) into the mixture. Stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.36), LCMS (RT = 0.147 min) and HNMR indicated compound **A105-1** was completely consumed and the product was detected. The reaction mixture was washed with saturated aqueous Na_2CO_3 . Added 1M HCl (50.0 mL) in the mixture, and the aqueous layer was adjusted to pH 8 with saturated aqueous Na_2CO_3 and extracted with DCM/IPA (3/1) (50.0 mL, 40.0 mL, 30.0 mL). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude product was used into the next step without further purification. Compound **A105-2** (16.0 g, 55.8 mmol, 64.1% yield) was obtained as a colorless oil. $^1\text{H NMR}$: 400 MHz, CDCl_3 δ 3.67 (s, 6H), 2.30 - 2.54 (m, 16H), 1.74 - 1.92 (m, 4H).

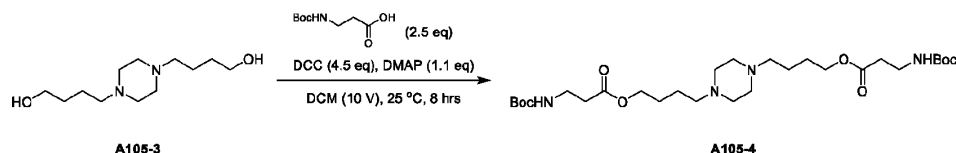
Example A105.2



[0590] Charged compound **A105-2** (16 g, 55.8 mmol, 1.00 eq) in THF (112 mL). Added LiAlH_4 (2.50 M, 67.0 mL, 3.00 eq) into the mixture at 0 °C. Stirred at 0 °C for 2 h. TLC (Dichloromethane: Methanol=10:1, R_f = 0) and HNMR indicated compound **A105-2** was completely consumed and the product was detected. Added H_2O (6.40 mL), 15% NaOH (6.40 mL), H_2O (19.2 mL) and Na_2SO_4 in the mixture at 0 °C. The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was used into the next step without further purification. Compound **A105-3** (9.80 g, 42.5 mmol, 76.1% yield) was obtained as a yellow solid. $^1\text{H NMR}$: 400 MHz, CDCl_3 δ 5.97 - 6.37 (m, 2H), 3.53 - 3.61 (m, 4H), 2.33 - 2.83

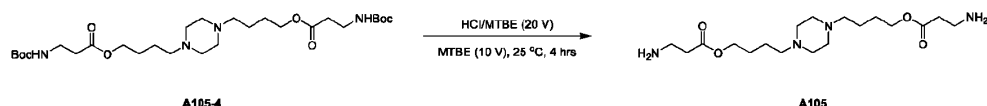
(m, 12H), 1.67 (br s, 8H).

Example A105.3

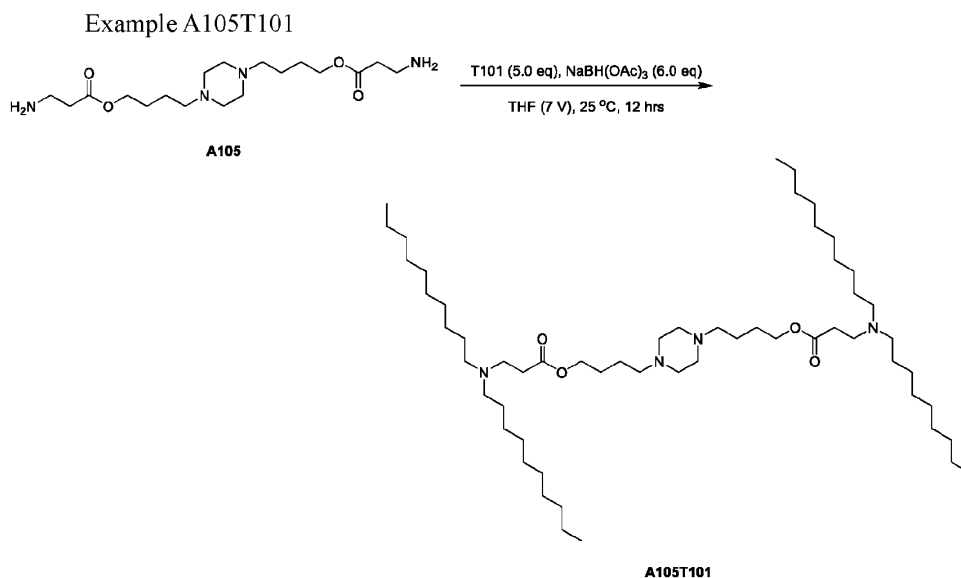


[0591] Charged compound **A105-3** (4.90 g, 21.2 mmol, 1.00 eq) in DCM (80.0 mL). Added acid (10.0 g, 53.1 mmol, 2.50 eq), DCC (19.7 g, 95.7 mmol, 19.3 mL, 4.50 eq) and DMAP (2.86 g, 23.4 mmol, 1.10 eq) into the mixture at 0 °C. Stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.27), LCMS (RT = 1.29 min) and HNMR indicated compound **A105-3** was completely consumed and the product was detected. The mixture was filtered and the filtrate was concentrated to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 80/1 to 0/1). Compound **A105-4** (5.00 g, 8.73 mmol, 41.0% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 5.02 (br s, 2H), 4.07 - 4.13 (m, 4H), 3.36 - 3.44 (m, 4H), 2.30 - 2.67 (m, 16H), 1.54 - 1.69 (m, 8H), 1.44 (s, 18H).

Example A105.4

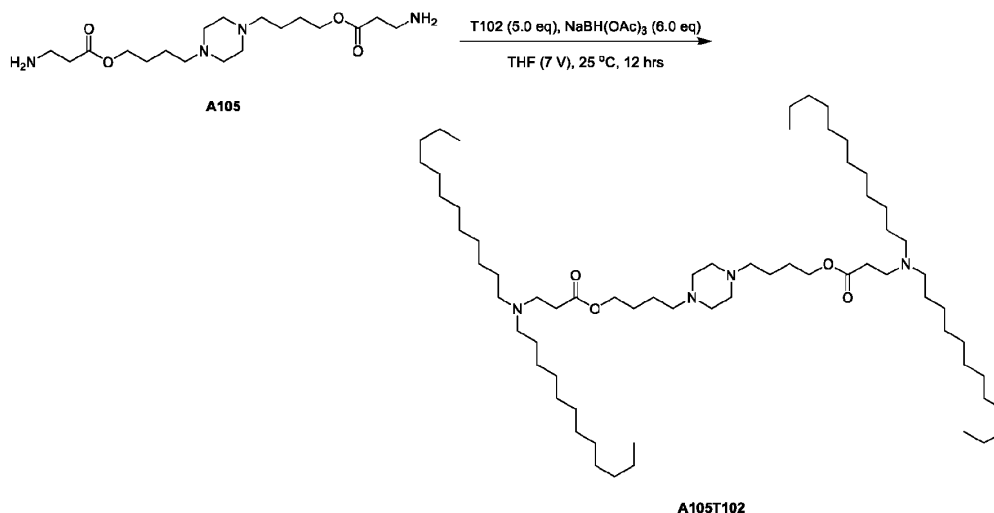


[0592] Charged compound **A105-4** (5.00 g, 8.73 mmol, 1.00 eq) in MTBE (20.0 mL) was added HCl/MTBE (4.00 M, 100 mL, 45.8 eq). The mixture was stirred at 25 °C for 12h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0) and HNMR indicated compound **A105-4** was completely consumed and the product was detected. The mixture was filtered and the filter cake was concentrated to give crude product. The crude product was used into the next step without further purification. Compound **A105** (3.20 g, 8.59 mmol, 98.4% yield) was obtained as a yellow solid. ¹H NMR: 400 MHz, DMSO δ 7.99 - 8.28 (m, 5H), 4.08 (br t, J = 6.2 Hz, 4H), 3.74 (br s, 4H), 3.39 - 3.52 (m, 4H), 3.10 - 3.23 (m, 4H), 2.95 - 3.09 (m, 5H), 2.62 - 2.82 (m, 5H), 1.62 - 1.87 (m, 8H).



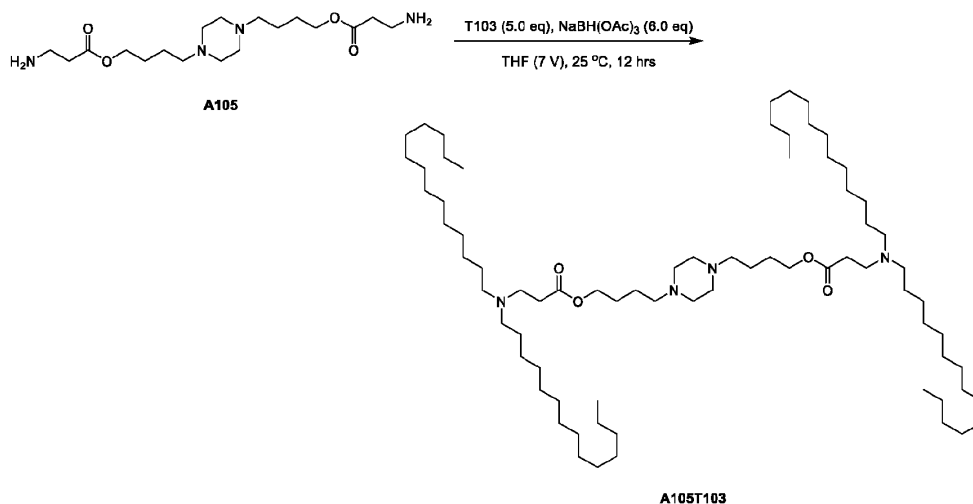
[0593] Charged compound **A105** (1.00 g, 2.68 mmol, 1.00 eq) and compound **T101** (2.10 g, 13.4 mmol, 2.53 mL, 5.00 eq) in THF (15.0 mL). Stirred at 20 °C for 30 min. Added $\text{NaBH}(\text{OAc})_3$ (3.41 g, 16.1 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT = 1.82 min) indicated compound **A105** was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na_2CO_3 , dried (Na_2SO_4) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: $[\text{H}_2\text{O} (0.05\%\text{HCl})\text{-THF: ACN}=1:3]$; gradient: 25%-55% B over 20.0 min). A105T101 (piperazine-1,4-diylbis(butane-4,1-diyl) bis(3-(didecylamino)propanoate), 0.80 g, 856 μmol , 32.0% yield) was obtained as a yellow oil. ^1H NMR: 400 MHz, CDCl_3 δ 4.08 (t, $J=6.4$ Hz, 4H), 2.78 (br t, $J=7.0$ Hz, 4H), 2.28 - 2.54 (m, 22H), 1.62 - 1.70 (m, 4H), 1.51 - 1.60 (m, 4H), 1.42 (br s, 9H), 1.27 (s, 57H), 0.86 - 0.93 (m, 12H).

Example A105T102



[0594] Charged compound **A105** (2.47 g, 13.4 mmol, 5.00 eq) and compound **T102** (2.47 g, 13.4 mmol, 5.00 eq) in THF (15.0 mL). Stirred at 20 °C for 30 min. Added NaBH(OAc)₃ (3.41 g, 16.1 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT = 2.16 min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: [H₂O (0.05% HCl)-THF: ACN=1:3]; gradient: 25%-60% B over 20.0 min). **A105T102** (piperazine-1,4-diylbis(butane-4,1-diyl) bis(3-(didodecylamino)propanoate), 600 mg, 573 μmol, 15.0% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.08 (t, J = 6.6 Hz, 4H), 2.78 (br t, J = 7.4 Hz, 4H), 2.32-2.53 (m, 22H), 1.62-1.69 (m, 5H), 1.51-1.60 (m, 5H), 1.41 (br s, 11H), 1.27 (s, 69H), 0.89 (t, J = 6.8 Hz, 12H).

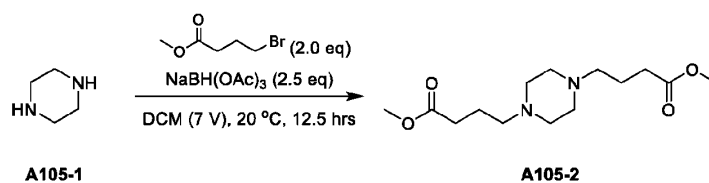
Example A105T103



[0595] Charged compound **A105** (1.20 g, 3.22 mmol, 1.00 eq) and compound **T103** (4.10 g, 19.3 mmol, 6.00 eq) in THF (20.0 mL). Stirred at 20 °C for 30 min. Added NaBH(OAc)₃ (4.10 g, 19.3 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT=2.4 min) indicated compound **A105** was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: [H₂O (0.05% HCl)-THF: CAN =1:3]; gradient: 20%-70% B over 20.0 min). **A105T103** (piperazine-1,4-diylbis(butane-4,1-diyl) bis(3-(ditetradecylamino)propanoate), 0.80 g, 690 μmol, 21.6% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.34 (t, *J* = 6.6 Hz, 4H), 2.93 (t, *J* = 6.6 Hz, 4H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.30 - 2.51 (m, 13H), 1.65 (dt, *J* = 15.2, 7.6 Hz, 3H), 1.42 (br d, *J* = 5.6 Hz, 10H), 1.27 (s, 90H), 0.89 (t, *J* = 6.8 Hz, 12H).

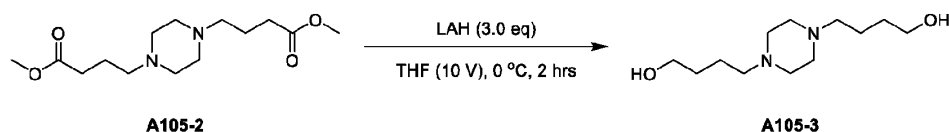
Example A106

Example A106.1



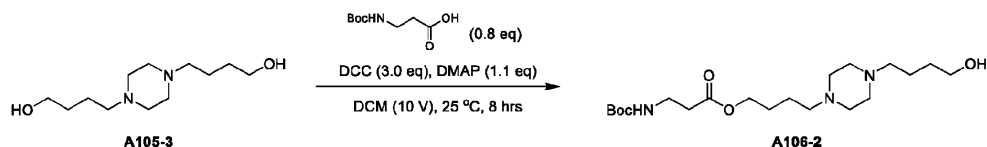
[0596] Charged compound **A105-1** (13.0 g, 150 mmol, 1.00 eq) in DCM (400 mL). Added methyl 4-oxobutanoate (35.0 g, 301 mmol, 2.00 eq) into the mixture. Stirred at 20 °C for 30 min. Added NaBH(OAc)₃ (79.9 g, 377 mmol, 2.50 eq) into the mixture. Stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.36), LCMS (RT = 0.147 min) and HNMR indicated compound **A105-1** was completely consumed and the product was detected. The reaction mixture was washed with saturated aqueous Na₂CO₃. Added 1M HCl in the mixture, and the aqueous layer was adjusted to pH 8 with saturated aqueous Na₂CO₃ and extracted with DCM/IPA (3/1) (50.0 mL, 40.0 mL, 30.0 mL). The organic layer was dried (Na₂SO₄) and evaporated to dryness. The crude product was used into the next step without further purification. Compound **A105-2** (27.0 g, 94.2 mmol, 62.4% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 3.67 (s, 6H), 2.27 - 2.62 (m, 16H), 1.82 (m, *J* = 7.2 Hz, 4H).

Example A106.2



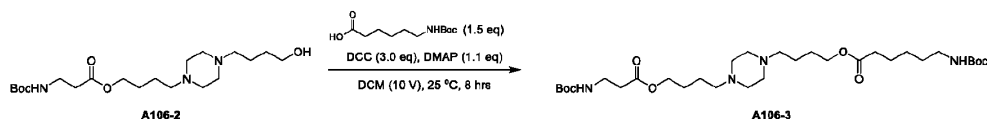
[0597] Charged compound **A105-2** (27.0 g, 94.2 mmol, 1.00 eq) in THF (210 mL). Added LiAlH₄ (2.50 M, 113 mL, 3.00 eq) into the mixture at 0 °C. Stirred at 0 °C for 2 h. TLC (Dichloromethane : Methanol = 10:1, R_f = 0) and HNMR indicated Reactant 1 was completely consumed and the product was detected. Added H₂O (11.0 mL), 15% NaOH (11.0 mL), H₂O (33.0 mL) and Na₂SO₄ in the mixture at 0 °C. The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was used into the next step without further purification. Compound **A105-3** (21.0 g, 91.1 mmol, 96.6% yield) was obtained as a white solid. ¹H NMR: 400 MHz, CDCl₃ δ 5.90-6.41 (m, 2H), 3.49-3.65 (m, 4H), 2.19-2.96 (m, 11H), 1.56-1.79 (m, 8H).

Example A106.3



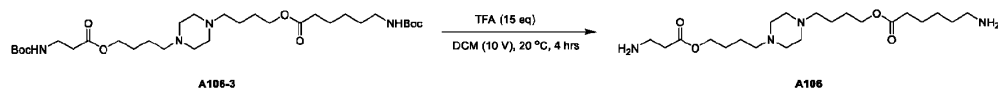
[0598] Charged compound **A105-3** (3.00 g, 13.0 mmol, 1.00 eq) in DCM (20.0 mL). Added acid (1.97 g, 10.4 mmol, 0.80 eq), DCC (8.06 g, 39.0 mmol, 7.90 mL, 3.00 eq) and DMAP (1.75 g, 14.3 mmol, 1.10 eq) into the mixture. Stirred at 35 °C for 1 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.13), LCMS (R_f = 1.014 min) and HNMR indicated compound **A105-3** was completely consumed and the product was detected. The mixture was filtered and the filtrate was washed with saturated aqueous Na₂CO₃. The organic layer was concentrated to give crude product. The residue was purified by column chromatography (SiO₂, Dichloromethane: Methanol = 20/1 to 0/1). Compound **A106-2** (10.0 g, 24.9 mmol, 27.3% yield) was obtained as a yellow solid. ¹H NMR: 400 MHz, CDCl₃ δ 6.48-6.52 (m, 6H), 4.98-5.09 (m, 1H), 3.56 (br d, J = 5.4 Hz, 2H), 2.32-2.60 (m, 10H), 1.44 (s, 9H).

Example A106.4



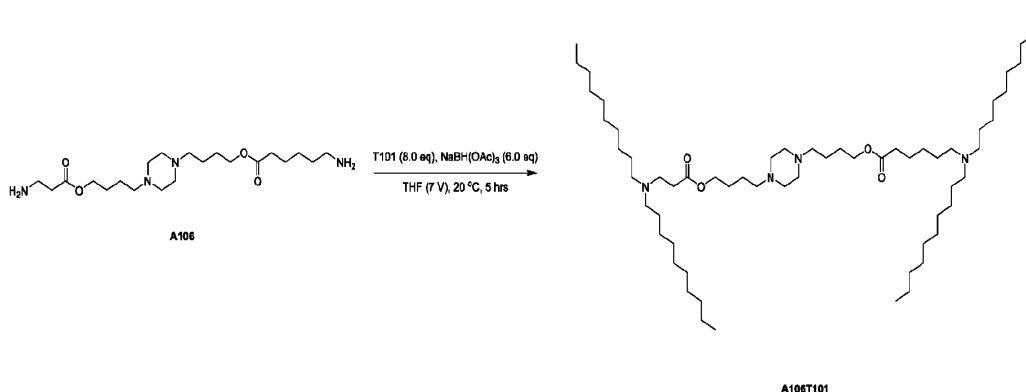
[0599] Charged compound **A106-2** (10.0 g, 24.9 mmol, 1.00 eq) in DCM (300 mL). Added acid (8.64 g, 37.3 mmol, 1.50 eq), DCC (15.4 g, 74.7 mmol, 15.1 mL, 3.00 eq) and DMAP (3.35 g, 27.3 mmol, 1.10 eq) into the mixture. The mixture was stirred at 35 °C for 1 h. TLC (Dichloromethane: Methanol=10:1, R_f = 0.43), LCMS R_f = 1.0 min) and HNMR indicated compound **A106-2** was completely consumed and the product was detected. The mixture was filtered and the filtrate was washed with saturated aqueous Na₂CO₃. The organic layer was concentrated to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 8/1 to 0/1). Compound **A106-3** (10.0 g, 16.2 mmol, 65.3% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 5.04 (br s, 1H), 4.60 (br d, J = 1.6 Hz, 1H), 4.04-4.14 (m, 4H), 3.39 (q, J = 5.8 Hz, 2H), 3.11 (q, J = 6.4 Hz, 2H), 2.26-2.56 (m, 14H), 1.29-1.73 (m, 35H).

Example A106.5



[0600] Charged compound **A106-3** (3.00 g, 4.88 mmol, 1.00 eq) in DCM (21.0 mL). Added TFA (8.35 g, 73.1 mmol, 5.44 mL, 15.0 eq) into the mixture. Stirred at 20 °C for 4 h. LCMS (RT = 0.094 min) and HNMR indicated Reactant 1 was completely consumed and the product was detected. The mixture was concentrated in vacuo. The crude product was used into the next step without further purification. Compound **A106** (2.00 g, 4.82 mmol, 98.8% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, DMSO δ 4.05 (dt, J = 18.9, 6.0 Hz, 4H), 2.98-3.15 (m, 6H), 2.72-2.82 (m, 2H), 2.66-2.66 (m, 1H), 2.62-2.68 (m, 1H), 2.29 (t, J = 7.4 Hz, 2H), 1.47-1.75 (m, 14H), 1.24-1.35 (m, 2H).

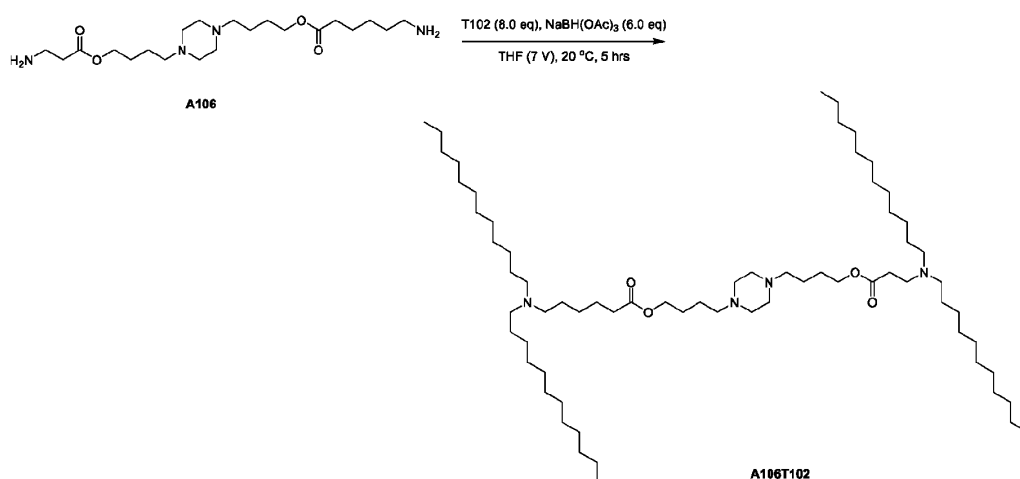
Example A106T101



[0601] Charged compound **A106** (1.00 g, 2.41 mmol, 1.00 eq) in THF (10.0 mL). Added compound **T101** (3.02 g, 19.3 mmol, 3.64 mL, 8.00 eq) and NaBH(OAc)₃ (3.07 g, 14.4 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 5 h. LCMS (R_f = 1.8 min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 250*50mm*10um; mobile phase: [H₂O(0.05% HCl)-ACN: THF=1:1]; gradient: 20%-60% B over 20.0 min). The residue was purified

by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 30/1 to 0/1). **A106T101** (4-(4-(4-((3-(didecylamino)propanoyl)oxy)butyl)piperazin-1-yl)butyl 6-(didecylamino)hexanoate, 0.60 g, 614 μmol, 66.6% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.08 (t, J = 6.4 Hz, 4H), 2.78 (br t, J = 7.4 Hz, 2H), 2.33-2.48 (m, 20H), 1.40-1.68 (m, 22H), 1.23-1.35 (m, 62H), 0.89 (t, J = 6.8 Hz, 12H).

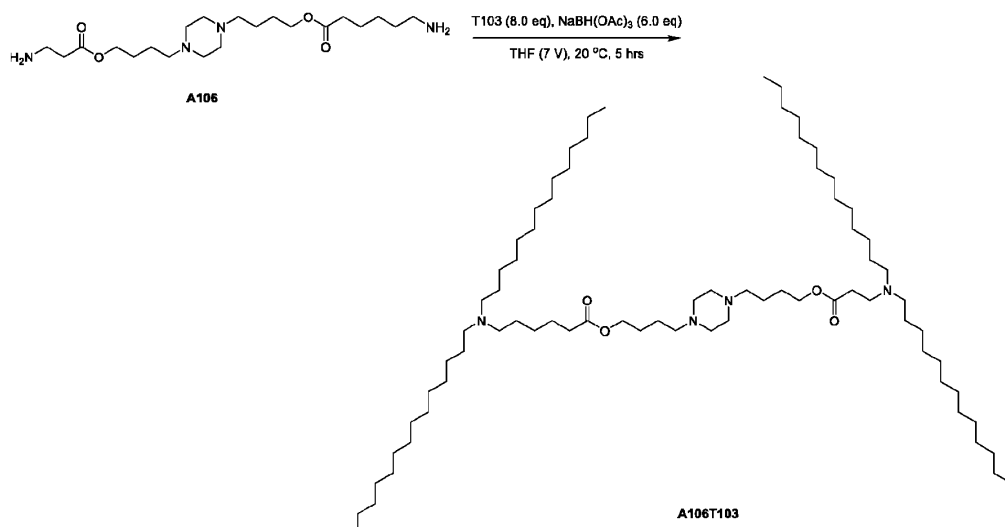
Example A106T102



[0602] Charged compound **A106** (1.00 g, 2.41 mmol, 1.00 eq) in THF (10.0 mL). Added compound **T102** (3.56 g, 19.3 mmol, 8.00 eq) and NaBH(OAc)₃ (3.07 g, 14.4 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 5 h. LCMS (R_f = 2.1 min) indicated compound **A106** was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and was washed with saturated aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The residue was purified by prep-HPLC (column: Phenomenex Gemini C18 75*40mm*3um; mobile phase: [H₂O (0.05% NH₃H₂O)-ACN]; B%: %, isocratic elution mode). **A106T102** (4-(4-(4-((3-(didodecylamino)propanoyl)oxy)butyl)piperazin-1-yl)butyl 6-(didodecylamino)hexanoate, 0.70 g, 643 μmol, 26.9% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.08 (t, J = 6.4 Hz, 4H), 2.77 (t, J = 7.4 Hz, 2H), 2.26-2.59 (m, 26H), 1.52-1.69 (m, 11H), 1.37-1.47 (m,

12H), 1.27 (s, 71H), 0.89 (t, J = 6.8 Hz, 12H).

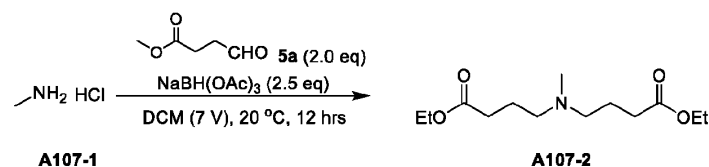
Example A106T103



[0603] Charged compound **A106** (1.20 g, 3.22 mmol, 1.00 eq) and compound **T103** (4.10 g, 19.3 mmol, 6.00 eq) in THF (20.0 mL). Stirred at 20 °C for 30 min. Added $\text{NaBH}(\text{OAc})_3$ (4.10 g, 19.3 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT=2.4 min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was filtered, and the filtrate was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na_2CO_3 , dried (Na_2SO_4) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: $[\text{H}_2\text{O} (0.05\%\text{HCl})\text{-THF: ACN}=1:3]$; gradient: 20%-70% B over 20.0 min). The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 30/1 to 0/1). Compound **A106T103** (4-(4-(4-((3-(ditetradecylamino)propanoyl)oxy)butyl)piperazin-1-yl)butyl 6-(ditetradecylamino)hexanoate, 0.70 g, 583 μmol , 70.0% yield) was obtained as a yellow oil. **¹H NMR**: 400 MHz, CDCl_3 δ 4.02-4.15 (m, 4H), 2.77 (br d, J = 7.2 Hz, 2H), 2.26-2.49 (m, 20H), 1.36-1.75 (m, 22H), 1.14-1.35 (m, 94H), 0.84-0.92 (m, 12H).

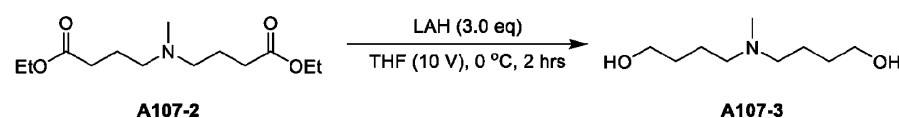
Example A107

Example A107.1



[0604] Charged compound **A107-1** (2.70 g, 39.9 mmol, 1.00 eq, HCl) in DCM (100 mL). Added compound **5a** (9.29 g, 79.9 mmol, 2.00 eq) into the mixture. Stirred at 20 °C for 30 min. Added NaBH(OAc)_3 (21.1 g, 99.9 mmol, 2.50 eq) into the mixture. Stirred at 20 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.36), LCMS (R_T = 0.105 min) and HNMR indicated compound **A107-1** was completely consumed and the product was detected. The reaction mixture was washed with saturated aqueous Na_2CO_3 . Added 1M HCl (50.0 mL) in the mixture, and the aqueous layer was adjusted to pH 8 with saturated aqueous Na_2CO_3 and extracted with DCM/IPA (3/1) (50.0 mL, 40.0 mL, 30.0 mL). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude product was used into the next step without further purification. Compound **A107-2** (4.40 g, 19.0 mmol, 47.5% yield) was obtained as a colorless oil. $^1\text{H NMR}$: 400 MHz, CDCl_3 δ 3.66 (s, 6H), 2.31-2.36 (m, 8H), 2.18 (s, 3H), 1.73-1.80 (m, 5H).

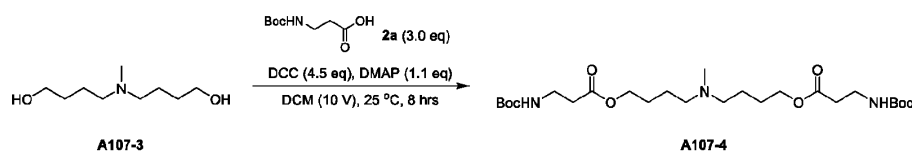
Example A107.2



[0605] Charged compound **A107-2** (4.40 g, 19.0 mmol, 1.00 eq) in THF (50.0 mL). Added LiAlH_4 (2.50 M, 22.8 mL, 3.00 eq) into the mixture at 0 °C. Stirred at 0 °C for 2 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0) and HNMR indicated Reactant 1 was completely consumed and the product was detected. Added H_2O (2.20 mL), 15% NaOH (2.20 mL), H_2O (6.60 mL) and Na_2SO_4 in the mixture at 0 °C. The mixture was filtered and the filtrate was concentrated to give crude product. The crude product was used into the next step without further purification. Compound **A107-3** (3.30 g, 18.8 mmol, 98.9% yield) was obtained as a colorless oil. $^1\text{H NMR}$: 400 MHz, CDCl_3 δ 5.90 - 6.41 (m, 2H), 3.49 - 3.65 (m, 4H), 2.19 - 2.96 (m, 11H),

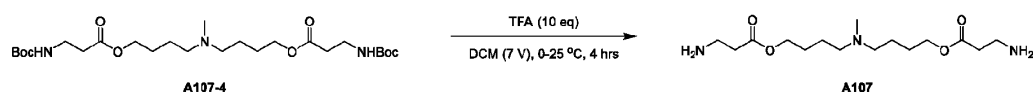
1.56 - 1.79 (m, 8H).

Example A107.3



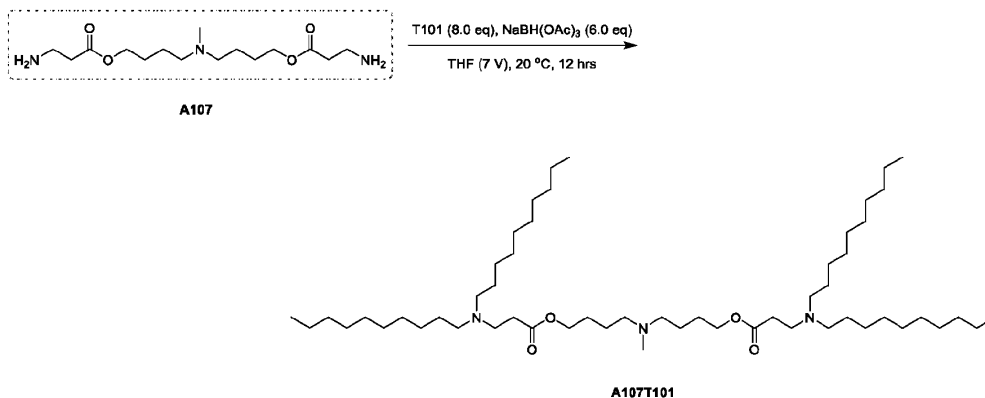
[0606] Charged compound **A107-3** (3.30 g, 18.8 mmol, 1.00 eq) in DCM (66.0 mL). Added compound **2a** (8.91 g, 47.0 mmol, 2.50 eq), DCC (17.4 g, 84.7 mmol, 17.1 mL, 4.50 eq) and DMAP (2.53 g, 20.7 mmol, 1.10 eq) at 0 °C. The mixture was stirred at 25 °C for 12 h. TLC (Dichloromethane: Methanol = 10:1, R_f = 0.27) LCMS (RT = 1.499 min) and HNMR indicated compound **A107-3** was completely consumed and the product was detected. The mixture was filtered and the filtrate was concentrated to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 80/1 to 0/1). Compound **A107-4** (5.00 g, 9.66 mmol, 51.3% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.96-5.15 (m, 2H), 4.09 - 4.14 (m, 4H), 3.40 (q, J = 5.6 Hz, 4H), 2.53 (t, J = 6.0 Hz, 4H), 2.36 (t, J = 7.2 Hz, 4H), 2.21 (s, 3H), 1.61-1.71 (m, 4H), 1.51-1.56 (m, 4H), 1.44 (s, 18H).

Example A107.4



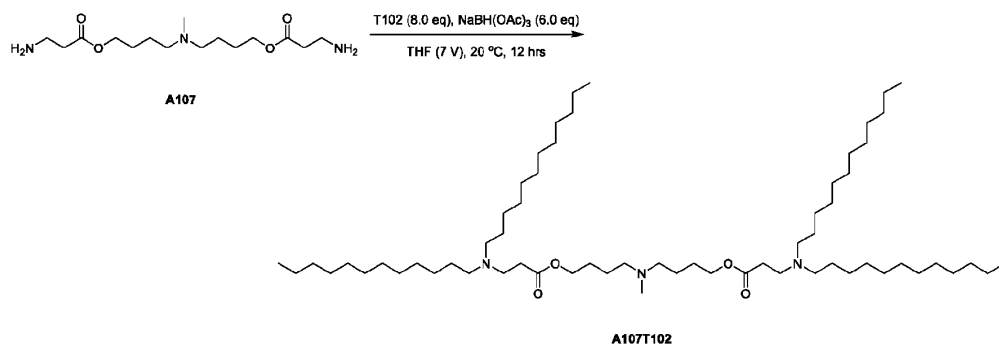
[0607] Charged compound **A107-4** (3.57 g, 6.90 mmol, 1.00 eq) in DCM (25.0 mL). Added TFA (7.86 g, 68.9 mmol, 5.12 mL, 10.0 eq) into the mixture at 0 °C. Stirred at 20 °C for 5 h. TLC (Dichloromethane: Methanol = 5:1, R_f = 0) and HNMR indicated compound **A107-4** was completely consumed and the product was detected. The mixture was evaporated to afford the crude product. The crude product was used into the next step without further purification. Compound **A107** (2.10 g, 6.62 mmol, 95.9% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, DMSO δ 7.91 (br s, 6H), 4.08 (t, J = 6.1 Hz, 4H), 2.98-3.15 (m, 8H), 2.74 (d, J = 4.6 Hz, 3H), 2.66 (t, J = 7.0 Hz, 4H), 1.66 (dt, J = 17.6, 5.4 Hz, 8H).

Example A107T101



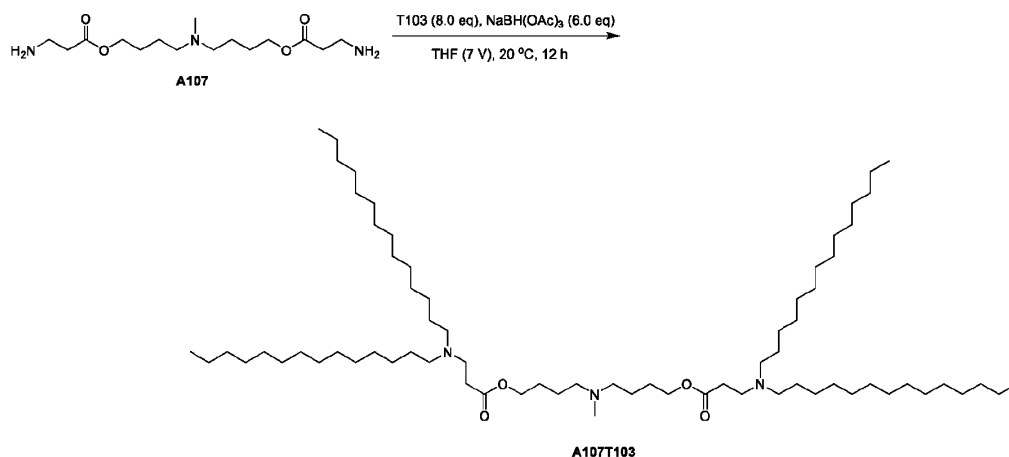
[0608] Charged compound **A107** (700 mg, 2.21 mmol, 1.00 eq) in THF (10.0 mL). Added compound **T101** (2.76 g, 17.6 mmol, 3.33 mL, 8.00 eq) and $\text{NaBH}(\text{OAc})_3$ (2.80 g, 13.23 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS ($\text{RT} = 1.918$ min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na_2CO_3 , dried (Na_2SO_4) and evaporated to dryness. The crude product was used into the next step without further purification. **A107T101** ((methylazanediyl)bis(butane-4,1-diyl) bis(3-(didecylamino)propanoate), 1.90 g, 2.16 mmol, 98.0% yield) was obtained as a yellow oil. **^1H NMR**: 400 MHz, CDCl_3 δ 4.08 (t, $J = 6.6$ Hz, 4H), 2.78 (t, $J = 7.4$ Hz, 4H), 2.39 (tt, $J = 18.2, 7.4$ Hz, 15H), 2.20 (s, 3H), 1.60–1.70 (m, 4H), 1.48–1.57 (m, 4H), 1.38–1.46 (m, 8H), 1.27 (s, 54H), 0.89 (t, $J = 6.8$ Hz, 12H).

Example A107T102



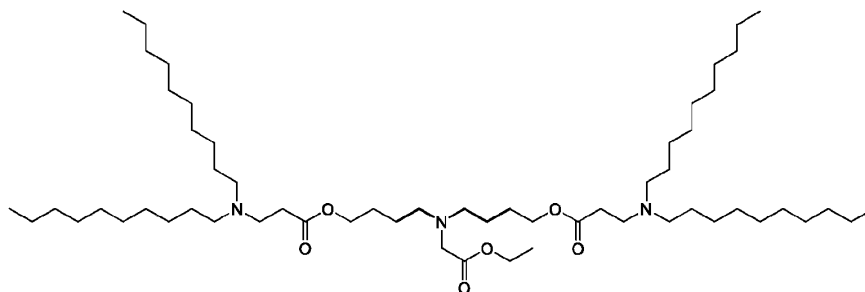
[0609] Charged compound **A107** (700 mg, 2.21 mmol, 1.00 eq) in THF (10.0 mL). Added compound **T102** (3.25 g, 17.6 mmol, 8.00 eq) and $\text{NaBH}(\text{OAc})_3$ (2.80 g, 13.2 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT = 2.2 min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na_2CO_3 , dried (Na_2SO_4) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: $[\text{H}_2\text{O}$ (0.05% HCl)-THF: ACN=1:3]; gradient:20%-65% B over 20.0 min). **A107T102** ((methylazanediy)bis(butane-4,1-diyl) bis(3-(didodecylamino)propanoate), 800 mg, 807 μmol , 38.1% yield) was obtained as a yellow oil. ^1H NMR: 400 MHz, CDCl_3 δ 4.08 (t, J = 6.8 Hz, 4H), 2.78 (t, J = 7.2 Hz, 4H), 2.39 (tt, J = 18.2, 7.4 Hz, 16H), 2.20 (s, 3H), 1.63-1.65 (m, 4H), 1.52-1.54 (m, 5H), 1.42 (m, 9H), 1.28 (s, 78H), 0.89 (t, J = 6.8 Hz, 12H).

Example A107T103



[0610] Charged compound **A107** (700 mg, 2.21 mmol, 1.00 eq) in THF (10.0 mL). Added compound **T103** (3.75 g, 17.6 mmol, 8.00 eq) and NaBH(OAc)₃ (2.80 g, 13.2 mmol, 6.00 eq) into the mixture. Stirred at 20 °C for 12 h. LCMS (RT=2.5 min) indicated Reactant 1 was completely consumed and the product was detected. The mixture was concentrated to give crude product. Charged the crude product in DCM (15.0 mL), and washed with saturated aqueous Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The residue was purified by prep-HPLC (column: Welch Xtimate C1 100*30mm*5um; mobile phase: [H₂O (0.04% HCl)-THF: ACN=1:3]; gradient: 25%-75% B over 20.0 min). **A107T103** ((methylazanediy)bis(butane-4,1-diyl) bis(3-(ditetradecylamino)propanoate), 900 mg, 816 μmol, 37.5% yield) was obtained as a yellow oil. ¹H NMR: 400 MHz, CDCl₃ δ 4.01 (t, J = 6.6 Hz, 4H), 2.70 (br d, J = 6.2 Hz, 4H), 2.22-2.43 (m, 16H), 2.13 (s, 3H), 1.52-1.63 (m, 5H), 1.42-1.50 (m, 4H), 1.35 (br d, J = 3.2 Hz, 8H), 1.19 (s, 87H), 0.81 (t, J = 6.8 Hz, 12H).

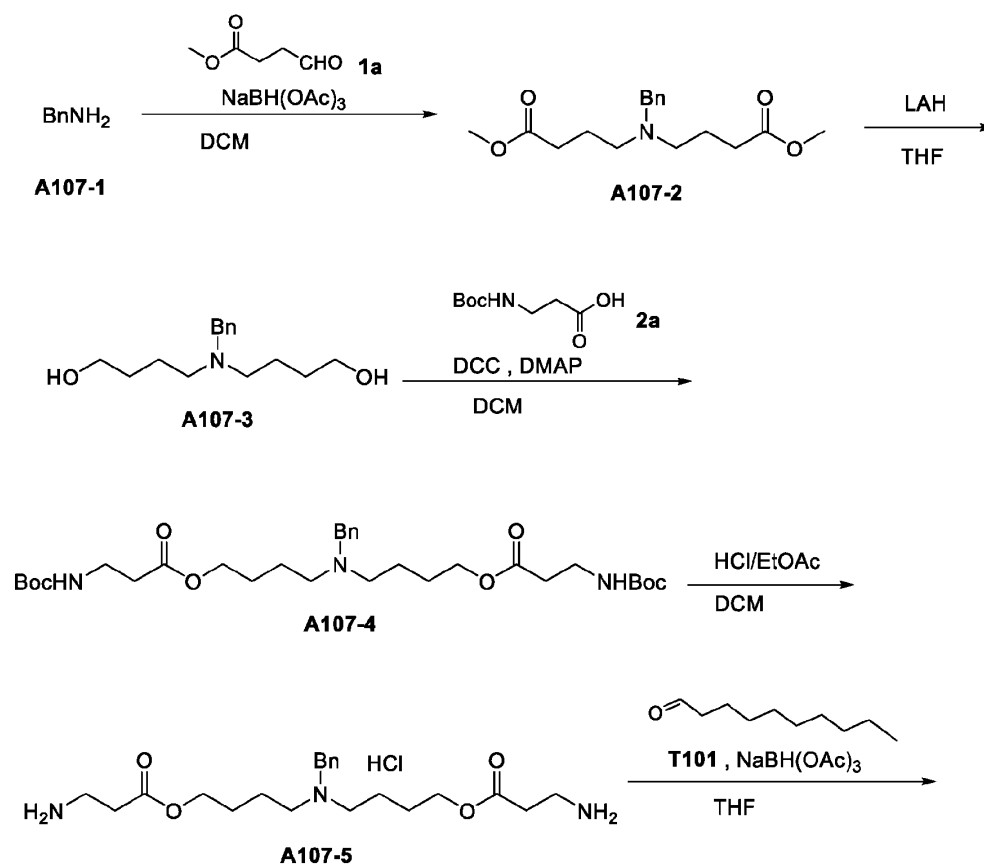
Example A109T101

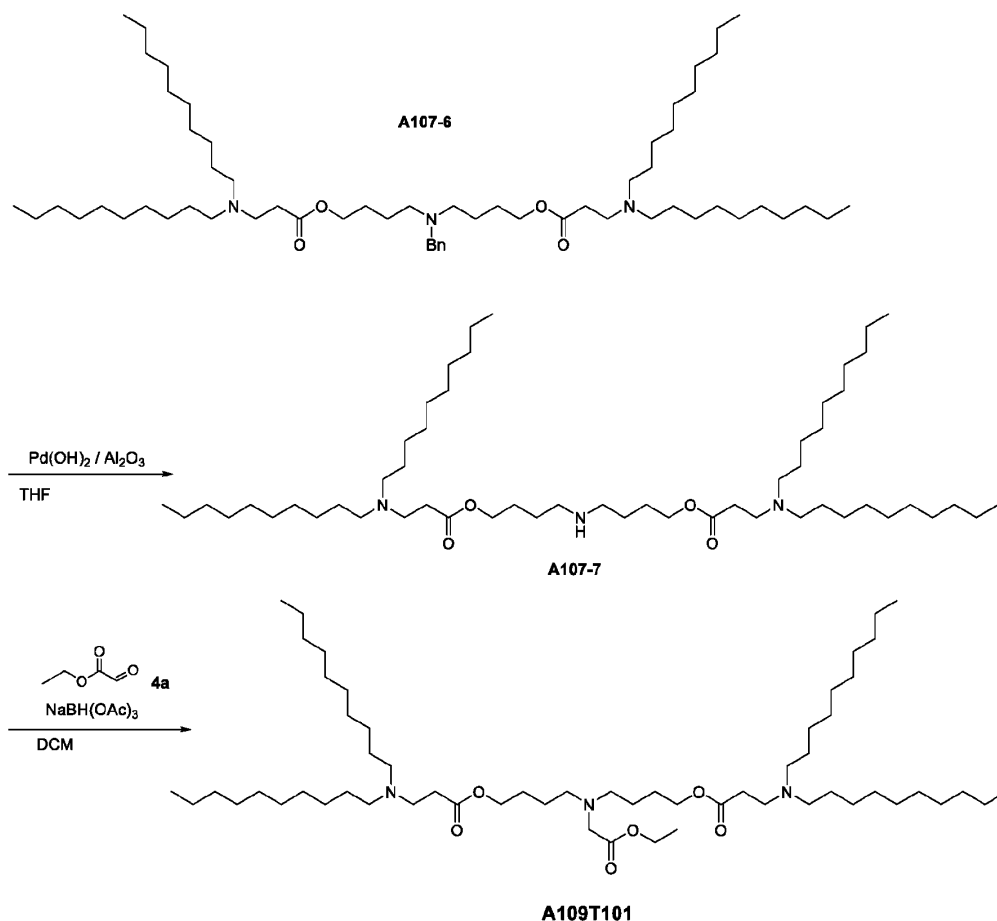


A109T101

((2-ethoxy-2-oxoethyl)azanediyl)bis(butane-4,1-diyl) bis(3-(didecylamino)propanoate)

[0611] This compound preparation, and that of some intermediates used in the same, were made as follows:





[0612] To a solution of compound **A107-1** (2.31 g, 21.5 mmol, 2.35 mL, 1.0 *eq*) and compound **1a** (5.00 g, 43.1 mmol, 2.0 *eq*) in DCM (100 mL) was added NaBH(OAc)₃ (11.4 g, 53.8 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 12h. LC-MS showed compound **A107-1** was consumed completely and desired mass was detected. The pH of the reaction solution was adjusted to 9 with sodium carbonate. Then to the mixture was added 100 mL water, the aqueous phase was extracted with DCM (100 mL ×3). The combined organic phase was washed with brine (100 mL ×3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (column: Welch Ultimate XB-CN 250*50*10um; mobile phase: [Hexane-EtOH (0.1% NH₃·H₂O)]; gradient: 1%-15% B over 10 min). Compound **A107-2** (3.90 g, 12.7 mmol, 58.9% yield) was obtained as a white solid which

was confirmed by HNMR. LCMS: R_t = 0.209 min. ^1H NMR (400 MHz, CDCl_3): δ = 7.23 - 7.30 (m, 5H), 3.65 (s, 6H), 3.54 (s, 2H), 2.43 (br t, J = 6.8 Hz, 4H), 2.33 (t, J = 7.4 Hz, 4H), 1.78 (br t, J = 7.1 Hz, 4H).

[0613] To a solution of compound **A107-2** (4.10 g, 13.3 mmol, 1.0 *eq*) in THF (40 mL) was added dropwise LiAlH_4 (2.5 M, 10.67 mL, 2.0 *eq*) at 0 °C over 5 min. The resulting mixture was stirred at 0 °C for 115 min. LC-MS showed that compound **A107-2** was consumed completely and the desired mass was detected. Dilute with appropriate amount of THF and cool to 0 °C, slowly added 1 mL water, 1 mL sodium hydroxide solution of 15% and 3 mL water, warmed to room temperature and stirred for 15 minutes. The reaction was added some anhydrous Na_2SO_4 , stirred for 15 minutes, filter and remove salt. Compound **A107-3** (3.20 g, 12.7 mmol, 95.4% yield) was obtained as a white solid which was confirmed by HNMR. LCMS: R_t = 0.146 min.

[0614] ^1H NMR (400 MHz, CDCl_3): δ = 7.19 - 7.26 (m, 5H), 4.17 - 4.29 (m, 2H), 3.50 - 3.54 (m, 6H), 2.39 (t, J = 6.4 Hz, 4H), 1.54 - 1.59 (m, 4H), 1.48 - 1.52 (m, 4H).

[0615] To a solution of compound **A107-3** (3.02 g, 12.7 mmol, 1.0 *eq*) in DCM (80 mL) was added compound **2a** (5.06 g, 26.73 mmol, 2.1 *eq*), DCC (10.5 g, 50.9 mmol, 10.3 mL, 4 *eq*) and DMAP (1.56 g, 12.7 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 8 h. LC-MS showed compound **A107-3** was consumed completely and the desired mass was detected. The reaction mixture was filtered and filtered liquid was co-evaporated to remove the DCM under reduced pressure to give product. The residue was purified by flash silica gel chromatography (column: Welch Ultimate XB-CN 250*50*10um; mobile phase: [Hexane-EtOH(0.1%IPAm)]; gradient: 1%-40% B over 15 min). Compound **A107-4** (7.00 g, 11.6 mmol, 91.6% yield, 99% purity) was obtained as a colorless oil which was confirmed by HNMR. LCMS: R_t = 0.359 min.

[0616] ^1H NMR (400 MHz, CDCl_3): δ = 7.27 - 7.30 (m, 5H), 5.04 (br s, 2H), 4.05 (t, J = 6.6 Hz, 4H), 3.53 (s, 2H), 3.38 (br d, J = 5.9 Hz, 4H), 2.50 (t, J = 6.0 Hz, 4H), 2.42 (s, 4H), 1.62 (br d, J = 8.3 Hz, 4H), 1.51 (br s, 4H), 1.44 (s, 18H).

[0617] To a solution of compound **A107-4** (3.50 g, 5.89 mmol, 1.0 *eq*) in HCl/EtOAc (2 M, 23.58 mL, 8 *eq*). The mixture was stirred at 25 °C for 3h. LC-MS showed compound **A107-4** was consumed completely and the desired mass was detected. The reaction mixture was co-

evaporated under reduced pressure to give residue. Compound **A107-5** (5.00 g, 11.6 mmol, 98.6% yield, HCl) was obtained as a white solid. LCMS: R_t = 0.090 min.

[0618] To a solution of compound **A107-5** (2.50 g, 5.81 mmol, 1.0 *eq*, HCl) in DCM (80 mL) was added NMM (588 mg, 5.81 mmol, 639 μ L, 1.0 *eq*). After addition, the mixture was stirred at this temperature for 15 min and then compound **T101** (5.45 g, 34.89 mmol, 6.58 mL, 6.0 *eq*), AcOH (349 mg, 5.81 mmol, 332 μ L, 1.0 *eq*), NaBH(OAc)₃ (7.39 g, 34.8 mmol, 6.0 *eq*) was added at 25°C. The mixture was stirred at 25 °C for 105 min. LC-MS showed compound **A107-5** was consumed completely and desired mass was detected. The pH of the reaction solution was adjusted to 9 with saturated sodium carbonate solution. The reaction mixture was added 100 mL water. The aqueous phase was extracted with DCM (80 mL $\times$ 3). The combined organic phase was washed with brine (50 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: C1 250 $\times$ 80mm, 10 μ m; mobile phase: [water (TFA)-ACN]; gradient: 35%-65% B over 25 min). Compound **A107-6** (3 g, 3.14 mmol, 54.05% yield) was obtained as a white solid which was confirmed by HNMR. LCMS: R_t = 0.495 min. ¹H NMR (400 MHz, CDCl₃):

[0619] δ = 7.30 (d, J = 4.4 Hz, 4H), 7.22 - 7.26 (m, 1H), 4.03 (t, J = 6.5 Hz, 4H), 3.63 - 3.66 (m, 4H), 3.54 (s, 2H), 2.79 (br s, 2H), 2.41 - 2.44 (m, 14H), 1.58 (br d, J = 6.9 Hz, 4H), 1.43 (m, 4H), 1.27 (m, 64H), 0.89 (m, 12H).

[0620] Compound **A107-6** (3.0 g, 3.14 mmol, 1.0 *eq*) was dissolved in THF (75 mL). The solution was added Pd(OH₂)/Al₂O₃ (3.14 mmol, 5% purity), then degassed and purged with H₂ (633.51 μ g, 314.27 μ mol, 0.1 *eq*) for 3 times. The solution was stirred under 2.5 Mpa at 60 °C for 7 h. LC-MS showed that compound **A107-6** was consumed completely and the desired mass was detected. The reaction mixture was co-evaporated under reduced pressure to give residue. Compound **A107-7** (2.5 g, crude) was obtained as a colorless oil. LCMS: R_t = 0.496 min.

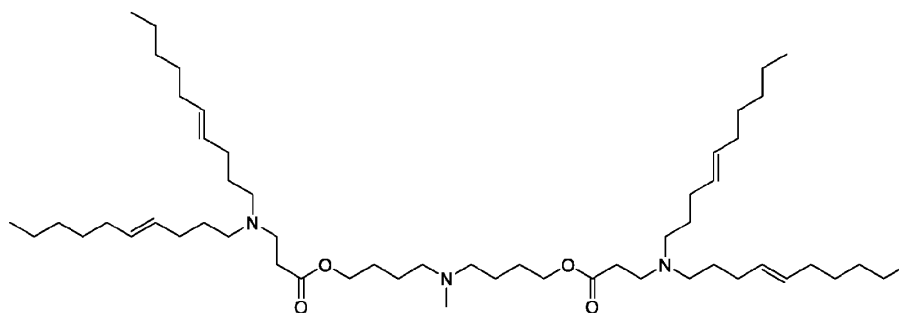
[0621] To a solution compound **4a** (519 mg, 2.54 mmol, 1.1 *eq*) and compound **A107-7** (2 g, 2.31 mmol, 1 *eq*) and in DCM (24 mL) was added NaBH(OAc)₃ (980.69 mg, 4.63 mmol, 2.0 *eq*). The mixture was stirred at 25°C for 1h. LC-MS showed that compound **A107-7** was consumed completely and the desired mass was detected. The reaction mixture was added 40 mL water, the aqueous phase was extracted with DCM (30 mL $\times$ 3). The combined organic phase was washed with brine (20 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and

concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10um; mobile phase: [water (TFA)-ACN];gradient:40%-70% B over 10 min). CAD showed that the compound purity was 95.58%. Compound **A109T101** (800 mg, 841.62 μ mol, 36.38% yield) was obtained as a yellow oil which was confirmed by HNMR.

[0622] LCMS: product: RT = 0.491 min. CAD product: RT = 6.351 min.

[0623] ^1H NMR (400 MHz, CDCl_3): δ = 4.17 (d, J = 7.3 Hz, 2H), 4.08 (t, J = 6.6 Hz, 4H), 3.33 (s, 2H), 2.79 (br s, 4H), 2.60 (t, J = 7.3 Hz, 4H), 2.41 (br s, 12H), 1.62 - 1.68 (m, 4H), 1.51 (br d, J = 6.6 Hz, 3H), 1.43 - 1.48 (m, 8H), 1.26 - 1.30 (m, 60H), 0.87 - 0.90 (m, 12H).

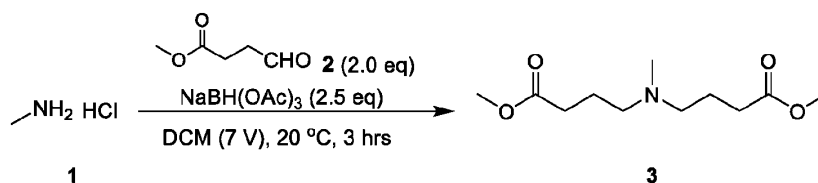
Example A107T104



A107T104

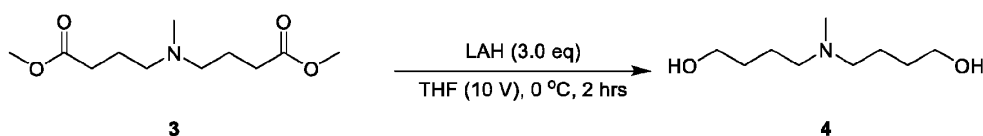
(methylazanediy1)bis(butane-4,1-diyl) bis(3-(di((E)-dec-4-en-1-yl)amino)propanoate)

[0624] This compound preparation, and that of some intermediates used in the same, were made as follows:

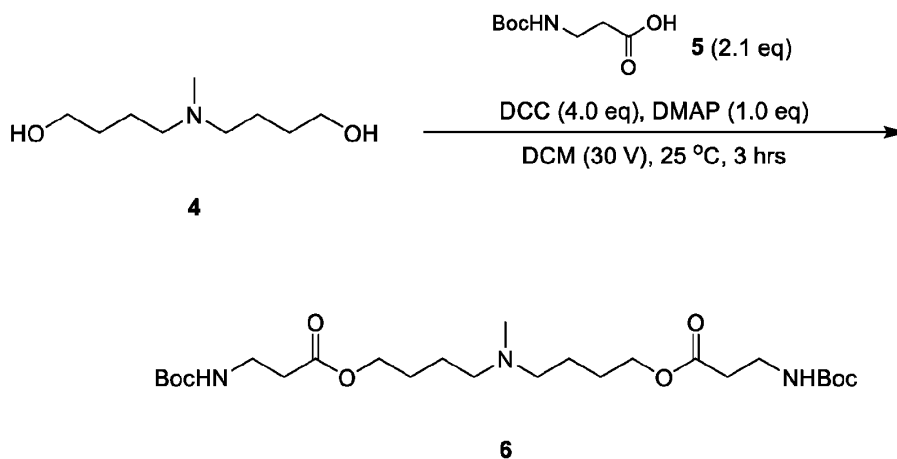


[0625] To a solution of **1** (290 mg, 4.31 mmol, 1.0 *eq*) and compound **2** (1.00 g, 8.61 mmol, 2.0 *eq*) in DCM (13 mL) was added $\text{NaBH}(\text{OAc})_3$ (2.28 g, 10.7 mmol, 2.5 *eq*). The mixture was stirred at 25 °C for 3 h. LC-MS showed Reactant **1** was consumed completely and desired mass was detected. Adjust the pH of the reaction solution to 8 with saturated sodium

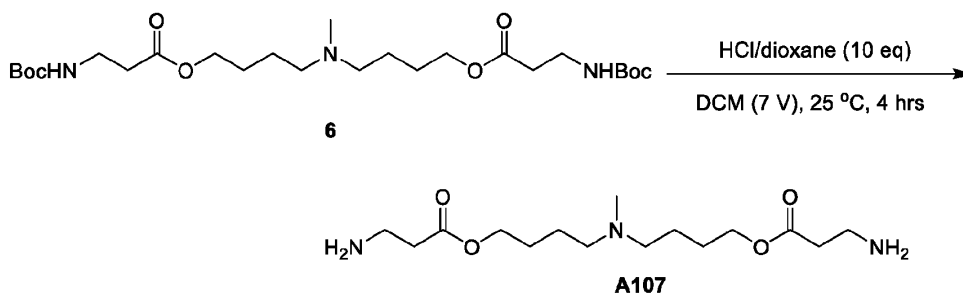
carbonate solution. The reaction mixture was added 40 mL water, the aqueous phase was extracted with DCM (20 mL $\times$ 3). The combined organic phase was washed with brine (20 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, DCM: MeOH= 10:1). Compound **3** (850 mg, 3.01 mmol, 69.9% yield, 82% purity) was obtained as a colorless oil, which was confirmed by ¹H NMR (400 MHz, CDCl₃): δ = 3.67 (s, 6H), 2.41 (t, J = 7.3 Hz, 4H), 2.35 (t, J = 7.4 Hz, 4H), 2.23 (s, 3H), 1.80 (t, J = 7.3 Hz, 4H).



[0626] To a solution of compound **3** (850 mg, 3.68 mmol, 1.0 *eq*) in THF (8.5 mL) was added dropwise LiAlH₄ (2.5 M, 2.94 mL, 2.0 *eq*) at 0 °C over 5 min. The resulting mixture was stirred at 0 °C for 115 min. LC-MS showed Reactant 1 was consumed completely and desired mass was detected. The reaction was diluted with 5 mL THF and cooled to 0 °C, then 0.2 mL water, 0.2 mL 15% NaOH solution, 0.6 mL water was added slowly. Then the reaction was heated to room temperature and stirred for 15 min., some anhydrous Na₂SO₄ was added and stirred for 15 min. Compound **4** (500 mg, 2.85 mmol, 77.6% yield) was obtained as a colorless oil, which was confirmed by HNMR. LCMS R_t = 0.071 min. ¹H NMR (400 MHz, CDCl₃): δ = 3.72 - 3.77 (m, 2H), 3.60 (t, J = 5.4 Hz, 4H), 2.37 - 2.44m, 4H), 2.24 (s, 3H), 1.59 - 1.67 (m, 8H).

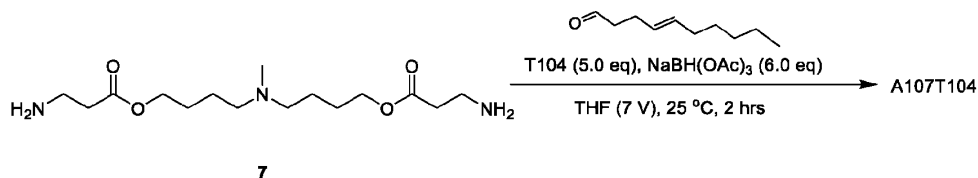


[0627] To a solution of **4** (500 mg, 2.85 mmol, 1.0 *eq*) and compound **5** (1.13 g, 5.99 mmol, 2.1 *eq*) in DCM (15 mL) was added DCC (2.35 g, 11.4 mmol, 2.31 mL, 4.0 *eq*) and DMAP (348 mg, 2.85 mmol, 1.0 *eq*). The mixture was stirred at 25 °C for 3 hrs. LC-MS showed Reactant 1 was consumed completely and desired mass was detected. The reaction mixture was filtered and the filtrate was co-evaporated under reduced pressure to give product. The residue was purified by column chromatography (SiO₂, DCM: MeOH=10:1). Compound **6** (320 mg, 618 μmol, 21.7% yield) was obtained as a colorless oil, which was confirmed by HNMR. LCMS RT = 0.313 min. ¹H NMR (400 MHz, CDCl₃): δ = 5.04 (brs, 2H), 4.11 (t, *J* = 6.6 Hz, 4H), 3.39 (br s, 4H), 2.52 (t, *J* = 6.0 Hz, 4H), 2.27 - 2.44 (m, 4H), 2.22 (s, 3H), 1.62 - 1.70 (m, 4H), 1.53 (td, *J* = 7.4, 14.4Hz, 4H), 1.44 (s, 18H).



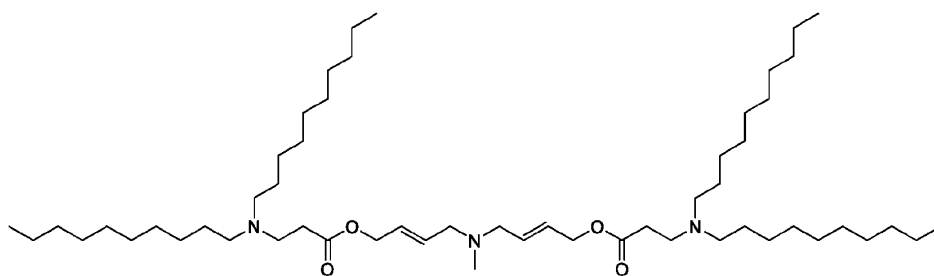
[0628] To a solution of compound **6** (320 mg, 618 μmol, 1.0 *eq*) was added HCl/EtOAc (2 M, 10.0 mL, 32.3 *eq*). The mixture was stirred at 25 °C for 4 h. LC-MS showed Reactant 1 was consumed completely and the desired mass was detected. The reaction mixture was co-evaporated

under reduced pressure to give residue. Compound A107 (218 mg, 616 μ mol, 99.7% yield, HCl) was obtained as a white solid. LCMS R_t = 0.066 min.



[0629] To a solution of compound **7** (218 mg, 616 μ mol, 1.0 *eq*, HCl) and T104 (475 mg, 3.08 mmol, 5.0 *eq*) in DCM (7 mL) was added NaBH(OAc)₃ (783 mg, 3.70 mmol, 6.0 *eq*). The mixture was stirred at 25 °C for 2 h. LC-MS showed Reactant 1 was consumed completely and the desired mass was detected. The reaction mixture was added 20 mL water, the aqueous phase was extracted with DCM (20 mL $\times$ 3). The combined organic phase was washed with brine (20 mL $\times$ 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by reversed-phase HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10 μ m; mobile phase: [water (TFA)-ACN]; gradient: 38%-68% B over 10 min). CAD showed the compound purity was 98%. Compound A107T104 (170 mg, 191.50 μ mol, 31.09% yield, 98.05% purity) was obtained as a yellow oil, which was confirmed by HNMR. LCMS product: R_t = 0.470 min. CAD product: R_t = 12.932 min. ¹H NMR (400 MHz, CDCl₃): δ = 5.57 - 5.18 (m, 8H), 4.07 (br s, 4H), 3.46 - 3.33 (m, 7H), 3.07 (s, 20H), 1.97 (dt, J = 6.5, 12.4 Hz, 16H), 1.48 (quin, J = 6.9 Hz, 8H), 1.44 - 1.10 (m, 28H), 0.87 (br t, J = 6.5 Hz, 12H).

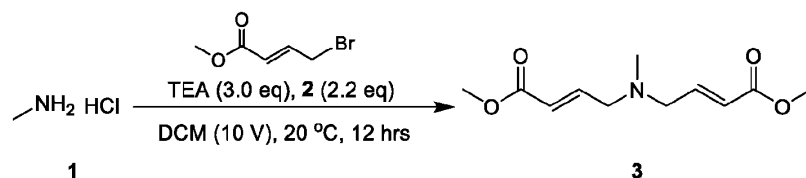
Example A110T101



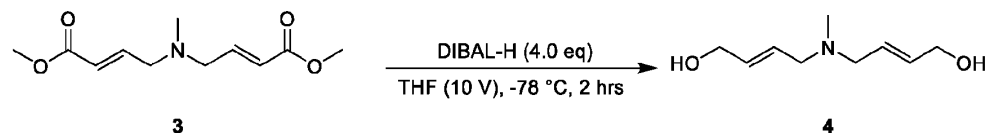
A110T101

(2*E*,2'*E*)-(methylazanediyl)bis(but-2-ene-4,1-diyl) bis(3-(didecylamino)propanoate)

[0630] This compound preparation, and that of some intermediates used in the same, were made as follows:

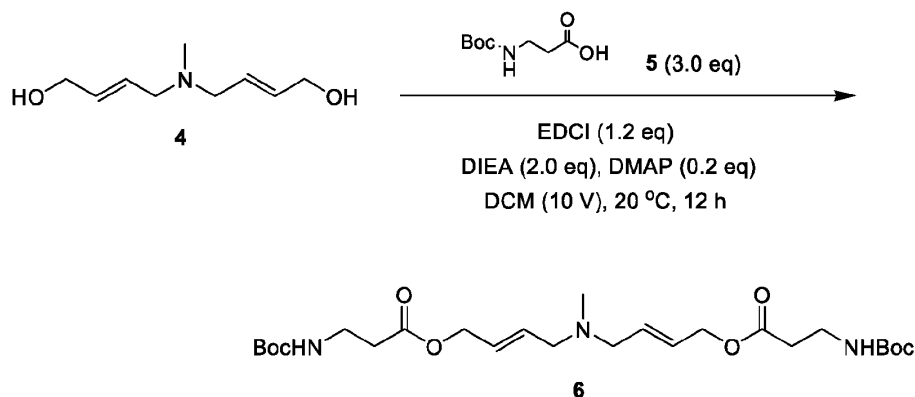


[0631] To a solution of compound **1** (2.20 g, 32.5 mmol, 1.0 eq) in DCM (30 mL) was added TEA (9.89 g, 97.7 mmol, 13.6 mL, 3.0 eq) and compound **2** (12.8 g, 71.6 mmol, 8.43 mL, 2.2 eq) at 0 °C. The mixture was stirred at 20 °C for 12 h. LC-MS showed compound **1** was consumed completely and one main peak with the desired mass was detected. The residue was diluted with water 30 mL and extracted with dichloromethane 30 mL (30 mL * 3). The combined organic layers was washed with brine 30 mL (30 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 70 mL/min). Compound **3** (1.10 g, 4.84 mmol, 14.8% yield) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.95 (td, J = 6.4, 15.7 Hz, 2H), 6.02 (td, J = 1.6, 15.6 Hz, 2H), 3.75 (s, 6H), 3.17 (br d, J = 5.2 Hz, 4H), 2.27 (s, 3H).

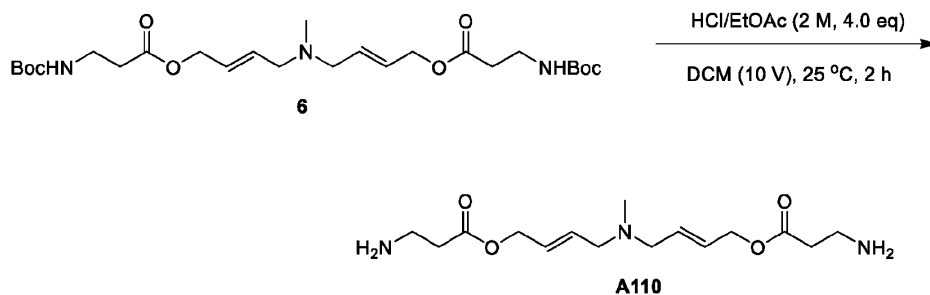


[0632] A mixture of compound **3** (1.40 g, 6.16 mmol, 1.0 eq) in THF (14 mL) was degassed and purged with N_2 for 3 times. The mixture was cooled to -78 °C. The DIBAL-H (1 M, 24.64 mL, 4.0 eq) was added slowly. The mixture was stirred at -78 °C for 2h under N_2 . TLC (Petroleum ether: Ethyl acetate=1:1, R_f = 0.0) indicated compound **3** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction was quenched by adding excess $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (35 g) and stirred for 20 min. The reaction mixture was filtered and the filtrate was concentrated. Compound **4** (660 mg, 3.85 mmol, 62.5% yield) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 5.54 - 5.67 (m, 4H), 4.65 (t, J = 5.6 Hz, 2H),

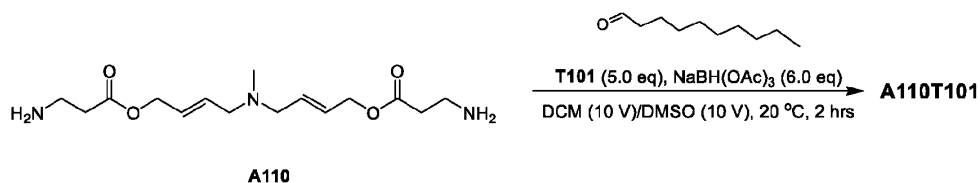
3.91 (br t, $J = 4.8$ Hz, 4H), 2.89 (br d, $J = 6.0$ Hz, 4H), 2.07 (s, 3H).



[0633] To a solution of compound **5** (2.19 g, 11.5 mmol, 3.0 *eq*) in DCM (10 mL) was added DIEA (996 mg, 7.71 mmol, 1.34 mL, 2.0 *eq*), EDCI (886 mg, 4.63 mmol, 1.2 *eq*) and DMAP (94.2 mg, 770 μ mol, 0.2 *eq*). The mixture was stirred at 20 °C for 0.5 hrs. Compound **4** (660 mg, 3.85 mmol, 1.0 *eq*) was added. The mixture was stirred at 20 °C for 11.5 h. LC-MS showed Compound **4** was consumed completely and the desired mass was detected. The residue was diluted with water 30 mL and extracted with dichloromethane 30 mL (30 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 50 mL/min). Compound **6** (450 mg, 876 μ mol, 22.7% yield) was obtained as a yellow oil. LCMS product: RT = 0.308 min. ^1H NMR (400 MHz, CDCl_3): δ = 5.73 - 5.85 (m, 4H), 5.02 (br d, $J = 3.2$ Hz, 1H), 4.60 (br d, $J = 5.6$ Hz, 4H), 3.41 (br d, $J = 5.6$ Hz, 4H), 3.04 (br s, 3H), 2.55 (br t, $J = 6.0$ Hz, 4H), 2.24 (br s, 2H), 1.56 (br d, $J = 10.0$ Hz, 3H), 1.45 (s, 18H).

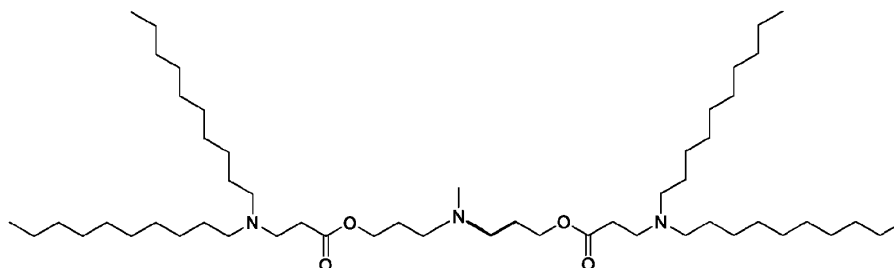


[0634] To a solution of compound **6** (750 mg, 1.46 mmol, 1.0 *eq*) in DCM (7 mL) was added HCl/EtOAc (2 M, 2.92 mL, 4.0 *eq*). The mixture was stirred at 25 °C for 2 h. LC-MS showed compound **6** was consumed completely and the desired mass was detected. The reaction mixture concentrated. Compound **A110** (500 mg, crude, HCl) was obtained as a yellow solid. LCMS product: RT = 0.083 min.



[0635] To a solution of compound **A110** (500 mg, 1.43 mmol, 1.0 *eq*, HCl) and compound **T101** (1.12 g, 7.15 mmol, 1.35 mL, 5.0 *eq*) in DCM (5 mL) and DMSO (5 mL) was added NaBH(OAc)₃ (1.82 g, 8.58 mmol, 6.0 *eq*). The mixture was stirred at 20 °C for 2h. LC-MS showed compound **A110** was consumed completely and desired mass was detected. The residue was diluted with water 30 mL and extracted with dichloromethane 30 mL (30 mL * 3). The combined organic layers were washed with brine 30 mL (30 mL * 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Ultimate C1 250*70mm*10um; mobile phase: [water(TFA)-ACN]; gradient: 35%-65% B over 25 min). Compound A110T101 (200 mg, 221 μmol, 15.4% yield, 96.6% purity) was obtained as a light yellow oil. LCMS: product: RT = 0.486 min. CAD product: RT = 6.366 min. ¹H NMR (400 MHz, CDCl₃): δ = 5.70 - 5.82 (m, 4H), 4.57 (d, *J* = 5.6 Hz, 4H), 3.00 (d, *J* = 6.0 Hz, 4H), 2.81 (br s, 4H), 2.41 - 2.48 (m, 12H), 2.20 (s, 3H), 1.26-1.32 (m, 60H), 0.87 - 0.86 (m, 12H).

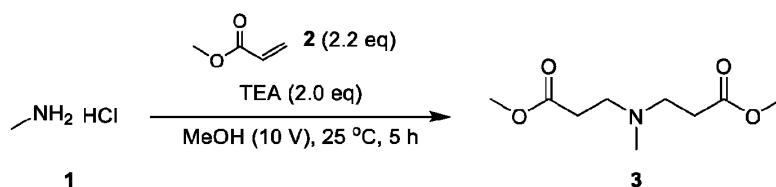
Example A108T101



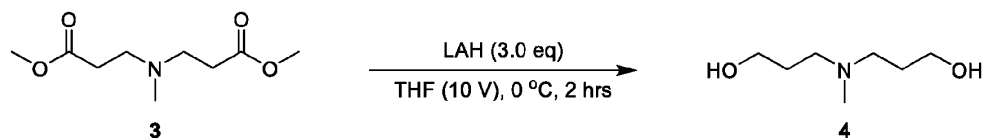
A108T101

methylazanediy)bis(propane-3,1-diyl) bis(3-(didecylamino)propanoate

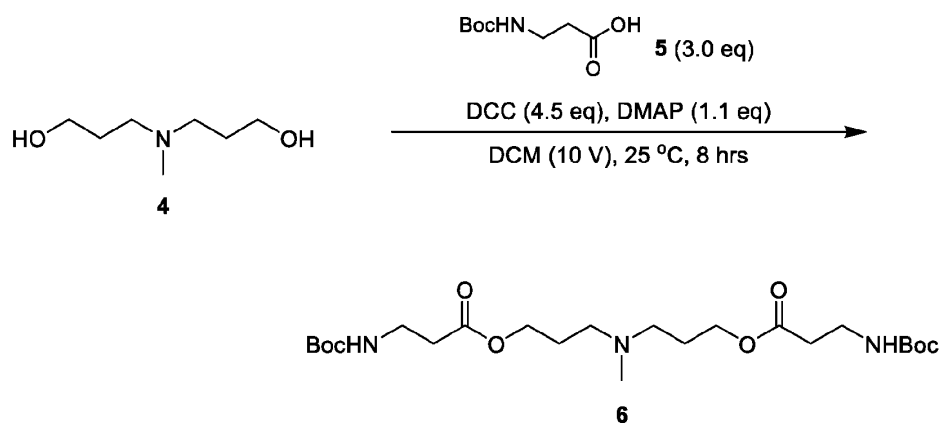
[0636] This compound preparation, and that of some intermediates used in the same, were made as follows:



[0637] To a solution of **1** (1.0 g, 14.8 mmol, 1.0 eq) in MeOH (10 mL) was added TEA (1.50 g, 14.8 mmol, 2.06 mL, 1.0 eq) at 25 °C before cooling the reaction to 0 °C. Then compound **2** (3.27 g, 37.9 mmol, 3.42 mL, 2.56 eq) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 5 h. LCMS showed that compound **3** (RT = 0.068 min, [M+H]⁺ = 204.1) was the main peak. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. Compound **3** (2.60 g, 12.63 mmol, 85.3% yield, 98.7% purity) was obtained as a yellow oil, which was confirmed by H NMR. The crude product was used for next step directly without purification. LCMS product: RT = 0.068 min. ¹H NMR (400 MHz, CDCl₃): δ 3.62 - 3.73 (m, 6H), 2.68 - 2.75 (m, 4H), 2.44 - 2.52 (m, 4H), 2.22 - 2.29 (m, 3H).

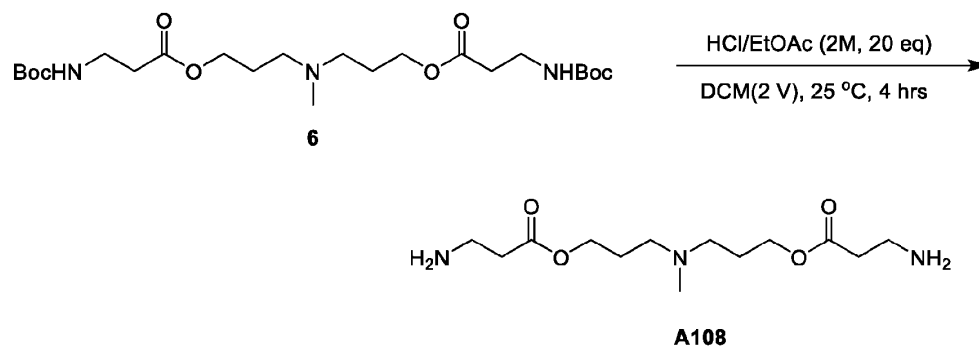


[0638] Compound **3** (2.6 g, 12.79 mmol, 1 eq) was added into THF (18 mL). The LiAlH₄ solution (2.5 M, 15.35 mL, 3.0 eq) was added dropwise into the mixture at 0 °C. Then the mixture was stirred at 0 °C for 2 h. TLC (DCM : MeOH=10:1) showed that compound **3** (R_f = 0.41) was consumed completely and one new major spot (R_f = 0.04) was detected. Then the reaction was diluted with THF (10 mL) and cooled to 0 °C. To this mixture was then successively added water (1.5 mL), 15% NaOH solution (1.5 mL) and water (4.5 mL) slowly. The reaction mixture was warmed to 20 °C and stirred for 15 mins, anhydrous Na₂SO₄ was added, and the mixture was stirred for 15 mins. Compound **4** (1.80 g, 12.1 mmol, 94.8% yield, 99.2% purity) was obtained as white solid, which was confirmed by H NMR. The crude product was used into the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 4.34 - 3.93 (m, 2H), 3.84 - 3.57 (m, 4H), 2.63 - 2.40 (m, 4H), 2.27 - 2.24 (m, 3H), 1.86 - 1.65 (m, 4H).

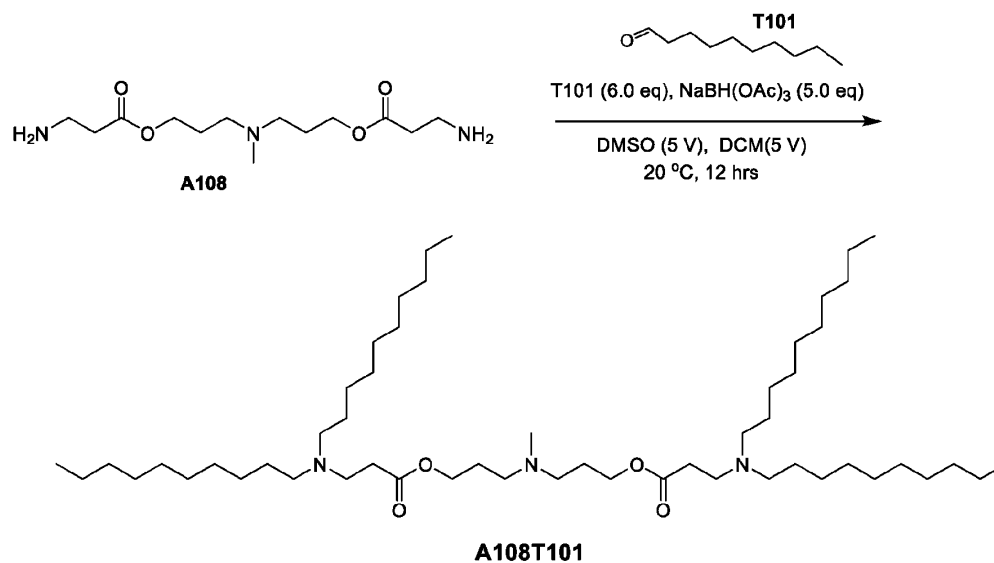


[0639] To a solution of **4** (500 mg, 3.40 mmol, 1.0 eq) and compound **5** (1.93 g, 10.1 mmol, 3.0 eq) in DCM (10 mL) was added DCC (3.15 g, 15.3 mmol, 3.09 mL, 4.5 eq) and DMAP (456 mg, 3.74 mmol, 1.1 eq) at 0 °C. Then the mixture was stirred at 20 °C for 12 h. LCMS showed the product (RT = 0.301 min, [M+H] = 490.2) was the main peak. The mixture was filtered and the filtrate was concentrated to give crude product. The residue was purified by normal phase-HPLC (column: Welch Ultimate XB-Diol 250 * 50 * 10 μm; mobile phase: [Hexane-EtOH (0.1% IPAm)]; gradient: 4%-34% B over 20 min). Compound **6** (1.0 g, 2.04 mmol, 30.1% yield, 100% purity) was obtained as a yellow oil, which was confirmed by H NMR. LCMS product: RT = 0.301 min. ¹H NMR (400 MHz, CDCl₃): δ 5.08 (br s, 2H), 4.15 (t, *J* = 6.5 Hz, 4H), 3.40 (q, *J* = 5.7 Hz, 4H), 2.53 (t, *J* = 6.0 Hz, 4H), 2.42 (br s, 3H), 2.23 (br s, 3H), 1.88 -

1.76 (m, 4H), 1.44 (s, 18H).



[0640] To a solution of **6** (500 mg, 1.02 mmol, 1.0 eq) in DCM (3 mL) was added HCl/EtOAc (2 M, 10.21 mL, 20 eq). The mixture was stirred at 25 °C for 4 h. LCMS showed the product (RT = 0.063 min, [M+1] = 290.2) was the main peak. The mixture was concentrated in vacuum to give **A108** (665 mg, crude, HCl) as a colorless oil, which was directly used into the next step without further purification. LCMS product: RT = 0.063 min.



[0641] To a solution of **A108** (665 mg, 2.04 mmol, 1.0 eq, HCl) in DMSO (2.0 mL) and DCM (2.0 mL) was added **T101** (1.91 g, 12.2 mmol, 2.31 mL, 6.0 eq). The mixture was stirred at 20 °C for 30 mins. Then NaBH(OAc)₃ (2.16 g, 10.2 mmol, 5.0 eq) was added into the mixture

and the mixture was stirred at 20 °C for 12 h. LCMS showed the product (RT=0.496 min, [M+H]=851.0) was the main peak. The mixture was poured into water (30 mL) and adjusted to pH = 9 with saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with DCM (30 mL × 2). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: CD12-ACCHROM phenyl-Hexyl 150*25*10um;mobile phase: [water(TFA)-ACN];gradient:30%-60% B over 15 min). The residue was further purified by prep-HPLC (column: Welch Ultimate C1 250*70mm*10um;mobile phase: [water(TFA)-ACN]; gradient:35%-65% B over 25 min). **A108T101** (800 mg, 936 μmol, 45.9% yield, 99.6% purity) was obtained as a yellow oil, which was confirmed by HNMR. LCMS product: RT = 0.496 min. CAD product: RT = 13.596 min.

[0642] ¹H NMR (400 MHz,CDCl₃): δ 4.11 (t, *J* = 6.4 Hz, 4H), 2.86 - 2.72 (m, 4H), 2.50 - 2.33 (m, 16H), 2.22 (s, 3H), 1.82 - 1.76 (m, 4H), 1.43 (br s, 8H), 1.27 (s, 56H), 0.89 (t, *J* = 6.8 Hz, 12H).

[0643] All possible combinations of the above-indicated embodiments of compounds of formula (G2) and their tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates are considered to be embraced within the scope of this application.

Compositions

[0644] In one aspect of the invention, compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof, are used in combination with a therapeutic agent (*e.g.*, polynucleotide, small molecule, protein, nucleic acids, peptide) to be delivered to a cell or a subject to form microparticles, nanoparticles, liposomes, or micelles. The recitation “compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof” refers, but is not limited, to at least one compound of any one of formulae (G1.1), (G1.2), (G2), mixtures of compounds of any one of such formulae, and mixtures of compounds of at least any two of such formulae, unless it is indicated explicitly that it is to be restricted in a specified way.

[0645] The agent to be delivered by the particles, liposomes, or micelles can be in the form of a gas, liquid, or solid, and the agent can be a polynucleotide (DNA such as dsDNA, pDNA, or RNA such as mRNA or siRNA), protein, peptide, or small molecule. The agents

include immunomodulatory agents such as immunostimulatory or immunoinhibitory agents, antigens, antibodies and antibody fragments such as antigen-binding antibody fragments, adjuvants, cytokines such as interleukins, anti-bacterial agents, anti-viral agents, anti-fungal agents, anti-parasitic agents, anti-cancer agents, anti-inflammatory agents. In some embodiments, the agent includes, but is not limited to plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme. Nucleic acids include naturally occurring, synthetic, and intentionally modified or altered polynucleotides. The compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof, can be combined with other lipid compounds, polymers (synthetic or natural), surfactants, cholesterol, carbohydrates, proteins, lipids, etc., to form the particles.

[0646] The particles comprising compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof as indicated above can optionally be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition. Examples of pharmaceutically acceptable carriers include a non-toxic (in the amount used) solid, semi-solid or liquid filler, diluent, encapsulating material, or formulation. Guidance concerning formulations for small molecule, vaccines, proteins and antibodies can be found, for example, in Remington (2020) *The Science and Practice of Pharmacy* 23rd Edition; D'Amico, *et al.*, (2021) *Drug Deliv. and Transl. Res.* 11, 353–372; and in Strickley and Lambert (2021) *Journal of Pharmaceutical Sciences* 110: 2590-2608.

[0647] In some embodiments, LNPs according to this invention comprise a therapeutic agent that is an mRNA. In some of such embodiments, the lipid nanoparticle with said mRNA is a vaccine.

[0648] In some embodiments, LNPs according to this invention are used in LNP drug delivery, vaccine delivery or cancer immunotherapy.

[0649] In some embodiments, LNPs according to this invention are comprised in or are an mRNA LNP vaccine.

[0650] In some embodiments, LNPs according to this invention are used for vaccine delivery and the vaccine is an mRNA LNP.

[0651] An immune response may be induced in a subject by a method that comprises providing the subject a pharmaceutical composition with LNPs according to this invention.

[0652] In some embodiments, pharmaceutical compositions according to this invention

comprise a therapeutic agent that in turn comprises an mRNA. In some of such embodiments, the mRNA LNP is a vaccine.

[0653] The form of the pharmaceutical compositions, the route of administration, the dosage and the regimen depend upon the condition to be treated, such as the severity of the illness, the age, weight, and sex of the patient. Pharmaceutical compositions can be formulated for different modes of administration such as for topical, oral, intranasal, parenteral, intraocular, intravenous, intramuscular, or subcutaneous administration.

[0654] In an embodiment, the pharmaceutical composition contains a formulation capable of injection into a subject. Examples of injectable formulation components isotonic, sterile, saline solutions (*e.g.*, monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride and mixtures of such salts), buffered saline, sugars (*e.g.*, dextrose), and water for injection. Pharmaceutical compositions include dry, for example, freeze-dried compositions which upon addition, depending on the case, of sterilized water or physiological saline, permit the constitution of injectable solutions. The doses used for the administration can be adapted as a function of various parameters such as mode of administration, relevant pathology, and duration of treatment.

[0655] Other pharmaceutically acceptable forms include tablets or other solids for oral administration, including time-release capsules.

[0656] Embodiments of compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof are used in lipid nanoparticle compositions ("LNPs"). Some of such compositions are used for tropism analysis. Some of such compositions are used for lipid nanoparticle delivery vehicles. In this application, "lipid nanoparticle composition(s)" and "lipid nanoparticle formulation(s)" are used indistinguishably. When referring below to embodiments of LNPs, reference is made to illustrative embodiments of LNPs that comprise compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof.

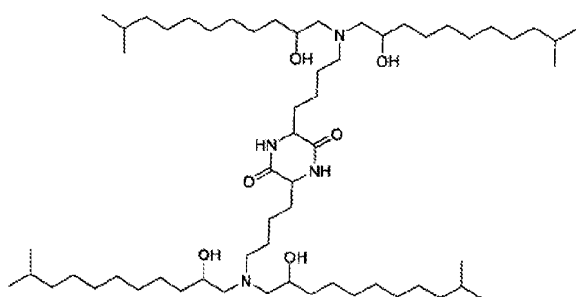
[0657] Lipid nanoparticles comprise one or more lipid species, including, but not limited to, cationic/ionizable lipids, non-cationic lipids, structural lipids, phospholipids, and helper lipids. Any of these lipids can be conjugated to polyethylene glycol ("PEG") and can be referred to as PEGylated lipids or PEG-modified lipids.

[0658] In some embodiments, a lipid nanoparticle composition includes one or more cationic and/or ionizable lipids. Cationic lipids have a head group with positive charges. Ionizable

lipids are protonated at low pH, which makes them positively charged. A positive charge on the LNP promotes association with the negatively charged cell membrane to enhance cellular uptake.

[0659] In some embodiments, the ionizable lipids, include, without limitations, amino lipids and compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof. Compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof are also referred to herein as lipids of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof.

[0660] The ionizable lipid bckk-E12 (Patent Publication WO2024/054882) were used in tests conducted herein as a comparative reference ionizable lipid. It has the following structure:



[0661] Additional ionizable lipids that were used as a comparative reference ionizable lipids in tests conducted herein include (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-M-C3-DMA, also known as MC3); 9Z,12Z-octadecadienoic acid, 3-[4,4-bis(octyloxy)-1-oxobutoxy]-2-[[[3-(diethylamino)propoxy]carbonyl]oxy]methyl]propyl ester (also known as LP-01); 8-[(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino]-octanoic acid, 1-octylnonyl ester (also known as SM-102), salts thereof, and mixtures thereof.

[0662] In certain embodiments of LNPs, the ionizable lipid(s) are present in amounts from about 10 mol% of the LNP to about 85 mol% of the LNP, from about 15 mol% of the LNP to about 75 mol% of the LNP, or from about 16 mol% of the LNP to about 60 mol% of the LNP.

[0663] “Structural lipids” are lipids that primarily function to build and maintain the structure of cell membranes, particularly the lipid bilayer. Structural lipids can be, but are not limited to, a sterol, phospholipids, sphingolipids, and glycolipids. “Sterol” refers to any naturally occurring sterol of plant (phytosterols) or animal (zoosterols) and non-naturally occurring synthetic sterols. In some embodiments, a sterol has a hydroxyl group at the 3-position of the steroid A-ring. In certain embodiments, a sterol is a cholesterol. Phytosterols include campesterol,

sitosterol, and stigmasterol. Sterols also include sterol-modified lipids.

[0664] In certain embodiments of LNPs, structural lipids are present in amounts from about 5 mol% of the LNP to about 70 mol% of the LNP, from about 10 mol% of the LNP to about 60 mol% of the LNP, from about 20 mol% of the LNP to about 60 mol% of the LNP, or from about 30 mol% of the LNP to about 60 mol% of the LNP.

[0665] The helper lipid is a non-cationic lipid. Helper lipids can be, but are not limited to, neutral lipids, zwitterionic lipid, or anionic lipids. In certain embodiments, a helper lipid comprises at least one fatty acid chain of at least 8C and at least one polar head group moiety. In certain embodiments, the LNPs include 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), or DSPC substitute as the helper lipid. In certain embodiments, the DSPC substitute is a lipid that is not a phospholipid. In certain embodiments, the LNPs comprise other helper lipids including oleic acid or oleic acid analogs.

[0666] In certain LNP embodiments, LNPs comprise a neutral lipid. Neutral lipids include any lipid species that exists either in an uncharged or neutral zwitterionic form at physiological pH. Such lipids include, without limitation, diacylphosphatidylcholine, diacylphosphatidylethanolamine, ceramide, sphingomyelin, dihydrosphingomyelin, cephalin, and cerebroside.

[0667] In certain LNP embodiments, lipids with mono or diunsaturated fatty acids with carbon chain lengths of C14 to C22 are used. In certain LNP embodiments, lipids having mixtures of saturated and unsaturated fatty acid chains are used. Illustrative embodiments of neutral lipids include, without limitation, 1,2-dioleoyl-sn-glycero-3-phosphatidyl-ethanolamine (DOPE), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), or any related phosphatidylcholine. Neutral lipids also comprise sphingomyelin, dihydrosphingomyelin, or phospholipids with other head groups.

[0668] In certain embodiments, the neutral lipid(s) are present in an amount from about 0.1 mol% of the lipid nanoparticle to about 75 mol% of the LNP, or from about 5 mol% of the LNP to about 66 mol% of the LNP, or from about 10 mol% of the LNP to about 50 mol% of the LNP, or from about 12 mol% of the LNP to about 30 mol% of the LNP.

[0669] In some LNP embodiments, the LNPs comprise PEGylated lipids or lipids conjugated to other stabilizing moieties (or stabilizers). In some embodiments, PEG-modified lipids (or lipid-polyoxyethylene conjugates) have a variety of “anchoring” lipid portions to secure

the PEG portion to the surface of the lipid vesicle. Polyethylene glycol (PEG) is a water-soluble polymer of ethylene ether repeating units, and can be linear or branched. PEGs are classified by their molecular weights, for example, PEG 2000 has an average molecular weight of about 2,000 Daltons, and PEG 5000 has an average molecular weight of about 5,000 Daltons. Commercially available PEGs (for example from Sigma Chemical Co., and other companies) include monomethoxypolyethylene glycol (MePEG-OH), monomethoxypolyethylene glycol-succinate (MePEG-S), monomethoxypolyethylene glycol-succinimidyl succinate (MePEG-S-NHS), monomethoxypolyethylene glycol-amine (MePEG-NH₂), monomethoxypolyethylene glycol-tresylate (MePEG-TRES), and monomethoxypolyethylene glycol-imidazolyl-carbonyl (MePEG-IM).

[0670] In certain LNP embodiments, the LNPs do not include PEG. In certain embodiments, the LNPs include HO-PEG. In other embodiments, the LNPs include a PEG substitute.

[0671] When PEG is used as the stabilizer, it can be conjugated to lipid(s). The stabilizer, either in a conjugated or an unconjugated form, accounts for 0.01 to 10 mol % of the LNP, or it is less than 7 mol% of the LNP. In certain embodiments, LNPs contain less than 5 mol% of PEG lipids.

[0672] In certain non-limiting examples, an LNP comprises the following components: (1) ionizable lipid(s); (2) helper lipid(s) (*e.g.*, a phospholipid such as DSPC); (3) structural lipid(s) (*e.g.*, a sterol such as cholesterol); and (4) PEG and/or PEG- modified lipid(s).

[0673] In some embodiments, the LNP comprises about 15 to 60 mol % ionizable lipid(s), 10 to 30 mol % helper lipid(s), 30 to 65 mol % structural lipid(s), and 0.01 to 10 mol % PEGylated lipid(s).

[0674] In certain embodiments, the LNPs comprise about 35 mol % ionizable lipids, 16 mol % helper lipids, 2.5 mol % PEGylated lipids, and 46.5 mol % structural lipids.

[0675] In certain embodiments, the LNPs comprise about 50 mol % ionizable lipids, 16 mol % helper lipids, 2.5 mol % PEGylated lipids, and 31.5 mol % structural lipids.

[0676] In certain embodiments, the LNPs comprise about 35 mol % ionizable lipids, 16 mol % helper lipids, 3.5 mol % PEGylated lipids, and 45.5 mol % structural lipids.

[0677] In certain embodiments, the LNPs comprise about 35 mol % ionizable lipids, 16 mol % helper lipids, 2.5 mol % PEGylated lipids, and 46.5 mol % structural lipids.

[0678] In certain embodiments, the LNPs comprise about 35 mol % ionizable lipids, 25 mol % helper lipids, 2.5 mol % PEGylated lipids, and 37.5 mol % structural lipids.

[0679] In certain embodiments, the LNPs comprise about 18.7 mol % ionizable lipids, 20 mol % helper lipids, 3.1 mol % PEGylated lipids, and 58.1 mol % structural lipids.

[0680] In certain embodiments, the LNPs comprise about 35 mol % ionizable lipids, 16 mol % helper lipids, 2.5 mol % PEGylated lipids, and 46.5 mol % structural lipids.

[0681] In certain embodiments, the LNPs have a size in any of the following illustrative ranges: from about 10 nm to 500 nm, from about 20 nm to about 400 nm, from about 40 nm to about 200 nm, from about 50 nm to about 180, from 55 nm to about 125 nm, or from 58 nm to about 100 nm.

[0682] In certain embodiments, the LNPs have a size of 55 nm. In certain embodiments, the LNPs have a size of 60 nm. In certain embodiments, the LNPs have a size of 65 nm. In certain embodiments, the LNPs have a size of 70 nm. In certain embodiments, the LNPs have a size of 75 nm. In certain embodiments, the LNPs have a size of 80 nm. In certain embodiments, the LNPs have a size of 85 nm. In certain embodiments, the LNPs have a size of 90 nm. In certain embodiments, the LNPs have a size of 95 nm. In certain embodiments, the LNPs have a size of 100 nm.

[0683] Illustrative embodiments of lipid nanoparticles according to this invention include the following.

[0684] In some embodiments, lipid nanoparticles comprise one or more than one ionizable lipids, wherein at least one of the ionizable lipids is a compound of any formulae (G1.1), (G1.2) and (G2), and any of the embodiments of the same described above. In some embodiments, lipid nanoparticles comprise one or more than one ionizable lipids, wherein at least one of the ionizable lipids is any compound according to the present invention named above or in the experiments described herein. In some embodiments, lipid particles comprise one or more than one ionizable lipids, wherein at least one of the ionizable lipids is any compound selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

[0685] In some embodiments, lipid nanoparticles comprise any one of the compounds referred to above, and further comprise one or more than one helper lipid, one or more than one structural lipids, and one or more than one PEG-lipids.

[0686] In some embodiments of lipid nanoparticles referred to above, the one or more than one ionizable lipid is present in a total ionizable lipid mole percentage from about 15% to about 60%; the one or more than one helper lipid is present in a total helper lipid mole percentage from about 10% to about 30%; the structural lipid is present in a total structural lipid mole percentage from about 30% to about 65%; and the PEG lipid is present in a total PEG lipid mole percentage from about 0.01% to about 10%. At least one ionizable lipid in such illustrative embodiments is selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

[0687] Further illustrative embodiments are provided by LNPs of this invention with any one of the compositions described above for such LNP embodiments that comprise a compound of this invention as those referred to above generically or specifically as an ionizable lipid, a helper lipid, a structural lipid, and a PEG lipid. Some of such LNP embodiments have a particle size as described above.

[0688] In some embodiments of lipid nanoparticles comprise one ionizable lipid that is a compound of this invention as those referred to above generically or specifically, and any of the compositional features described herein.

[0689] In some embodiments of lipid nanoparticles comprise one or more than one ionizable lipid, where at least one of such ionizable lipids is a compound of this invention as those referred to above generically or specifically, any of the compositional features described herein, and further comprise a therapeutic agent. Such therapeutic agent is in some embodiments a nucleic acid. In some of such embodiments, the therapeutic agent is a nucleic acid selected from minigenes, plasmids, minicircles, small interfering RNA (siRNA), microRNA (miRNA), antisense oligonucleotides (ASO), ribozymes, closed ended double stranded DNA (*e.g.*, ceDNA, CELiD), linear covalently closed DNA (“ministring”), Doggybone™ protelomere closed ended DNA, or dumbbell linear DNA, dicer-substrate dsRNA, small hairpin RNA (shRNA),

asymmetrical interfering RNA (aiRNA), microRNA (miRNA), mRNA, tRNA, rRNA, and DNA viral vectors, viral RNA vector, and any combination thereof.

[0690] As used herein, the term “nucleic acid,” is meant to refer to a polymer containing at least two nucleotides (*i.e.*, deoxyribonucleotides or ribonucleotides) in either single- or double-stranded form and includes DNA, RNA, and hybrids thereof. DNA may be in the form of, *e.g.*, antisense molecules, plasmid DNA, DNA-DNA duplexes, pre-condensed DNA, PCR products, vectors (P1, PAC, BAC, YAC, artificial chromosomes), expression cassettes, chimeric sequences, chromosomal DNA, or derivatives and combinations of these groups. DNA may be in the form of minicircle, plasmid, bacmid, minigene, ministring DNA (linear covalently closed DNA vector), closed-ended linear duplex DNA (CELiD or ceDNA), Doggybone™ DNA, dumbbell shaped DNA, minimalistic immunological-defined gene expression (MIDGE)-vector, viral vector or nonviral vectors. RNA may be in the form of small interfering RNA (siRNA), Dicer-substrate dsRNA, small hairpin RNA (shRNA), asymmetrical interfering RNA (aiRNA), microRNA (miRNA), mRNA, rRNA, tRNA, viral RNA (vRNA), and combinations thereof. Nucleic acids include nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, and which have similar binding properties as the reference nucleic acid. Examples of such analogs and/or modified residues include, without limitation, phosphorothioates, phosphorodiamidate morpholino oligomer (morpholino), phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2'-O-methyl ribonucleotides, locked nucleic acid (LNA™), and peptide nucleic acids (PNAs). Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated.

[0691] As used herein, the phrases “nucleic acid”, “nucleic acid therapeutics”, “therapeutic nucleic acid” and “TNA” are used interchangeably and refer to any modality of therapeutic using nucleic acids as an active component of therapeutic agent to treat a disease or disorder. As used herein, these phrases refer to RNA-based therapeutics and DNA-based therapeutics. Non-limiting examples of RNA-based therapeutics include mRNA, antisense RNA and oligonucleotides, ribozymes, aptamers, interfering RNAs (RNAi), dicer-substrate dsRNA,

small hairpin RNA (shRNA), asymmetrical interfering RNA (aiRNA), and microRNA (miRNA). Non-limiting examples of DNA-based therapeutics include minicircle DNA, minigene, viral DNA (e.g., Lentiviral or AAV genome) or non-viral DNA vectors, closed-ended linear duplex DNA (ceDNA/CELiD), plasmids, bacmids, Doggybone™ DNA vectors, minimalistic immunological-defined gene expression (MIDGE)-vector, nonviral ministring DNA vector (linear-covalently closed DNA vector), and dumbbell-shaped DNA minimal vector (“dumbbell DNA”).

[0692] Furthermore, such nucleic acid in embodiments of LNPs according to this invention is any one of those referred to herein. In some of such embodiments, the nucleic acid is at least one of an oligonucleotide, an RNA, and a DNA. In some of such embodiments, the nucleic acid is at least one of a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

[0693] In some embodiments, pharmaceutical compositions according to the present invention comprise a lipid nanoparticle as in any of the embodiments described herein and a pharmaceutically acceptable carrier. Use of such pharmaceutical compositions include providing them to a subject in need of treating a disease or disorder such as those referred to herein, to a subject for inducing an immune response, to a subject for modulating the expression of a target gene in a cell, or to a subject for delivering a therapeutic level of active agent.

[0694] Compounds of this invention as those referred to above generically or specifically are comprised in embodiments for use in LNP drug delivery or cancer immunotherapy. Such drug is dsDNA, DNA, mRNA, siRNA, a small molecule drug, or any other of the drugs referred to herein.

Methods of Manufacture

[0695] Methods of making other cationic/ionizable lipids, lipid nanoparticles containing them, and pharmaceutical compositions containing the cationic/ionizable lipids and/or lipid nanoparticles are described in, for example, International Publication Nos. WO2017/099823, U.S. Patent No. 8,492,359, and U.S. Patent Publication Nos. 2023/0142731, each of which is incorporated by reference in its entirety. Such synthesis methodologies, in addition to the methodologies described hereinbelow for LNPs according to this invention, may be used in formulating lipid nanoparticles and pharmaceutical compositions with compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof, and in making constituents used with compounds of this invention in such particles and compositions that contain them.

[0696] In some embodiments, a solution of one or more lipids in an organic solution (e.g., ethanol) is prepared. Similarly, a solution of one or more active (therapeutic) agents (for example an RNA molecule) in an aqueous buffered solution is prepared. The two solutions are mixed and diluted to form a colloidal suspension of lipid nanoparticles. In some embodiments, the dispersion is filtered through micron filters, concentrated, and filtered by tangential flow filtration.

[0697] LNP-nucleic acid formulations can be generated through, but not limited to, detergent dialysis, the ethanol loading technique, rapid-mixing methods, microfluidic mixing approaches, microfluidic hydrodynamic, and staggered herringbone mixing.

Methods of Use

[0698] In other general aspects, provided are compounds and pharmaceutical compositions described herein for treating various diseases, in particular, for the use in the delivery of therapeutic agents or drugs (e.g., polynucleotide, small molecule, protein, peptide) to a subject, such as in cancer immunotherapy, gene editing, and gene writing applications, and in the formulation of vaccines, personalized cancer vaccines and tolerogenic vaccines. For example, compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof may be used in nanoparticle formulations to deliver DNA, RNA, or other polynucleotides to a subject or to a cell. For example, lipid nanoparticles (LNPs) comprising compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof may be used for delivery of RNA interference (RNAi) therapeutics.

[0699] As used herein, “cancer immunotherapy,” also known as immuno-oncology, is a form of cancer treatment that uses the power of the body's own immune system to prevent, control, and eliminate cancer. Cancer immunotherapy comes in a variety of forms, including targeted antibodies, cancer vaccines, adoptive cell transfer, tumor-infecting viruses, checkpoint inhibitors, cytokines, and adjuvants. mRNA is widely used in cancer immunotherapy. For example, one of the applications of mRNA is therapeutic vaccination, which can leverage the capability of mRNA to deliver immune stimulants like cytokines and chemokines.

[0700] In some embodiments, compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof may be used as biodegradable lipids because these compounds contain ester groups and can undergo hydrolysis. With the biodegradable functionality, these lipids may display rapid elimination from plasma and tissues, and thus may improve their biocompatibility and facilitate their elimination once they have served their purpose to deliver therapeutic agents or

drugs to the appropriate intracellular compartments *in vivo*.

[0701] In certain embodiments, compounds of formula (G1.1), formula (G1.2), formula (G2), and mixtures thereof can be used in nanoparticle formulations to facilitate intracellular delivery of a DNA vector to a subject. The DNA vector can deliver a variety of different transgene that can be expressed to provide a protein having a desired activity. Examples of transgenes include those providing a healthy copy of gene in a subject where the gene is defective or a new, a modified gene that can help treat a disease or disorder, or a new gene encoding for protein providing a beneficial effect.

[0702] In different embodiments, a transgene encodes GAA (acid alpha-glucosidase) for treatment of Pompe disease; TPP1 (tripeptidyl peptidase-1) for treatment of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2); ATP7B (copper transporting ATPase2) for treatment of Wilson's disease; alpha galactosidase for treatment of Fabry disease; ASS1 (arginosuccinate synthase) for treatment of Citrullinemia Type 1; beta-glucocerebrosidase for treatment of Gaucher disease Type 1; beta-hexosaminidase A for treatment of Tay-Sachs disease; SERPING1 (C1 protease inhibitor or C1 esterase inhibitor) for treatment of hereditary angioedema (HAE), also known as C1 inhibitor deficiency type I and type II; or glucose-6-phosphatase for treatment of glycogen storage disease type I (GSDI).

[0703] In different embodiments, the transgene encodes insulin, glucagon, growth hormone (GH), parathyroid hormone (PTH), growth hormone releasing factor (GRF), follicle stimulating hormone (FSH), luteinizing hormone (LH), human chorionic gonadotropin (hCG), vascular endothelial growth factor (VEGF), angiopoietins, angiostatin, granulocyte colony stimulating factor (GCSF), erythropoietin (EPO), connective tissue growth factor (CTGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), transforming growth factor α (TGF α), platelet-derived growth factor (PDGF), insulin growth factors I or II (IGF-I or IGF-II), TGF β , activins, bone morphogenic protein (BMP), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins NT-3 or NT4/5, ciliary neurotrophic factor (CNTF), glial cell line derived neurotrophic factor (GDNF), neurturin, agrin, netrin-1 or netrin-2, hepatocyte growth factor (HGF), ephrins, noggin, sonic hedgehog or tyrosine hydroxylase.

[0704] In different embodiments, the transgene encodes thrombopoietin (TPO), an interleukin (IL-1 through IL-36), monocyte chemoattractant protein, leukemia inhibitory factor,

granulocyte-macrophage colony stimulating factor, Fas ligand, tumor necrosis factors α or β , interferons α , β , or γ , stem cell factor, flk-2/flt3 ligand, IgG, IgM, IgA, IgD or IgE, chimeric immunoglobulins, an antibody, humanized antibodies, single chain antibodies, T cell receptors, chimeric T cell receptors, single chain T cell receptors, class I or class II MHC molecules. Antibodies and immunoglobulins can, for example, be provided targeting cancer cells or other disease or disorder causing cells.

[0705] In different embodiments, the transgene encodes CFTR (cystic fibrosis transmembrane regulator protein), a blood coagulation (clotting) factor (Factor XIII, Factor IX (FIX), Factor VIII (FVIII), Factor X, Factor VII, Factor VIIa, or protein C) a gain of function blood coagulation factor, erythropoietin, LDL receptor, lipoprotein lipase, ornithine transcarbamylase, β -globin, α -globin, spectrin, α -antitrypsin, adenosine deaminase (ADA), a metal transporter (ATP7A or ATP7), sulfamidase, an enzyme involved in lysosomal storage disease (ARSA), hypoxanthine guanine phosphoribosyl transferase, β -25 glucocerebrosidase, sphingomyelinase, lysosomal hexosaminidase, branched-chain keto acid dehydrogenase, a hormone, a growth factor, insulin-like growth factor 1 or 2, platelet derived growth factor, epidermal growth factor, nerve growth factor, neurotrophic factor -3 and -4, brain-derived neurotrophic factor, glial derived growth factor, transforming growth factor α and β , a cytokine, α -interferon, β -interferon, interferon- γ , interleukin-2, interleukin-4, interleukin 12, granulocyte-macrophage colony stimulating factor, lymphotoxin, a suicide gene product, herpes simplex virus thymidine kinase, cytosine deaminase, diphtheria toxin, cytochrome P450, deoxycytidine kinase, tumor necrosis factor, a drug resistance protein, a tumor suppressor protein (*e.g.*, p53, Rb, Wt-1, NF1, Von Hippel–Lindau (VHL), adenomatous polyposis coli (APC)), a peptide with immunomodulatory properties, a tolerogenic or immunogenic peptide or protein Tregitope or hCDR1, insulin, glucokinase, guanylate cyclase 2D (LCA-GUCY2D), retinal pigment epithelium-specific 65 kDa protein (RPE65), Rab escort protein 1 (choroideremia), LCA 5 (LCA-lebercilin), ornithine ketoacid aminotransferase (gyrate atrophy), retinoschisin 1 (X-linked retinoschisis), X-linked retinitis pigmentosa GTPase (XLRP), MER proto-oncogene tyrosine kinase (MERTK) (autosomal recessive (AR) forms of retinitis pigmentosa (RP)), ABCA4 (Stargardt), ACHM 2, 3 and 4 (achromatopsia), an anti-vascular endothelial growth factor (VEGF) agent polypeptide (*e.g.*, bevacizumab, brolicizumab, ranibizumab, aflibercept), DFNB1 (connexin 26 deafness), USH1C (Usher's syndrome 1C), PKD-1 or PKD-2 (polycystic kidney disease), TPP1 (tripeptidyl

peptidase-1), a sulfatase, N-acetylglucosamine-1-phosphate transferase, cathepsin A, GM2-AP, NPC1, VPC2, a sphingolipid activator protein, or one or more donor sequences used as repair templates for genome editing.

[0706] In different embodiments, the transgene encodes erythropoietin (EPO) for treatment of anemia; interferon-alpha, interferon-beta, and interferon-gamma for treatment of various immune disorders, viral infections and cancer; an interleukin (IL), including any one of IL-1 through IL-36, and corresponding receptors, for treatment of various inflammatory diseases or immuno-deficiencies; a chemokine, including chemokine (C-X-C motif) ligand 5 (CXCL5) for treatment of immune disorders; granulocyte-colony stimulating factor (G-CSF) for treatment of immune disorders such as Crohn's disease; granulocyte-macrophage colony stimulating factor (GM-CSF) for treatment of various human inflammatory diseases; macrophage colony stimulating factor (M-CSF) for treatment of various human inflammatory diseases; keratinocyte growth factor (KGF) for treatment of epithelial tissue damage; chemokines such as monocyte chemoattractant protein-1 (MCP-1) for treatment of recurrent miscarriage, HIV-related complications, and insulin resistance; tumor necrosis factor (TNF) and receptors for treatment of various immune disorders; alpha1-antitrypsin for treatment of emphysema or chronic obstructive pulmonary disease (COPD); alpha-L-iduronidase for treatment of mucopolysaccharidosis I (MPS I); ornithine transcarbamoylase (OTC) for treatment of OTC deficiency; phenylalanine hydroxylase (PAH) or phenylalanine ammonia-lyase (PAL) for treatment of phenylketonuria (PKU); lipoprotein lipase for treatment of lipoprotein lipase deficiency; apolipoproteins for treatment of apolipoprotein (Apo) A-I deficiency; low-density lipoprotein receptor (LDL-R) for treatment of familial hypercholesterolemia (FH); albumin for treatment of hypoalbuminemia; lecithin cholesterol acyltransferase (LCAT); carbamoyl synthetase I; argininosuccinate synthetase; argininosuccinate lyase; arginase; fumarylacetoacetate hydrolase; porphobilinogen deaminase; cystathionine beta-synthase for treatment of homocystinuria; branched chain ketoacid decarboxylase; isovaleryl-CoA dehydrogenase; propionyl CoA carboxylase; methylmalonyl-CoA mutase; glutaryl CoA dehydrogenase; insulin; pyruvate carboxylase; hepatic phosphorylase; phosphorylase kinase; glycine decarboxylase; H-protein; T-protein; cystic fibrosis transmembrane regulator (CFTR); ATP-binding cassette, sub-family A (ABC1), member 4 (ABCA4) for the treatment of Stargardt disease; or dystrophin.

[0707] In a further embodiment, the transgene encodes a protein for treating a disease or

disorder selected from the group consisting of: hereditary angioedema, Pompe disease, hemophilia A, hemophilia B, Fabry, wet macular degeneration, Leber hereditary optic neuropathy, Huntington's disease, Parkinson's disease, glaucoma, age-related macular degeneration, and Stargardt disease.

Preparation of Lipid Nanoparticle Formulations using Microfluidics Device

[0708] Lipid nanoparticle (LNP) formulations comprising lipids described herein were prepared as follows. Preparation methodologies have been described in WO2024/054901 and WO2024/054882, which are incorporated herein by reference in their entireties.

[0709] The DNA or mRNA solution was prepared in 10-100 mM citrate buffer solution at pH 3-5, while the lipid mixtures were dissolved in ethanol. The DNA or mRNA aqueous solution and the lipid ethanolic solution were mixed on NanoAssemblr at 5:1 to 3:1 flow rate ratio with total flow rate of 12 mL/min. Subsequently, the LNP solution was transferred to dialysis cassettes, and dialyzed against 1x DPBS buffer for 2 hours, then another 2 hours against newly made 1x DPBS at room temperature. Finally, they were dialyzed against another newly made 1x DPBS solution overnight at 0 °C.

[0710] The intermediate LNP was concentrated with Amicon Ultra-15 (10 kD MWCO) tube at 2000g, 23 °C till it was concentrated about 5-15 times. Then the LNP was filtered through a 0.2 µm pore sterile filter. The particle size of LNP was determined by quasielastic light scattering using a Malvern Zetasizer Nano ZS, and the DNA or mRNA encapsulation as well as quantification was measured by Quant-iT RiboGreen mRNA Assay Kit. Based on the DNA or mRNA quantification results, the LNP solutions were further diluted with 1x DPBS buffer as well as 60% w/w sucrose solution, and stored at -80 °C.

Lipid Nanoparticle Formulation Characterizations

[0711] Upon preparation of the lipid nanoparticle formulations, lipid nanoparticle size and zeta potential, and encapsulation efficiency of nucleic acid into the lipid nanoparticles were analyzed. Particle size was determined by dynamic light scattering and zeta potential was measured by electrophoretic light scattering (Zetasizer Nano ZS, Malvern Instruments).

[0712] Encapsulation efficiency (ee%) of DNA or mRNA in lipid nanoparticles as well as the quantification was determined by RiboGreen® (Thermo Scientific) kit. Ribogreen® is an ultra-sensitive fluorescent nucleic acid stain for quantitating mRNA but can also be used to quantify dsDNA. The ee % was determined by performing a membrane impermeable fluorescent

dye exclusion assay. Each LNP sample was divided into two groups, one was treated with TE buffer, and the other was treated with Triton-X 100, a nonionic surfactant known to break the LNPs. In addition, a series of known concentrations of the DNA or mRNA solution were also prepared as the standard solutions for quantification. Subsequently, all the wells were treated with Ribogreen[®], and after 5-10 mins the fluorescence readings were taken. The ee% is calculations as $ee\% = (I_{\text{Triton}} - I_{\text{TE}}) / I_{\text{Triton}}$, where I_{Triton} is the fluorescence of the Triton-X100 treated LNP samples, while the I_{TE} was the fluorescence of the TE buffer treated LNP group. For the quantification of the DNA or mRNA, a standard linear curve was constructed based on the fluorescence intensity vs. known concentrations of the DNA or mRNA standard solutions. To obtain the DNA or mRNA total quantification of the LNP samples, the I_{Triton} fluorescence value was plugged into the standard linear curve to calculate the DNA or mRNA concentration of the relevant LNP.

In vivo evaluation of lipid nanoparticles

[0713] LNPs were formulated as above with either FIX expression cassette DNA or EPO mRNA as a payload. C57BL/6 mice were intravenously dosed with DNA-LNP or mRNA-LNP via tail vein injection. For DNA-LNPs, mice were pre-treated with an anti-IFNAR antibody and dexamethasone, and then dosed with up to 50 µg DNA payload. For mRNA-LNPs, mice were dosed with up to 2 µg mRNA payload. At various time points thereafter, plasma was sampled for protein expression and cytokine stimulation.

HepG2 Cell Culture:

[0714] The culture flask (Corning[®]) was removed from the incubator (37°C, 5% CO₂, 80% RH), and the supernatant was removed from the culture flask and the cell layer was rinsed with 1x DPBS. Trypsin- EDTA (Gibco) was added to the cell layer and flask was placed in the incubator for cell detachment. Growth medium (DMEM (Gibco) with 10% FBS (Gibco), and 1% Pen-Strep (Gibco)) was added to the flask. An aliquot of the cell suspension was diluted in 0.4% Trypan blue (Gibco) for cell counting. Cells were passed into a gelatin-coated culture flask with growth media and flask was placed in the incubator.

[0715] When seeding cell plates for assay, 200 µL of cell suspension at 1.5×10^5 cells/mL was transferred to a gelatin-coated, 96-well flat-bottom tissue culture plate (Costar). Cell seeding was performed the day before the assay.

Cell-based Assays

[0716] LNPs were formulated with *Gaussia* pDNA or mRNA. LNPs were diluted to 4

pg/mL and 25 μ L were added to each well in a 96-well plate containing 200 μ L HepG2 cells. ApoE4 was diluted in culture media to 10 pg/mL and 25 μ L were added to 96-well plates containing either cell line. The final amount of LNP added and final ApoE4 concentration in 250 μ L media was 100 ng per well and 1 pg/mL, respectively.

[0717] *Gaussia* luciferase expression by HepG2 cells was determined by collecting supernatant after 24 hours for mRNA-LNPs and after 48 hours for pDNA-LNPs. Supernatants were diluted 1:2.5 in QUANTIT-Luc. Luminescence units were determined using a luminometer.

FIX ELISA Assay Protocol

[0718] 96-well ELISA plates (Costar) were coated with capture antibody (Affinity Biologicals) then sealed and incubated at RT. Plates were washed 3 times with PBS-Tween wash buffer and blotted to remove excess liquid. Standards were prepared by serial-diluting human pooled normal plasma (George King Biomedical) in mouse control plasma (BioIVT). Prepared standards and samples were diluted in sample diluent. Transferred standard and sample dilutions to plates and incubated at RT. Plates were washed 3 times with wash buffer and blotted to remove excess liquid. Detection antibody (Affinity Biologicals) was added to each well of the plates and incubated at RT. Plates were washed 3 times with PBS-Tween wash buffer and blotted to remove excess liquid. TMB (Thermo Scientific) was added to each well of the plates and incubated in the dark at RT. Sulfuric acid was added to each well and plates were read for absorbance at 450 nm on a plate reader (Biotek). A 4-parameter curve was generated for the standards. Samples results were interpolated on the standard curve.

Example 1: In vitro Screening of Delivery of DNAs and RNAs LNPs

[0719] Briefly, a pDNA or mRNA solution was prepared in 10-100 mM citrate buffer solution at pH 3-5, while the lipid mixture was dissolved in ethanol. The DNA or mRNA aqueous solution and the lipid ethanolic solution were mixed on Tecan liquid handler at ratio of 2:1. Subsequently, the LNP solution was dialyzed against 1x DPBS using Microdialysis Plates with fist buffer exchange after 2 hours at room temperature followed by overnight dialysis at 4 °C. The DNA or mRNA encapsulation as well as quantification was measured by Quant-iT RiboGreen mRNA Assay Kit (Thermo Fisher Scientific).

[0720] Some lipids according to the present invention were synthesized and screened *in vitro* for LNP delivery of mRNA and/or pDNA. Using the compound name $Ai''L1Tk''$ introduced above, the screened lipids are compounds $Ai''L1Tk''$, where i'' is 1-9, 11, 12, 14, 16-

37, and k'' is 1-15, thus the entries (along the abscissa axis in the tabular summary shown in FIG. 1) A1 to A9, A11, A12, A14, and A16 to A37 (see also Table 1 for the formulae of the corresponding amino compounds), and T1 to T15 (see also Tables 2 and T2) along the ordinate axis in the tabular summary shown in FIG. 1. LNPs were formulated by liquid handler with either *Gaussia* luciferase mRNA and/or pDNA payloads. HepG2 cells were transfected in vitro with those LNPs (100 ng/well of nucleic acid), and *Gaussia* luciferase protein expression was measured by luminescence assay. FIG. 1 shows preliminary screening results of LNPs with such non-optimized lipids resulting in expressions of *Gaussia* luciferase from mRNA, pDNA, or both payloads (“mRNA”, “pDNA” and “Both”, respectively, in FIG. 1).

Example 2: DNA-LNPs in vivo Data

[0721] DNA-LNPs comprising an hFIX transgene expression construct were administered via tail vein injection to wild-type mice with standard immunosuppression. FIG. 2A and 2B show the circulating levels of FIX protein expressed from the transgene, and FIG. 2C and 2D show circulating IL-6 levels (representative cytokine response) after administration of DNA-LNPs, with lipids according to this invention, such as lipids of Formula (G1.1) and Formula (G2). Circulating hFIX levels were measured 7 days post-dosing and circulating IL-6 levels were measured 4 hours after dosing.

[0722] As shown in FIG. 2A, 7 days after dosing hFIX DNA-LNPs comprising A4L1T14, A5L1T15, A7L1T14, and A9L1T15, average circulating FIX levels were 48, 146, 242, and 277 ng/ml, respectively. As shown in FIG. 2B, 7 days after dosing hFIX DNA-LNPs comprising A106T101, and A107T101, average circulating FIX levels were 80, and 76 ng/ml, respectively.

[0723] As shown in FIG. 2C, 4 hours after dosing of DNA-LNPs comprising A4L1T14, A5L1T15, A7L1T14, and A9L1T15, average circulating IL-6 levels were 13804, 53888, 30554, 27540, and 18539 pg/ml, respectively. As shown in FIG. 2D, 4 hours after dosing of DNA LNPs comprising A106T101, and A107T101, average circulating IL-6 levels were 394, and 644 pg/ml, respectively. All these readings in FIG. 2A-2D were above the LLOQ for the experiments.

Example 3: In vivo Efficacy of Varied Lipid Nanoparticle Compositions with the Same Ionizable Lipid

[0724] As shown in FIG. 3A, the LNPs 1788, 1790, 1791, 1792, 1793, and 1794 had the same ionizable lipid A4L1T14, but comprised different formulation compositions, and each of them expressed different *in vivo* efficacy (FIG. 3B). The term “mass ratio” in the tables shown in

FIG. 3A and FIG. 5A means the ratio of ionizable lipid mass to nucleic acid mass used to prepare the formulation.

[0725] Varied lipid nanoparticle compositions comprising the same ionizable lipid A4L1T14 resulted in different levels of circulating hFIX protein (as expressed from a FIX DNA transgene) and different levels of circulating IL-6 *in vivo*. As shown in FIG. 3B, 7 days after dosing the DNA-LNP with different lipid nanoparticle compositions, the LNPs 1788, 1790, 1791, 1792, 1793, and 1794 resulted in circulating hFIX levels of 189, 40, 22, 59, 31, and 26 ng/ml respectively. As shown in FIG. 3C, four hours after dosing various formulations of DNA-LNP compositions, the LNPs 1788, 1790, 1791, 1792, 1793, and 1794 resulted in circulating IL-6 levels of 16349, 14319, 5374, 10301, 7483, and 826 pg/ml respectively. All these readings in FIG. 3B and 3C showed efficacies above the LLOQ for the experiments.

Example 4: mRNA-LNPs *in vivo* Data

[0726] *In vivo* potency data of hEPO mRNA-LNPs formulated with lipids of formula (G1.1) were generated after IV dosing.

[0727] As shown in FIG. 4A, 6 hours after single IV dosing of the mRNA-LNPs of A4L1T14, the subjects had plasma hEPO levels of 853, 182, and 63 ng/ml, for the corresponding doses of 2 µg, 0.7 µg, and 0.2 µg, respectively. In reference to another lipid, 6 hours after single IV dosing of the mRNA-LNPs of A5L1T15, the subjects had plasma hEPO levels of 156, 63, and 63 ng/ml, for the doses of 2 µg, 0.7 µg, and 0.2 µg, respectively. The readings at the top of each bar in the graph shown in FIG. 4A for reference lipids MC3 and bcKK-E12, from left to right and given in the same units as indicated in the ordinate axis of the graph, are as follows: 533, 153, 63, 801, 216, and 63.

[0728] As shown in FIG. 4B, 6 hours after single IV dosing of the mRNA-LNPs of A4L1T14, the plasma MCP-1 cytokine levels were 18, 13, and 10 pg/ml, for the corresponding doses of 2 µg, 0.7 µg, and 0.2 µg. While 6 hours after single IV dosing of the mRNA-LNPs of A5L1T15, the plasma MCP-1 cytokine levels were 15, 9, and 8 pg/ml, for the doses of 2 µg, 0.7 µg, and 0.2 µg, respectively. The readings at the top of each bar in the graph shown in FIG. 4B, from left to right and given in the same units as indicated in the ordinate axis of the graph, are as follows: 7 (pre-bleed), 9, 7, 7, (reference lipid MC3) and 7, 7, and 7 (reference lipid bcKK-E12). All these readings in FIG. 4A and 4B showed potencies above (for higher doses) or at (for some lower doses) the LLOQ for the experiments.

[0729] FIG. 4C shows hEPO expression after two IV doses of hEPO mRNA-LNPs. 2 µg hEPO mRNA-LNP was dosed on day 0 and day 14, respectively. The plasma hEPO levels from both A4L1T14 and A5L1T15 mRNA-LNPs increased to the peak within 12 hours after IV dosing, and returned to the baseline seven days after dosing. 14 days after the first dose, a second dose was administered, and the plasma hEPO levels demonstrated similar fluctuation patterns as the plasma hEPO levels after the first dose. As shown in FIG. 4C (graph on the left), from day 0 to day 2, the A4L1T14-based mRNA-LNPs expressed the highest level of plasma hEPO (top line in the graph), the bCKK-E12-based mRNA-LNPs expressed a lower level of plasma hEPO (line in the graph slightly below the A4L1T14 line), the MC3-based mRNA-LNPs expressed a comparatively lower level of plasma hEPO (line in the graph below the two top ones and above the lowest one), while the A5L1T15-based mRNA-LNPs demonstrated the comparatively lowest level of plasma hEPO (line at the bottom in the graph). As shown in FIG. 4C (graph on the right), from day 14 to day 20, the bCKK-E12-based mRNA-LNPs expressed the highest level of plasma hEPO pattern (line at the top in the graph), the A4L1T14-based mRNA-LNPs expressed a comparatively lower level of plasma hEPO (line right below the top line), the MC3-based mRNA-LNPs expressed a comparatively lower level of plasma hEPO (third line in the graph from top to bottom), while the A5L1T15-based mRNA-LNPs level of plasma hEPO corresponds to the comparatively lowest level (line at the bottom in the graph).

[0730] Example 5: mRNA-LNPs Comprising Lipids of the Present Invention Can Be Re-dosed *in vivo*

[0731] The mRNA-LNPs formulated with lipids of the present invention, such as A4L1T14, can be re-dosed *in vivo*. FIG. 5A shows multiple compositions of mRNA-LNPs comprising A4L1T14, such as LNP1, LNP2, and LNP3.

[0732] As shown in FIG. 5B, various formulations of hEPO mRNA-LNPs comprising A4L1T14 were administered IV at least five times in each mouse. Six hours after each IV dosing, plasma hEPO levels were measured. 2 µg hEPO mRNA-LNPs were dosed intravenously. The interval between Dose-1 and Dose-2 was 14 days, and the interval for all subsequent doses was 21 days. The hEPO level was measured from plasma samples 6 hours after dosing. Dosing with LNP1 resulted in average plasma hEPO levels of 556, 669, 636, 863, and 1068 ng/ml, after dose one, two, three, four, and five, respectively. Dosing with LNP2, resulted in average plasma hEPO levels of 324, 524, 375, 511, and 229 ng/ml, after dose one, two, three, four, and five,

respectively. Dosing with LNP3, resulted in average plasma hEPO levels of 797, 782, 1177, 1175, and 1441 ng/ml, after dose one, two, three, four, and five, respectively.

[0733] Example 6: In vivo Data of mRNA-LNPs Comprising Lipids of the Present Invention

[0734] mRNA-LNPs containing various ionizable lipids, including lipids according to the present invention (Formula (G1.1) and (G2)), were administered via tail vein injection to wild-type mice. The hEPO expressions from mRNA-LNPs, based on circulating hEPO, was measured 6 hours post-injection.

[0735] As shown in FIG. 6, hEPO mRNA-LNPs comprising lipids of formula (G1.1), or formula (G2) demonstrated average plasma hEPO levels ranging from 2 ng/ml to 942 ng/ml. The readings at the top of each bar in the graph shown in FIG. 6, from left to right and given in the same units as indicated in the ordinate axis of the graph, are as follows: 81, 408, 329, 304, 170, 32, 604, 6, 310, 942, 103, 185, 4, 4, 63, 2, 3, 2, 4, 2, 2, 2, 82, 17, 84, (in reference to LNPs of this invention), and 197, and 902 (in reference to LNPs LP-01 and MC3). Readings in FIG. 6 for LNPs according to the present invention were above or at about the LLOQ for these experiments.

[0736] Example 7: In vivo Potency Data for Delivery of Firefly Luciferase mRNA-LNPs

[0737] In vivo potency data of firefly luciferase mRNA-LNPs are shown in FIG. 7. The luciferase mRNA-LNPs were formulated with various lipids of Formula (G1.1) listed along the abscissa axis. Firefly luciferase expression was measured by *ex vivo* IVIS imaging of whole liver tissues 24 hours post-dosing of 2 µg mRNA-LNP.

[0738] As shown in FIG. 7, after IV administrations, mRNA-LNPs formulated with lipids of A4L1T14, A4L1T15, A5L1T15, A7L1T15, and A14L1T15, expressed firefly luciferase in liver tissues, with average total Flux of 5.4×10^8 , 2.3×10^8 , 1.1×10^8 , 6.9×10^7 , and 1.6×10^8 (Photons/sec), respectively. LNPs formulated with lipids according to the present invention displayed a delivery potency greater than, and in some cases comparable to, that of LNPs formulated with reference lipids LP-01, MC3 and SM-102.

[0739] Example 8: In-vivo Data Showing Responses to A4L1T14-based mRNA-LNPs

[0740] Mice were intramuscularly dosed with 5 µg of OVA mRNA-LNP formulated with A4L1T14 as ionizable lipid, and with OVA mRNA-LNPs formulated with reference lipids MC3 and SM-102 at day 0, and 1 µg of OVA mRNA-LNP at day 24. 10 µg of OVA protein was administered with Alhydrogel adjuvant on day 0 and day 24. Anti-OVA IgG was measured from

plasma using Mouse Anti-OVA IgG Antibody Assay Kit (Chondrex). At day 28, splenocytes were stained for Thy1.2, CD8, and CD4, and with H-2Kb SIINFEKL tetramer, and I-Ab OVA323-339 tetramer. For restimulation, splenocytes were treated with 1 µg/mL of OVA 257-264 or OVA 323-339 peptide in the presence of protein transport inhibitor (ebioscience) for 4 hours. Stimulated cells were surface stained for Thy1.2, CD8, CD4, and intracellularly stained for IFN-γ using Cyto-Fast Fix-Perm buffer set (BioLegend).

[0741] OVA mRNA-LNP comprising A4L1T14, was delivered intramuscularly. As shown in FIG. 8A, the strength of anti-OVA IgG antibody response was measured on day 14 and day 28 post injection. Compared to day 14, the average anti-OVA IgG antibody level increased on day 28. There was anti-OVA IgG response with Alhydrogel, MC3 and SM-102 formulations that showed also an increase of the average anti-OVA IgG antibody level on day 28 in comparison with the level at day 14.

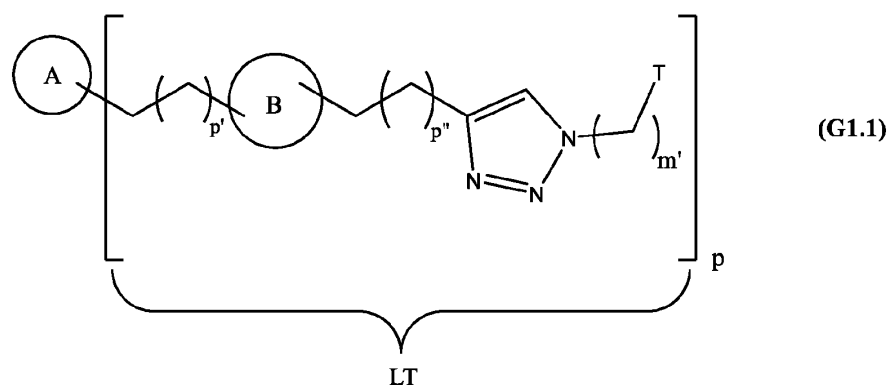
[0742] mRNA-LNP *in-vivo* data in FIG. 8B showed immune responses to A4L1T14-based LNP formulations, and the strength of antigen-specific T cell (MHC-I tetramer+ CD8 cells) responses induced by A4L1T14-based LNP formulations was measured. As shown in FIG. 8B, A4L1T14-based OVA mRNA-LNPs induced antigen-specific CD8 T cell responses in spleen and draining lymph node (dLN), as identified using MHC-I-tetramer. Moreover, the induced antigen-specific T cell (MHC-I tetramer+ CD8 cells) response in spleen was stronger than the CD8 T cells in dLN. As also shown in FIG. 8B, MC3- and SM-102-based OVA mRNA-LNPs induced antigen-specific CD8 T cell responses, but no response was induced when Alhydrogel was used.

[0743] mRNA-LNP *in vivo* data in FIG. 8C show immune responses to A4L1T14-based LNP formulations. The strength of antigen-specific T cell (IFN-γ+ CD8 cells) responses induced by A4L1T14-based LNP formulations was measured. As shown in FIG. 8C, A4L1T14-based OVA m-RNA-LNPs increased antigen-specific T cell (IFN-γ+ CD8 cells) responses when mouse splenocytes were tested in the presence of the model ovalbumin K^b-binding peptide SIINFEKL, while no CD8 T cells were detected in the absence of SIINFEKL peptide. As also shown in FIG. 8C, SM-102- and MC3-based OVA m-RNA-LNPs increased antigen-specific T cell (IFN-γ+ CD8 cells) responses when mouse splenocytes were tested in the presence of the model ovalbumin K^b-binding peptide SIINFEK, while no CD8 T cells were detected in the absence of SIINFEKL peptide, but no response was induced when Alhydrogel was used.

[0744] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the present description. All documents cited herein are incorporated by reference in their entirety.

CLAIMS

1. A compound of formula (G1.1)



wherein

moiety B is C(O)O, OC(O), C(O)NH, HNC(O), or CH₂CH₂,

p = 1-6;

p' = 0-4;

p'' = 0-4;

m' = 0, 1;

moiety T is selected from

CH((CH₂)_{ll}CH₃)-(CH₂)_{ll'}-CH₃, ll = 2-6, ll' = 2-6

CH₃-(CH₂)_k-CH₂, k = 2-14;

(CH₃-(CH₂)_{k'})₂-CH-(CH₂)_{k''}-CH₂, k' = 0-8, k'' = 0-9;

CH₃-(CH₂)_{kk}-CH=CH-(CH₂)_{kk'}-CH₂, kk = 5-8, kk' = 5-8;

CH₃-(CH₂)_{k_p}-CH=CH-(CH₂)_{k_p'}-CH=CH-(CH₂)_{k_p''}-CH₂, k_p = 5-7, k_p' = 5-7,

k_p' = 1-3;

CH₃-(CH₂)_l-O-C(O)-(CH₂)_{kk''}-CH₂, l = 2-7, kk'' = 0-4; and

$(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH-MS-C(O)}-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is O or NH;

and when $p > 1$, then each one of the plurality of T moieties is the same or different from the remaining T moieties in the same molecule,

and

A is an amino moiety, and said amino moiety A is chosen depending on the p-value as follows, wherein the term * is used to refer to a N-binding site of an LT moiety, and *(*) (or (*)*) indistinguishably is used to refer to two separate N-binding sites of two LT moieties:

when $p = 1$, then A is

$*N((\text{CH}_2)_{ir}-N(\text{NT}_1)(\text{NT}_2))(X-(\text{CH}_2)_2-\text{Y-OCO-CH}(\text{TA}_1)(\text{TA}_2))$,

$ir = 2-4$,

NT_1 is H, or CH_3 ,

NT_2 is CH_3 , $(\text{CH}_2)_r-\text{OCO}-(\text{CH}_2)_{r'}-\text{CH}_3$, $(\text{CH}_2)_r-\text{OH}$, or

$(\text{CH}_2)_r-\text{CH}_3$, with $r = 1-3$, $r' = 1-3$, and $r'' = 1-3$,

X is C(O)-O , C(O)-CH_2 , $(\text{CH}_2)_{mm}-\text{OCO}$ with $mm = 1-3$, or

$\text{CH}_2-(\text{CH}_2)_{mm}$ with $mm = 0-3$,

Y is $\text{S-S}-(\text{CH}_2)_n$, $n = 2,3$, or $(\text{CH}_2)_q$, $q = 3-6$,

OCO is O-C(O) or C(O)-O ,

TA_1 is H or $(\text{CH}_2)_m-\text{CH}_3$, and

TA_2 is $(\text{CH}_2)_{m'}-\text{CH}_3$,

with $m = 5-8$ and $m' = 5-8$;

when $p = 2$, then A is $*(*)N-(\text{CH}_2)_t-\text{Z}$,

$t = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH_3 , OH, $\text{N}(\text{CH}_2-\text{CH}_3)_2$,

or $\text{N}(\text{CH}_3)_2$,

when $p = 4$, then A is $*(*)N-(\text{CH}_2)_{w1}-\text{E}-(\text{CH}_2)_{w2}-N(*)^*$,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-

O, $\text{O}-(\text{CH}_2)_{w3}$ -(substituted or unsubstituted 1,4-

piperazinediyl)-(CH₂)_{w4}-O, substituted or unsubstituted 1,4-piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-cyclohexanediyl)-EE, or EE-(1,3-cyclohexanediyl)-EE, wherein w3 = 0-4, w4 = 0-4, XS is C(O)-O-(CH₂)₂, and EE is O, C(O)-O or C(O)-NH,

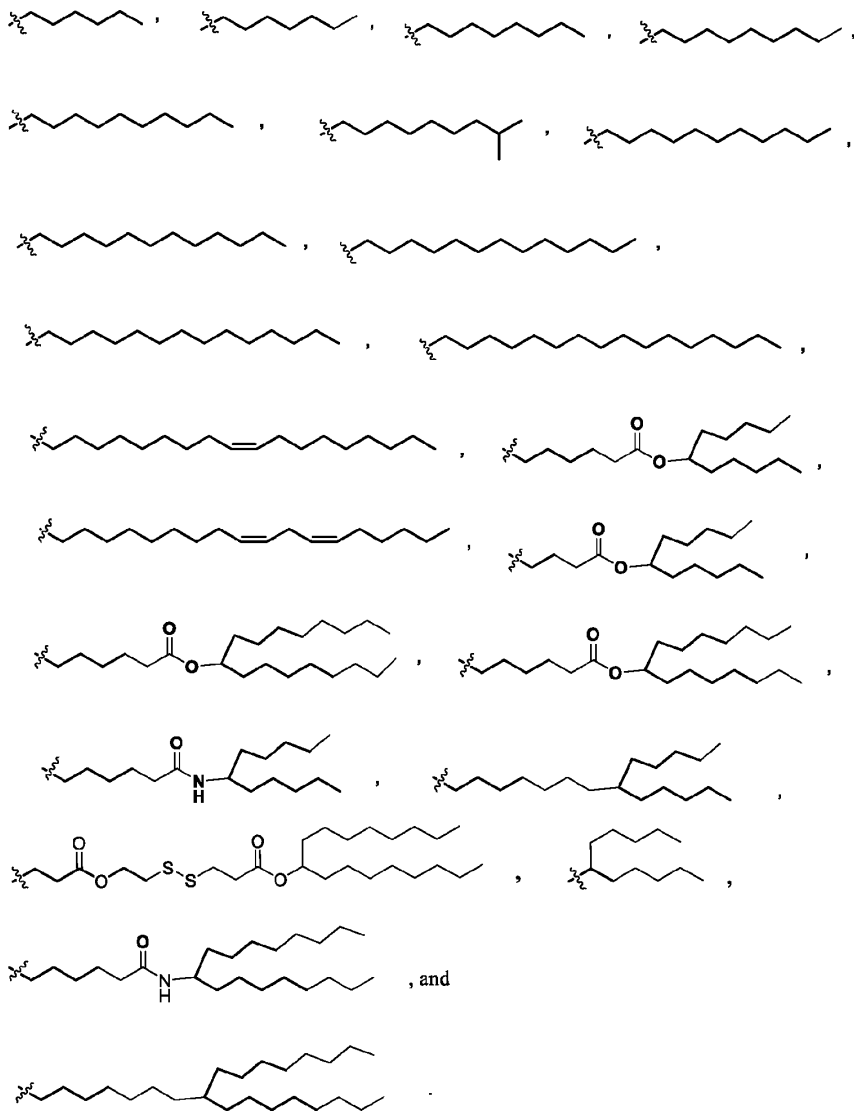
when p = 5, then A is ^{*}(^{*})N-(CH₂)_{p1}-N^{*}-(CH₂)_{p2}-N(^{*})^{*}, p1 = 2-5, p2 = 2-5, and

when p = 6, then A is ^{*}(^{*})N-(CH₂)_{q1}-N((CH₂)_{q2}-N(^{*})^{*})-(CH₂)_{q3}-N(^{*})^{*}, q1 = 2-4, q2 = 2-4, and q3 = 2-4.

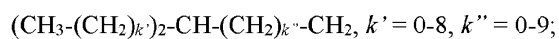
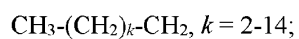
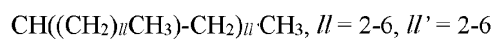
wherein, when p > 1, then each one of the plurality of LT moieties is the same or different from the remaining LT moieties in the same molecule, or a stereoisomer, tautomer, constitutional isomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof.

2. A compound of claim 1, wherein p = 2, 4, 5 or 6, and wherein all the LT moieties are identical.
3. A compound of claim 1, wherein p = 2, 4, 5 or 6, and wherein at least two LT moieties are the same and at least two LT moieties are different.
4. A compound of claim 1, wherein p = 2, 4, 5 or 6, and wherein all the LT moieties are different.
5. A compound of claim 1, wherein p' = 1.
6. A compound of claim 1, wherein p'' = 1.
7. A compound of claim 1, wherein m' = 1.
8. A compound of claim 1, wherein p' = 1 and p'' = 1.

9. A compound of claim 8, wherein B is CH₂CH₂, C(O)NH, or C(O)O.
10. A compound of claim 8, wherein B is C(O)O.
11. A compound of claim 8, wherein B is CH₂CH₂.
12. A compound of claim 8, wherein B is C(O)NH.
13. A compound of claim 1, wherein p' = p'' = 1, and B is CH₂CH₂, C(O)NH, HNC(O), C(O)O or OC(O).
14. A compound of claim 1, wherein p is one of 1, 2, 3, 4, 5 and 6, and when p is one of 2, 3, 4, 5 and 6, then p' = p'' = 1 in each LT.
15. A compound of claim 1, wherein p is one of 1, 2, 3, 4, 5 and 6, and when p is 1, then p' = p'' = 1 in each LT.
16. A compound of claim 1, wherein, when p = 2-6, all the T moieties are identical.
17. A compound of any one of claims 1-16 wherein T for each LT moiety is selected from the following moieties:



18. A compound of claim 1, wherein moiety T is selected from



$\text{CH}_3-(\text{CH}_2)_{kk}-\text{CH}=\text{CH}-(\text{CH}_2)_{kk'}-\text{CH}_2$, $kk = 5-8$, $kk' = 5-8$;
 $\text{CH}_3-(\text{CH}_2)_{kp}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp''}-\text{CH}_2$, $kp = 5-7$, $kp'' = 5-7$,
 $kp' = 1-3$;
 $\text{CH}_3-(\text{CH}_2)_l-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-4$; and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{MS}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is
 O or NH;
 and when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is the
 same in each of said LT moieties.

19. A compound of claim 1, wherein moiety T is selected from

$\text{CH}((\text{CH}_2)_n\text{CH}_3)-\text{CH}_2)_{ll'}-\text{CH}_3$, $ll = 2-6$, $ll' = 2-6$
 $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 2-14$;
 $(\text{CH}_3-(\text{CH}_2)_{k'})_2-\text{CH}-(\text{CH}_2)_{k''}-\text{CH}_2$, $k' = 0-8$, $k'' = 0-9$;
 $\text{CH}_3-(\text{CH}_2)_{kk}-\text{CH}=\text{CH}-(\text{CH}_2)_{kk'}-\text{CH}_2$, $kk = 5-8$, $kk' = 5-8$;
 $\text{CH}_3-(\text{CH}_2)_{kp}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp''}-\text{CH}_2$, $kp = 5-7$, $kp'' = 5-7$,
 $kp' = 1-3$;
 $\text{CH}_3-(\text{CH}_2)_l-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-4$; and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{MS}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is
 O or NH;
 $p = 1, 2, 4, 5$, or 6 ;
 and when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is
 different from the remaining T moieties in each of said LT moieties.

20. A compound of claim 1, wherein moiety T is selected from

$\text{CH}((\text{CH}_2)_n\text{CH}_3)-\text{CH}_2)_{ll'}-\text{CH}_3$, $ll = 2-6$, $ll' = 2-6$
 $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 2-14$;
 $(\text{CH}_3-(\text{CH}_2)_{k'})_2-\text{CH}-(\text{CH}_2)_{k''}-\text{CH}_2$, $k' = 0-8$, $k'' = 0-9$;
 $\text{CH}_3-(\text{CH}_2)_{kk}-\text{CH}=\text{CH}-(\text{CH}_2)_{kk'}-\text{CH}_2$, $kk = 5-8$, $kk' = 5-8$;
 $\text{CH}_3-(\text{CH}_2)_{kp}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp''}-\text{CH}_2$, $kp = 5-7$, $kp'' = 5-7$,
 $kp' = 1-3$;
 $\text{CH}_3-(\text{CH}_2)_l-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-4$; and

$(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{MS}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is
 O or NH;
 $p = 1, 2, 4, 5$, or 6 ,
 when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is the
 same as or different from the remaining T moieties in each of said LT
 moieties; and
 $m' = 1$ in each of said LT moieties.

21. A compound of claim 20, wherein, when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is the same as the remaining T moieties in each of said LT moieties.

22. A compound of claim 20, wherein, when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is different from the remaining T moieties in each of said LT moieties.

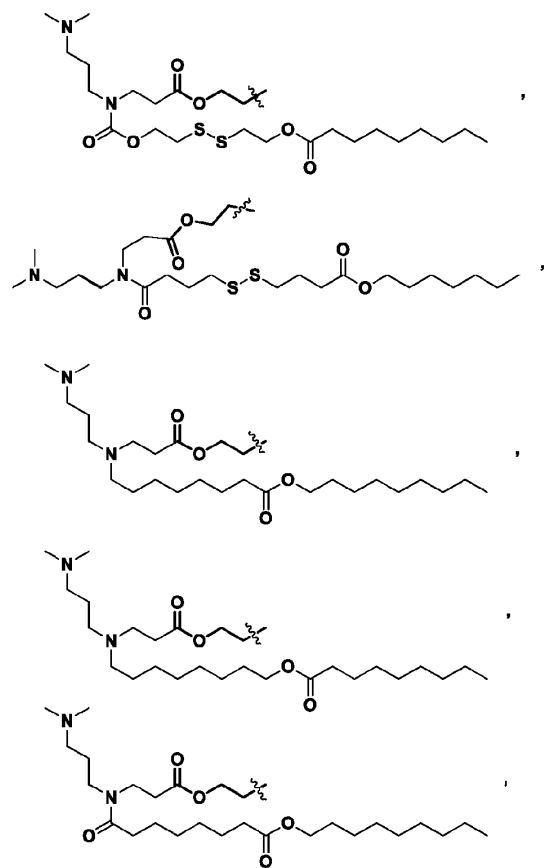
23. A compound of claim 1, wherein moiety T is selected from

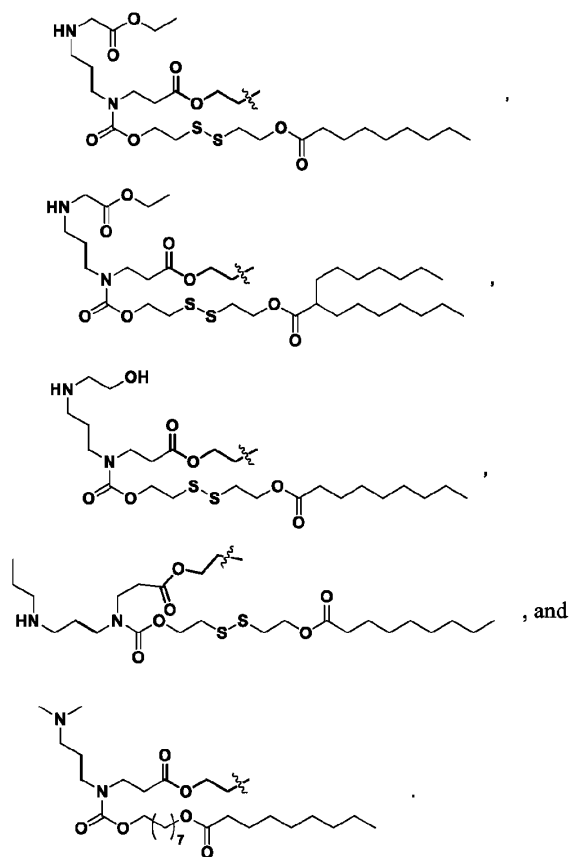
$\text{CH}((\text{CH}_2)_n\text{CH}_3)-\text{CH}_2)_{ll'}-\text{CH}_3$, $ll' = 2-6$, $ll' = 2-6$
 $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 2-14$;
 $(\text{CH}_3-(\text{CH}_2)_{k'})_2-\text{CH}-(\text{CH}_2)_{kk''}-\text{CH}_2$, $k' = 0-8$, $kk'' = 0-9$;
 $\text{CH}_3-(\text{CH}_2)_{kk'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kk''}-\text{CH}_2$, $kk' = 5-8$, $kk'' = 5-8$;
 $\text{CH}_3-(\text{CH}_2)_{kp}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp''}-\text{CH}_2$, $kp = 5-7$, $kp'' = 5-7$,
 $kp' = 1-3$;
 $\text{CH}_3-(\text{CH}_2)_l-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-4$; and
 $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{MS}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is
 O or NH;
 $p = 1, 2, 4, 5$, or 6 ,
 when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is the
 same as or different from the remaining T moieties in each of said LT
 moieties; and
 $m' = 0$ in each of said LT moieties.

24. A compound of claim 23, wherein, when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is the same as the remaining T moieties in each of said LT moieties.

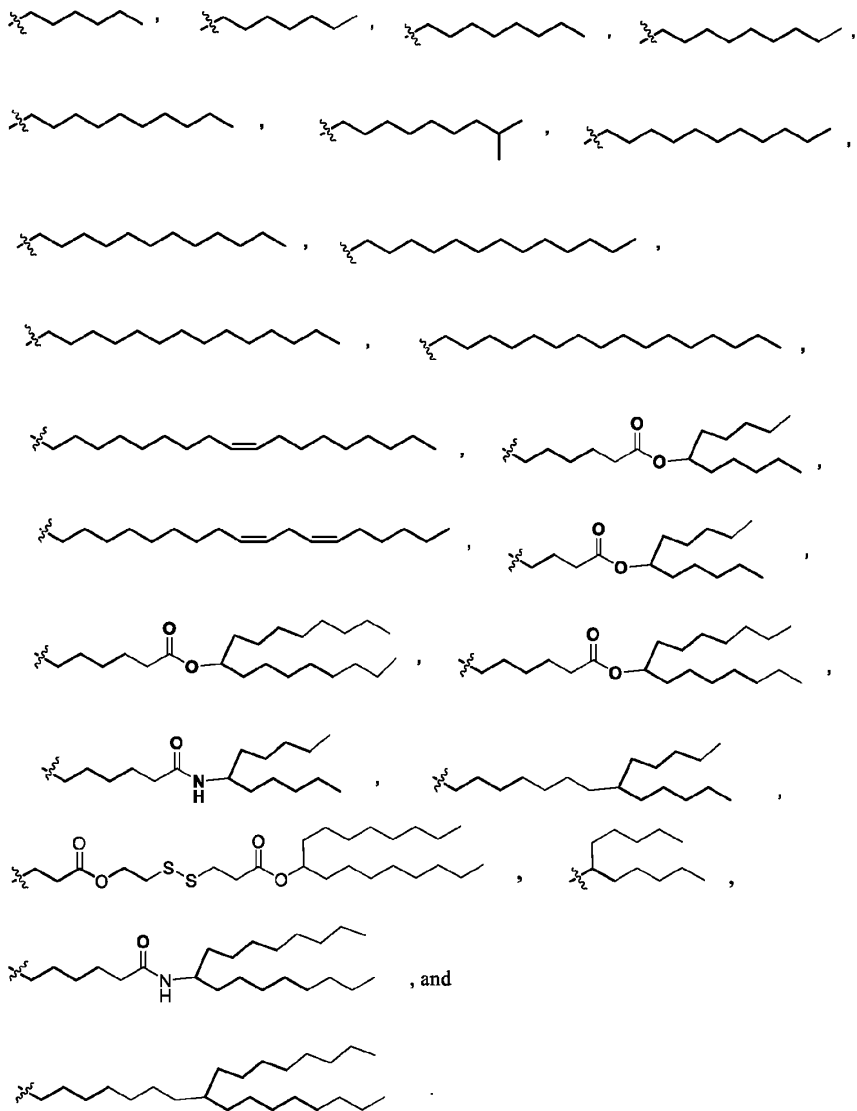
25. A compound of claim 23, wherein, when $p = 2, 4, 5$ or 6 , then each one of the plurality of T moieties is different from the remaining T moieties in each of said LT moieties.

26. A compound of claim 1, wherein $p = 1$, and the moiety $A-CH_2-(CH_2)_p-B-CH_2(CH_2)_{p'}-J$ in (G1.1), wherein $p' = p'' = 1$ and B is $C(O)O$, is selected from the following moieties:

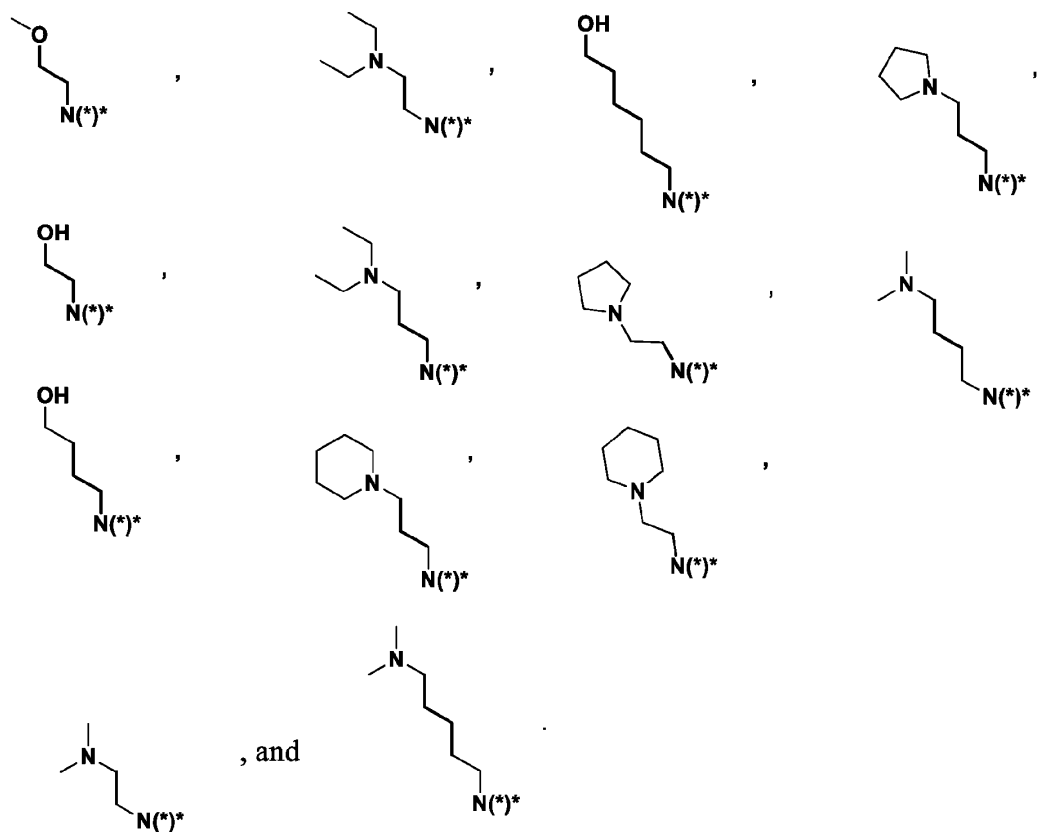




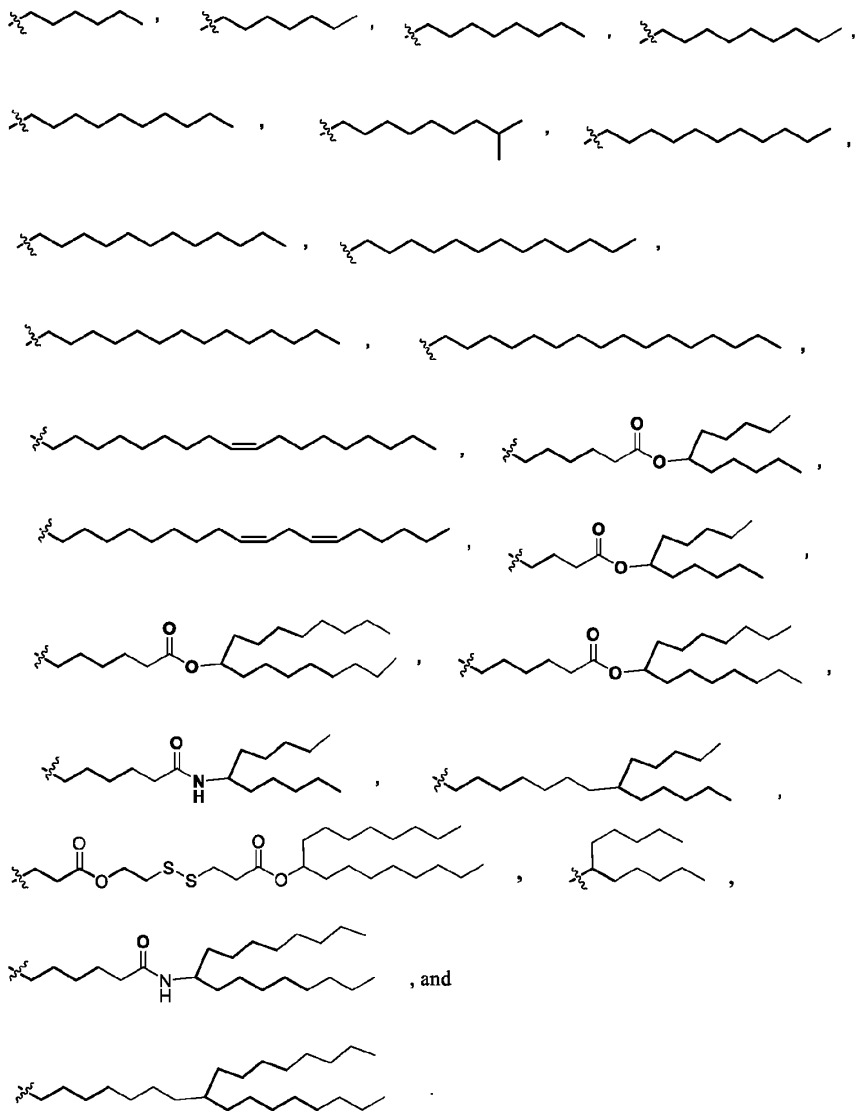
27. A compound of claim 26, wherein moiety T is selected from the following moieties:



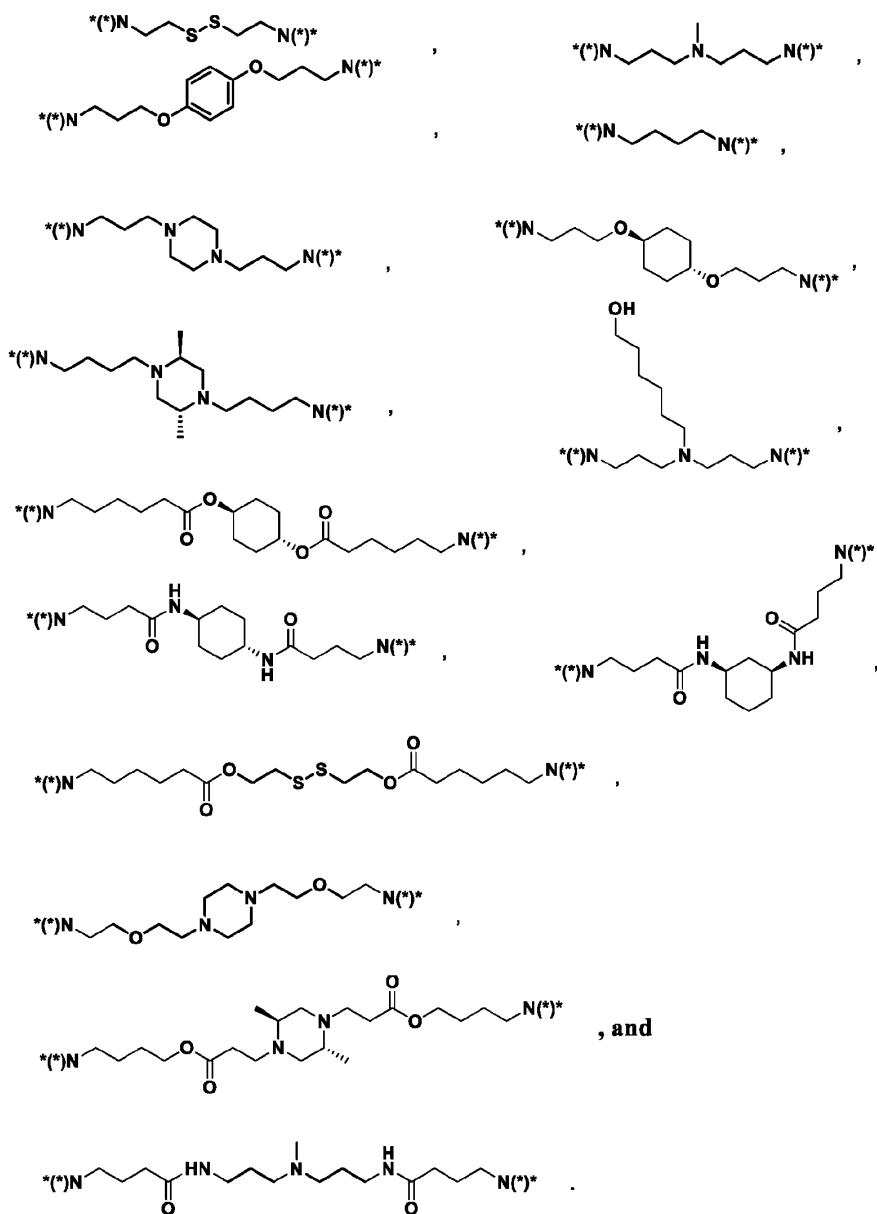
28. A compound of claim 1, wherein $p = 2$ and A is selected from the following moieties:



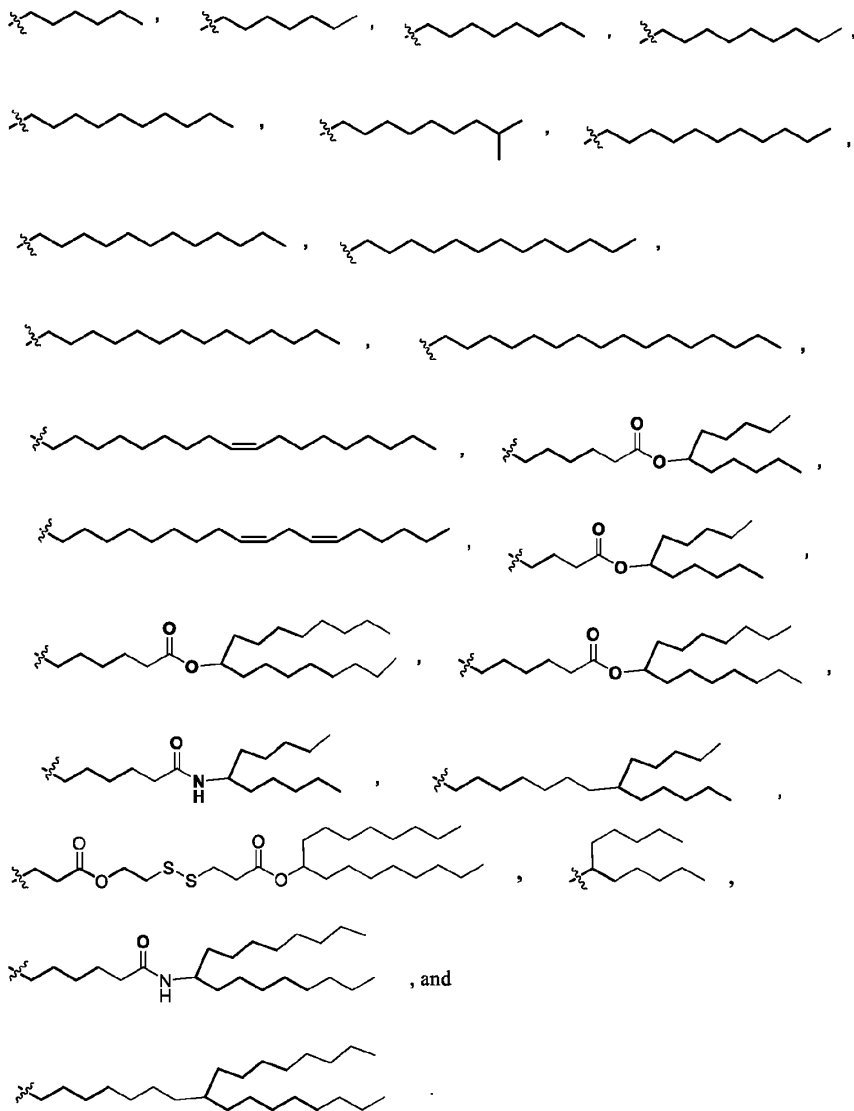
29. A compound of claim 28, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:



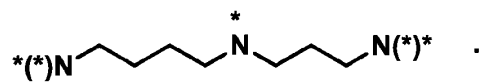
30. A compound of claim 1, wherein p = 4 and A is selected from the following moieties:



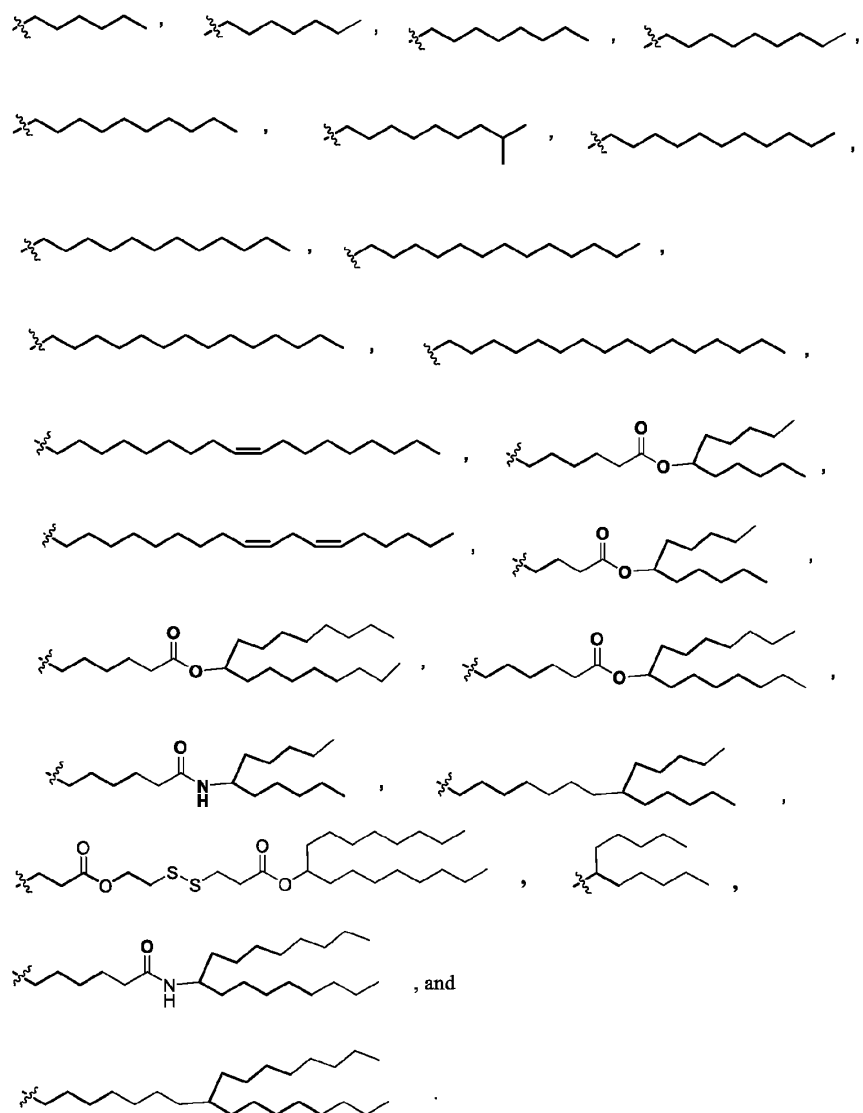
31. A compound of claim 30, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:



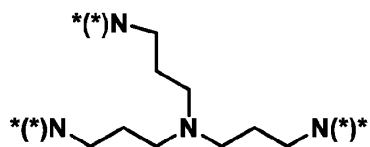
32. A compound of claim 1, wherein $p = 5$ and A is the following moiety:



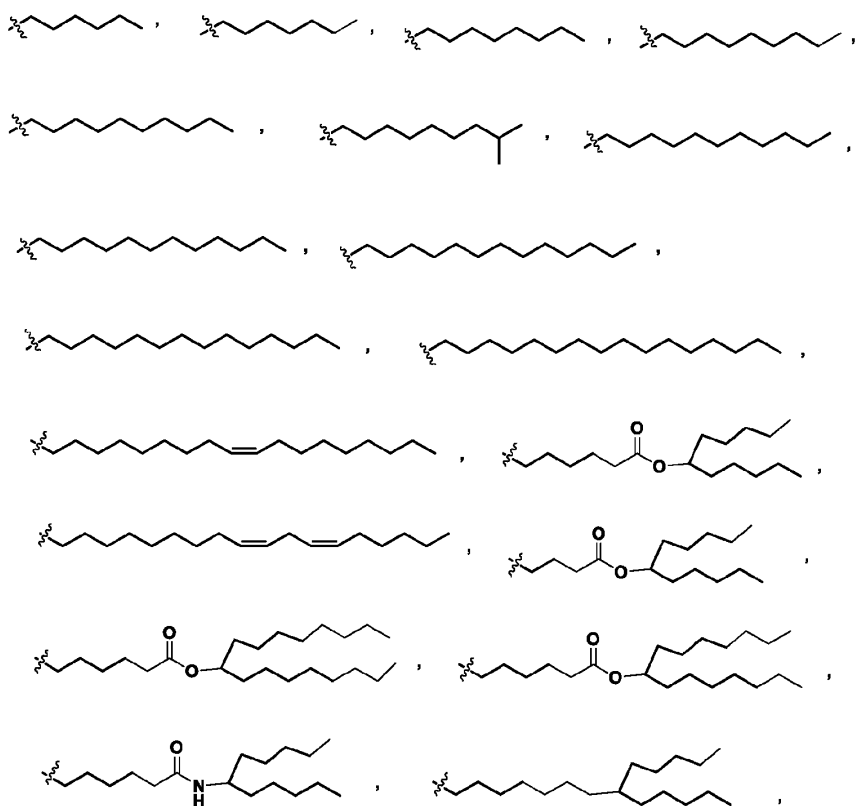
33. A compound of claim 32, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:

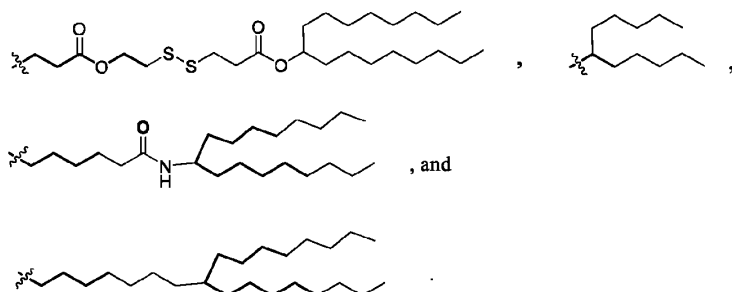


34. A compound of claim 1, wherein $p = 6$ and A is the following moiety:



35. A compound of claim 34, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:





36. A compound of claim 35, B is C(O)O.

37. A compound of claim 1, wherein $p = 4$, E is unsubstituted O-phenylen-O, $w_1 = w_2 = 3$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$ and $m' = 1$.

38. A compound of claim 1, wherein $p = 4$, the substituted amino in E is $\text{-}\frac{3}{5}\text{N}\frac{3}{5}\text{-}$, $w_1 = w_2 = 3$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 5$ and $m' = 1$.

39. A compound of claim 1, wherein $p = 4$, E is unsubstituted O-phenylen-O, $w_1 = w_2 = 3$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 9$, and $m' = 1$.

40. A compound of claim 1, wherein $p = 4$, E is S-S, $w_1 = w_2 = 2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 3$, and $m' = 1$.

41. A compound of claim 1, wherein $p = 5$, $p_1 = 3$, $p_2 = 4$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 6$, and $m' = 1$.

42. A compound of claim 1, wherein $p = 4$, E is unsubstituted 1,4-piperazindiyl, $w_1 = w_2 = 3$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 7$, and $m' = 1$.

43. A compound of claim 1, wherein $p = p' = p'' = 1$, $m' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ and $k = 6$.

44. A compound of claim 1, wherein $p = p' = p'' = 1$, $m' = 0$, T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ and $k = 6$.

45. A compound of claim 1, wherein $p = 2$, $t = 3$, Z is N-piperidino, $p' = 1$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 10$, and $m' = 1$.
46. A compound of claim 1, wherein $p = 4$, E is substituted 1,4-piperazindiy1, $w_1 = w_2 = 4$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.
47. A compound of claim 1, wherein $p = 4$, $w_1 = w_2 = 3$, E is unsubstituted $\text{C(O)-NH-(1,3-cyclohexanediy1)-NH-C(O)}$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.
48. A compound of claim 1, wherein $p = 4$, E is $\text{O-(CH}_2\text{)}_{w_3}\text{-(substituted or unsubstituted 1,4-piperazinediy1)-(CH}_2\text{)}_{w_4}\text{-O}$, $w_1 = w_2 = w_3 = w_4 = 2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 4$, and $m' = 1$.
49. A compound of claim 1, wherein $p = 2$, $t = 2$, Z is $\text{N(CH}_2\text{-CH}_3\text{)}_2$, and for each LT moiety each T is $\text{CH}_3\text{-(CH}_2\text{)}_7\text{-CH=CH-(CH}_2\text{)}_6\text{-CH}_2$, $m' = 1$, and $p' = p'' = 1$.
50. A compound of claim 1, wherein $p = 2$, $t = 2$, Z is $\text{N(CH}_2\text{-CH}_3\text{)}_2$, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 11$.
51. A compound of claim 1, wherein $p = 2$, $t = 2$, Z is N-piperidino, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 8$.
52. A compound of claim 1, wherein $p = 2$, $t = 3$, Z is N-pyrrolidino, and for each LT moiety $m' = 1$, $p' = p'' = 1$, and each T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$, with $k = 8$.
53. A compound of claim 1, wherein $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_4\text{-CH=CH-CH}_2\text{-CH=CH-(CH}_2\text{)}_6\text{-CH}_2$, X is C(O)-O , Y is $\text{S-S-(CH}_2\text{)}_n$ with $n = 2$, OCO is O-C(O) , and $m = 7$.

54. A compound of claim 1, wherein $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_3-\text{CH}_2$, with $l = 3$, X is $\text{C}(\text{O})-\text{CH}_2$, Y is $\text{S}-\text{S}-(\text{CH}_2)_n$ with $n = 3$, OCO is $\text{O}-\text{C}(\text{O})$, and $m = 6$.
55. A compound of claim 1, wherein $p = 1$, $m' = 1$, $p' = p'' = 1$, T is $(\text{CH}_3)_2-\text{CH}-(\text{CH}_2)_4-\text{CH}_2$, X is CH_2-CH_2 , Y is $(\text{CH}_2)_q$ with $q = 4$, OCO is $\text{O}-\text{C}(\text{O})$, and $m = 7$.
56. A compound of claim 1, wherein $p = 4$, $w_1 = w_2 = 4$, E is XS-(substituted 1,4-piperazinediyl)-XS, XS is $\text{O}-\text{C}(\text{O})-(\text{CH}_2)_2$, and for each LT moiety $p' = p'' = 1$, $m' = 1$, T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 4$.
57. A compound of claim 1, wherein $p = 4$, $w_1 = w_2 = 2$, E is S-S, and for each LT moiety $p' = p'' = 1$, $m' = 1$, T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 3$.
58. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 2$, Z is OH, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 5$.
59. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 4$, Z is OH, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 6$.
60. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 6$, Z is OH, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 5$.
61. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 2$, Z is $\text{N}(\text{CH}_3)_2$, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 9$.
62. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 4$, Z is $\text{N}(\text{CH}_3)_2$, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 6$.
63. A compound of claim 1, wherein $p = 2$, $p' = p'' = 1$, $t = 5$, Z is $\text{N}(\text{CH}_3)_2$, and for each LT moiety $m' = 1$, and T is $\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$ with $k = 8$.

64. A compound of claim 1, wherein $p = 4$, $w_1 = w_2 = 5$, E is EE-(1,4-cyclohexanediyl)-EE, EE is C(O)-O, and for each LT moiety $m' = 1$, $p' = p'' = 1$, T is $\text{CH}_3\text{-(CH}_2\text{)}_k\text{-CH}_2$ with $k = 7$.

65. A compound of claim 1, wherein $p = 4$, $w_1 = w_2 = 5$, E is XS-S-S-XS, XS is C(O)-O-(CH₂)₂, and for each LT moiety $m' = 1$, $p' = p'' = 1$, T is (CH₃)₂-CH-(CH₂)₅-CH₂.

66. A compound selected from the group: A1L1T1, A1L1T2, A1L1T3, A1L1T4, A1L1T5, A1L1T6, A1L1T7, A1L1T8, A1L1T9, A1L1T10, A1L1T11, A1L1T12, A1L1T13, A1L1T14, A1L1T15, A2L1T1, A2L1T2, A2L1T3, A2L1T4, A2L1T5, A2L1T6, A2L1T7, A2L1T8, A2L1T9, A2L1T10, A2L1T11, A2L1T12, A2L1T13, A2L1T14, A2L1T15, A3L1T1, A3L1T2, A3L1T3, A3L1T4, A3L1T5, A3L1T6, A3L1T7, A3L1T8, A3L1T9, A3L1T10, A3L1T11, A3L1T12, A3L1T13, A3L1T14, A3L1T15, A4L1T1, A4L1T2, A4L1T3, A4L1T4, A4L1T5, A4L1T6, A4L1T7, A4L1T8, A4L1T9, A4L1T10, A4L1T11, A4L1T12, A4L1T13, A4L1T14, A4L1T15, A4L1T16, A4L1T17, A4L1T18, A4L1T19, A4L2T18, A4L2T14, A4L3T19, A4L3T14, A5L1T1, A5L1T2, A5L1T3, A5L1T4, A5L1T5, A5L1T6, A5L1T7, A5L1T8, A5L1T9, A5L1T10, A5L1T11, A5L1T12, A5L1T13, A5L1T14, A5L1T15, A5L2T21, A5L3T22, A6L1T1, A6L1T2, A6L1T3, A6L1T4, A6L1T5, A6L1T6, A6L1T7, A6L1T8, A6L1T9, A6L1T10, A6L1T11, A6L1T12, A6L1T13, A6L1T14, A6L1T15, A6L2T18, A6L3T19, A7L1T1, A7L1T2, A7L1T3, A7L1T4, A7L1T5, A7L1T6, A7L1T7, A7L1T8, A7L1T9, A7L1T10, A7L1T11, A7L1T12, A7L1T13, A7L1T14, A7L1T15, A8L1T1, A8L1T2, A8L1T3, A8L1T4, A8L1T5, A8L1T6, A8L1T7, A8L1T8, A8L1T9, A8L1T10, A8L1T11, A8L1T12, A8L1T13, A8L1T14, A8L1T15, A9L1T1, A9L1T2, A9L1T3, A9L1T4, A9L1T5, A9L1T6, A9L1T7, A9L1T8, A9L1T9, A9L1T10, A9L1T11, A9L1T12, A9L1T13, A9L1T14, A9L1T15, A10L1T19, A11L1T1, A11L1T2, A11L1T3, A11L1T4, A11L1T5, A11L1T6, A11L1T7, A11L1T8, A11L1T9, A11L1T10, A11L1T11, A11L1T12, A11L1T13, A11L1T14, A11L1T15, A12L1T1, A12L1T2, A12L1T3, A12L1T4, A12L1T5, A12L1T6, A12L1T7, A12L1T8, A12L1T9, A12L1T10, A12L1T11, A12L1T12, A12L1T13, A12L1T14, A12L1T15,

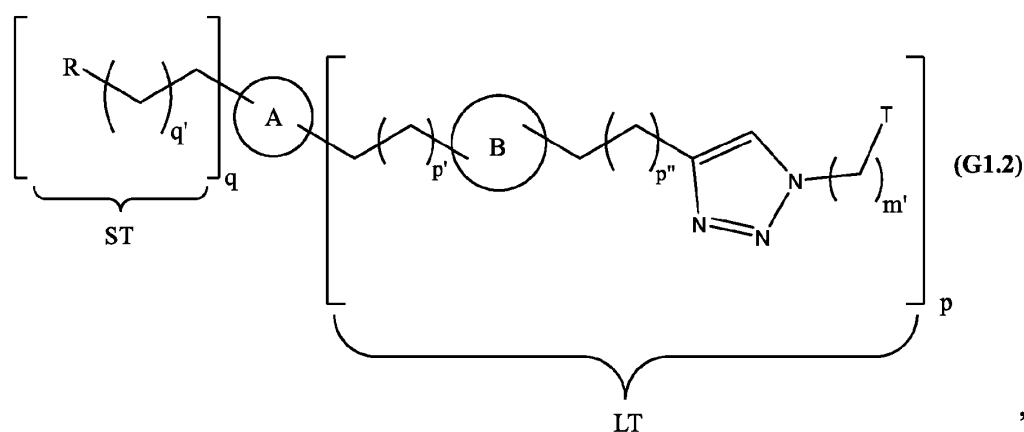
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A28L1T1, A28L1T2, A28L1T3, A28L1T4, A28L1T5, A28L1T6, A28L1T7, A28L1T8,
A28L1T9, A28L1T10, A28L1T11, A28L1T12, A28L1T13, A28L1T14, A28L1T15,
A29L1T1, A29L1T2, A29L1T3, A29L1T4, A29L1T5, A29L1T6, A29L1T7, A29L1T8,
A29L1T9, A29L1T10, A29L1T11, A29L1T12, A29L1T13, A29L1T14, A29L1T15,

A30L1T1, A30L1T2, A30L1T3, A30L1T4, A30L1T5, A30L1T6, A30L1T7, A30L1T8, A30L1T9, A30L1T10, A30L1T11, A30L1T12, A30L1T13, A30L1T14, A30L1T15, A31L1T1, A31L1T2, A31L1T3, A31L1T4, A31L1T5, A31L1T6, A31L1T7, A31L1T8, A31L1T9, A31L1T10, A31L1T11, A31L1T12, A31L1T13, A31L1T14, A31L1T15, A32L1T1, A32L1T2, A32L1T3, A32L1T4, A32L1T5, A32L1T6, A32L1T7, A32L1T8, A32L1T9, A32L1T10, A32L1T11, A32L1T12, A32L1T13, A32L1T14, A32L1T15, A33L1T1, A33L1T2, A33L1T3, A33L1T4, A33L1T5, A33L1T6, A33L1T7, A33L1T8, A33L1T9, A33L1T10, A33L1T11, A33L1T12, A33L1T13, A33L1T14, A33L1T15, A34L1T1, A34L1T2, A34L1T3, A34L1T4, A34L1T5, A34L1T6, A34L1T7, A34L1T8, A34L1T9, A34L1T10, A34L1T11, A34L1T12, A34L1T13, A34L1T14, A34L1T15, A35L1T1, A35L1T2, A35L1T3, A35L1T4, A35L1T5, A35L1T6, A35L1T7, A35L1T8, A35L1T9, A35L1T10, A35L1T11, A35L1T12, A35L1T13, A35L1T14, A35L1T15, A36L1T1, A36L1T2, A36L1T3, A36L1T4, A36L1T5, A36L1T6, A36L1T7, A36L1T8, A36L1T9, A36L1T10, A36L1T11, A36L1T12, A36L1T13, A36L1T14, A36L1T15, A37L1T1, A37L1T2, A37L1T3, A37L1T4, A37L1T5, A37L1T6, A37L1T7, A37L1T8, A37L1T9, A37L1T10, A37L1T11, A37L1T12, A37L1T13, A37L1T14, A37L1T15, A38L1T15, A39L1T15, A40L1T15, A41L1T15, and A42L1T20, and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof.

67. A compound of claim 66, selected from the group: A2L1T2, A3L1T3, A8L1T8, A1L1T1, A4L1T4, A5L1T5, A5L1T15, A34L1T4, A11L1T11, A26L1T9, A6L1T2, A12L1T2, A14L1T2, A21L1T13, A24L1T12, A25L1T10, A22L1T7, A27L1T7, A30L1T13, A30L1T15, A31L1T14, A33L1T6, A37L1T2, A4L1T4, A18L1T3, A19L1T4, A20L1T3, A23L1T8, A28L1T4, A29L1T7, A35L1T5, A36L1T6, A4L1T16, A4L1T17, A4L1T19, A4L2T18, A4L2T14, A4L3T19, A4L3T14, A40L1T15, A41L1T15, A5L2T21, A5L3T22, A6L2T18, A6L3T19, A10L1T19, A38L1T15, A39L1T15, and A42L1T20, and tautomers, stereoisomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof.

68. A compound selected from the group: A1L1, A2L1, A3L1, A4L1, A5L1, A6L1, A7L1, A8L1, A9L1, A11L1, A12L1, A14L1, A16L1, A17L1, A18L1, A19L1, A20L1, A21L1, A22L1, A23L1, A24L1, A25L1, A26L1, A27L1, A28L1, A29L1, A30L1, A31L1, A32L1, A33L1, A34L1, A35L1, A36L1, A37L1, A10L1, A38L1, A39L1, A40L1, A41L1, A42L1, A4L2, A5L2, A6L2, A4L3, A5L3, and A6L3.

69. A compound of formula (G1.2)



wherein

$p = 1-5$ when $q = 1-5$, and $p = 1-6$ when $q = 0-5$, with $(p + q) = 1-6$ and $p \neq 0$;

when $p > 1$, then each one of the plurality of LT moieties is the same or different from the remaining LT moieties in the same molecule, and

when $q > 1$, then each one of the plurality of ST moieties is the same or different from the remaining ST moieties in the same molecule;

R, in each ST moiety, is OH, COOH, CHO, OR', COOR', C(O)NH₂, or C(O)NHR', with R' being H or (CH₂)_{q'}CH₃, with $q' = 1-4$, $q'' = 1-4$, $q \geq 1$;

wherein

moiety B is C(O)O, OC(O), C(O)NH, HNC(O), or CH₂CH₂,

$p' = 0-4$;

$p'' = 0-4$;

$m' = 0, 1$;

moiety T is selected from

$\text{CH}((\text{CH}_2)_l\text{CH}_3)-\text{CH}_2)_{ll'}\text{CH}_3$, $ll' = 2-6$, $ll' = 2-6$

$\text{CH}_3-(\text{CH}_2)_k-\text{CH}_2$, $k = 2-14$;

$(\text{CH}_3-(\text{CH}_2)_k)_2-\text{CH}-(\text{CH}_2)_{k''}-\text{CH}_2$, $k' = 0-8$, $k'' = 0-9$;

$\text{CH}_3-(\text{CH}_2)_{kk'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kk''}-\text{CH}_2$, $kk' = 5-8$, $kk'' = 5-8$;

$\text{CH}_3-(\text{CH}_2)_{kp}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp'}-\text{CH}=\text{CH}-(\text{CH}_2)_{kp''}-\text{CH}_2$, $kp = 5-7$, $kp'' = 5-7$,

$kp' = 1-3$;

$\text{CH}_3-(\text{CH}_2)_l-\text{O}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-4$; and

$(\text{CH}_3-(\text{CH}_2)_l-\text{CH}_2)_2-\text{CH}-\text{MS}-\text{C}(\text{O})-(\text{CH}_2)_{kk''}-\text{CH}_2$, $l = 2-7$, $kk'' = 0-5$, MS is

O or NH;

and when $p > 1$, then each one of the plurality of T moieties is the same or different from the remaining T moieties in the same molecule,

and

A is an amino moiety, and said amino moiety A is selected depending on the (p+q)-value as follows, wherein the term * is used to refer to a N-binding site of an LT moiety, and *(*) (or (*)*) indistinguishably is used to refer to two separate N-binding sites of two LT moieties:

when $p = 1$ and $q = 1$, then A is *(*)N-(CH₂)_l-Z,

$l = 2-6$,

Z is N-pyrrolidino, N-piperidino, OCH₃, OH, N(CH₂-CH₃)₂, or N(CH₃)₂,

when $p+q = 4$, with $p \geq 1$ and $q \geq 1$, then A is

()N-(CH₂)_{w1}-E-(CH₂)_{w2}-N(*)*,

$w1 = 2-6$,

$w2 = 2-6$,

E is bond, substituted or unsubstituted amino, O-phenylene-

O, O-(CH₂)_{w3}-(substituted or unsubstituted 1,4-

piperazinediyl)-(CH₂)_{w4}-O, substituted or unsubstituted 1,4-

piperazinediyl, S-S, XS-S-S-XS, XS-(substituted or

unsubstituted 1,4-piperazinediyl)-XS, EE-(1,4-cyclohexanediyl)-EE, or EE-(1,3-cyclohexanediyl)-EE, wherein $w_3 = 0-4$, $w_4 = 0-4$, XS is C(O)-O-(CH₂)₂, and EE is O, C(O)-O or C(O)-NH,

when $p+q = 5$, with $p \geq 1$ and $q \geq 1$, then A is

$^{*}(\text{N}-(\text{CH}_2)_{p1}-\text{N}^{*}-(\text{CH}_2)_{p2}-\text{N}(\text{N}^{*})^{*})^{*}$, $p1 = 2-5$,

$p2 = 2-5$, and

when $p+q = 6$, with $p \geq 1$ and $q \geq 1$, then A is

$^{*}(\text{N}-(\text{CH}_2)_{q1}-\text{N}((\text{CH}_2)_{q2}-\text{N}(\text{N}^{*})^{*})-(\text{CH}_2)_{q3}-\text{N}(\text{N}^{*})^{*})^{*}$,

$q1 = 2-4$, $q2 = 2-4$, and $q3 = 2-4$;

or a stereoisomer, tautomer, constitutional isomer, constitutional isomer, pharmaceutically acceptable salt or solvate thereof.

70. A compound of claim 69, wherein $p = 2$ and $q = 3$.

71. A compound of claim 69, wherein $p = 3$, and $q = 2$.

72. A compound of claim 69, wherein $p + q = 5$, and A is $^{*}(\text{N}-(\text{CH}_2)_{p1}-\text{N}^{*}-(\text{CH}_2)_{p2}-\text{N}(\text{N}^{*})^{*})^{*}$, $p1 = 2-5$, $p2 = 2-5$.

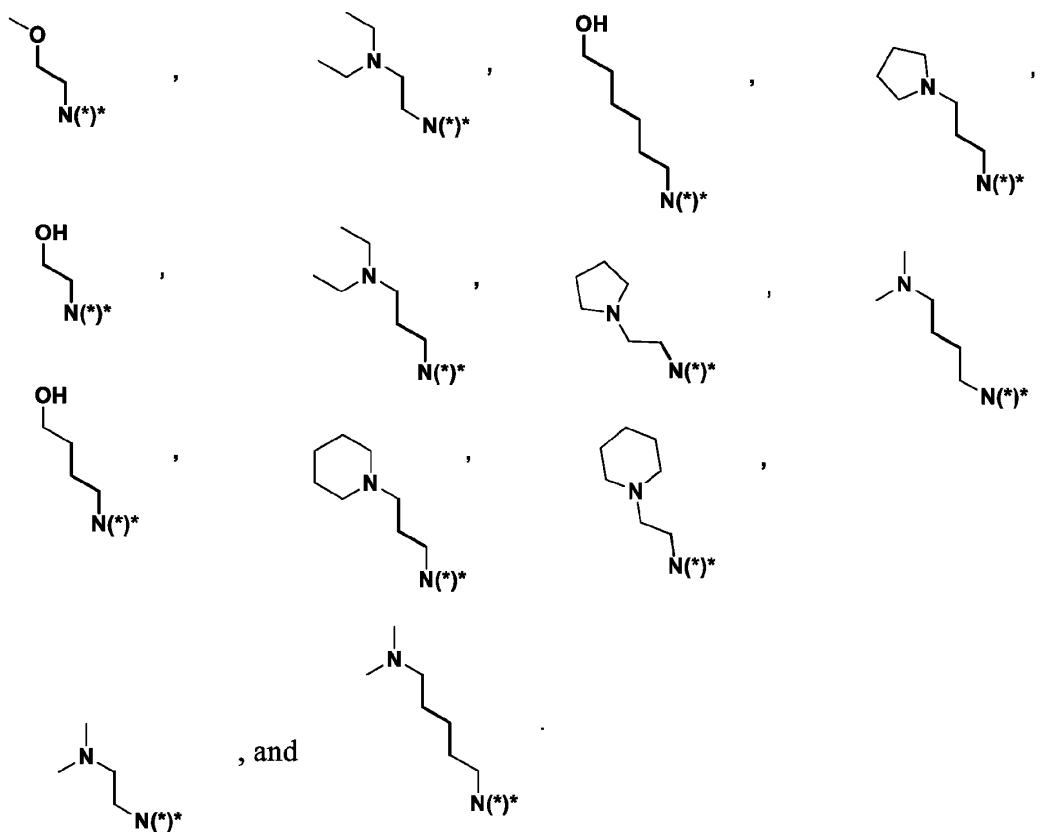
73. A compound of claim 69, wherein $p + q = 5$, and A is $^{*}(\text{N}-(\text{CH}_2)_4-\text{N}^{*}-(\text{CH}_2)_3-\text{N}(\text{N}^{*})^{*})^{*}$.

74. A compound of claim 69, wherein $q \geq 2$, and all the ST moieties are the same.

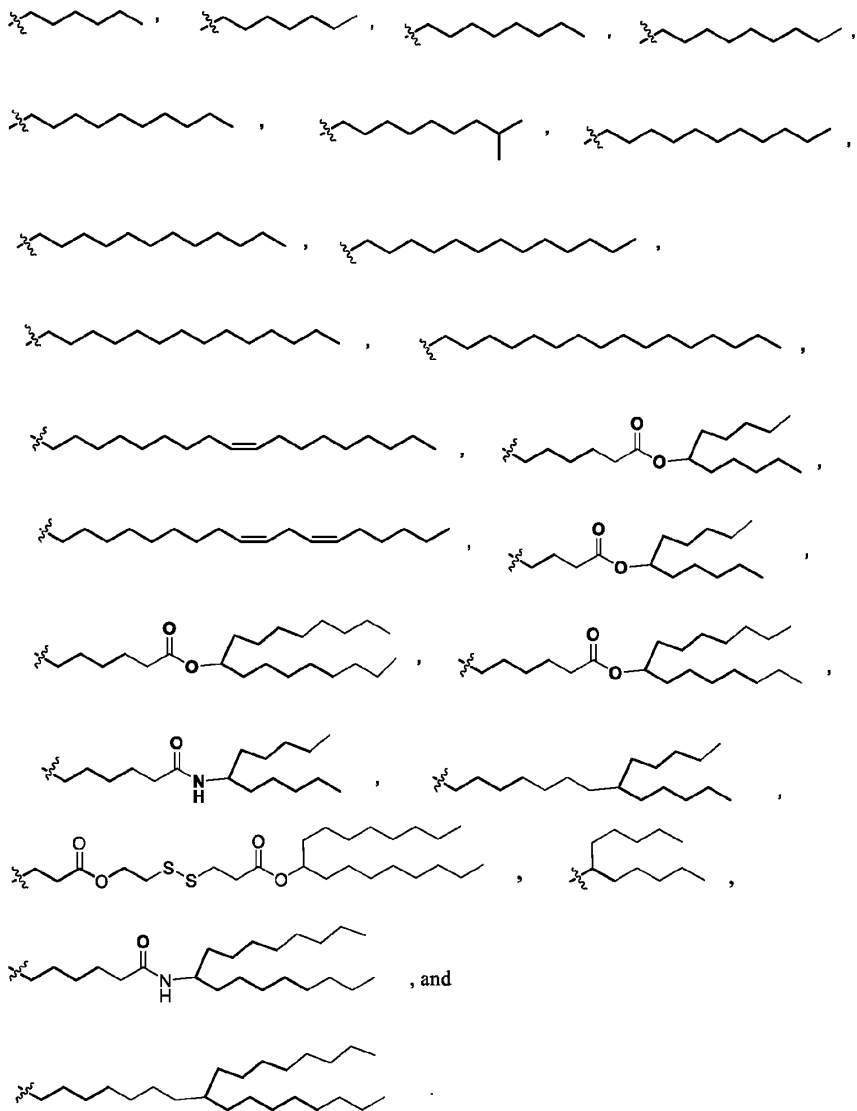
75. A compound of claim 69, wherein $p \geq 2$, and all the LT moieties are the same.

76. A compound of claim 69, wherein $p \geq 2$ and $q \geq 2$, and all the ST moieties are the same and all the LT moieties are the same.

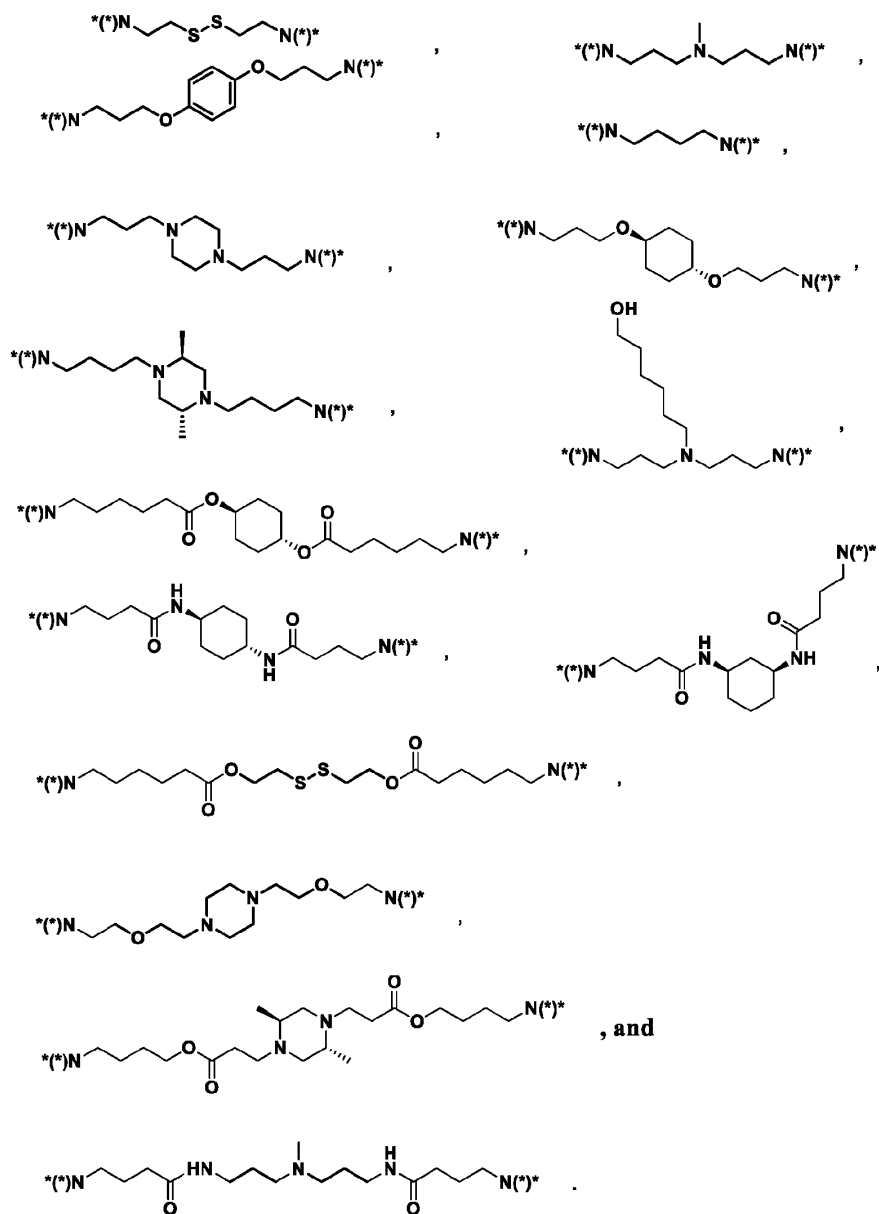
77. A compound of claim 69, wherein $p + q = 2$, $p = 1$ and $q = 1$, wherein said compound has formulae A(ST)(LT), wherein the amine moiety A is selected from the following moieties:



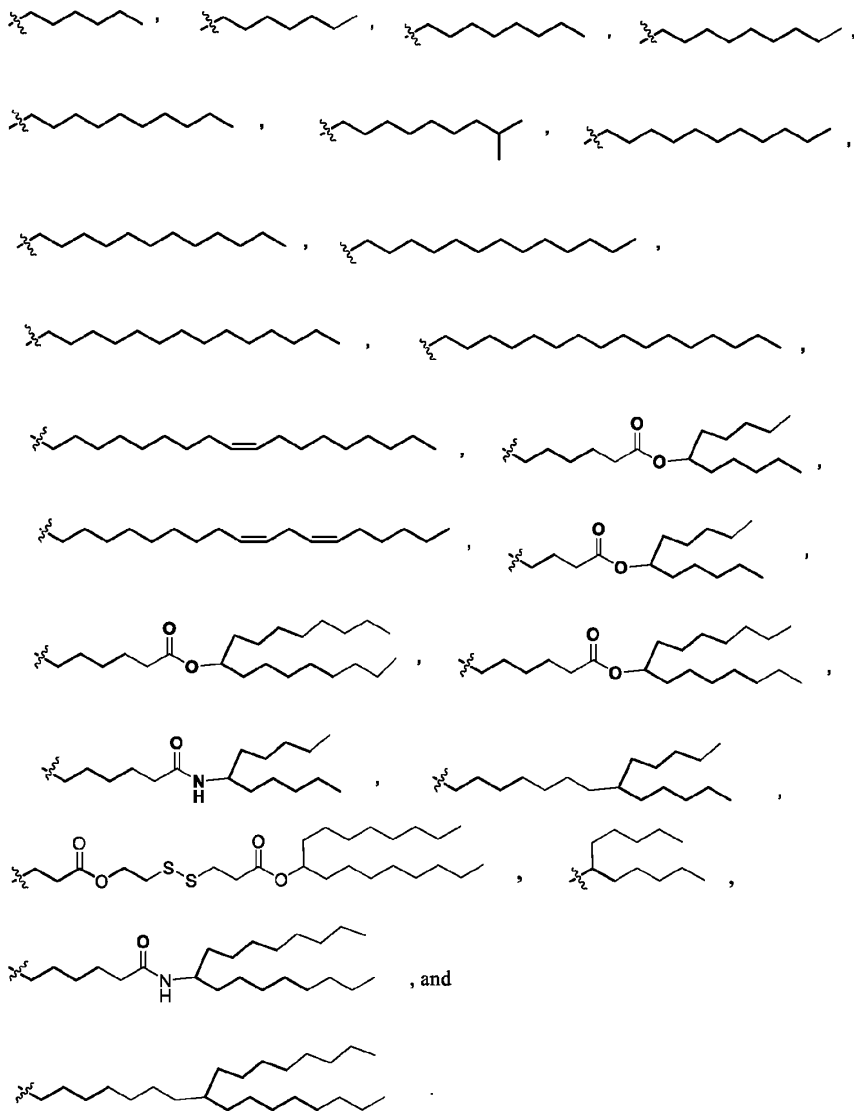
78. A compound of claim 77, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:



79. A compound of claim 69, wherein $p + q = 4$, $p + q = 2$, $p \geq 1$ and $q \geq 1$, and A is selected from the following moieties:

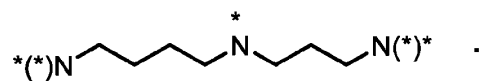


80. A compound of claim 79, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:

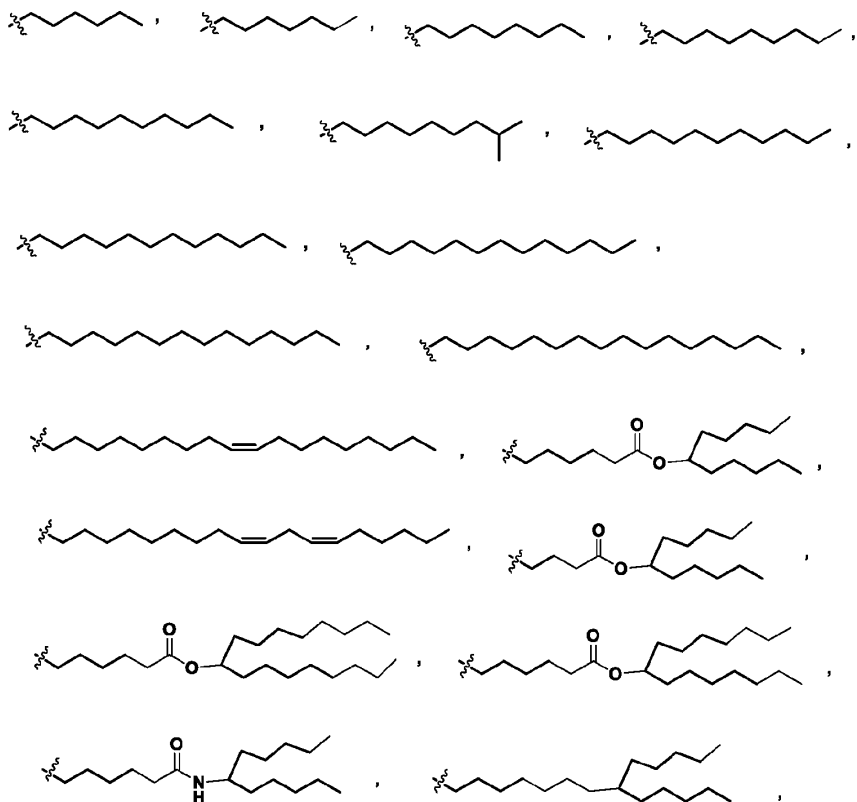


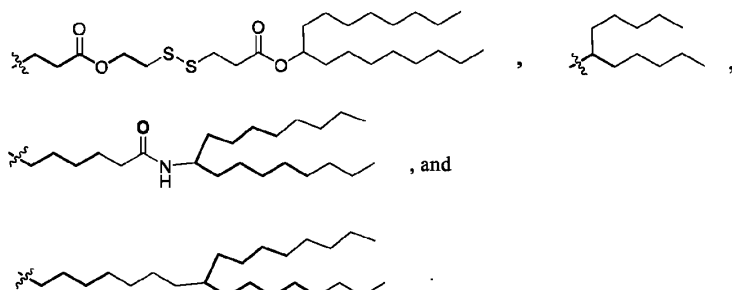
81. A compound of claim 80, wherein the [p, q] pair value is one of [p = 1, q = 3]; [p = 2, q = 2]; and [p = 3, q = 1].

82. A compound of claim 69, wherein $p+q = 5$, $p \geq 1$ and $q \geq 1$ and A is the following moiety:



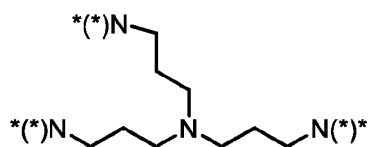
83. A compound of claim 82, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and moiety T is selected from the following moieties:



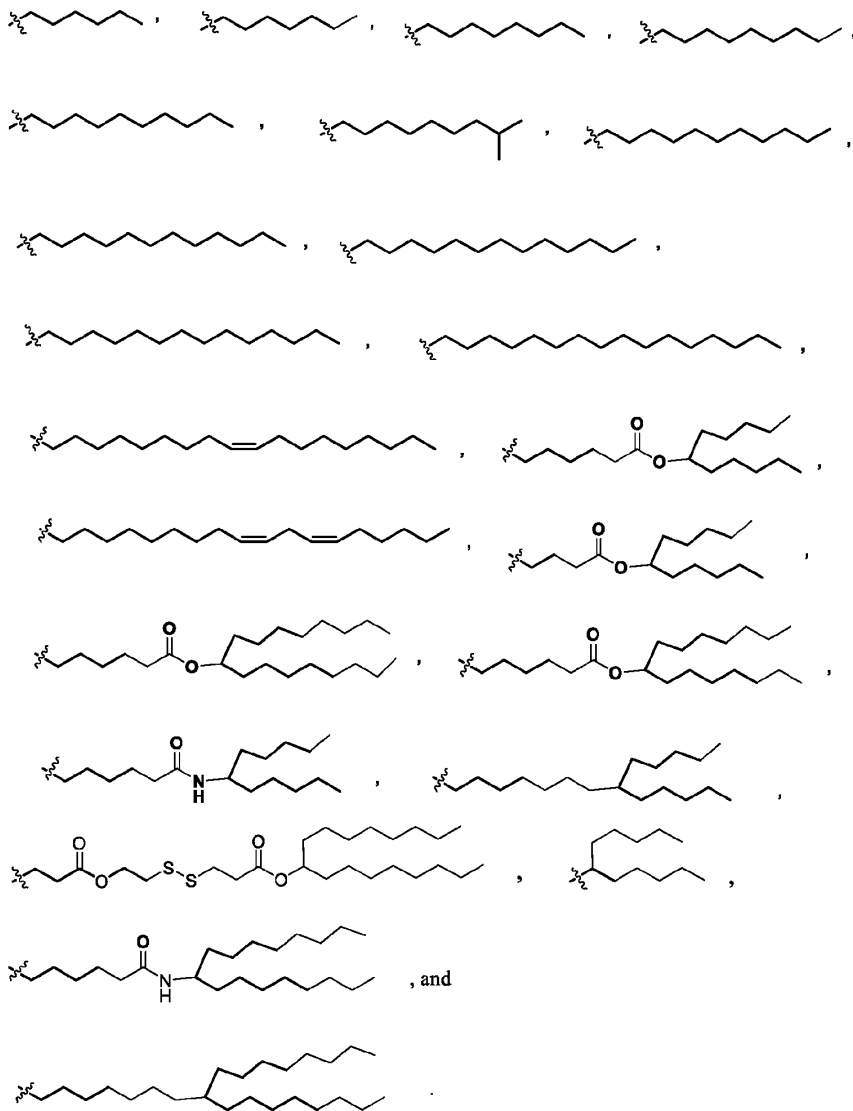


84. A compound of claim 83, wherein the [p, q] pair value is one of [p = 1, q = 4]; [p = 2, q = 3]; [p = 3, q = 2], and [p = 4, q = 1].

85. A compound of claim 69, wherein $p+q=6$, $p \geq 1$ and $q \geq 1$ and A is the following moiety:



86. A compound of claim 85, wherein $p' = p'' = 1$, B is C(O)O, C(O)NH or CH₂CH₂, and T is selected from the following moieties:



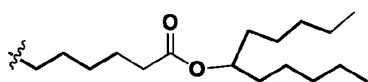
87. A compound of claim 86, wherein the [p, q] pair value is one of [p = 1, q = 5]; [p = 2, q = 4]; [p = 3, q = 3], [p = 4, q = 2], and [p = 5, q = 1].

88. A compound of claim 82, wherein B is C(O)O.

89. A compound of claim 88, wherein all the LT moieties are the same, all the ST moieties are the same.

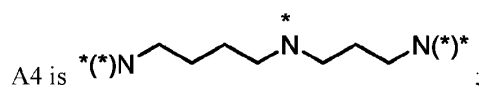
90. A compound of claim 89, wherein each ST is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, and $[p = 3 \text{ and } q = 2]$ or $[p = 2 \text{ and } q = 3]$.

91. A compound of claim 90, wherein moiety T is

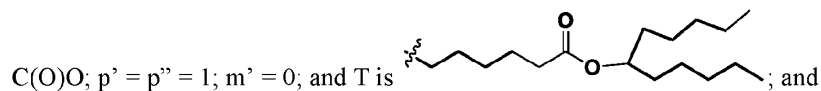


92. A compound of claim 69, wherein $(p + q) = 5$, and the compound is selected from compounds:

$\text{A4}(\text{L1T14})_3(\text{ST1})_2$, and $\text{A4}(\text{L1T14})_2(\text{ST1})_3$; wherein



all the LT moieties are the same L1T14, wherein each of said L1T14 is defined by B being



all ST moieties are the same ST1, wherein each of said ST1 moieties is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$.

93. A compound of claim 92, wherein the compound is selected from the group:

$\text{A4}(\text{L1T14})_{1-1}(\text{L1T14})_{2-4}(\text{ST1})_{2-3(1)}$, $\text{A4}(\text{L1T14})_{1-1}(\text{ST1})_{2-4}(\text{L1T14})_{2-3(1)}$,

$\text{A4}(\text{L1T14})_{2-4}(\text{ST1})_{1-1}(\text{L1T14})_{1-3(1)}(\text{ST1})_{1-3(1)}$,

$\text{A4}(\text{L1T14})_{1-4}(\text{ST1})_{1-4}(\text{ST1})_{1-1}(\text{L1T14})_{2-3(1)}$, $\text{A4}(\text{L1T14})_{1-3(1)}(\text{ST1})_{1-3(1)}(\text{ST1})_{1-1}(\text{L1T14})_{2-4}$,

and $\text{A4}(\text{L1T14})_{1-1}(\text{ST1})_{1-1}(\text{ST1})_{1-1}(\text{L1T14})_{2-3(1)}$.

94. A compound of claim 93, wherein the compound is selected from the group:

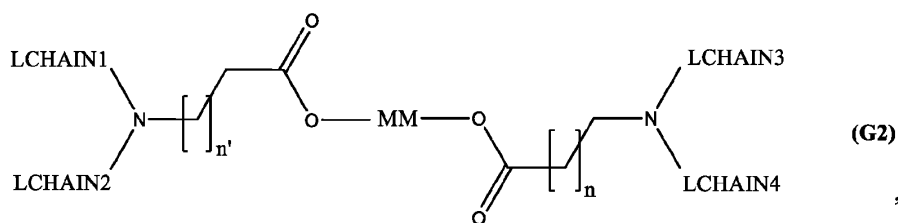
$\text{A4}(\text{L1T14})_{1-1}(\text{L1T14})_{2-4}(\text{ST1})_{2-3(1)}$, and $\text{A4}(\text{L1T14})_{1-1}(\text{ST1})_{2-4}(\text{L1T14})_{2-3(1)}$.

95. A compound of claim 92, wherein the compound is selected from the group:

A4(ST1)₁₋₁(ST1)₂₋₄(L1T14)₂₋₃₍₁₎, A4(ST1)₁₋₁(L1T14)₂₋₄(ST1)₂₋₃₍₁₎,
 A4(ST1)₂₋₄(L1T14)₁₋₁(ST1)₁₋₃₍₁₎(L1T14)₁₋₃₍₁₎,
 A4(ST1)₁₋₄(L1T14)₁₋₄(L1T14)₁₋₁(ST1)₂₋₃₍₁₎, A4(ST1)₁₋₃₍₁₎(L1T14)₁₋₃₍₁₎(L1T14)₁₋₁(ST1)₂₋₄,
 and A4(ST1)₁₋₁(L1T14)₁₋₁(L1T14)₁₋₁(ST1)₂₋₃₍₁₎.

96. A compound of claim 95, wherein the compound is selected from the group: A4(L1T14)₂₋₄(ST1)₁₋₁(ST1)₂₋₃₍₁₎, and A4(ST1)₂₋₄(ST1)₁₋₁(L1T14)₂₋₃₍₁₎.

97. A compound of formula (G2) or a tautomer, stereoisomer, constitutional isomer, pharmaceutically acceptable salt or solvates thereof,



wherein:

MM is $-\zeta-\text{C}_6\text{H}_{10}-\zeta-$, (MM1),

$-\zeta-\text{CH}_2\text{CH}_2\text{S}-\text{CH}_2\text{CH}_2-\zeta-$, (MM2),

$-\zeta-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2\text{CH}_2-\zeta-$, (MM3),

$-\zeta-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2\text{CH}_2-\zeta-$, $t = 0-3$, $t' = 0-3$, (MM4), or

$-\zeta-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2\text{CH}_2-\zeta-$, $t1 = 1-3$, $t2 = 1-3$, $t3 = 1-3$, $t4 = 1-3$, (MM5)

wherein each one of LCHAIN1, LCHAIN2, LCHAIN3 and LCHAIN4 is
 a linear or branched C_a-alkyl, with $a = 9-15$, or
 $\text{CH}_2(\text{CH}_2)_v\text{CH}=\text{CH}(\text{CH}_2)_{v'}\text{CH}_3$, with $v' = 1-4$, $v'' = 2-5$;

and each occurrence of LCHAIN1 - LCHAIN4 is the same or different from each of any of the other three occurrences of LCHAIN1 - LCHAIN4;

$n = 0 - 4$;

$n' = 0 - 4$, and each occurrence of n is the same or different from each occurrence of n' ;

Q is $(CH_2)_rCH_3$ with $r = 0-2$, or $CH_2(CH_2)_rC(O)O(CH_2)_{r'}CH_3$ with $r' = 0-3$ and $r'' = 1-3$.

98. A compound of claim 97, wherein each of LCHAIN1 - LCHAIN4 is a linear C_a -alkyl, with $a = 9-15$.

99. A compound of claim 97, at least one of LCHAIN1 - LCHAIN4 is a branched C_a -alkyl, with $a = 9-15$.

99. A compound of claim 98, wherein LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 = linear C_a -alkyl, with $a = 9-15$.

100. A compound of claim 99, wherein LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is $CH_3-(CH_2)_8-CH_2$, $CH_3-(CH_2)_{10}-CH_2$, or $CH_3-(CH_2)_{12}-CH_2$.

101. A compound of claim 97, LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is $CH_2(CH_2)_{\nu}CH=CH(CH_2)_{\nu'}CH_3$, with $\nu' = 2$, $\nu'' = 4$.

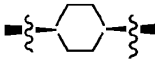
102. A compound of claim 97, wherein $n = n'$.

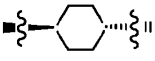
103. A compound of claim 102, wherein $n = n' = 1$.

104. A compound of claim 97, $n = 1$ and $n' = 4$.

105. A compound of claim 97, wherein $n = 4$ and $n' = 1$.

106. A compound of claim 97, wherein MM is MM1.

107. A compound of claim 106, wherein MM1 is  (MM1.1).

108. A compound of claim 106, wherein MM1 is  (MM1.2).

109. A compound of claim 107, wherein $n = n' = 1$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is $\text{CH}_3\text{-(CH}_2)_8\text{-CH}_2$, $\text{CH}_3\text{-(CH}_2)_{10}\text{-CH}_2$, or $\text{CH}_3\text{-(CH}_2)_{12}\text{-CH}_2$.

110. A compound of claim 108, wherein $n = n' = 1$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is $\text{CH}_3\text{-(CH}_2)_8\text{-CH}_2$, $\text{CH}_3\text{-(CH}_2)_{10}\text{-CH}_2$, or $\text{CH}_3\text{-(CH}_2)_{12}\text{-CH}_2$.

111. A compound of claim 97, wherein MM is MM2.

112. A compound of claim 97, wherein MM is MM3.

113. A compound of claim 97, wherein MM is MM4.

114. A compound of claim 113, wherein Q is $(\text{CH}_2)_r\text{CH}_3$ with $r = 0-1$, or $\text{CH}_2(\text{CH}_2)_r\text{C(O)O(CH}_2)_{r'}\text{CH}_3$ with $r' = 1-2$ and $r'' = 1-3$.

115. A compound of claim 113, wherein Q is CH_3 , or $\text{CH}_2(\text{CH}_2)_r\text{C(O)O(CH}_2)_{r'}\text{CH}_3$ with $r' = 1$ and $r'' = 1$.

116. A compound of claim 113, wherein Q is CH_3 , or $\text{CH}_2(\text{CH}_2)_r\text{C(O)O(CH}_2)_{r'}\text{CH}_3$ with $r' = r'' = 1$, and $t = t' = 1, 2$.

117. A compound of claim 113, wherein $t = 1, 2$ and $t' = 1, 2$.

118. A compound of claim 113, wherein $t = t' = 1, 2$.

119. A compound of claim 97, wherein MM is MM5.
120. A compound of claim 119, wherein $t1 = 1, 2$, $t2 = 1, 2$, $t3 = 1, 2$, $t4 = 1, 2$.
121. A compound of claim 119, wherein $t1 = t2 = t3 = t4 = 1, 2$.
122. A compound of claim 119, wherein $t1 = t2 = t3 = t4 = 1$.
123. A compound of claim 119, wherein $t1 = t2 = t3 = t4 = 1$, Q is CH₃. 124. A compound of claim 111, wherein $n = n' = 1$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
125. A compound of claim 111, wherein $n = 1$, $n' = 4$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
126. A compound of claim 112, wherein $n = n' = 1$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
127. A compound of claim 112, wherein $n = 1$, $n' = 4$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
128. A compound of claim 113, wherein $n = n' = 1$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
129. A compound of claim 113, wherein $n = 1$, $n' = 4$, and LCHAIN1 = LCHAIN2 = LCHAIN3 = LCHAIN4 is CH₃-(CH₂)₈-CH₂, CH₃-(CH₂)₁₀-CH₂, or CH₃-(CH₂)₁₂-CH₂.
130. A compound of any one of claims 98-101, 102-105, 109, 110, 125-129, wherein MM is selected from MM1, MM2 and MM3.

131. A compound of any one of claims 98-101, 102-105, 109, 110, 125-129, wherein MM is MM4, Q is $(\text{CH}_2)_r\text{CH}_3$ with $r = 0-2$, or $\text{CH}_2(\text{CH}_2)_r\text{C}(\text{O})\text{O}(\text{CH}_2)_{r'}\text{CH}_3$ with $r' = 0-3$ and $r'' = 1-3$, $t = 0-3$, and $t' = 0-3$.

132. A compound of any one of claims 98-101, 102-105, 109, 110, 125-129, wherein MM is MM5, Q is $(\text{CH}_2)_r\text{CH}_3$ with $r = 0-2$, or $\text{CH}_2(\text{CH}_2)_r\text{C}(\text{O})\text{O}(\text{CH}_2)_{r'}\text{CH}_3$ with $r' = 0-3$ and $r'' = 1-3$, $t1 = 1-3$, $t2 = 1-3$, $t3 = 1-3$, and $t4 = 1-3$.

133. A compound selected from the group: A101T101, A101T102, A101T103, A102T101, A102T102, A102T103, A103T101, A103T102, A103T103, A104T101, A104T102, A104T103, A105T101, A105T102, A105T103, A106T101, A106T102, A106T103, A107T101, A107T102, A107T103, A109T101, A107T104, A110T101, A108T101, and tautomers, stereoisomers, constitutional isomers, constitutional isomers, pharmaceutically acceptable salts and solvates thereof.

134. A compound of any one of claims 1, 26-36, 66-69, 77-96, 97-133, wherein the compound is in the form of a pharmaceutically acceptable salt.

135. A lipid nanoparticle comprising one or more than one ionizable lipids, wherein at least one of said ionizable lipids is a compound of any one of claims 1, 26-36, 66-69, 77-96, 97-133.

136. A lipid nanoparticle of claim 135, wherein said at least one of said ionizable lipids is selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

137. A lipid nanoparticle of claim 135, further comprising one or more than one helper lipid, one or more than one structural lipids, and one or more than one PEG-lipids.

138. A lipid nanoparticle of claim 137, wherein said at least one ionizable lipid is selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

139. A lipid nanoparticle of claim 137, wherein said one or more than one ionizable lipid is present in a total ionizable lipid mole percentage from about 15% to about 60%; said one or more than one helper lipid is present in a total helper lipid mole percentage from about 10% to about 30%; said structural lipid is present in a total structural lipid mole percentage from about 30% to about 65%; and said PEG lipid is present in a total PEG lipid mole percentage from about 0.01% to about 10%.

140. A lipid nanoparticle of claim 139, wherein said at least one ionizable lipid is selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

141. A lipid nanoparticle of claim 140, wherein said at least one ionizable lipid is selected from compounds A4L1T14 and A5L1T15.

142. A lipid nanoparticle of claim 139, wherein

said total ionizable lipid mole percentage is about 35%; said one total helper lipid mole percentage is about 16%; said total structural lipid mole percentage is about 46.5%; and said total PEG lipid mole percentage is about 2.5%;

said total ionizable lipid mole percentage is about 50%; said one total helper lipid mole percentage is about 16%; said total structural lipid mole percentage is about 31.5%; and said total PEG lipid mole percentage is about 2.5%;

said total ionizable lipid mole percentage is about 35%; said one total helper lipid mole percentage is about 16%; said total structural lipid mole percentage is about 45.5%; and said total

PEG lipid mole percentage is about 3.5%;

said total ionizable lipid mole percentage is about 35%; said one total helper lipid mole percentage is about 16%; said total structural lipid mole percentage is about 46.5%; and said total PEG lipid mole percentage is about 2.5%;

said total ionizable lipid mole percentage is about 35%; said one total helper lipid mole percentage is about 25%; said total structural lipid mole percentage is about 37.5%; and said total PEG lipid mole percentage is about 2.5%;

said total ionizable lipid mole percentage is about 18.7%; said one total helper lipid mole percentage is about 20%; said total structural lipid mole percentage is about 58.1%; and said total PEG lipid mole percentage is about 3.1%; or

said total ionizable lipid mole percentage is about 35%; said one total helper lipid mole percentage is about 16%; said total structural lipid mole percentage is about 46.5%; and said total PEG lipid mole percentage is about 2.5%.

143. A lipid nanoparticle of claim 142, wherein said one or more than one ionizable lipid is one compound and said compound is selected from compounds A4L1T14, A5L1T15, A7L1T14, A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

144. A lipid nanoparticle of claim 143, wherein said one or more than one ionizable lipid is one compound and said compound is selected from compounds A4L1T14 and A5L1T15.

145. A lipid nanoparticle of claim 142, wherein the lipid nanoparticle is an LNP and said LNP has a size in any of the following ranges: from about 10 nm to about 500 nm, from about 20 nm to about 400 nm, from about 40 nm to about 200 nm, from about 50 nm to about 180, from 55 nm to about 125 nm, and from 58 nm to about 100 nm.

146. A lipid nanoparticle of claim 145, wherein said one or more than one ionizable lipid is one compound and said compound is selected from compounds A4L1T14, A5L1T15, A7L1T14,

A9L1T15, A3L1T14, A4L1T16, A4L1T17, A4L2T14, A4L2T18, A4L3T14, A6L1T16, A6L1T15, A5L1T15, A7L1T15, A9L1T2, A4L1T14, A12L1T3, A14L1T15, A16L1T13, A22L1T15, A24L1T15, A26L1T12, A27L1T12, A19L1T15, A32L1T15, A4L1T15, A106T101, and A107T101.

147. A lipid nanoparticle of claim 146, wherein said one or more than one ionizable lipid is one compound and said compound is selected from compounds A4L1T14 and A5L1T15.

148. A lipid nanoparticle of claim 135, further comprising a therapeutic agent.

149. A lipid nanoparticle of claim 148, wherein the therapeutic agent is a nucleic acid.

150. A lipid nanoparticle of claim 149, wherein the nucleic acid selected from an oligonucleotide, an RNA, and a DNA.

151. A lipid nanoparticle of claim 148, wherein the therapeutic agent is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

152. A lipid nanoparticle of claim 148, wherein the therapeutic agent is a nucleic acid selected from a minigene, a plasmid, a minicircle, a small interfering RNA (siRNA), a microRNA (miRNA), an antisense oligonucleotides (ASO), a ribozyme, a closed ended double stranded DNA, a linear covalently closed DNA (ministring), a doggybone protelomere closed-ended DNA, a dumbbell linear DNA, a dicer-substrate dsRNA, a small hairpin RNA (shRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), an mRNA, a tRNA, an rRNA, a DNA viral vectors, a viral RNA vector, and any combination thereof.

153. A lipid nanoparticle of claim 146, further comprising a therapeutic agent that is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an mRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

154. A lipid nanoparticle of claim 153, wherein the therapeutic agent is an mRNA and the lipid nanoparticle with said mRNA is a vaccine.

155. A pharmaceutical composition comprising a lipid nanoparticle of claim 148 and a pharmaceutically acceptable carrier.

156. A compound of any one of claims 1-67, 69-133, for use in LNP drug delivery, vaccine delivery or cancer immunotherapy.

157. A compound of claim 156 for use in vaccine delivery.

158. A compound of claim 156 for use in vaccine delivery, wherein the vaccine is an mRNA LNP.

159. A compound of claim 155, wherein the drug is dsDNA, DNA, mRNA, siRNA, or small molecule.

160. A method of treating a disease or disorder, comprising providing the subject a pharmaceutical composition of claim 155.

161. A method of inducing an immune response in a subject, comprising providing the subject a pharmaceutical composition of claim 15.

162. A method of claim 161, wherein said therapeutic agent within said pharmaceutical composition comprises an mRNA.

163. A method of claim 162, wherein the mRNA LNP is a vaccine.

164. A method of modulating the expression of a target gene in a cell, comprising providing the subject a pharmaceutical composition of claim 155.

165. A method for delivering a therapeutic level of active agent to a subject, comprising administering to the subject a pharmaceutical composition of claim 155.