

RAPIDLY-METABOLIZED LIPID COMPOUND

[0001] The present application claims the priority of the Chinese Patent Application No. 202310720951.5 filed on June 16, 2023, Chinese Patent Application No. 202310723466.3 filed on June 16, 2023, and Chinese Patent Application No. 202410115561.X filed on January 26, 2024. The Chinese Patent Applications mentioned above are incorporated herein by reference as part of the disclosure of the present application.

TECHNICAL FIELD

[0002] The present disclosure relates to a novel class of ionizable cationic lipid compounds, or pharmaceutically acceptable salts, isotopic variants, tautomers, or stereoisomers thereof. The present disclosure also relates to lipid nanoparticles and pharmaceutical compositions comprising said compound, and the application of the lipid nanoparticles in the delivery of biologically active substances such as nucleic acids (e.g., mRNA, siRNA, ASO, and DNA).

BACKGROUND

[0003] Gene therapy refers to the introduction of exogenous genes into target cells to correct or compensate for genetic defects or abnormalities within the cell, so as to achieve the purpose of treatment. In the past few decades, research related to the treatment of clinical diseases through gene therapy has received more and more attention. Especially in recent years, siRNA-related drugs and mRNA vaccines have been approved by the FDA for clinical treatment, which has further promoted research and related investment in the field of gene therapy.

[0004] Nucleic acid substances are easily degraded by nucleases in organisms, and nucleic acid substances themselves are negatively charged, which makes it difficult for them to enter the cell through the cell membrane. As a nucleic acid delivery material, lipid nanoparticles (LNP) are one of the most important nucleic acid delivery systems

with the advantages of easy to prepare, good biodegradability, no immunogenicity and good safety. The main components of LNP include cationic lipids, cholesterol, neutral lipids and polyethylene glycol-conjugated lipids. Among them, cationic lipid molecules are the core of LNP delivery system, and their molecular structure plays a decisive role in the delivery efficiency, targeting, and formulation stability, and the like, of the entire liposome nanoparticles.

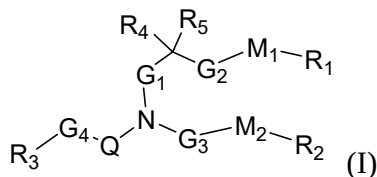
[0005] Due to the different requirements of the delivery system for the delivery of different kinds of nucleic acid substances and the specific delivery of different targets, in order to meet the different needs of gene therapy, new lipid molecules need to be further developed.

SUMMARY

[0006] The present disclosure develops a new class of ionizable cationic lipid compounds that can be used to deliver various biologically active substances with high delivery efficiency.

[0007] The inventor's prior patent CN115850104A discloses that a class of cationic lipid compounds with a pair of geminal dialkyl in each tail has high delivery efficiency. Unexpectedly, after further research, it was found that when the geminal dialkyl structure was applied to cationic lipids containing central nitrogen atoms, the cationic lipids degraded slowly in the liver, making them suitable for applications with slow degradation. For some application scenarios that require accelerating metabolism in vivo, a new class of ionizable lipid compounds is developed.

[0008] the present disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof:



[0009] wherein each group is as defined herein.

[0010] In another aspect, the present disclosure provides a nanoparticle composition comprising lipid components, and optionally a load, wherein the lipid component comprises the compound of the present disclosure.

[0011] US11246933B1 discloses that incorporation of a biodegradable group into the tail chain of a lipid compound in a lipid nanoparticle results in faster metabolism and removal of the lipid from the body following delivery of the active agent to a target area. As a result, these lipids which contain the biodegradable groups have lower toxicity than similar lipids without the biodegradable groups. The tail chain of the cationic lipid compound of the present disclosure has biodegradable group(s), thereby has superior toxicity profile to similar lipids without biodegradable groups, such as DLin-MC3-DMA.

[0012] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure or a nanoparticle composition of the present disclosure, and optionally pharmaceutically acceptable excipient(s), such as carrier(s), adjuvant(s) or vehicle(s).

[0013] In another aspect, the present disclosure provides use of the compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure in the manufacture of a medicament for treating, diagnosing, or preventing a disease. In one embodiment, the medicament for treating, diagnosing, or preventing a disease is a therapeutic or prophylactic mRNA vaccine.

[0014] In another aspect, the present disclosure provides use of the compound of the present disclosure, the nanoparticle composition of the present disclosure, or the pharmaceutical composition of the present disclosure in preparing a medicament for delivering a loading. In another aspect, the present disclosure provides the use of a compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure in the manufacture of a medicament for delivering a load.

[0015] In another aspect, the present disclosure provides a method of treating, diagnosing, or preventing a disease in a subject, comprising administering to the subject a compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure.

[0016] In another aspect, the present disclosure provides a compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure, for use in treating, diagnosing, and/or preventing a disease.

[0017] In another aspect, the present disclosure provides a method of delivering a load in a subject, comprising administering to the subject a compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure.

[0018] In another aspect, the present disclosure provides a compound of the present disclosure, a nanoparticle composition of the present disclosure, or a pharmaceutical composition of the present disclosure, for use in delivering a load.

[0019] In a specific embodiment, the load is selected from one or more of therapeutic agents, prophylactic agents, and diagnostic agents; alternatively, the therapeutic agent, prophylactic agent, or diagnostic agent is a nucleic acid.

[0020] In a more specific embodiment, the nucleic acid is selected from one or more of ASO, RNA and DNA.

[0021] In a more specific embodiment, the RNA is selected from one or more of small interfering RNA (siRNA), short hairpin RNA (shRNA), antisense RNA (aRNA), messenger RNA (mRNA), long non-coding RNA (lncRNA), microRNA (miRNA), small activating RNA (saRNA), multimeric coding nucleic acid (MCNA), polymeric coding nucleic acid (PCNA), guide RNA (gRNA), CRISPRRNA (crRNA), and a ribozyme, alternatively mRNA, and more alternatively modified mRNA.

Definitions

Chemical definitions

[0022] Definitions of specific functional groups and chemical terms are described in more detail below.

[0023] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁₋₆ alkyl” includes C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0024] “C₁₋₂₀ alkyl” refers to a linear or branched saturated hydrocarbon group having 1 to 20 carbon atoms. In some embodiments, C₄₋₂₀ alkyl, C₆₋₁₄ alkyl, C₇₋₁₂ alkyl, C₈₋₁₂ alkyl, C₉₋₁₂ alkyl, C₄₋₁₀ alkyl, C₇₋₁₁ alkyl, C₈₋₁₁ alkyl, C₉₋₁₁ alkyl, C₁₀₋₁₁ alkyl, C₆₋₁₀ alkyl, C₇₋₁₀ alkyl, C₈₋₁₀ alkyl, C₉₋₁₀ alkyl, C₁₀ alkyl, C₈₋₉ alkyl, C₄₋₉ alkyl, C₆₋₉ alkyl, C₇₋₉ alkyl, C₉ alkyl, C₁₀ alkyl, C₁₁ alkyl, C₂₋₈ alkyl, C₄₋₈ alkyl, C₅₋₈ alkyl, C₆₋₈ alkyl, C₇₋₈ alkyl, C₈ alkyl, C₆₋₇ alkyl, C₇ alkyl, C₄₋₆ alkyl, C₁₋₂₀ alkyl, C₁₋₁₄ alkyl, C₂₋₁₄ alkyl, C₁₋₁₃ alkyl, C₁₋₁₂ alkyl, C₁₋₁₀ alkyl, C₁₋₉ alkyl, C₁₋₈ alkyl, C₁₋₇ alkyl, C₂₋₇ alkyl, C₁₋₆ alkyl, C₂₋₆ alkyl, C₁₋₅ alkyl, C₅ alkyl, C₁₋₄ alkyl, C₂₋₄ alkyl, C₁₋₃ alkyl, C₂₋₃ alkyl, C₁₋₂ alkyl, and Me are preferred. Examples of C₁₋₆ alkyl include: methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), isobutyl (C₄), n-pentyl (C₅), 3-pentyl (C₅), pentyl (C₅), neopentyl (C₅), 3-methyl-2-butyl (C₅), tert-pentyl (C₅), and n-hexyl (C₆). The term “C₁₋₆ alkyl” also includes heteroalkyl, wherein one or more (e.g., 1, 2, 3, or 4) carbon atoms are substituted with heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, or phosphorus). An alkyl group may optionally be substituted with one or more substituents, for example, 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. Conventional abbreviations of alkyl groups include: Me (-CH₃), Et (-CH₂CH₃), iPr (-CH(CH₃)₂), nPr (-CH₂CH₂CH₃), n-Bu (-CH₂CH₂CH₂CH₃), or i-Bu (-CH₂CH(CH₃)₂). In some embodiments, alkyl is preferably linear alkyl.

[0025] “C₂₋₁₃ alkenyl” refers to a linear or branched hydrocarbon group having 2 to 13 carbon atoms and at least one carbon-carbon double bond. “C₄₋₂₀ alkenyl” refers to a linear or branched hydrocarbon group having 4 to 20 carbon atoms and at least one carbon-carbon double bond. In some embodiments, C₄₋₁₄ alkenyl, C₆₋₁₄ alkenyl, C₇₋₁₂ alkenyl, C₄₋₁₀ alkenyl, C₂₋₁₀ alkenyl, C₂₋₉ alkenyl, C₂₋₆ alkenyl, and C₂₋₄ alkenyl are preferred. Examples of C₂₋₆ alkenyl include: ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), etc. The term “C₂₋₆ alkenyl” also includes heteroalkenyl where one or more (e.g., 1, 2, 3, or 4) carbon atoms are replaced with heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, or phosphorus). An alkenyl group may optionally be substituted with one or more substituents, for example, 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0026] “C₂₋₁₃ alkynyl” refers to a linear or branched hydrocarbon group having 2 to 13 carbon atoms, at least one carbon-carbon triple bond, and optionally one or more carbon-carbon double bonds. “C₄₋₂₀ alkynyl” refers to a linear or branched hydrocarbon group having 4 to 20 carbon atoms, at least one carbon-carbon triple bond, and optionally one or more carbon-carbon double bonds. In some embodiments, C₄₋₁₄ alkynyl, C₆₋₁₄ alkynyl, C₇₋₁₂ alkynyl, C₄₋₁₀ alkynyl, C₂₋₁₀ alkynyl, C₂₋₉ alkynyl, C₂₋₆ alkynyl, and C₂₋₄ alkynyl are preferred. Examples of C₂₋₆ alkynyl include, but are not limited to: ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), hexynyl (C₆), and the like. The term “C₂₋₆ alkynyl” also includes heteroalkynyl where one or more (e.g., 1, 2, 3, or 4) carbon atoms are replaced with heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, or phosphorus). An alkynyl group may optionally be substituted with one or more substituents, for example, 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0027] “C₁₋₂₀ alkylene” refers to a bivalent group formed by removing another hydrogen of C₁₋₂₀ alkyl, and can be substituted or unsubstituted. In some embodiments, C₄₋₂₀ alkylene, C₆₋₁₄ alkylene, C₇₋₁₂ alkylene, C₈₋₁₂ alkylene, C₄₋₁₀ alkylene, C₇₋₁₁ alkylene, C₈₋₁₁ alkylene, C₈₋₁₀ alkylene, C₉₋₁₀ alkylene, C₈₋₉ alkylene, C₄₋₉ alkylene, C₆₋₉ alkylene, C₇₋₉ alkylene, C₉ alkylene, C₂₋₈ alkylene, C₅₋₈ alkylene, C₇₋₈ alkylene, C₄₋₆ alkylene, C₁₋₂₀ alkylene, C₁₋₁₄ alkylene, C₂₋₁₄ alkylene, C₁₋₁₃ alkylene, C₁₋₁₂ alkylene, C₁₋₁₀ alkylene, C₁₋₉ alkyl, C₁₋₈ alkylene, C₁₋₇ alkylene, C₂₋₇ alkylene, C₁₋₆ alkylene, C₂₋₆ alkylene, C₁₋₅ alkylene, C₅ alkylene, C₁₋₄ alkylene, C₂₋₄ alkylene, C₁₋₃ alkylene, C₂₋₃ alkylene, C₁₋₂ alkylene, and methylene are preferred. Unsubstituted alkylene groups include, but are not limited to: methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), hexylene (-CH₂CH₂CH₂CH₂CH₂CH₂-), etc. Exemplary of substituted alkylene groups, such as those substituted with one or more alkyl (methyl) groups, include, but are not limited to: substituted methylene (-CH(CH₃)-, and -C(CH₃)₂-), substituted ethylene (-CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂-), substituted propylene (-CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH(CH₃)-, -C(CH₃)₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂C(CH₃)₂-), etc.

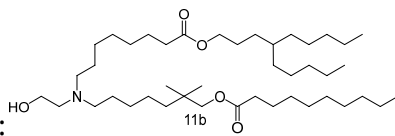
[0028] “C₂₋₁₃ alkenylene” refers to a bivalent group formed by removing another hydrogen of C₂₋₁₃ alkenyl, and can be substituted or unsubstituted. “C₄₋₁₄ alkenylene” refers to a bivalent group formed by removing another hydrogen of C₄₋₁₄ alkenyl, and can be substituted or unsubstituted. In some embodiments, C₆₋₁₄ alkenylene, C₄₋₁₀ alkenylene, C₂₋₁₀ alkenylene, C₂₋₉ alkenylene, C₂₋₆ alkenylene, and C₂₋₄ alkenylene are particularly preferred. Exemplary unsubstituted forms of the alkenylene include, but are not limited to: ethenylene (-CH=CH-) and propenylene (e.g., -CH=CHCH₂- and -CH₂-CH=CH-). Exemplary substituted alkenylene groups, for example, alkenylene substituted with one or more alkyl (methyl), include, but are not limited to: substituted ethenylene (-C(CH₃)=CH- and -CH=C(CH₃)-), substituted propenylene (-C(CH₃)=CHCH₂-, -CH=C(CH₃)CH₂-, -CH=CHCH(CH₃)-, -CH=CHC(CH₃)₂-, -CH(CH₃)-CH=CH-, -C(CH₃)₂-CH=CH-, -CH₂-C(CH₃)=CH-, -CH₂-CH=C(CH₃)-), etc.

[0029] “C₂₋₁₃ alkynylene” refers to a bivalent group formed by removing another hydrogen of C₂₋₁₃ alkynyl, and can be substituted or unsubstituted. “C₄₋₁₄ alkynylene” refers to a bivalent group formed by removing another hydrogen of C₄₋₁₄ alkynyl, and can be substituted or unsubstituted. In some embodiments, C₆₋₁₄ alkynylene, C₄₋₁₀ alkynylene, C₂₋₁₀ alkynylene, C₂₋₉ alkynylene, C₂₋₆ alkynylene, and C₂₋₄ alkynylene are particularly preferred. Exemplary alkynylene groups include, but are not limited to: ethynylene (-C≡C-), substituted or unsubstituted propynylene (-C≡CCH₂-), etc.

[0030] “C₀₋₆ alkylene” refers to a chemical bond and the “C₁₋₆ alkylene” described above. “C₀₋₄ alkylene” refers to a chemical bond and the “C₁₋₄ alkylene” described above.

[0031] The term "variable A and variable B have a total length of x carbon atoms" means that the total number of carbon atoms of the main chain in the group represented by variable A and the number of carbon atoms of the main chain in the group represented by variable B is x.

[0032] The term “the substitution site of R_{1s} on R₂ is separated from M₂ by x carbon atoms” means that the sum of the number of carbon atoms (including N atoms replaced by -NR'-) between the sites substituted by variable R_{1s} on variable R₂, and so on for other



situations. For example: , in compound 11b, the substitution site of R_{1s} on R₂ is separated from M₂ by 3 carbon atoms.

[0033] “Halo” or “halogen” refers to fluorine (F), chlorine (Cl), bromine (Br), and iodine (I).

[0034] Thus, “C₁₋₁₀ haloalkyl” refers to the above “C₁₋₁₀ alkyl”, which is substituted with one or more halogen. In some embodiments, C₁₋₈ haloalkyl, C₁₋₆ haloalkyl, C₁₋₄ haloalkyl, and C₁₋₃ haloalkyl are particularly preferred, still alternatively C₁₋₂ haloalkyl. Exemplary haloalkyl groups include, but are not limited to: -CF₃, -CH₂F, -CHF₂, -CHFCH₂F, -CH₂CHF₂, -CF₂CF₃, -CCl₃, -CH₂Cl, -CHCl₂, 2,2,2-trifluoro-1,1-dimethyl-ethyl, etc. A haloalkyl group can be substituted at any accessible point of attachment with, for example, 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0035] “C₃₋₁₄ cycloalkyl” or “3- to 14-membered cycloalkyl” refers to a radical of a non-aromatic cyclic hydrocarbon group having 3 to 14 ring carbon atoms and zero heteroatoms, optionally containing 1, 2, or 3 double or triple bonds. In some embodiments, 3- to 10-membered cycloalkyl, 5- to 10-membered cycloalkyl, 3- to 8-membered cycloalkyl, 3- to 7-membered cycloalkyl, and 3- to 6-membered cycloalkyl are particularly preferred, still alternatively 5- to 7-membered cycloalkyl, 4- to 6-membered cycloalkyl, 3- to 5-membered cycloalkyl, 3- to 4-membered cycloalkyl, and 5- to 6-membered cycloalkyl, still alternatively 5-membered cycloalkyl, still alternatively 6-membered cycloalkyl, and still alternatively cyclopropyl. The cycloalkyl also includes a ring system in which the cycloalkyl ring described above is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the cycloalkyl ring, and in such case, the number of carbon atoms continues to represent the number of carbon atoms in the cycloalkyl system. The cycloalkyl further comprises the cycloalkyl described above, in which the substituents on any non-adjacent carbon atoms are connected to form a bridged ring, together forming a polycyclic alkane sharing two or more carbon atoms. The cycloalkyl further comprises the cycloalkyl described above, in which the substituents on the same carbon atom are connected to form a ring, together forming a polycyclic alkane sharing one carbon atom. Exemplary cycloalkyl groups

include, but are not limited to: cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), etc. A cycloalkyl can optionally be substituted with one or more substituents, for example, 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0036] “C₃₋₁₄ cycloalkylene” refers to a bivalent group formed by removing another hydrogen of C₃₋₁₄ cycloalkyl and may be substituted or unsubstituted. In some embodiments, C₃₋₁₀ cycloalkylene, C₃₋₇ cycloalkylene, C₃₋₆ cycloalkylene, C₃₋₅ cycloalkylene, and C₃₋₄ cycloalkylene are particularly preferred, even still alternatively cyclopropylene.

[0037] “3-14 membered heterocyclyl” or “3- to 14-membered heterocyclyl” refers to a saturated or unsaturated group of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, optionally wherein 1, 2 or 3 double or triple bonds are contained. In a heterocyclyl containing one or more nitrogen atoms, the point of attachment can be a carbon atom or a nitrogen atom as long as the valence permits. In some embodiments, 3- to 10-membered heterocyclyl is preferred, which is a radical of 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms; in some embodiments, 5- to 10-membered heterocyclyl is preferred, which is a radical of 5- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 5 ring heteroatoms; in some embodiments, 3- to 8-membered heterocyclyl is preferred, which is a radical of 3- to 8-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms; in some embodiments, 3- to 7-membered heterocyclyl is preferred, which is a radical of 3- to 7-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms; 5- to 7-membered heterocyclyl is preferred, which is a radical of 5- to 7-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 3- to 6-membered heterocyclyl is preferred, which is a radical of 3- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 4- to 6-membered heterocyclyl is preferred, which is a radical of 4- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring

heteroatoms; 5- to 6-membered heterocyclyl is more preferred, which is a radical of 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 5-membered heterocyclyl is preferred, which is a radical of 5-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms; 6-membered heterocyclyl is preferred, which is a radical of 6-membered non-aromatic ring system having ring carbon atoms and 1 to 3 ring heteroatoms. The heterocyclyl also includes a ring system wherein the heterocyclyl described above is fused with one or more cycloalkyl groups, wherein the point of attachment is on the heterocyclyl ring, or the heterocyclyl described above is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring; and in such cases, the number of ring members continues to represent the number of ring members in the heterocyclyl ring system. The heterocyclyl further comprises the heterocyclyl described above, in which the substituents on any non-adjacent carbon or nitrogen atoms are connected to form a bridge ring, together forming a polycyclic heteroalkane sharing two or more carbon or nitrogen atoms. The heterocyclyl further comprises the heterocyclyl described above, in which the substituents on the same carbon atom are connected to form a ring, together forming a polycyclic heteroalkane sharing one carbon atom. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, but are not limited to: aziridinyl, oxiranyl, and thioirenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, but are not limited to: azetidiny, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, but are not limited to: tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, but are not limited to: pyrazolidinyl, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, but are not limited to: triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, but are not limited to: piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, but are not limited to: piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl

groups containing three heteroatoms include, but are not limited to: triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, but are not limited to: azepanyl, oxepanyl, and thiepanyl. Exemplary 5-membered heterocyclyl groups fused with a C₆ aryl ring (also referred to as 5,6-bicyclic heterocyclyl herein) include, but are not limited to: indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused with a C₆ aryl ring (also referred to as 6,6-bicyclic heterocyclyl herein) include, but are not limited to: tetrahydroquinolinyl, tetrahydroisoquinolinyl, etc. Heterocyclyl also includes the above heterocyclyl that shares one or two atoms with one cycloalkyl, heterocyclyl, aryl, or heteroaryl to form a bridged or spiro ring, where the shared atom may be a carbon or nitrogen atom as long as the valency permits. The heterocyclyl further includes the heterocyclyl described above, which optionally can be substituted with one or more substituents, e.g., with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0038] “C₆₋₁₀ aryl” refers to a radical of monocyclic or polycyclic (e.g., bicyclic) 4n+2 aromatic ring system having 6-10 ring carbon atoms and zero heteroatoms (e.g., having 6 or 10 shared π electrons in a cyclic array). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). The aryl group also includes a ring system in which the aryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the aryl ring, in which case the number of carbon atoms continues to represent the number of carbon atoms in the aryl ring system. The aryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

[0039] “5- to 14-membered heteroaryl” refers to a radical of 5- to 14-membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6, 10 or 14 shared π electrons in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur. In the heteroaryl group containing one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom as long as the valence permits. heteroaryl bicyclic systems may include one or more heteroatoms in one or two rings. heteroaryl also includes ring

systems wherein the heteroaryl ring described above is fused with one or more cycloalkyl or heterocyclyl groups, and the point of attachment is on the heteroaryl ring. In such case, the number the carbon atoms continues to represent the number of carbon atoms in the heteroaryl ring system. In some embodiments, 5- to 10-membered heteroaryl groups are alternative, which are radicals of 5- to 10-membered monocyclic or bicyclic $4n+2$ aromatic ring systems having ring carbon atoms and 1-4 ring heteroatoms. In other embodiments, 5- to 6-membered heteroaryl groups are yet alternative, which are radicals of 5- to 6-membered monocyclic or bicyclic $4n+2$ aromatic ring systems having ring carbon atoms and 1-4 ring heteroatoms. Exemplary 5-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyrrolyl, furyl and thienyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, but are not limited to, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, but are not limited to, triazolyl, oxadiazolyl (such as, 1,2,4-oxadiazolyl), and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, but are not limited to, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, but are not limited to, pyridyl or pyridonyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, but are not limited to, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, but are not limited to, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, but are not limited to, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, but are not limited to, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzoxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, indolizinyl and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, but are not limited to, naphthyridinyl, pteridinyl, quinolyl, isoquinolyl, cinnolinyl, quinoxalinyl, phthalazinyl and quinazolinyl. The heteroaryl can be substituted with one or more substituents, for example, with 1 to 5 substituents, 1 to 3 substituents or 1 substituent.

- [0040] “Hydroxyalkyl” refers to an alkyl group that is substituted with one or more hydroxy groups.
- [0041] “Alkoxy” refers to an oxyether form of a linear or branched-chain alkyl group, i.e., an -O-alkyl group. Similarly, “methoxy” refers to -O-CH₃.
- [0042] “Optionally substituted with ...” means .it can be substituted with the specified substituents or unsubstituted.
- [0043] Bivalent groups formed by removing another hydrogen from the groups defined above such as alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl are collectively referred to as “ylene”. Ring-forming groups such as cycloalkyl, heterocyclyl, aryl, and heteroaryl are collectively referred to as “cyclic groups”.
- [0044] alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, etc, as defined herein are optionally substituted groups.
- [0045] Exemplary substituents on carbon atoms include, but are not limited to: halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -ON(R^{bb})₂, -N(R^{bb})₂, -N(R^{bb})₃⁺X⁻, -N(OR^{cc})R^{bb}, -SH, -SR^{aa}, -SSR^{cc}, -C(=O)R^{aa}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, -NR^{bb}C(=O)R^{aa}, -NR^{bb}CO₂R^{aa}, -NR^{bb}C(=O)N(R^{bb})₂, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -OC(=NR^{bb})R^{aa}, -OC(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})₂, -OC(=NR^{bb})N(R^{bb})₂, -NR^{bb}C(=NR^{bb})N(R^{bb})₂, -C(=O)NR^{bb}SO₂R^{aa}, -NR^{bb}SO₂R^{aa}, -SO₂N(R^{bb})₂, -SO₂R^{aa}, -SO₂OR^{aa}, -OSO₂R^{aa}, -S(=O)R^{aa}, -OS(=O)R^{aa}, -Si(R^{aa})₃, -OSi(R^{aa})₃, -C(=S)N(R^{bb})₂, -C(=O)SR^{aa}, -C(=S)SR^{aa}, -SC(=S)SR^{aa}, -SC(=O)SR^{aa}, -OC(=O)SR^{aa}, -SC(=O)OR^{aa}, -SC(=O)R^{aa}, -P(=O)₂R^{aa}, -OP(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -OP(=O)(R^{aa})₂, -OP(=O)(OR^{cc})₂, -P(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -P(=O)(NR^{bb})₂, -OP(=O)(NR^{bb})₂, -NR^{bb}P(=O)(OR^{cc})₂, -NR^{bb}P(=O)(NR^{bb})₂, -P(R^{cc})₂, -P(R^{cc})₃, -OP(R^{cc})₂, -OP(R^{cc})₃, -B(R^{aa})₂, -B(OR^{cc})₂, -BR^{aa}(OR^{cc}), alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;
- [0046] or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =NN(R^{bb})₂, =NNR^{bb}C(=O)R^{aa}, =NNR^{bb}C(=O)OR^{aa}, =NNR^{bb}S(=O)₂R^{aa}, =NR^{bb}, or =NOR^{cc};

- [0047] each of the R^{aa} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or two R^{aa} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;
- [0048] each of the R^{bb} is independently selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or two R^{bb} groups are combined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;
- [0049] each of the R^{cc} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or two R^{cc} groups are joined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;
- [0050] Each of the R^{dd} is independently selected from: halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{ee}, -NR^{ff}C(=O)N(R^{ff})₂, -C(=NR^{ff})OR^{ee}, -OC(=NR^{ff})R^{ee}, -OC(=NR^{ff})OR^{ee}, -C(=NR^{ff})N(R^{ff})₂, -OC(=NR^{ff})N(R^{ff})₂, -NR^{ff}C(=NR^{ff})N(R^{ff})₂, -NR^{ff}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{ee}, -S(=O)R^{ee}, -Si(R^{ee})₃, -OSi(R^{ee})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{ee}, -C(=S)SR^{ee}, -SC(=S)SR^{ee}, -P(=O)₂R^{ee}, -P(=O)(R^{ee})₂, -OP(=O)(R^{ee})₂, -OP(=O)(OR^{ee})₂, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents may be combined to form =O or =S;
- [0051] each of the R^{ee} is independently selected from alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl, wherein each of the alkyl, alkenyl, alkynyl,

cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

[0052] each of the R^{ff} is independently selected from hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or two R^{ff} groups are combined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

[0053] each of the R^{gg} is independently: halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl)⁺X⁻, -NH₃⁺X⁻, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHCO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₆-C₁₀ aryl, 3-7 membered heterocyclyl, or 5-10 membered heteroaryl; or two geminal R^{gg} substituents may be combined to form =O or =S; wherein, X⁻ is a counter ion.

[0054] exemplary substituents on nitrogen atoms include, but are not limited to:

hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or two R^{cc} groups attached to a nitrogen atom are

combined to form a heterocyclyl or heteroaryl ring, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as described above.

[0055] “Nucleic acids” refers to single- or double-stranded deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) molecules and their heterozygous molecules. Examples of nucleic acid molecules include, but are not limited to, messenger RNA (mRNA), microRNA (miRNA), small interfering RNA (siRNA), self-amplified RNA (saRNA), and antisense oligonucleotides (ASO), etc. Nucleic acids may be further chemically modified, and the chemical modifier selected from one of, or a combination of: pseudouridine, N1-methyl-pseudouridine, 5-methoxyuridine, 5-methylcytosine. mRNA molecules contain protein coding regions and may further contain expression regulatory sequences. Typical expression regulatory sequences include, but are not limited to, 5' cap, 5' untranslated region (5' UTR), 3' untranslated region (3' UTR), polyadenylate sequence (PolyA), miRNA binding sites.

[0056] “Cationic lipid” refers to a lipid molecule capable of being positively charged at physiological pH. In some embodiments, the cationic lipid is an amino lipid.

[0057] “Neutral lipid” refers to a lipid molecule that is not charged at specific pH, e.g., physiological pH. Examples of neutral lipids include, but are not limited to, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE), and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE).

[0058] “Structure lipids” refers to lipids that enhance the stability of nanoparticles by filling the gaps between lipids, commonly such as steroids. The steroid is a compound having a perhydrocyclopentanophenanthrene carbon framework. In an alternative embodiment, the steroid is selected from cholesterol, sitosterol, coprosterol, fucosterol, brassicasterol, ergosterol, tomatine, ursolic acid, α -tocopherol, stigmasterol, avenasterol, ergocalciferol and campesterol.

- [0059] “Polymer lipids” refers to molecules containing a polymer moiety and a lipid moiety. In some embodiments, the polymer lipid is a polyethylene glycol (PEG) lipid. Other lipids that can reduce aggregation, such as products of compounds having uncharged, hydrophilic, space-barrier moieties coupled with lipid may also be used.
- [0060] “Lipid nanoparticles” refers to particles containing lipid components of nanoscale size.
- [0061] “Biodegradable groups” refers to functional groups that contain biodegradable bonds, such as esters, disulfide bonds and amides, etc. Biodegradation may affect the process of removing compounds from the body. The biodegradable groups of the present disclosure are oriented from the head to the tail in ionizable lipid molecules.

Other definitions

- [0062] The term “treating” as used herein relates to reversing, alleviating or inhibiting the progression or prevention of the disorders or conditions to which the term applies, or of one or more symptoms of such disorders or conditions. The noun “treatment” as used herein relates to the action of treating, which is a verb, and the latter is as just defined.
- [0063] The term “pharmaceutically acceptable salt” as used herein refers to those carboxylate and amino acid addition salts of the compounds of the present disclosure, which are suitable for the contact with patients’ tissues within a reliable medical judgment, and do not produce inappropriate toxicity, irritation, allergy, etc. They are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use. The term includes, if possible, the zwitterionic form of the compounds of the disclosure.
- [0064] The pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali metal and alkaline earth metal hydroxides or organic amines. Examples of the metals used as cations include sodium, potassium, magnesium, calcium, etc. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine.
- [0065] The base addition salt of the acidic compound can be prepared by contacting the free acid form with a sufficient amount of the required base to form a salt in a conventional manner. The free acid can be regenerated by contacting the salt form with

an acid in a conventional manner and then isolating the free acid. The free acid forms are somewhat different from their respective salt forms in their physical properties, such as solubility in polar solvents. But for the purposes of the present disclosure, the salts are still equivalent to their respective free acids.

[0066] The salts can be prepared from the inorganic acids, which include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogen phosphates, dihydrogen phosphates, metaphosphates, pyrophosphates, chlorides, bromides and iodides. Examples of the acids include hydrochloric acid, nitric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, etc. The representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthalate, methanesulfonate, glucoheptanate, lactobionate, lauryl sulfonate, isethionate, etc. The salts can also be prepared from the organic acids, which include aliphatic monocarboxylic and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxyalkanoic acids, alkanedioic acid, aromatic acids, aliphatic and aromatic sulfonic acids, etc. The representative salts include acetate, propionate, octanoate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methyl benzoate, dinitrobenzoate, naphthoate, besylate, tosylate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, etc. The pharmaceutically acceptable salts can include cations based on alkali metals and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, etc., as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, etc. Salts of amino acids are also included, such as arginine salts, gluconates, galacturonates, etc. (for example, see Berge S. M. et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977; 66: 1- 19 for reference).

[0067] "Subjects" to which administration is contemplated include, but are not limited to, humans (e.g., males or females of any age group, e.g., paediatric subjects (e.g., infants, children, adolescents) or adult subjects (e.g., young adults, middle-aged adults or older adults) and/or non-human animals, such as mammals, e.g., primates (e.g., cynomolgus

monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats and/or dogs. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human animal. The terms “human”, “patient” and “subject” can be used interchangeably herein.

[0068] “Disease”, “disorder”, and “condition” can be used interchangeably herein.

[0069] Unless otherwise indicated, the term “treatment” as used herein includes the effect on a subject who is suffering from a particular disease, disorder, or condition, which reduces the severity of the disease, disorder, or condition, or delays or slows the progression of the disease, disorder or condition (“therapeutic treatment”). The term also includes the effect that occurs before the subject begins to suffer from a specific disease, disorder or condition (“prophylactic treatment”).

[0070] Generally, the “effective amount” of a pharmaceutical composition refers to an amount sufficient to elicit a target biological response. As understood by those skilled in the art, the effective amount of the pharmaceutical composition of the disclosure can vary depending on the following factors, such as the desired biological endpoint, the pharmacokinetics of the pharmaceutical composition, the diseases being treated, the mode of administration, and the age, health status and symptoms of the subjects. The effective amount includes therapeutically effective amount and prophylactically effective amount.

[0071] Unless otherwise indicated, the “therapeutically effective amount” of the pharmaceutical composition as used herein is an amount sufficient to provide therapeutic benefits in the course of treating a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. The therapeutically effective amount of a pharmaceutical composition refers to the amount of the therapeutic agent that, when used alone or in combination with other therapies, provides a therapeutic benefit in the treatment of a disease, disorder or condition. The term “therapeutically effective amount” can include an amount that improves the overall treatment, reduces or avoids the symptoms or causes of the disease or condition, or enhances the therapeutic effect of other therapeutic agents.

[0072] Unless otherwise indicated, the “prophylactically effective amount” of the pharmaceutical composition as used herein is an amount sufficient to prevent a disease,

disorder or condition, or an amount sufficient to prevent one or more symptoms associated with a disease, disorder or condition, or an amount sufficient to prevent the recurrence of a disease, disorder or condition. The prophylactically effective amount of a pharmaceutical composition refers to the amount of a therapeutic agent that, when used alone or in combination with other agents, provides a prophylactic benefit in the prevention of a disease, disorder or condition. The term “prophylactically effective amount” can include an amount that improves the overall prevention, or an amount that enhances the prophylactic effect of other preventive agents.

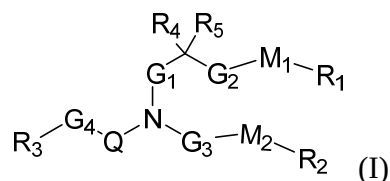
[0073] “Combination” and related terms refer to the simultaneous or sequential administration of the pharmaceutical compositions of the present disclosure and other therapeutic agents. For example, the pharmaceutical compositions of the present disclosure can be administered simultaneously or sequentially in separate unit dosage with other therapeutic agents, or simultaneously in a single unit dosage with other therapeutic agents.

DETAILED DESCRIPTION

[0074] As used herein, “compounds of the present disclosure” refers to the following compounds, pharmaceutically acceptable salts, isotopic variants, tautomers or stereoisomers thereof.

[0075] In the present disclosure, compounds are named using standard nomenclature. For compounds having an asymmetric center, it should be understood, unless otherwise stated, that all optical isomers and mixtures thereof are included. Furthermore, unless otherwise specified, all isomer compounds and carbon-carbon double bonds included in the present disclosure may occur in the form of Z and E. Compounds which exist in different tautomeric forms, one of which is not limited to any particular tautomer, but is intended to cover all tautomeric forms.

[0076] In one embodiment, the present disclosure relates to a compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer or stereoisomer thereof:



- [0077] wherein
- [0078] G_1 and G_2 are independently selected from a chemical bond, C_{1-13} linear alkylene, C_{2-13} linear alkenylene, and C_{2-13} linear alkynylene, each of which is optionally substituted with one or more $\text{R}_{\text{G}1}$;
- [0079] G_1 and G_2 have a total length of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 carbon atoms;
- [0080] $\text{R}_{\text{G}1}$ is independently H, C_{1-14} alkyl, $-\text{L}_a-\text{OR}_a$, $-\text{L}_a-\text{SR}_a$, or $-\text{L}_a-\text{NR}_a\text{R}'_a$;
- [0081] G_3 is C_{4-14} linear alkylene, C_{4-14} linear alkenylene, or C_{4-14} linear alkynylene, each of which is optionally substituted with one or more $\text{R}_{\text{G}3}$;
- [0082] $\text{R}_{\text{G}3}$ is independently H, $-\text{L}_a-\text{OR}_a$, $-\text{L}_a-\text{SR}_a$, or $-\text{L}_a-\text{NR}_a\text{R}'_a$;
- [0083] L_a is independently a chemical bond or C_{1-14} alkylene;
- [0084] R_a and R'_a are independently selected from H, C_{1-14} alkyl, C_{3-14} cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0085] G_4 is a chemical bond, C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene, each of which is optionally substituted with one or more $\text{R}_{\text{G}4}$;
- [0086] $\text{R}_{\text{G}4}$ is independently H, C_{1-6} alkyl, $-\text{L}_b-\text{OR}_b$, $-\text{L}_b-\text{SR}_b$, or $-\text{L}_b-\text{NR}_b\text{R}'_b$;
- [0087] L_b is independently a chemical bond or C_{1-6} alkylene;
- [0088] R_b and R'_b are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocyclyl;
- [0089] or, two $\text{R}_{\text{G}4}$ attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C_{3-14} cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4g} ;
- [0090] R_{4g} is independently H, halogen, cyano, C_{1-8} alkyl, C_{1-8} haloalkyl, $-\text{L}_e-\text{OR}_e$, $-\text{L}_e-\text{SR}_e$, or $-\text{L}_e-\text{NR}_e\text{R}'_e$;
- [0091] L_e is independently a chemical bond or C_{1-8} alkylene;
- [0092] R_e and R'_e are independently selected from H, C_{1-8} alkyl, C_{3-14} cycloalkyl, and 3- to 14-membered heterocyclyl;

- [0093] M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -O-, -SC(O)O-, -OC(O)NR-, -NRC(O)NR-, -OC(O)S-, -OC(O)O-, -NRC(O)O-, -SC(O)-, -C(O)S-, -NR-, -C(O)NR-, -NRC(O)-, -NRC(O)S-, -SC(O)NR-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR-, -NRC(S)O-, -S-S-, and -S(O)₀₋₂-;
- [0094] Q is selected from a chemical bond, -C(O)O-, -O-, -SC(O)O-, -OC(O)NR_f-, -NR_fC(O)NR_f-, -OC(O)S-, -OC(O)O-, -NR_fC(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NR_f-, -C(O)NR_f-, -NR_fC(O)-, -NR_fC(O)S-, -SC(O)NR_f-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR_f-, -NR_fC(S)O-, -S-S-, -S(O)₀₋₂-, phenylene, and pyridinylene, wherein the phenylene or the pyridinylene is optionally substituted with one or more R*;
- [0095] R* is independently H, halogen, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, -L_f-OR_f, -L_f-SR_f, or -L_f-NR_fR'_f;
- [0096] L_f is independently a chemical bond or C₁₋₈ alkylene;
- [0097] R_f and R'_f are independently selected from H, C₁₋₁₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0098] R₁ and R₂ are independently selected from C₄₋₂₀ alkyl, C₄₋₂₀ alkenyl, and C₄₋₂₀ alkynyl, each of which is optionally substituted with one or more R_{1s}, and wherein one or more methylene units are optionally and independently replaced with -NR'-;
- [0099] R_{1s} is independently H, C₁₋₂₀ alkyl, -L_c-OR_c, -L_c-SR_c, or -L_c-NR_cR'_c;
- [0100] R and R' are independently H or C₁₋₂₀ alkyl;
- [0101] L_c is independently a chemical bond or C₁₋₂₀ alkylene;
- [0102] R_c and R'_c are independently selected from H, C₁₋₂₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0103] R₃ is selected from CN, -OR_g, -C(O)R_g, -OC(O)R_g, -NR''C(O)R_g, -NR_gR'_g-, -NR''C(O)NR_gR'_g-, -NR''C(O)R_g-, -NR''S(O)₂R_g-, -OC(O)NR_gR'_g-, -NR''C(O)OR_g-, -N(OR_g)C(O)R_g-, -N(OR_g)S(O)₂R_g-, -N(OR_g)C(O)OR_g-, -N(OR_g)C(O)R_gR'_g-, 3- to 14-membered heterocyclyl, and 5- to 14-membered heteroaryl;
- [0104] R_g and R'_g are independently H, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl;
- [0105] R'' is independently H or C₁₋₆ alkyl;
- [0106] R₄ and R₅ are independently C₁₋₈ alkyl, which is optionally substituted with one or more R_{4s};

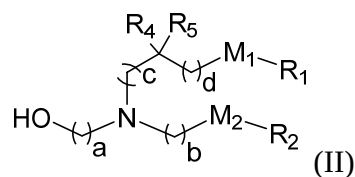
[0107] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4s};

[0108] R_{4s} is independently H, halogen, cyano, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -L_d-OR_d, -L_d-SR_d, or -L_d-NR_dR'_d;

[0109] L_d is independently a chemical bond or C₁₋₈ alkylene;

[0110] R_d and R'_d are independently H, C₁₋₈ alkyl, C₃₋₁₄ cycloalkyl, or 3- to 14-membered heterocyclyl.

[0111] In another embodiment, the present disclosure relates to a compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, which has a structure of formula (II):



[0112] wherein

[0113] a = 1, 2, 3, 4, 5, or 6;

[0114] b = 4, 5, 6, 7, 8, 9, or 10;

[0115] c = 1, 2, 3, 4, 5, or 6;

[0116] d = 0, 1, 2, 3, or 4;

[0117] c + d = 3, 4, 5, 6, 7, 8, or 9;

[0118] the other groups are as defined herein.

[0119]

[0120] G₁ and G₂

[0121] In one embodiment, G₁ is a chemical bond; in another embodiment, G₁ is C₁₋₁₃ linear alkylene, alternatively C₁₋₉ linear alkylene, alternatively C₁₋₆ linear alkylene, and alternatively C₂₋₆ linear alkylene; in another embodiment, G₁ is C₂₋₁₃ linear alkenylene, alternatively C₂₋₉ linear alkenylene, and alternatively C₂₋₆ linear alkenylene; in another embodiment, G₁ is C₂₋₁₃ linear alkynylene, alternatively C₂₋₉ linear alkynylene, and alternatively C₂₋₆ linear alkynylene; in another embodiment, G₁ is optionally substituted with one or more R_{G1}; in another embodiment, G₁ is optionally substituted with 1, 2, 3, or 4 R_{G1}; in another embodiment, G₁ is unsubstituted.

- [0122] In a more specific embodiment, G₁ is a chemical bond, C₁₋₉ linear alkylene, C₂₋₉ linear alkenylene, or C₂₋₉ linear alkynylene; in another more specific embodiment, G₁ is C₁₋₆ linear alkylene, C₂₋₆ linear alkenylene, or C₂₋₆ linear alkynylene; in another more specific embodiment, G₁ is C₁₋₆ linear alkylene; in another more specific embodiment, G₁ is C₂₋₆ linear alkylene.
- [0123] In one embodiment, G₂ is a chemical bond; in another embodiment, G₂ is C₁₋₁₃ linear alkylene, alternatively C₁₋₉ linear alkylene, alternatively C₁₋₆ linear alkylene, and alternatively C₁₋₄ linear alkylene; in another embodiment, G₂ is C₂₋₁₃ linear alkenylene, alternatively C₂₋₉ linear alkenylene, and alternatively C₂₋₆ linear alkenylene; in another embodiment, G₂ is C₂₋₁₃ linear alkynylene, alternatively C₂₋₉ linear alkynylene, and alternatively C₂₋₆ linear alkynylene; in another embodiment, G₂ is optionally substituted with one or more R_{G1}; in another embodiment, G₂ is optionally substituted with 1, 2, 3, or 4 R_{G1}; in another embodiment, G₂ is unsubstituted.
- [0124] In a more specific embodiment, G₂ is a chemical bond, C₁₋₉ linear alkylene, C₂₋₉ linear alkenylene, or C₂₋₉ linear alkynylene; in another more specific embodiment, G₂ is a chemical bond, C₁₋₆ linear alkylene, C₂₋₆ linear alkenylene, or C₂₋₆ linear alkynylene; in another more specific embodiment, G₂ is a chemical bond or C₁₋₆ linear alkylene; in another more specific embodiment, G₂ is a chemical bond or C₁₋₄ linear alkylene.
- [0125] In one embodiment, G₁ and G₂ have a total length of 3 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 4 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 5 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 6 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 7 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 8 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 9 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 10 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 11 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 12 carbon atoms; in another embodiment, G₁ and G₂ have a total length of 13 carbon atoms.
- [0126] In a more specific embodiment, G₁ and G₂ have a total length of 3, 4, 5, 6, 7, 8, or 9 carbon atoms; in another more specific embodiment, G₁ and G₂ have a total length of 4, 5, or 6 carbon atoms; in another more specific embodiment, G₁ and G₂ have a total length

of 5 or 6 carbon atoms; in another more specific embodiment, G_1 and G_2 have a total length of 5, 6, or 7 carbon atoms; in another more specific embodiment, G_1 and G_2 have a total length of 6 or 7 carbon atoms.

[0127] R_{G1}

[0128] In one embodiment, R_{G1} is H; in another embodiment, R_{G1} is C_{1-14} alkyl, alternatively C_{1-10} alkyl, and alternatively C_{1-6} alkyl; in another embodiment, R_{G1} is $-L_a-OR_a$; in another embodiment, R_{G1} is $-L_a-SR_a$; in another embodiment, R_{G1} is $-L_a-NR_aR'_a$.

[0129] In a more specific embodiment, R_{G1} is independently H or C_{1-10} alkyl; in another more specific embodiment, R_{G1} is independently H or C_{1-6} alkyl.

[0130] G_3

[0131] In one embodiment, G_3 is C_{4-14} linear alkylene, alternatively C_{4-10} linear alkylene, alternatively C_{4-9} linear alkylene, and alternatively C_{5-8} linear alkylene; in another embodiment, G_3 is C_{4-14} linear alkenylene; in another embodiment, G_3 is C_{4-14} linear alkynylene; in another embodiment, G_3 is optionally substituted with one or more R_{G3} ; in another embodiment, G_3 is optionally substituted with 1, 2, 3, or 4 R_{G3} ; in another embodiment, G_3 is unsubstituted.

[0132] In a more specific embodiment, G_3 is C_{4-10} linear alkylene, C_{4-10} linear alkenylene, or C_{4-10} linear alkynylene; in another more specific embodiment, G_3 is C_{4-9} linear alkylene; in another more specific embodiment, G_3 is C_{5-8} linear alkylene.

[0133] R_{G3}

[0134] In one embodiment, R_{G3} is H; in another embodiment, R_{G3} is $-L_a-OR_a$; in another embodiment, R_{G3} is $-L_a-SR_a$; in another embodiment, R_{G3} is $-L_a-NR_aR'_a$.

[0135] L_a , R_a , and R'_a

[0136] In one embodiment, L_a is a chemical bond; in another embodiment, L_a is C_{1-14} alkylene, alternatively C_{1-10} alkylene, and alternatively C_{1-6} alkylene.

[0137] In a more specific embodiment, L_a is independently a chemical bond or C_{1-10} alkylene; in another more specific embodiment, L_a is a chemical bond or C_{1-6} alkylene.

- [0138] In one embodiment, R_a is H; in another embodiment, R_a is C₁₋₁₄ alkyl, alternatively C₁₋₁₀ alkyl, alternatively C₁₋₆ alkyl; in another embodiment, R_a is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R_a is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0139] In one embodiment, R'_a is H; in another embodiment, R'_a is C₁₋₁₄ alkyl, alternatively C₁₋₁₀ alkyl, and alternatively C₁₋₆ alkyl; in another embodiment, R'_a is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R'_a is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0140] In a more specific embodiment, R_a and R'_a are independently H, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl; in another more specific embodiment, R_a and R'_a are independently H or C₁₋₆ alkyl.

[0141] G₄

- [0142] In one embodiment, G₄ is a chemical bond; in another embodiment, G₄ is C₁₋₆ alkylene, alternatively C₁₋₄ alkylene, alternatively C₂₋₄ alkylene, and alternatively C₂₋₃ alkylene; in another embodiment, G₄ is C₂₋₆ alkenylene; in another embodiment, G₄ is C₂₋₆ alkynylene; in another embodiment, G₄ is optionally substituted with one or more R_{G4}; in another embodiment, G₄ is optionally substituted with 1, 2, 3, or 4 R_{G4}; in another embodiment, G₄ is unsubstituted.
- [0143] In a more specific embodiment, G₄ is C₁₋₄alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene; in another more specific embodiment, G₄ is C₂₋₄ alkylene; in another more specific embodiment, G₄ is C₂₋₃ alkylene.

[0144] R_{G4}

- [0145] In one embodiment, R_{G4} is H; in another embodiment, R_{G4} is C₁₋₆ alkyl, alternatively C₁₋₄ alkyl; in another embodiment, R_{G4} is -L_b-OR_b; in another embodiment, R_{G4} is -L_b-SR_b; in another embodiment, R_{G4} is -L_b-NR_bR'_b.
- [0146] In a more specific embodiment, R_{G4} is independently H or C₁₋₆ alkyl.
- [0147] In one embodiment, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene, alternatively C₃₋₁₀ cycloalkylene, alternatively C₃₋₇ cycloalkylene; in another embodiment, two R_{G4}

attached to the same carbon atom are taken together with the carbon atom to which they are attached to form 3- to 14-membered heterocyclylene, alternatively 3- to 10-membered heterocyclylene, alternatively 3- to 7-membered heterocyclylene; in another embodiment, a ring formed by two R_{G4} taken together with the carbon atom to which they are attached is optionally substituted with one or more R_{4g}; in another embodiment, a ring formed by two R_{G4} taken together with the carbon atom to which they are attached is optionally substituted with 1, 2, or 3 R_{4g}; in another embodiment, a ring formed by two R_{G4} taken together with the carbon atom to which they are attached is unsubstituted.

[0148] In a more specific embodiment, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₁₀ cycloalkylene or 3- to 10-membered heterocyclylene; in another more specific embodiment, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkylene or 3- to 7-membered heterocyclylene.

[0149] L_b, R_b, and R'_b

[0150] In one embodiment, L_b is a chemical bond; in another embodiment, L_b is C₁₋₆ alkylene, alternatively C₁₋₄ alkylene.

[0151] In a more specific embodiment, L_b is independently a chemical bond or C₁₋₄ alkylene.

[0152] In one embodiment, R_b is H; in another embodiment, R_b is C₁₋₆ alkyl, alternatively C₁₋₄ alkyl; in another embodiment, R_b is C₃₋₁₀ cycloalkyl, alternatively C₃₋₇ cycloalkyl; in another embodiment, R_b is 3- to 10-membered heterocyclyl, alternatively 3- to 7-membered heterocyclyl.

[0153] In one embodiment, R'_b is H; in another embodiment, R'_b is C₁₋₆ alkyl, alternatively C₁₋₄ alkyl; in another embodiment, R'_b is C₃₋₁₀ cycloalkyl, alternatively C₃₋₇ cycloalkyl; in another embodiment, R'_b is 3- to 10-membered heterocyclyl, alternatively 3- to 7-membered heterocyclyl.

[0154] In a more specific embodiment, R_b and R'_b are independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocyclyl; in another more specific embodiment, R_b

and R'_b are independently H or C₁₋₆ alkyl; in another more specific embodiment, R_b and R'_b are independently H or C₁₋₄ alkyl.

[0155] R_{4g}

[0156] In one embodiment, R_{4g} is H; in another embodiment, R_{4g} is halogen; in another embodiment, R_{4g} is cyano; in another embodiment, R_{4g} is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl; in another embodiment, R_{4g} is C₁₋₈ haloalkyl, alternatively C₁₋₆ haloalkyl; in another embodiment, R_{4g} is -L_e-OR_e; in another embodiment, R_{4g} is -L_e-SR_e; in another embodiment, R_{4g} is -L_e-NR_eR'_e.

[0157] In a more specific embodiment, R_{4g} is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

[0158] L_e, R_e, and R'_e

[0159] In one embodiment, L_e is a chemical bond; in another embodiment, L_e is C₁₋₈ alkylene, alternatively C₁₋₆ alkylene, and alternatively C₁₋₄ alkylene.

[0160] In a more specific embodiment, L_e is independently a chemical bond or C₁₋₆ alkylene; in another more specific embodiment, L_a is a chemical bond or C₁₋₄ alkylene.

[0161] In one embodiment, R_e is H; in another embodiment, R_e is C₁₋₈ alkyl, alternatively C₁₋₆ alkylene, and alternatively C₁₋₄ alkylene; in another embodiment, R_e is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R_e is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.

[0162] In one embodiment, R'_e is H; in another embodiment, R'_e is C₁₋₈ alkyl, alternatively C₁₋₆ alkylene, and alternatively C₁₋₄ alkylene; in another embodiment, R'_e is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R'_e is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.

[0163] In a more specific embodiment, R_e and R'_e are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl; in another more specific embodiment, R_e and R'_e are independently H or C₁₋₄ alkyl.

[0164] M₁ and M₂

[0165] In one embodiment, M₁ is -C(O)O-; in another embodiment, M₁ is -OC(O)-; in another embodiment, M₁ is -O-; in another embodiment, M₁ is -SC(O)O-; in another embodiment, M₁ is -OC(O)NR-; in another embodiment, M₁ is -NRC(O)NR-; in another embodiment, M₁ is -OC(O)S-; in another embodiment, M₁ is -OC(O)O-; in another embodiment, M₁ is -NRC(O)O-; in another embodiment, M₁ is -SC(O)-; in another embodiment, M₁ is -C(O)S-; in another embodiment, M₁ is -NR-; in another embodiment, M₁ is -C(O)NR-, for example, -C(O)NH-; in another embodiment, M₁ is -NRC(O)-, for example, -NHC(O)-; in another embodiment, M₁ is -NRC(O)S-; in another embodiment, M₁ is -SC(O)NR-; in another embodiment, M₁ is -C(O)-; in another embodiment, M₁ is -OC(S)-; in another embodiment, M₁ is -C(S)O-; in another embodiment, M₁ is -OC(S)NR-; in another embodiment, M₁ is -NRC(S)O-; in another embodiment, M₁ is -S-S-; in another embodiment, M₁ is -S(O)₀₋₂-, such as -S-, -S(O)-, and -S(O)₂-.

[0166] In one embodiment, M₂ is -C(O)O-; in another embodiment, M₂ is -OC(O)-; in another embodiment, M₂ is -O-; in another embodiment, M₂ is -SC(O)O-; in another embodiment, M₂ is -OC(O)NR-; in another embodiment, M₂ is -NRC(O)NR-; in another embodiment, M₂ is -OC(O)S-; in another embodiment, M₂ is -OC(O)O-; in another embodiment, M₂ is -NRC(O)O-; in another embodiment, M₂ is -SC(O)-; in another embodiment, M₂ is -C(O)S-; in another embodiment, M₂ is -NR-; in another embodiment, M₂ is -C(O)NR-; in another embodiment, M₂ is -NRC(O)-; in another embodiment, M₂ is -NRC(O)S-; in another embodiment, M₂ is -SC(O)NR-; in another embodiment, M₂ is -C(O)-; in another embodiment, M₂ is -OC(S)-; in another embodiment, M₂ is -C(S)O-; in another embodiment, M₂ is -OC(S)NR-; in another embodiment, M₂ is -NRC(S)O-; in another embodiment, M₂ is -S-S-; in another embodiment, M₂ is -S(O)₀₋₂-, such as -S-, -S(O)-, and -S(O)₂-.

[0167] In a more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -OC(O)O-, -SC(O)-, -C(O)S-, -C(O)NR-, and -NRC(O)-; in another more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-; in another more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-; in another more specific embodiment, M₁ and M₂ are independently selected from -C(O)O- and -OC(O)-.

[0168] In a more specific embodiment, M₁ and M₂ are independently selected from -C(O)O- and -C(O)S-; in another more specific embodiment, M₁ and M₂ are -C(O)O-.

[0169] In a more specific embodiment, one of M₁ and M₂ is -C(O)O- or -C(O)S-, and the other is -OC(O)- or -SC(O)-; in another more specific embodiment, one of M₁ and M₂ is -C(O)O-, and the other is -OC(O)-.

[0170] In a more specific embodiment, M₁ is -OC(O)- or -SC(O)-; in another more specific embodiment, M₁ is -OC(O)-; in another more specific embodiment, M₂ is -C(O)O- or -C(O)S-; in another more specific embodiment, M₂ is -C(O)O-.

[0171] In a more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NHC(O)-, and -C(O)NH-; in another more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -C(O)S-, and -C(O)NH-; in another more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, and -C(O)S-; in another more specific embodiment, one of M₁ and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-, and the other is -C(O)O-, -C(O)S-, -C(O)NH-, -OC(O)-, or -SC(O)-, alternatively -C(O)O-, -C(O)S-, -C(O)NH-, or -OC(O)-, alternatively -C(O)O-, -C(O)S-, -OC(O)-, or -SC(O)-, alternatively -C(O)O-, -C(O)S-, or -OC(O)-; in another more specific embodiment, one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-, alternatively -C(O)O- or -OC(O)-; in another more specific embodiment, M₁ is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-, alternatively -C(O)O- or -OC(O)-, alternatively -C(O)O-, alternatively -OC(O)-, and M₂ is -OC(O)O-; in another more specific embodiment, M₁ is -OC(O)O-, and M₂ is -OC(O)- or -C(O)O-, alternatively -OC(O)-; in another more specific embodiment, M₁ and M₂ are independently -C(O)O-, -C(O)S-, -OC(O)-, -SC(O)-, or -OC(O)O-; in another more specific embodiment, M₁ and M₂ are independently -C(O)O-, -OC(O)-, or -OC(O)O-; in another more specific embodiment, M₁ and M₂ are not simultaneously -OC(O)O-.

[0172] Q

[0173] In one embodiment, Q is a chemical bond; in another more specific embodiment, Q is -C(O)O-; in another more specific embodiment, Q is -O-; in another more specific embodiment, Q is -SC(O)O-; in another more specific embodiment, Q is -OC(O)NR_t-; in

another more specific embodiment, Q is $\text{-NR}_f\text{C(O)NR}_f\text{-}$; in another more specific embodiment, Q is -OC(O)S- ; in another more specific embodiment, Q is -OC(O)O- ; in another more specific embodiment, Q is $\text{-NR}_f\text{C(O)O-}$; in another more specific embodiment, Q is -OC(O)- ; in another more specific embodiment, Q is -SC(O)- ; in another more specific embodiment, Q is -C(O)S- ; in another more specific embodiment, Q is $\text{-NR}_f\text{-}$; in another more specific embodiment, Q is $\text{-C(O)NR}_f\text{-}$; in another more specific embodiment, Q is $\text{-NR}_f\text{C(O)-}$; in another more specific embodiment, Q is $\text{-NR}_f\text{C(O)S-}$; in another more specific embodiment, Q is $\text{-SC(O)NR}_f\text{-}$; in another more specific embodiment, Q is -C(O)- ; in another more specific embodiment, Q is -OC(S)- ; in another more specific embodiment, Q is -C(S)O- ; in another more specific embodiment, Q is $\text{-OC(S)NR}_f\text{-}$; in another more specific embodiment, Q is $\text{-NR}_f\text{C(S)O-}$; in another more specific embodiment, Q is -S-S- ; in another more specific embodiment, Q is $\text{-S(O)}_{0-2}\text{-}$; in another more specific embodiment, Q is phenylene; in another more specific embodiment, Q is pyridinylene; in another more specific embodiment, when Q is phenylene, Q is optionally substituted with one or more R^* , alternatively optionally substituted with 1, 2 or 3 R^* ; in another more specific embodiment, Q is unsubstituted phenylene; in another more specific embodiment, when Q is pyridinylene, Q is optionally substituted with one or more R^* , alternatively optionally substituted with 1, 2 or 3 R^* ; in another more specific embodiment, Q is unsubstituted pyridinylene.

[0174] in another more specific embodiment, Q is a chemical bond, -OC(O)- , or -SC(O)- ; in another more specific embodiment, Q is a chemical bond or -SC(O)- ; in another more specific embodiment, Q is phenylene or pyridinylene, which is optionally substituted with 1, 2 or 3 R^* .

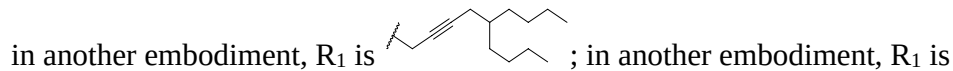
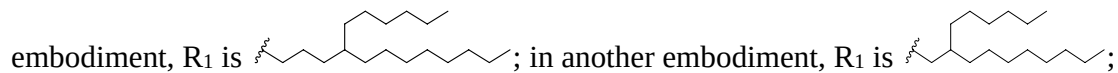
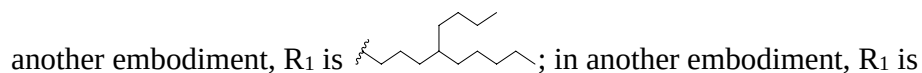
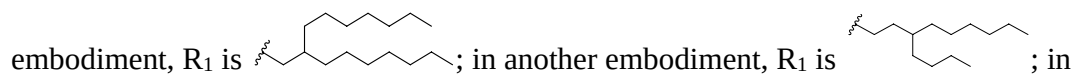
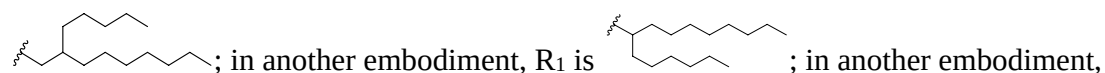
[0175] R^*

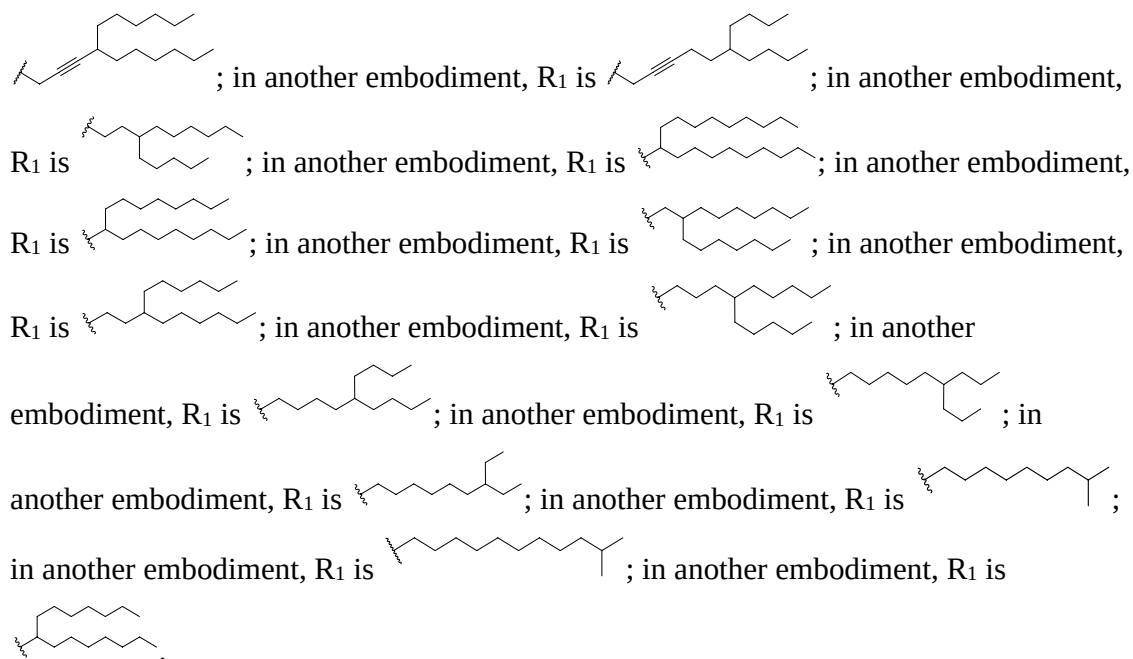
[0176] In one embodiment, R^* is H; in another more specific embodiment, Q is halogen; in another more specific embodiment, R^* is cyano; in another more specific embodiment, R^* is C_{1-10} alkyl, alternatively C_{1-6} alkyl; in another more specific embodiment, R^* is C_{1-10} haloalkyl, alternatively C_{1-6} haloalkyl; in another more specific embodiment, R^* is $\text{-L}_f\text{-OR}_f$; in another more specific embodiment, R^* is $\text{-L}_f\text{-SR}_f$; in another more specific embodiment, R^* is $\text{-L}_f\text{-NR}_f\text{R}'_f$.

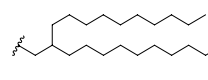
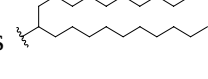
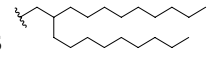
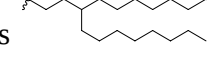
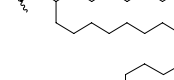
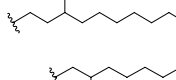
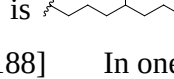
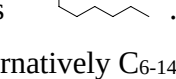
- [0177] In a more specific embodiment, R* is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.
- [0178] L_f, R_f, and R'_f
- [0179] In one embodiment, L_f is a chemical bond; in another embodiment, L_f is C₁₋₈ alkylene, alternatively C₁₋₆ alkylene, alternatively C₁₋₄ alkylene.
- [0180] In a more specific embodiment, L_f is independently a chemical bond or C₁₋₆ alkylene; in another more specific embodiment, L_f is independently a chemical bond or C₁₋₄ alkylene.
- [0181] In one embodiment, R_f is H; in another embodiment, R_f is C₁₋₁₀ alkyl, alternatively C₁₋₆ alkyl, and alternatively C₁₋₄ alkyl; in another embodiment, R_f is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R_f is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0182] In one embodiment, R'_f is H; in another embodiment, R'_f is C₁₋₁₀ alkyl, alternatively C₁₋₆ alkyl, alternatively C₁₋₄ alkyl; in another embodiment, R'_f is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R'_f is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0183] In a more specific embodiment, R_f and R'_f are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl; in another more specific embodiment, R_f and R'_f are independently H or C₁₋₆ alkyl; in another more specific embodiment, R_f and R'_f are independently H or C₁₋₄ alkyl.
- [0184] R₁ and R₂
- [0185] In one embodiment, R₁ is C₄₋₂₀ alkyl, alternatively C₆₋₁₄ alkyl, alternatively C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₈₋₁₁ alkyl, alternatively C₉₋₁₁ alkyl, alternatively C₈₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₈₋₉ alkyl, alternatively C₉ alkyl, alternatively C₈₋₁₂ linear alkyl, alternatively C₇₋₁₁ linear alkyl, alternatively C₈₋₁₁ linear alkyl, alternatively C₉₋₁₁ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl, alternatively C₈₋₁₀ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₈₋₉ linear alkyl, alternatively C₁₁ linear alkyl, alternatively C₁₀ linear alkyl, and alternatively C₉ linear alkyl; in another embodiment, R₁ is C₄₋₂₀ alkenyl, alternatively C₆₋₁₄ alkenyl, alternatively

C₇₋₁₂ alkenyl; alternatively C₈₋₁₂ alkenyl; in another embodiment, R₁ is C₄₋₂₀ alkynyl, alternatively C₆₋₁₄ alkynyl, alternatively C₇₋₁₂ alkynyl, alternatively C₈₋₁₂ alkynyl; in another embodiment, R₁ is optionally substituted with one or more R_{1s}; in another embodiment, R₁ is optionally substituted with 1, 2, 3, or 4 R_{1s}, alternatively optionally substituted with 1 R_{1s}; in another embodiment, R₁ is unsubstituted; in another embodiment, one or more methylene units in R₁ are optionally and independently replaced with -NR'-, alternatively one methylene unit in R₁ is optionally replaced with -NR'-; in another embodiment, R₁ is optionally substituted with 1 C₁₋₉ alkyl (alternatively C₆₋₉ alkyl, alternatively C₆₋₇ alkyl).

[0186] In one embodiment, R₁ is -(CH₂)₅CH₃; in another embodiment, R₁ is -(CH₂)₆CH₃; in another embodiment, R₁ is -(CH₂)₇CH₃; in another embodiment, R₁ is -(CH₂)₈CH₃; in another embodiment, R₁ is -(CH₂)₉CH₃; in another embodiment, R₁ is -(CH₂)₁₀CH₃; in another embodiment, R₁ is -(CH₂)₁₁CH₃; in another embodiment, R₁ is -CH₂-C≡C-(CH₂)₅CH₃; in another embodiment, R₁ is -CH₂-C≡C-(CH₂)₆CH₃; in another embodiment, R₁ is -(CH₂)₂-C≡C-(CH₂)₅CH₃; in another embodiment, R₁ is -(CH₂)₄-C≡C-(CH₂)₃CH₃; in another embodiment, R₁ is -CH₂-CH=CH-(CH₂)₅CH₃; in another embodiment, R₁ is -CH₂-CH=CH-(CH₂)₆CH₃; in another embodiment, R₁ is -(CH₂)₂-CH=CH-(CH₂)₅CH₃; in another embodiment, R₁ is -(CH₂)₄-CH=CH-(CH₂)₃CH₃; in another embodiment, R₁ is -(CH₂)₅-CH=CH-CH₂CH₃; in another embodiment, R₁ is





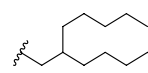
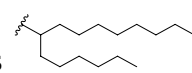
[0187] In one embodiment, R₁ is $-(CH_2)_2-C\equiv C-(CH_2)_4CH_3$; in another embodiment, R₁ is $-(CH_2)_3-C\equiv C-(CH_2)_3CH_3$; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  ; in another embodiment, R₁ is  .

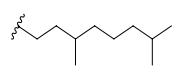
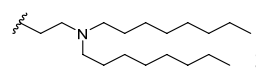
[0188] In one embodiment, R₂ is C₄₋₂₀ alkyl, alternatively C₆₋₁₄ alkyl, alternatively C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₂ alkyl, alternatively C₈₋₁₁ alkyl, alternatively C₉₋₁₁ alkyl, alternatively C₈₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₁₀ alkyl, alternatively C₉ alkyl, alternatively C₈₋₁₂ linear alkyl, alternatively C₇₋₁₁ linear alkyl, alternatively C₈₋₁₁ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl, alternatively C₁₁ linear alkyl, alternatively C₁₀ linear alkyl, alternatively C₈₋₁₀ linear alkyl, alternatively C₉₋₁₀ linear alkyl, and alternatively C₉ linear alkyl; in another embodiment, R₂ is C₄₋₂₀ alkenyl, alternatively C₆₋₁₄ alkenyl, alternatively C₇₋₁₂ alkenyl, alternatively C₈₋₁₂ alkenyl; in another embodiment, R₂ is C₄₋₂₀ alkynyl, alternatively C₆₋₁₄ alkynyl, alternatively C₇₋₁₂ alkynyl, alternatively C₈₋₁₂ alkynyl; in another embodiment, R₂ is optionally substituted

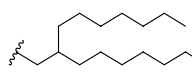
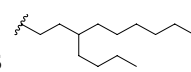
with one or more R_{1s}; in another embodiment, R₂ is optionally substituted with 1, 2, 3, or 4 R_{1s}, alternatively optionally substituted with 1 R_{1s}, alternatively optionally substituted with 1 C₁₋₃ alkyl, alternatively optionally substituted with 1 methyl; in another embodiment, R₂ is unsubstituted; in another embodiment, one or more methylene units in R₂ are optionally and independently replaced with -NR'-, alternatively one methylene unit in R₂ is optionally replaced with -NR'-.

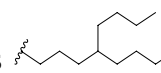
[0189] In one embodiment, only one of R₁ and R₂ is substituted; in another embodiment, R₁ is substituted with R_{1s}, and R₂ is not substituted with R_{1s}; in another embodiment, R₂ is substituted with R_{1s}, and R₁ is not substituted with R_{1s};

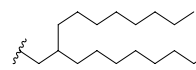
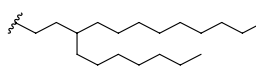
[0190] In one embodiment, R₂ is -(CH₂)₅CH₃; in another embodiment, R₂ is -(CH₂)₆CH₃; in another embodiment, R₂ is -(CH₂)₇CH₃; in another embodiment, R₂ is -(CH₂)₈CH₃; in another embodiment, R₂ is -(CH₂)₉CH₃; in another embodiment, R₂ is -(CH₂)₁₀CH₃; in another embodiment, R₂ is -(CH₂)₁₁CH₃; in another embodiment, R₂ is -CH₂-C≡C-(CH₂)₅CH₃; in another embodiment, R₂ is -CH₂-C≡C-(CH₂)₆CH₃; in another embodiment, R₂ is -(CH₂)₂-C≡C-(CH₂)₅CH₃; in another embodiment, R₂ is -(CH₂)₄-C≡C-(CH₂)₃CH₃; in another embodiment, R₂ is -CH₂-CH=CH-(CH₂)₅CH₃; in another embodiment, R₂ is -CH₂-CH=CH-(CH₂)₆CH₃; in another embodiment, R₂ is -(CH₂)₂-CH=CH-(CH₂)₅CH₃; in another embodiment, R₂ is -(CH₂)₄-CH=CH-(CH₂)₃CH₃; in another embodiment, R₂ is -(CH₂)₅-CH=CH-CH₂CH₃; in another embodiment, R₂ is

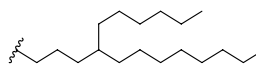
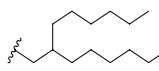
; in another embodiment, R₂ is ; in another embodiment,

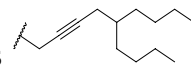
R₂ is ; in another embodiment, R₂ is ; in another

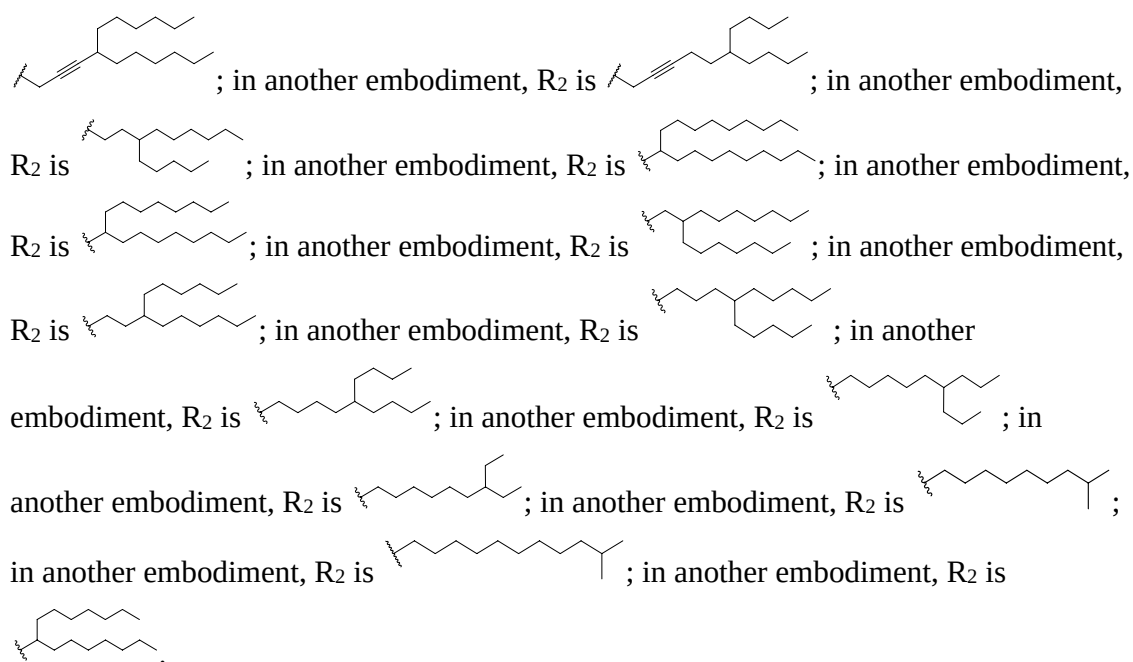
embodiment, R₂ is ; in another embodiment, R₂ is ; in

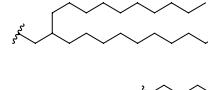
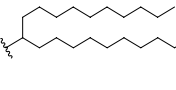
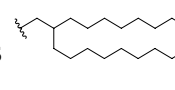
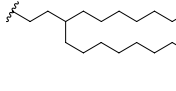
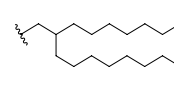
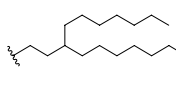
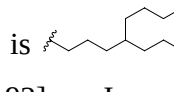
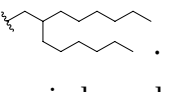
another embodiment, R₂ is ; in another embodiment, R₂ is

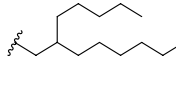
; in another embodiment, R₂ is ; in another

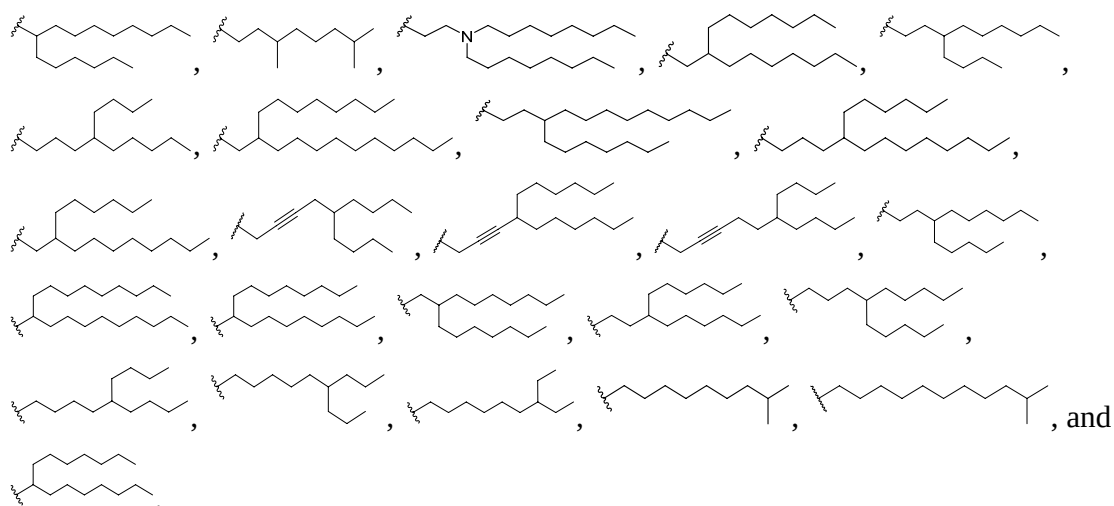
embodiment, R₂ is ; in another embodiment, R₂ is ;

in another embodiment, R₂ is ; in another embodiment, R₂ is



[0191] In one embodiment, R₂ is $-(CH_2)_2-C\equiv C-(CH_2)_4CH_3$; in another embodiment, R₂ is $-(CH_2)_3-C\equiv C-(CH_2)_3CH_3$; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  ; in another embodiment, R₂ is  .

[0192] In a more specific embodiment, R₁ and R₂ are independently selected from C₆₋₁₄ alkyl, C₆₋₁₄ alkenyl, and C₆₋₁₄ alkynyl; in another more specific embodiment, R₁ and R₂ are independently selected from C₇₋₁₂ alkyl, C₇₋₁₂ alkenyl, and C₇₋₁₂ alkynyl; in another more specific embodiment, R₁ and R₂ are independently selected from C₈₋₁₂ alkyl, C₈₋₁₂ alkenyl, and C₈₋₁₂ alkynyl; in another more specific embodiment, R₁ and R₂ are independently selected from the following groups: $-(CH_2)_5CH_3$, $-(CH_2)_6CH_3$, $-(CH_2)_7CH_3$, $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_{11}CH_3$, $-CH_2-C\equiv C-(CH_2)_5CH_3$, $-CH_2-C\equiv C-(CH_2)_6CH_3$, $-(CH_2)_2-C\equiv C-(CH_2)_5CH_3$, $-(CH_2)_4-C\equiv C-(CH_2)_3CH_3$, $-CH_2-CH=CH-(CH_2)_5CH_3$, $-CH_2-CH=CH-(CH_2)_6CH_3$, $-(CH_2)_2-CH=CH-(CH_2)_5CH_3$, $-(CH_2)_4-CH=CH-(CH_2)_3CH_3$, $-(CH_2)_5-CH=CH-CH_2CH_3$,  ,

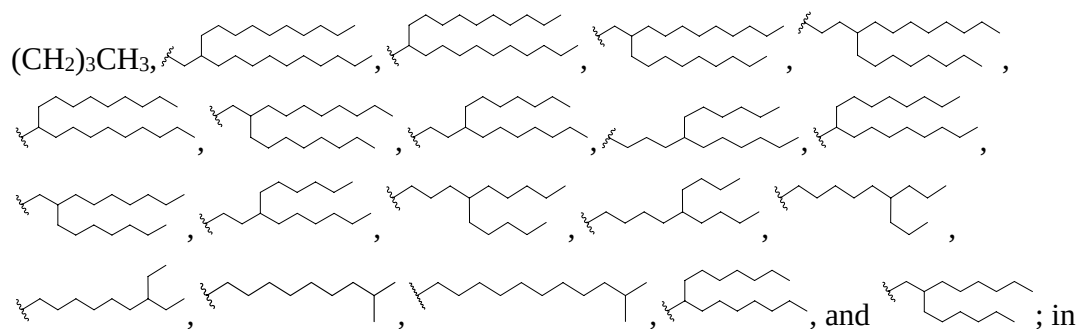


[0193] In a more specific embodiment, R_1 and R_2 are independently selected from C_{7-12} alkyl, alternatively C_{8-12} alkyl, alternatively C_{9-11} alkyl, alternatively C_{9-10} alkyl, which is optionally substituted with 1 R_{1s} ; and only one of R_1 and R_2 is substituted.

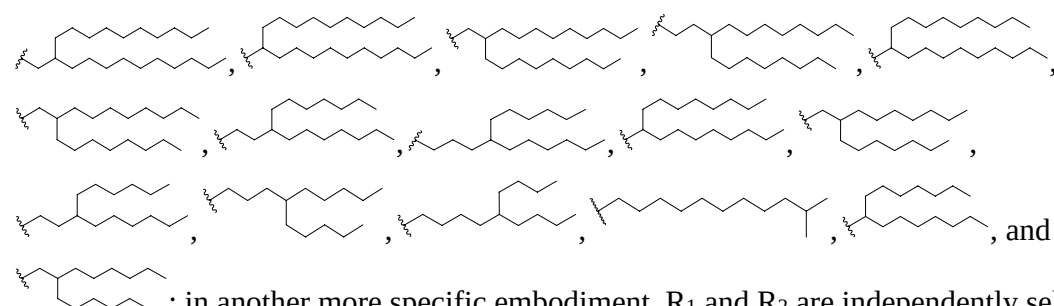
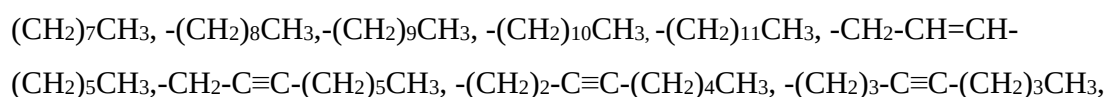
[0194] In a more specific embodiment, R_1 and R_2 are independently selected from: - $(CH_2)_6CH_3$, $-(CH_2)_7CH_3$, $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_{11}CH_3$, , and ; in another more specific embodiment, R_1 and R_2 are independently selected

from: $-(CH_2)_7CH_3$, $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_{11}CH_3$, , , , , , , and ; in another more specific embodiment, R_1 and R_2 are independently selected from: $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_{11}CH_3$, , , , , , , and .

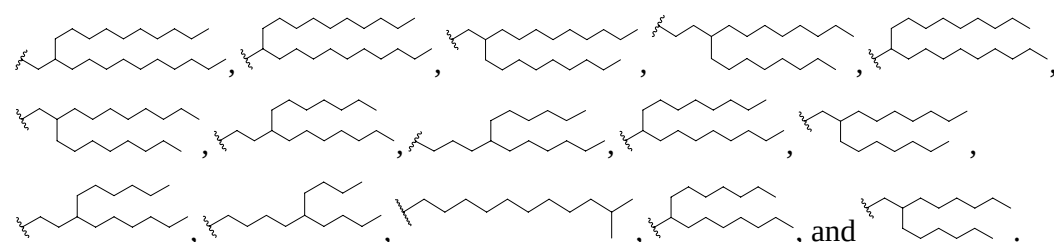
[0195] In a more specific embodiment, R_1 and R_2 are independently selected from: - $(CH_2)_6CH_3$, $-(CH_2)_7CH_3$, $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, $-(CH_2)_{11}CH_3$, $-CH_2-CH=CH-(CH_2)_5CH_3$, $-CH_2-C\equiv C-(CH_2)_5CH_3$, $-(CH_2)_2-C\equiv C-(CH_2)_4CH_3$, $-(CH_2)_3-C\equiv C-$



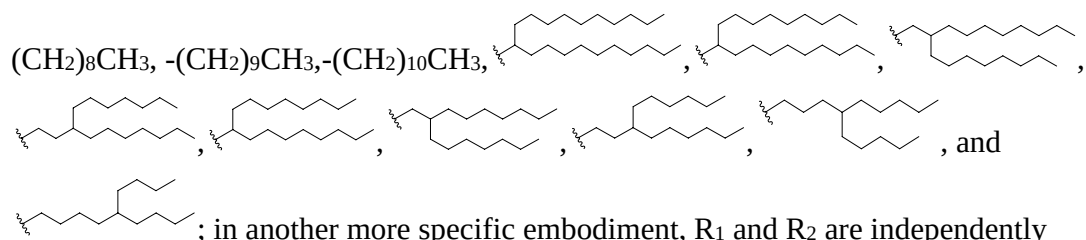
another more specific embodiment, R_1 and R_2 are independently selected from: -

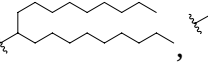
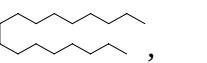
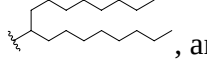
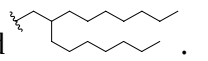


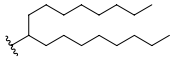
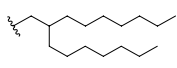
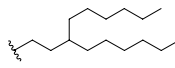
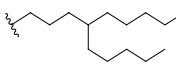
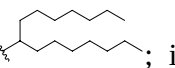
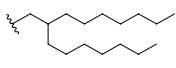
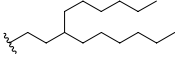
from: $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$,
 $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$,

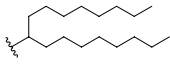
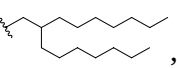
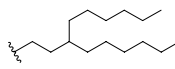
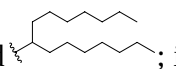
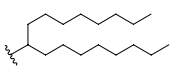
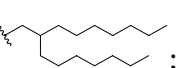
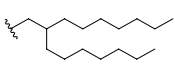
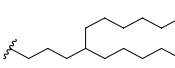
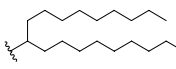
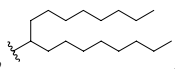
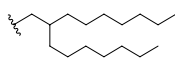
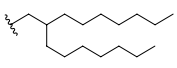
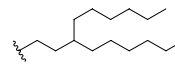


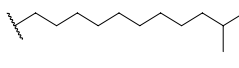
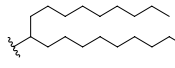
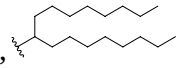
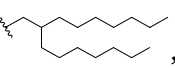
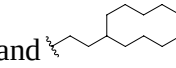
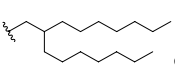
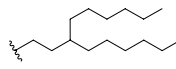
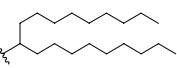
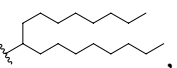
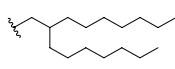
[0196] In a more specific embodiment, R_1 and R_2 are independently selected from: -

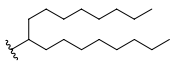
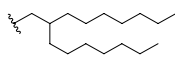
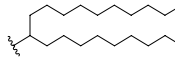
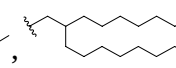
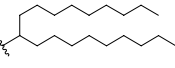
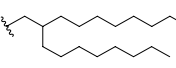
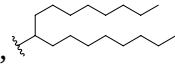
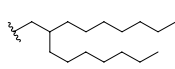
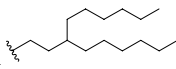
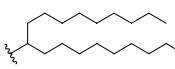
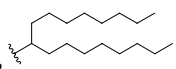
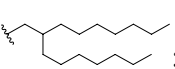


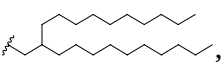
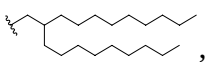
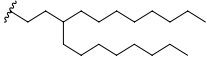
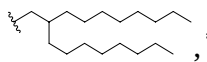
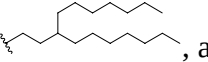
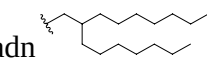
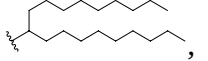
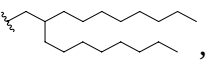
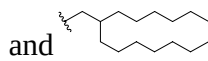
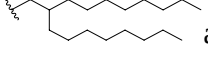
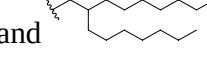
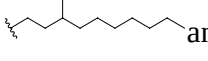
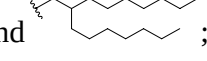
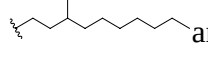
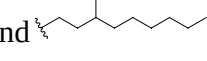
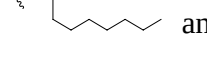
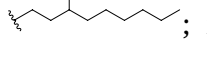
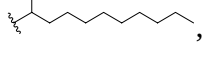
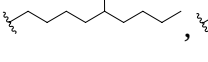
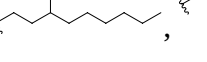
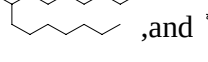
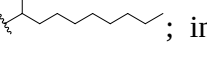
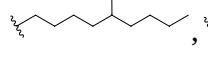
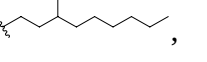
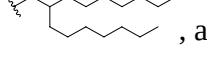
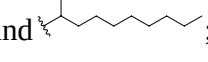
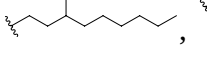
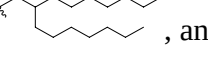
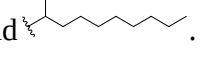
selected from: $-(\text{CH}_2)_7\text{CH}_3$, $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, , ,
, and  .

[0197] In a more specific embodiment, R₁ is selected from: , , , , and ; in another more specific embodiment, R₁ is selected from:  and .

[0198] In a more specific embodiment, R₁ is selected from: , , , and ; in another more specific embodiment, R₁ is selected from:  and ; in another more specific embodiment, R₁ is selected from: $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, , and ; in another more specific embodiment, R₁ is selected from: , , and ; in another more specific embodiment, R₁ is selected from:  and .

[0199] In a more specific embodiment, R₂ is selected from: $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, and ; in another more specific embodiment, R₂ is selected from: , , , and ; in another more specific embodiment, R₂ is selected from:  and ; in another more specific embodiment, R₂ is selected from: , , and .

[0200] In a more specific embodiment, R₂ is selected from:  and ; in another more specific embodiment, R₂ is selected from: , , , , , , and ; in another more specific embodiment, R₂ is selected from: , , and ; in another more specific

embodiment, R₂ is selected from: , , , , , and ; in another more specific embodiment, R₂ is selected from: , , and ; in another more specific embodiment, R₂ is selected from: , and ; in another more specific embodiment, R₂ is selected from: , and ; in another more specific embodiment, R₂ is selected from: , and ; in another more specific embodiment, R₂ is selected from:  and ; in another more specific embodiment, R₂ is selected from: , , , , and ; in another more specific embodiment, R₂ is selected from: , , , and ; in another more specific embodiment, R₂ is selected from: , , and .

[0201] R_{1s}

[0202] In one embodiment, R_{1s} is H; in another embodiment, R_{1s} is H; in another embodiment, R_{1s} is C₁₋₂₀ alkyl, alternatively C₁₋₁₄ alkyl, alternatively C₁₋₁₀ alkyl, alternatively C₁₋₉ alkyl, alternatively C₇₋₉ alkyl, alternatively C₈₋₉ alkyl, alternatively C₁₋₆ alkyl, and alternatively C₁₋₄ alkyl, alternatively C₇₋₁₁ alkyl, alternatively C₄₋₁₀ alkyl, alternatively C₆₋₁₀ alkyl, alternatively C₇₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₄₋₉ alkyl, alternatively C₆₋₉ alkyl, alternatively C₁₋₈ alkyl, alternatively C₄₋₈ alkyl, alternatively C₆₋₈ alkyl, alternatively C₇₋₈ alkyl, alternatively C₆₋₇ alkyl, alternatively C₉ alkyl, alternatively C₈ alkyl, alternatively C₇ alkyl; in another embodiment, R_{1s} is -L_c-OR_c; in another embodiment, R_{1s} is -L_c-SR_c; in another embodiment, R_{1s} is -L_c-NR_cR'_c.

[0203] In one embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 0 carbon atom; in another embodiment, the substitution site of R_{1s} on R₁ is separated from

M₁ by 1 carbon atom; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 2 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 3 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 4 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 5 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 6 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 7 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 8 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 9 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₁ is separated from M₁ by 10 carbon atoms.

[0204] In one embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 0 carbon atom; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 1 carbon atom; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 2 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 3 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 4 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 5 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 6 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 7 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 8 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 9 carbon atoms; in another embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 10 carbon atoms.

[0205] In a more specific embodiment, R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c; in another more specific embodiment, R_{1s} is independently H or C₁₋₁₄ alkyl; in another more specific embodiment, R_{1s} is independently H or C₁₋₁₀ alkyl; in another more specific embodiment, R_{1s} is independently H or C₁₋₉ alkyl; in another more specific embodiment, R_{1s} is independently H or C₁₋₆ alkyl; in another more specific embodiment, R_{1s} is independently H or C₁₋₄ alkyl.

[0206] In a more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 0-10 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 0-6 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 0-4 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 0-2 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 0 carbon atom.

[0207] In a more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 1-10 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 1-6 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 1-4 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 1-2 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 2-10 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 2-6 carbon atoms; in another more specific embodiment, the substitution site of R_{1s} on R_1 or R_2 is separated from M_1 or M_2 by 2-4 carbon atoms.

[0208] In another more specific embodiment, R_1 is not substituted with R_{1s} , and the substitution site of R_{1s} on R_2 is separated from M_2 by 0-10 carbon atoms, alternatively 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; In another more specific embodiment, R_1 is not substituted with R_{1s} , and the substitution site of R_{1s} on R_2 is separated from M_2 by 0-10 carbon atoms, alternatively 0-6 carbon atom, alternatively 0-4 carbon atoms, alternatively 0-2 carbon atoms; alternatively 0 carbon atom; In another more specific embodiment, R_1 is not substituted with R_{1s} , and the substitution site of R_{1s} on R_2 is separated from M_2 by 2-10 carbon atoms, alternatively 2-6 carbon atom, alternatively 2-4 carbon atoms.

[0209] R and R'

- [0210] In one embodiment, R is H; in another embodiment, R is C₁₋₂₀ alkyl, alternatively C₁₋₁₄ alkyl, alternatively C₁₋₉ alkyl, and alternatively C₁₋₆ alkyl.
- [0211] In one embodiment, R' is H; in another embodiment, R' is C₁₋₂₀ alkyl, alternatively C₁₋₁₄ alkyl, alternatively C₁₋₉ alkyl, and alternatively C₁₋₆ alkyl.
- [0212] In a more specific embodiment, R and R' are each independently H or C₁₋₂₀ alkyl; in another more specific embodiment, R and R' are each independently H or C₁₋₁₄ alkyl; in another more specific embodiment, R and R' are each independently H or C₁₋₉ alkyl; in another more specific embodiment, R and R' are each independently H or C₁₋₆ alkyl; in another more specific embodiment, R is H.
- [0213] L_c, R_c, and R'_c
- [0214] In one embodiment, L_c is a chemical bond; in another embodiment, L_c is C₁₋₂₀ alkylene, alternatively C₁₋₁₄ alkylene, alternatively C₁₋₁₀ alkylene, and alternatively C₁₋₆ alkylene.
- [0215] In a more specific embodiment, L_c is independently a chemical bond or C₁₋₁₄ alkylene; in another more specific embodiment, L_c is independently a chemical bond or C₁₋₁₀ alkylene; in another more specific embodiment, L_c is independently a chemical bond or C₁₋₆ alkylene.
- [0216] In one embodiment, R_c is H; in another embodiment, R_c is C₁₋₂₀ alkyl, alternatively C₁₋₁₄ alkyl, alternatively C₁₋₁₀ alkyl, and alternatively C₁₋₆ alkyl; in another embodiment, R_c is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R_c is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0217] In one embodiment, R'_c is H; in another embodiment, R'_c is C₁₋₂₀ alkyl, alternatively C₁₋₁₄ alkyl, alternatively C₁₋₁₀ alkyl, and alternatively C₁₋₆ alkyl; in another embodiment, R'_c is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R'_c is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.
- [0218] In a more specific embodiment, R_c and R'_c are independently H or C₁₋₁₄ alkyl; in another more specific embodiment, R_c and R'_c are independently H or C₁₋₁₀ alkyl; in another more specific embodiment, R_c and R'_c are independently H or C₁₋₆ alkyl.

[0219] R_3

[0220] In one embodiment, R_3 is CN; in another embodiment, R_3 is $-OR_g$, for example, -OH; in another embodiment, R_3 is $-C(O)R_g$; in another embodiment, R_3 is $-OC(O)R_g$; in another embodiment, R_3 is $-NR''C(O)R_g$; in another embodiment, R_3 is $-NR_gR'_g$, for example, $-N(CH_3)_2$; in another embodiment, R_3 is $-NR''C(O)NR_gR'_g$; in another embodiment, R_3 is $-NR''C(O)R_g$; in another embodiment, R_3 is $-NR''S(O)_2R_g$; in another embodiment, R_3 is $-OC(O)NR_gR'_g$; in another embodiment, R_3 is $-NR''C(O)OR_g$; in another embodiment, R_3 is $-N(OR_g)C(O)R_g$; in another embodiment, R_3 is $-N(OR_g)S(O)_2R_g$; in another embodiment, R_3 is $-N(OR_g)C(O)OR_g$; in another embodiment, R_3 is $-N(OR_g)C(O)R_gR'_g$; in another embodiment, R_3 is 3- to 14-membered heterocyclyl; in another embodiment, R_3 is 5- to 14-membered heteroaryl.

[0221] In a more specific embodiment, R_3 is CN, $-OR_g$, or $-NR_gR'_g$; in another more specific embodiment, R_3 is $-OR_g$ or $-NR_gR'_g$; in another more specific embodiment, R_3 is -OH or $-N(CH_3)_2$; in another more specific embodiment, R_3 is $-OR_g$; in another more specific embodiment, R_3 is -OH.

[0222] R_g and R'_g

[0223] In one embodiment, R_g is H; in another embodiment, R_g is C_{1-10} alkyl, alternatively C_{1-6} alkyl, alternatively C_{1-4} alkyl, for example, methyl; in another embodiment, R_g is C_{3-10} cycloalkyl, alternatively C_{3-7} cycloalkyl; in another embodiment, R_g is 3- to 10-membered heterocyclyl, alternatively 3- to 7-membered heterocyclyl.

[0224] In one embodiment, R'_g is H; in another embodiment, R'_g is C_{1-10} alkyl, alternatively C_{1-6} alkyl, and alternatively C_{1-4} alkyl; in another embodiment, R'_g is C_{3-10} cycloalkyl, alternatively C_{3-7} cycloalkyl; in another embodiment, R'_g is 3- to 10-membered heterocyclyl, alternatively 3- to 7-membered heterocyclyl.

[0225] In a more specific embodiment, R_g and R'_g are independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl; in another more specific embodiment, R_g and R'_g are independently H or C_{1-6} alkyl; in another more specific embodiment, R_g and R'_g are independently H or C_{1-4} alkyl; in another more specific embodiment, R_g and R'_g are independently H or methyl.

[0226] R"

[0227] In one embodiment, R" is H; in another embodiment, R" is C₁₋₆ alkyl, alternatively C₁₋₄ alkyl.

[0228] R₄ and R₅

[0229] In one embodiment, R₄ is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl, alternatively C₁₋₃ alkyl, and alternatively methyl; in another embodiment, R₄ is optionally substituted with one or more R_{4s}; in another embodiment, R₄ is optionally substituted with 1, 2, or 3 R_{4s}; in another embodiment, R₄ is unsubstituted.

[0230] In one embodiment, R₅ is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl, alternatively C₁₋₃ alkyl, and alternatively methyl; in another embodiment, R₅ is optionally substituted with one or more R_{4s}; in another embodiment, R₅ is optionally substituted with 1, 2, or 3 R_{4s}; in another embodiment, R₅ is unsubstituted.

[0231] In one embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene, alternatively C₃₋₁₀ cycloalkylene, alternatively C₃₋₆ cycloalkylene (e.g., cyclopropylene, cyclobutylene, cyclopentylene, and cyclohexylene), alternatively C₃₋₅ cycloalkylene, alternatively C₃₋₄ cycloalkylene, alternatively cyclopropylene, alternatively cyclopentylene; in another embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form 3- to 14-membered heterocyclylene, alternatively 3- to 10-membered heterocyclylene, alternatively 3- to 6-membered heterocyclylene; in another embodiment, a ring formed by R₄, R₅ taken together with the carbon atom to which they are attached is optionally substituted with one or more R_{4s}; in another embodiment, a ring formed by R₄, R₅ taken together with the carbon atom to which they are attached is optionally substituted with 1, 2, or 3 R_{4s}; in another embodiment, a ring formed by R₄, R₅ taken together with the carbon atom to which they are attached is unsubstituted.

[0232] In a more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₁₀ cycloalkylene or 3- to 10-membered heterocyclylene; in another more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-

membered heterocyclene; in another more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene (e.g., cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene); in another more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₅ cycloalkylene; in another more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene or cyclopentylene; in another more specific embodiment, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene; in another more specific embodiment, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring.

[0233] R_{4s}

[0234] In one embodiment, R_{4s} is H; in another embodiment, R_{4s} is halogen; in another embodiment, R_{4s} is cyano; in another embodiment, R_{4s} is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl, alternatively C₁₋₃ alkyl; in another embodiment, R_{4s} is C₁₋₈ haloalkyl, alternatively C₁₋₆ haloalkyl, and alternatively C₁₋₃ haloalkyl; in another embodiment, R_{4s} is -L_d-OR_d; in another embodiment, R_{4s} is -L_d-SR_d; in another embodiment, R_{4s} is -L_d-NR_dR'_d.

[0235] In a more specific embodiment, R_{4s} is independently H, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -L_d-OR_d, -L_d-SR_d, or -L_d-NR_dR'_d; in another more specific embodiment, R_{4s} is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; in another more specific embodiment, R_{4s} is independently H, C₁₋₃ alkyl, or C₁₋₃ haloalkyl.

[0236] L_d, R_d, and R'_d

[0237] In one embodiment, L_d is a chemical bond; in another embodiment, L_d is C₁₋₈ alkylene, alternatively C₁₋₆ alkylene, and alternatively C₁₋₃ alkylene.

[0238] In a more specific embodiment, L_d is independently a chemical bond or C₁₋₆ alkylene; in another more specific embodiment, L_d is independently a chemical bond or C₁₋₃ alkylene.

[0239] In one embodiment, R_d is H; in another embodiment, R_d is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl; in another embodiment, R_d is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in

another embodiment, R_d is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.

[0240] In one embodiment, R'_d is H; in another embodiment, R'_d is C₁₋₈ alkyl, alternatively C₁₋₆ alkyl; in another embodiment, R'_d is C₃₋₁₄ cycloalkyl, alternatively C₃₋₁₀ cycloalkyl; in another embodiment, R'_d is 3- to 14-membered heterocyclyl, alternatively 3- to 10-membered heterocyclyl.

[0241] In a more specific embodiment, R_d and R'_d are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl; in another more specific embodiment, R_d and R'_d are independently H or C₁₋₆ alkyl.

[0242] a, b, c, and d

[0243] In one embodiment, a is 1; in another embodiment, a is 2; in another embodiment, a is 3; in another embodiment, a is 4; in another embodiment, a is 5; in another embodiment, a is 6.

[0244] In a more specific embodiment, a = 2, 3, 4, 5, or 6; in another more specific embodiment, a = 2, 3, or 4; in another more specific embodiment, a = 2 or 4; in another more specific embodiment, a = 2 or 3; in another more specific embodiment, a = 3 or 4.

[0245] In one embodiment, b is 4; in another embodiment, b is 5; in another embodiment, b is 6; in another embodiment, b is 7; in another embodiment, b is 8; in another embodiment, b is 9; in another embodiment, b is 10.

[0246] In a more specific embodiment, b = 5, 6, 7, or 8; in another more specific embodiment, b = 5, 6, or 7; in another more specific embodiment, b = 5 or 7; in another more specific embodiment, b = 6 or 7.

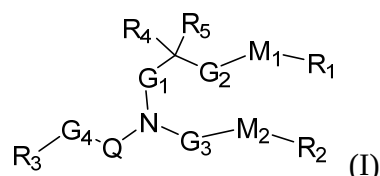
[0247] In a more specific embodiment, b = 4, 5, 6, 7, 8, 9, or 10; in another more specific embodiment, b = 4, 5, 6, 7, 8, or 9; in another more specific embodiment, b = 4, 5, 6, or 7; in another more specific embodiment, b = 5 or 6; in another more specific embodiment, b = 6, 7, or 8; in another more specific embodiment, b = 5, 6, 7, or 8.

[0248] In one embodiment, c is 1; in another embodiment, c is 2; in another embodiment, c is 3; in another embodiment, c is 4; in another embodiment, c is 5; in another embodiment, c is 6.

- [0249] In a more specific embodiment, $c = 2, 3, 4, 5$, or 6 ; in another more specific embodiment, $c = 2, 3$, or 4 ; in another more specific embodiment, $c = 3$ or 4 ; in another more specific embodiment, $c = 5$ or 6 .
- [0250] In a more specific embodiment, $c = 2, 4, 5$, or 6 ; in another more specific embodiment, $c = 4, 5$, or 6 ; in another more specific embodiment, $c = 4$ or 6 ; in another more specific embodiment, $c = 2, 3, 4$, or 5 ; in another more specific embodiment, $c = 2, 4$, or 5 ; in another more specific embodiment, $c = 2$ or 5 .
- [0251] In one embodiment, d is 0 ; in another embodiment, d is 1 ; in another embodiment, d is 2 ; in another embodiment, d is 3 ; in another embodiment, d is 4 .
- [0252] In a more specific embodiment, $d = 0, 1, 2$, or 4 ; in another more specific embodiment, $d = 2, 3$, or 4 ; in another more specific embodiment, $d = 0$ or 1 .
- [0253] In a more specific embodiment, $d = 0, 1, 2, 3$, or 4 ; in another more specific embodiment, $d = 0, 1$, or 2 ; in another more specific embodiment, $d = 0$ or 2 ; in another more specific embodiment, d is not 0 ; in another more specific embodiment, $d = 1, 2, 3$, or 4 ; in another more specific embodiment, $d = 1$ or 2 ; in another more specific embodiment, $d = 1, 2$ or 4 ; in another more specific embodiment, $d = 1$ or 4 .
- [0254] In one embodiment, $c + d = 3$; in another embodiment, $c + d = 4$; in another embodiment, $c + d = 5$; in another embodiment, $c + d = 6$; in another embodiment, $c + d = 7$; in another embodiment, $c + d = 8$; in another embodiment, $c + d = 9$.
- [0255] In a more specific embodiment, $c + d = 4, 5$, or 6 ; in another more specific embodiment, $c + d = 5$ or 6 .
- [0256] In a more specific embodiment, $c + d = 3, 4, 5, 6, 7, 8$, or 9 ; in another more specific embodiment, $c + d = 4, 5, 6$, or 7 ; in another more specific embodiment, $c + d = 4, 5$, or 6 ; in another more specific embodiment, $c + d = 5, 6$, or 7 ; in another more specific embodiment, $c + d = 6, 7$, or 8 ; in another more specific embodiment, $c + d = 6$ or 7 .
- [0257] Any of the above technical solutions in any specific embodiment or any combination thereof may be combined with any technical solution or any combination thereof in other specific embodiments. For example, any technical solutions of G_1 , or any combination thereof, may be combined with any technical solution of $G_2, R_{G1}, G_3, R_{G3}, L_a, R_a, R'_a, G_4, R_{G4}, L_b, R_b, R'_b, R_{4g}, L_e, R_e, R'_e, M_1, M_2, Q, R^*, L_f, R_f, R'_f, R_1, R_2, R_{1s}, R,$

R', L_c, R_c, R'_c, R₃, R_g, R'_g, R'', R₄, R₅, R_{4s}, L_d, R_d, R'_d, a, b, c, and d, etc. The present disclosure is intended to include all of these combinations of technical solutions and, for reasons of space, will not be listed.

[0258] In a more specific embodiment, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof:



[0259] wherein

[0260] G₁ and G₂ are independently selected from a chemical bond, C₁₋₁₃ linear alkylene, C₂₋₁₃ linear alkenylene, and C₂₋₁₃ linear alkynylene, each of which is optionally substituted with one or more R_{G1};

[0261] G₁ and G₂ have a total length of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 carbon atoms;

[0262] R_{G1} is independently H, C₁₋₁₄ alkyl, -L_a-OR_a, -L_a-SR_a, or -L_a-NR_aR'_a;

[0263] G₃ is C₄₋₁₄ linear alkylene, C₄₋₁₄ linear alkenylene, or C₄₋₁₄ linear alkynylene, each of which is optionally substituted with one or more R_{G3};

[0264] R_{G3} is independently H, -L_a-OR_a, -L_a-SR_a, or -L_a-NR_aR'_a;

[0265] L_a is independently a chemical bond or C₁₋₁₄ alkylene;

[0266] R_a and R'_a are independently selected from H, C₁₋₁₄ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;

[0267] G₄ is a chemical bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆ alkynylene, each of which is optionally substituted with one or more R_{G4};

[0268] R_{G4} is independently H, C₁₋₆ alkyl, -L_b-OR_b, -L_b-SR_b, or -L_b-NR_bR'_b;

[0269] L_b is independently a chemical bond or C₁₋₆ alkylene;

[0270] R_b and R'_b are independently selected from H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocyclyl;

[0271] or, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4g};

- [0272] R_{4g} is independently H, halogen, cyano, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -L_e-OR_e, -L_e-SR_e, or -L_e-NR_eR'_e;
- [0273] L_e is independently a chemical bond or C₁₋₈ alkylene;
- [0274] R_e and R'_e are independently selected from H, C₁₋₈ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0275] M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -O-, -SC(O)O-, -OC(O)NR-, -NRC(O)NR-, -OC(O)S-, -OC(O)O-, -NRC(O)O-, -SC(O)-, -C(O)S-, -NR-, -C(O)NR-, -NRC(O)-, -NRC(O)S-, -SC(O)NR-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR-, -NRC(S)O-, -S-S-, and -S(O)₀₋₂-;
- [0276] Q is selected from a chemical bond, -C(O)O-, -O-, -SC(O)O-, -OC(O)NR_f-, -NR_fC(O)NR_f-, -OC(O)S-, -OC(O)O-, -NR_fC(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NR_f-, -C(O)NR_f-, -NR_fC(O)-, -NR_fC(O)S-, -SC(O)NR_f-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR_f-, -NR_fC(S)O-, -S-S-, -S(O)₀₋₂-, phenylene, and pyridinylene, wherein the phenylene or the pyridinylene is optionally substituted with one or more R*;
- [0277] R* is independently H, halogen, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, -L_f-OR_f, -L_f-SR_f, or -L_f-NR_fR'_f;
- [0278] L_f is independently a chemical bond or C₁₋₈ alkylene;
- [0279] R_f and R'_f are independently selected from H, C₁₋₁₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0280] R₁ and R₂ are independently selected from C₄₋₂₀ alkyl, C₄₋₂₀ alkenyl, and C₄₋₂₀ alkynyl, each of which is optionally substituted with one or more R_{1s}, and wherein one or more methylene units are optionally and independently replaced with -NR'-;
- [0281] R_{1s} is independently H, C₁₋₂₀ alkyl, -L_c-OR_c, -L_c-SR_c, or -L_c-NR_cR'_c;
- [0282] R and R' are independently H or C₁₋₂₀ alkyl;
- [0283] L_c is independently a chemical bond or C₁₋₂₀ alkylene;
- [0284] R_c and R'_c are independently selected from H, C₁₋₂₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;
- [0285] R₃ is selected from CN, -OR_g, -C(O)R_g, -OC(O)R_g, -NR''C(O)R_g, -NR_gR'_g, -NR''C(O)NR_gR'_g, -NR''C(O)R_g, -NR''S(O)₂R_g, -OC(O)NR_gR'_g, -NR''C(O)OR_g, -N(OR_g)C(O)R_g, -N(OR_g)S(O)₂R_g, -N(OR_g)C(O)OR_g, -N(OR_g)C(O)R_gR'_g, 3- to 14-membered heterocyclyl, and 5- to 14-membered heteroaryl;

- [0286] R_g and R'_g are independently H, C_{1-10} alkyl, C_{3-10} cycloalkyl, or 3- to 10-membered heterocyclyl;
- [0287] R'' is independently H or C_{1-6} alkyl;
- [0288] R_4 and R_5 are independently C_{1-8} alkyl, which is optionally substituted with one or more R_{4s} ;
- [0289] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-14} cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4s} ;
- [0290] R_{4s} is independently H, halogen, cyano, C_{1-8} alkyl, C_{1-8} haloalkyl, $-L_d-OR_d$, $-L_d-SR_d$, or $-L_d-NR_dR'_d$;
- [0291] L_d is independently a chemical bond or C_{1-8} alkylene;
- [0292] R_d and R'_d are independently H, C_{1-8} alkyl, C_{3-14} cycloalkyl, or 3- to 14-membered heterocyclyl..
- [0293] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G_1 and G_2 are independently a chemical bond, C_{1-9} linear alkylene, C_{2-9} linear alkenylene, or C_{2-9} linear alkynylene.
- [0294] In a more specific embodiment, G_1 is C_{1-6} linear alkylene, C_{2-6} linear alkenylene, or C_{2-6} linear alkynylene, alternatively C_{1-6} linear alkylene, alternatively C_{2-6} linear alkylene.
- [0295] In a more specific embodiment, G_2 is a chemical bond, C_{1-6} linear alkylene, C_{2-6} linear alkenylene, or C_{2-6} linear alkynylene, alternatively a chemical bond or C_{1-6} linear alkylene, alternatively a chemical bond or C_{1-4} linear alkylene.
- [0296] In a more specific embodiment, G_1 and G_2 have a total length of 3, 4, 5, 6, 7, 8, or 9 carbon atoms, alternatively a total length of 4, 5, or 6 carbon atoms, alternatively a total length of 5 or 6 carbon atoms; alternatively a total length of 5,6 or 7 carbon atoms; alternatively a total length of 6 or 7 carbon atoms.
- [0297] alternatively, G_1 and G_2 are optionally substituted with 1, 2, 3, or 4 R_{G1} .
- [0298] In a more specific embodiment, the present disclosure provides the compound of formula (I) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or

stereoisomer thereof, wherein R_{G1} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₆ alkyl.

[0299] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G₃ is C₄₋₁₀ linear alkylene, C₄₋₁₀ linear alkenylene, or C₄₋₁₀ linear alkynylene, alternatively C₄₋₉ linear alkylene, alternatively C₅₋₈ linear alkylene.

[0300] In a more specific embodiment, G₃ is optionally substituted with 1, 2, 3, or 4 R_{G3}.

[0301] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_a is independently a chemical bond or C₁₋₁₀ alkylene, alternatively a chemical bond or C₁₋₆ alkylene.

[0302] In a more specific embodiment, R_a and R'_a are independently H, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl.

[0303] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G₄ is C₁₋₄ alkylene, C₂₋₄ alkenylene, or C₂₋₄ alkynylene, alternatively C₂₋₄ alkylene, alternatively C₂₋₃ alkylene.

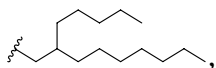
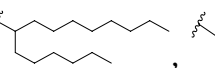
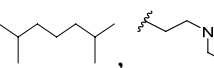
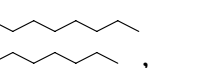
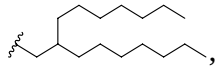
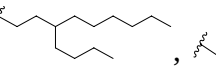
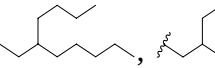
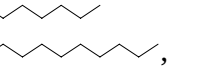
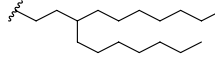
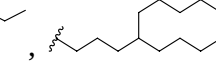
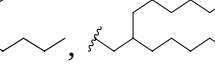
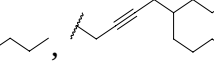
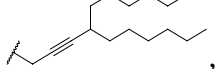
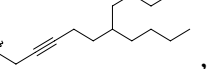
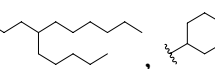
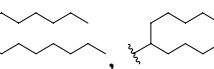
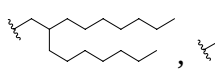
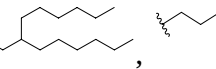
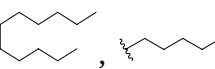
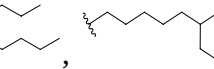
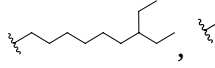
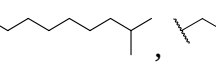
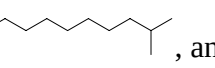
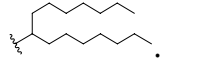
[0304] In a more specific embodiment, G₄ is optionally substituted with 1, 2, 3, or 4 R_{G4}.

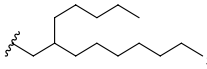
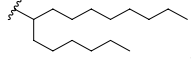
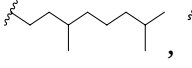
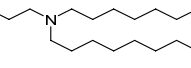
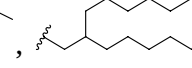
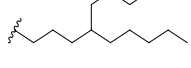
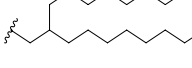
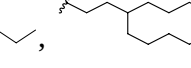
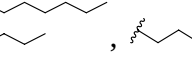
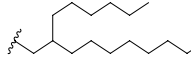
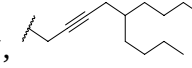
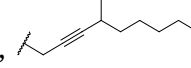
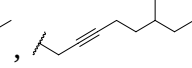
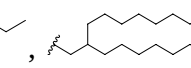
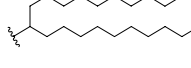
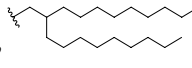
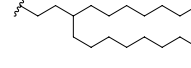
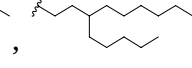
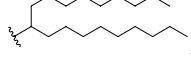
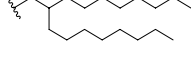
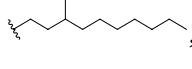
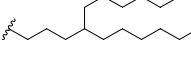
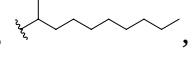
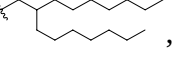
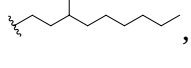
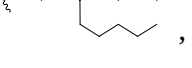
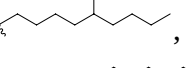
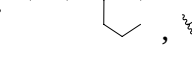
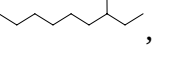
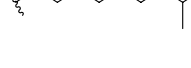
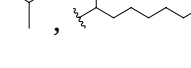
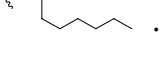
[0305] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{G4} is independently H or C₁₋₆ alkyl, alternatively C₁₋₄ alkyl.

[0306] In a more specific embodiment, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₁₀ cycloalkylene or 3- to 10-membered heterocyclylene, alternatively C₃₋₇ cycloalkylene or 3- to 7-membered heterocyclylene, each of which is optionally substituted with 1, 2, or 3 R_{4g}.

[0307] In a more specific embodiment, R_{4g} is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

- [0308] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_b is independently a chemical bond or C_{1-4} alkylene.
- [0309] In a more specific embodiment, R_b and R'_b are independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl, alternatively H or C_{1-6} alkyl, alternatively H or C_{1-4} alkyl.
- [0310] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-SC(O)-$, $-C(O)S-$, $-C(O)NR-$, and $-NRC(O)-$, alternatively $-C(O)O-$, $-OC(O)O-$, $-OC(O)-$, $-SC(O)-$, and $-C(O)S-$, alternatively $-C(O)O-$, $-OC(O)-$, $-SC(O)-$, and $-C(O)S-$, alternatively $-C(O)O-$ and $-OC(O)-$.
- [0311] In a more specific embodiment, M_1 and M_2 are independently selected from $-C(O)O-$ and $-C(O)S-$, alternatively $-C(O)O-$.
- [0312] In a more specific embodiment, one of M_1 and M_2 is $-C(O)O-$ or $-C(O)S-$, alternatively $-C(O)O-$, and the other is $-OC(O)-$ or $-SC(O)-$, alternatively $-OC(O)-$.
- [0313] In a more specific embodiment, M_1 is $-OC(O)-$ or $-SC(O)-$, alternatively $-OC(O)-$; and M_2 is $-C(O)O-$ or $-C(O)S-$, alternatively $-C(O)O-$.
- [0314] In a more specific embodiment, M_1 is $-C(O)O-$, and M_2 is $-C(O)O-$ or $-C(O)S-$.
- [0315] In a more specific embodiment, M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, $-SC(O)-$, $-C(O)S-$, $-NHC(O)-$, and $-C(O)NH-$.
- [0316] In a more specific embodiment, M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, $-C(O)S-$, and $-C(O)NH-$, alternatively $-C(O)O-$, $-OC(O)-$, and $-C(O)S-$.
- [0317] In a more specific embodiment, one of M_1 and M_2 is $-C(O)O-$ or $-C(O)S-$, alternatively $-C(O)O-$, and the other is selected from $-C(O)O-$, $-C(O)S-$, $-C(O)NH-$, $-OC(O)-$, and $-SC(O)-$, alternatively $-C(O)O-$, $-C(O)S-$, $-C(O)NH-$, and $-OC(O)-$, alternatively $-C(O)O-$, $-C(O)S-$, $-OC(O)-$, and $-SC(O)-$, alternatively $-C(O)O-$, $-C(O)S-$, and $-OC(O)-$.
- [0318] In a more specific embodiment, one of M_1 and M_2 is $-OC(O)O-$, and the other is selected from $-C(O)O-$, $-OC(O)-$, $-SC(O)-$, and $-C(O)S-$, alternatively $-C(O)O-$ and $-OC(O)-$.

- [0319] In a more specific embodiment, M₁ is selected from -C(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-, alternatively -C(O)O- and -OC(O)-, alternatively -C(O)O-, alternatively -OC(O)-, M₂ is -OC(O)O-.
- [0320] In a more specific embodiment, M₁ is -OC(O)O-, M₂ is -OC(O)- or -C(O)O-, alternatively -OC(O)-.
- [0321] In a more specific embodiment, M₁ and M₂ are independently selected from -C(O)O-, -C(O)S-, -OC(O)-, -SC(O)-, and -OC(O)O-, alternatively -C(O)O-, -OC(O)-, and -OC(O)O-; alternatively M₁ and M₂ are not simultaneously -OC(O)O-.
- [0322] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R₁ and R₂ are independently C₆₋₁₄ alkyl, C₆₋₁₄ alkenyl, or C₆₋₁₄ alkynyl, alternatively C₆₋₁₄ alkyl, alternatively C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl.
- [0323] In a more specific embodiment, R₁ and R₂ are independently C₇₋₁₂ alkyl, C₇₋₁₂ alkenyl, or C₇₋₁₂ alkynyl, alternatively C₈₋₁₂ alkyl, C₈₋₁₂ alkenyl, or C₈₋₁₂ alkynyl.
- [0324] In a more specific embodiment, R₁ and R₂ are optionally substituted with 1, 2, 3, or 4 R_{1s}, alternatively optionally substituted with 1 R_{1s}.
- [0325] In a more specific embodiment, R₁ and R₂ are independently selected from the following groups: -(CH₂)₅CH₃, -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, -CH₂-C≡C-(CH₂)₅CH₃, -CH₂-C≡C-(CH₂)₆CH₃, -(CH₂)₂-C≡C-(CH₂)₅CH₃, -(CH₂)₄-C≡C-(CH₂)₃CH₃, -CH₂-CH=CH-(CH₂)₅CH₃, -CH₂-CH=CH-(CH₂)₆CH₃, -(CH₂)₂-CH=CH-(CH₂)₅CH₃, -(CH₂)₄-CH=CH-(CH₂)₃CH₃, -(CH₂)₅-CH=CH-CH₂CH₃, , , , , , , , , , , , , , , , , , , , , , , , and .

[0326] In a more specific embodiment, R₁ and R₂ are independently selected from the following groups: -(CH₂)₅CH₃, -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, -CH₂-C≡C-(CH₂)₅CH₃, -CH₂-C≡C-(CH₂)₆CH₃, -(CH₂)₂-C≡C-(CH₂)₅CH₃, -(CH₂)₂-C≡C-(CH₂)₄CH₃, -(CH₂)₃-C≡C-(CH₂)₃CH₃, -(CH₂)₄-C≡C-(CH₂)₃CH₃, -CH₂-CH=CH-(CH₂)₅CH₃, -CH₂-CH=CH-(CH₂)₆CH₃, -(CH₂)₂-CH=CH-(CH₂)₅CH₃, -(CH₂)₄-CH=CH-(CH₂)₃CH₃, -(CH₂)₅-CH=CH-CH₂CH₃, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

[0327] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c, alternatively H or C₁₋₁₄ alkyl, alternatively H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alky.

[0328] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R and R' are each independently H or C₁₋₂₀ alkyl, alternatively H or C₁₋₁₄ alkyl, alternatively H or C₁₋₉ alkyl, alternatively H or C₁₋₆ alkyl; alternatively, R is H.

[0329] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or

stereoisomer thereof, wherein L_c is independently a chemical bond or C_{1-14} alkylene, alternatively a chemical bond or C_{1-10} alkylene, alternatively a chemical bond or C_{1-6} alkylene.

[0330] In a more specific embodiment, R_c and R'_c are independently H or C_{1-14} alkyl, alternatively H or C_{1-10} alkyl, alternatively H or C_{1-6} alkyl.

[0331] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_3 is CN, $-OR_g$, or $-NR_gR'_g$, alternatively $-OR_g$ or $-NR_gR'_g$, alternatively $-OR_g$, alternatively $-OH$.

[0332] In a more specific embodiment, R_3 is OH or $-N(CH_3)_2$.

[0333] In a more specific embodiment, R_g and R'_g are independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl, alternatively H or C_{1-6} alkyl, alternatively H or C_{1-4} alkyl, alternatively H or methyl.

[0334] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_4 and R_5 are independently C_{1-6} alkyl, alternatively C_{1-3} alkyl, alternatively methyl.

[0335] In a more specific embodiment, R_4 and R_5 are optionally substituted with 1, 2, or 3 R_{4s} .

[0336] In a more specific embodiment, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkylene or 3- to 10-membered heterocyclylene, alternatively C_{3-6} cycloalkylene or 3- to 6-membered heterocyclylene, alternatively C_{3-6} cycloalkylene (e.g., cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene), alternatively C_{3-5} cycloalkylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene.

[0337] In a more specific embodiment, a ring formed by R_4 and R_5 with the carbon atom to which they are attached to is optionally substituted with 1, 2, or 3 R_{4s} .

[0338] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{4s} is independently H, halogen, cyano, C_{1-6} alkyl, C_{1-6}

haloalkyl, -L_d-OR_d, -L_d-SR_d, or -L_d-NR_dR'_d, alternatively H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, alternatively H, C₁₋₃ alkyl, or C₁₋₃ haloalkyl.

[0339] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_d is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₃ alkylene.

[0340] In a more specific embodiment, R_d and R'_d are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl.

[0341] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_e is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₄ alkylene.

[0342] In a more specific embodiment, R_e and R'_e are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.

[0343] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein Q is a chemical bond, -OC(O)-, or -SC(O)-, alternatively a chemical bond or -SC(O)-.

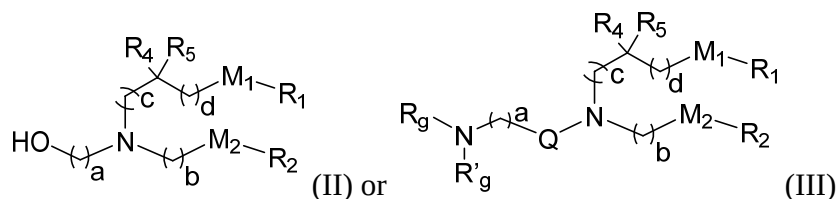
[0344] In a more specific embodiment, when Q is phenylene or pyridinylene, Q is optionally substituted with 1, 2, or 3 R*.

[0345] In a more specific embodiment, R* is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl.

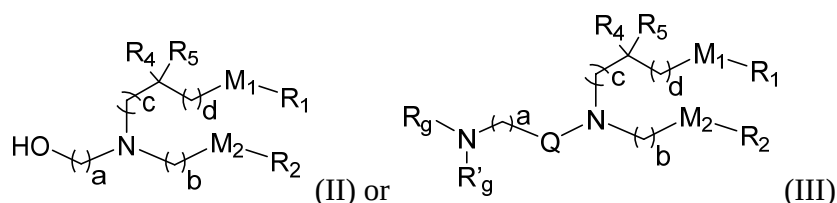
[0346] In a more specific embodiment, L_f is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₄ alkylene.

[0347] In a more specific embodiment, R_f and R'_f are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.

[0348] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, which has a structure of formula (II) or formula (III):



- [0349] wherein
- [0350] a = 1, 2, 3, 4, 5, or 6;
- [0351] b = 4, 5, 6, 7, 8, 9, or 10;
- [0352] c = 1, 2, 3, 4, 5, or 6;
- [0353] d = 0, 1, 2, 3, or 4;
- [0354] c + d = 3, 4, 5, 6, 7, 8, or 9;
- [0355] the other groups are as defined herein.
- [0356] In a more specific embodiment, the present disclosure provides the compound of formula (II) or formula (III), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



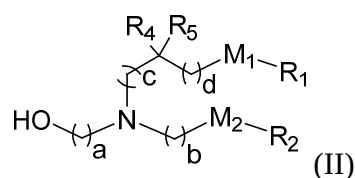
- [0357] wherein, the substitution site of R_{1s} on R₁ or R₂ is separated from M₁ or M₂ by 0-10 carbon atoms, alternatively 0-6 carbon atoms, alternatively 0-4 carbon atoms, alternatively 0-2 carbon atoms, alternatively 0 carbon atom.
- [0358] In a more specific embodiment, the substitution site of R_{1s} on R₂ is separated from M₂ by 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, alternatively 2-4 carbon atoms.
- [0359] In a more specific embodiment, R₁ is not substituted with R_{1s}, and the substitution site of R_{1s} on R₂ is separated from M₂ by 0-10 carbon atoms, alternatively 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, alternatively 2-4 carbon atoms.

[0360] In a more specific embodiment, R₁ is substituted with R_{1s}, and R₂ is not substituted with R_{1s}.

[0361] In a more specific embodiment, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring.

[0362] In a more specific embodiment, d is not 0.

[0363] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0364] wherein

[0365] a = 2, 3, 4, 5, or 6;

[0366] b = 4, 5, 6, 7, 8, 9, or 10;

[0367] c = 1, 2, 3, 4, 5, or 6;

[0368] d = 0, 1, 2, 3, or 4;

[0369] c + d = 3, 4, 5, 6, 7, 8, or 9; alternatively c + d = 4, 5, or 6;

[0370] M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-; alternatively, M₁ and M₂ are independently selected from -C(O)O- and -C(O)S-; alternatively, one of M₁ and M₂ is -C(O)O- or -C(O)S-, and the other is -OC(O)- or -SC(O)-;

[0371] R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

[0372] R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c, alternatively H or C₁₋₁₄alkyl;

[0373] L_c is independently a chemical bond or C₁₋₁₄ alkylene;

[0374] R_c and R'_c are independently H or C₁₋₁₄ alkyl;

[0375] R₄ and R₅ are independently C₁₋₆ alkyl;

[0376] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

[0377] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0378] $a = 2, 3, \text{ or } 4$;

[0379] $b = 4, 5, 6, 7, 8, \text{ or } 9$; alternatively $b = 5, 6, 7, \text{ or } 8$; alternatively $b = 5, 6, \text{ or } 7$;

[0380] $c = 2, 3, 4, 5, \text{ or } 6$;

[0381] $d = 0, 1, 2, 3, \text{ or } 4$;

[0382] $c + d = 5 \text{ or } 6$;

[0383] M_1 and M_2 are independently $-C(O)O-$ or $-OC(O)-$; alternatively, M_1 and M_2 are $-C(O)O-$; alternatively, one of M_1 and M_2 is $-C(O)O-$, and the other is $-OC(O)-$;

[0384] R_1 and R_2 are independently C_{7-12} alkyl, alternatively C_{8-12} alkyl, which is optionally substituted with 1 R_{1s} ;

[0385] R_{1s} is independently H or C_{1-10} alkyl, alternatively H or C_{1-9} alkyl;

[0386] R_4 and R_5 are independently C_{1-3} alkyl;

[0387] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-6} cycloalkylene, alternatively C_{3-5} cycloalkylene.

[0388] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0389] $a = 2, 3, \text{ or } 4$;

[0390] $b = 4, 5, 6, 7, 8, \text{ or } 9$; alternatively $b = 5, 6, 7, \text{ or } 8$; alternatively $b = 5 \text{ or } 7$;

[0391] $c = 2, 3, 4, 5, \text{ or } 6$;

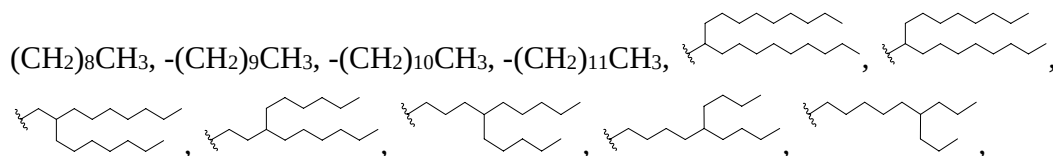
[0392] $d = 0, 1, 2, 3, \text{ or } 4$; alternatively $d = 0, 1, 2, \text{ or } 4$;

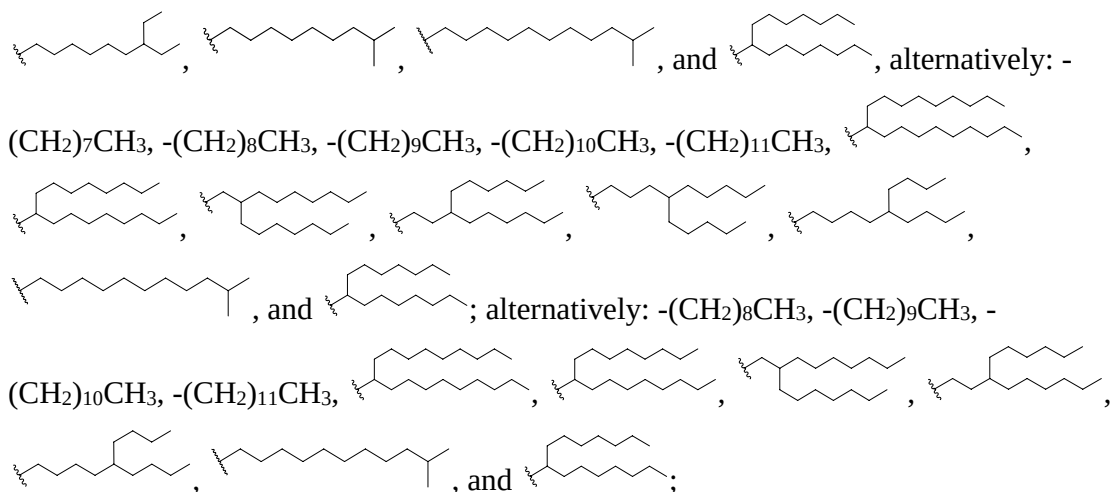
[0393] $c + d = 5 \text{ or } 6$; alternatively $c + d = 6$;

[0394] M_1 and M_2 are $-C(O)O-$;

[0395] or, one of M_1 and M_2 is $-C(O)O-$, and the other is $-OC(O)-$;

[0396] R_1 and R_2 are independently selected from: $-(CH_2)_6CH_3$, $-(CH_2)_7CH_3$, -





[0397] R_4 and R_5 are methyl;

[0398] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene.

[0399] In a more specific embodiment, only one of R_1 and R_2 is substituted.

[0400] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0401] $a = 2$;

[0402] $b = 5$;

[0403] $c = 2, 3, 4, 5$, or 6 ; alternatively $c = 6$;

[0404] $d = 0, 1, 2, 3$, or 4 ; alternatively $d = 0$;

[0405] $c + d = 5$ or 6 , alternatively 6 ;

[0406] M_1 and M_2 are $-\text{C}(\text{O})\text{O}-$;

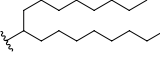
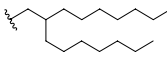
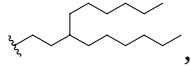
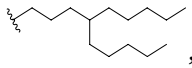
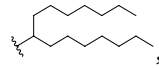
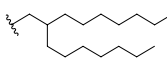
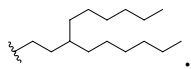
[0407] R_1 is C_{7-12} alkyl, alternatively C_{8-12} alkyl, alternatively C_{8-9} alkyl, or alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;

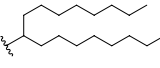
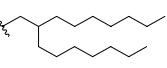
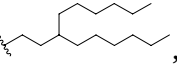
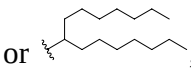
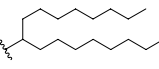
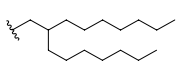
[0408] R_{1s} is independently H or C_{1-10} alkyl, alternatively H or C_{1-9} alkyl, alternatively C_{5-8} alkyl, alternatively C_{6-8} alkyl, alternatively C_{7-8} alkyl;

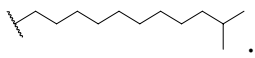
[0409] R_2 is C_{7-11} linear alkyl, alternatively C_{10-11} linear alkyl, alternatively C_{11} linear alkyl, which is optionally substituted with 1 C_{1-3} alkyl, alternatively optionally substituted with 1 methyl;

[0410] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;

[0411] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0412] In a more specific embodiment, R₁ is , , , , or , alternatively  or .

[0413] In a more specific embodiment, R₁ is , , , or , alternatively  or .

[0414] In a more specific embodiment, R₂ is -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, or .

[0415] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0416] a = 2, 3, or 4; alternatively a = 2;

[0417] b = 7;

[0418] c = 2, 3, 4, 5, or 6; alternatively c = 2, 3, or 4; alternatively c = 2;

[0419] d = 0, 1, 2, 3, or 4; alternatively d = 2, 3, or 4; alternatively d = 4;

[0420] c + d = 5 or 6, alternatively 6;

[0421] M₁ and M₂ are -C(O)O-;

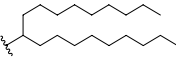
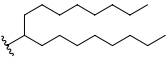
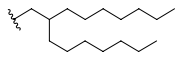
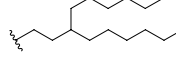
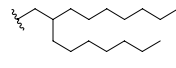
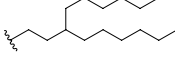
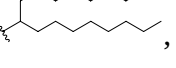
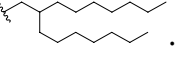
[0422] R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

[0423] R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0424] R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively C₆₋₉ alkyl, alternatively C₇₋₈ alkyl;

[0425] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0426] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0427] In a more specific embodiment, R₂ is , , , or , alternatively  or , alternatively , and .

[0428] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0429] a = 2;

[0430] b = 7;

[0431] c = 3 or 4; alternatively c = 4;

[0432] d = 2;

[0433] M₁ and M₂ are -C(O)O-;

[0434] R₁ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₈₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0435] R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl;

[0436] R₂ is C₇₋₁₁ linear alkyl, alternatively C₉ linear alkyl;

[0437] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0438] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0439] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0440] a = 2, 3, or 4; alternatively a = 2 or 4;

[0441] b = 6 or 7; alternatively b = 7;

[0442] c = 2, 3, 4, 5, or 6; alternatively c = 5 or 6;

[0443] d = 0, 1, 2, 3, or 4; alternatively d = 0 or 1;

[0444] c + d = 5 or 6, alternatively 6;

[0445] M₁ is -OC(O)-; and M₂ is -C(O)O-;

[0446] R₁ is C₇₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl;

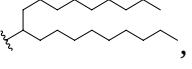
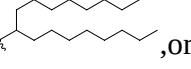
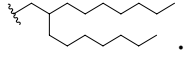
[0447] R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ linear alkyl, which is optionally substituted with 1 R_{1s};

[0448] R_{1s} is independently C₇₋₉ alkyl;

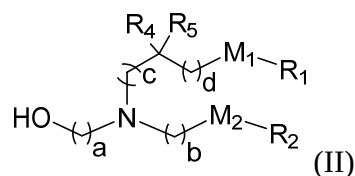
[0449] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0450] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0451] In a more specific embodiment, when a = 4, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring; alternatively, R_{1s} is independently C₈₋₉ alkyl.

[0452] In a more specific embodiment, R₂ is , , or .

[0453] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0454] wherein

[0455] a = 2, 3, 4, 5, or 6;

[0456] b = 4, 5, 6, 7, 8, 9, or 10;

[0457] c = 1, 2, 3, 4, 5, or 6;

[0458] d = 0, 1, 2, 3, or 4;

[0459] c + d = 3, 4, 5, 6, 7, 8, or 9; alternatively c + d = 4, 5, 6, or 7;

[0460] M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NHC(O)-, and -C(O)NH-, alternatively -C(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-; alternatively, one of M₁ and M₂ is -C(O)O- or -C(O)S-, and the other is -C(O)O-, -C(O)S-, -C(O)NH-, -OC(O)- or -SC(O)-, alternatively -C(O)O-, -C(O)S-, -OC(O)- or -SC(O)-;

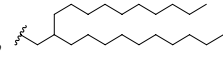
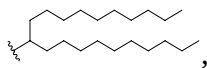
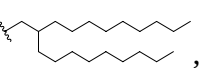
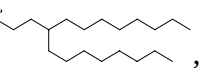
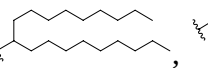
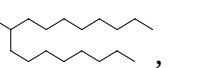
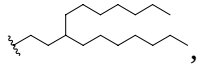
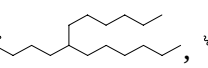
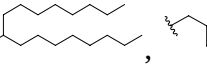
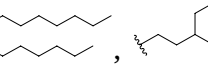
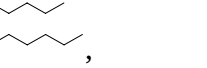
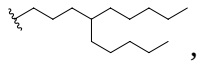
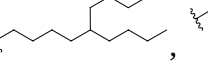
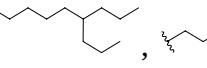
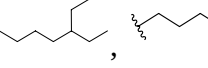
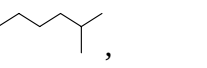
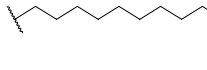
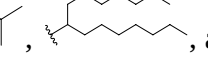
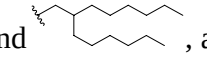
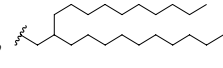
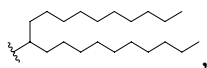
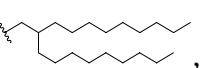
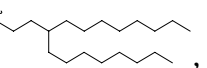
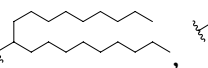
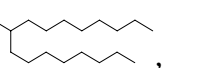
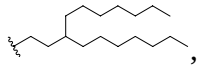
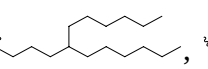
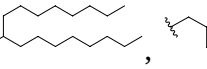
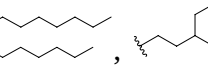
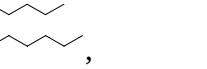
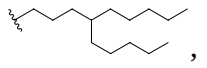
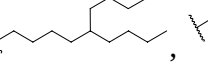
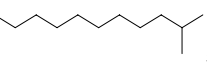
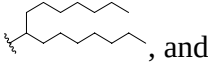
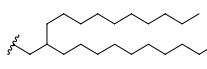
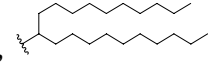
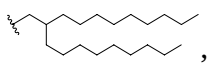
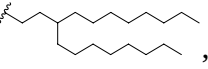
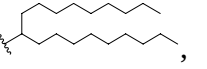
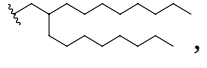
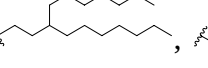
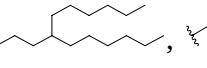
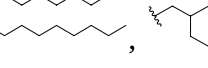
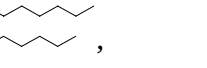
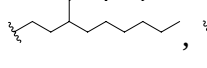
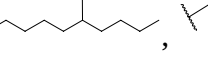
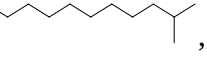
[0461] R₁ and R₂ are independently C₆₋₁₄ alkyl, C₆₋₁₄ alkenyl, or C₆₋₁₄ alkynyl, each of which is optionally substituted with 1, 2, 3, or 4 R_{1s};

[0462] R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c, alternatively H or C₁₋₁₄ alkyl;

- [0463] L_c is independently a chemical bond or C_{1-14} alkylene;
- [0464] R_c and R'_c are independently H or C_{1-14} alkyl;
- [0465] R_4 and R_5 are independently C_{1-6} alkyl;
- [0466] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-6} cycloalkylene or 3- to 6-membered heterocyclylene.
- [0467] In a more specific embodiment, the present disclosure provides the compound of formula (II) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0468] $a = 2, 3, \text{ or } 4$;
- [0469] $b = 4, 5, 6, 7, 8, \text{ or } 9$, alternatively $b = 5, 6, 7, \text{ or } 8$, alternatively $b = 5, 6, \text{ or } 7$;
- [0470] $c = 2, 3, 4, 5, \text{ or } 6$;
- [0471] $d = 0, 1, 2, 3, \text{ or } 4$;
- [0472] $c + d = 5, 6, \text{ or } 7$;
- [0473] M_1 and M_2 are independently $-C(O)O-$, $-OC(O)-$, $-C(O)S-$ or $-C(O)NH-$, alternatively $-C(O)O-$, $-OC(O)-$, or $-C(O)S-$; alternatively, one of M_1 and M_2 is $-C(O)O-$, and the other is $-C(O)O-$, $-C(O)S-$, $-C(O)NH-$, or $-OC(O)-$, alternatively $-C(O)O-$, $-C(O)S-$, or $-OC(O)-$;
- [0474] R_1 and R_2 are independently C_{7-12} alkyl, C_{7-12} alkenyl, or C_{7-12} alkynyl, alternatively C_{8-12} alkyl, C_{8-12} alkenyl, or C_{8-12} alkynyl, each of which is optionally substituted with 1 R_{1s} ;
- [0475] R_{1s} is independently H or C_{1-10} alkyl;
- [0476] R_4 and R_5 are independently C_{1-3} alkyl;
- [0477] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-6} cycloalkylene, alternatively C_{3-5} cycloalkylene.
- [0478] In a more specific embodiment, the present disclosure provides the compound of formula (II) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0479] $a = 2, 3, \text{ or } 4$;
- [0480] $b = 4, 5, 6, 7, 8, \text{ or } 9$; alternatively $b = 5, 6, 7, \text{ or } 8$; alternatively $b = 5 \text{ or } 7$;
- [0481] $c = 2, 3, 4, 5, \text{ or } 6$;
- [0482] $d = 0, 1, 2, 3, \text{ or } 4$;

[0483] $c + d = 5, 6, \text{ or } 7$; alternatively $c + d = 6$;

[0484] one of M_1 and M_2 is $-\text{C}(\text{O})\text{O}-$, and the other is $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{O})\text{NH}-$, or $-\text{OC}(\text{O})-$, alternatively $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, or $-\text{OC}(\text{O})-$;

[0485] R_1 and R_2 are independently selected from: $-(\text{CH}_2)_6\text{CH}_3$, $-(\text{CH}_2)_7\text{CH}_3$, $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$, , , , , , , , , , , , , , , , , , , and , alternatively: $-(\text{CH}_2)_7\text{CH}_3$, $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$, , , , , , , , , , , , , , , and ; alternatively: $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$, , , , , , , , , , , , , and ;

[0486] R_4 and R_5 are methyl;

[0487] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene;

[0488] In a more specific embodiment, only one of R_1 and R_2 is substituted.

[0489] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0490] $a = 2$;

[0491] $b = 5$;

[0492] $c = 5$ or 6 ; alternatively $c = 6$;

[0493] $d = 0$ or 1 ; alternatively $d = 0$;

[0494] $c + d = 5$ or 6 , alternatively 6 ;

[0495] M_1 is $-C(O)O-$, and M_2 is $-C(O)O-$ or $-C(O)S-$; alternatively M_1 and M_2 are $-C(O)O-$;

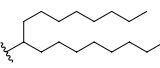
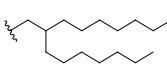
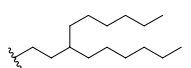
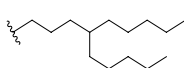
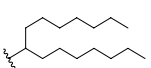
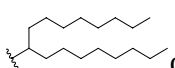
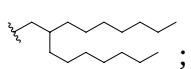
[0496] R_1 is C_{7-12} alkyl, alternatively C_{8-12} alkyl, alternatively C_{8-9} alkyl, or alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;

[0497] R_{1s} is independently H or C_{1-10} alkyl, alternatively H or C_{1-9} alkyl, alternatively C_{6-8} alkyl, alternatively C_{7-8} alkyl;

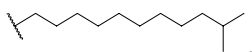
[0498] R_2 is C_{7-11} linear alkyl, alternatively C_{10-11} linear alkyl, alternatively C_{11} linear alkyl, which is optionally substituted with 1 C_{1-3} alkyl, alternatively optionally substituted with 1 methyl;

[0499] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;

[0500] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively cyclopropylene;

[0501] In a more specific embodiment, R_1 is , , , , or , alternatively  or  ;

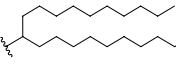
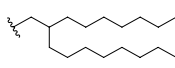
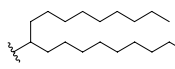
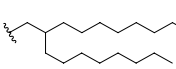
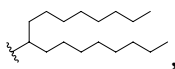
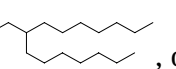
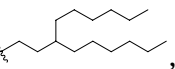
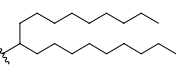
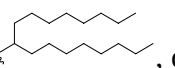
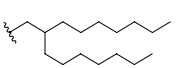
[0502] In a more specific embodiment, R_2 is $-(CH_2)_9CH_3$, $-(CH_2)_{10}CH_3$, or



[0503] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0504] $a = 2, 3$, or 4 ; alternatively $a = 2$;

- [0505] $b = 5, 6, \text{ or } 7$; alternatively $b = 7$;
- [0506] $c = 2, 3, 4, 5, \text{ or } 6$; alternatively $c = 2, 3, \text{ or } 4$; alternatively $c = 2$;
- [0507] $d = 0, 1, 2, 3, \text{ or } 4$; alternatively $d = 2, 3, \text{ or } 4$; alternatively $d = 4$;
- [0508] $c + d = 5 \text{ or } 6$, alternatively 6;
- [0509] M_1 and M_2 are $-\text{C}(\text{O})\text{O}-$;
- [0510] R_1 and R_2 are independently C_{7-12} alkyl, alternatively C_{8-12} alkyl, alternatively C_{9-11} alkyl, alternatively C_{9-10} alkyl, which is optionally substituted with 1 R_{1s} ; and only one of R_1 and R_2 is substituted;
- [0511] R_{1s} is independently H or C_{1-10} alkyl, alternatively C_{6-10} alkyl, alternatively C_{7-9} alkyl;
- [0512] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;
- [0513] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring;
- [0514] In a more specific embodiment, R_1 is C_{8-12} linear alkyl, alternatively C_{9-11} linear alkyl, alternatively C_{9-10} linear alkyl;
- [0515] R_2 is C_{7-12} alkyl, alternatively C_{8-12} alkyl, alternatively C_{9-11} alkyl, alternatively C_{9-10} alkyl, which is optionally substituted with 1 R_{1s} ; when R_2 is C_{10} linear alkyl, R_{1s} is C_{9-10} alkyl, alternatively C_9 alkyl.

- [0516] In a more specific embodiment, R_2 is , , , , , , or , alternatively , , or .

- [0517] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0518] $a = 2, 3, \text{ or } 4$;
- [0519] $b = 6$;
- [0520] $c = 4, 5, \text{ or } 6$; alternatively $c = 5 \text{ or } 6$; alternatively $c = 5$;
- [0521] $d = 1 \text{ or } 2$; alternatively $d = 1$;
- [0522] $c + d = 6, 7, \text{ or } 8$; alternatively 6 or 7; alternatively 6;
- [0523] M_1 is $-\text{OC}(\text{O})-$; M_2 is $-\text{C}(\text{O})\text{O}-$;

[0524] R₁ is C₇₋₁₂ linear alkyl, alternatively C₈₋₁₁ linear alkyl, alternatively C₉₋₁₁ linear alkyl;

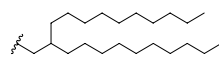
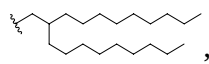
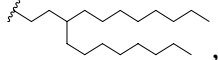
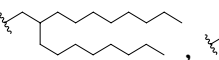
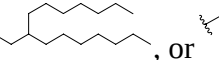
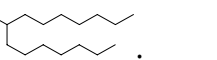
[0525] R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₂ alkyl, which is optionally substituted with 1 R_{1s};

[0526] R_{1s} is independently C₇₋₁₁ alkyl, alternatively C₇₋₁₀ alkyl;

[0527] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0528] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

[0529] provided that, when c=4, a=2 or 3.

[0530] In a more specific embodiment, R₂ is , , , , , or .

[0531] In a more specific embodiment, a=2 or 4; b=6; c=5 or 6, alternatively c=5; d=1;

[0532] R₁ is C₈₋₉ linear alkyl, alternatively C₉ linear alkyl;

[0533] R₂ is C₉₋₁₀ alkyl, alternatively C₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0534] R_{1s} is independently C₇₋₈ alkyl;

[0535] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl.

[0536] In a more specific embodiment, a=2, 3 or 4, alternatively 2 or 4; b=6; c=5; d=2;

[0537] R₁ is C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

[0538] R₂ is C₉₋₁₁ alkyl, which is optionally substituted with 1 R_{1s};

[0539] R_{1s} is independently C₇₋₉ alkyl,

[0540] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl.

[0541] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0542] a = 2, 3, or 4; alternatively a = 2 or 4;

[0543] b = 7;

[0544] c = 5 or 6; alternatively c = 5;

[0545] d = 0 or 1; alternatively d = 1;

[0546] c + d = 5 or 6, alternatively 6;

[0547] M₁ is -OC(O)-; M₂ is -C(O)O-;

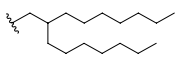
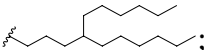
[0548] R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, which is optionally substituted with 1 C₁₋₉ alkyl (alternatively C₆₋₉ alkyl, alternatively C₆₋₇ alkyl);

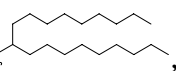
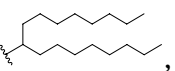
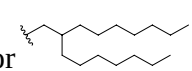
[0549] R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0550] R_{1s} is independently C₇₋₉ alkyl;

[0551] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0552] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0553] In a more specific embodiment, R₁ is -(CH₂)₈CH₃, -(CH₂)₉CH₃, , or ;

[0554] R₂ is , , or .

[0555] In a more specific embodiment, when a=4,

[0556] R₁ is C₉₋₁₀ linear alkyl;

[0557] R₂ is C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0558] R_{1s} is C₈₋₉ alkyl;

[0559] R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring.

[0560] In a more specific embodiment, when a=2,

[0561] R₁ is C₁₀ linear alkyl;

[0562] alternatively R_{1s} is C₈₋₉ alkyl, alternatively C₉ alkyl.

[0563] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0564] a = 2, 3, or 4; alternatively a = 2 or 4;

[0565] b = 7;

[0566] c = 4;

[0567] d = 2;

[0568] M₁ is -OC(O)-; M₂ is -C(O)O-;

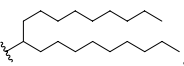
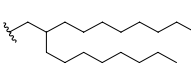
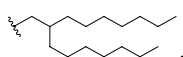
[0569] R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl;

[0570] R₂ is C₈₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0571] R_{1s} is independently C₇₋₉ alkyl;

[0572] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0573] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring.

[0574] In a more specific embodiment, R₂ is , , or .

[0575] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0576] a = 2, 3, or 4; alternatively a = 2;

[0577] b = 8;

[0578] c = 5;

[0579] d = 1;

[0580] M₁ is -OC(O)-; M₂ is -C(O)O-;

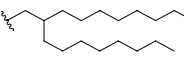
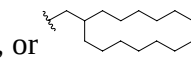
[0581] R₁ is C₈₋₁₂ linear alkyl, alternatively C₉₋₁₁ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl;

[0582] R₂ is C₈₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0583] R_{1s} is independently C₇₋₉ alkyl, alternatively C₇₋₈ alkyl;

[0584] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

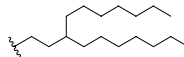
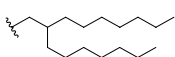
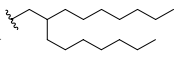
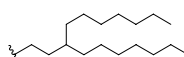
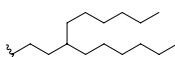
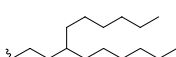
[0585] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring.

[0586] In a more specific embodiment, R₂ is , or .

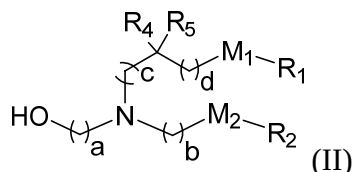
[0587] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0588] a = 2;

[0589] b = 6, 7, or 8, alternatively b = 7;

- [0590] $c = 5$;
- [0591] $d = 1$;
- [0592] M_1 is $-\text{OC}(\text{O})-$; M_2 is $-\text{C}(\text{O})\text{O}-$;
- [0593] R_1 is C_{8-11} linear alkyl, alternatively C_{9-10} linear alkyl, alternatively C_9 linear alkyl;
- [0594] R_2 is C_{8-11} alkyl, alternatively C_{9-10} alkyl, alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;
- [0595] R_{1s} is independently C_7 alkyl;
- [0596] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl.
- [0597] In a more specific embodiment, R_2 is  or ,
alternatively .
- [0598] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0599] $a = 2$ or 3 , alternatively $a = 2$;
- [0600] $b = 7$;
- [0601] $c = 3$;
- [0602] $d = 3$;
- [0603] M_1 is $-\text{OC}(\text{O})-$; M_2 is $-\text{C}(\text{O})\text{O}-$;
- [0604] R_1 is C_{8-11} linear alkyl, alternatively C_{9-10} linear alkyl, alternatively C_9 linear alkyl;
- [0605] R_2 is C_{8-11} alkyl, alternatively C_{9-10} alkyl, alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;
- [0606] R_{1s} is independently C_{6-7} alkyl, alternatively C_7 alkyl;
- [0607] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl.
- [0608] In a more specific embodiment, R_2 is  or ,
alternatively .

[0609] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0610] wherein

[0611] a=2, 3, 4, 5, or 6;

[0612] b=4, 5, 6, 7, 8, 9, or 10;

[0613] c=1, 2, 3, 4, 5, or 6;

[0614] d=0, 1, 2, 3, or 4;

[0615] c+d=3, 4, 5, 6, 7, 8, or 9, alternatively c+d=4, 5, or 6;

[0616] one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-;

[0617] R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

[0618] R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c; alternatively H or C₁₋₁₄ alkyl;

[0619] L_c is independently a chemical bond or C₁₋₁₄ alkylene;

[0620] R_c and R'_c are independently H or C₁₋₁₄ alkyl;

[0621] R₄ and R₅ are independently C₁₋₆ alkyl;

[0622] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

[0623] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

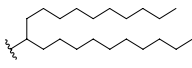
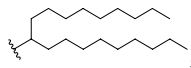
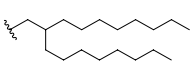
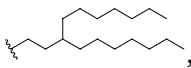
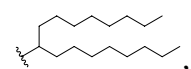
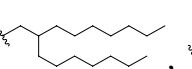
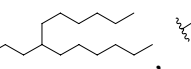
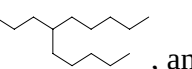
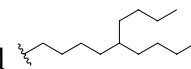
[0624] a=2, 3, or 4;

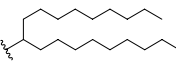
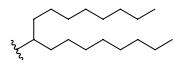
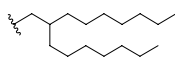
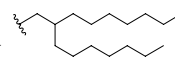
[0625] b=4, 5, 6, or 7, alternatively b=5 or 6, alternatively b=6;

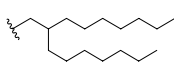
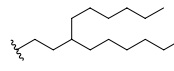
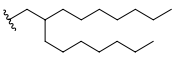
[0626] c= 2, 3, 4, 5, or 6; alternatively c= 2, 4, 5, or 6;

[0627] d=0, 1, 2, 3, or 4; alternatively d=0, 1, 2, or 4;

[0628] c+d=5 or 6, alternatively c+d=6;

- [0629] one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O- or -OC(O)-;
- [0630] R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₉₋₁₁ alkyl, which is optionally substituted with 1 R_{1s};
- [0631] R_{1s} is independently H or C₁₋₁₀ alkyl; alternatively H or C₄₋₁₀ alkyl;
- [0632] R₄ and R₅ are independently C₁₋₃ alkyl;
- [0633] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene, alternatively C₃₋₄ cycloalkylene.
- [0634] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0635] a=2, 3, or 4;
- [0636] b=4, 5, 6, or 7, alternatively b=5 or 6, alternatively b=6;
- [0637] c= 2, 3, 4, 5, or 6; alternatively c= 2, 4, 5, or 6;
- [0638] d=0, 1, 2, 3, or 4; alternatively d=0, 1, 2, or 4;
- [0639] c+d=5 or 6, alternatively c+d=6;
- [0640] one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O- or -OC(O)-;
- [0641] R₁ and R₂ are independently selected from -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, , , , , , , , , , and ;
- [0642] R₄ and R₅ are methyl;
- [0643] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene.
- [0644] In a more specific embodiment, only one of R₁ and R₂ is substituted;
- [0645] In a more specific embodiment, M₁ is -C(O)O- or -OC(O)-, alternatively -C(O)O-, and M₂ is -OC(O)O-.
- [0646] In a more specific embodiment, M₁ is -OC(O)O-, and M₂ is -OC(O)-.
- [0647] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0648] a=2;

- [0649] $b=5$ or 6 , alternatively $b=6$;
- [0650] $c=4, 5$, or 6 ; alternatively $c=4$ or 6 ; alternatively $c=6$;
- [0651] $d=0, 1$, or 2 ; alternatively $d=0$ or 2 ;
- [0652] $c+d=6$;
- [0653] M_1 is $-C(O)O-$, and M_2 is $-OC(O)O-$;
- [0654] R_1 is C_{8-11} alkyl, alternatively C_{9-10} alkyl, alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;
- [0655] R_{1s} is C_{7-9} alkyl, alternatively C_7 alkyl;
- [0656] R_2 is C_{8-11} linear alkyl, alternatively C_{9-10} linear alkyl, alternatively C_9 linear alkyl;
- [0657] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;
- [0658] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively not to form a ring.
- [0659] In a more specific embodiment, R_1 is , , or , alternatively .
- [0660] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0661] $a=2$;
- [0662] $b=6$;
- [0663] $c=4, 5$, or 6 ; alternatively $c=5$ or 6 ; alternatively $c=6$;
- [0664] $d=0, 1$, or 2 ; alternatively $d=0$ or 1 ;
- [0665] $c+d=6$;
- [0666] M_1 is $-C(O)O-$, and M_2 is $-OC(O)O-$;
- [0667] R_1 is C_{8-10} linear alkyl, alternatively C_{9-10} linear alkyl, alternatively C_9 linear alkyl;
- [0668] R_2 is C_{8-10} alkyl, alternatively C_{9-10} alkyl, alternatively C_9 alkyl, which is optionally substituted with 1 R_{1s} ;
- [0669] R_{1s} is C_{6-7} alkyl, alternatively C_7 alkyl;
- [0670] R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;
- [0671] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively not to form a ring.

[0672] In a more specific embodiment, R₂ is  or ,
alternatively  .

[0673] In a more specific embodiment, the present disclosure provides the compound of formula (II) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0674] a=2;

[0675] b=5 or 6; alternatively b=6;

[0676] c=5;

[0677] d=1;

[0678] M₁ is -OC(O)-, and M₂ is -OC(O)O-;

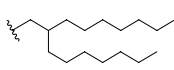
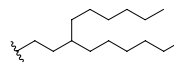
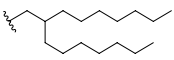
[0679] R₁ is C₈₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

[0680] R_{1s} is C₆₋₈ alkyl, alternatively C₆₋₇ alkyl;

[0681] R₂ is C₈₋₁₂ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl;

[0682] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0683] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring.

[0684] In a more specific embodiment, R₁ is  or ,
alternatively  .

[0685] In a more specific embodiment, the present disclosure provides the compound of formula (II) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0686] a=2, 3 or 4; alternatively a=2;

[0687] b=5, 6, 7, or 8; alternatively b=6 or 7; alternatively b=7;

[0688] c=4, 5, or 6; alternatively c=4;

[0689] d=0, 1, or 2; alternatively d=1;

[0690] c+d=5 or 6; alternatively c+d=5;

[0691] M₁ is -OC(O)O-, M₂ is -OC(O)-;

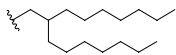
[0692] R₁ is C₈₋₁₂ alkyl, alternatively C₈₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

[0693] R_{1s} is C₆₋₁₀ alkyl, alternatively C₆₋₈ alkyl;

[0694] R₂ is C₈₋₁₂ linear alkyl, alternatively C₈₋₁₀ linear alkyl;

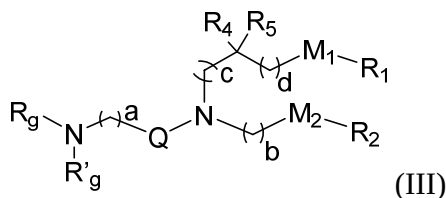
[0695] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0696] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring.

[0697] In a more specific embodiment, R₁ is .

[0698] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0699] In a more specific embodiment, the present disclosure provides the compound of formula (III), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0700] wherein

[0701] Q is -SC(O)- or -OC(O)-;

[0702] R_g and R'_g are independently C₁₋₆ alkyl;

[0703] a = 2, 3, 4, 5, or 6; alternatively a = 2, 3, or 4;

[0704] b = 4, 5, 6, 7, 8, or 9; alternatively b = 5, 6, or 7;

[0705] c = 2, 3, 4, 5, or 6;

[0706] d = 0, 1, 2, 3, or 4;

[0707] c+d=5 or 6;

[0708] M₁ and M₂ are independently selected from -C(O)O-, -C(O)S-, -OC(O)-, -SC(O)-, and -OC(O)O-;

[0709] R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

- [0710] R_{1s} is independently H, C_{1-14} alkyl, $-L_c-OR_c$, or $-L_c-NR_cR'_c$; alternatively H or C_{1-14} alkyl;
- [0711] L_c is independently a chemical bond or C_{1-14} alkylene;
- [0712] R_c and R'_c are independently H or C_{1-14} alkyl;
- [0713] R_4 and R_5 are independently C_{1-6} alkyl,
- [0714] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-6} cycloalkylene or 3- to 6-membered heterocyclylene.
- [0715] In a more specific embodiment, the present disclosure provides the compound of formula (III) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0716] Q is $-SC(O)-$ or $-OC(O)-$;
- [0717] R_g and R'_g are independently C_{1-3} alkyl;
- [0718] $a = 3$ or 4 ;
- [0719] $b = 6$ or 7 ;
- [0720] $c = 2, 3, 4$, or 5 ; alternatively 2 or 5 ;
- [0721] $d = 1, 2, 3$, or 4 ; alternatively 1 or 4 ;
- [0722] $c+d=5$ or 6 ;
- [0723] M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, and $-OC(O)O-$; alternatively, M_1 and M_2 are not simultaneously $-OC(O)O-$;
- [0724] R_1 and R_2 are independently C_{7-12} alkyl, alternatively C_{8-10} alkyl, which is optionally substituted with 1 R_{1s} ;
- [0725] R_{1s} is independently H or C_{1-10} alkyl; alternatively H or C_{1-9} alkyl;
- [0726] R_4 and R_5 are independently C_{1-3} alkyl,
- [0727] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-6} cycloalkylene.
- [0728] In a more specific embodiment, the present disclosure provides the compound of formula (III) , or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- [0729] Q is $-SC(O)-$;
- [0730] R_g and R'_g are methyl;
- [0731] $a = 3$ or 4 ;

[0732] $b = 6$ or 7 ;

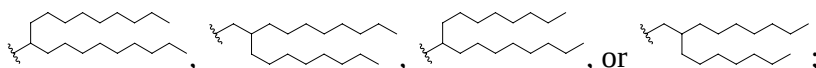
[0733] $c = 2, 4$, or 5 ; alternatively 2 or 5 ;

[0734] $d = 1, 2$, or 4 ; alternatively 1 or 4 ;

[0735] $c+d=6$;

[0736] M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, and $-OC(O)O-$;
alternatively, M_1 and M_2 are not simultaneously $-OC(O)O-$;

[0737] R_1 and R_2 are independently $-(CH_2)_7CH_3$, $-(CH_2)_8CH_3$, $-(CH_2)_9CH_3$,

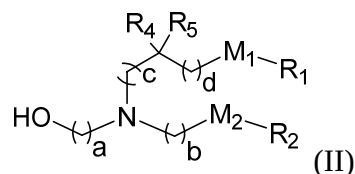


[0738] R_4 and R_5 are methyl;

[0739] or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form cyclopropylene, alternatively not to form a ring.

[0740] In a more specific embodiment, only one of R_1 and R_2 is substituted; alternatively, R_1 is unsubstituted, and R_2 is substituted.

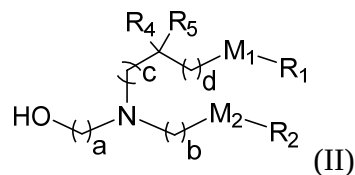
[0741] In a more specific embodiment, the present disclosure provides the compound of formula (II), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0742] wherein M_1 and M_2 are independently selected from $-C(O)O-$ and $-C(O)S-$,
alternatively $-C(O)O-$;

[0743] the other groups are as defined herein.

[0744] In a more specific embodiment, the present disclosure provides the compound of formula (II) or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0745] wherein one of M_1 and M_2 is $-C(O)O-$ or $-C(O)S-$, alternatively $-C(O)O-$, and the other is $-OC(O)-$ or $-SC(O)-$, alternatively $-OC(O)-$;

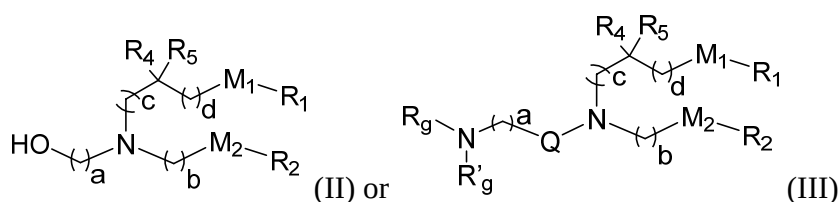
[0746] the other groups are as defined herein.

[0747] In a more specific embodiment, R_{1s} is independently H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.

[0748] In a more specific embodiment, M₁ is -OC(O)- or -SC(O)-, alternatively -OC(O)-; and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-.

[0749] In a more specific embodiment, R_{1s} is independently C₁₋₈ alkyl, alternatively C₄₋₈ alkyl, alternatively C₆₋₈ alkyl, alternatively C₇₋₈ alkyl, alternatively C₈ alkyl;

[0750] In a more specific embodiment, the present disclosure provides the compound of formula (II) or formula (III), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



[0751] wherein

[0752] Q is a chemical bond, -SC(O)- or -OC(O)-;

[0753] R_g and R'_g are independently C₁₋₆ alkyl;

[0754] a = 2, 3, 4, 5, or 6;

[0755] b = 6 or 7;

[0756] c = 5 or 6;

[0757] d = 0 or 1;

[0758] c + d = 5 or 6;

[0759] M₁ is -OC(O)- or -SC(O)-; and M₂ is -C(O)O- or -C(O)S-;

[0760] R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, which is optionally substituted with 1 R_{1s};

[0761] R_{1s} is independently H or C₁₋₁₀ alkyl;

[0762] R₄ and R₅ are independently C₁₋₆ alkyl,

[0763] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene.

[0764] In a more specific embodiment, only one of R₁ and R₂ is substituted; alternatively, R₁ is unsubstituted, and R₂ is substituted.

[0765] In a more specific embodiment, the present disclosure provides the compound of formula (II) or formula (III), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

[0766] Q is -SC(O)- or -OC(O)-, alternatively -SC(O)- ;

[0767] R_g and R'_g are independently C₁₋₃ alkyl, alternatively methyl;

[0768] a = 2, 3, or 4; alternatively a = 2 or 4; alternatively a = 4;

[0769] b = 6 or 7; alternatively b = 7;

[0770] c = 5 or 6; alternatively c = 5;

[0771] d = 0 or 1; alternatively d = 1;

[0772] c + d = 5 or 6; alternatively c + d = 6;

[0773] M₁ is -OC(O)-; M₂ is -C(O)O-;

[0774] R₁ is C₇₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl; alternatively C₉ linear alkyl;

[0775] R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

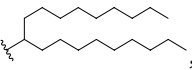
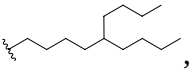
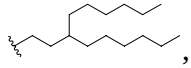
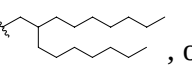
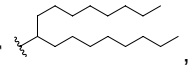
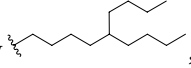
[0776] R_{1s} is independently C₁₋₉ alkyl, alternatively C₁₋₈ alkyl, alternatively C₄₋₉ alkyl, alternatively C₄₋₈ alkyl;

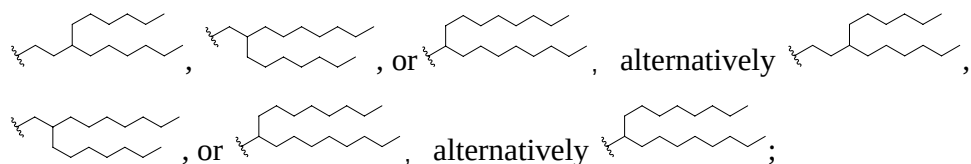
[0777] R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

[0778] or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.

[0779] In a more specific embodiment, the substitution site of R_{1s} on R₁ or R₂ is separated from M₁ or M₂ by 0-10 carbon atoms, alternatively 0-6 carbon atoms, alternatively 0-4 carbon atoms, alternatively 0-2 carbon atoms, alternatively 0 carbon atom.

[0780] In a more specific embodiment, R₁ is not substituted with R_{1s}, and the substitution site of R_{1s} on R₂ is separated from M₂ by 0-10 carbon atoms, alternatively 1-10 carbon atoms, alternatively 1-6 carbon atoms, 1-4 carbon atoms, 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, 2-4 carbon atoms.

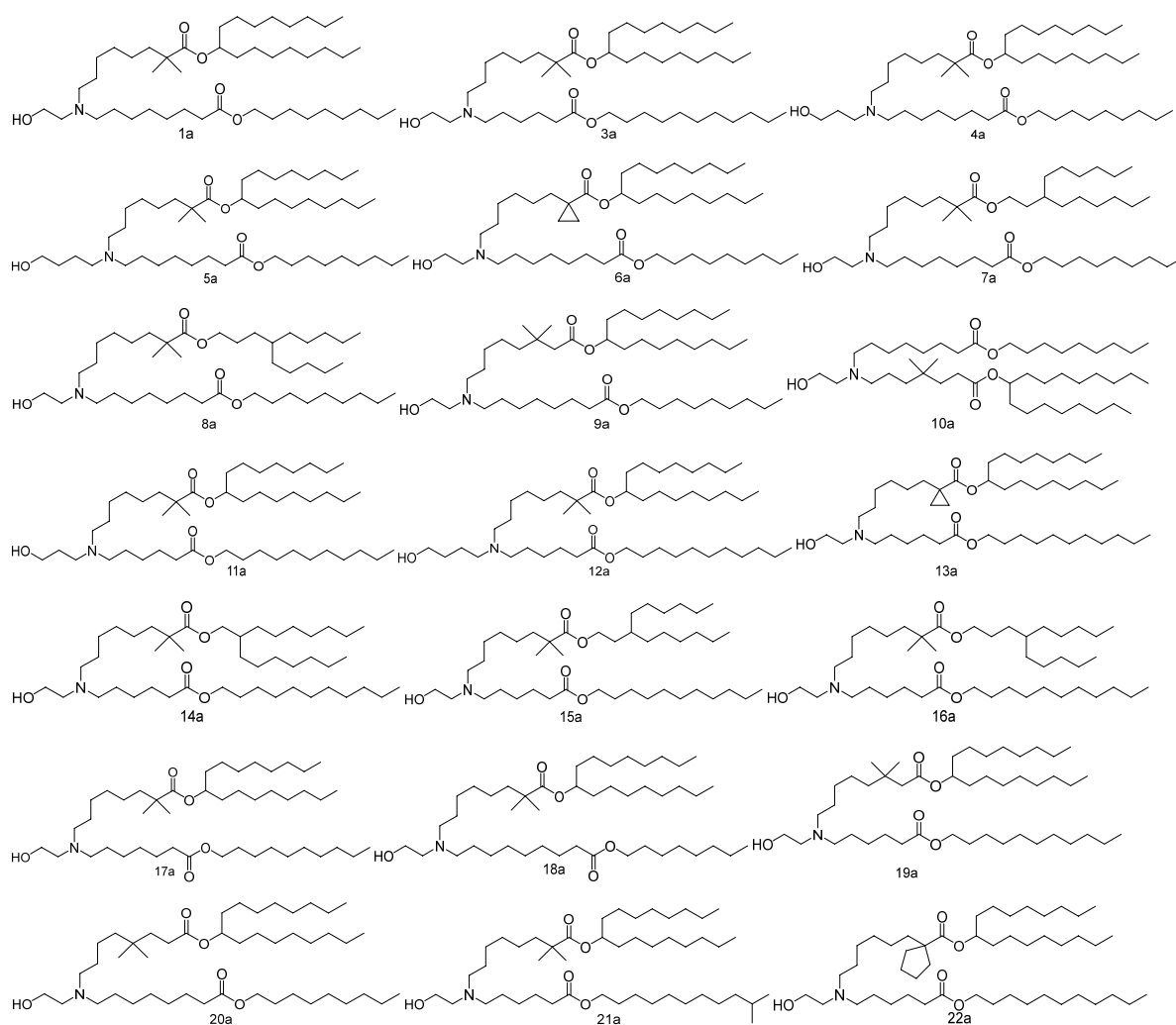
[0781] In a more specific embodiment, R₂ is , , , , or , alternatively .

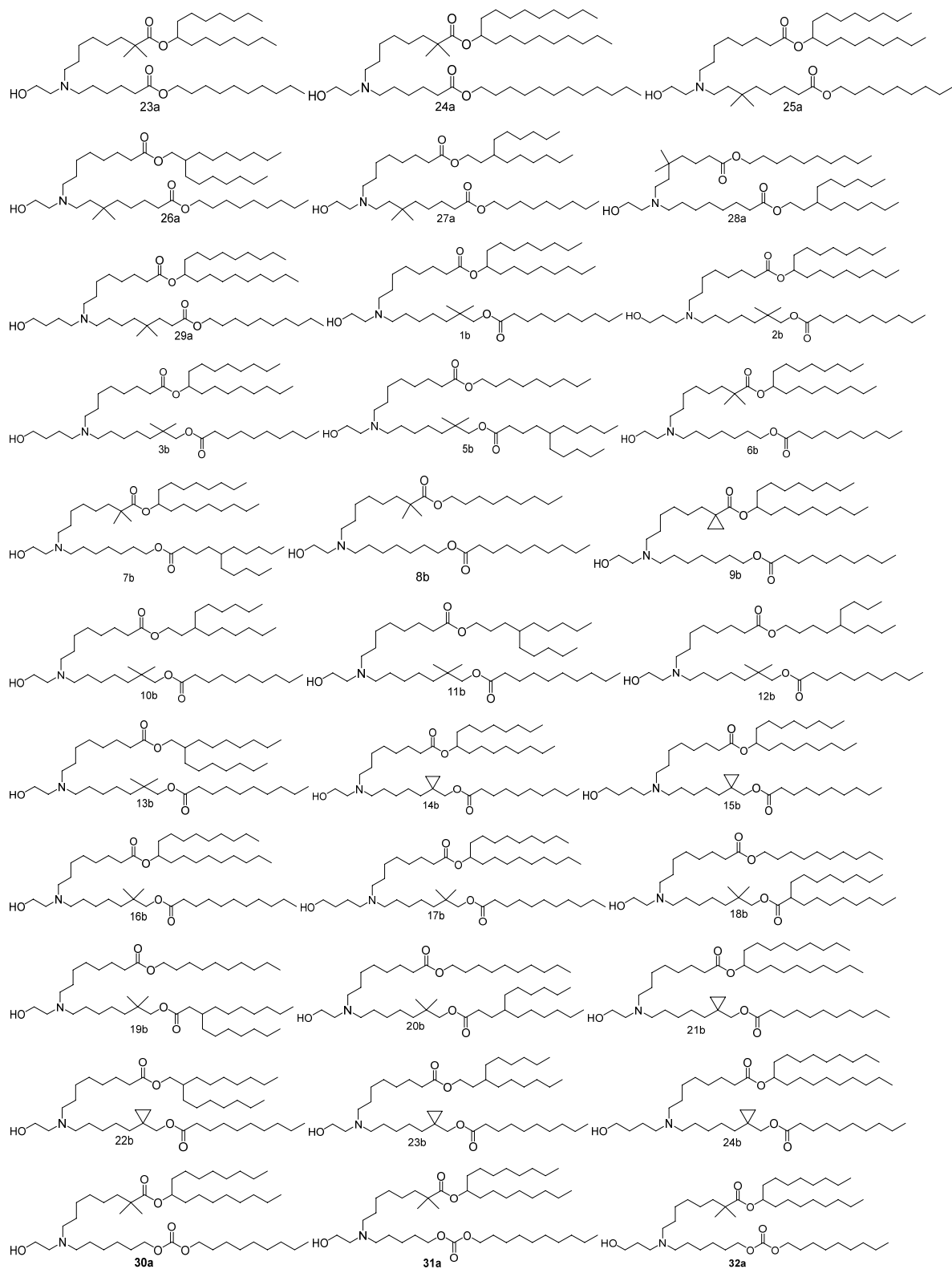


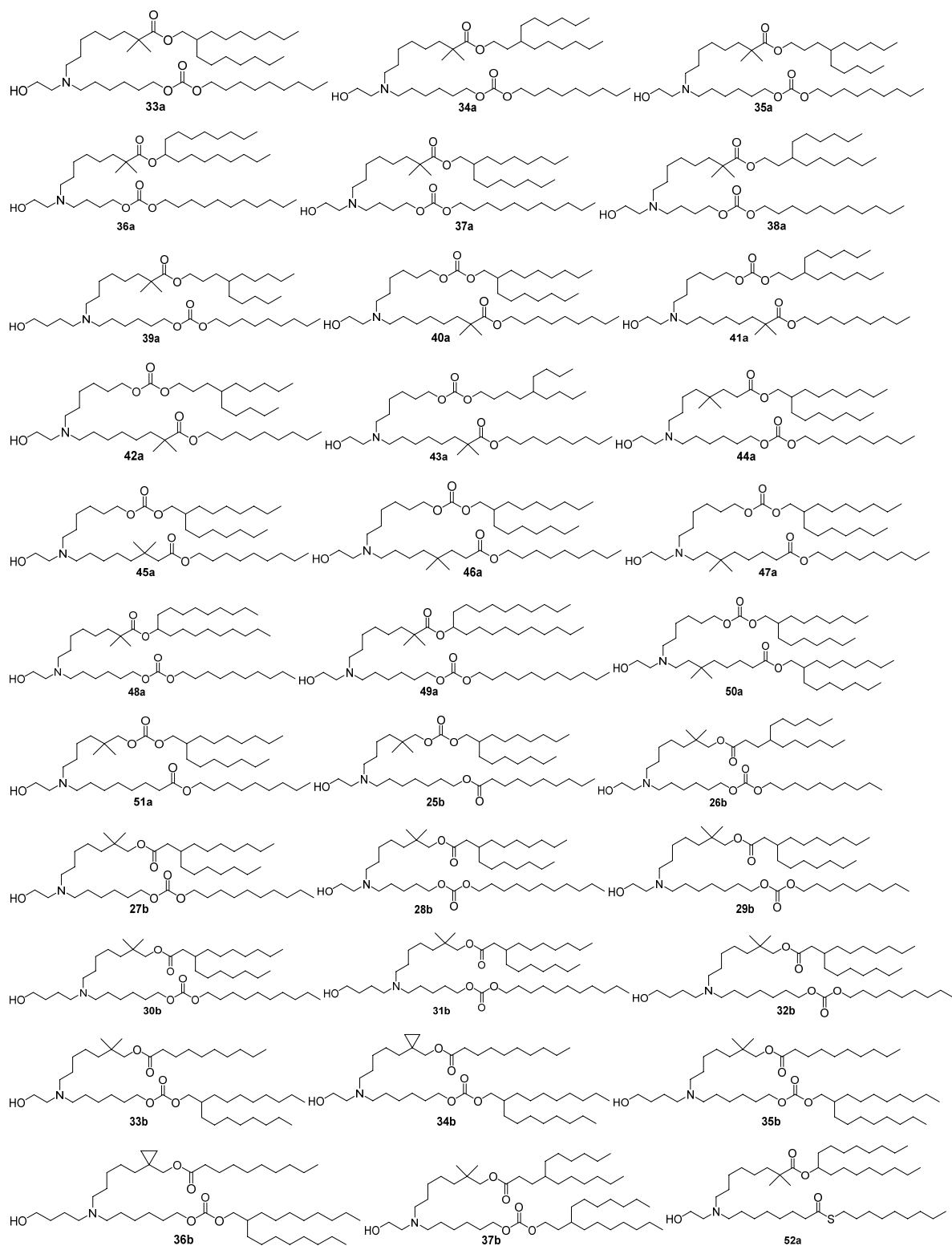
[0782] In a more specific embodiment, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring.

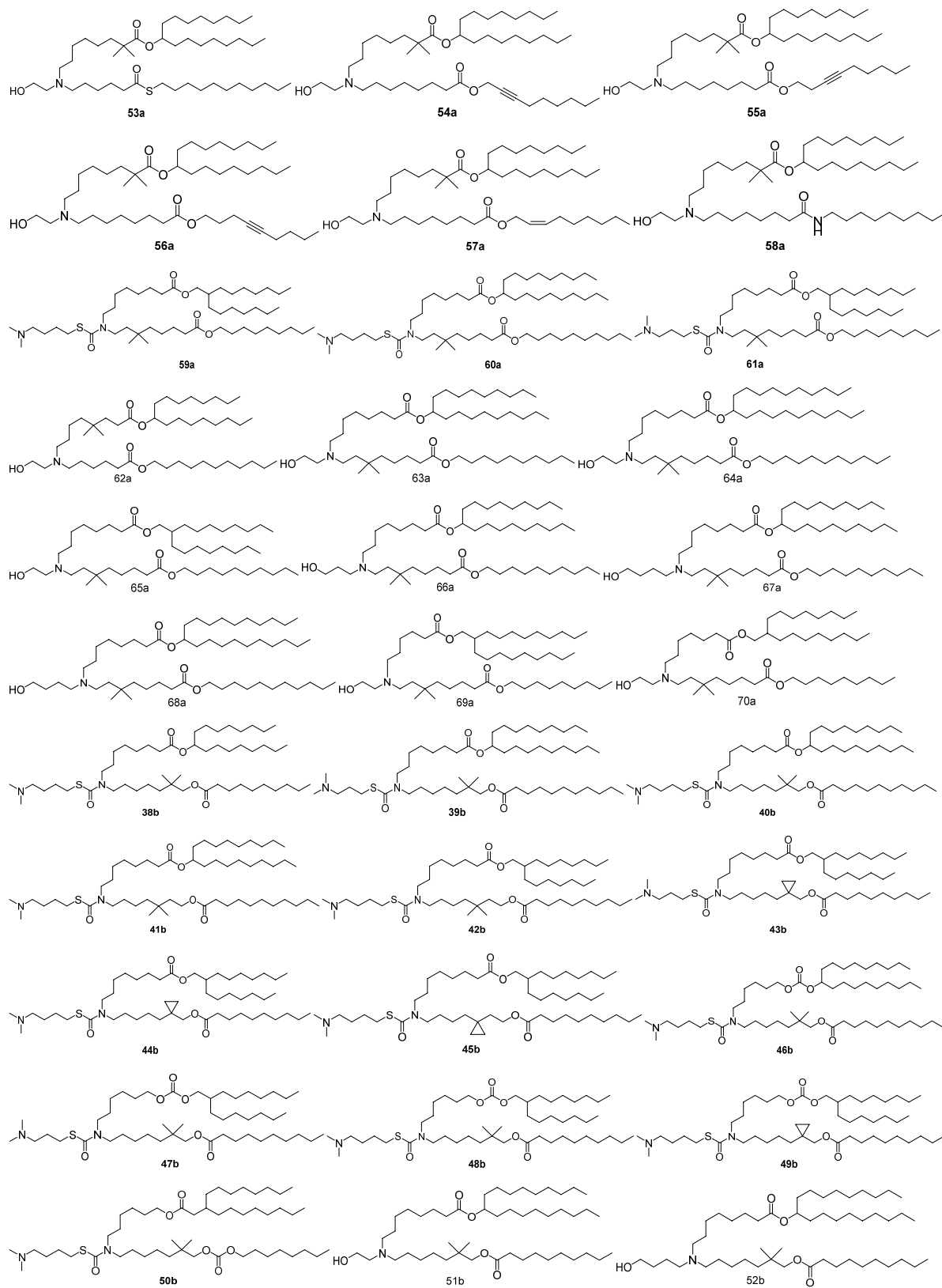
[0783] In a more specific embodiment, the present disclosure provides the compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein the compound is selected from the compounds in Table (I).

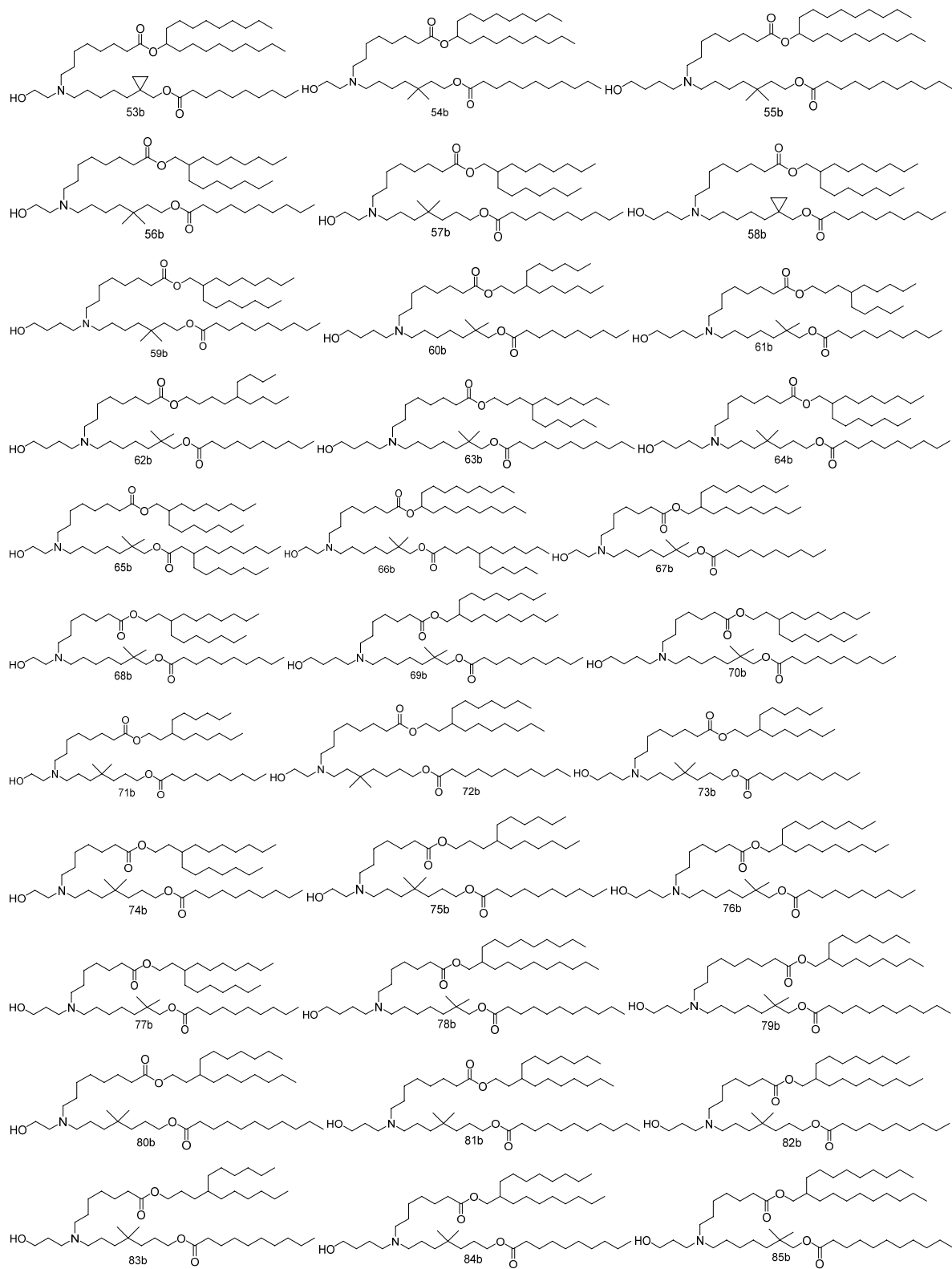
Table (I)

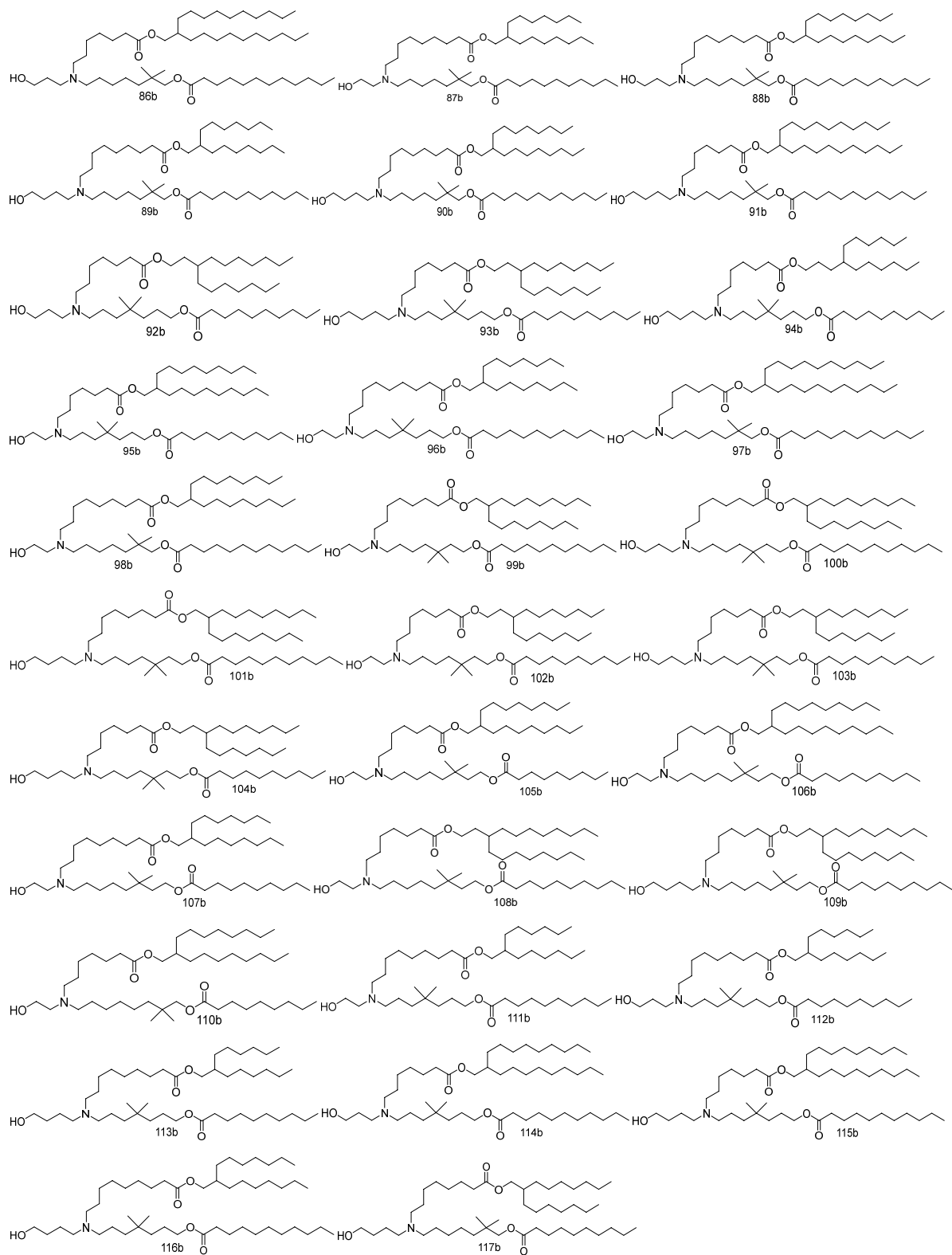


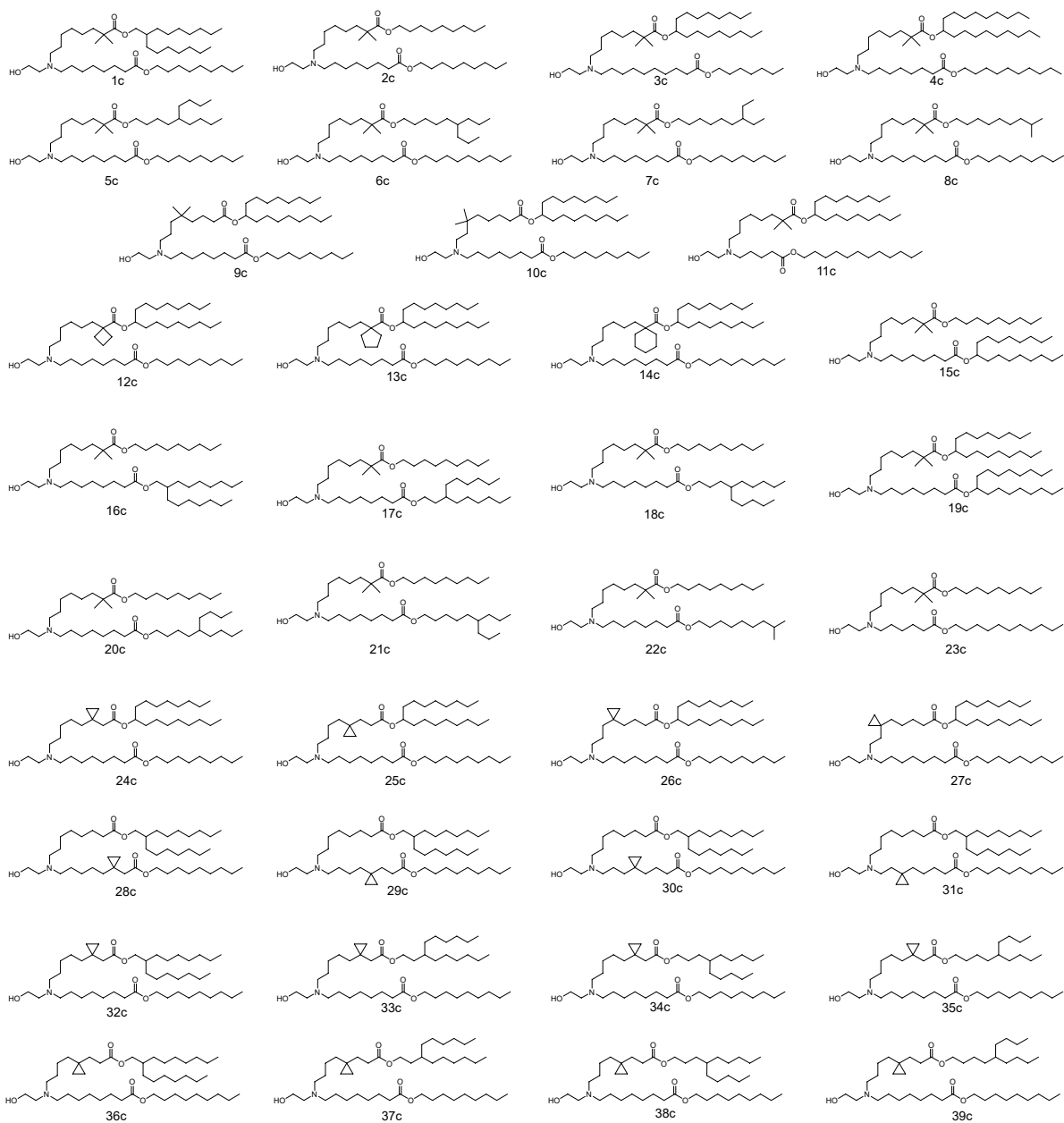


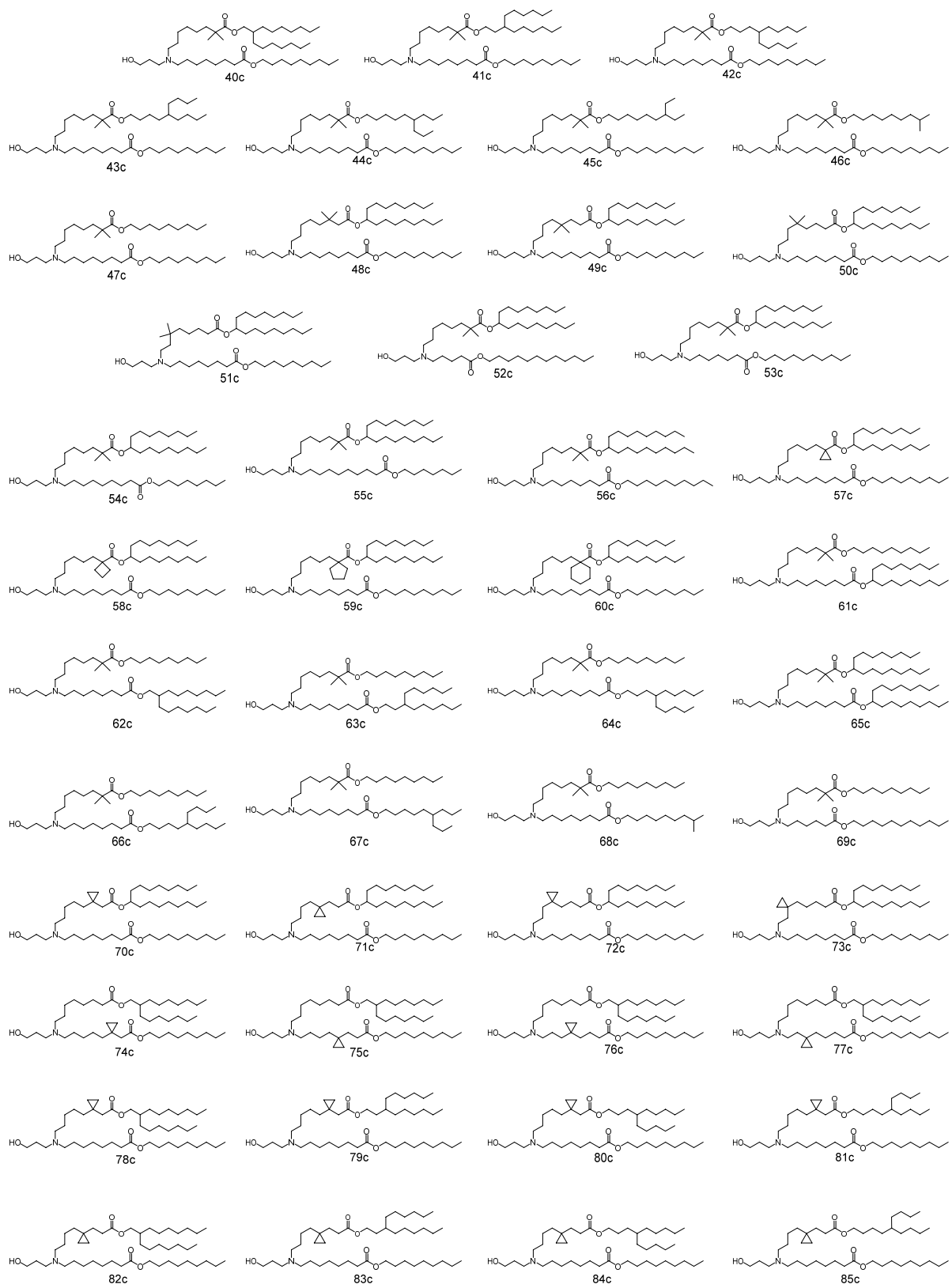


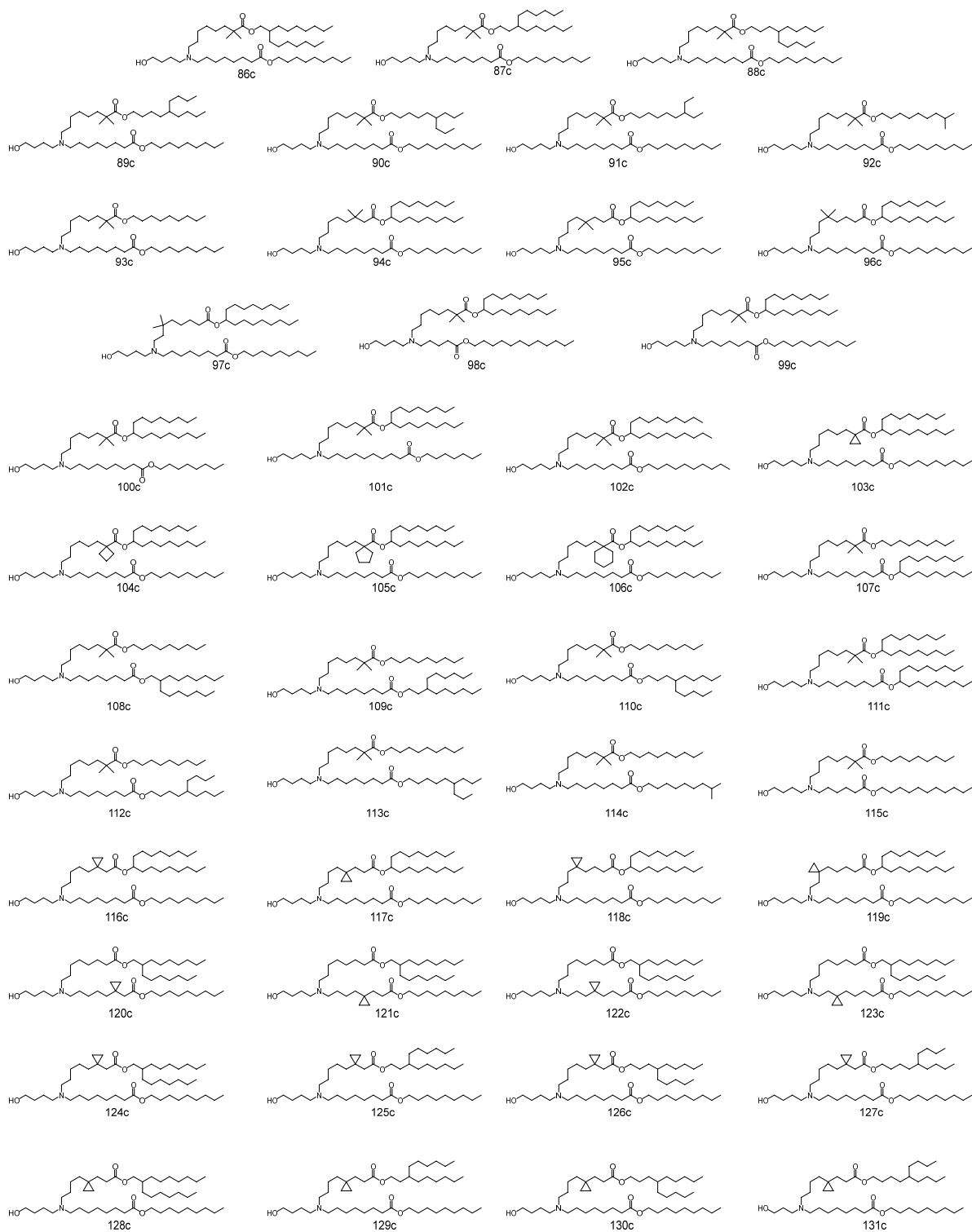


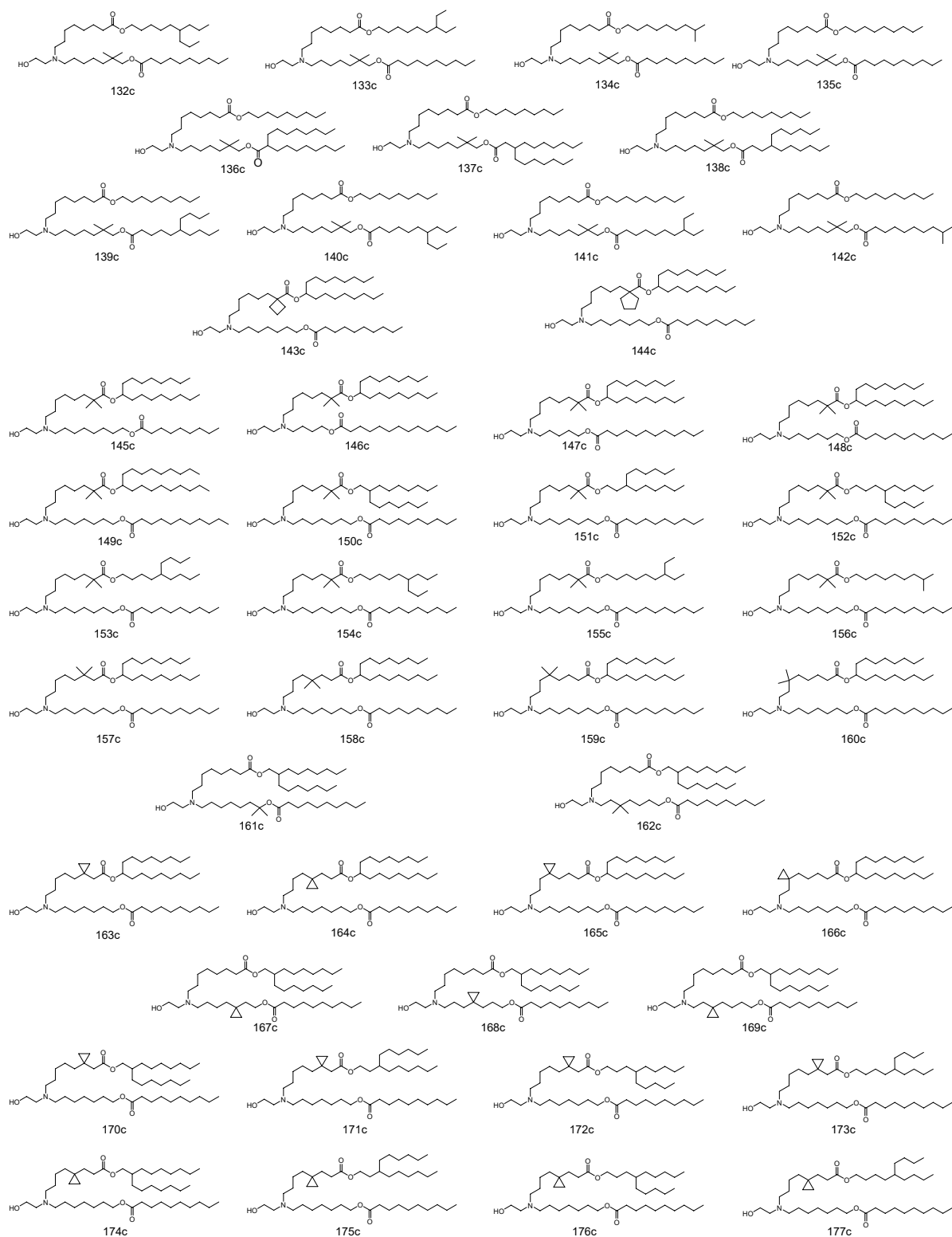


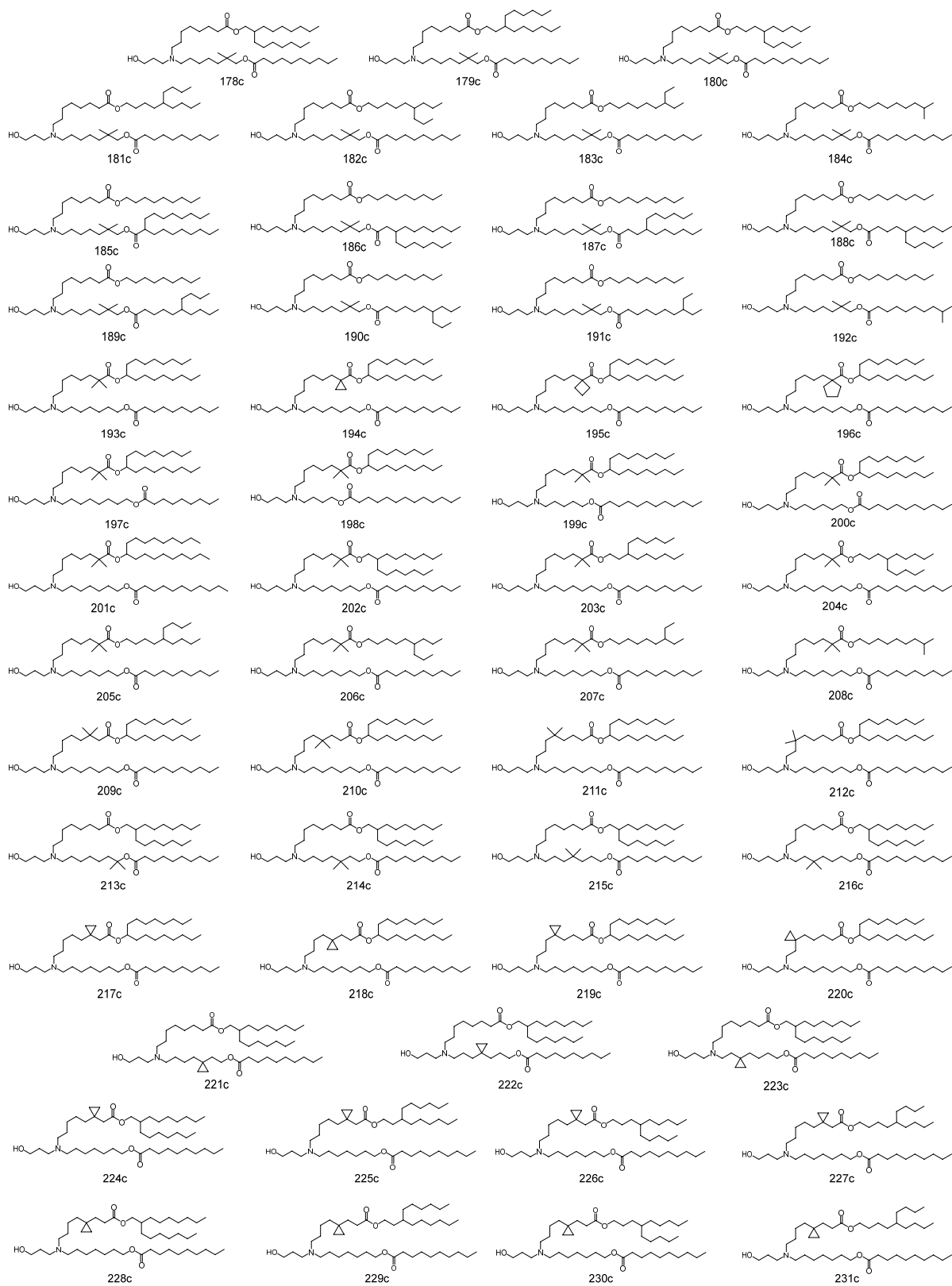


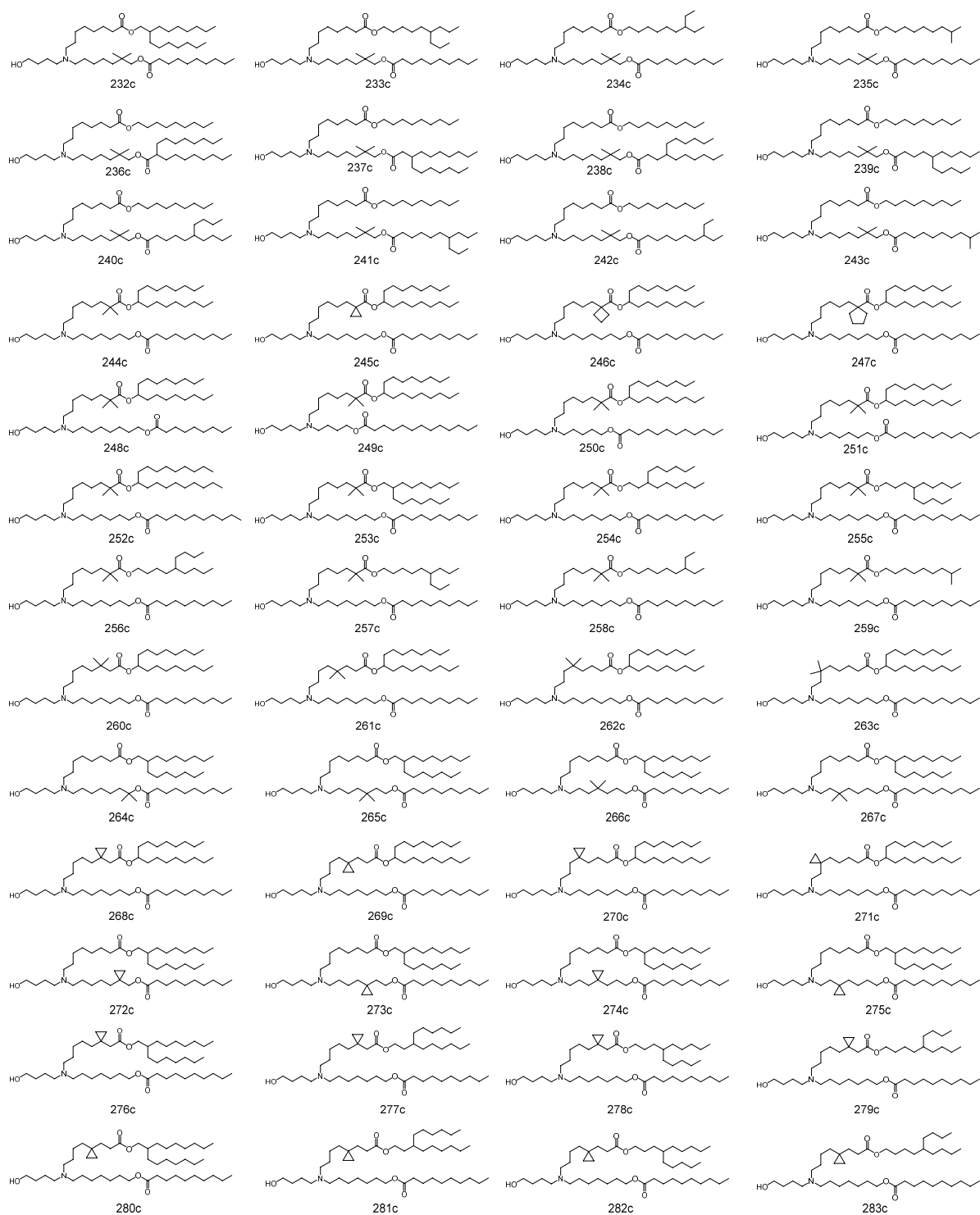






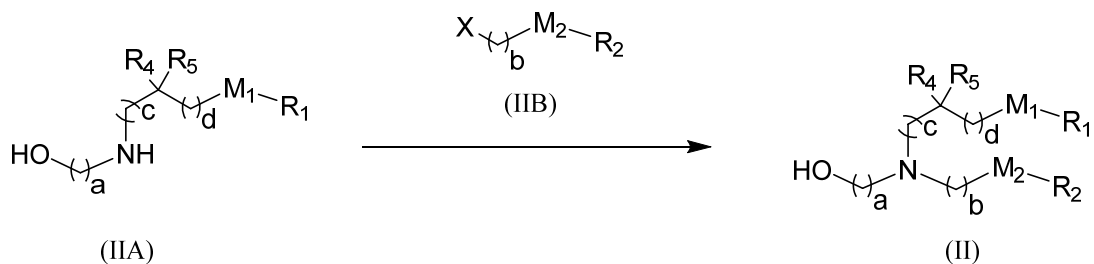






[0784] The present disclosure further provides a method for preparing a compound of formula (II), comprising:

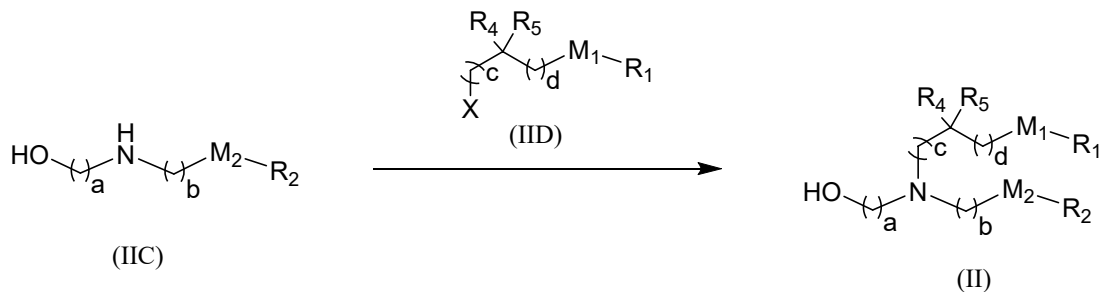
[0785] reacting a compound of formula (IIA) with a compound of formula (IIB) to give the compound of formula (II),



[0786] wherein X is halogen, and the other variables are as defined herein.

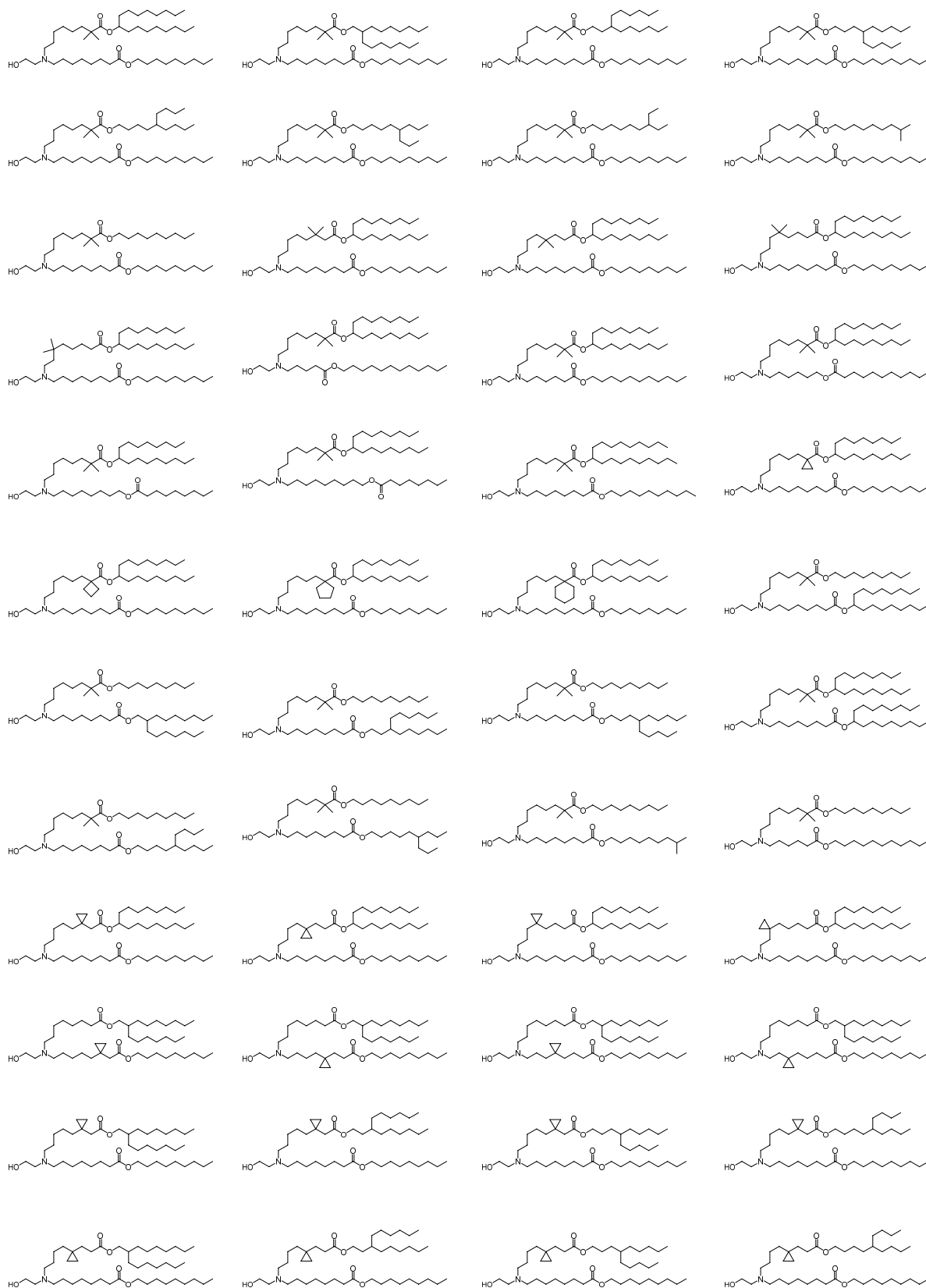
[0787] The present disclosure further provides a method for preparing a compound of formula (II), comprising:

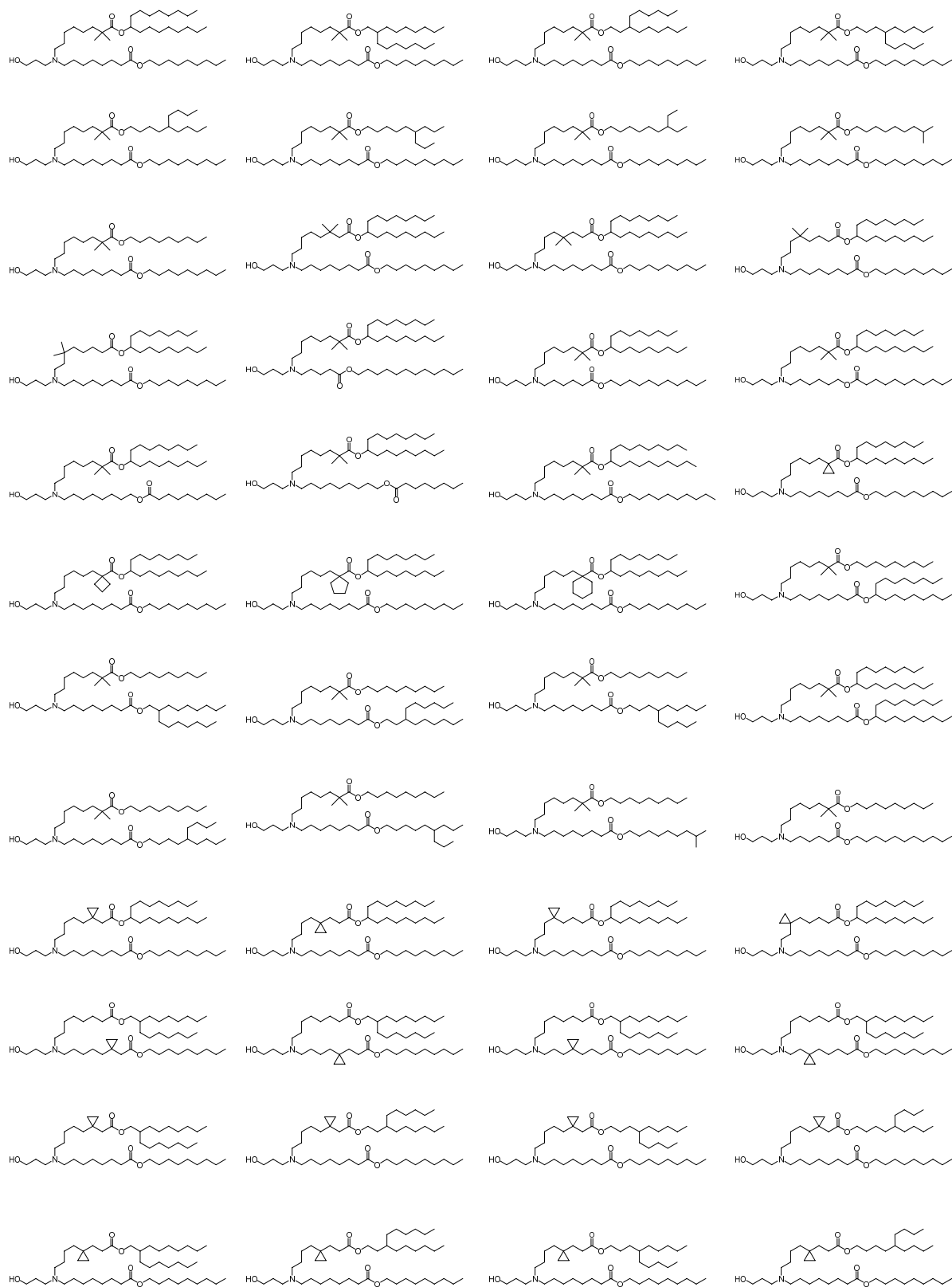
[0788] reacting a compound of formula (IIC) with a compound of formula (IID) to give the compound of formula (II),

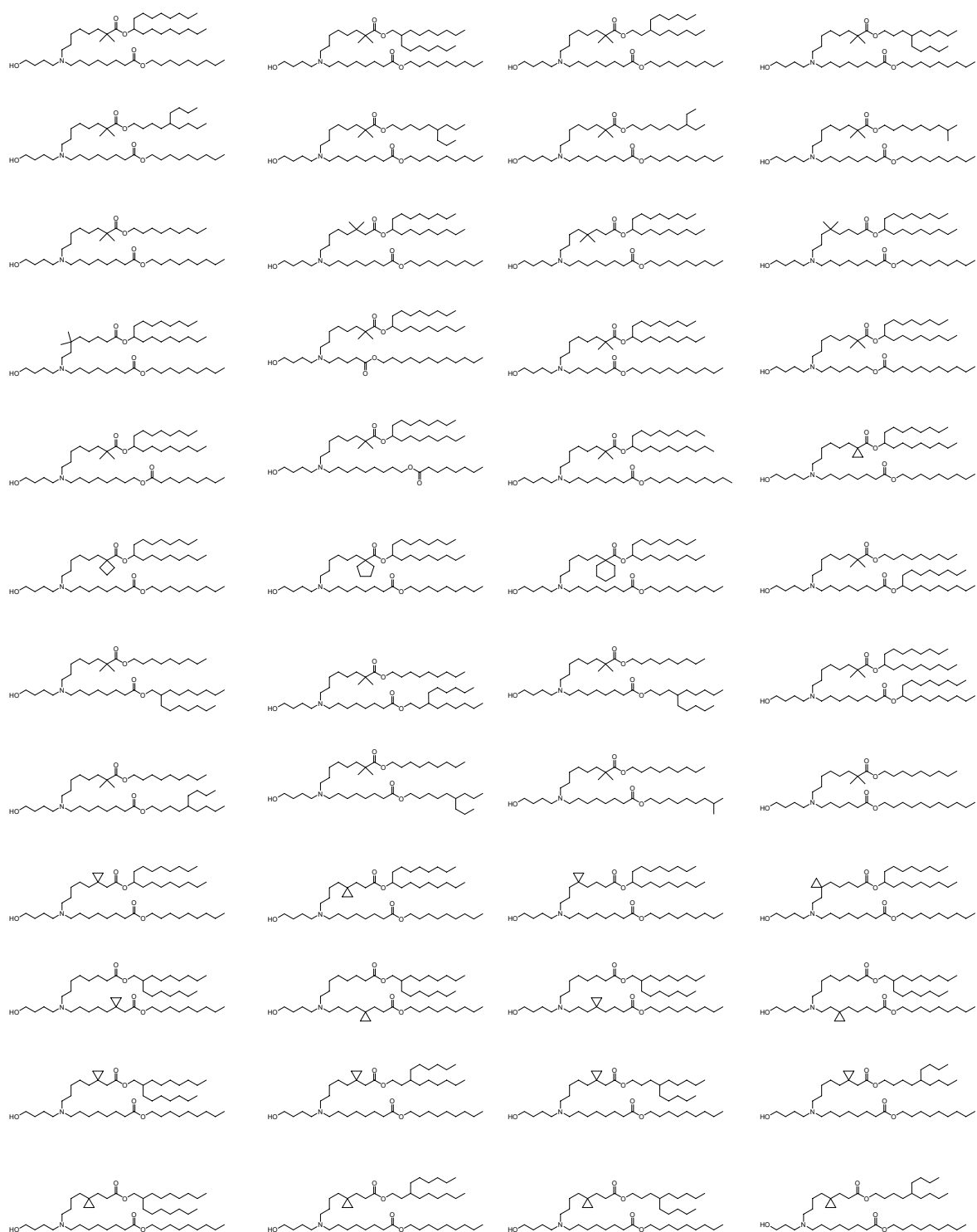


[0789] wherein X is halogen, and the other variables are as defined herein.

[0790] In a specific embodiment, the compound is selected from:







[0791] In a more specific embodiment, the present disclosure provides a nanoparticle composition comprising a lipid component, and optionally a load, wherein the lipid component comprises the compound of the present disclosure.

- [0792] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the lipid component comprises the following components in molar percentage:
- [0793] ionizable cationic lipids 20 mol%-85 mol%;
- [0794] structural lipids 10 mol%-75 mol%;
- [0795] neutral lipids 1.0 mol%-30 mol%;
- [0796] polymeric lipids 0.25 mol%-10 mol%.
- [0797] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the lipid component comprises the following components in molar percentage:
- [0798] any of the above-mentioned compound of the present disclosure 50 mol%;
- [0799] neutral lipids 10 mol%;
- [0800] structural lipids 38.5 mol%;
- [0801] polymeric lipids 1.5 mol%.
- [0802] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the neutral lipids are selected from one or more of DSPC, DMPC, DOPC, DPPC, POPC, DOPE, DMPE, POPE and DPPE, alternatively DSPC and/or DOPE.
- [0803] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the structure lipids are selected from one or more of cholesterol, sitosterol, coprosterol, fucosterol, brassicasterol, ergosterol, tomatine, ursolic acid, α -tocopherol, stigmasterol, avenasterol, ergocalciferol and campesterol, alternatively cholesterol and/or β -sitosterol, still alternatively cholesterol.
- [0804] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the polymer lipids are polyethylene glycolated lipids.
- [0805] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein,, the polyethylene glycolated lipids are selected from one or more of: PEG modified phosphatidylethanolamine, PEG modified phosphatidic acid, PEG modified ceramide, PEG modified dialkyl amine, PEG modified diacylglycerol, and PEG modified dialkylglycerol.

- [0806] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the polyethylene glycolated lipids contain a PEG moiety of about 1000 Da to about 20 kDa, alternatively a PEG moiety of about 1000 Da to about 5000 Da.
- [0807] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the polyethylene glycolated lipids are selected from one or more of DMPE-PEG1000, DPPE-PEG1000, DSPE-PEG1000, DOPE-PEG1000, DMG-PEG2000, Ceramide-PEG2000, DMPE-PEG2000, DPPE-PEG2000, DSPE-PEG2000, Azido-PEG2000, DSPE-PEG2000-Mannose, Ceramide-PEG5000, and DSPE-PEG5000, alternatively DMG-PEG2000.
- [0808] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the load is selected from one or more of therapeutic, prophylactic and diagnostic agents.
- [0809] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the therapeutic, prophylactic or diagnostic agent is a nucleic acid.
- [0810] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the nucleic acid is selected from one or more of ASO, RNA and DNA.
- [0811] In a more specific embodiment, the present disclosure provides the nanoparticle composition described above, wherein, the RNA is selected from one or more of interfering RNA (RNAi), small interfering RNA (siRNA), short hairpin RNA (shRNA), antisense RNA (aRNA), messenger RNA (mRNA), modified messenger RNA (mmRNA), long non-coding RNA (lncRNA), microRNA (miRNA), small activating RNA (saRNA), multimeric coding nucleic acid (MCNA), polymeric coding nucleic acid (PCNA), guide RNA (gRNA), CRISPRRNA (crRNA), and nucleases, alternatively mRNA, still alternatively, modified mRNA.
- [0812] The compounds of the present disclosure may include one or more asymmetric centers, and thus may exist in a variety of stereoisomeric forms, for example, enantiomers and/or diastereomers. For example, the compounds of the present disclosure may be in

the form of an individual enantiomer, diastereomer or geometric isomer (e.g., cis- and trans-isomers), or may be in the form of a mixture of stereoisomers, including racemic mixture and a mixture enriched in one or more stereoisomers. The isomers can be separated from the mixture by the methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or alternative isomers can be prepared by asymmetric synthesis.

[0813] The compounds of the present disclosure may exist in tautomer forms. The tautomer is a functional group isomer resulting from the rapid shift of an atom between two positions in a molecule. The tautomer is a special functional group isomer, wherein a pair of tautomers can convert between each other, but usually exist in a relatively stable isomer as its main form. The most important examples are the enol and keto tautomers.

[0814] The present disclosure also comprises compounds that are labeled with isotopes (isotope variants), which are equivalent to those described in formula (IV), but one or more atoms are replaced with atoms having an atom mass or mass number that are different from that of atoms that are common in nature. Examples of isotopes which may be introduced into the compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present disclosure that comprise the above isotopes and/or other isotopes of other atoms, prodrugs thereof and pharmaceutically acceptable salts of said compounds or prodrugs all are within the scope of the present disclosure. Certain isotope-labeled compounds of the present disclosure, such as those incorporating radioactive isotopes (e.g., ^3H and ^{14}C), can be used for the measurement of the distribution of drug and/or substrate in tissue. Tritium, which is ^3H and carbon-14, which is ^{14}C isotope, are yet alternative, because they are easy to prepare and detect. Furthermore, replaced with heavier isotopes, such as deuterium, which is ^2H , may provide therapeutic benefits due to the higher metabolic stability, such as prolonging the half-life *in vivo* or decreasing the dosage requirements, and thus may be alternative in some cases. Isotope-labeled compounds of formula (I) of the present disclosure and prodrugs thereof can be prepared generally by using readily available isotope-labeled reagents to replace non-isotope-labeled reagents in the

following schemes and/or the procedures disclosed in the examples and preparation examples.

[0815] The present disclosure also provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of formula (I), or therapeutically acceptable salts thereof, and pharmaceutically acceptable carriers, diluents or excipients thereof. All of these forms belong to the present disclosure.

[0816] Pharmaceutical compositions and kits

[0817] In another aspect, the present disclosure provides a pharmaceutical composition comprising nanoparticle compositions of the present disclosure and pharmaceutically acceptable excipient(s), the nanoparticle composition comprises the compounds of the present disclosure.

[0818] A pharmaceutically acceptable excipient for use in the present disclosure refers to a non-toxic carrier, adjuvant or vehicle which does not destroy the pharmacological activity of the compound formulated together. Pharmaceutically acceptable carriers, adjuvants, or vehicles that may be used in the compositions of the present disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (e.g., human serum albumin), buffer substances (such as phosphate), glycine, sorbic acid, potassium sorbate, a mixture of partial glycerides of saturated plant fatty acids, water, salt or electrolyte (such as protamine sulfate), disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salt, silica gel, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based materials, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylate, wax, polyethylene-polyoxypropylene block polymers, polyethylene glycol and lanolin.

[0819] The present disclosure also includes kits (e.g., pharmaceutical packs). Kits provided may include a nanoparticle composition of the present disclosure and other therapeutic, or diagnostic, or prophylactic agents, and a first and a second containers (e.g., vials, ampoules, bottles, syringes, and/or dispersible packages or other materials) containing the nanoparticle composition of the present disclosure or other therapeutic, or diagnostic, or prophylactic agents. In some embodiments, kits provided can also optionally include a third container containing a pharmaceutically acceptable excipient

for diluting or suspending the nanoparticle composition of the present disclosure and/or other therapeutic, or diagnostic, or prophylactic agent. In some embodiments, the nanoparticle composition of the present disclosure provided in the first container and the other therapeutic, or diagnostic, or prophylactic agents provided in the second container is combined to form a unit dosage form.

[0820] Administration

[0821] The pharmaceutical composition provided by the present disclosure can be administered by a variety of routes including, but not limited to, oral administration, parenteral administration, inhalation administration, topical administration, rectal administration, nasal administration, oral administration, vaginal administration, administration by implant or other means of administration. For example, parenteral administration as used herein includes subcutaneous administration, intradermal administration, intravenous administration, intramuscular administration, intra-articular administration, intraarterial administration, intrasynovial administration, intrasternal administration, intracerebroventricular administration, intralesional administration, and intracranial injection or infusion techniques.

[0822] Generally, the pharmaceutical compositions provided herein are administered in an effective amount. The amount of the pharmaceutical composition actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated or prevented, the chosen route of administration, the actual pharmaceutical composition administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0823] When used to prevent the disorder of the present disclosure, the pharmaceutical compositions provided herein will be administered to a subject at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Subjects at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0824] The pharmaceutical compositions provided herein can also be administered chronically (“chronic administration”). Chronic administration refers to administration of a compound or pharmaceutical composition thereof over an extended period of time, *e.g.*, for example, over 3 months, 6 months, 1 year, 2 years, 3 years, 5 years, *etc.*, or may be continued indefinitely, for example, for the rest of the subject’s life. In certain embodiments, the chronic administration is intended to provide a constant level of the compound in the blood, *e.g.*, within the therapeutic window over the extended period of time.

[0825] The pharmaceutical compositions of the present disclosure may be further delivered using a variety of dosing methods. For example, in certain embodiments, the pharmaceutical composition may be given as a bolus, *e.g.*, in order to raise the concentration of the compound in the blood to an effective level. The placement of the bolus dose depends on the systemic levels of the active ingredient desired throughout the body, *e.g.*, an intramuscular or subcutaneous bolus dose allows a slow release of the active ingredient, while a bolus delivered directly to the veins (*e.g.*, through an IV drip) allows a much faster delivery which quickly raises the concentration of the active ingredient in the blood to an effective level. In other embodiments, the pharmaceutical composition may be administered as a continuous infusion, *e.g.*, by IV drip, to provide maintenance of a steady-state concentration of the active ingredient in the subject’s body. Furthermore, in still yet other embodiments, the pharmaceutical composition may be administered as first as a bolus dose, followed by continuous infusion.

[0826] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses, generally in an amount ranging from about 0.01 to about 20% by weight, alternatively from about 0.1 to about 20% by weight, alternatively from about 0.1 to about 10% by weight, and still alternatively from about 0.5 to about 15% by weight.

[0827] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[0828] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable excipients known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable excipient and the like.

Example

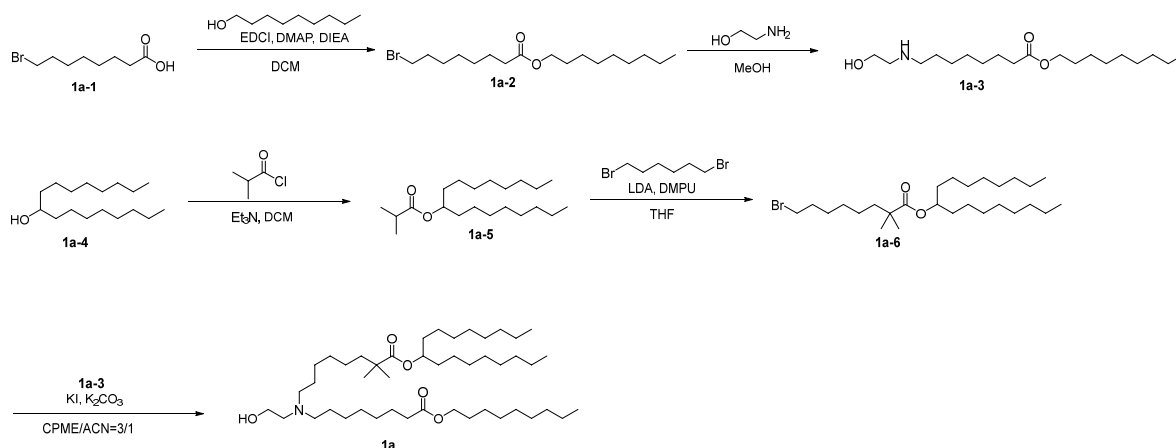
[0829] In order to make the technical solutions of the present disclosure clearer and more explicit, the present disclosure is further elaborated through the following examples. The following examples are used only to illustrate specific embodiments of the present disclosure so that a person skilled in the art can understand the present disclosure, but are not intended to limit the scope of protection of the present disclosure. The technical means or methods, etc. not specifically described in the specific embodiments of the present disclosure are conventional technical means or methods, etc. in the art. The materials, reagents, etc. used in examples are commercially available if not otherwise specified.

Table 1

Chemical formula or abbreviation	Full Name
THF	Tetrahydrofuran
ACN	Acetonitrile
DCM	Dichloromethane
MeOH	Methanol
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
MTBE	<i>tert</i> -Butyl methyl ether
CDCl ₃	Deuterated chloroform

TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
LDA	Lithium diisopropylamide
DMAP	4-Dimethylaminopyridine
(COCl) ₂	Oxalyl chloride
NaI	Sodium iodide
NaH	Sodium hydride
K ₂ CO ₃	Potassium carbonate
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
DIEA	<i>N,N</i> -diisopropylethylamine
LiAlH ₄	Lithium aluminum hydride
CMPE	Cyclopentyl methyl ether
DMPU	<i>N,N</i> -dimethylpropyleneurea
TMSCl	Trimethylchlorosilane
TMSOK	Potassium trimethylsilanolate
TEA	Triethylamine

[0830] Example 1: Synthesis of Compound 1a



[0831] To a 500 mL three-neck round-bottom flask were added 1-nonanol (15 g, 104.0 mmol, 1.0 eq.), 8-bromooctanoic acid (25.5 g, 114.0 mmol, 1.1 eq.), DMAP (2.54 g, 20.8 mmol, 0.2 eq.), DIEA (40.3 g, 312.0 mmol, 3.0 eq.), and EDCI (25.9 g, 135 mmol, 1.3

eq.) at room temperature, and 250 mL of DCM was added. The reaction liquid was stirred at room temperature for 4 h, and the reaction was completed as monitored by TLC. The reaction liquid was poured into 200 mL of a saturated aqueous ammonium chloride solution, and the mixture was extracted with 3 × 100 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 21 g of a yellow oily compound 1a-2.

[0832] To a 250 mL three-neck round-bottom flask were added compound 1a-2 (21 g, 60.1 mmol, 1.0 eq.) and 2-aminoethanol (110 g, 1.80 mol, 30.0 eq.) at room temperature, and the mixture was dissolved in 100 mL of methanol. The mixture was heated to 60 °C, stirred for reaction for 18 h, and concentrated to remove the reaction solvent. Then a saturated aqueous ammonium chloride solution and ethyl acetate were added thereto, and the mixture was extracted after layer separation. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 14 g of a yellow oily compound 1a-3.

[0833] To a 250 mL three-neck round-bottom flask were added 9-heptadecanol (9.8 g, 38.2 mmol, 1.0 eq.) and triethylamine (15.5 g, 152.8 mmol, 4.0 eq.) at room temperature, and the mixture was dissolved in 100 mL of DCM. The reaction system was cooled in an ice bath, and then 2-methylpropionyl chloride (9.8 g, 91.7 mmol, 2.4 eq.) was slowly added. The mixture was warmed to room temperature and reacted overnight. After the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 8.7 g of a yellow oily compound 1a-5.

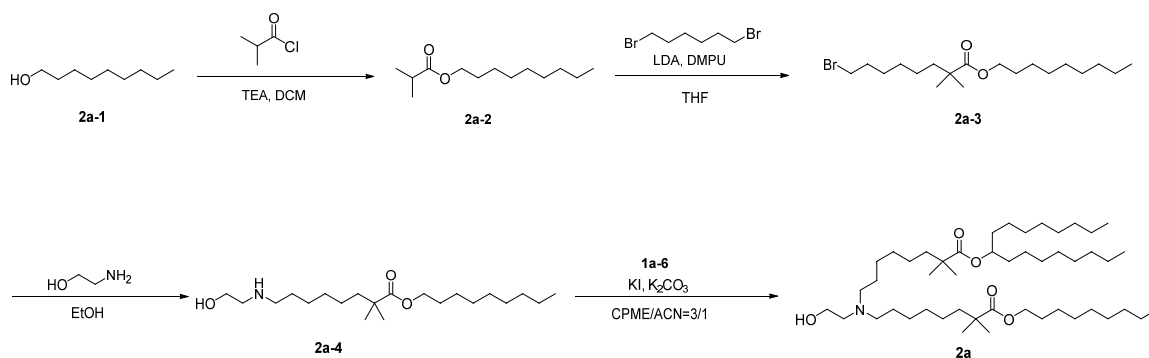
[0834] To a 250 mL three-neck round-bottom flask was added compound 1a-5 (8.7 g, 26.6 mmol, 1.0 eq.) at room temperature, and the mixture was dissolved in 60 mL of THF. The reaction system was cooled to -40 °C, and then LDA (13.1 mL, 26.2 mmol, 0.98 eq.) was slowly added dropwise. The mixture was stirred for reaction for 1 h, and

then 1,6-dibromohexane (9.03 g, 37.0 mmol, 1.39 eq.) and DMPU (0.48 g, 3.73 mmol, 0.14 eq.) were added to the reaction system. The mixture was warmed to room temperature and reacted overnight. After the reaction was completed as monitored by TLC, a saturated ammonium chloride ice water solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 10.1 g of a yellow oily compound 1a-6.

[0835] To a 20 mL round-bottom flask were added compound 1a-6 (1.48 g, 3.04 mmol, 2.0 eq.), compound 1a-3 (500 mg, 1.52 mmol, 1.0 eq.), K₂CO₃ (628.2 mg, 4.55 mmol, 3.0 eq.), KI (302.3 mg, 1.82 mmol, 1.2 eq.), cyclopentyl methyl ether (7.5 mL), and acetonitrile (2.5 mL). The mixture was warmed to 80 °C and reacted. After the reaction was completed as monitored by TLC, a saturated ammonium chloride ice water solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 96.98 mg of an oily compound **1a**.

[0836] ¹H NMR (400 MHz, CDCl₃) δ: 4.86-4.80 (m, 1H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.57 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 4H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.62 (m, 4H), 1.51-1.45 (m, 10H), 1.38-1.23 (m, 49H), 1.15 (s, 6H), 0.88 (t, *J* = 7.2 Hz, 9H); ESI-MS *m/z*: 738.60 [M+H]⁺.

[0837] Example 2: Synthesis of Compound 2a



[0838] To a 250 mL three-neck round-bottom flask were added 1-nonanol (8.8 g, 61.0 mmol, 1.0 eq.) and triethylamine (24.7 g, 244.0 mmol, 4.0 eq.) at room temperature, and

the mixture was dissolved in 100 mL of DCM. The reaction system was cooled in an ice bath, and then 2-methylpropionyl chloride (15.6 g, 146.4 mmol, 2.4 eq.) was slowly added. The mixture was warmed to room temperature and reacted. After the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 10.8 g of a yellow oily compound 2a-2.

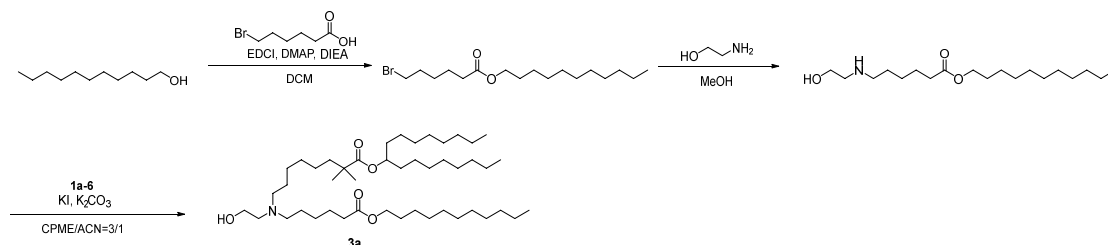
[0839] To a 250 mL three-neck round-bottom flask was added compound 2a-2 (4.8 g, 22.4 mmol, 1.0 eq.) at room temperature, and the mixture was dissolved in 50 mL of THF. The reaction system was cooled to -40 °C, and then LDA (11.0 mL, 21.9 mmol, 0.98 eq.) was slowly added dropwise. The mixture was stirred for reaction for 1 h, and then 1,6-dibromohexane (7.59 g, 31.1 mmol, 1.39 eq.) and DMPU (0.57 g, 4.48 mmol, 0.2 eq.) were added to the reaction system. The mixture was warmed to room temperature and reacted overnight. After the reaction was completed as monitored by TLC, a saturated ammonium chloride ice water solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 4.6 g of a yellow oily compound 2a-3.

[0840] To a 250 mL three-neck round-bottom flask were added compound 2a-3 (4.6 g, 12.2 mmol, 1.0 eq.) and 2-aminoethanol (14.9 g, 244.0 mmol, 20.0 eq.) at room temperature, and the mixture was dissolved in 50 mL of ethanol. The mixture was heated to 60 °C, stirred for reaction for 18 h, and concentrated to remove the reaction solvent. Then a saturated aqueous ammonium chloride solution and ethyl acetate were added thereto, and the mixture was extracted after layer separation. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 2.2 g of a yellow oily compound 2a-4.

[0841] To a 20 mL round-bottom flask were added compound 2a-4 (500 mg, 1.4 mmol, 1.0 eq.), compound 1a-6 (1.37 g, 2.8 mmol, 2.0 eq.), K₂CO₃ (579 mg, 4.2 mmol, 3.0 eq.), KI (279 mg, 1.68 mmol, 1.2 eq.), cyclopentyl methyl ether (7.5 mL), and acetonitrile (2.5 mL). The mixture was warmed to 80 °C and reacted. After the reaction was completed as monitored by TLC, a saturated ammonium chloride ice water solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 137.9 mg of an oily compound **2a**.

[0842] **¹H NMR** (400 MHz, CDCl₃) δ : 4.83 (m, 1H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 2.60 (t, *J* = 5.6 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 4H), 1.62 (m, 2H), 1.52-1.40 (m, 12H), 1.36-1.20 (m, 48H), 1.15 (m, 12H), 0.88 (t, *J* = 7.2 Hz, 9H); **ESI-MS** *m/z*: 766.50 [M+H]⁺.

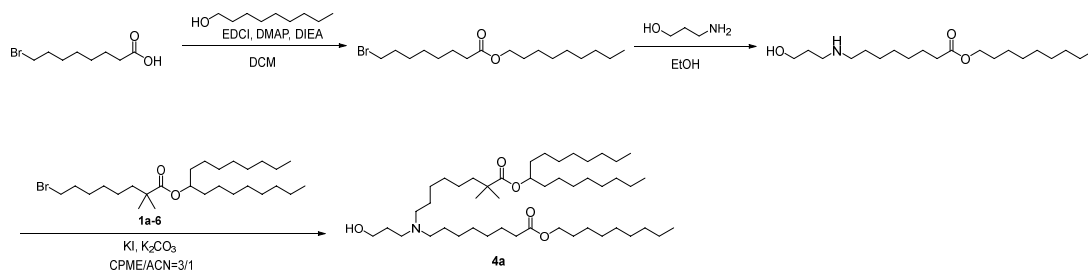
[0843] Example 3: Synthesis of Compound 3a



[0844] Compound 3a was prepared referring to the method of Example 1 to give 114.7 mg of an oily product.

[0845] **¹H NMR** (400 MHz, CDCl₃) δ : 4.83 (m, 1H), 4.06 (t, *J* = 7.2 Hz, 2H), 3.59 (m, 2H), 2.66 (m, 2H), 2.54 (m, 4H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.70-1.56 (m, 4H), 1.50 (m, 10H), 1.32-1.26 (m, 49H), 1.15 (s, 6H), 0.88 (t, *J* = 7.2 Hz, 9H); **ESI-MS** *m/z*: 738.55 [M+H]⁺.

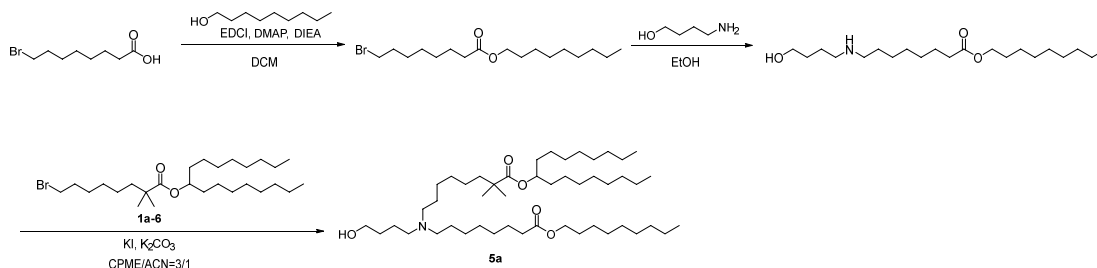
[0846] Example 4: Synthesis of Compound 4a



[0847] Compound **4a** was prepared referring to the method of Example 1 to give 112.1 mg of an oily product.

[0848] ¹H NMR (400 MHz, CDCl₃) δ: 4.83 (m, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.80 (t, *J* = 5.4 Hz, 2H), 2.51-2.73 (m, 6H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.65-1.44 (m, 16H), 1.26 (m, 49H), 1.15 (s, 6H), 0.93-0.82 (m, 9H); **ESI-MS** *m/z*: 752.70 [M+H]⁺.

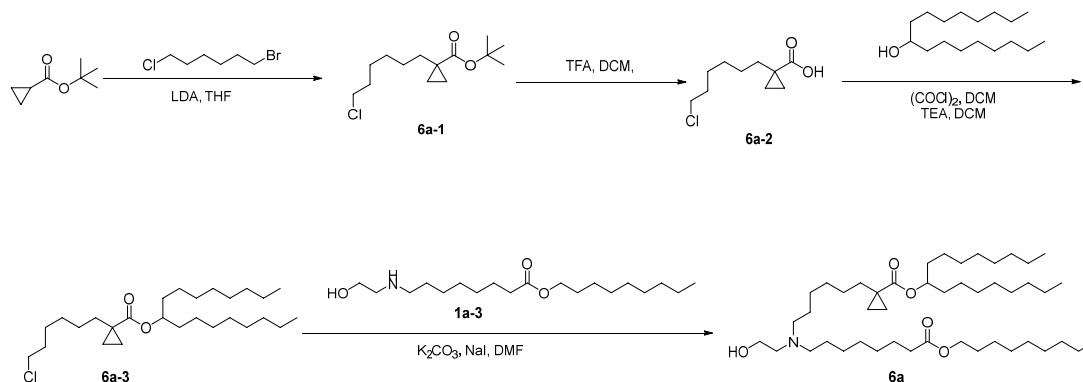
[0849] Example 5: Synthesis of Compound 5a



[0850] Compound **5a** was prepared referring to the method of Example 1 to give 150.8 mg of an oily product.

[0851] ¹H NMR (300 MHz, CDCl₃) δ: 4.84 (m, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.60 (m, 2H), 2.41-2.63 (m, 4H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.65-1.44 (m, 18H), 1.26-1.34 (m, 51H), 1.14 (s, 6H), 0.93-0.82 (m, 9H); **ESI-MS** *m/z*: 766.70 [M+H]⁺.

[0852] Example 6: Synthesis of Compound 6a



[0853] *tert*-Butyl cyclopropanecarboxylate (15.0 g, 150.0 mmol, 1.0 eq.) was dissolved in 150 mL of anhydrous tetrahydrofuran, and the mixture was cooled to -60 °C. LDA (150.0 mL, 300.0 mmol, 2.0 eq.) was added to the reaction liquid under nitrogen atmosphere. After the mixture was stirred at the same temperature for reaction for 1 h, 1-bromo-6-chlorohexane (44.9 g, 225.0 mmol, 1.5 eq.) was added, and the mixture was stirred at room temperature for reaction for another 3 h. After the reaction was completed as monitored by TLC, the reaction was quenched with a saturated aqueous ammonium

chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 19 g of a colorless oily compound 6a-1.

[0854] To a solution of compound 6a-1 (10.0 g, 38.3 mmol) in DCM (30.0 mL) was added 10.0 mL of trifluoroacetic acid, and the mixture was stirred at room temperature for 3 h. The reaction solvent was removed by pressurized rotary evaporation to give a crude product, which was purified by silica gel column chromatography to give 6.9 g of a colorless oily compound 6a-2.

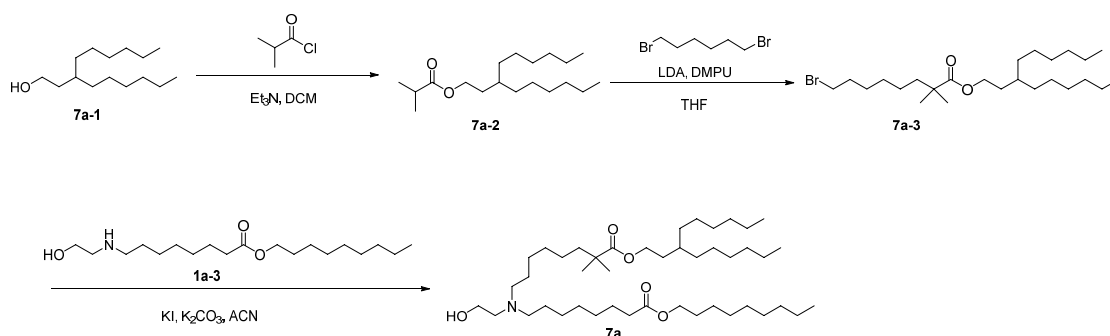
[0855] Compound 6a-2 (500.0 mg, 2.45 mmol, 2.0 eq.) was dissolved in DCM (5.0 mL), and 2-3 drops of DMF and oxalyl chloride (311.1 mg, 2.45 mmol, 2.0 eq.) were added to the reaction system under an ice bath. After the mixture was stirred for 30 min, the solvent was removed by rotary evaporation under reduced pressure to give an acyl chloride intermediate. The resulting acyl chloride was dissolved in DCM (5.0 mL), then 9-heptadecanol (312.3 mg, 1.22 mmol, 1.0 eq.) and triethylamine (247.5 mg, 2.45 mmol, 2.0 eq.) were added, and the mixture was reacted at room temperature for 5 h. After the reaction was completed, the reaction liquid was poured into 50 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 240 mg of an oily compound 6a-3.

[0856] To a solution of compound 6a-3 (200.0 mg, 0.45 mmol, 1.5 eq.) in DMF (3.0 mL) were added potassium carbonate (124.2 mg, 0.90 mmol, 3.0 eq.), sodium iodide (112.5 mg, 0.75 mmol, 2.5 eq.), and compound 1a-3 (99.0 mg, 0.30 mmol, 1.0 eq.). The reaction liquid was heated to 80 °C and stirred for reaction for 5 h. After the reaction was completed, the reaction system was cooled to room temperature. The reaction was quenched with a saturated aqueous sodium chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by preparative liquid chromatography to give 75.2 mg of compound **6a**. (Column model: XSelect C18 (19 × 150 mm, 5 μm), mobile

phase A: water:acetonitrile = 90:10 (10 mmol/L ammonium bicarbonate + 0.5% aqueous ammonia), mobile phase B: isopropanol: acetonitrile = 90: 10; flow rate: 25 mL/min; gradient: the proportion of B was 75%-80% in 0-12 min, and the proportion of B was 90% after 12 min).

[0857] **¹H NMR** (400 MHz, CDCl₃) δ : 4.82 (m, 1H), 4.05 (t, J = 7.2 Hz, 2H), 2.57 (m, 6H), 2.29 (t, J = 7.2 Hz, 2H), 1.61 (m, 7H), 1.52 (m, 13H); 1.21-1.37 (m, 45H), 1.16 (q, J = 4.4 Hz, 2H), 0.88 (t, J = 7.2 Hz, 9H), 0.64 (q, J = 4.4 Hz, 2H); **ESI-MS** m/z : 736.55 [M+H]⁺.

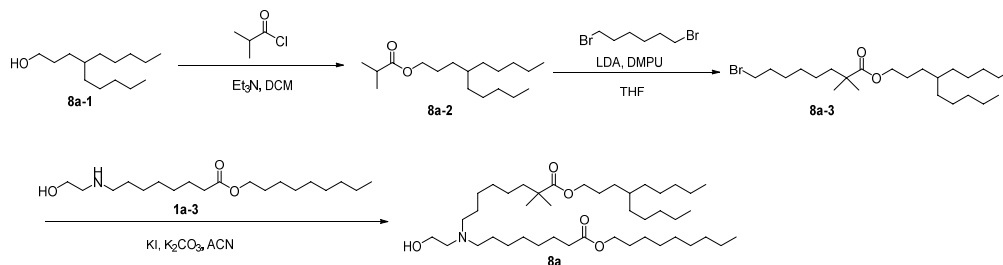
[0858] Example 7: Synthesis of Compound 7a



[0859] Compound **7a** was prepared referring to the method of Example 1 to give 102.4 mg of an oily product.

[0860] **¹H NMR** (300 MHz, CDCl₃) δ : 4.08 (td, J = 7.2 Hz, 4H), 3.58 (m, 2H), 2.57 (d, J = 40.6 Hz, 6H), 2.31 (t, J = 7.2 Hz, 2H), 1.73-1.40 (m, 14H), 1.20-1.39 (m, 45H), 1.17 (s, 6H), 0.96-0.85 (m, 9H); **ESI-MS** m/z : 710.55 [M+H]⁺.

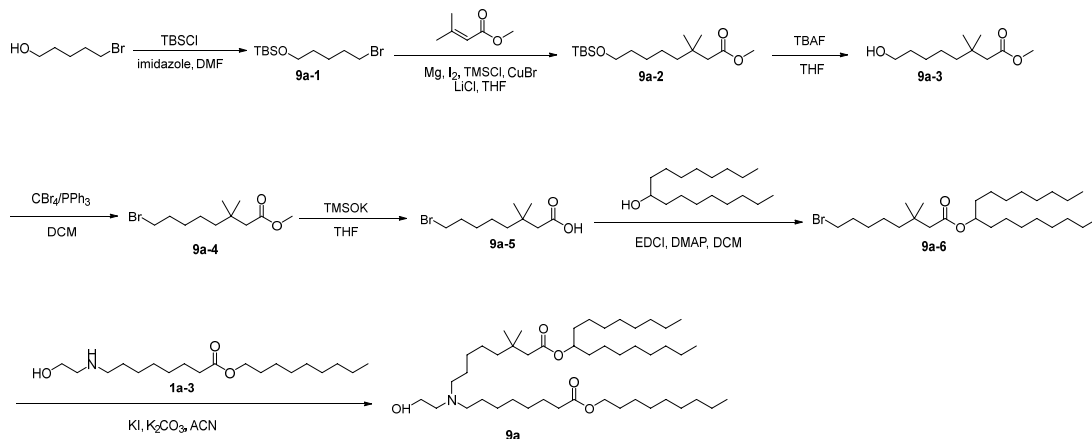
[0861] Example 8: Synthesis of Compound 8a



[0862] Compound **8a** was prepared referring to the method of Example 1 to give 44.9 mg of an oily product.

[0863] **¹H NMR** (300 MHz, CDCl₃) δ : 4.07-3.91 (m, 4H), 3.56 (m, 2H), 2.31-2.62 (m, 6H), 2.29 (t, J = 7.2 Hz, 2H), 1.73-1.40 (m, 12H), 1.39-1.20 (m, 44H), 1.16 (s, 6H), 0.93-0.82 (m, 9H); **ESI-MS** m/z : 696.50 [M+H]⁺.

[0864] Example 9: Synthesis of Compound 9a



[0865] In a 250 mL round-bottom flask, 5-bromo-1-pentanol (30 g, 180.0 mmol, 1.0 eq.) and imidazole (30.6 g, 449.0 mmol, 2.5 eq.) were dissolved in 120 mL of DMF. The reaction system was placed in an ice bath, and TBSCl (29.8 g, 198 mmol, 1.1 eq.) was added to the reaction system. The mixture was warmed to room temperature and reacted overnight. After the reaction was completed as monitored by TLC, a saturated aqueous sodium bicarbonate solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 26 g of a light yellow oily compound 9a-1.

[0866] In a 250 mL three-neck round-bottom flask, Mg (1.70 g, 70.1 mmol, 1.6 eq.), I₂ (0.01 g, 0.039 mmol), and 50 mL of anhydrous THF were added. The reaction system was warmed to 37 °C, then compound 9a-1 (18.5 g, 65.7 mmol, 1.5 eq.) was slowly added within 30 min, and the mixture was reacted until magnesium powder almost disappeared completely to give a Grignard reagent. In a 250 mL three-neck round-bottom flask, CuBr (0.63 g, 4.38 mmol, 0.1 eq.), LiCl (0.37 g, 8.76 mmol, 0.2 eq.), and 50 mL of anhydrous THF were added under nitrogen atmosphere. After the mixture was stirred at 0 °C for 30 min, to the obtained copper-lithium reagent solution were added methyl 3,3-dimethacrylate (5 g, 43.8 mmol, 1.0 eq.) and TMSCl (7.14 g, 65.7 mmol, 1.5 eq.)

dropwise. After the dropwise addition was completed, the mixture was stirred at 0 °C for another 30 min. The prepared Grignard reagent was slowly added dropwise to the reaction liquid, and after the dropwise addition was completed, the mixture was reacted for another 2 h. After the reaction was completed as monitored by TLC, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 13 g of a light yellow oily compound 9a-2.

[0867] To a solution of compound 9a-2 (13 g, 41.1 mmol, 1.0 eq.) in THF was added TBAF (21.5 g, 82.1 mmol, 2.0 eq.) in batches under an ice bath, and the mixture was stirred at room temperature for 2 h. A saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product of 9a-3, which was directly used in the next step without purification.

[0868] Compound 9a-3 (14 g, 69.2 mmol, 1.0 eq.) and PPh₃ (21.8 g, 83.0 mmol, 1.2 eq.) were dissolved in 140 mL of dichloromethane, the reaction system was cooled to 0 °C, and then CBr₄ (25.3 g, 76.1 mmol, 1.1 eq.) was added in batches. The mixture was stirred at room temperature for reaction until the reaction was completed as monitored by TLC. The reaction was quenched with an ice saturated aqueous sodium chloride solution, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 7.6 g of a light yellow oily compound 9a-4.

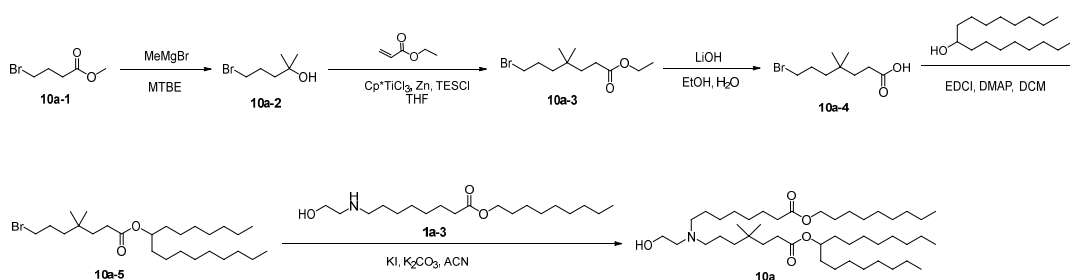
[0869] To 60 mL of a solution of compound 9a-4 (6 g, 22.6 mmol, 1 eq.) in THF was added TMSOK (4.35 g, 33.9 mmol, 1.5 eq.). The mixture was stirred at room temperature for reaction until the reaction was completed as monitored by TLC, the pH of the reaction system was adjusted to 4.0 with 2.0 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a

crude product, which was purified by silica gel column chromatography to give 2.5 g of a light yellow oily compound 9a-5.

[0870] Compound **9a** was prepared referring to the method of Example 1 to give 81.7 mg of an oily product.

[0871] ¹H NMR (300 MHz, CDCl₃) δ: 4.85 (m, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.66 (s, 2H), 2.59 (m, 4H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 2H), 1.64-1.43 (m, 12H), 1.22-1.38 (m, 51H), 1.12 (s, 6H), 0.95-0.85 (m, 9H); ESI-MS *m/z*: 738.65 [M+H]⁺.

[0872] Example 10: Synthesis of Compound 10a



[0873] In a 100 mL round-bottom flask, methyl 4-bromobutyrate (4 g, 22.1 mmol, 1.0 eq.) was dissolved in 40 mL of MTBE, the reaction system was placed in an ice bath, and methylmagnesium bromide (22.1 mL, 66.3 mmol, 3.0 eq.) was added to the reaction system. The mixture was warmed to room temperature and reacted until the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with EtOAc. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 3.5 g of compound 10a-2.

[0874] To a 100 mL round-bottom flask were added compound 10a-2 (3 g, 16.6 mmol, 1.0 eq.) triethylchlorosilane (7.49 g, 49.7 mmol, 3.0 eq.), zinc powder (3.25 g, 49.7 mmol, 3.0 eq.), Cp*TiCl₃ (519 mg, 1.80 mmol, 0.1 eq.), and 5A molecular sieves (2.4 g) under nitrogen atmosphere, and then 24 mL of anhydrous THF was added. The reaction system was heated to 50 °C, and then ethyl acrylate (2.49 g, 24.9 mmol, 1.5 eq.) was added to the reaction system. The mixture was heated to 60 °C for reaction for another 12 h. The reaction liquid was cooled to room temperature, a saturated aqueous sodium chloride solution was added to quench the reaction, and the mixture was extracted with EtOAc. The organic phases were combined and dried over anhydrous sodium sulfate. The

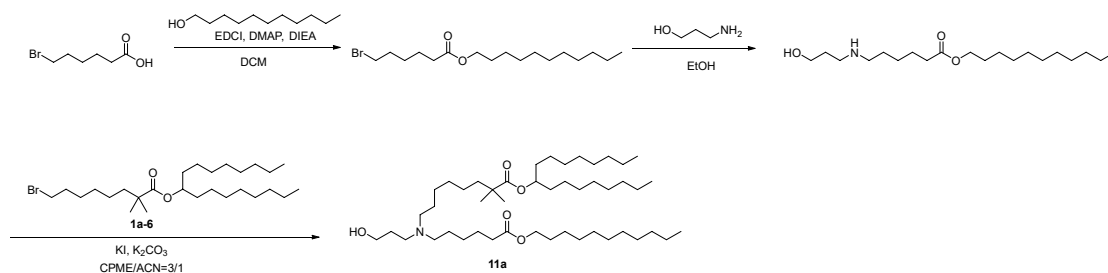
mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 2.4 g of compound 10a-3.

[0875] In a 40 mL reaction flask, compound 10a-3 (1 g, 3.77 mmol, 1.0 eq.) was dissolved in a mixed solution of 10 mL ethanol and 2 mL water, and then lithium hydroxide (0.27 g, 11.3 mmol, 3.0 eq.) was added to the reaction system. The mixture was reacted at room temperature until the reaction was completed as monitored by TLC, the organic solvent was removed by rotary evaporation, and the pH of the solution was adjusted to about 4 with 2.0 M dilute hydrochloric acid. A saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with EtOAc. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 800 mg of compound 10a-4.

[0876] Compound **10a** was prepared referring to the method of Example 1 to give 93.4 mg of an oily product.

[0877] ¹H NMR (300 MHz, CDCl₃) δ: 4.92-4.72 (m, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.59 (m, 2H), 2.64-2.51 (m, 6H), 2.33-2.18 (m, 4H), 1.55 (m, 14H), 1.34-1.24 (m, 45H), 0.83 (m, 15H); **ESI-MS** *m/z*: 724.55 [M+H]⁺.

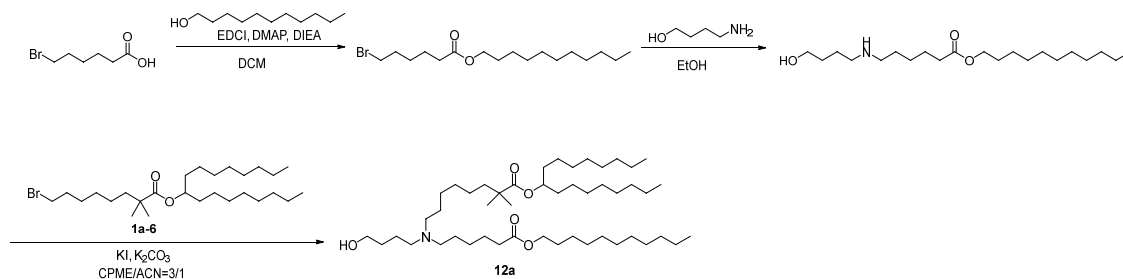
[0878] Example 11: Synthesis of Compound 11a



[0879] Compound **11a** was prepared referring to the method of Example 1 to give 69.5 mg of an oily product.

[0880] ¹H NMR (400 MHz, CDCl₃) δ: 4.90-4.80 (m, 1H), 4.08 (t, *J* = 7.2 Hz, 2H), 3.81 (t, *J* = 5.2 Hz, 2H), 2.55 (m, 6H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.71-1.46 (m, 16H), 1.40-1.26 (m, 49H), 1.17 (s, 6H), 0.90 (t, *J* = 7.2 Hz, 9H); **ESI-MS** *m/z*: 752.60 [M+H]⁺.

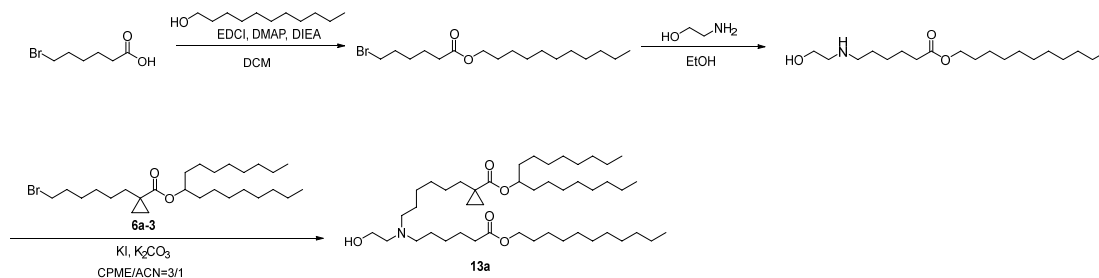
[0881] Example 12: Synthesis of Compound 12a



[0882] Compound **12a** was prepared referring to the method of Example 1 to give 178.6 mg of an oily product.

[0883] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.88-4.77 (m, 1H), 4.05 (t, $J = 7.2$ Hz, 2H), 3.60 (t, $J = 5.6$ Hz, 2H), 2.57 (m, 6H), 2.30 (t, $J = 7.2$ Hz, 2H), 1.71-1.46 (m, 12H), 1.43-1.15 (m, 55H), 1.11 (s, 6H), 0.89 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 766.70 $[\text{M}+\text{H}]^+$.

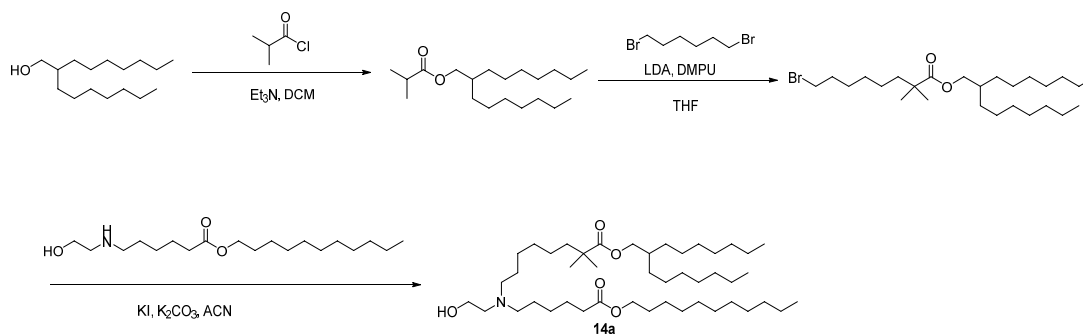
[0884] Example 13: Synthesis of Compound 13a



[0885] Compound **13a** was prepared referring to the method of Example 1 to give 43.5 mg of an oily product.

[0886] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.81 (p, $J = 6.4$ Hz, 1H), 4.06 (t, $J = 6.8$ Hz, 2H), 3.58 (m, 2H), 2.58-2.36 (m, 6H), 2.30 (t, $J = 7.6$ Hz, 2H), 1.70-1.51 (m, 16H), 1.48-1.16 (m, 47H), 1.14 (t, $J = 4.0$ Hz, 2H), 0.88 (t, $J = 7.2$ Hz, 9H), 0.64 (t, $J = 4.0$ Hz, 2H); **ESI-MS** m/z : 736.60 $[\text{M}+\text{H}]^+$.

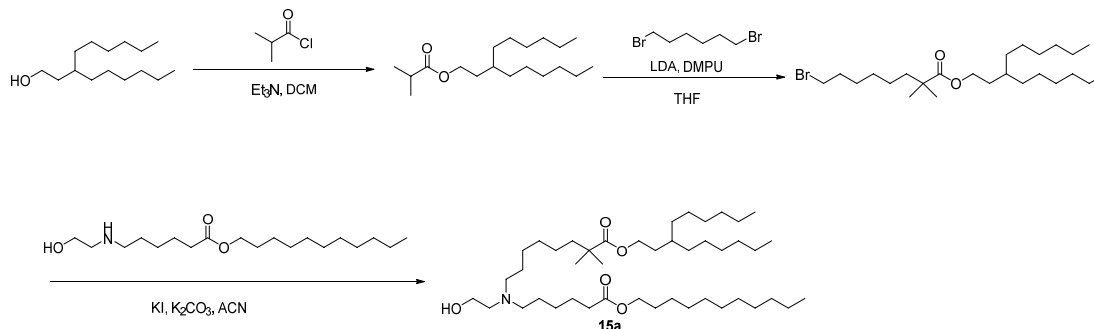
[0887] Example 14: Synthesis of Compound 14a



[0888] Compound **14a** was prepared referring to the method of Example 1 to give 56.3 mg of an oily product.

[0889] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.08 (t, $J = 6.8$ Hz, 2H), 4.01 (d, $J = 4.8$ Hz, 2H), 3.97 (d, $J = 5.6$ Hz, 2H), 3.17-3.06 (m, 5H), 2.36 (t, $J = 7.2$ Hz, 2H), 1.87-1.63 (m, 16), 1.57-1.29 (m, 45H), 1.19 (s, 6H), 0.91 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 724.55 $[\text{M}+\text{H}]^+$.

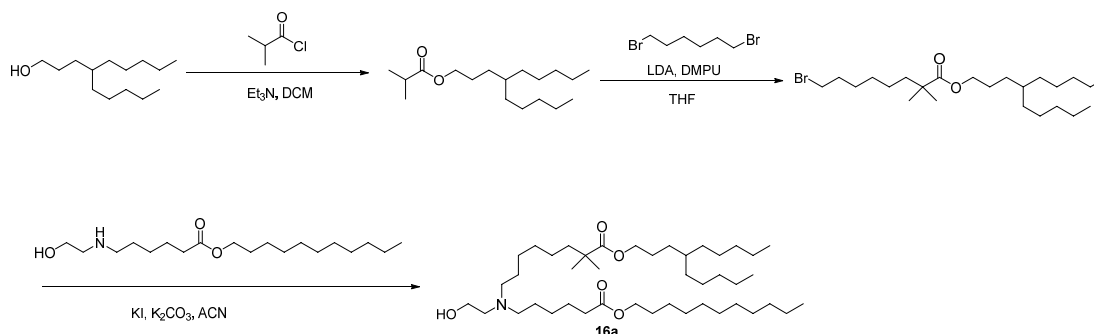
[0890] Example 15: Synthesis of Compound 15a



[0891] Compound **15a** was prepared referring to the method of Example 1 to give 120.3 mg of an oily product.

[0892] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.09-4.03 (m, 4H), 3.56 (m, 2H), 2.62-2.49 (m, 5H), 2.30 (t, $J = 6.0$ Hz, 2H), 1.66-1.55 (m, 14H), 1.52-1.26 (m, 45H), 1.15 (s, 6H), 0.88 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 710.55 $[\text{M}+\text{H}]^+$.

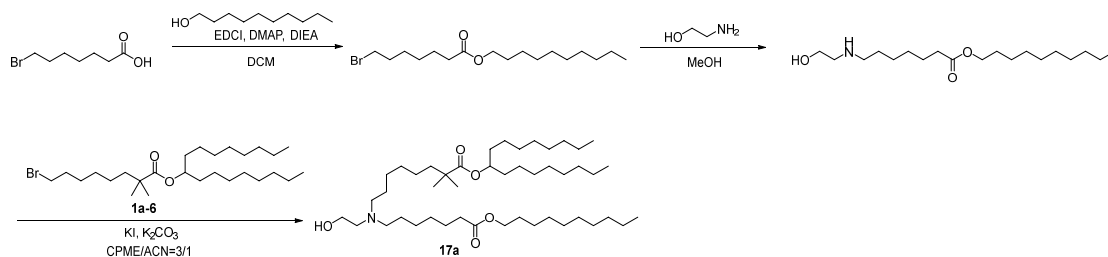
[0893] Example 16: Synthesis of Compound 16a



[0894] Compound **16a** was prepared referring to the method of Example 1 to give 80.8 mg of an oily product.

[0895] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.07-3.92 (m, 4H), 3.60 (m, 2H), 2.66-2.46 (m, 6H), 2.30 (t, $J = 7.6$ Hz, 2H), 1.68-1.44 (m, 12H), 1.38-1.07 (m, 44H), 1.05 (s, 6H), 0.88 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 696.55 $[\text{M}+\text{H}]^+$.

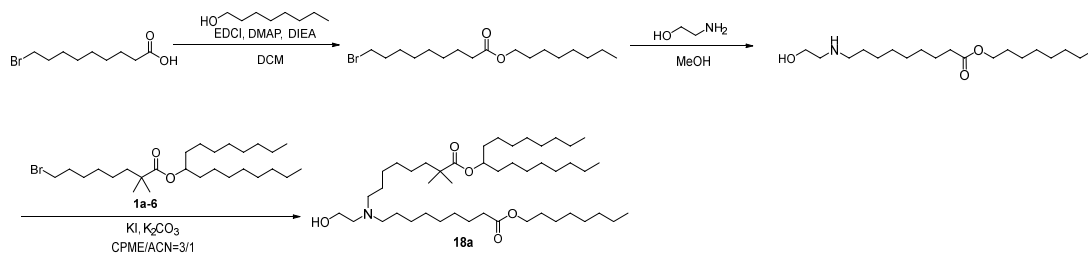
[0896] Example 17: Synthesis of Compound 17a



[0897] Compound **17a** was prepared referring to the method of Example 1 to give 125.7 mg of an oily product.

[0898] ^1H NMR (400 MHz, CDCl_3) δ : 4.86-4.80 (m, 1H), 4.05 (t, $J = 6.8$ Hz, 2H), 3.55 (m, 2H), 2.60-2.47 (m, 6H), 2.29 (t, $J = 7.6$ Hz, 2H), 1.66-1.48 (m, 14H), 1.43-1.26 (m, 49H), 1.15 (s, 6H), 0.88 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 738.65 $[\text{M}+\text{H}]^+$.

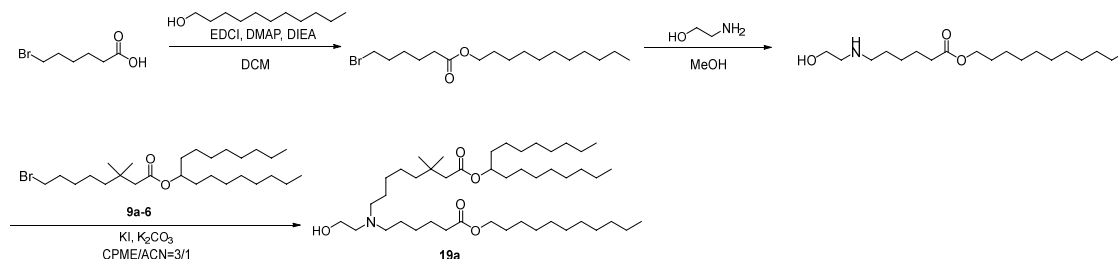
[0899] Example 18: Synthesis of Compound 18a



Compound **18a** was prepared referring to the method of Example 1 to give 127.4 mg of an oily product.

[0900] ^1H NMR (400 MHz, CDCl_3) δ : 4.86-4.80 (m, 1H), 4.06 (t, $J = 6.8$ Hz, 2H), 3.53 (t, $J = 4.8$ Hz, 2H), 2.58 (t, $J = 4.8$ Hz, 2H), 2.43 (t, $J = 4.8$ Hz, 4H), 2.29 (t, $J = 7.6$ Hz, 2H), 1.65-1.43 (m, 14H), 1.38-1.18 (m, 49H), 1.15 (s, 6H), 0.88 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 738.66 $[\text{M}+\text{H}]^+$.

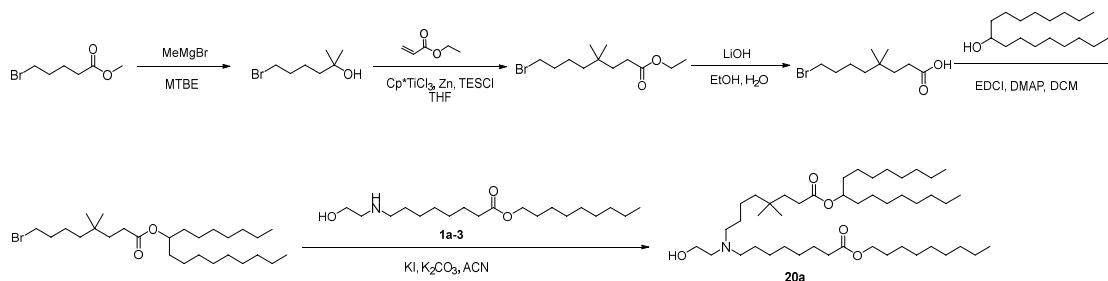
[0901] Example 19: Synthesis of Compound 19a



[0902] Compound **19a** was prepared referring to the method of Example 9 to give 79.7 mg of an oily product.

[0903] **¹H NMR** (300 MHz, CDCl₃) δ: 4.89-4.82 (m, 1H), 4.06 (t, *J* = 6.9 Hz, 2H), 3.67 (m, 2H), 2.70-2.34 (m, 4H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.17 (s, 2H), 1.70-1.49 (m, 12H), 1.38-1.18 (m, 49H), 0.99 (s, 6H), 0.88 (t, *J* = 6.9 Hz, 9H); **ESI-MS** *m/z*: 738.65 [M+H]⁺.

[0904] Example 20: Synthesis of Compound 20a

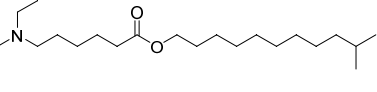
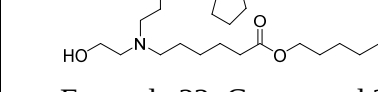
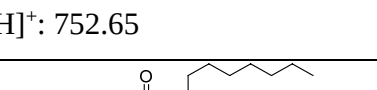
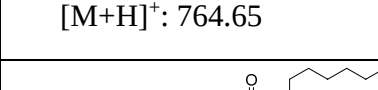
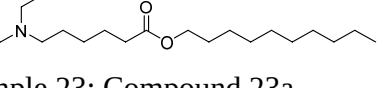
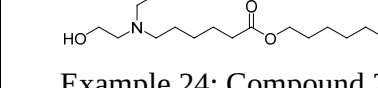


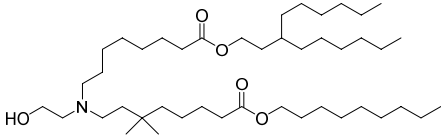
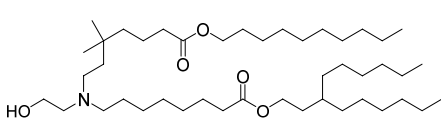
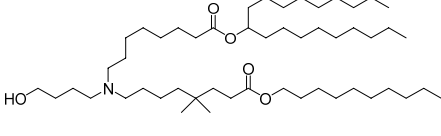
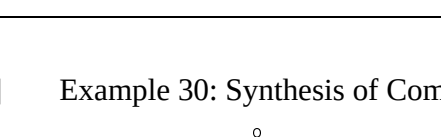
[0905] Compound **20a** was prepared referring to the method of Example 10 to give 74.5 mg of an oily product.

[0906] **¹H NMR** (400 MHz, CDCl₃) δ: 4.89-4.85 (m, 1H), 4.06 (t, *J* = 7.2 Hz, 2H), 3.63 (m, 2H), 2.69-2.57 (m, 6H), 2.35-2.20 (m, 4H), 1.71-1.53 (m, 15H), 1.39-1.19 (m, 46H), 0.94-0.85 (m, 15H); **ESI-MS** *m/z*: 738.45 [M+H]⁺.

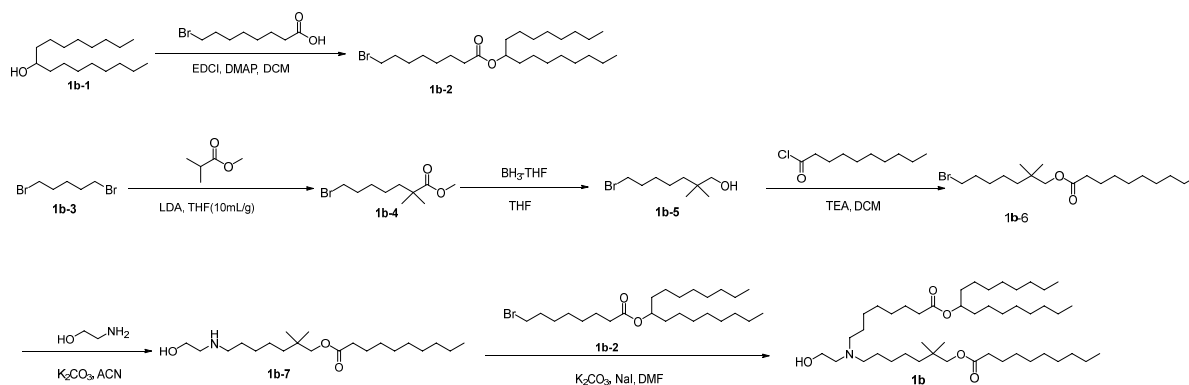
[0907] The compounds in Table 2 were synthesized using the methods of the above examples, or using similar methods of the corresponding intermediates.

Table 2

 Example 21: Compound 21a [M+H]⁺: 752.65	 Example 22: Compound 22a [M+H]⁺: 764.65
 Example 23: Compound 23a [M+H]⁺: 696.65	 Example 24: Compound 24a [M+H]⁺: 780.65
	

Example 25: Compound 25a $[M+H]^+$: 738.60 	Example 26: Compound 26a $[M+H]^+$: 724.55 
Example 27: Compound 27a $[M+H]^+$: 710.50 	Example 28: Compound 28a $[M+H]^+$: 710.50 
Example 29: Compound 29a $[M+H]^+$: 808.70 	

[0908] Example 30: Synthesis of Compound 1b



[0909] 9-Heptadecanol 1b-1 (200.0 mg, 0.78 mmol, 1.0 eq.) was dissolved in DCM (2.0 mL), and 8-bromooctanoic acid (226.2 mg, 1.01 mmol, 1.3 eq.), EDCI (179.4 mg, 0.94 mmol, 1.2 eq.), and DMAP (42.9 mg, 1.17 mmol, 1.5 eq.) were added to the solution. The reaction liquid was stirred at room temperature for 3 h, the reaction liquid was poured into 10 mL of a saturated aqueous sodium chloride solution, and the mixture was extracted with 3 × 20 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 300 mg of a yellow oily compound 1b-2.

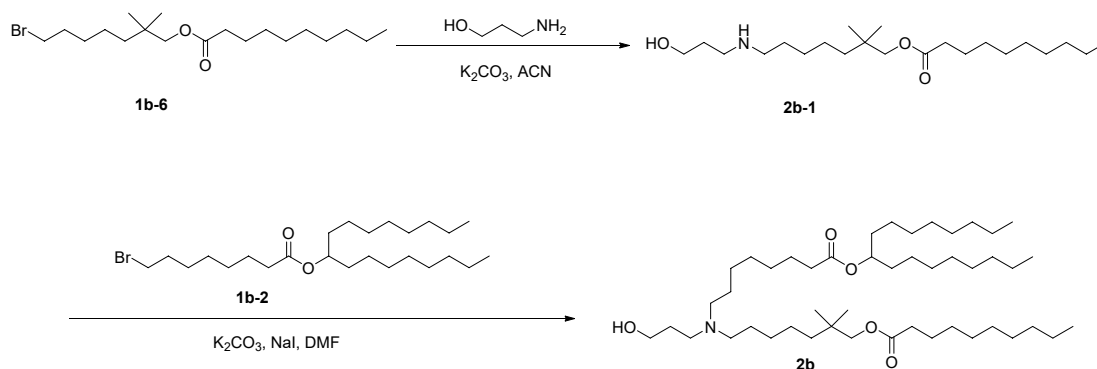
- [0910] Methyl isobutyrate (21 g, 205.0 mmol, 1.0 eq.) was dissolved in 200 mL of anhydrous THF, the mixture was cooled to 0 °C, and LDA (205 mL, 410.0 mmol, 2.0 eq.) was added to the reaction liquid under nitrogen atmosphere. The reaction was heated to room temperature. After stirring for 30 min, 1,5-dibromopentane (47 g, 205.0 mmol, 1.0 eq.) was added. After the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with 3 × 300 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 30 g of a yellow oily compound 1b-4.
- [0911] Compound 1b-4 (15.0 g, 40.0 mmol, 1.0 eq.) was dissolved in 30 mL of THF, the mixture was cooled to 0 °C, and a borane-tetrahydrofuran solution (1 M, 100.0 mL) was added dropwise to the reaction system under nitrogen atmosphere. The mixture was heated to 75 °C and stirred for reaction for 3 h. After the reaction was completed, the reaction system was cooled to room temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution, and the mixture was extracted with 3 × 300 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product of 1b-5 (13.6 g), which was directly used in the next step without purification.
- [0912] Caprinoyl chloride (11.0 g, 58.0 mmol, 1.3 eq.) was added to a solution of compound 1b-5 (10.0 g, 44.0 mmol, 1.0 eq.) in DCM (100 mL), triethylamine (13.5 g, 134.0 mmol, 3.0 eq.) was added to the reaction system, and the mixture was reacted at room temperature for 3 h. The reaction liquid was poured into 100 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 10 g of compound 1b-6.
- [0913] Potassium carbonate (1.5 g, 11.1 mmol, 3.0 eq.) and compound 1b-6 (1.4 g, 3.7 mmol, 1.0 eq.) were added to a solution of ethanolamine (2.3 g, 37.2 mmol, 10.0 eq.) in acetonitrile (15.0 mL). The mixture was heated to 70 °C and stirred for reaction for 3 h.

The reaction liquid was poured into 30 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 1.4 g of compound 1b-7. **¹H NMR** (300 MHz, CD₃Cl) δ : 0.85-0.89 (m, 9H), 1.20-1.26 (m, 21H), 1.59-1.62 (m, 4H), 2.29-2.34 (m, 2H), 2.73-2.76 (m, 2H), 2.87-2.91 (m, 2H), 3.72-3.77 (m, 3H).

[0914] Compound 1b-2 (300.0 mg, 0.84 mmol, 1.0 eq.) and compound 1b-7 (503.4 mg, 1.09 mmol, 1.3 eq.) were dissolved in DMF (3.0 mL), then potassium carbonate (289.9 mg, 2.1 mmol, 2.5 eq.) and sodium iodide (314.4 mg, 2.1 mmol, 2.5 eq.) were added, and the mixture was heated to 70 °C and stirred for reaction for 2 h. The reaction liquid was poured into 20 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give compound **1b** (158.9 mg).

[0915] **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 0.85-0.95 (m, 15H), 1.17-1.34 (m, 48H), 1.52-1.59 (m, 8H), 1.62-1.64 (m, 4H), 2.27-2.35 (m, 4H), 2.48-2.53 (m, 4H), 2.63 (t, *J* = 6.3 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 2H), 4.84-4.89 (m, 1H); **ESI-MS** *m/z*: 738.65 [M+H]⁺.

[0916] Example 31: Synthesis of Compound 2b



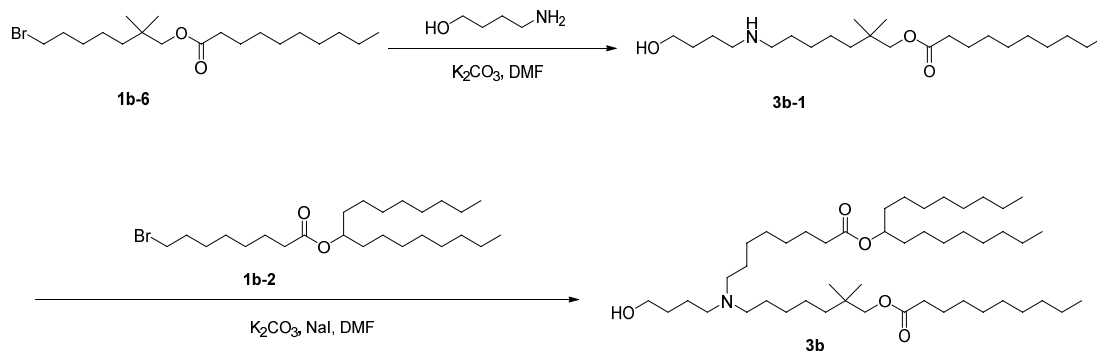
[0917] Potassium carbonate (549.3 mg, 4.0 mmol, 3.0 eq.) and compound 1b-6 (500.0 mg, 1.33 mmol, 1.0 eq.) were added to a solution of 3-amino-1-propanol (1.0 g, 13.3 mmol, 10.0 eq.) in acetonitrile (10.0 mL). The mixture was heated to 70 °C and stirred for reaction for 3 h. The reaction liquid was poured into 30 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous

sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 350 mg of a colorless oily compound 2b-1.

[0918] Compound 1b-2 (565 mg, 1.22 mmol, 1.3 eq.) and compound 2b-1 (350 mg, 0.94 mmol, 1.0 eq.) were dissolved in DMF (5.0 mL), then potassium carbonate (389 mg, 2.82 mmol, 3.0 eq.) and sodium iodide (353 mg, 2.35 mmol, 2.5 eq.) were added, and the mixture was heated to 70 °C and stirred for reaction for 5 h. The reaction liquid was poured into 20 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give compound **2b** (160 mg).

[0919] ¹H NMR (400 MHz, Methanol-*d*₄) δ: 0.85-0.95 (m, 15H), 1.20-1.40 (m, 48H), 1.62-1.70 (m, 12H), 1.72-1.78 (m, 2H), 2.28-2.35 (m, 4H), 2.60-2.66 (m, 4H), 2.74-2.79 (m, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.80 (s, 2H), 4.82-4.89 (m, 1H); ESI-MS *m/z*: 752.65 [M+H]⁺.

[0920] Example 32: Synthesis of Compound 3b

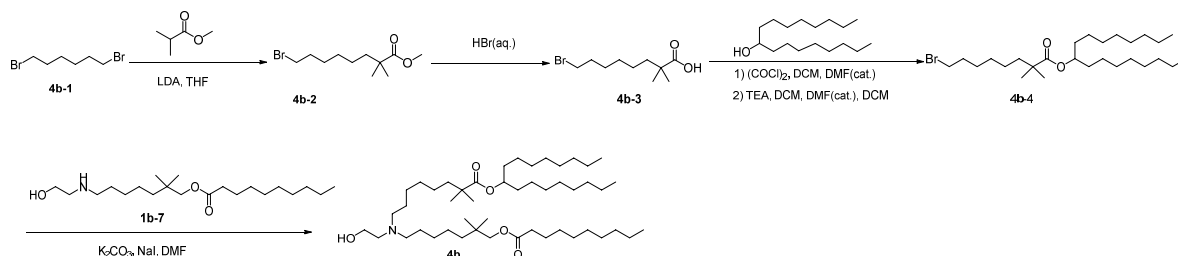


[0921] Potassium carbonate (549 mg, 4.0 mmol, 3.0 eq.) and compound 1b-6 (500 mg, 1.33 mmol, 1.0 eq.) were added to a solution of 4-amino-1-butanol (1.2 g, 13.3 mmol, 10.0 eq.) in DMF (10.0 mL). The mixture was heated to 70 °C and stirred for reaction for 3 h. The reaction liquid was poured into 30 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 300 mg of a colorless oily compound 3b-1.

[0922] Compound 1b-2 (462 mg, 1.0 mmol, 1.3 eq.) and compound 3b-1 (297 mg, 0.77 mmol, 1.0 eq.) were dissolved in DMF (5.0 mL), then potassium carbonate (269 mg, 1.9 mmol, 2.5 eq.) and sodium iodide (285 mg, 1.9 mmol, 2.5 eq.) were added, and the mixture was heated to 70 °C and stirred for reaction for 5 h. The reaction liquid was poured into 20 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give compound **3b** (228 mg).

[0923] **¹H NMR** (400 MHz, CDCl₃) δ: 0.80-0.90 (m, 15H), 1.25-1.40 (m, 48H), 1.49-1.66 (m, 8H), 1.74-1.81 (m, 8H), 2.24-2.37 (m, 4H), 2.47-2.58 (m, 6H), 3.56 (s, 2H), 3.77 (s, 2H), 4.81-4.88 (m, 1H); **ESI-MS** m/z: 766.85 [M+H]⁺.

[0924] Example 33: Synthesis of Compound 4b



[0925] Methyl isobutyrate (21 g, 205 mmol, 1.0 eq.) was dissolved in 200 mL of anhydrous THF, the mixture was cooled to 0 °C, and LDA (205 mL, 410 mmol, 2.0 eq.) was added to the reaction liquid under nitrogen atmosphere. The reaction was heated to room temperature. After stirring for 30 min, 1,6-dibromohexane (50 g, 205 mmol, 1.0 eq.) was added. After the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with 3 × 300 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 34 g of a yellow oily compound 4b-2. **¹H NMR** (400 MHz, CD₃Cl) δ: 1.05-1.52 (m, 14H), 1.78-1.91 (m, 2H), 3.36-3.42 (m, 2H), 3.71 (s, 3H).

[0926] Compound 4b-2 (10.0 g, 37.6 mmol, 1.0 eq.) was added to a hydrobromic acid aqueous solution (50.0 mL). The reaction liquid was heated to 100 °C and stirred for reaction for 24 h. After the reaction was completed, the reaction system was cooled to

room temperature. The reaction was quenched with a saturated aqueous sodium chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 7.4 g of a yellow oily compound 4b-3. ¹H NMR (400 MHz, CD₃Cl) δ: 1.19 (s, 6H), 1.25-1.28 (m, 4H), 1.30-1.56 (m, 4H), 1.80-1.89 (m, 2H), 3.37-3.42 (m, 2H).

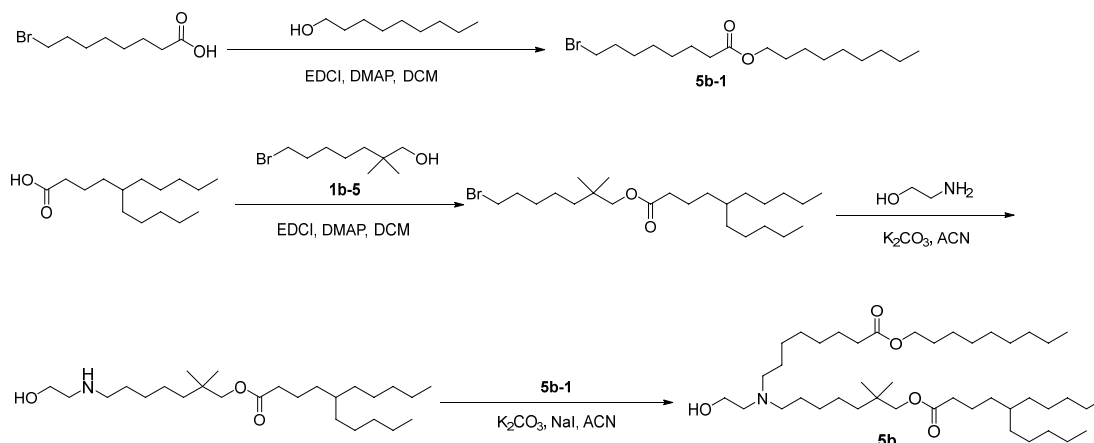
[0927] Compound 4b-3 (5.0 g, 19.9 mmol, 1.0 eq.) was dissolved in DCM (50.0 mL), and DMF (291.0 mg, 3.98 mmol, 0.2 eq.) and oxalyl chloride (5.1 g, 39.8 mmol, 2.0 eq.) were added to the reaction system under an ice bath. After the mixture was stirred for 30 min, the solvent was removed by rotary evaporation under reduced pressure to give an acyl chloride intermediate. The resulting acyl chloride was dissolved in DCM (50.0 mL), then 9-heptadecanol (4.08 g, 15.9 mmol, 0.8 eq.) and triethylamine (6.03 g, 59.7 mmol, 3.0 eq.) were added, and the mixture was reacted at room temperature overnight. After the reaction was completed, the reaction liquid was poured into 300 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 4.3 g of an oily compound 4b-4.

[0928] To a solution of compound 4b-4 (492.9 mg, 1.0 mmol, 1.2 eq.) in DMF (3.0 mL) were added potassium carbonate (347.8 mg, 2.5 mmol, 3.0 eq.), sodium iodide (314.4 mg, 2.1 mmol, 2.5 eq.), and compound 1b-7 (300.0 mg, 0.8 mmol, 1.0 eq.). The reaction liquid was heated to 70 °C and stirred for reaction for 2 h. After the reaction was completed, the reaction system was cooled to room temperature. The reaction was quenched with a saturated aqueous sodium chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by preparative liquid chromatography to give 106 mg of compound 4b. (Column model: XBridge Shield RP18 OBD Column 19 × 150 mm, 5 μm; mobile phase A: acetonitrile: water (10 mmol/L ammonium bicarbonate + 0.05% aqueous ammonia), mobile phase B: isopropanol: acetonitrile; flow rate: 20

mL/min; gradient: the proportion of mobile phase B was gradually increased from 75% B to 95% B within 9 min).

[0929] **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 0.85-0.95 (m, 15H), 1.15 (s, 6H), 1.20-1.40 (m, 48H), 1.47-1.54 (m, 10H), 1.60-1.64 (m, 2H), 2.31-2.34 (m, 2H), 2.47-2.51 (m, 4H), 2.61 (t, *J* = 6.4 Hz, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.80 (s, 2H), 4.81-4.88 (m, 1H); **ESI-MS** *m/z*: 766.70 [M+H]⁺.

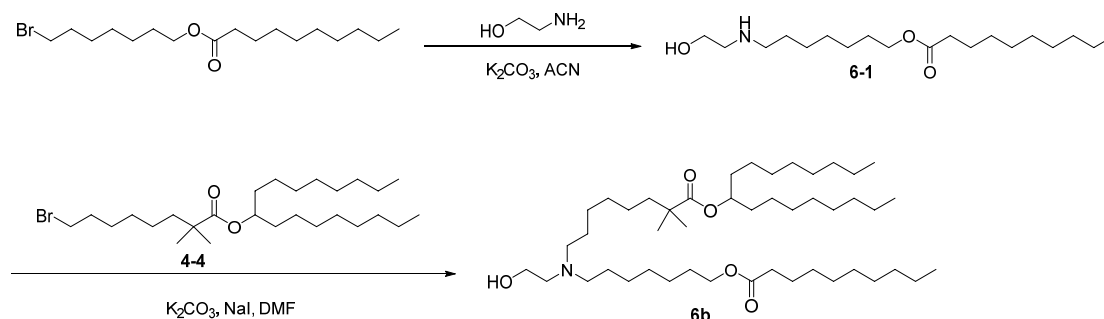
[0930] Example 34: Synthesis of Compound 5b



[0931] Compound **5b** was prepared referring to the method of Example 30 to give 174 mg of an oily product.

[0932] **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 0.85-0.95 (m, 15H), 1.20-1.40 (m, 43H), 1.50-1.60 (m, 4H), 1.61-1.70 (m, 7H), 2.28-2.33 (m, 4H), 2.48-2.64 (m, 5H), 3.51-3.63 (m, 2H), 3.80 (s, 2H), 4.04-4.08 (m, 2H); **ESI-MS** *m/z*: 696.60 [M+H]⁺.

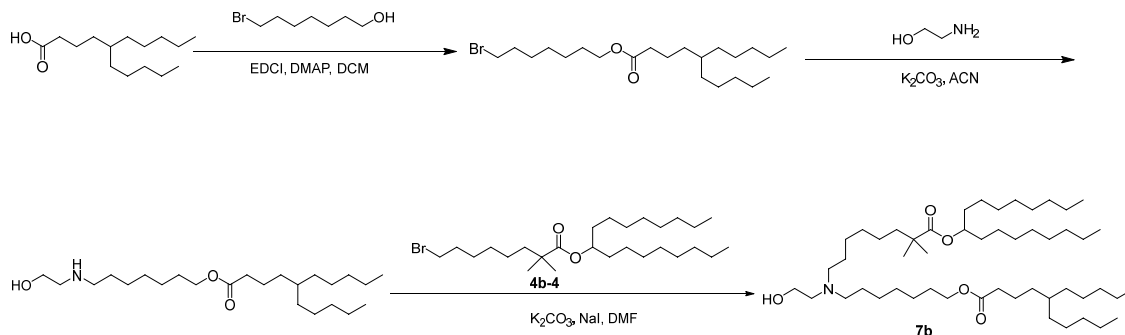
[0933] Example 35: Synthesis of Compound 6b



[0934] Compound **6b** was prepared referring to the method of Example 30 to give 113 mg of an oily product.

[0935] **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 0.85-0.95 (m, 9H), 1.25 (s, 6H), 1.35-1.55 (m, 48H), 1.58-1.65 (m, 14H), 2.27-2.32 (m, 2H), 2.46-2.51 (m, 4H), 2.58-2.62 (m, 2H), 3.58-3.64 (m, 2H), 4.04-4.08 (m, 2H), 4.83-4.87 (m, 1H); **ESI-MS** *m/z*: 738.65 [M+H]⁺.

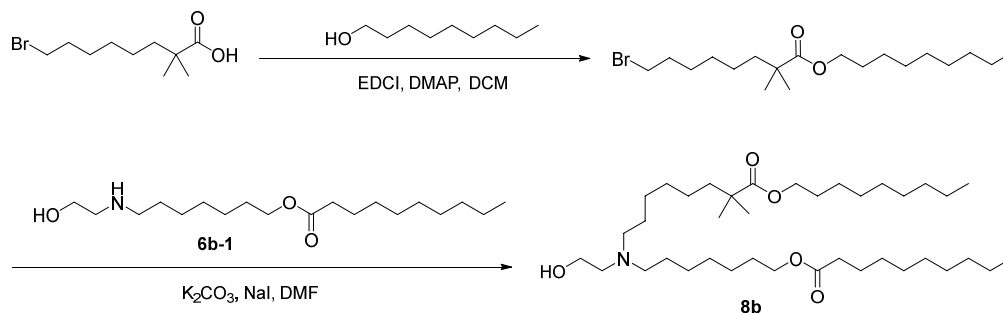
[0936] Example 36: Synthesis of Compound 7b



[0937] Compound **7b** was prepared referring to the method of Example 30 to give 91 mg of an oily product.

[0938] **¹H NMR** (400 MHz, CDCl₃) δ : 0.85-0.90 (m, 12H), 1.14 (s, 6H), 1.23-1.49 (m, 56H), 1.56-1.64 (m, 14H), 2.24-2.29 (m, 2H), 2.51-2.65 (m, 5H), 3.60 (s, 2H), 4.03-4.07 (m, 2H), 4.80-4.84 (m, 1H); **ESI-MS** *m/z*: 809.05 [M+H]⁺.

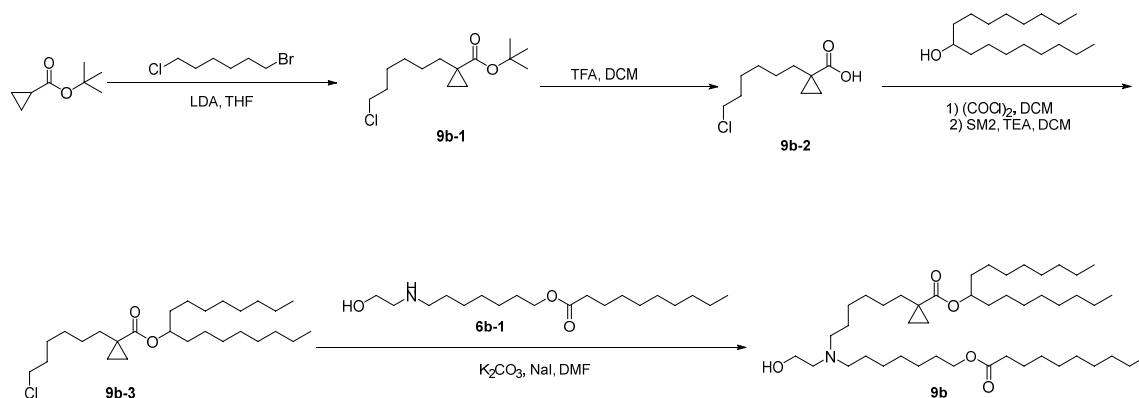
[0939] Example 37: Synthesis of Compound 8b



[0940] Compound **8b** was prepared referring to the method of Example 30 to give 124 mg of an oily product.

[0941] **¹H NMR** (400 MHz, CDCl₃) δ : 0.85-0.95 (m, 6H), 1.27-1.49 (m, 42H), 1.52-1.63 (m, 12H), 2.26-2.31 (m, 2H), 2.52-2.57 (m, 4H), 2.65-2.68 (m, 2H), 3.47-3.64 (m, 2H), 4.01-4.07 (m, 4H); **ESI-MS** *m/z*: 626.65 [M+H]⁺.

[0942] Example 38: Synthesis of Compound 9b



[0943] *tert*-Butyl cyclopropanecarboxylate (15.0 g, 150.0 mmol, 1.0 eq.) was dissolved in 150 mL of anhydrous tetrahydrofuran, and the mixture was cooled to -60 °C. LDA (150.0 mL, 300.0 mmol, 2.0 eq.) was added to the reaction liquid under nitrogen atmosphere. After the mixture was stirred at the same temperature for reaction for 1 h, 1-bromo-6-chlorohexane (44.9 g, 225.0 mmol, 1.5 eq.) was added, and the mixture was stirred at room temperature for reaction for another 3 h. After the reaction was completed as monitored by TLC, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the mixture was extracted with 3 × 300 mL of DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 19 g of a colorless oily compound 9b-1.

[0944] To a solution of compound 9b-1 (10.0 g, 38.3 mmol) in DCM (30.0 mL) was added 10.0 mL of trifluoroacetic acid, and the mixture was stirred at room temperature for 3 h. The reaction solvent was removed by pressurized rotary evaporation to give a crude product, which was purified by silica gel column chromatography to give 6.9 g of a colorless oily compound 9b-2.

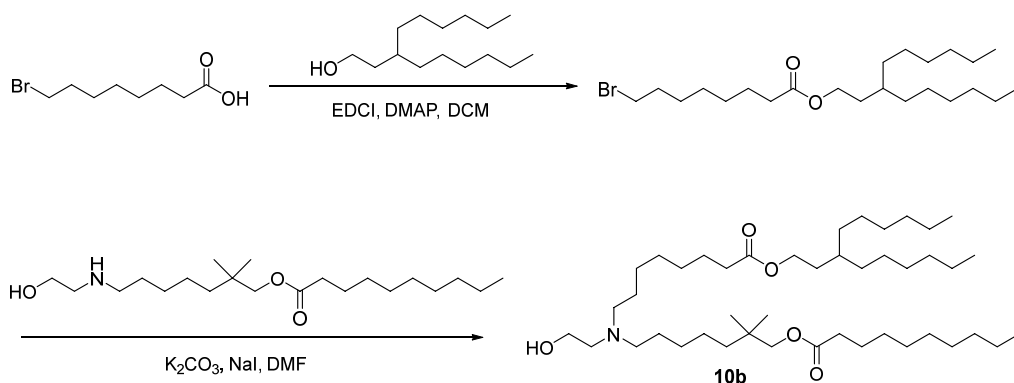
[0945] Compound 9b-2 (500.0 mg, 2.45 mmol, 2.0 eq.) was dissolved in DCM (5.0 mL), and 2-3 drops of DMF and oxalyl chloride (311.1 mg, 2.45 mmol, 2.0 eq.) were added to the reaction system under an ice bath. After the mixture was stirred for 30 min, the solvent was removed by rotary evaporation under reduced pressure to give an acyl chloride intermediate. The resulting acyl chloride was dissolved in DCM (5.0 mL), then 9-heptadecanol (312.3 mg, 1.22 mmol, 1.0 eq.) and triethylamine (247.5 mg, 2.45 mmol,

2.0 eq.) were added, and the mixture was reacted at room temperature for 5 h. After the reaction was completed, the reaction liquid was poured into 50 mL of water, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 240 mg of an oily compound 9b-3.

[0946] To a solution of compound 9b-3 (200.0 mg, 0.45 mmol, 1.5 eq.) in DMF (3.0 mL) were added potassium carbonate (124.2 mg, 0.90 mmol, 3.0 eq.), sodium iodide (112.5 mg, 0.75 mmol, 2.5 eq.), and compound 6b-1 (99.0 mg, 0.30 mmol, 1.0 eq.). The reaction liquid was heated to 70 °C and stirred for reaction for 5 h. After the reaction was completed, the reaction system was cooled to room temperature. The reaction was quenched with a saturated aqueous sodium chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by preparative liquid chromatography to give 85.4 mg of compound 9b. (Column model: XBridge Shield RP18 OBD Column 19 × 150 mm, 5 μm; mobile phase A: acetonitrile: water (10 mmol/L ammonium bicarbonate + 0.05% aqueous ammonia), mobile phase B: isopropanol: acetonitrile; flow rate: 20 mL/min; gradient: 75% B to 95% B in 9 min).

[0947] **¹H NMR** (400 MHz, CDCl₃) δ: 0.60-0.70 (m, 2H), 0.85-0.95 (m, 9H), 1.13-1.31 (m, 48H), 1.46-1.48 (m, 12H), 1.57-1.63 (m, 4H), 2.26-2.31 (m, 2H), 2.42-2.47 (m, 4H), 2.56-2.59 (m, 2H), 3.50-3.54 (m, 2H), 4.03-4.07 (m, 2H), 4.80-4.84 (m, 1H); **ESI-MS** m/z: 736.65 [M+H]⁺.

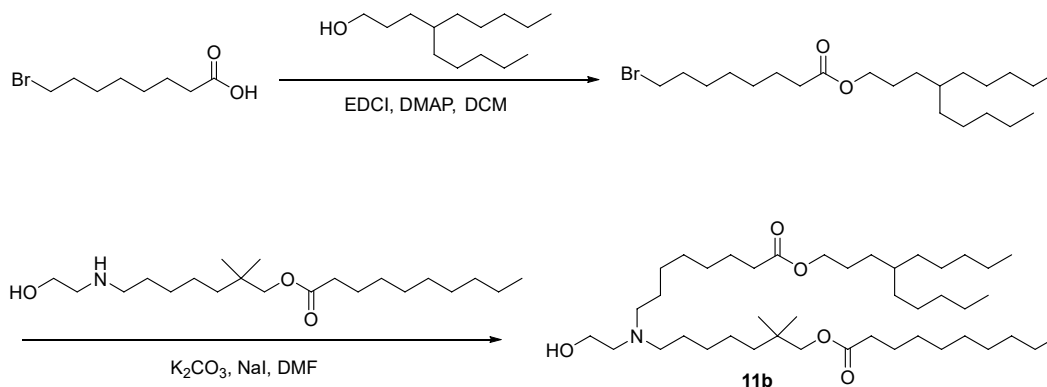
[0948] Example 39: Synthesis of Compound 10b



[0949] Compound **10b** was prepared referring to the method of Example 30 to give 128 mg of an oily product.

[0950] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 0.85-0.95 (m, 15H), 1.12-1.36 (m, 43H), 1.40-1.63 (m, 12H), 2.26-2.31 (m, 4H), 2.42-2.65 (m, 6H), 3.50-3.54 (m, 2H), 3.78 (s, 2H), 4.08 (t, $J = 7.2$ Hz, 2H); **ESI-MS** m/z : 710.80 $[\text{M}+\text{H}]^+$.

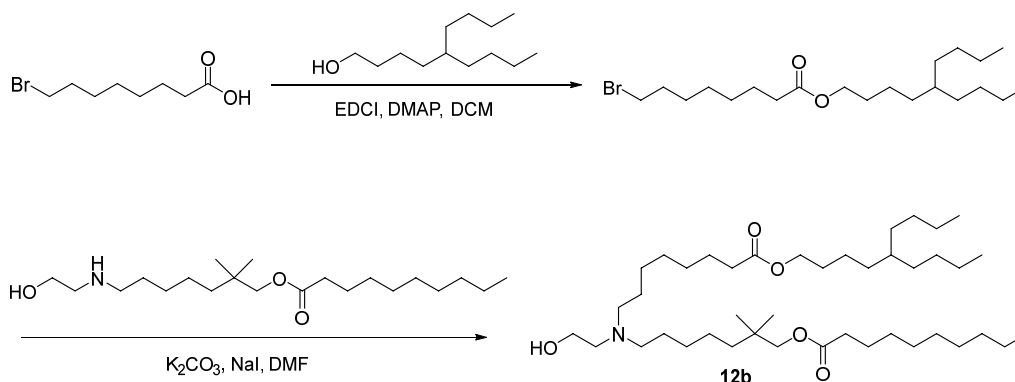
[0951] Example 40: Synthesis of Compound 11b



[0952] Compound **11b** was prepared referring to the method of Example 30 to give 92 mg of an oily product.

[0953] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 0.83-0.94 (m, 15H), 1.18-1.42 (m, 43H), 1.48-1.67 (m, 10H), 2.28-2.35 (m, 4H), 2.46-2.52 (m, 4H), 2.61 (t, $J = 6.6$ Hz, 2H), 3.61 (t, $J = 6.6$ Hz, 2H), 3.80 (s, 2H), 4.05 (t, $J = 6.6$ Hz, 2H); **ESI-MS** m/z : 696.60 $[\text{M}+\text{H}]^+$.

[0954] Example 41: Synthesis of Compound 12b



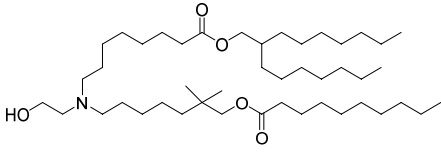
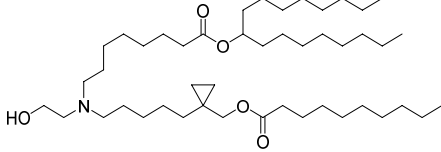
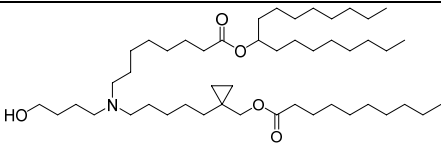
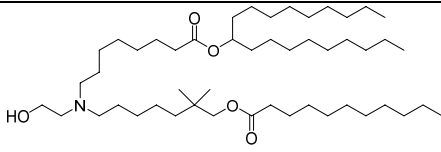
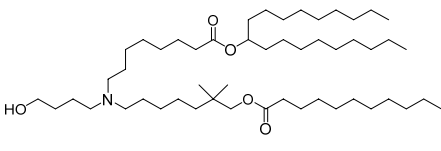
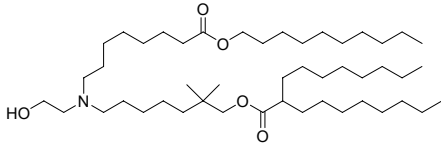
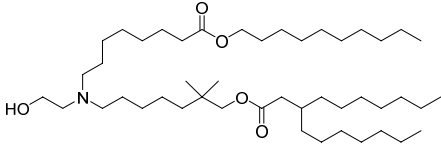
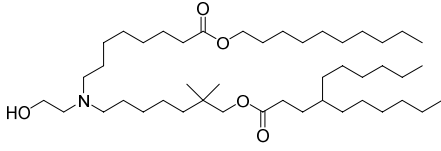
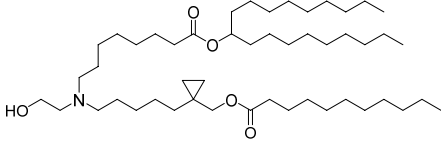
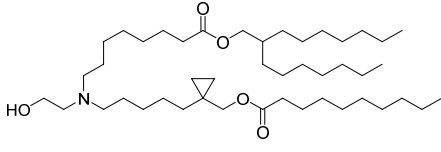
[0955] Compound **12b** was prepared referring to the method of Example 30 to give 105 mg of an oily product.

[0956] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 0.85-0.95 (m, 15H), 1.19-1.34 (m, 41H), 1.42-1.58 (m, 4H), 1.59-1.63 (m, 6H), 2.23 (q, $J = 7.6$ Hz, 4H), 2.53 (q, $J = 7.6$ Hz, 4H), 2.62

(q, $J = 7.6$ Hz, 2H), 3.62 (t, $J = 6.4$ Hz, 2H), 3.80 (s, 2H), 4.07 (t, $J = 6.4$ Hz, 2H); **ESI-MS** m/z : 682.60 $[M+H]^+$.

[0957] The compounds in Table 3 were synthesized using the methods of the above examples, or using similar methods of the corresponding intermediates.

Table 3

 Example 42: Compound 13b $[M+H]^+$: 724.80	 Example 43: Compound 14b $[M+H]^+$: 736.70
 Example 44: Compound 15b $[M+H]^+$: 764.70	 Example 45: Compound 16b $[M+H]^+$: 780.80
 Example 46: Compound 17b $[M+H]^+$: 808.80	 Example 47: Compound 18b $[M+H]^+$: 752.85
 Example 48: Compound 19b $[M+H]^+$: 738.65	 Example 49: Compound 20b $[M+H]^+$: 724.80
 Example 50: Compound 21b $[M+H]^+$: 778.75	 Example 51: Compound 22b $[M+H]^+$: 722.75

by rotary evaporation to give a crude compound 1a-6, which was directly used in the next step without purification.

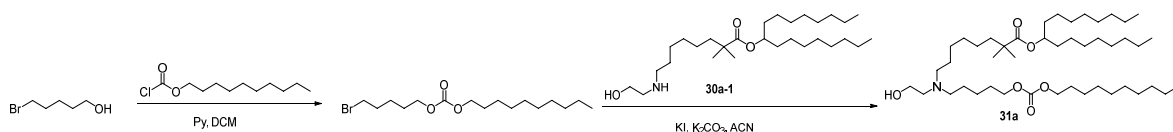
[0961] Compound 1a-6 (15 g, 30.6 mmol, 1.0 eq.) and ethanolamine (37.4 g, 612.0 mmol, 20.0 eq.) were dissolved in 80 mL of ethanol, and the reaction system was heated to 60 °C and reacted for 2 h. After the reaction was completed, the reaction system was cooled to room temperature, the ethanol solvent was removed by rotary evaporation, the crude product was dissolved in ethyl acetate, and then a saturated sodium chloride solution was added. After extraction, the organic phases were combined, dried over anhydrous Na₂SO₄, and filtered to remove the drying agent, and the solvent was removed by rotary evaporation. The resulting crude product was purified by silica gel column chromatography to give a yellow oily compound 30a-1 (12.4 g).

[0962] In a 50 mL reaction flask, 6-bromo-1-hexanol (1.5 g, 8.3 mmol, 1.0 eq.) and pyridine (1.31 g, 16.6 mmol, 2.0 eq.) were dissolved in 15 mL of DCM, *n*-nonyl chloroformate (1.88 g, 9.1 mmol, 1.1 eq.) was added dropwise within 15 min under an ice bath, and the mixture was left at room temperature overnight. A saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with DCM. The organic phases were combined, dried over anhydrous Na₂SO₄, and filtered to remove the drying agent, and the solvent was removed by rotary evaporation. The resulting crude product was purified by silica gel column chromatography to give a yellow oily compound 30a-4 (2.5 g).

[0963] In an 8 mL sealed tube, compound 30a-4 (200 mg, 0.57 mmol, 1.0 eq.), compound 30a-1 (294.2 mg, 0.63 mmol, 1.1 eq.), KI (113.4 mg, 0.68 mmol, 1.2 eq.), K₂CO₃ (236.0 mg, 1.71 mmol, 3.0 eq.), and 5.0 mL of anhydrous acetonitrile were added. The mixture was heated to 80 °C, stirred for reaction overnight, cooled to room temperature, and filtered. After the filter cake was washed with acetonitrile, the organic phases were combined, and the solvent was removed by rotary evaporation to give a reaction crude product. The crude product was purified by preparative liquid chromatography to give compound 30a (87.9 mg).

[0964] ¹H NMR (400 MHz, CDCl₃) δ: 4.83 (m, 1H), 4.12 (t, *J* = 6.6 Hz, 4H), 3.61 (m, 2H), 2.62 (m, 6H), 1.70–1.63 (m, 4H), 1.50 (m, 8H), 1.26 (m, 49H), 1.15 (s, 6H), 0.88 (t, *J* = 6.6 Hz, 9H); ESI-MS *m/z*: 740.55 [M+H]⁺.

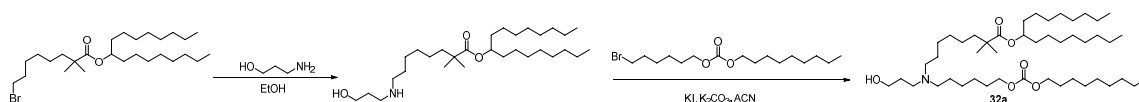
[0965] Example 55: Synthesis of Compound 31a



[0966] Compound 31a was prepared referring to the method of Example 54 to give 80.7 mg of an oily product.

[0967] **¹H NMR** (400 MHz, CDCl₃) δ : 4.83 (p, J = 6.6 Hz, 1H), 4.12 (td, J = 7.2, 2.4 Hz, 4H), 3.61 (m, 2H), 2.61 (m, 6H), 1.68 (m, 4H), 1.50 (m, 8H), 1.26 (m, 49H), 1.15 (s, 6H), 0.88 (t, J = 6.6 Hz, 9H); **ESI-MS** m/z : 740.65 [M+H]⁺.

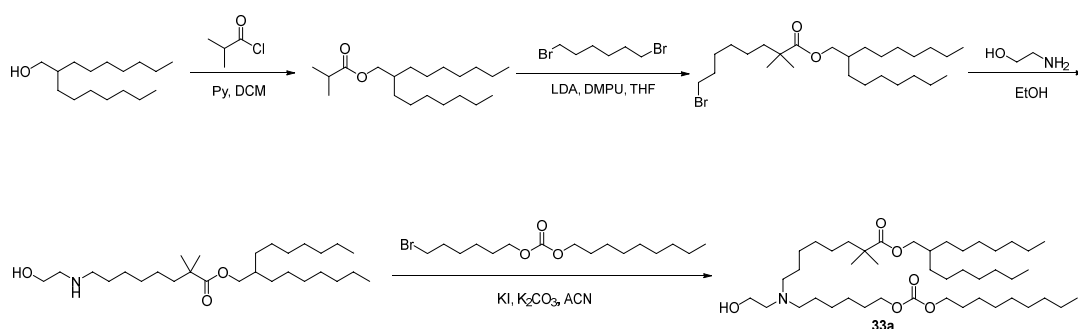
[0968] Example 56: Synthesis of Compound 32a



[0969] Compound 32a was prepared referring to the method of Example 54 to give 93.9 mg of an oily product.

[0970] **¹H NMR** (300 MHz, CDCl₃) δ : 4.85 (p, J = 6.6 Hz, 1H), 4.12 (t, J = 6.6 Hz, 4H), 3.79 (t, J = 5.1 Hz, 2H), 2.65 (m, 2H), 2.42 (m, 4H), 1.77-1.64 (m, 6H), 1.51 (t, J = 6.0 Hz, 10H), 1.28 (d, J = 4.5 Hz, 47H), 1.17 (s, 6H), 0.88 (t, J = 6.6 Hz, 9H); **ESI-MS** m/z : 754.60 [M+H]⁺.

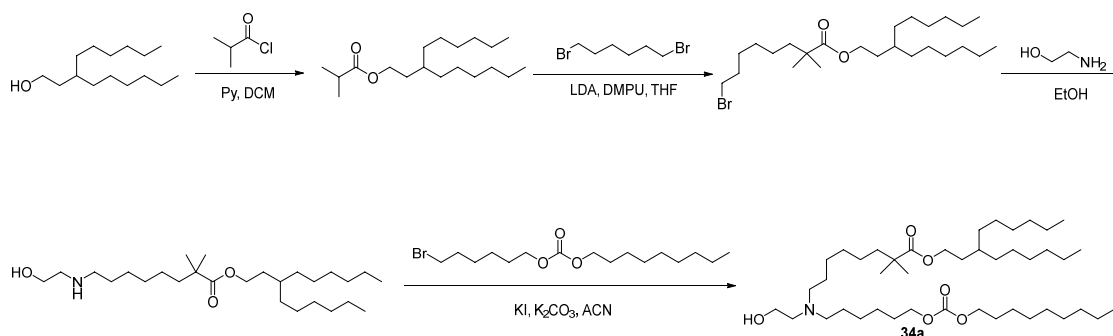
[0971] Example 57: Synthesis of Compound 33a



[0972] Compound 33a was prepared referring to the method of Example 54 to give 164.2 mg of an oily product.

[0973] **¹H NMR** (400 MHz, CDCl₃) δ : 4.12 (t, J = 6.8 Hz, 4H), 3.95 (d, J = 5.6 Hz, 2H), 3.54 (t, J = 5.2 Hz, 2H), 2.59 (t, J = 5.2 Hz, 2H), 2.50-2.41 (m, 4H), 1.67 (m, 5H), 1.53 - 1.19 (m, 53H), 1.16 (s, 6H), 0.88 (t, J = 6.8 Hz, 9H); **ESI-MS** m/z : 726.50 [M+H]⁺.

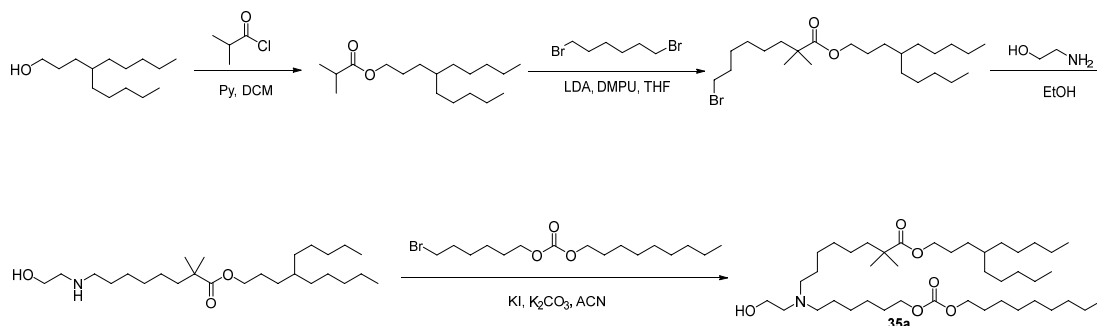
[0974] Example 58: Synthesis of Compound 34a



[0975] Compound 34a was prepared referring to the method of Example 54 to give 150.1 mg of an oily product.

[0976] **¹H NMR** (400 MHz, CDCl₃) δ : 4.12 (t, J = 6.8 Hz, 4H), 4.08 (t, J = 6.8 Hz, 2H), 3.56 (m, 2H), 2.61-2.48 (m, 6H), 1.66 (m, 5H), 1.61-1.26 (m, 51H), 1.15 (s, 6H), 0.88 (t, J = 6.8 Hz, 9H); **ESI-MS** m/z : 712.60 [M+H]⁺.

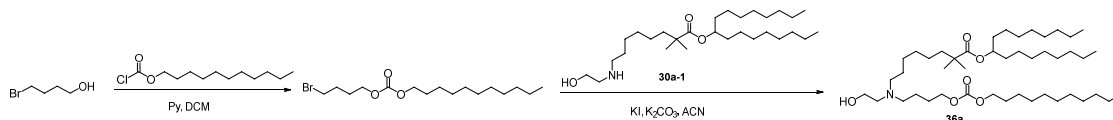
[0977] Example 59: Synthesis of Compound 35a



[0978] Compound 35a was prepared referring to the method of Example 54 to give 217.9 mg of an oily product.

[0979] **¹H NMR** (400 MHz, CDCl₃) δ : 4.12 (t, J = 6.8 Hz, 4H), 4.03 (t, J = 6.8 Hz, 2H), 3.53 (t, J = 5.2 Hz, 2H), 2.58 (t, J = 5.2 Hz, 2H), 2.47-2.40 (m, 4H), 1.73-1.62 (m, 6H), 1.60-1.19 (m, 48H), 1.16 (s, 6H), 0.88 (t, J = 6.8 Hz, 9H); **ESI-MS** m/z : 698.55 [M+H]⁺.

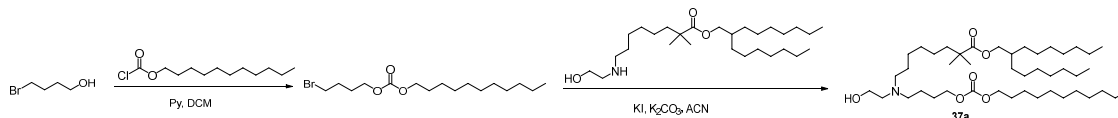
[0980] Example 60: Synthesis of Compound 36a



[0981] Compound 36a was prepared referring to the method of Example 54 to give 169.7 mg of an oily product.

[0982] **¹H NMR** (300 MHz, CDCl₃) δ : 4.83 (p, J = 6.6 Hz, 1H), 4.16-4.10 (m, 4H), 3.53 (t, J = 5.1 Hz, 2H), 2.58 (t, J = 5.1 Hz, 2H), 2.52-2.42 (m, 4H), 1.67 (m, 4H), 1.59-1.18 (m, 57H), 1.15 (s, 6H), 0.89 (t, J = 6.6 Hz, 9H); **ESI-MS** m/z : 740.60 [M+H]⁺.

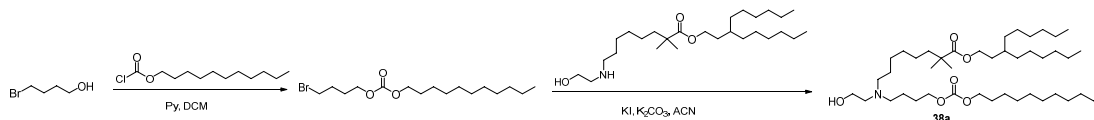
[0983] Example 61: Synthesis of Compound 37a



[0984] Compound 37a was prepared referring to the method of Example 54 to give 59.4 mg of an oily product.

[0985] **¹H NMR** (400 MHz, CDCl₃) δ : 4.12 (q, J = 6.8 Hz, 4H), 3.95 (d, J = 5.2 Hz, 2H), 3.58 (m, 2H), 2.64-2.51 (m, 6H), 1.74-1.43 (m, 12H), 1.39-1.19 (m, 46H), 1.16 (s, 6H), 0.88 (t, J = 6.8 Hz, 9H); **ESI-MS** m/z : 726.50 [M+H]⁺.

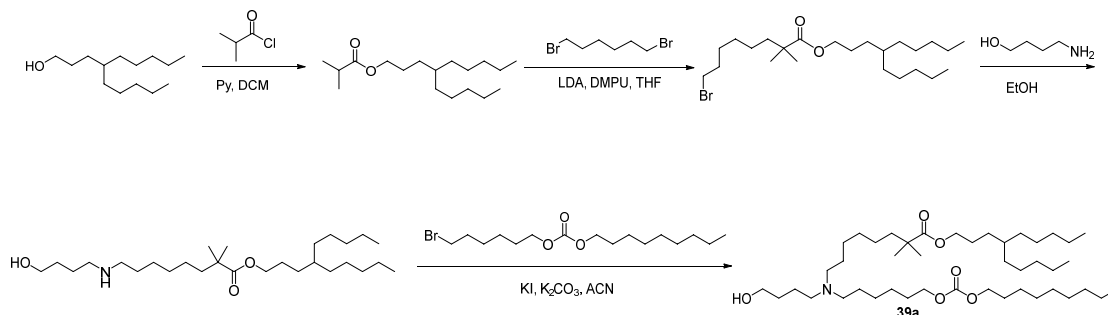
[0986] Example 62: Synthesis of Compound 38a



[0987] Compound 38a was prepared referring to the method of Example 54 to give 44.8 mg of an oily product.

[0988] **¹H NMR** (300 MHz, CDCl₃) δ : 4.16-4.04 (m, 6H), 3.62 (m, 2H), 2.69-2.58 (m, 6H), 1.74-1.41 (m, 12H), 1.39-1.18 (m, 44H), 1.15 (s, 6H), 0.92-0.87 (m, 9H); **ESI-MS** m/z : 712.55 [M+H]⁺.

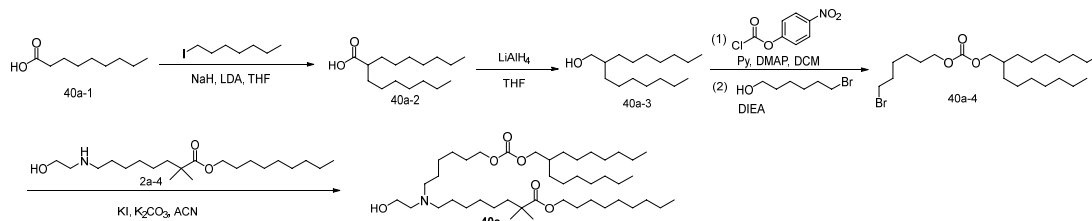
[0989] Example 63: Synthesis of Compound 39a



[0990] Compound 39a was prepared referring to the method of Example 54 to give 105.4 mg of an oily product.

[0991] **¹H NMR** (400 MHz, CDCl₃) δ : 4.13-4.10 (m, 4H), 4.03 (t, J = 6.8 Hz, 2H), 3.56 (m, 2H), 2.46 (m, 6H), 1.73-1.67 (m, 8H), 1.64-1.19 (m, 50H), 1.15 (s, 6H), 0.88 (m, 9H); **ESI-MS** m/z : 726.50 [M+H]⁺.

[0992] Example 64: Synthesis of Compound 40a



[0993] In a 500 mL round-bottom flask, nonanoic acid (15.0 g, 94.8 mmol, 1.0 eq.) and THF (150 mL), were added at room temperature under nitrogen atmosphere. The system was cooled to 0 °C, NaH (3.64 g, 151.7 mmol, 1.6 eq.) was sequentially added in batches, and LDA (85.3 mL, 170.6 mmol, 1.8 eq., 2 M in THF) was added dropwise. The mixture was stirred at room temperature for 1 h, and 1-iodoheptane (23.6 g, 104.3 mmol, 1.1 eq.) was added to the system at 0 °C. The system was stirred at 80 °C overnight. The reaction was monitored by TLC, and a new spot of the product was found. The reaction was cooled to room temperature, ice water was added to quench the reaction, and the mixture was extracted 3 times with DCM. The organic phases were combined and washed once with a saturated NaCl solution, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography to give yellow oily 2-heptylnonanoic acid (16.36 g).

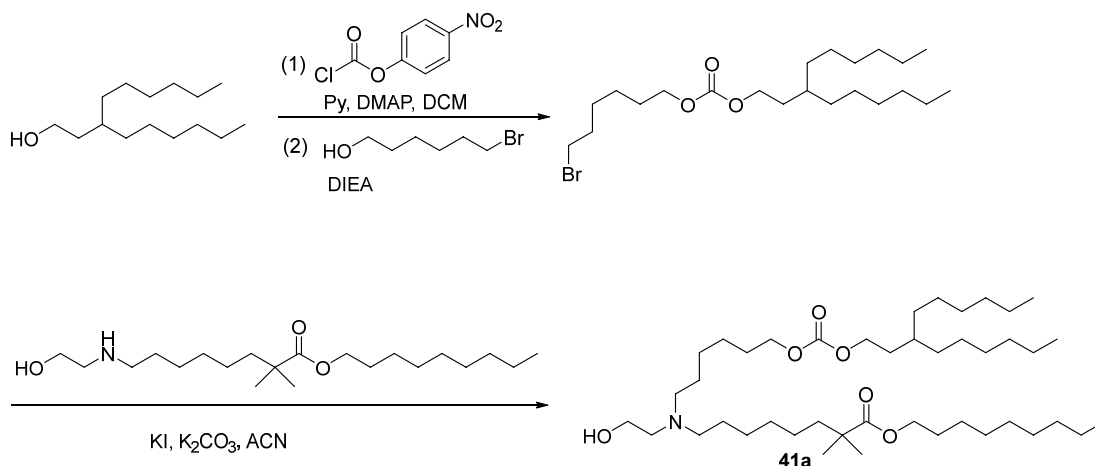
[0994] In a 250 mL round-bottom flask, 2-heptylnonanoic acid (7.0 g, 27.3 mmol, 1.0 eq.) was dissolved in 70 mL of anhydrous THF at room temperature, the system was cooled to 0 °C, and LiAlH₄ (16.38 mL, 2.5 M in THF) was added dropwise within 30 min. After the dropwise addition was completed, the mixture was warmed to room temperature and stirred for 2 h. The reaction was monitored by TLC, and the conversion of the starting material was completed. The reaction liquid was poured into a saturated sodium chloride solution to quench the reaction, the mixture was extracted with ethyl acetate, and the organic phases were combined, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography to give a light yellow oily product of 2-heptylnonanol (6.97 g).

[0995] In a 50 mL three-neck round-bottom flask, 2-heptylnonanol (400 mg, 1.65 mmol, 1.0 eq.), pyridine (261.0 mg, 3.30 mmol, 2.0 eq.), DMAP (40.3 mg, 0.33 mmol, 0.2 eq.), *p*-nitrophenyl chloroformate (399.0 mg, 1.98 mmol, 1.2 eq.), and DCM (4 mL) were added at room temperature. The reaction system was stirred at room temperature for 1 h. Thereafter, 6-bromo-1-hexanol (896.2 mg, 4.95 mmol, 3.0 eq.) and DIEA (639.7 mg, 4.95 mmol, 3.0 eq.) were added to the reaction system. The system was stirred at room temperature overnight. The mixture was diluted with DCM (4 mL) and washed once with a saturated sodium bicarbonate solution (6 mL). The organic phase was washed once with saturated NaCl (5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography to give a light yellow oily carbonate intermediate compound 40a-4 (325 mg).

[0996] In an 8 mL sealed tube, compound 40a-4 (250 mg, 0.56 mmol, 1.0 eq.) obtained in the previous step, compound 2a-4 (179.0 mg, 0.50 mmol, 0.9 eq.), potassium iodide (110.8 mg, 0.67 mmol, 1.2 eq.), potassium carbonate (230.6 mg, 1.68 mmol, 3.0 eq.), and acetonitrile (2.5 mL) were added at room temperature. The mixture was heated to 80 °C and stirred for reaction overnight. The reaction was monitored by LC-MS, and the reaction system was cooled to room temperature. The mixture was filtered, concentrated, and purified by Prep-HPLC to give a light yellow oily product of compound 40a (84.3 mg).

[0997] **¹H NMR** (400 MHz, CDCl₃) δ: 4.14 (t, *J* = 6.8 Hz, 2H), 4.06 (dd, *J* = 8.0, 6.0 Hz, 4H), 3.60 (m, 2H), 2.65-2.53 (m, 6H), 1.73-1.60 (m, 12H), 1.42-1.22 (m, 46H), 1.18 (s, 6H), 0.90 (t, *J* = 6.8 Hz, 9H); **ESI-MS** *m/z*: 726.50 [M+H]⁺.

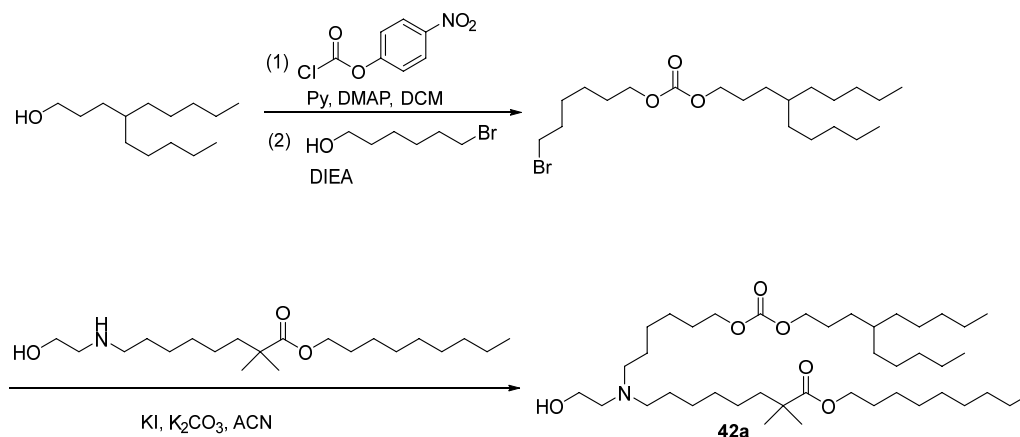
[0998] Example 65: Synthesis of Compound 41a



[0999] Compound 41a was prepared referring to the method of Example 64 to give 113.3 mg of an oily product.

[1000] **¹H NMR** (400 MHz, CDCl₃) δ : 4.14 (td, J = 9.2, 6.8 Hz, 4H), 4.06 (t, J = 6.8 Hz, 2H), 3.57 (m, 2H), 2.62-2.49 (m, 6H), 1.71-1.63 (m, 6H), 1.57-1.22 (m, 50H), 1.17 (s, 6H), 0.90 (t, J = 6.8 Hz, 9H); **ESI-MS** m/z : 712.55 [M+H]⁺.

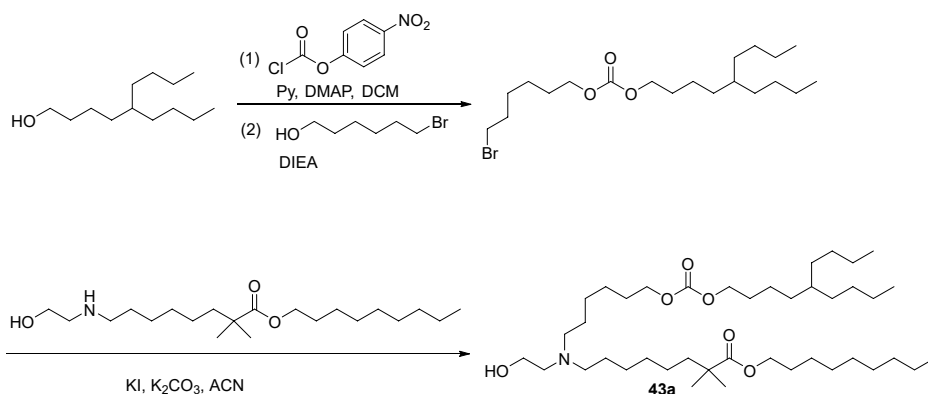
[1001] Example 66: Synthesis of Compound 42a



[1002] Compound 42a was prepared referring to the method of Example 64 to give 124.2 mg of an oily product.

[1003] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (td, J = 6.6, 4.8 Hz, 4H), 4.04 (t, J = 6.6 Hz, 2H), 3.55 (t, J = 5.7 Hz, 2H), 2.60-2.47 (m, 6H), 1.72-1.62 (m, 6H), 1.59-1.19 (m, 48H), 1.15 (s, 6H), 0.93-0.83 (m, 9H); **ESI-MS** m/z : 698.55 [M+H]⁺.

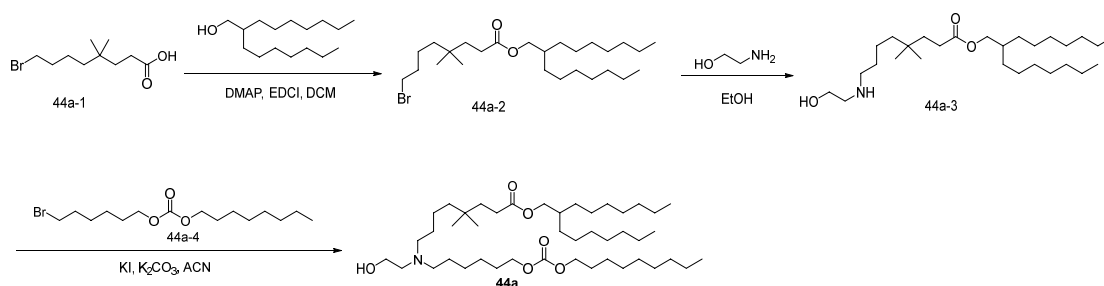
[1004] Example 67: Synthesis of Compound 43a



[1005] Compound 43a was prepared referring to the method of Example 64 to give 97.7 mg of an oily product.

[1006] ¹H NMR (400 MHz, CDCl₃) δ: 4.15 (td, *J* = 6.8, 1.6 Hz, 4H), 4.06 (t, *J* = 6.8 Hz, 2H), 3.64 (m, 2H), 2.68-2.56 (m, 6H), 1.76-1.60 (m, 8H), 1.54-1.22 (m, 44H), 1.18 (s, 6H), 0.96-0.86 (m, 9H); ESI-MS *m/z*: 684.45 [M+H]⁺.

[1007] Example 68: Synthesis of Compound 44a

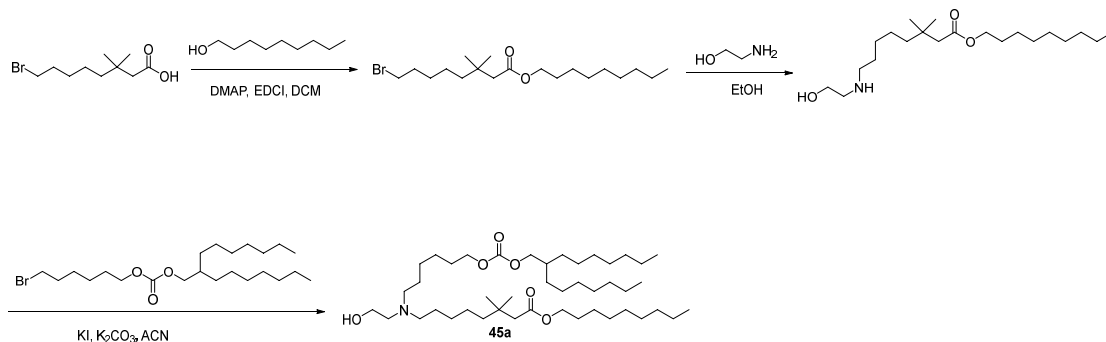


[1008] In a 20 mL round-bottom flask, compound 44a-1 (587.58 mg, 2.34 mmol, 1.2 eq.), 2-heptylnonan-1-ol (500 mg, 1.95 mmol, 1.0 eq.), EDCI (560.58 mg, 2.93 mmol, 1.5 eq.), and DMAP (47.63 mg, 0.39 mmol, 0.2 eq.) were dissolved in 5 mL of dichloromethane, and the mixture was reacted at room temperature overnight. After the reaction was completed, a saturated aqueous sodium chloride solution was added to quench the reaction, the mixture was extracted with dichloromethane, and the organic phases were combined, dried over Na₂SO₄, filtered, and concentrated to give 1 g of crude 44a-2, which was directly used in the subsequent reaction.

[1009] Compound 44a was prepared referring to the method of Example 54 to give 165.3 mg of an oily product.

[1010] **¹H NMR** (400 MHz, CDCl₃) δ : 4.12 (t, J = 6.8 Hz, 4H), 3.96 (d, J = 5.6 Hz, 2H), 3.59 (m, 2H), 2.53-2.42 (m, 6H), 2.26-2.20 (m, 2H), 1.70-1.63 (m, 7H), 1.56-1.19 (m, 49H), 0.92-0.83 (m, 15H); **ESI-MS** m/z : 726.50 [M+H]⁺.

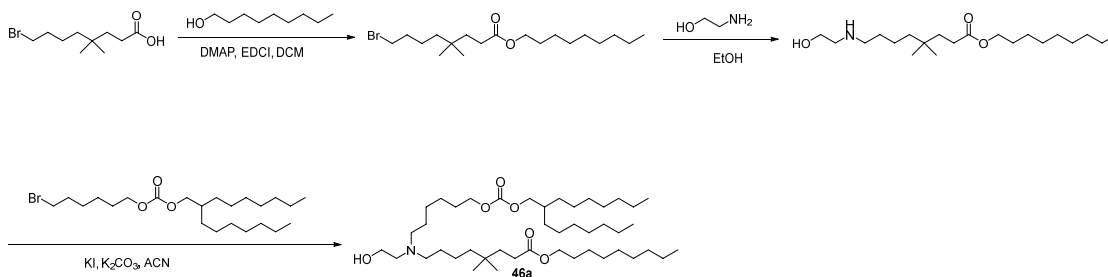
[1011] Example 69: Synthesis of Compound 45a



[1012] Compound 45a was prepared referring to the method of Example 68 to give 107.2 mg of an oily product.

[1013] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (t, J = 6.6 Hz, 2H), 4.04 (t, J = 6.6 Hz, 4H), 3.57 (m, 2H), 2.63-2.51 (m, 6H), 2.18 (s, 2H), 1.73-1.61 (m, 5H), 1.59-1.21 (m, 51H), 0.98 (s, 6H), 0.93-0.83 (m, 9H); **ESI-MS** m/z : 726.55 [M+H]⁺.

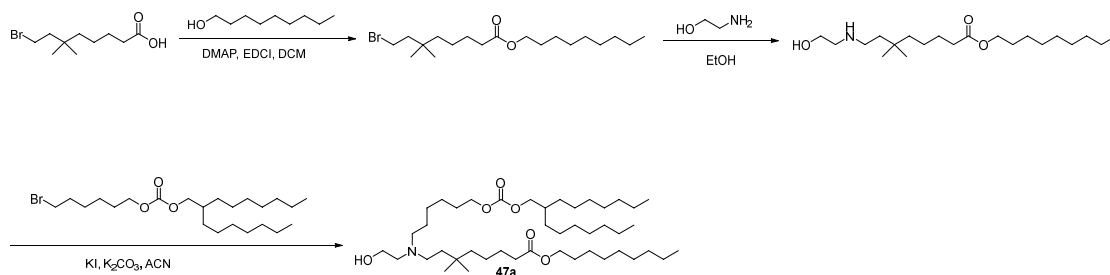
[1014] Example 70: Synthesis of Compound 46a



[1015] Compound 46a was prepared referring to the method of Example 68 to give 116.7 mg of an oily product.

[1016] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (t, J = 6.6 Hz, 2H), 4.07-4.02 (m, 4H), 3.58 (m, 2H), 2.64-2.49 (m, 6H), 2.27-2.21 (m, 2H), 1.73-1.60 (m, 5H), 1.56-1.21 (m, 51H), 0.93-0.82 (m, 15H); **ESI-MS** m/z : 726.45 [M+H]⁺.

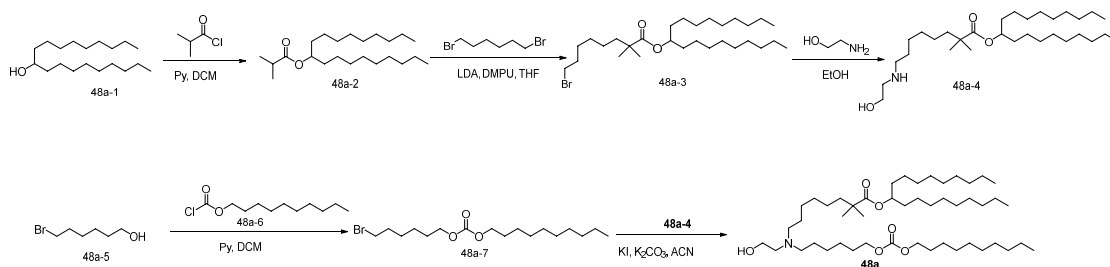
[1017] Example 71: Synthesis of Compound 47a



[1018] Compound 47a was prepared referring to the method of Example 68 to give 24.2 mg of an oily product.

[1019] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.12 (t, $J = 6.8$ Hz, 2H), 4.07-4.02 (m, 4H), 3.73 (m, 2H), 2.81-2.63 (m, 6H), 2.31 (t, $J = 6.8$ Hz, 2H), 1.76-1.59 (m, 10H), 1.58-1.22 (m, 46H), 0.92-0.87 (m, 15H); **ESI-MS** m/z : 726.55 $[\text{M}+\text{H}]^+$.

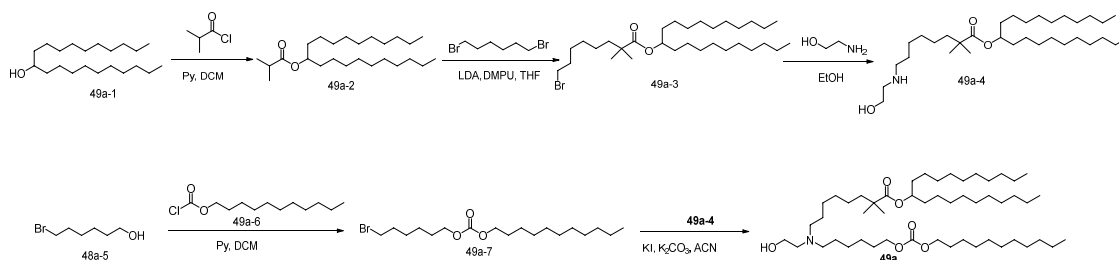
[1020] Example 72: Synthesis of Compound 48a



[1021] Compound 48a was prepared referring to the method of Example 54 to give 258.1 mg of an oily product.

[1022] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.85 (p, $J = 6.0$ Hz, 1H), 4.12 (t, $J = 6.6$ Hz, 4H), 3.59 (m, 2H), 2.65-2.52 (m, 6H), 1.67-1.62 (m, 5H), 1.49-1.20 (m, 60H), 1.15 (s, 6H), 0.88 (t, $J = 6.6$ Hz, 9H); **ESI-MS** m/z : 782.72 $[\text{M}+\text{H}]^+$.

[1023] Example 73: Synthesis of Compound 49a



[1024] Compound 49a was prepared referring to the method of Example 54 to give 27.9 mg of an oily product.

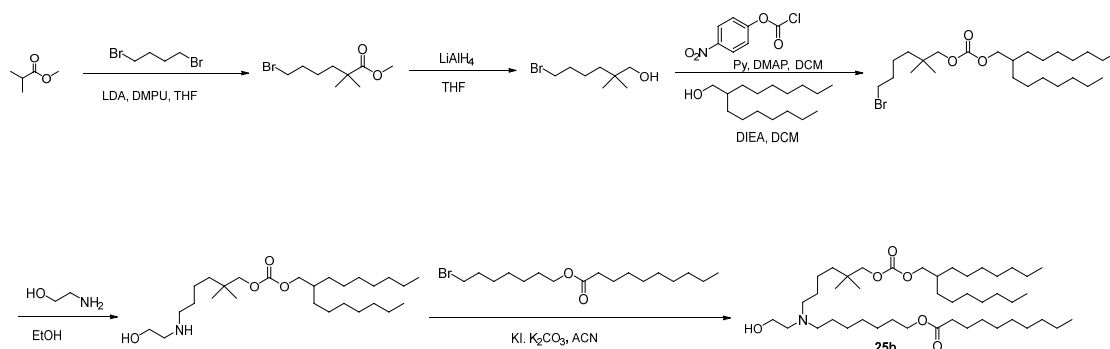
were combined, dried over Na₂SO₄, filtered, and concentrated, and the organic solvent was removed by rotary evaporation to give 7.5 g of a crude compound of methyl 2,2-dimethyl-6-bromohexanoate.

[1031] In a 250 mL round-bottom flask, methyl 2,2-dimethyl-6-bromohexanoate (7.5 g, crude) was dissolved in 75 mL of anhydrous THF. After the mixture was cooled to 0 °C, LiAlH₄ (10.12 mL, 25.3 mmol, 2.5 M in THF) was added dropwise. After the dropwise addition was completed, the mixture was reacted for another 30 min. After the reaction was completed, a saturated aqueous ammonium chloride solution was added to quench the reaction, the mixture was extracted with ethyl acetate, the organic phases were combined, dried over Na₂SO₄, filtered, and concentrated, and the organic solvent was removed by rotary evaporation to give 7.5 g of a crude product, which was purified by silica gel column chromatography to give 2.5 g of the compound 2,2-dimethyl-6-bromohexanol.

[1032] Compound 51a was prepared referring to the method of Example 64 to give 205.5 mg of an oily product.

[1033] **¹H NMR** (300 MHz, CDCl₃) δ: 4.08-4.02 (m, 4H), 3.85 (s, 2H), 3.54 (t, *J* = 5.1 Hz, 2H), 2.59 (t, *J* = 5.1 Hz, 2H), 2.49-2.43 (m, 4H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.66-1.57 (m, 6H), 1.55-1.22 (m, 50H), 0.92-0.83 (m, 15H); **ESI-MS** *m/z*: 726.80 [M+H]⁺.

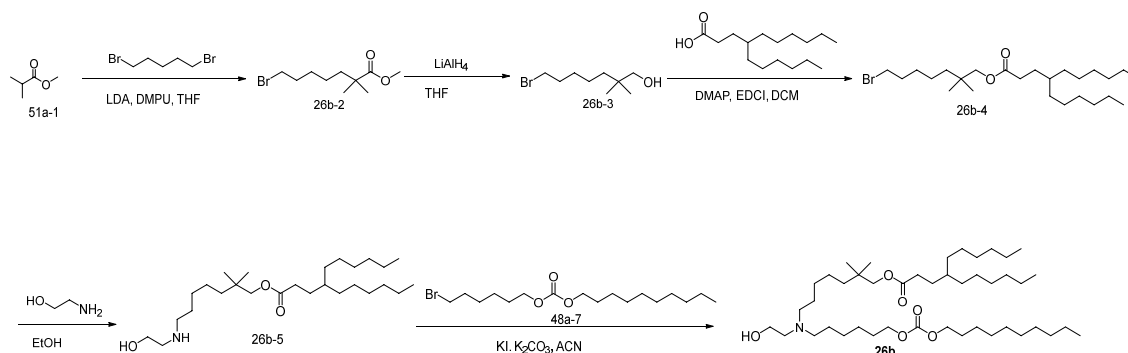
[1034] Example 76: Synthesis of Compound 25b



[1035] Compound 25b was prepared referring to the method of Example 75 to give 152.1 mg of an oily product.

[1036] **¹H NMR** (300 MHz, CDCl₃) δ: 4.08-4.02 (m, 4H), 3.85 (s, 2H), 3.58 (m, 2H), 2.64-2.51 (m, 6H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.79-1.59 (m, 6H), 1.47-1.24 (m, 50H), 0.95-0.85 (m, 15H); **ESI-MS** *m/z*: 726.50 [M+H]⁺.

[1037] Example 77: Synthesis of Compound 26b



[1038] Methyl isobutyrate (21 g, 205.0 mmol, 1.0 eq.) was dissolved in 200 mL of anhydrous THF, the mixture was cooled to 0 °C, and LDA (205 mL, 410.0 mmol, 2.0 eq.) was added to the reaction liquid under nitrogen atmosphere. The reaction was heated to room temperature. After stirring for 30 min, 1,5-dibromopentane (47 g, 205.0 mmol, 1.0 eq.) was added. After the reaction was completed as monitored by TLC, a saturated aqueous ammonium chloride solution was added to quench the reaction, and the mixture was extracted with DCM (3 × 300 mL). The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 30 g of a yellow oily compound methyl 2,2-dimethyl-7-bromoheptanoate.

[1039] Methyl 2-dimethyl-7-bromoheptanoate (15.0 g, 40.0 mmol, 1.0 eq.) was dissolved in 30 mL of THF, the mixture was cooled to 0 °C, and a lithium aluminum hydride solution (2 M, 50.0 mL) was added dropwise to the reaction system under nitrogen atmosphere. The mixture was stirred for reaction for 3 h. After the reaction was completed, the reaction was quenched with a saturated aqueous ammonium chloride solution, and the mixture was extracted with DCM (3 × 300 mL). The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product of 2,2-dimethyl-7-bromoheptanol (13.6 g), which was directly used in the next step without purification.

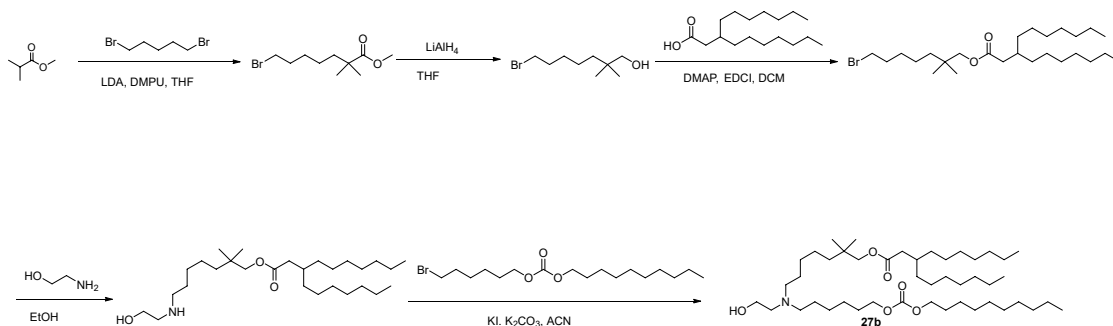
[1040] 2,2-Dimethyl-7-bromoheptanol (500.0 mg, 2.24 mmol, 1.0 eq.) was dissolved in DCM (10.0 mL), and 4-hexyldecanoic acid (746.2 mg, 2.91 mmol, 1.3 eq.), EDCI (515.7 mg, 2.69 mmol, 1.2 eq.), and DMAP (410.5 mg, 3.36 mmol, 1.5 eq.) were added to the

solution. The reaction liquid was stirred at room temperature for 3 h, the reaction liquid was poured into 10 mL of a saturated aqueous sodium chloride solution, and the mixture was extracted with DCM. The organic phases were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography to give 858 mg of a yellow oily compound 26b-4.

[1041] Compound 26b was prepared referring to the method of Example 64 to give 99.0 mg of an oily product.

[1042] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.86-0.91 (m, 15H), 1.21-1.40 (m, 50H), 1.58-1.71 (m, 6H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.48-2.53 (m, 4H), 2.62 (t, *J* = 6.6 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 2H), 4.10 (td, *J* = 2.7, 6.3 Hz, 4H); **ESI-MS** *m/z*: 726.70 [M+H]⁺.

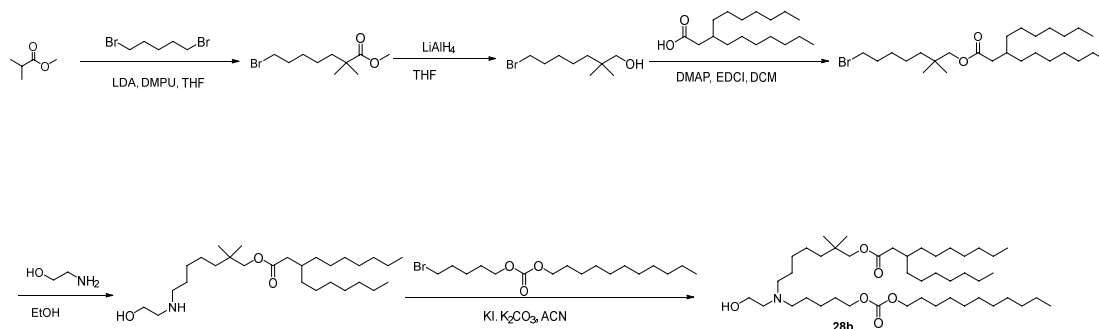
[1043] Example 78: Synthesis of Compound 27b



[1044] Compound 27b was prepared referring to the method of Example 77 to give 70.0 mg of an oily product.

[1045] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.85-0.95 (m, 15H), 1.25-1.55 (m, 48H), 1.59-1.83 (m, 10H), 2.25 (d, *J* = 6.6 Hz, 2H), 2.48-2.53 (m, 4H), 2.62 (t, *J* = 6.3 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 2H), 4.11 (td, *J* = 3.0, 6.6 Hz, 4H); **ESI-MS** *m/z*: 740.65 [M+H]⁺.

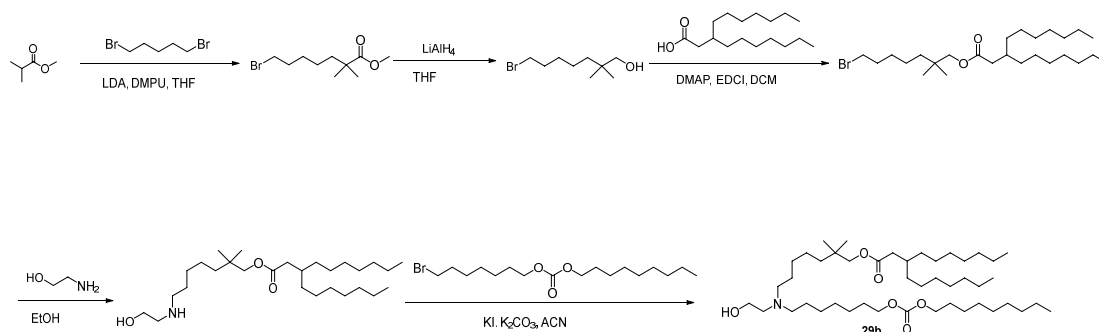
[1046] Example 79: Synthesis of Compound 28b



[1047] Compound 28b was prepared referring to the method of Example 77 to give 97.8 mg of an oily product.

[1048] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.85-0.95 (m, 15H), 1.21-1.55 (m, 48H), 1.60-1.84 (m, 10H), 2.25 (d, *J* = 6.6 Hz, 2H), 2.47-2.53 (m, 4H), 2.61 (t, *J* = 6.3 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 2H), 4.11 (td, *J* = 4.5, 6.3 Hz, 4H); **ESI-MS** *m/z*: 740.80 [M+H]⁺.

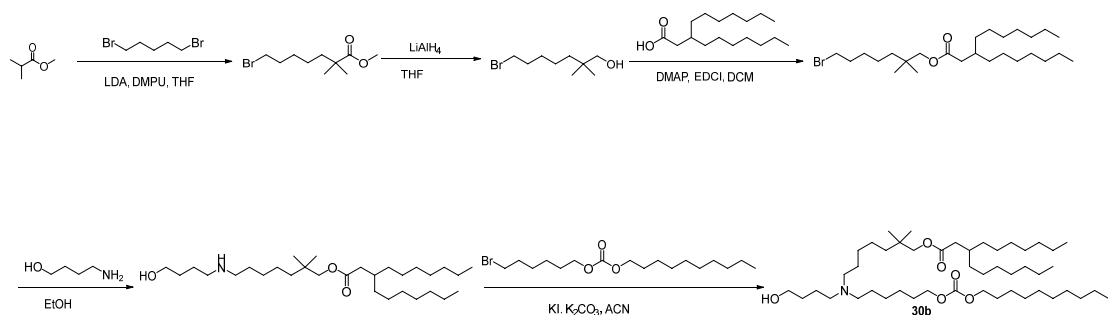
[1049] Example 80: Synthesis of Compound 29b



[1050] Compound 29b was prepared referring to the method of Example 77 to give 107.7 mg of an oily product.

[1051] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.85-0.95 (m, 15H), 1.21-1.55 (m, 53H), 1.60-1.84 (m, 5H), 2.25 (d, *J* = 6.6 Hz, 2H), 2.50-2.55 (m, 4H), 2.64 (t, *J* = 6.3 Hz, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 2H), 4.11 (td, *J* = 1.8, 6.6 Hz, 4H); **ESI-MS** *m/z*: 740.60 [M+H]⁺.

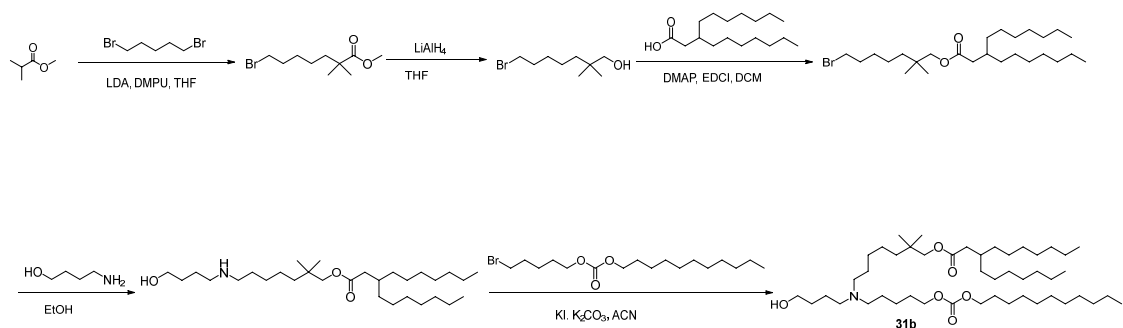
[1052] Example 81: Synthesis of Compound 30b



[1053] Compound 30b was prepared referring to the method of Example 77 to give 82.4 mg of an oily product.

[1054] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.87-0.92 (m, 15H), 1.21-1.53 (m, 49H), 1.55-1.83 (m, 13H), 2.25 (d, *J* = 6.9 Hz, 2H), 2.46-2.52 (m, 6H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.79 (s, 2H), 4.11 (td, *J* = 3.0, 6.6 Hz, 4H); **ESI-MS** *m/z*: 768.70 [M+H]⁺.

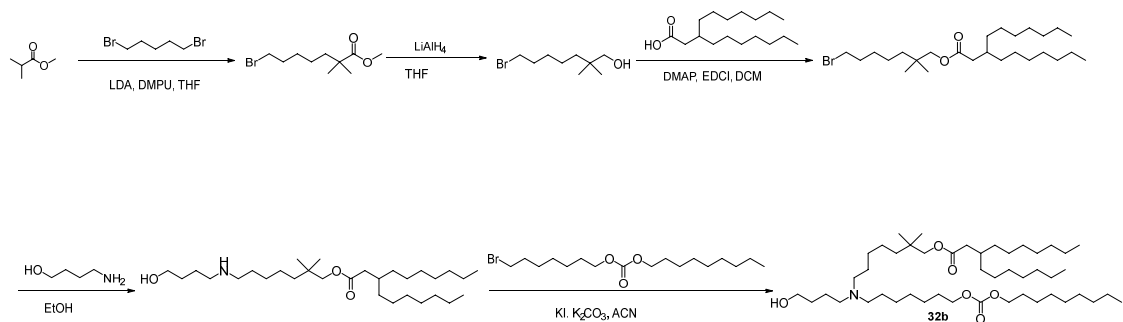
[1055] Example 82: Synthesis of Compound 31b



[1056] Compound 31b was prepared referring to the method of Example 77 to give 107.7 mg of an oily product.

[1057] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.86-0.92 (m, 15H), 1.21-1.53 (m, 49H), 1.55-1.83 (m, 13H), 2.25 (d, *J* = 6.6 Hz, 2H), 2.47-2.54 (m, 6H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.79 (s, 2H), 4.10 (td, *J* = 6.6, 12.3 Hz, 4H); **ESI-MS** *m/z*: 768.70 [M+H]⁺.

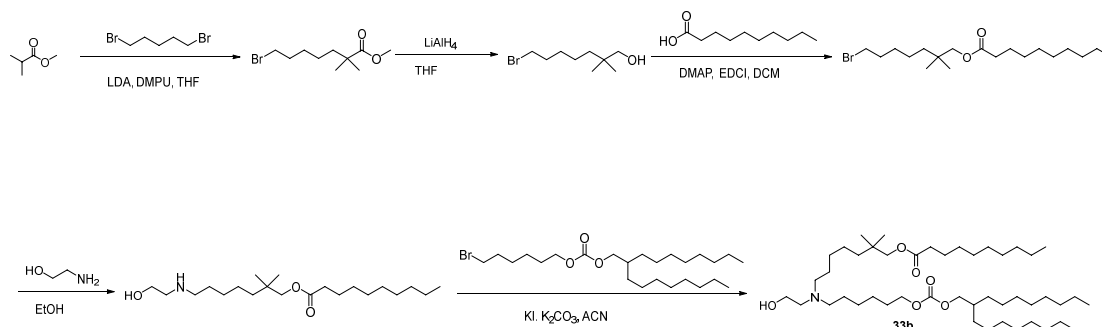
[1058] Example 83: Synthesis of Compound 32b



[1059] Compound 32b was prepared referring to the method of Example 77 to give 84.3 mg of an oily product.

[1060] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.88-0.93 (m, 15H), 1.22-1.53 (m, 49H), 1.56-1.83 (m, 13H), 2.25 (d, *J* = 6.6 Hz, 2H), 2.49-2.54 (m, 6H), 3.55 (t, *J* = 5.4 Hz, 2H), 3.79 (s, 2H), 4.10 (td, *J* = 2.1, 6.6 Hz, 4H); **ESI-MS** *m/z*: 768.65 [M+H]⁺.

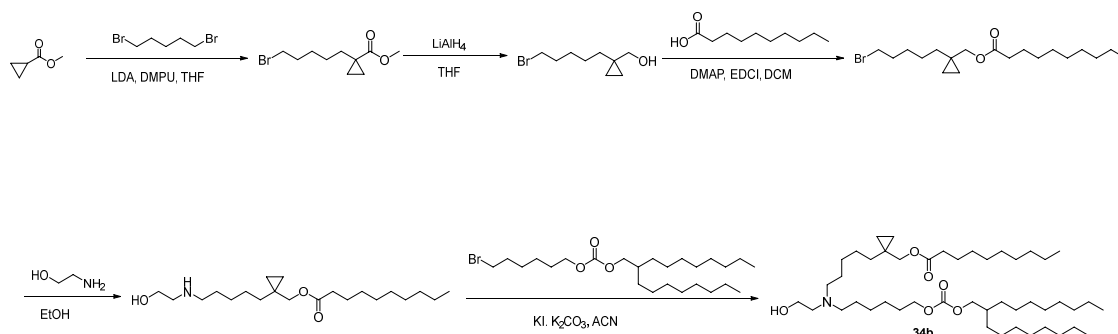
[1061] Example 84: Synthesis of Compound 33b



[1062] Compound 33b was prepared referring to the method of Example 77 to give 74.9 mg of an oily product.

[1063] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.88-0.92 (m, 15H), 1.22-1.53 (m, 51H), 1.48-1.69 (m, 9H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.50-2.55 (m, 4H), 2.63 (t, *J* = 6.3 Hz, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 2H), 4.02 (d, *J* = 5.7 Hz, 2H), 4.11 (t, *J* = 6.6 Hz, 2H); **ESI-MS** *m/z*: 754.60 [M+H]⁺.

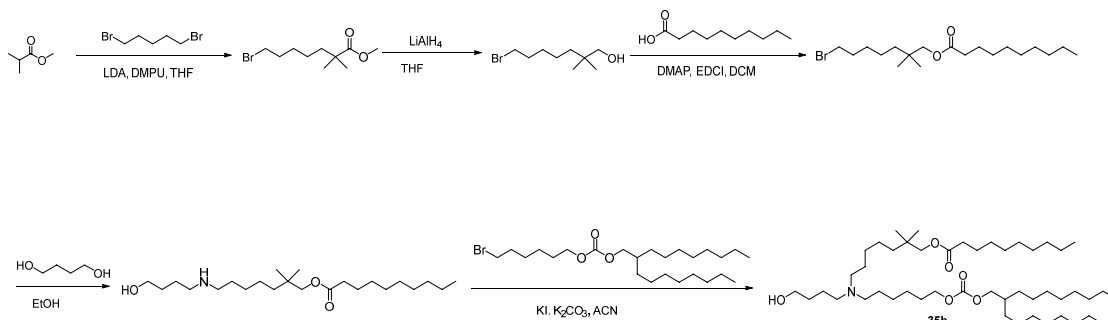
[1064] Example 85: Synthesis of Compound 34b



[1065] Compound 34b was prepared referring to the method of Example 77 to give 76.6 mg of an oily product.

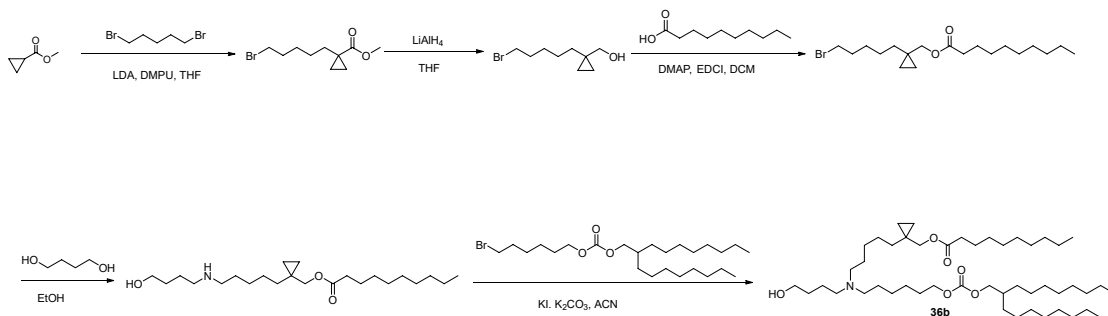
[1066] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.36-0.46 (m, 4H), 0.88-0.92 (m, 9H), 1.20-1.51 (m, 55H), 1.56-1.69 (m, 5H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.51-2.55 (m, 4H), 2.64 (t, *J* =

[1067] Example 86: Synthesis of Compound 35b



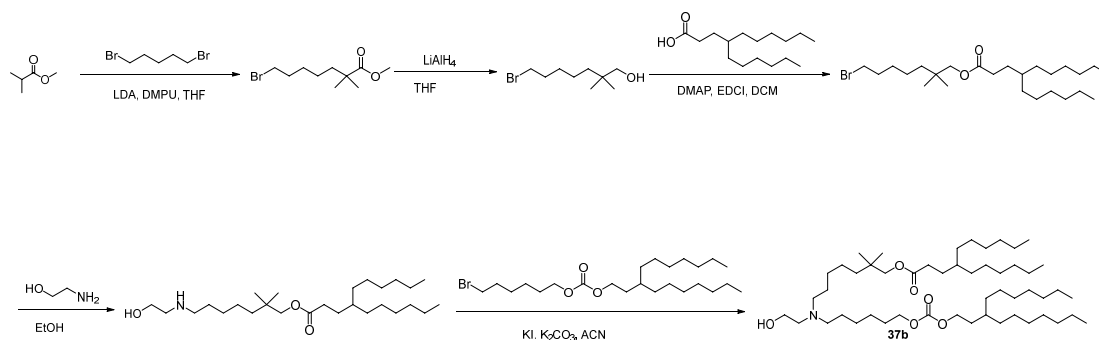
[1069] **¹H NMR** (300 MHz, MeOH-*d*₄) δ : 0.88-0.92 (m, 15H), 1.24-1.72 (m, 64H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.45-2.51 (m, 6H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.80 (s, 2H), 4.02 (d, *J* = 5.7 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H); **ESI-MS** *m/z*: 782.65 [*M*+*H*]⁺.

[1070] Example 87: Synthesis of Compound 36b



[1072] **¹H NMR** (300 MHz, MeOH-*d*₄) δ: 0.34-0.46 (m, 4H), 0.87-0.92 (m, 9H), 1.22-1.72 (m, 64H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.45-2.51 (m, 6H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.92 (s, 2H), 4.02 (d, *J* = 5.7 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H); **ESI-MS** *m/z*: 780.80 [M+H]⁺.

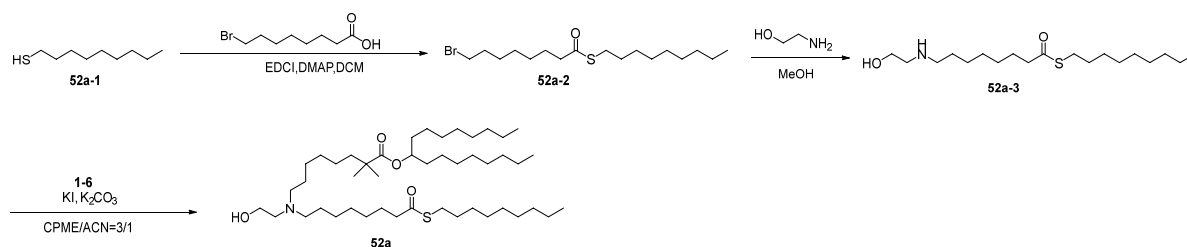
[1073] Example 88: Synthesis of Compound 37b



[1074] Compound 37b was prepared referring to the method of Example 77 to give 71.6 mg of an oily product.

[1075] $^1\text{H NMR}$ (300 MHz, $\text{MeOH-}d_4$) δ : 0.89-0.94 (m, 18H), 1.24-1.69 (m, 67H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.50-2.55 (m, 4H), 2.64 (t, $J = 6.3$ Hz, 2H), 3.62 (t, $J = 6.3$ Hz, 2H), 3.80 (s, 2H), 4.11 (td, $J = 6.3, 14.7$ Hz, 4H); **ESI-MS** m/z : 824.70 $[\text{M}+\text{H}]^+$.

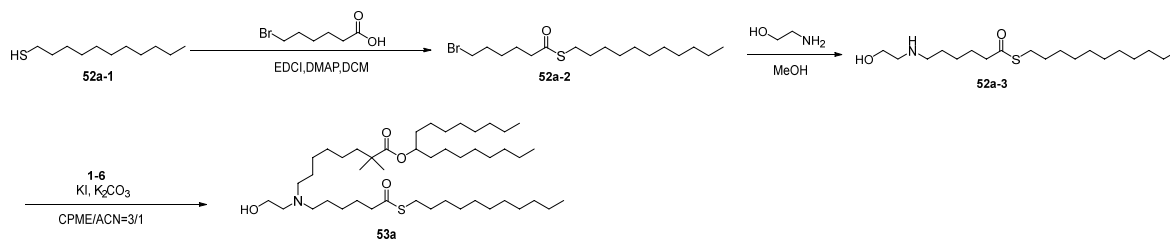
[1076] Example 89: Synthesis of Compound 52a



[1077] Compound 52a was prepared referring to the method of Example 1 to give 243.8 mg of an oily product.

[1078] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.87-4.81 (m, 1H), 3.59 (m, 2H), 2.86 (t, $J = 7.2$ Hz, 2H), 2.65-2.51 (m, 8H), 1.64-1.58 (m, 4H), 1.57-1.43 (m, 11H), 1.39-1.19 (m, 48H), 1.15 (s, 6H), 0.90 (t, $J = 7.2$ Hz, 9H); **ESI-MS** m/z : 754.60 $[\text{M}+\text{H}]^+$.

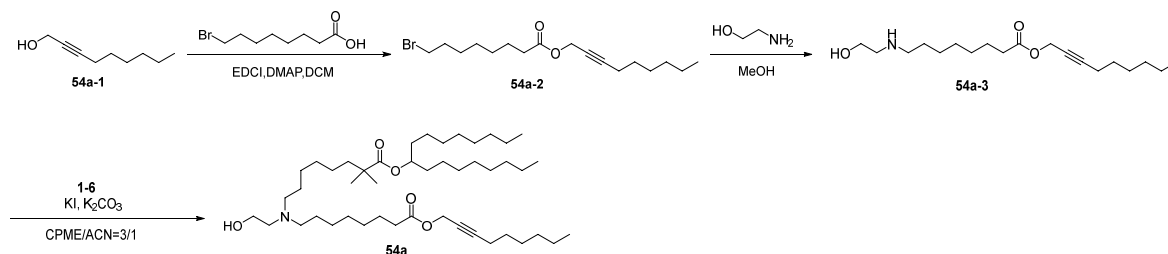
[1079] Example 90: Synthesis of Compound 53a



[1080] Compound 53a was prepared referring to the method of Example 1 to give 262.7 mg of an oily product.

[1081] **¹H NMR** (300 MHz, CDCl₃) δ : 4.90-4.78 (m, 1H), 3.56 (t, J = 5.1 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.63-2.48 (m, 8H), 1.81-1.19 (m, 63H), 1.16 (s, 6H), 0.89 (t, J = 7.2 Hz, 9H); **ESI-MS** m/z : 754.60 [M+H]⁺.

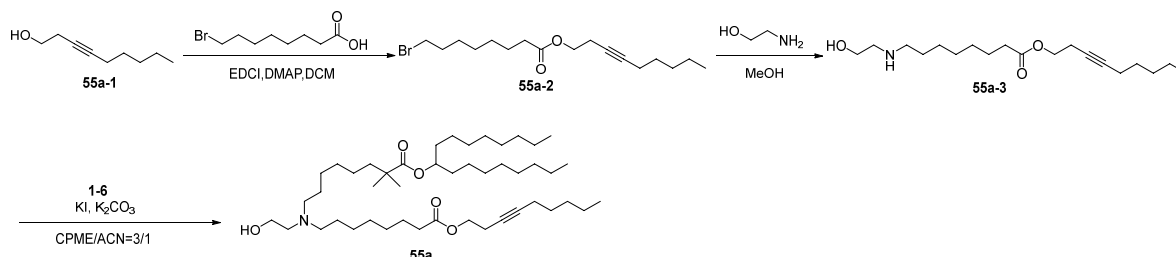
[1082] Example 91: Synthesis of Compound 54a



[1083] Compound **54a** was prepared referring to the method of Example 1 to give 287.7 mg of an oily product.

[1084] **¹H NMR** (300 MHz, CDCl₃) δ : 4.89-4.79 (m, 1H), 4.66 (t, J = 2.1 Hz, 2H), 3.53 (t, J = 5.4 Hz, 2H), 2.58 (t, J = 5.4 Hz, 2H), 2.45 (t, J = 7.2 Hz, 4H), 2.34 (t, J = 7.2 Hz, 2H), 2.24-2.20 (m, 2H), 1.79-1.17 (m, 57H), 1.15 (s, 6H), 0.88 (t, J = 7.2 Hz, 9H); **ESI-MS** m/z : 734.60 [M+H]⁺.

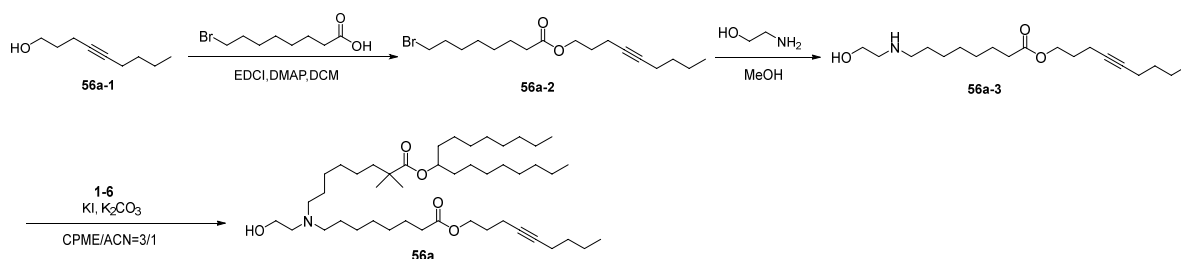
[1085] Example 92: Synthesis of Compound 55a



[1086] Compound **55a** was prepared referring to the method of Example 1 to give 173.5 mg of an oily product.

[1087] **¹H NMR** (300 MHz, CDCl₃) δ : 4.89-4.78 (m, 1H), 4.13 (t, J = 7.2 Hz, 2H), 3.56 (m, 2H), 2.63 (m, 2H), 2.51-2.45 (m, 6H), 2.31 (t, J = 7.2 Hz, 2H), 2.16-2.10 (m, 2H), 1.78-1.17 (m, 55H), 1.15 (s, 6H), 0.90 (m, 9H); **ESI-MS** m/z : 734.50 [M+H]⁺.

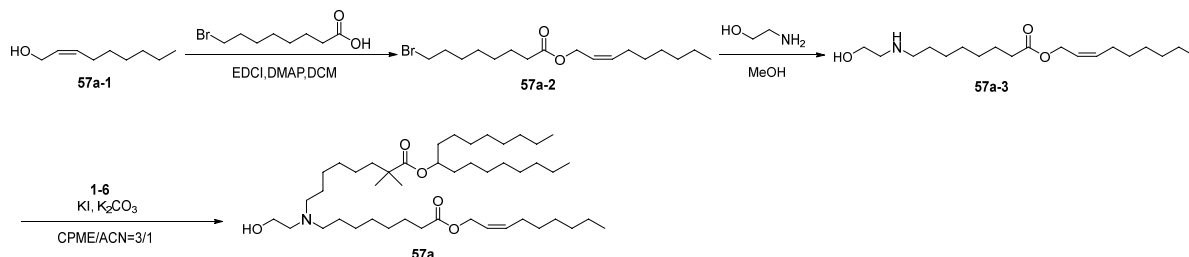
[1088] Example 93: Synthesis of Compound 56a



[1089] Compound **56a** was prepared referring to the method of Example 1 to give 112.2 mg of an oily product.

[1090] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.87-4.79 (m, 1H), 4.16 (t, $J = 6.6$ Hz, 2H), 3.60 (m, 2H), 2.67-2.53 (m, 6H), 2.32-2.11 (m, 6H), 2.32-2.11 (m, 6H), 1.85-1.76 (m, 2H), 1.66-1.18 (m, 53H), 1.14 (s, 6H), 0.88 (m, 9H); **ESI-MS** m/z : 734.55 $[\text{M}+\text{H}]^+$.

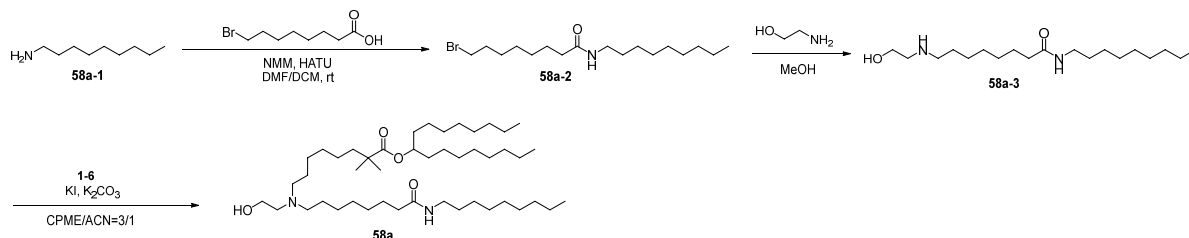
[1091] Example 94: Synthesis of Compound 57a



[1092] Compound **57a** was prepared referring to the method of Example 1 to give 45.0 mg of an oily product.

[1093] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 5.68-5.49 (m, 2H), 4.85-4.79 (m, 1H), 4.63 (d, $J = 6.8$ Hz, 2H), 3.84 (m, 2H), 2.95-2.76 (m, 6H), 2.31 (t, $J = 7.2$ Hz, 2H), 2.12-2.07 (m, 2H), 1.66-1.18 (m, 57H), 1.16 (s, 6H), 0.88 (m, 9H); **ESI-MS** m/z : 736.60 $[\text{M}+\text{H}]^+$.

[1094] Example 95: Synthesis of Compound 58a



[1095] In a 50 mL round-bottom flask, the reactants 1-nonanamine (286.5 mg, 2.0 mmol, 1.0 eq.), 8-bromooctanoic acid (535.5 mg, 2.4 mmol, 1.2 eq.), NMM (202.3 mg, 2.0 mmol, 1.0 eq.), and HATU (1.14 g, 3.0 mmol, 1.5 eq.) were dissolved in a mixed solution of DMF (2.0 mL) and DCM (10.0 mL), and the mixture was stirred at room temperature

remove the drying agent, and the solvent was removed to give 2.45 g of a colorless oily compound 59a-3.

[1101] In a 100 mL three-neck flask, compound 59a-6 (1.5 g, 5.8 mmol, 1.0 eq.), 2-heptyl-1-nonanol (1.40 g, 5.8 mmol, 1.0 eq.), EDCI (1.66 g, 8.7 mmol, 1.5 eq.), and DMAP (0.35 g, 2.9 mmol, 0.5 eq.) were dissolved in 20 mL of dichloromethane, and the mixture was stirred at room temperature overnight. The mixture was washed with water (3 × 15 mL). The organic phase was subjected to rotary evaporation under reduced pressure, directly mixed with silica gel, and purified by silica gel column chromatography to give 3.3 g of compound 59a-7.

[1102] In a 100 mL three-neck flask, compound 59a-7 (2.8 g, 5.8 mmol, 1.0 eq.) was dissolved in 20 mL of dichloromethane, HCl/dioxane (4 M, 14 mL) was added, and the mixture was stirred at room temperature overnight. The organic solvent was removed by rotary evaporation, the reaction liquid was adjusted to neutrality with a saturated sodium bicarbonate solution, and the mixture was extracted with DCM (3 × 20 mL). The organic phase was collected and dried over anhydrous Na₂SO₄. The organic phase was purified by silica gel column chromatography to give 1.95 g of compound 8.

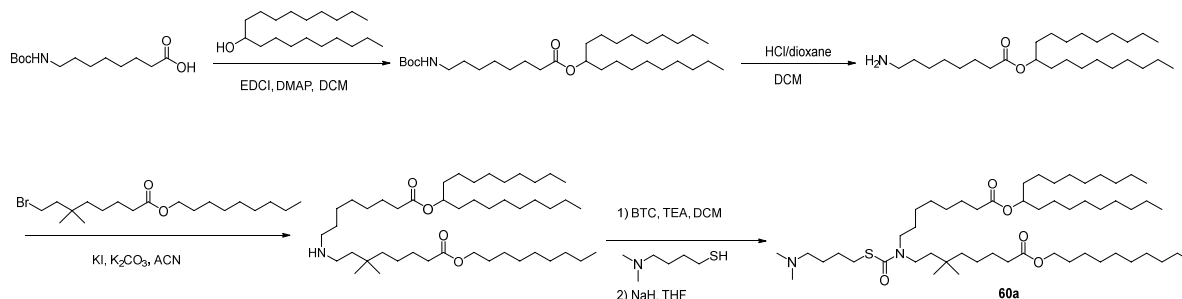
[1103] In a 40 mL sealed tube, compound 59a-8 (680 mg, 1.8 mmol, 1.0 eq.), KI (365 mg, 2.2 mmol, 1.2 eq.), K₂CO₃ (745 mg, 5.4 mmol, 3.0 eq.), and 59a-5 (668.9 mg, 1.8 mmol, 1.0 eq.) were dissolved in 10 mL of acetonitrile. The mixture was heated to 80 °C and stirred for reaction overnight. After the reaction was completed, the mixture was cooled to room temperature and filtered, and the filter cake was washed with acetonitrile (5 mL × 2). The filtrate was collected and concentrated by rotary evaporation to dryness. The residue was purified by column chromatography to give 580 mg of a yellow oily compound 59a-9.

[1104] In a 20 mL sealed tube, compound 59a-9 (200 mg, 0.29 mmol, 1.0 eq.) was dissolved in 5 mL of DCM. After the reaction system was cooled to 5 °C, TEA (59.5 mg, 0.59 mmol, 2.0 eq.) and BTC (87.3 mg, 0.29 mmol, 1.0 eq.) were added dropwise. The temperature was kept at 5 °C, the mixture was stirred for reaction for 1 h and concentrated to remove DCM, and 5 mL of tetrahydrofuran was added. In another 20 mL sealed tube, compound 59a-3 (101.9 mg, 0.76 mmol, 2.6 eq.) was dissolved in 5 mL of tetrahydrofuran. After the mixture was cooled to 0 °C, NaH (60%, 58.0 mg, 1.45 mmol,

5.0 eq.) was added. After stirring at 0 °C for 1 h, the above prepared THF mixed solution was added dropwise, and the mixture was reacted for another 1 h. The reaction liquid was poured into 10 mL of ice water, and the mixture was extracted with ethyl acetate. The organic phases were combined, dried over anhydrous sodium sulfate, and filtered to remove the drying agent, and the solvent was removed to give a crude product. The crude product was purified by Prep-HPLC (Column: XSelect C18 (30 × 150 mm, 5 μm); Eluent A: H₂O/ACN 60/40, 10 mM NH₄HCO₃ + 1% NH₃•H₂O; Eluent B: IPA/ACN 90/10; Flow rate: 60 mL/min; Gradient program: 65%-85% B in 0-12 min) to give 126.9 mg of a light yellow oily compound 59a.

[1105] **¹H NMR** (300 MHz, CDCl₃) δ: 4.06 (t, *J* = 6.6 Hz, 2H), 3.96 (d, *J* = 5.7 Hz, 2H), 3.36-3.15 (m, 4H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.41 (s, 2H), 2.31-2.24 (m, 10H), 1.64-1.16 (m, 61H), 0.93-0.77 (m, 15H); **ESI-MS** *m/z*: 839.65 [M+H]⁺.

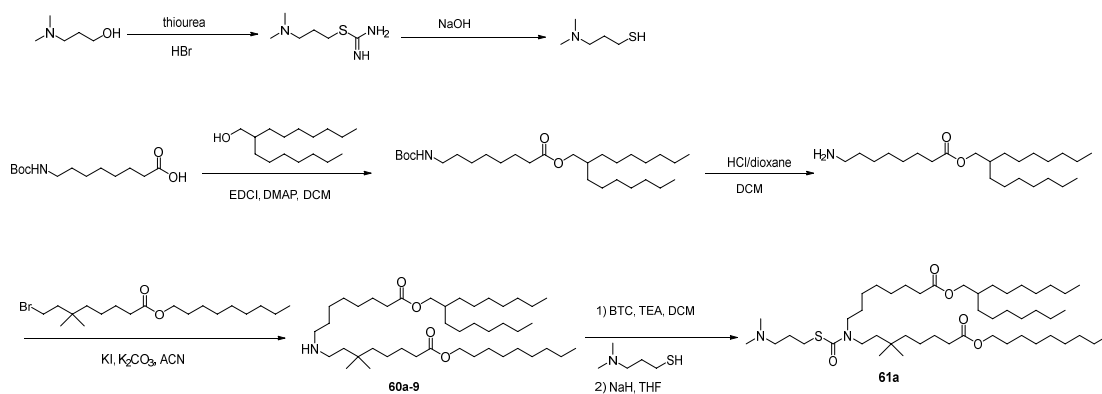
[1106] Example 97: Synthesis of Compound 60a



[1107] Compound 60a was prepared referring to the method of Example 96 to give 157.3 mg of an oily product.

[1108] **¹H NMR** (300 MHz, CDCl₃) δ: 4.86 (p, *J* = 6.3 Hz, 1H), 4.06 (t, *J* = 6.9 Hz, 2H), 3.37-3.17 (m, 4H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.39-2.25 (m, 12H), 1.79-1.18 (m, 70H), 0.93-0.83 (m, 15H); **ESI-MS** *m/z*: 895.80 [M+H]⁺.

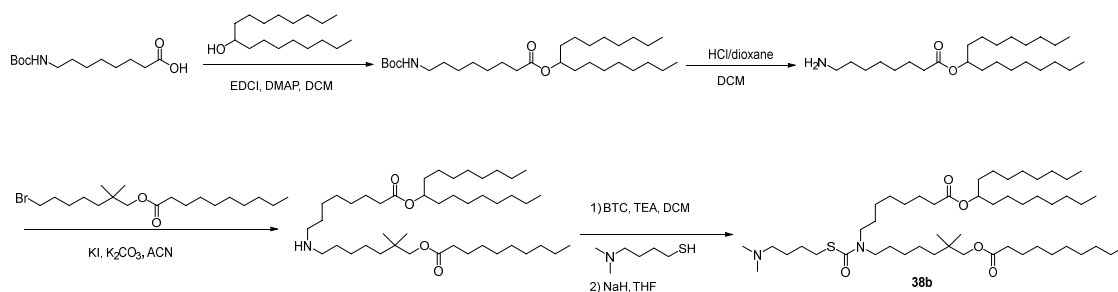
[1109] Example 98: Synthesis of Compound 61a



[1110] Compound 61a was prepared referring to the method of Example 96 to give 184.0 mg of an oily product.

[1111] **¹H NMR** (300 MHz, CDCl₃) δ : 4.06 (t, J = 6.9 Hz, 2H), 3.96 (d, J = 5.7 Hz, 2H), 3.35-3.18 (m, 4H), 2.91 (t, J = 7.2 Hz, 2H), 2.43-2.27 (m, 12H), 1.87-1.77 (m, 2H), 1.61-1.18 (m, 57H), 0.93-0.84 (m, 15H); **ESI-MS** m/z : 825.55 [M+H]⁺.

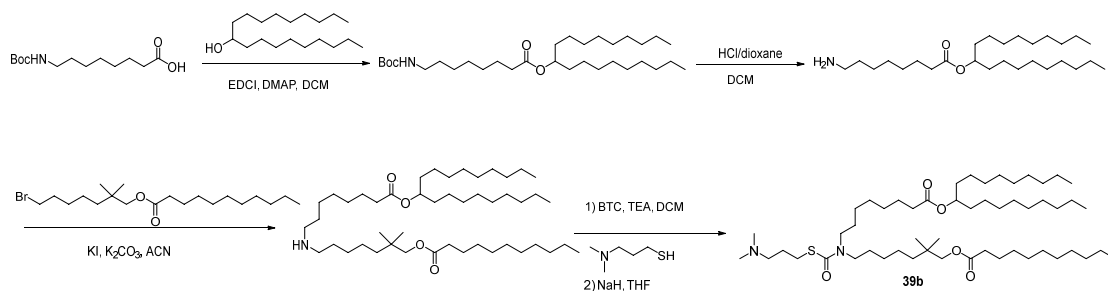
[1112] Example 99: Synthesis of Compound 38b



[1113] Compound 38b was prepared referring to the method of Example 96 to give 228 mg of an oily product.

[1114] **¹H NMR** (300 MHz, CDCl₃) δ : 4.86 (p, J = 6.3 Hz, 1H), 3.78 (s, 2H), 3.33-3.18 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.38-2.25 (m, 12H), 1.69-1.44 (m, 16H), 1.34-1.17 (m, 48H), 0.90-0.85 (m, 15H); **ESI-MS** m/z : 853.65 [M+H]⁺.

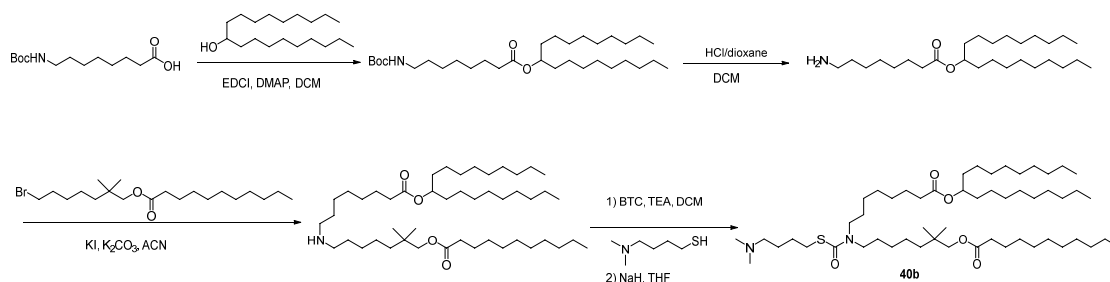
[1115] Example 100: Synthesis of Compound 39b



[1116] Compound 39b was prepared referring to the method of Example 96 to give 117.9 mg of an oily product.

[1117] **¹H NMR** (300 MHz, CDCl₃) δ : 4.86 (p, J = 6.3 Hz, 1H), 3.78 (s, 2H), 3.36-3.17 (m, 4H), 2.92 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.34-2.22 (m, 10H), 1.90-1.80 (m, 3H), 1.62-1.49 (m, 14H), 1.34-1.17 (m, 51H), 0.93-0.86 (m, 15H); **ESI-MS** m/z : 881.65 [M+H]⁺.

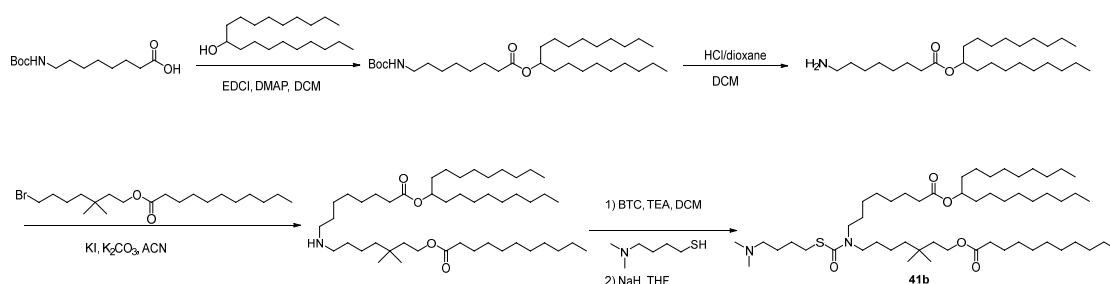
[1118] Example 101: Synthesis of Compound 40b



[1119] Compound 40b was prepared referring to the method of Example 96 to give 75.3 mg of an oily product.

[1120] **¹H NMR** (300 MHz, CDCl₃) δ : 4.86 (p, J = 6.3 Hz, 1H), 3.78 (s, 2H), 3.36-3.17 (m, 4H), 2.91 (t, J = 6.6 Hz, 2H), 2.48-2.28 (m, 12H), 1.89-1.60 (m, 10H), 1.51-1.16 (m, 60H), 0.93-0.87 (m, 15H); **ESI-MS** m/z : 895.70 [M+H]⁺.

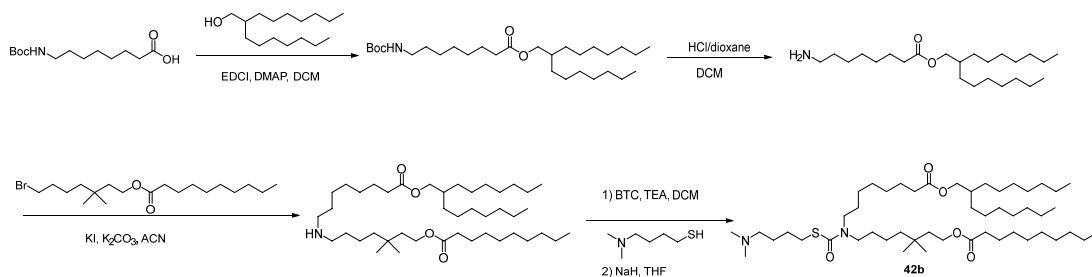
[1121] Example 102: Synthesis of Compound 41b



[1122] Compound 41b was prepared referring to the method of Example 96 to give 95.1 mg of an oily product.

[1123] **¹H NMR** (400 MHz, CDCl₃) δ : 4.86 (p, J = 6.4 Hz, 1H), 4.09 (t, J = 7.6 Hz, 2H), 3.31-3.24 (m, 4H), 2.90 (t, J = 7.6 Hz, 2H), 2.40-2.26 (m, 12H), 1.63-1.50 (m, 21H), 1.32-1.16 (m, 49H), 0.90-0.86 (m, 15H); **ESI-MS** m/z : 895.80 [M+H]⁺.

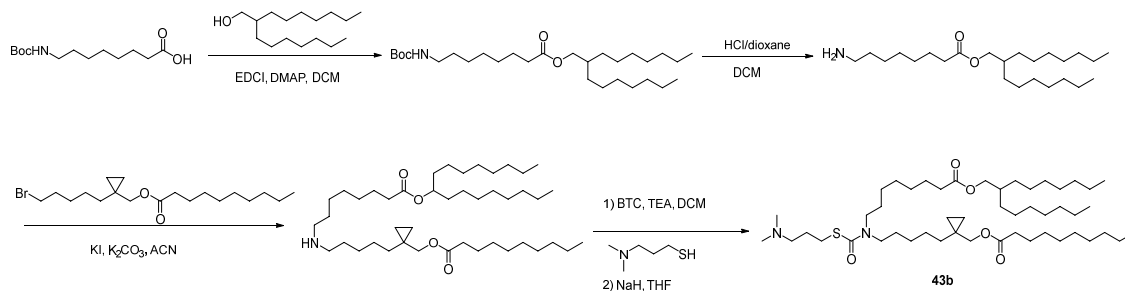
[1124] Example 103: Synthesis of Compound 42b



[1125] Compound 42b was prepared referring to the method of Example 96 to give 63.6 mg of an oily product.

[1126] **¹H NMR** (400 MHz, CDCl₃) δ : 4.09 (p, J = 7.6 Hz, 2H), 3.96 (d, J = 6.0 Hz, 2H), 3.31-3.24 (m, 4H), 2.90 (t, J = 7.2 Hz, 2H), 2.57-2.26 (m, 12H), 1.67-1.43 (m, 20H), 1.32-1.16 (m, 41H), 0.90-0.86 (m, 15H); **ESI-MS** m/z : 839.70 [M+H]⁺.

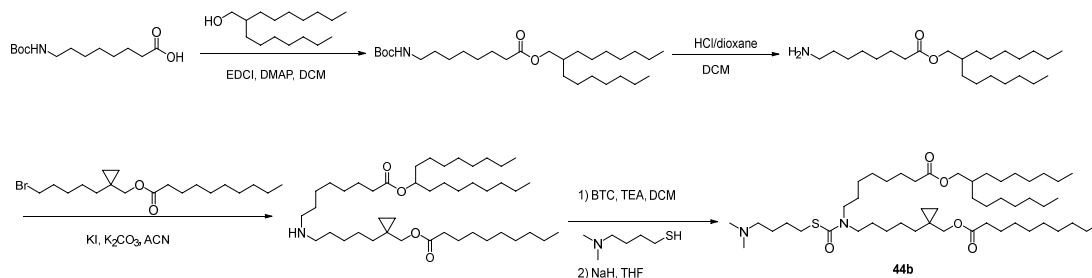
[1127] Example 104: Synthesis of Compound 43b



[1128] Compound 43b was prepared referring to the method of Example 96 to give 130.5 mg of an oily product.

[1129] **¹H NMR** (300 MHz, CDCl₃) δ : 3.96 (d, J = 6.0 Hz, 2H), 3.89 (s, 2H), 3.35-3.18 (m, 4H), 2.91 (t, J = 7.2 Hz, 2H), 2.44-2.28 (m, 12H), 1.87-1.79 (m, 2H), 1.77-1.60 (m, 10H), 1.34-1.17 (m, 47H), 0.90-0.85 (m, 9H), 0.52-0.32 (m, 4H); **ESI-MS** m/z : 823.60 [M+H]⁺.

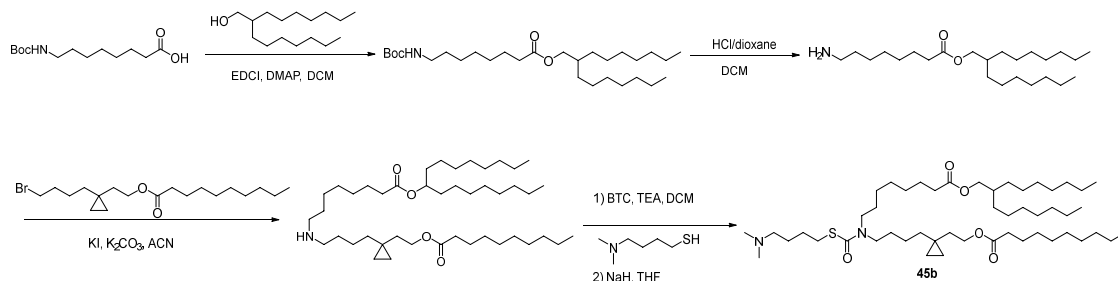
[1130] Example 105: Synthesis of Compound 44b



[1131] Compound 44b was prepared referring to the method of Example 96 to give 79.4 mg of an oily product.

[1132] **¹H NMR** (300 MHz, CDCl₃) δ : 3.95 (d, J = 5.7 Hz, 2H), 3.90 (s, 2H), 3.35-3.19 (m, 4H), 2.90 (t, J = 7.2 Hz, 2H), 2.67 (s, 4H), 2.34-2.27 (m, 4H), 1.72-1.51 (m, 16H), 1.29-1.21 (m, 49H), 0.90-0.83 (m, 9H), 0.46-0.36 (m, 4H); **ESI-MS** m/z : 837.75 [M+H]⁺.

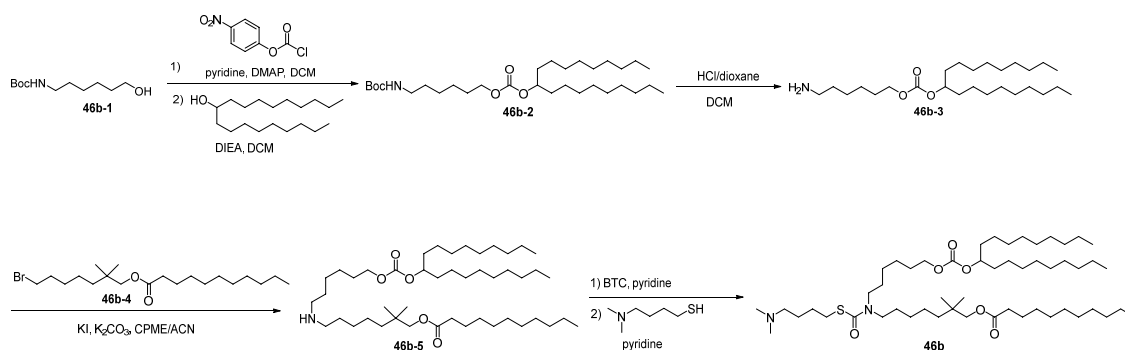
[1133] Example 106: Synthesis of Compound 45b



[1134] Compound 45b was prepared referring to the method of Example 96 to give 41 mg of an oily product.

[1135] **¹H NMR** (400 MHz, CDCl₃) δ : 4.13 (s, 2H), 3.96 (d, J = 6.0 Hz, 2H), 3.31-3.24 (m, 4H), 2.90 (t, J = 6.8 Hz, 2H), 2.54-2.26 (m, 10H), 1.67-1.45 (m, 18H), 1.29-1.21 (m, 45H), 0.90-0.82 (m, 9H), 0.32-0.29 (m, 4H); **ESI-MS** m/z : 837.70 [M+H]⁺.

[1136] Example 107: Synthesis of Compound 46b

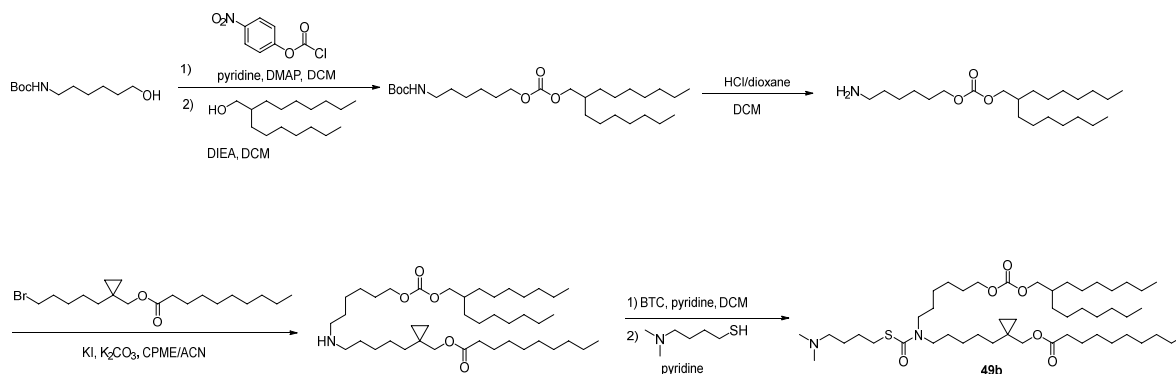


[1137] In a 100 mL three-neck round-bottom flask, compound 46b-1 (1.0 g, 4.60 mmol, 1.0 eq.), pyridine (0.74 mL, 9.2 mmol, 2.0 eq.), DMAP (112.4 mg, 0.92 mmol, 0.2 eq.), and *p*-nitrophenyl chloroformate (1.11 g, 5.52 mmol, 1.2 eq.) were dissolved in 20 mL of dichloromethane at room temperature under nitrogen atmosphere. After the reaction system was stirred at room temperature for 1 h, 2-nonyl-1-decanol (3.93 g, 13.8 mmol, 3.0 eq.) and DIEA (2.40 mL, 13.8 mmol, 3.0 eq.) were added to the reaction system. The reaction system was stirred at room temperature overnight. The reaction was monitored by TLC, and a new spot of the product was found. The mixture was diluted with DCM (20 mL) and washed once with a saturated sodium bicarbonate solution (10 mL). The

[1144] Compound 48b was prepared referring to the method of Example 107 to give 129.4 mg of an oily product.

[1145] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (t, J = 6.6 Hz, 2H), 4.02 (d, J = 5.7 Hz, 2H), 3.78 (s, 2H), 3.36-3.21 (m, 4H), 2.90 (t, J = 6.9 Hz, 2H), 2.36-2.26 (m, 10H), 1.63-1.41 (m, 13H), 1.26-1.18 (m, 46H), 0.89-0.86 (m, 15H); **ESI-MS** m/z : 841.65 [M+H]⁺.

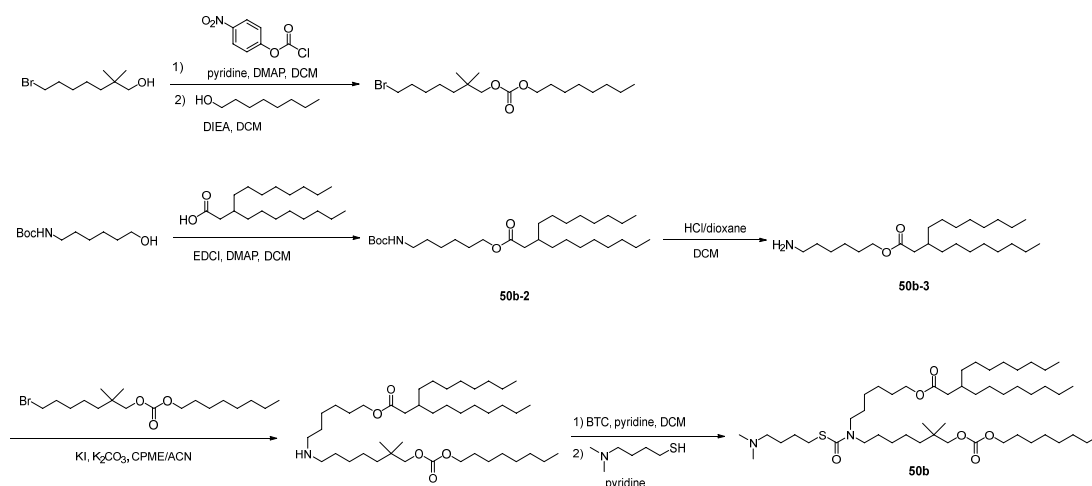
[1146] Example 110: Synthesis of Compound 49b



[1147] Compound 49b was prepared referring to the method of Example 107 to give 135.6 mg of an oily product.

[1148] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (t, J = 6.3 Hz, 2H), 4.02 (d, J = 5.7 Hz, 2H), 3.89 (s, 2H), 3.31-3.22 (m, 4H), 2.90 (t, J = 6.9 Hz, 2H), 2.34-2.26 (m, 10H), 1.65-1.48 (m, 13H), 1.27-1.19 (m, 46H), 0.90-0.86 (m, 9H), 0.45-0.35 (m, 4H); **ESI-MS** m/z : 839.50 [M+H]⁺.

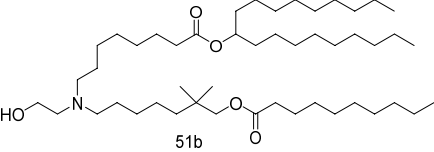
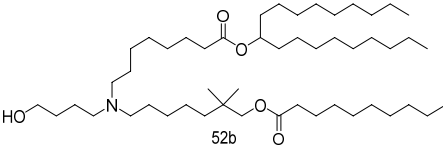
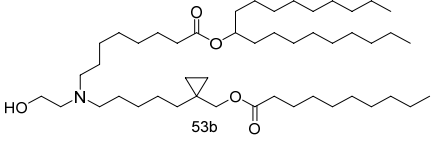
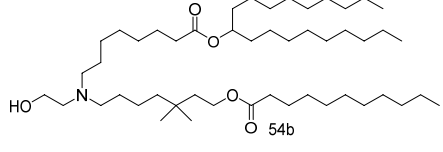
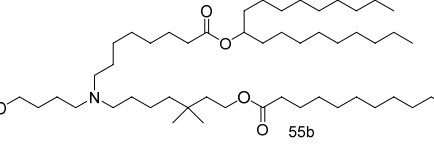
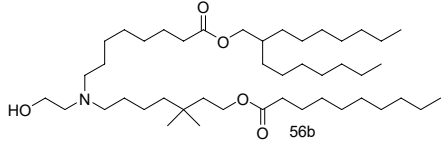
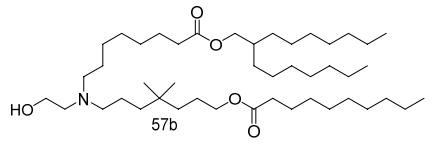
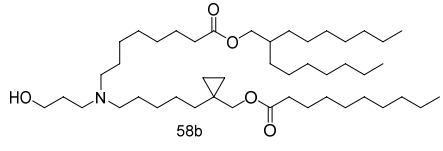
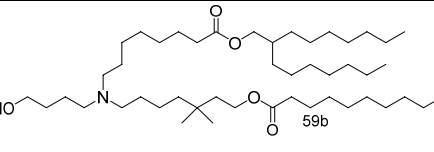
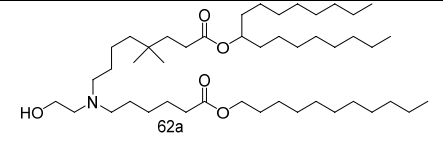
[1149] Example 111: Synthesis of Compound 50b

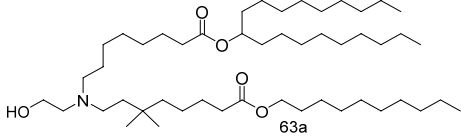
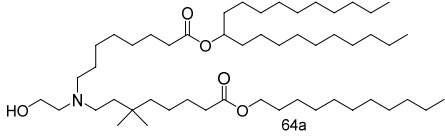
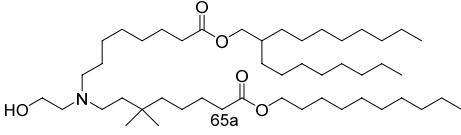
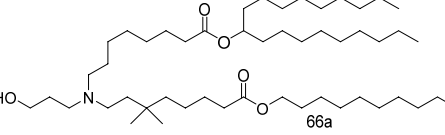
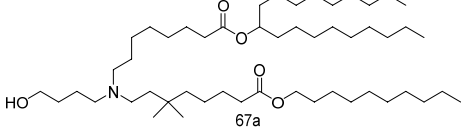
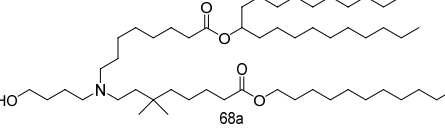
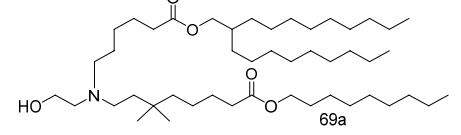
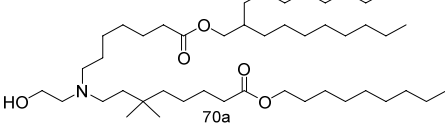
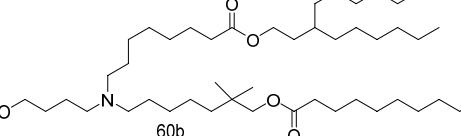
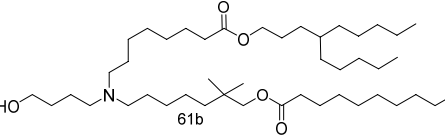
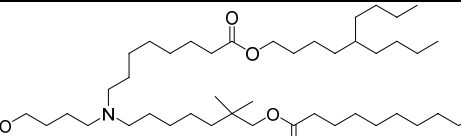
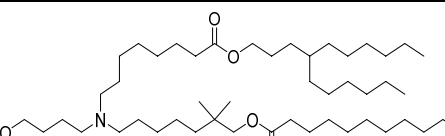


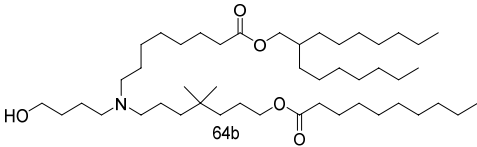
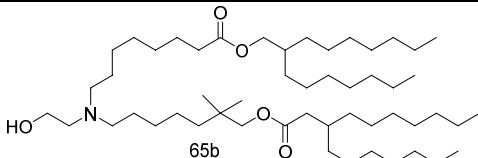
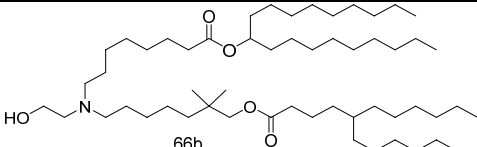
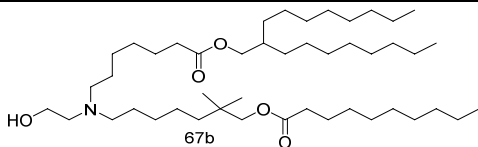
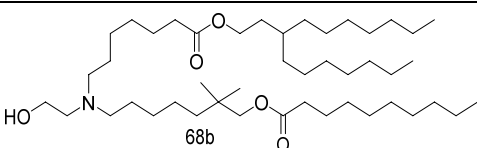
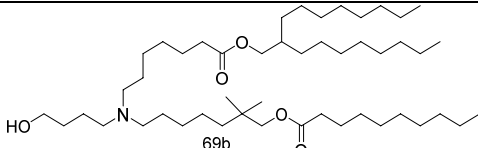
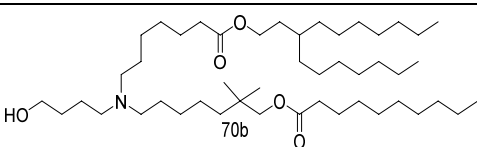
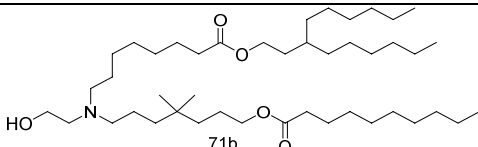
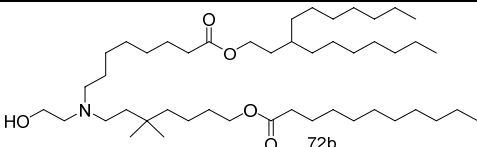
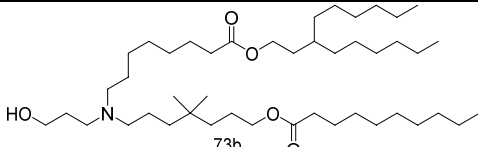
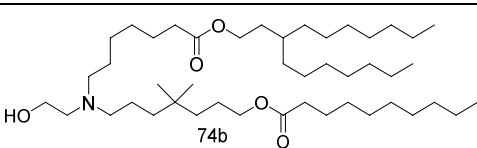
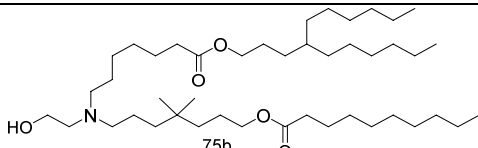
[1150] Compound 50b was prepared referring to the method of Example 107 to give 123.1 mg of an oily product.

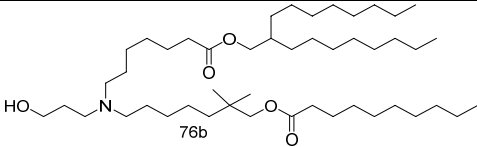
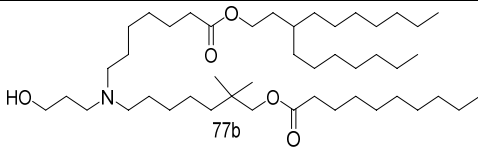
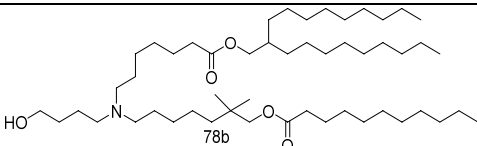
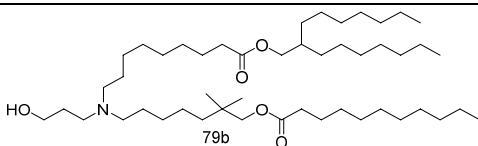
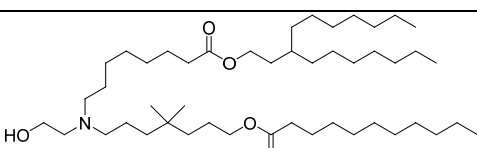
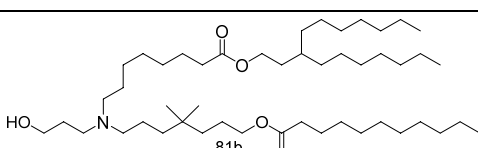
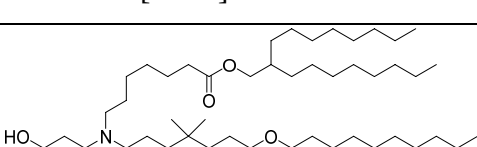
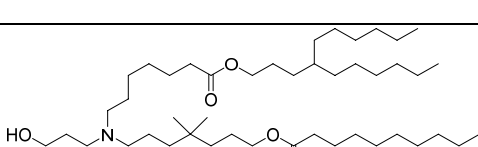
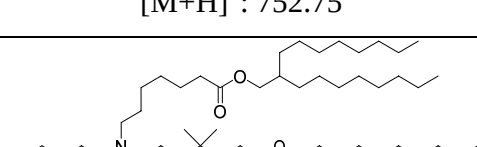
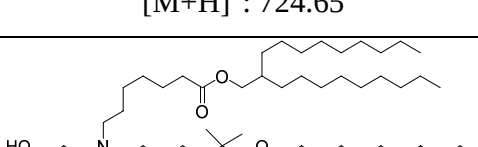
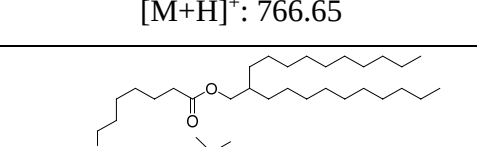
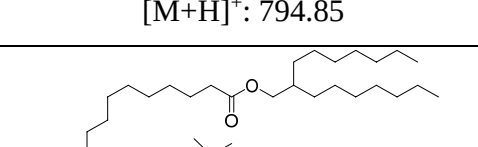
[1151] **¹H NMR** (300 MHz, CDCl₃) δ : 4.12 (t, J = 6.6 Hz, 2H), 4.02 (t, J = 6.6 Hz, 2H), 3.84 (s, 2H), 3.34-3.19 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.46-2.20 (m, 10H), 1.84 (m, 2H), 1.65-1.44 (m, 13H), 1.27-1.19 (m, 46H), 0.92-0.86 (m, 15H); **ESI-MS** m/z : 855.60 [M+H]⁺.

[1152] The compounds in Table below were synthesized using the methods of the above examples, or using similar methods of the corresponding intermediates.

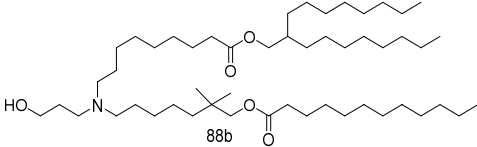
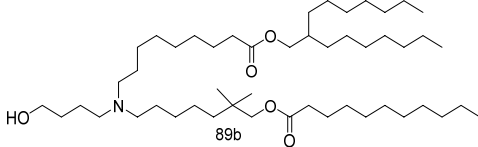
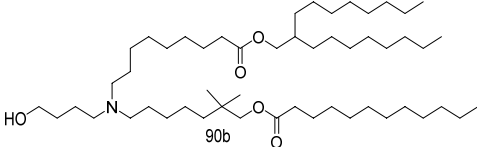
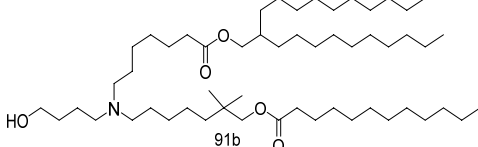
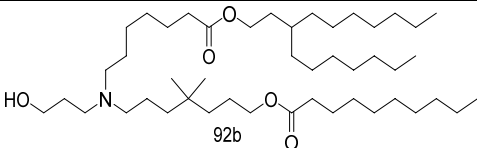
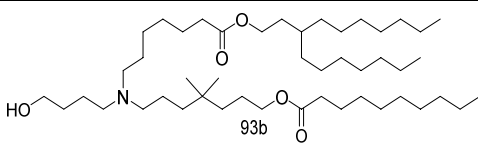
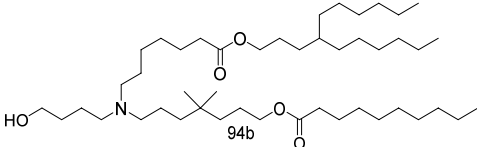
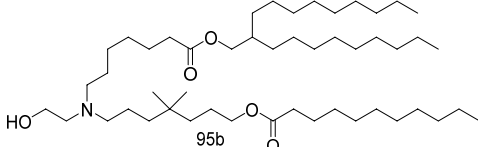
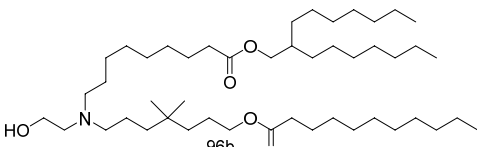
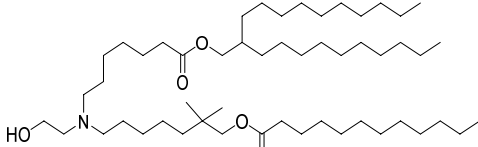
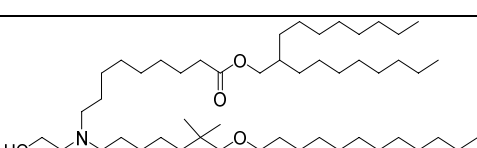
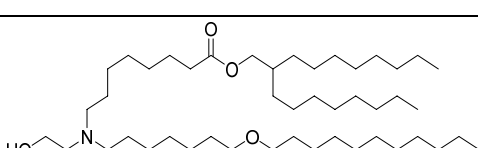
 51b Example 112 [M+H]⁺: 766.65	 52b Example 113 [M+H]⁺: 794.80
 53b Example 114 [M+H]⁺: 764.70	 54b Example 115 [M+H]⁺: 780.85
 55b Example 116 [M+H]⁺: 808.90	 56b Example 117 [M+H]⁺: 724.60
 57b Example 118 [M+H]⁺: 724.60	 58b Example 119 [M+H]⁺: 737.60
 59b Example 120 [M+H]⁺: 752.65	 62a Example 121 [M+H]⁺: 738.60

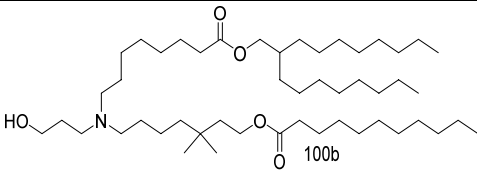
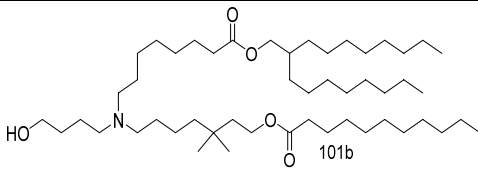
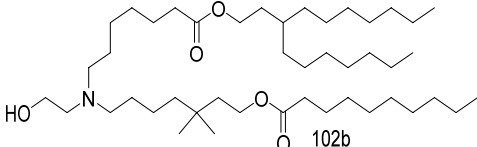
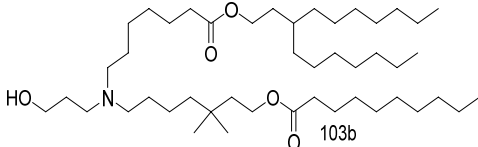
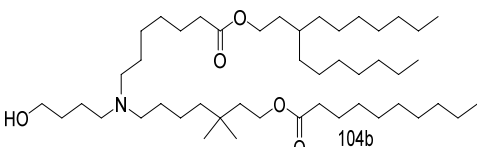
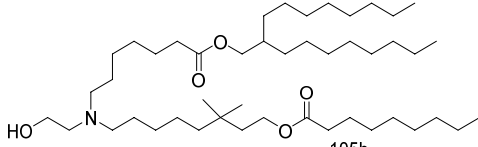
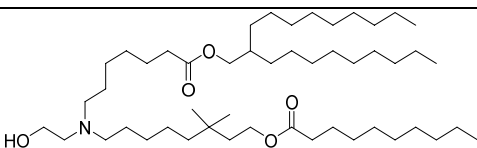
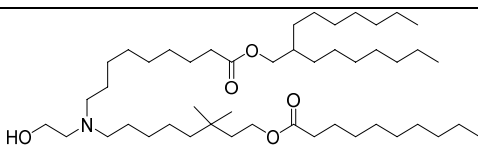
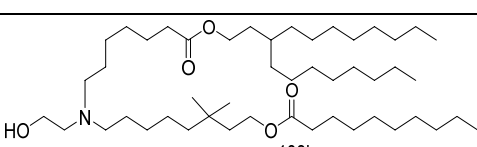
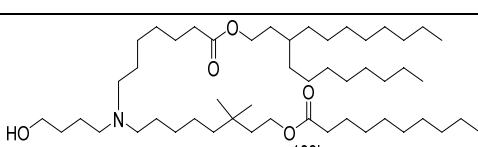
 Example 122 [M+H]⁺: 780.65	 Example 123 [M+H]⁺: 822.70
 Example 124 [M+H]⁺: 766.60	 Example 125 [M+H]⁺: 794.70
 Example 126 [M+H]⁺: 808.70	 Example 127 [M+H]⁺: 850.75
 Example 128 [M+H]⁺: 752.60	 Example 129 [M+H]⁺: 738.55
 Example 130 [M+H]⁺: 738.75	 Example 131 [M+H]⁺: 724.70
 Example 132 [M+H]⁺: 710.80	 Example 133 [M+H]⁺: 766.95

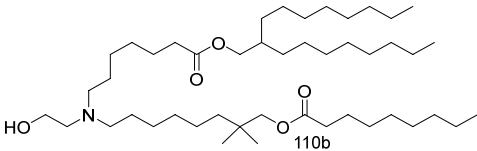
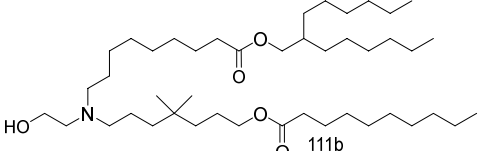
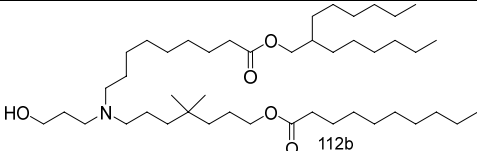
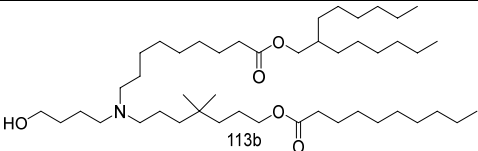
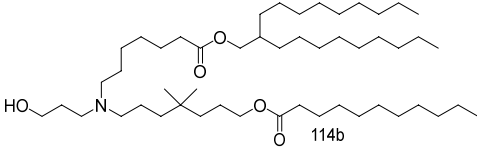
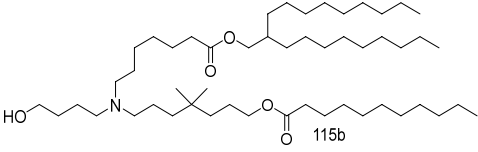
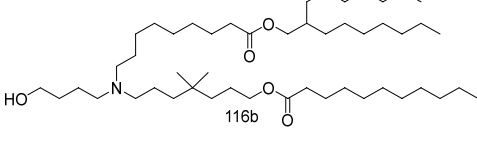
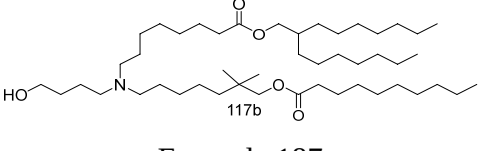
 Example 134 $[M+H]^+$: 752.65	 Example 135 $[M+H]^+$: 822.75
 Example 136 $[M+H]^+$: 864.85	 Example 137 $[M+H]^+$: 738.55
 Example 138 $[M+H]^+$: 724.70	 Example 139 $[M+H]^+$: 766.70
 Example 140 $[M+H]^+$: 752.75	 Example 141 $[M+H]^+$: 710.70
 Example 142 $[M+H]^+$: 752.70	 Example 143 $[M+H]^+$: 724.70
 Example 144	 Example 145

$[M+H]^+$: 724.65  76b Example 146 $[M+H]^+$: 156	$[M+H]^+$: 710.65  77b Example 147 $[M+H]^+$: 738.80
 78b Example 148 $[M+H]^+$: 808.70	 79b Example 149 $[M+H]^+$: 766.70
 80b Example 150 $[M+H]^+$: 752.65	 81b Example 151 $[M+H]^+$: 766.65
 82b Example 152 $[M+H]^+$: 752.75	 83b Example 153 $[M+H]^+$: 724.65
 84b Example 154 $[M+H]^+$: 766.65	 85b Example 155 $[M+H]^+$: 794.85
 86b Example 156	 87b Example 157

[M+H] ⁺ : 836.70	[M+H] ⁺ : 752.65
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 Example 158 [M+H]⁺: 808.70	 Example 159 [M+H]⁺: 780.65
 Example 160 [M+H]⁺: 822.75	 Example 161 [M+H]⁺: 850.80
 Example 162 [M+H]⁺: 738.65	 Example 163 [M+H]⁺: 752.70
 Example 164 [M+H]⁺: 738.65	 Example 165 [M+H]⁺: 780.90
 Example 166 [M+H]⁺: 752.90	 Example 167 [M+H]⁺: 822.75
 Example 168	 Example 169

$[M+H]^+$: 794.60  Example 170 $[M+H]^+$: 780.70	$[M+H]^+$: 766.65  Example 171 $[M+H]^+$: 794.75
 Example 172 $[M+H]^+$: 724.70	 Example 173 $[M+H]^+$: 738.65
 Example 174 $[M+H]^+$: 752.75	 Example 175 $[M+H]^+$: 738.60
 Example 176 $[M+H]^+$: 780.70	 Example 177 $[M+H]^+$: 752.65
 Example 178 $[M+H]^+$: 766.60	 Example 179 $[M+H]^+$: 794.75

 Example 180 [M+H]⁺: 738.70	 Example 181 [M+H]⁺: 710.60
 Example 182 [M+H]⁺: 724.85	 Example 183 [M+H]⁺: 738.85
 Example 184 [M+H]⁺: 794.75	 Example 185 [M+H]⁺: 808.80
 Example 186 [M+H]⁺: 780.75	 Example 187 [M+H]⁺: 752.90

[1153] Compounds 1c-283c were synthesized using the method as described in the above Examples, or similar methods using corresponding intermediates.

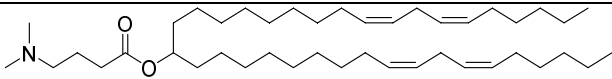
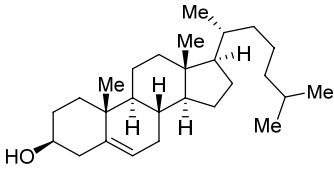
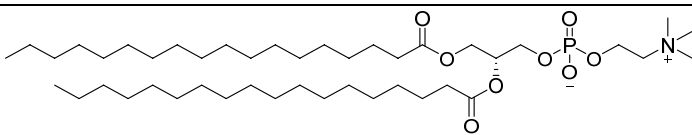
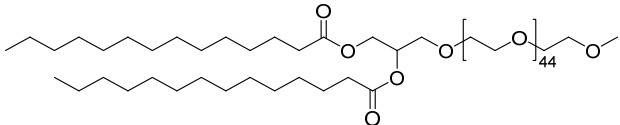
[1154] **Pharmacological experiments**

[1155] **Assay Example 1: Preparation of Nanoparticles**

[1156] Materials used for lipid nanoparticle assembly include: (1) ionizable lipid compounds: e.g., ionizable lipids designed and synthesized in the present disclosure or DLin-MC3-DMA (purchased from AVT) as a control; (2) structure lipids: e.g., Cholesterol (purchased from Sigma-Aldrich); (3) phospholipids: e.g., DSPC i.e., 1,2-distearoyl-SN-glycero-3-phosphocholine (Distearoylphosphatidylcholine, purchased from

AVT); (4) polyethylene glycolated lipids: e.g. DMG-PEG2000 i.e., dimyristoylglycero-polyethylene glycol 2000 (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000, purchased from AVT); (5) active ingredients of nucleic acid fragments: e.g. Luciferase mRNA, siRNA, CRISPR Cas 9 mRNA, etc. (manufactured in-house). The names of materials of the lipid nanoparticle assembly and their structural formulae are detailed in Table 4.

Table 4

No.	Structure name	Structural formula
1	DLin-MC3-DMA (MC3)	
2	Cholesterol	
3	DSPC	
4	DMG-PEG2000	

[1157] Lipid nanoparticles were prepared by (1) dissolving and mixing ionizable lipid compounds, cholesterol, phospholipids and polyethylene glycolated lipids in ethanol at (molar percentages) 50%, 38.5%, 10% and 1.5%, respectively; (2) dissolving the mRNA active ingredient in 25 mM sodium acetate solution (pH = 4.5); (3) using an automated high-throughput microfluidic system to mix the organic phase containing the lipid mixture and the aqueous phase containing the mRNA component in the flow ratio range of 1:1 to 1:4 at a mixing speed of 10 mL/min to 18 mL/min; (4) the prepared lipid nanoparticles (N/P ratio = 6) were diluted with phosphate buffer solution and the nanoparticle solutions were ultrafiltered to the original preparation volume using

ultrafiltration tubes (purchased from Millipore) with a cut-off molecular weight of 30 kDa; and (5) the obtained nanoparticles were filtered through a sterile 0.2 µm filter membrane and then stored in a sealed glass vial at low temperature.

[1158] The preparation method of lipid nanoparticles includes microfluidic mixing systems, but is not limited to this method, which also includes T-type mixers and ethanol injection method, and the like.

[1159] **Assay example 2: Characterization of physical properties of lipid nanoparticles**

[1160] The particle size and particle size dispersity index (PDI) of the prepared lipid nanoparticles were measured using a Zetasizer Pro (purchased from Malvern Instruments Ltd) and a DynaPro NanoStar (purchased from Wyatt) dynamic light scattering instrument. The degree of RNA encapsulation by lipid nanoparticles was characterized by the Encapsulation Efficiency%, which reflects the degree of binding of lipid nanoparticles to RNA fragments. This parameter was measured by the method of Quant-it™ RiboGreen RNA Assay (purchased from Invitrogen). Lipid nanoparticle samples were diluted in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH = 7.5). A portion of the sample solution was removed, to which 0.5% Triton (Triton X-100) was added, and then allowed to stand at 37 °C for 30 minutes. Immediately after the addition of RIBOGREEN® reaction solution, the fluorescence values were read on a Varioskan LUX multifunctional microplate reader (purchased from Thermofisher) at 485 nm for absorption and 528 nm for emission to give the encapsulation efficiency values.

[1161] **Assay example 3: Animal experiment**

[1162] The delivery effect and safety of nanoparticles encapsulated with luciferase mRNA (Trilink, L-7202) in mice were evaluated. The test mice were SPF-grade C57BL/6 mice, female, 6-8 weeks old, weighing 18-22 g, and were purchased from SPF (Beijing) Biotechnology Co., Ltd. All animals were acclimatized for more than 7 days prior to the experiment, and had free access to food and water during the experiment. The conditions include alternating light and dark for 12/12 h, the indoor temperature of 20-26 °C and the humidity of 40-70%. The mice were randomly grouped. The lipid

nanoparticles encapsulated with luciferase mRNA prepared above were injected into mice by intravenous administration at a single dose of 0.5 mg/kg mRNA, and the mice were subjected to in vivo bioluminescence assay using a Small Animal In Vivo Imaging System (IVIS LUMINA III, purchased from PerkinElmer) at 6 h after administration. The assay was performed as follows: D-luciferin solution was prepared in saline at a concentration of 15 mg/mL, and each mouse was given the substrate by intraperitoneal injection. At ten minutes after administration of the substrate, the mice were anesthetized in an anesthesia chamber with isoflurane at a concentration of 2.5%. The anesthetized mice were placed in IVIS for fluorescence imaging, and data acquisition and analysis were performed on the concentrated distribution area of fluorescence.

[1163] The in vivo delivery efficiency of lipid nanoparticle carriers was expressed as the mean values of fluorescence intensity and total photon count in different animals within the same subject group, as shown in Table 5 - Table 11. Higher values of fluorescence intensity and total photon count indicate higher in vivo delivery efficiency of this mRNA fragment by lipid nanoparticles. The lipid nanoparticles containing the cationic lipids of the present disclosure have good in vivo delivery efficiency.

Table 5

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after administration (Total Flux)
1a	113.08	0.022	94.61	3.52E+10
3a	89.72	0.021	94.23	1.03E+11
4a	103.7	0.005	92.87	3.25E+10
6a	90.67	0.018	87.22	2.88E+10
7a	103.32	0.018	90.92	5.26E+10
9a	103.03	0.031	89.64	2.06E+10
10a	131.09	0.032	89.69	7.08E+10
11a	98.01	0.021	89.36	2.05E+10
12a	104.85	0.021	85.24	1.39E+10

13a	110.20	0.018	92.96	5.01E+10
14a	90.99	0.012	91.67	1.09E+11
15a	95.94	0.021	90.77	4.15E+10
19a	109.37	0.035	87.90	4.73E+10
20a	102.13	0.032	87.83	1.18E+11
21a	110.00	0.016	88.37	8.84E+10
22a	99.48	0.010	97.25	1.74E+10
23a	99.25	0.011	96.30	9.84E+10
24a	109.53	0.052	88.89	3.07E+10
25a	86.99	0.051	95.62	1.33E+11
26a	106.37	0.050	91.18	1.11E+11
27a	136.43	0.016	93.52	4.31E+10
28a	110.30	0.018	93.90	4.30E+10
29a	88.59	0.012	97.30	5.46E+10
MC3	96.83	0.04	95.62	8.04E+09

Table 6

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after administration (Total Flux)
1b	88.59	0.031	89.89	9.34E+10
2b	104.61	0.013	80.17	8.31E+10
3b	102.32	0.015	74.43	1.41E+11
6b	99.55	0.029	80.01	7.42E+10
7b	101.67	0.030	88.68	2.00E+10
10b	114.72	0.052	72.72	3.15E+10
12b	104.60	0.031	91.04	1.19E+10
13b	99.02	0.018	89.27	1.81E+11

14b	99.73	0.013	83.54	1.05E+11
15b	120.27	0.015	69.69	8.22E+10
16b	101.90	0.028	89.09	1.28E+11
17b	109.87	0.030	87.72	1.74E+11
18b	100.46	0.037	89.34	3.91E+10
19b	109.53	0.036	83.01	6.13E+10
20b	107.83	0.032	87.69	4.82E+10
21b	94.58	0.051	92.37	4.95E+10
22b	99.44	0.050	93.03	8.78E+10
23b	115.70	0.031	93.14	3.92E+10
24b	83.05	0.019	94.52	7.06E+10
MC3	96.83	0.04	95.62	8.04E+09

Table 7

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after administration (Total Flux)
30a	107.40	0.12	86.94	8.32E+10
31a	115.56	0.11	86.08	7.04E+10
32a	129.00	0.10	83.51	1.24E+10
33a	111.60	0.17	86.98	1.09E+11
34a	116.67	0.12	95.73	3.14E+10
35a	126.63	0.22	95.00	3.01E+10
36a	104.80	0.15	92.41	2.51E+10
37a	110.67	0.15	92.14	3.54E+10
38a	114.03	0.13	94.51	1.39E+10
39a	144.83	0.08	93.59	2.24E+10
40a	120.90	0.18	95.08	2.03E+11

41a	114.03	0.13	94.51	1.11E+11
42a	104.13	0.17	95.54	3.47E+10
43a	105.63	0.15	97.03	2.23E+10
44a	92.67	0.20	96.84	1.06E+11
45a	114.73	0.15	94.63	1.22E+11
46a	110.83	0.16	93.03	9.06E+10
47a	104.47	0.21	93.23	3.10E+10
48a	81.22	0.16	96.13	8.16E+10
49a	100.56	0.14	94.85	2.28E+10
50a	78.03	0.12	98.67	2.86E+10
51a	92.08	0.15	94.81	3.11E+10
25b	94.39	0.15	95.59	1.11E+11
26b	113.77	0.14	94.58	6.53E+10
27b	91.10	0.18	97.83	5.59E+10
28b	94.55	0.16	96.19	4.18E+10
29b	112.43	0.10	96.28	3.52E+10
30b	115.83	0.08	95.02	4.03E+10
31b	118.73	0.07	95.73	1.87E+10
32b	116.50	0.16	95.31	3.52E+10
33b	85.80	0.15	94.85	8.23E+10
34b	85.20	0.19	97.61	2.78E+10
35b	100.40	0.21	96.35	3.77E+10
36b	112.50	0.19	96.10	3.84E+10
37b	83.72	0.16	95.15	3.72E+10
MC3	96.83	0.04	95.62	8.04E+09

Table 8

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after
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				administration (Total Flux)
52a	79.40	0.09	93.30	2.58E+10
53a	124.00	0.23	90.96	9.04E+10
54a	87.37	0.14	91.34	1.32E+10
55a	126.17	0.16	73.85	1.96E+10
56a	86.37	0.09	82.84	3.23E+10
57a	79.17	0.17	95.41	3.42E+10
58a	187.50	0.18	68.54	2.72E+10

Table 9

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after administration (Total Flux)
60a	92.74	0.15	97.44	1.75E+10
61a	111.90	0.09	95.87	1.32E+10
38b	102.50	0.11	98.29	1.49E+10
39b	102.67	0.07	93.58	7.16E+10
40b	97.10	0.11	96.74	3.70E+10
43b	121.89	0.08	95.26	1.29E+10
44b	92.63	0.15	97.45	1.16E+10
46b	98.91	0.09	97.78	2.44E+10
47b	122.40	0.07	97.27	2.84E+10
50b	98.36	0.13	98.50	1.01E+10

Table 10

Compound	Particle size (nm)	Particle-size distribution	Encapsulation efficiency	Total photon count in vivo at 6
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		(PDI)	(%)	hours after administration (Total Flux)
51b	91.96	0.12	95.92	7.60E+10
52b	105.97	0.06	90.84	1.01E+11
53b	125.03	0.42	91.92	1.00E+11
54b	81.37	0.17	96.69	5.71E+10
55b	90.37	0.11	94.65	1.02E+11
56b	98.59	0.16	93.87	8.35E+10
57b	98.23	0.18	94.15	3.86E+10
58b	112.93	0.15	92.88	6.17E+10
59b	127.23	0.12	80.27	1.04E+11
62a	98.07	0.17	89.88	1.20E+10
63a	80.23	0.17	95.56	1.17E+11
64a	86.99	0.15	96.72	9.82E+10
65a	95.88	0.16	95.93	6.53E+10
66a	105.77	0.11	92.88	9.31E+10
67a	111.33	0.06	91.57	6.07E+10
68a	103.93	0.04	94.47	7.55E+10
69a	107.20	0.34	96.65	7.41E+10
70a	86.08	0.15	96.69	9.33E+10

Table 11

Compound	Particle size (nm)	Particle-size distribution (PDI)	Encapsulation efficiency (%)	Total photon count in vivo at 6 hours after administration (Total Flux)
63b	165.53	0.09	84.27	2.72E+10
64b	143.67	0.09	89.27	3.36E+10

65b	80.60	0.16	97.75	1.25E+11
66b	81.83	0.17	97.18	4.35E+10
67b	88.28	0.23	96.30	1.71E+11
68b	88.33	0.20	96.31	2.88E+11
69b	99.05	0.13	93.85	1.52E+11
70b	96.20	0.09	96.91	1.15E+11
71b	95.59	0.17	95.95	1.70E+11
72b	92.45	0.12	95.13	7.01E+10
73b	119.37	0.14	92.71	4.73E+10
74b	93.18	0.17	94.92	7.13E+10
75b	91.60	0.19	95.99	7.05E+10
76b	91.27	0.18	94.97	9.41E+10
77b	93.16	0.16	95.88	9.72E+10
78b	98.88	0.12	92.27	5.51E+10
79b	99.27	0.15	92.85	1.62E+11
80b	93.39	0.18	93.59	8.94E+10
81b	107.43	0.19	92.87	5.20E+10
82b	99.57	0.16	90.71	5.03E+10
83b	100.67	0.10	95.70	1.62E+10
84b	123.77	0.11	89.17	6.68E+10
85b	92.14	0.17	95.44	9.61E+10
86b	92.26	0.13	94.74	1.01E+11
87b	92.25	0.22	94.16	1.35E+11
88b	98.16	0.12	94.68	4.51E+10
89b	122.20	0.08	84.88	5.51E+10
90b	109.57	0.08	91.21	4.72E+10
91b	96.43	0.12	91.95	8.66E+10
92b	99.90	0.15	92.47	3.74E+10
93b	141.73	0.10	90.17	2.45E+10
94b	125.60	0.11	93.55	2.23E+10

95b	84.62	0.15	95.41	2.44E+10
96b	97.75	0.15	92.10	3.77E+10
97b	85.56	0.14	93.79	9.01E+10
98b	87.99	0.18	93.04	1.07E+11
99b	85.13	0.15	92.70	4.78E+10
100b	101.50	0.12	91.14	8.51E+10
101b	126.00	0.10	81.76	5.39E+10
102b	92.12	0.16	93.92	7.52E+10
103b	96.82	0.11	94.07	5.95E+10
104b	135.57	0.09	91.51	3.20E+10
105b	89.73	0.16	94.38	9.24E+10
106b	88.22	0.15	94.89	1.42E+11
107b	88.13	0.16	94.05	1.98E+11
108b	86.61	0.16	94.16	1.38E+11
109b	95.32	0.13	93.00	1.90E+11
110b	133.93	0.21	85.48	1.36E+11
111b	187.13	0.21	63.26	3.98E+10
112b	175.67	0.17	69.74	1.31E+10
113b	147.03	0.09	88.21	2.09E+10
114b	103.40	0.13	93.55	4.53E+10
115b	100.25	0.12	93.91	3.71E+10
116b	120.13	0.09	90.71	1.96E+10
117b	151.17	0.09	72.51	1.73E+10

[1164] **Assay example 4: Evaluation of delivery efficiency and safety in vitro**

[1165] The delivery effect and safety of nanoparticles encapsulated with luciferase mRNA were evaluated at the cellular level in vitro. The cells used in the assay were human embryonic kidney cells 293 (HEK293T cells) cultured in DMEM (Dulbecco's Modified Eagle Medium) (purchased from Thermo Fisher) containing 10% fetal bovine serum and 5% penicillin-streptomycin double antibiotics at a indoor temperature of 37 °C and a CO₂ concentration of 5%. The cells were uniformly dispersed and spread in 48-well

plates, and incubated in the incubator for 24 h. Then a solution of the lipid nanoparticles encapsulated with luciferase mRNA were added. After 24 h, the cells were lysed, and the intracellular expression intensity and relative light units (RLU) of luciferase in each type of lipid nanoparticles were measured with a luciferase detection reagent (purchased from Promega). The higher the intensity of expression, the higher the delivery efficiency of the lipid material at the cellular level. Meanwhile, CCK-8 reagent (purchased from DOJINDO) was used in cytotoxicity testing for the parallel lipid nanoparticle-treated cell groups after 24 hours. In the test, the group of cells to which only PBS was added was used as a negative control. The procedure was as follows: after the addition of CCK-8 solution, the cells were left to stand in an incubator at 37 °C for 4 h. The absorbance values were read on a multifunctional microplate reader at an absorbance band of 450 nm. The ratio of the absorbance value of the nanoparticle-treated cells to that of the negative control was used as a characterization parameter for cell viability.

[1166] The delivery effects and the toxicity data of nanoparticles at the cellular level in vitro are shown in Table 12.

Table 12

Compound	Fluorescence intensity of cells (RLU)	Cell viability (%)
20a	6.55E+06	105.11
MC3	2.95E+06	97.84

[1167] **Assay Example 5: Evaluation of clearance rate of ionizable lipids *in vivo***

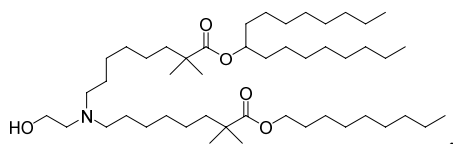
[1168] The 6-8 weeks old C57 WT female mice (n = 3) were injected by tail vein administration of 100 μ L of unloaded LNP (0.1 mg/mL) formed from the ionizable lipid, cholesterol, DSPC, and DMG-PEG 2000 at a ratio of 50:38.5:10:1.5. The experimental animals were executed by removing the cervical vertebrae and dissected for the liver at 24 h and 72 h after administration, respectively, while the same batch of non-dosed experimental animal livers were used as a blank control group. Water was added to the liver sample for homogenization, and the protein was precipitated. The content of the ionizable lipid in the sample was quantitatively analyzed using LC-MS/MS in comparison to a calibration standard prepared from matched blank liver tissues.

[1169] Clearance rate datas for ionizable lipids are shown in Table 13.

Table 13

Compound	Percentage of cationic lipids in the liver in the total dose, 24 h after administration (%)	Percentage of cationic lipids in the liver in the total dose, 72 h after administration (%)
1a	< 1	0
4a	< 1	0
1b	15±4.2	< 1
3b	12±3.8	< 1
10b	5±3.1	< 1
12b	< 1	0
13b	8±2.7	< 1
30a	4	< 2
26b	8	< 1
22b	2	< 1
39b	< 1	< 1
56a	< 1	< 1
Control group	92±3.5	89±4.7

[1170] The control compound is of the following structure:

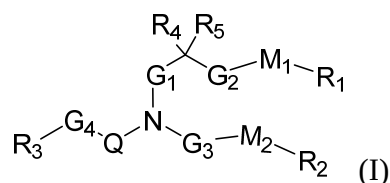


[1171] Datas in Table 13 show that the geminal dialkyl compound in the control group degrade slowly in the liver, and about 90% of it still remains in the liver 72 hours after administration. The compounds of the present invention has a faster degradation rate, and can be degraded in the liver in about 72 hours.

[1172] While the present disclosure has been fully described by way of its embodiments, it is worth noting that various variations and modifications are apparent to those skilled in the art. Such variations and modifications should all be included within the scope of the claims appended to this disclosure.

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof:



wherein,

G₁ and G₂ are independently selected from a chemical bond, C₁₋₁₃ linear alkylene, C₂₋₁₃ linear alkenylene, and C₂₋₁₃ linear alkynylene, each of which is optionally substituted with one or more R_{G1};

G₁ and G₂ have a total length of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 carbon atoms;

R_{G1} is independently H, C₁₋₁₄ alkyl, -L_a-OR_a, -L_a-SR_a, or -L_a-NR_aR'_a;

G₃ is C₄₋₁₄ linear alkylene, C₄₋₁₄ linear alkenylene, or C₄₋₁₄ linear alkynylene, each of which is optionally substituted with one or more R_{G3};

R_{G3} is independently H, -L_a-OR_a, -L_a-SR_a, or -L_a-NR_aR'_a;

L_a is independently a chemical bond or C₁₋₁₄ alkylene;

R_a and R'_a are independently selected from H, C₁₋₁₄ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;

G₄ is a chemical bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆ alkynylene, each of which is optionally substituted with one or more R_{G4};

R_{G4} is independently H, C₁₋₆ alkyl, -L_b-OR_b, -L_b-SR_b, or -L_b-NR_bR'_b;

L_b is independently a chemical bond or C₁₋₆ alkylene;

R_b and R'_b are independently selected from H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocyclyl;

or, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4g};

R_{4g} is independently H, halogen, cyano, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -L_e-OR_e, -L_e-SR_e, or -L_e-NR_eR'_e;

L_e is independently a chemical bond or C₁₋₈ alkylene;

R_e and R'_e are independently selected from H, C₁₋₈ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;

M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -O-, -SC(O)O-, -OC(O)NR-, -NRC(O)NR-, -OC(O)S-, -OC(O)O-, -NRC(O)O-, -SC(O)-, -C(O)S-, -NR-, -C(O)NR-, -NRC(O)-, -NRC(O)S-, -SC(O)NR-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR-, -NRC(S)O-, -S-S-, and -S(O)₀₋₂;

Q is selected from a chemical bond, -C(O)O-, -O-, -SC(O)O-, -OC(O)NR_f-, -NR_fC(O)NR_f-, -OC(O)S-, -OC(O)O-, -NR_fC(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NR_f-, -C(O)NR_f-, -NR_fC(O)-, -NR_fC(O)S-, -SC(O)NR_f-, -C(O)-, -OC(S)-, -C(S)O-, -OC(S)NR_f-, -NR_fC(S)O-, -S-S-, -S(O)₀₋₂-, phenylene, and pyridinylene, wherein the phenylene or the pyridinylene is optionally substituted with one or more R*;

R* is independently H, halogen, cyano, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, -L_f-OR_f, -L_f-SR_f, or -L_f-NR_fR'_f;

L_f is independently a chemical bond or C₁₋₈ alkylene;

R_f and R'_f are independently selected from H, C₁₋₁₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;

R₁ and R₂ are independently selected from C₄₋₂₀ alkyl, C₄₋₂₀ alkenyl, and C₄₋₂₀ alkynyl, each of which is optionally substituted with one or more R_{1s}, and wherein one or more methylene units are optionally and independently replaced with -NR'-;

R_{1s} is independently H, C₁₋₂₀ alkyl, -L_c-OR_c, -L_c-SR_c, or -L_c-NR_cR'_c;

R and R' are independently H or C₁₋₂₀ alkyl;

L_c is independently a chemical bond or C₁₋₂₀ alkylene;

R_c and R'_c are independently selected from H, C₁₋₂₀ alkyl, C₃₋₁₄ cycloalkyl, and 3- to 14-membered heterocyclyl;

R₃ is selected from CN, -OR_g, -C(O)R_g, -OC(O)R_g, -NR''C(O)R_g, -NR_gR'_g, -NR''C(O)NR_gR'_g, -NR''C(O)R_g, -NR''S(O)₂R_g, -OC(O)NR_gR'_g, -NR''C(O)OR_g, -N(OR_g)C(O)R_g, -N(OR_g)S(O)₂R_g, -N(OR_g)C(O)OR_g, -N(OR_g)C(O)R_gR'_g, 3- to 14-membered heterocyclyl, and 5- to 14-membered heteroaryl;

R_g and R'_g are independently H, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl;

R'' is independently H or C₁₋₆ alkyl;

R₄ and R₅ are independently C₁₋₈ alkyl, which is optionally substituted with one or more R_{4s}; or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₁₄ cycloalkylene or 3- to 14-membered heterocyclylene, each of which is optionally substituted with one or more R_{4s};

R_{4s} is independently H, halogen, cyano, C₁₋₈ alkyl, C₁₋₈ haloalkyl, -L_d-OR_d, -L_d-SR_d, or -L_d-NR_dR'_d;

L_d is independently a chemical bond or C₁₋₈ alkylene;

R_d and R'_d are independently H, C₁₋₈ alkyl, C₃₋₁₄ cycloalkyl, or 3- to 14-membered heterocyclyl.

2. The compound of formula (I) of claim 1, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G₁ and G₂ are independently a chemical bond, C₁₋₉ linear alkylene, C₂₋₉ linear alkenylene, or C₂₋₉ linear alkynylene;
alternatively, G₁ is C₁₋₆ linear alkylene, C₂₋₆ linear alkenylene, or C₂₋₆ linear alkynylene, alternatively C₁₋₆ linear alkylene, alternatively C₂₋₆ linear alkylene;
alternatively, G₂ is a chemical bond, C₁₋₆ linear alkylene, C₂₋₆ linear alkenylene, or C₂₋₆ linear alkynylene, alternatively a chemical bond or C₁₋₆ linear alkylene, alternatively a chemical bond or C₁₋₄ linear alkylene;
alternatively, G₁ and G₂ have a total length of 3, 4, 5, 6, 7, 8, or 9 carbon atoms, alternatively a total length of 4, 5, or 6 carbon atoms, alternatively a total length of 5 or 6 carbon atoms;
alternatively a total length of 5, 6, or 7 carbon atoms, alternatively a total length of 6 or 7 carbon atoms;
alternatively, G₁ and G₂ are optionally substituted with 1, 2, 3, or 4 R_{G1}.
3. The compound of formula (I) of claim 1 or 2, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{G1} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₆ alkyl.
4. The compound of formula (I) of any one of claims 1-3, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G₃ is C₄₋₁₀ linear alkylene, C₄₋₁₀ linear alkenylene, or C₄₋₁₀ linear alkynylene, alternatively C₄₋₉ linear alkylene, alternatively C₅₋₈ linear alkylene;
alternatively, G₃ is optionally substituted with 1, 2, 3, or 4 R_{G3}.

5. The compound of formula (I) of any one of claims 1-4, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_a is independently a chemical bond or C_{1-10} alkylene, alternatively a chemical bond or C_{1-6} alkylene; alternatively, R_a and R'_a are independently H, C_{1-10} alkyl, C_{3-10} cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C_{1-6} alkyl.
6. The compound of formula (I) of any one of claims 1-5, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein G_4 is C_{1-4} alkylene, C_{2-4} alkenylene, or C_{2-4} alkynylene, alternatively C_{2-4} alkylene, alternatively C_{2-3} alkylene; alternatively, G_4 is optionally substituted with 1, 2, 3, or 4 R_{G4} .
7. The compound of formula (I) of any one of claims 1-6, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{G4} is independently H or C_{1-6} alkyl, alternatively C_{1-4} alkyl; alternatively, two R_{G4} attached to the same carbon atom are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkylene or 3- to 10-membered heterocyclylene, alternatively C_{3-7} cycloalkylene or 3- to 7-membered heterocyclylene, each of which is optionally substituted with 1, 2, or 3 R_{4g} ; alternatively, R_{4g} is independently H, halogen, cyano, C_{1-6} alkyl, or C_{1-6} haloalkyl.
8. The compound of formula (I) of any one of claims 1-7, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_b is independently a chemical bond or C_{1-4} alkylene; alternatively, R_b and R'_b are independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or 3- to 7-membered heterocyclyl, alternatively H or C_{1-6} alkyl, alternatively H or C_{1-4} alkyl.
9. The compound of formula (I) of any one of claims 1-8, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein M_1 and M_2 are independently selected from $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-SC(O)-$, $-C(O)S-$, $-C(O)NR-$, and $-NRC(O)-$; alternatively $-C(O)O-$, $-OC(O)O-$, $-OC(O)-$, $-SC(O)-$, and $-C(O)S-$; alternatively $-C(O)O-$, $-OC(O)-$, $-SC(O)-$, and $-C(O)S-$; alternatively $-C(O)O-$ and $-OC(O)-$; alternatively, M_1 and M_2 are independently selected from $-C(O)O-$ and $-C(O)S-$, alternatively $-C(O)O-$; alternatively, one of M_1 and M_2 is $-C(O)O-$ or $-C(O)S-$, alternatively $-C(O)O-$, and the other is $-OC(O)-$ or $-SC(O)-$, alternatively $-OC(O)-$;

alternatively, M₁ is -OC(O)- or -SC(O)-, alternatively -OC(O)-; and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-;

alternatively, M₁ is -C(O)O-, and M₂ is -C(O)O- or -C(O)S-;

alternatively, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, -C(O)S-, -NHC(O)-, and -C(O)NH-;

alternatively, M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -C(O)S-, and -C(O)NH-, alternatively -C(O)O-, -OC(O)-, and -C(O)S-;

alternatively, one of M₁ and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-, and the other is -C(O)O-, -C(O)S-, -C(O)NH-, -OC(O)-, or -SC(O)-, alternatively -C(O)O-, -C(O)S-, -C(O)NH-, or -OC(O)-, alternatively -C(O)O-, -C(O)S-, -OC(O)-, or -SC(O)-, alternatively -C(O)O-, -C(O)S-, or -OC(O)-;

alternatively, one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-, alternatively -C(O)O- or -OC(O)-;

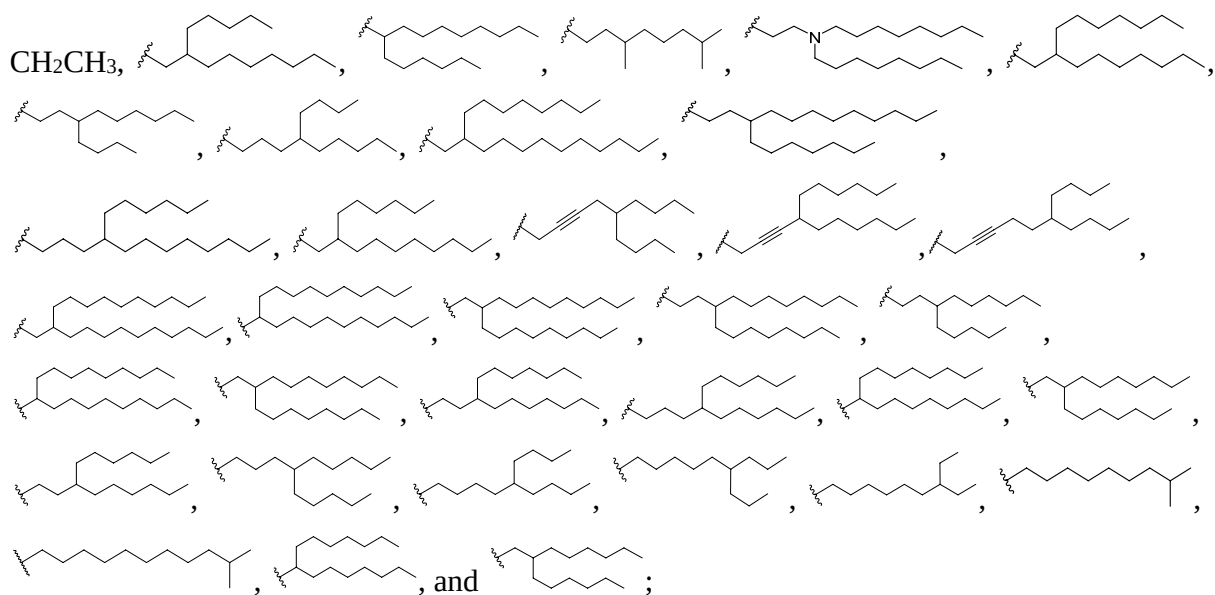
alternatively, M₁ is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-, alternatively -C(O)O- or -OC(O)-, alternatively -C(O)O-, alternatively -OC(O)-, and M₂ is -OC(O)O-;

alternatively, M₁ is -OC(O)O-, and M₂ is -OC(O)- or -C(O)O-, alternatively -OC(O)-;

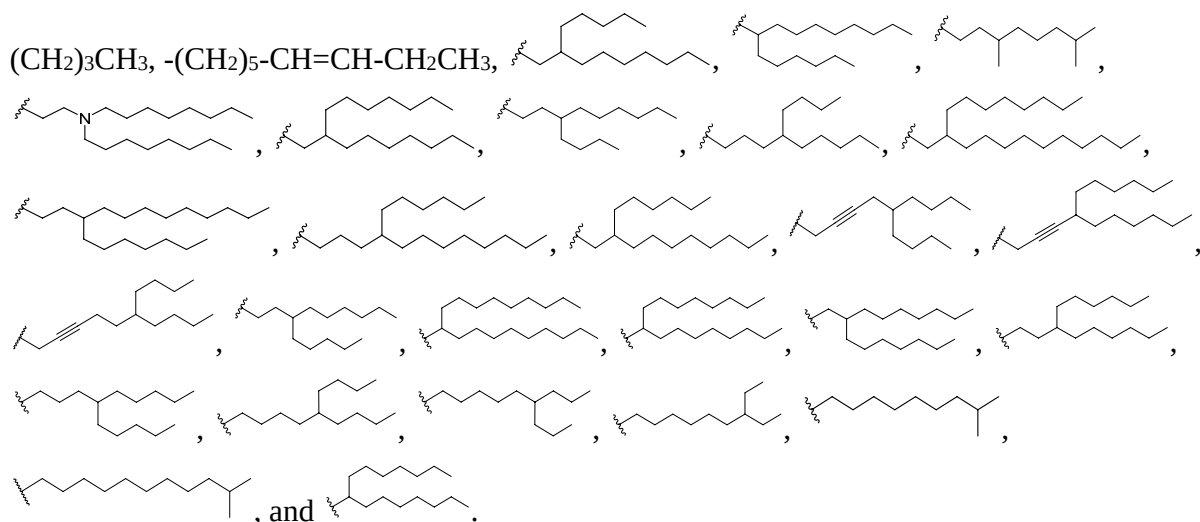
alternatively, M₁ and M₂ are independently selected from -C(O)O-, -C(O)S-, -OC(O)-, -SC(O)-, and -OC(O)O-, alternatively -C(O)O-, -OC(O)-, and -OC(O)O-; alternatively, M₁ and M₂ are not simultaneously -OC(O)O-.

10. The compound of formula (I) of any one of claims 1-9, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R₁ and R₂ are independently C₆₋₁₄ alkyl, C₆₋₁₄ alkenyl, or C₆₋₁₄ alkynyl, alternatively C₆₋₁₄ alkyl, alternatively C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl;
- alternatively, R₁ and R₂ are independently C₇₋₁₂ alkyl, C₇₋₁₂ alkenyl, or C₇₋₁₂ alkynyl, alternatively C₈₋₁₂ alkyl, C₈₋₁₂ alkenyl, or C₈₋₁₂ alkynyl;
- alternatively, R₁ and R₂ are optionally substituted with 1, 2, 3, or 4 R_{1s}, alternatively optionally substituted with 1 R_{1s};
- alternatively, R₁ and R₂ are independently selected from the following groups: -(CH₂)₅CH₃, -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, -CH₂-C≡C-(CH₂)₅CH₃, -CH₂-C≡C-(CH₂)₆CH₃, -(CH₂)₂-C≡C-(CH₂)₅CH₃, -(CH₂)₂-C≡C-(CH₂)₄CH₃, -(CH₂)₃-C≡C-(CH₂)₃CH₃, -(CH₂)₄-C≡C-(CH₂)₃CH₃, -CH₂-CH=CH-(CH₂)₅CH₃, -CH₂-CH=CH-

(CH₂)₆CH₃, -(CH₂)₂-CH=CH-(CH₂)₅CH₃, -(CH₂)₄-CH=CH-(CH₂)₃CH₃, -(CH₂)₅-CH=CH-



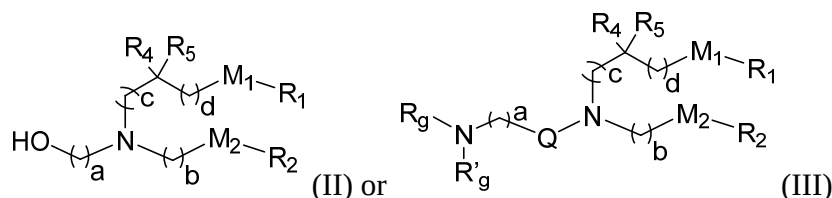
alternatively, R₁ and R₂ are independently selected from the following groups: -(CH₂)₅CH₃, -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, -CH₂-C≡C-(CH₂)₅CH₃, -CH₂-C≡C-(CH₂)₆CH₃, -(CH₂)₂-C≡C-(CH₂)₅CH₃, -(CH₂)₄-C≡C-(CH₂)₃CH₃, -CH₂-CH=CH-(CH₂)₅CH₃, -CH₂-CH=CH-(CH₂)₆CH₃, -(CH₂)₂-CH=CH-(CH₂)₅CH₃, -(CH₂)₄-CH=CH-



11. The compound of formula (I) of any one of claims 1-10, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c, alternatively H or C₁₋₁₄ alkyl, alternatively H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.

12. The compound of formula (I) of any one of claims 1-11, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R and R' are each independently H or C₁₋₂₀ alkyl, alternatively H or C₁₋₁₄ alkyl, alternatively H or C₁₋₉ alkyl, alternatively H or C₁₋₆ alkyl; alternatively, R is H.
13. The compound of formula (I) of any one of claims 1-12, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_c is independently a chemical bond or C₁₋₁₄ alkylene, alternatively a chemical bond or C₁₋₁₀ alkylene, alternatively a chemical bond or C₁₋₆ alkylene;
alternatively, R_c and R'_c are independently H or C₁₋₁₄ alkyl, alternatively H or C₁₋₁₀ alkyl, alternatively H or C₁₋₆ alkyl.
14. The compound of formula (I) of any one of claims 1-13, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R₃ is CN, -OR_g, or -NR_gR'_g, alternatively -OR_g or -NR_gR'_g, alternatively -OR_g, alternatively -OH;
alternatively, R₃ is -OH or -N(CH₃)₂;
alternatively, R_g and R'_g are independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or 3- to 7-membered heterocyclyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl, alternatively H or methyl.
15. The compound of formula (I) of any one of claims 1-14, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R₄ and R₅ are independently C₁₋₆ alkyl, alternatively C₁₋₃ alkyl, alternatively methyl;
alternatively, R₄ and R₅ are optionally substituted with 1, 2, or 3 R_{4s};
alternatively, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₁₀ cycloalkylene or 3- to 10-membered heterocyclylene, alternatively C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene, alternatively C₃₋₆ cycloalkylene (e.g., cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene), alternatively C₃₋₅ cycloalkylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene;
alternatively, a ring formed by R₄ and R₅ with the carbon atom to which they are attached is optionally substituted with 1, 2, or 3 R_{4s}.
16. The compound of formula (I) of any one of claims 1-15, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein R_{4s} is independently H, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -L_d-OR_d, -L_d-SR_d, or -L_d-NR_dR'_d, alternatively H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl, alternatively H, C₁₋₃ alkyl, or C₁₋₃ haloalkyl.

17. The compound of formula (I) of any one of claims 1-16, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_d is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₃ alkylene; alternatively, R_d and R'_d are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl.
18. The compound of formula (I) of any one of claims 1-17, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein L_e is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₄ alkylene; alternatively, R_e and R'_e are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.
19. The compound of formula (I) of any one of claims 1-18, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein Q is a chemical bond, -OC(O)-, or -SC(O)-; alternatively a chemical bond or -SC(O)-; alternatively, when Q is phenylene or pyridinylene, which is optionally substituted with 1, 2, or 3 R*;
alternatively, R* is independently H, halogen, cyano, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;
alternatively, L_f is independently a chemical bond or C₁₋₆ alkylene, alternatively a chemical bond or C₁₋₄ alkylene;
alternatively, R_f and R'_f are independently H, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, or 3- to 10-membered heterocyclyl, alternatively H or C₁₋₆ alkyl, alternatively H or C₁₋₄ alkyl.
20. The compound of formula (I) of any one of claims 1-19, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, which has a structure of formula (II) or formula (III):



wherein,

$a = 1, 2, 3, 4, 5$, or 6 ;

$b = 4, 5, 6, 7, 8, 9$, or 10 ;

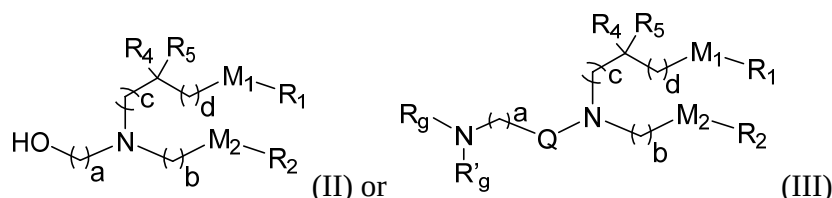
$c = 1, 2, 3, 4, 5$, or 6 ;

$d = 0, 1, 2, 3, \text{ or } 4$;

$c + d = 3, 4, 5, 6, 7, 8, \text{ or } 9$;

the other groups are as defined in any one of claims 1-19.

21. The compound of formula (II) or formula (III) of claims 20, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein,

the substitution site of R_{1s} on R₁ or R₂ is separated from M₁ or M₂ by 0-10 carbon atoms, alternatively 0-6 carbon atoms, alternatively 0-4 carbon atoms, alternatively 0-2 carbon atoms, alternatively 0 carbon atoms;

alternatively, the substitution site of R_{1s} on R₁ or R₂ is separated from M₁ or M₂ by 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, alternatively 2-4 carbon atoms;

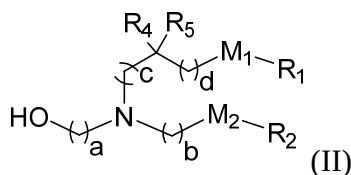
alternatively, R₁ is not substituted with R_{1s}, and the substitution site of R_{1s} on R₂ is separated from M₂ by 0-10 carbon atoms, alternatively 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, alternatively 2-4 carbon atoms;

alternatively, R₁ is substituted with R_{1s}, and R₂ is not substituted with R_{1s};

alternatively, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring;

alternatively, d is not 0.

22. The compound of formula (II) of claim 20 or 21, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein

a = 2, 3, 4, 5, or 6;

b = 4, 5, 6, 7, 8, 9, or 10;

c = 1, 2, 3, 4, 5, or 6;

d = 0, 1, 2, 3, or 4;

c + d = 3, 4, 5, 6, 7, 8, or 9; alternatively c + d = 4, 5, or 6;

M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, -SC(O)-, and -C(O)S-; alternatively, M₁ and M₂ are independently selected from -C(O)O- and -C(O)S-; alternatively, one of M₁ and M₂ is -C(O)O- or -C(O)S-, and the other is -OC(O)- or -SC(O)-;

R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c, alternatively H or C₁₋₁₄ alkyl;

L_c is independently a chemical bond or C₁₋₁₄ alkylene;

R_c and R'_c are independently H or C₁₋₁₄ alkyl;

R₄ and R₅ are independently C₁₋₆ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

23. The compound of formula (II) of claim 22, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4;

b = 4, 5, 6, 7, 8, or 9; alternatively b = 5, 6, 7, or 8; alternatively b = 5, 6, or 7;

c = 2, 3, 4, 5, or 6;

d = 0, 1, 2, 3, or 4;

c + d = 5 or 6;

M₁ and M₂ are independently -C(O)O- or -OC(O)-; alternatively, M₁ and M₂ are -C(O)O-; alternatively, one of M₁ and M₂ is -C(O)O-, and the other is -OC(O)-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene, alternatively C₃₋₅ cycloalkylene.

24. The compound of formula (II) of claim 23, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4;

b = 4, 5, 6, 7, 8, or 9; alternatively b = 5, 6, 7, or 8; alternatively b = 5 or 7;

c = 2, 3, 4, 5, or 6;

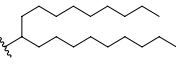
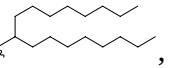
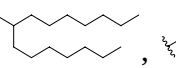
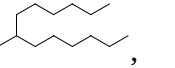
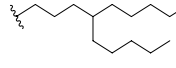
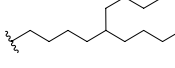
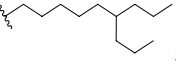
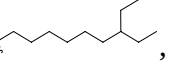
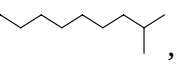
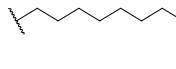
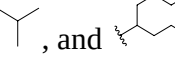
d = 0, 1, 2, 3, or 4; alternatively d = 0, 1, 2, or 4;

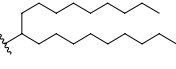
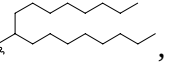
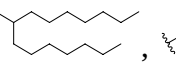
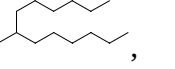
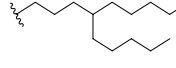
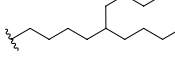
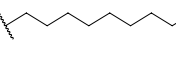
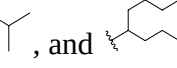
c + d = 5 or 6; alternatively c + d = 6;

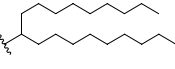
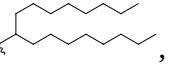
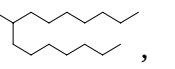
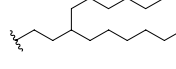
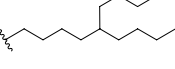
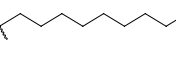
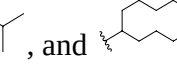
M₁ and M₂ are -C(O)O-;

or, one of M₁ and M₂ is -C(O)O-, and the other is -OC(O)-;

R₁ and R₂ are independently selected from: -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -

(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, , , , , , , , , , , , and ; alternatively -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -

(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, , , , , , , , and ; alternatively -(CH₂)₈CH₃,

-(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, , , , , , , , and ;

R₄ and R₅ are methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene;

alternatively, only one of R₁ and R₂ is substituted.

25. The compound of formula (II) of claim 23, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2;

b = 5;

c = 2, 3, 4, 5, or 6; alternatively c = 6;

d = 0, 1, 2, 3, or 4; alternatively d = 0;

c + d = 5 or 6, alternatively 6;

M₁ and M₂ are -C(O)O-;

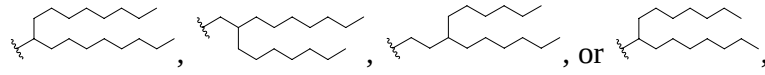
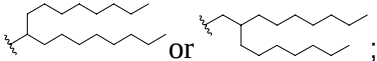
R₁ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₈₋₉ alkyl, or alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

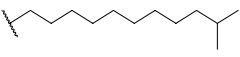
R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively C₆₋₈ alkyl, alternatively C₇₋₈ alkyl;

R₂ is C₇₋₁₁ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl, alternatively C₁₁ linear alkyl, which is optionally substituted with 1 C₁₋₃ alkyl, alternatively optionally substituted with 1 methyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, R₁ is , alternatively  ;

alternatively, R₂ is -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, or .

26. The compound of formula (II) of claim 23, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4; alternatively a = 2;

b = 7;

c = 2, 3, 4, 5, or 6; alternatively c = 2, 3, or 4; alternatively c = 2;

d = 0, 1, 2, 3, or 4; alternatively d = 2, 3, or 4; alternatively d = 4;

c + d = 5 or 6, alternatively 6;

M₁ and M₂ are -C(O)O-;

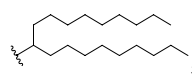
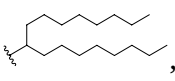
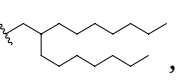
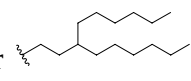
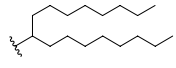
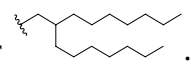
R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively C₆₋₉ alkyl, alternatively C₇₋₈ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, R₂ is , , , or , alternatively  or .

27. The compound of formula (II) of claim 23, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- a = 2;
 - b = 7;
 - c = 3 or 4; alternatively c = 4;
 - d = 2;
 - M₁ and M₂ are -C(O)O-;
 - R₁ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₈₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};
 - R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl;
 - R₂ is C₇₋₁₁ linear alkyl, alternatively C₉ linear alkyl;
 - R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;
 - or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene.
28. The compound of formula (II) of claim 23, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein
- a = 2, 3, or 4; alternatively a = 2 or 4;
 - b = 6 or 7; alternatively b = 7;
 - c = 2, 3, 4, 5, or 6; alternatively c = 5 or 6;
 - d = 0, 1, 2, 3, or 4; alternatively d = 0 or 1;
 - c + d = 5 or 6, alternatively 6;
 - M₁ is -OC(O)-; and M₂ is -C(O)O-;
 - R₁ is C₇₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl;
 - R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ linear alkyl, which is optionally substituted with 1 R_{1s};
 - R_{1s} is independently C₇₋₉ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, R₂ is , , or .

$$\text{HO}-(\text{---})_a\text{N}-(\text{---})_b\text{M}_2\text{---R}_2 \quad \text{---}(\text{---})_c\text{C}(\text{R}_4)(\text{R}_5)\text{---}(\text{---})_d\text{M}_1\text{---R}_1 \quad (\text{II})$$

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

30. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4;

b = 4, 5, 6, 7, 8, or 9, alternatively b = 5, 6, 7, or 8, alternatively b = 5, 6, or 7;

c = 2, 3, 4, 5, or 6;

d = 0, 1, 2, 3, or 4;

c + d = 5, 6, or 7;

M₁ and M₂ are independently -C(O)O-, -OC(O)-, -C(O)S- or -C(O)NH-, alternatively -C(O)O-, -OC(O)-, or -C(O)S-; alternatively, one of M₁ and M₂ is -C(O)O-, and the other is -C(O)O-, -C(O)S-, -C(O)NH-, or -OC(O)-, alternatively -C(O)O-, -C(O)S-, or -OC(O)-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, C₇₋₁₂ alkenyl, or C₇₋₁₂ alkynyl, alternatively C₈₋₁₂ alkyl, C₈₋₁₂ alkenyl, or C₈₋₁₂ alkynyl, each of which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene, alternatively C₃₋₅ cycloalkylene.

31. The compound of formula (II) of claim 30, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4;

b = 4, 5, 6, 7, 8, or 9; alternatively b = 5, 6, 7, or 8; alternatively b = 5 or 7;

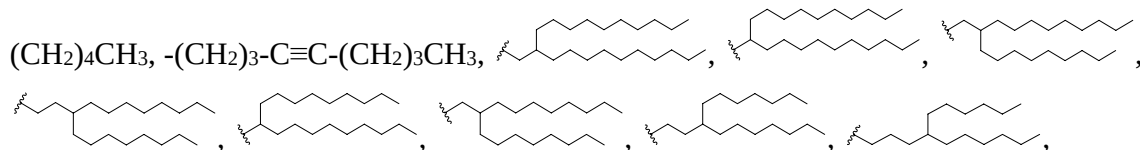
c = 2, 3, 4, 5, or 6;

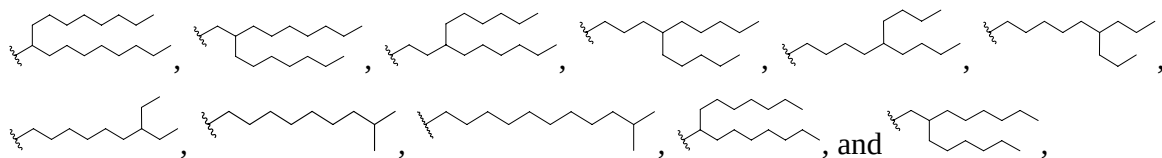
d = 0, 1, 2, 3, or 4;

c + d = 5, 6, or 7; alternatively c + d = 6;

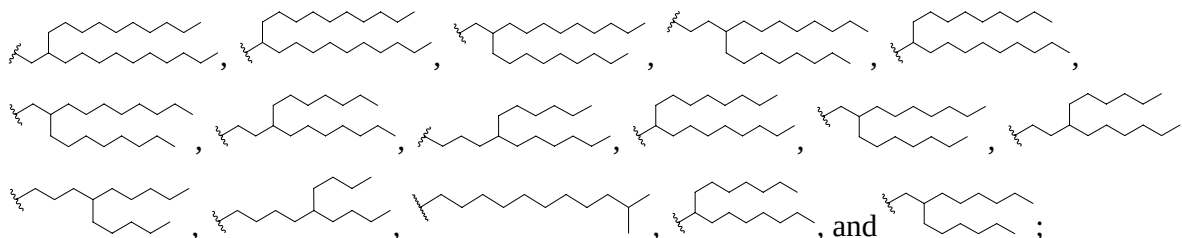
one of M₁ and M₂ is -C(O)O-, and the other is -C(O)O-, -C(O)S-, -C(O)NH-, or -OC(O)-, alternatively -C(O)O-, -C(O)S-, or -OC(O)-;

R₁ and R₂ are independently selected from: -(CH₂)₆CH₃, -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, -(CH₂)₁₁CH₃, -CH₂-CH=CH-(CH₂)₅CH₃, -CH₂-C≡C-(CH₂)₅CH₃, -(CH₂)₂-C≡C-

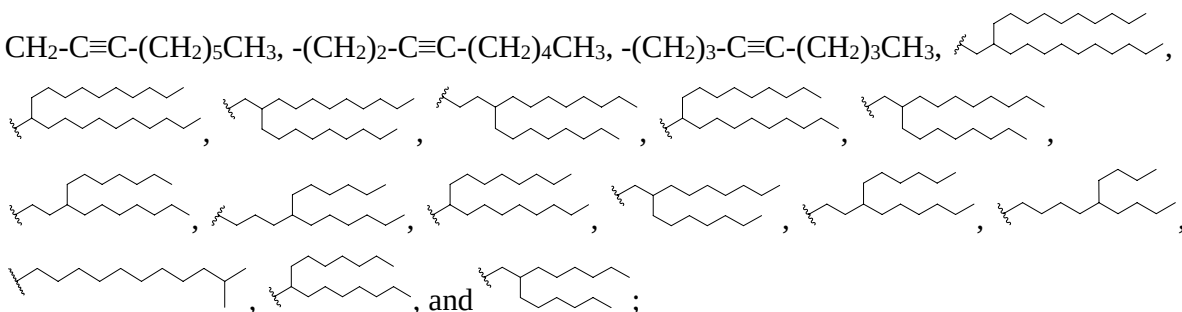




alternatively: $-(\text{CH}_2)_7\text{CH}_3$, $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$,



alternatively: $-(\text{CH}_2)_8\text{CH}_3$, $-(\text{CH}_2)_9\text{CH}_3$, $-(\text{CH}_2)_{10}\text{CH}_3$, $-(\text{CH}_2)_{11}\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_5\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{C}-(\text{CH}_2)_5\text{CH}_3$, $-(\text{CH}_2)_2-\text{C}\equiv\text{C}-(\text{CH}_2)_4\text{CH}_3$, $-(\text{CH}_2)_3-\text{C}\equiv\text{C}-(\text{CH}_2)_3\text{CH}_3$,



R_4 and R_5 are methyl;

or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form cyclopropylene, cyclobutylene, cyclopentylene, or cyclohexylene, alternatively cyclopropylene or cyclopentylene, alternatively cyclopropylene;

alternatively, only one of R_1 and R_2 is substituted.

32. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

$a = 2$;

$b = 5$;

$c = 5$ or 6 ; alternatively $c = 6$;

$d = 0$ or 1 ; alternatively $d = 0$;

$c + d = 5$ or 6 , alternatively 6 ;

M_1 is $-\text{C}(\text{O})\text{O}-$, and M_2 is $-\text{C}(\text{O})\text{O}-$ or $-\text{C}(\text{O})\text{S}-$; alternatively M_1 and M_2 are $-\text{C}(\text{O})\text{O}-$;

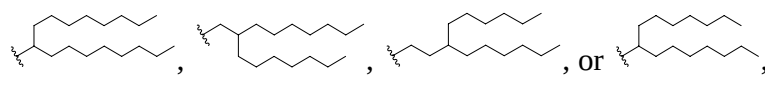
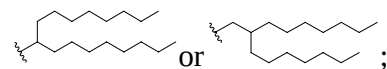
R₁ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₈₋₉ alkyl, or alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

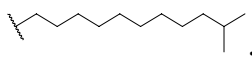
R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively H or C₁₋₉ alkyl, alternatively C₆₋₈ alkyl, alternatively C₇₋₈ alkyl;

R₂ is C₇₋₁₁ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl, alternatively C₁₁ linear alkyl, which is optionally substituted with 1 C₁₋₃ alkyl, alternatively optionally substituted with 1 methyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, R₁ is , alternatively  ;

alternatively, R₂ is -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, or .

33. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4; alternatively a = 2;

b = 5, 6, or 7; alternatively b = 7;

c = 2, 3, 4, 5, or 6; alternatively c = 2, 3, or 4; alternatively c = 2;

d = 0, 1, 2, 3, or 4; alternatively d = 2, 3, or 4; alternatively d = 4;

c + d = 5 or 6, alternatively 6;

M₁ and M₂ are -C(O)O-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s}; and only one of R₁ and R₂ is substituted;

R_{1s} is independently H or C₁₋₁₀ alkyl, alternatively C₆₋₁₀ alkyl, alternatively C₇₋₉ alkyl;

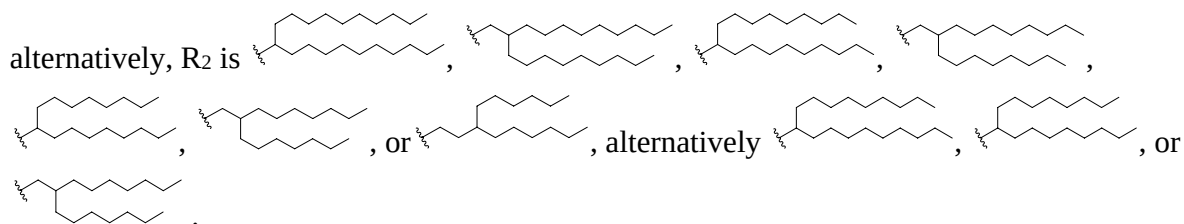
R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring;

alternatively,

R₁ is C₈₋₁₂ linear alkyl, alternatively C₉₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl;

R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s}; when R₂ is C₁₀ linear alkyl, R_{1s} is C₉₋₁₀ alkyl, alternatively C₉ alkyl;



34. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a = 2, 3, or 4;

b = 6;

c = 4, 5, or 6; alternatively c = 5 or 6; alternatively c = 5;

d = 1 or 2; alternatively d = 1;

c+d=6, 7, or 8; alternatively 6 or 7; alternatively 6;

M₁ is -OC(O)-; M₂ is -C(O)O-;

R₁ is C₇₋₁₂ linear alkyl, alternatively C₈₋₁₁ linear alkyl, alternatively C₉₋₁₁ linear alkyl;

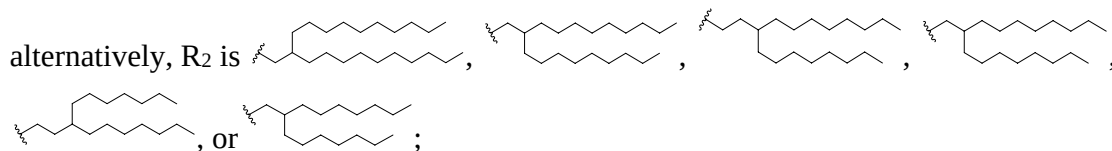
R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₂ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₇₋₁₁ alkyl, alternatively C₇₋₁₀ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

provided that, when c=4, a=2 or 3;



alternatively,

a=2 or 4; b=6; c=5 or 6, alternatively c=5; d=1;

R₁ is C₈₋₉ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₉₋₁₀ alkyl, alternatively C₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₇₋₈ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;
alternatively,

a=2, 3 or 4, alternatively 2 or 4; b=6; c=5; d=2;

R₁ is C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₉₋₁₁ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₇₋₉ alkyl,

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl.

35. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a =2, 3, or 4; alternatively a = 2 or 4;

b = 7;

c = 5 or 6; alternatively c = 5;

d = 0 or 1; alternatively d = 1;

c + d = 5 or 6, alternatively 6;

M₁ is -OC(O)-; M₂ is -C(O)O-;

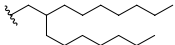
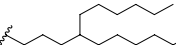
R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, which is optionally substituted with 1 C₁₋₉ alkyl (alternatively C₆₋₉ alkyl, alternatively C₆₋₇ alkyl);

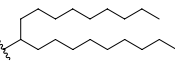
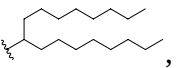
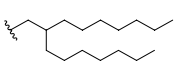
R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₇₋₉ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, R₁ is -(CH₂)₈CH₃, -(CH₂)₉CH₃, , or ;

R₂ is , , or ;

alternatively, when a=4,

R₁ is C₉₋₁₀ linear alkyl;

R₂ is C₉₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is C₈₋₉ alkyl;

R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring;

alternatively, when $a=2$,

R_1 is C_{10} linear alkyl;

alternatively R_{1s} is C_{8-9} alkyl, alternatively C_9 alkyl.

36. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

$a=2, 3$, or 4 ; alternatively $a=2$ or 4 ;

$b=7$;

$c=4$;

$d=2$;

M_1 is $-OC(O)-$; M_2 is $-C(O)O-$;

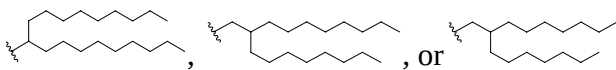
R_1 is C_{8-11} linear alkyl, alternatively C_{9-10} linear alkyl;

R_2 is C_{8-11} alkyl, alternatively C_{9-10} alkyl, which is optionally substituted with 1 R_{1s} ;

R_{1s} is independently C_{7-9} alkyl;

R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;

or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring;

alternatively, R_2 is .

37. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

$a=2, 3$, or 4 ; alternatively $a=2$;

$b=8$;

$c=5$;

$d=1$;

M_1 is $-OC(O)-$; M_2 is $-C(O)O-$;

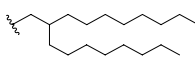
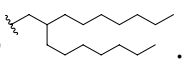
R_1 is C_{8-12} linear alkyl, alternatively C_{9-11} linear alkyl, alternatively C_{10-11} linear alkyl;

R_2 is C_{8-11} alkyl, alternatively C_{9-10} alkyl, which is optionally substituted with 1 R_{1s} ;

R_{1s} is independently C_{7-9} alkyl, alternatively C_{7-8} alkyl;

R_4 and R_5 are independently C_{1-3} alkyl, alternatively methyl;

or, R_4 and R_5 are taken together with the carbon atom to which they are attached to form C_{3-4} cycloalkylene, alternatively cyclopropylene, alternatively not to form a ring;

alternatively, R₂ is  , or  .

38. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a =2;

b = 6, 7, or 8, alternatively b=7;

c = 5;

d =1;

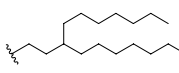
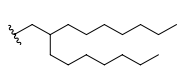
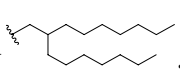
M₁ is -OC(O)-; M₂ is -C(O)O-;

R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₈₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₇ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

alternatively, R₂ is  or  , alternatively  .

39. The compound of formula (II) of claim 29, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

a =2 or 3, alternatively a=2;

b =7;

c = 3;

d =3;

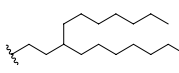
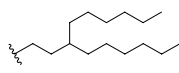
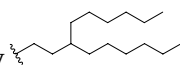
M₁ is -OC(O)-; M₂ is -C(O)O-;

R₁ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

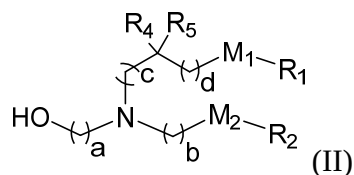
R₂ is C₈₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently C₆₋₇ alkyl, alternatively C₇ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

alternatively, R₂ is  or  , alternatively  .

40. The compound of formula (II) of claim 20 or 21, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein,

a=2, 3, 4, 5, or 6;

b=4, 5, 6, 7, 8, 9, or 10;

c=1, 2, 3, 4, 5, or 6;

d=0, 1, 2, 3, or 4;

c+d=3, 4, 5, 6, 7, 8, or 9, alternatively c+d=4, 5, or 6;

one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O-, -OC(O)-, -SC(O)-, or -C(O)S-;

R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR'_c; alternatively H or C₁₋₁₄ alkyl;

L_c is independently a chemical bond or C₁₋₁₄ alkylene;

R_c and R'_c are independently H or C₁₋₁₄ alkyl;

R₄ and R₅ are independently C₁₋₆ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

41. The compound of formula (II) of claim 40, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2, 3, or 4;

b=4, 5, 6, or 7, alternatively b=5 or 6, alternatively b=6;

c= 2, 3, 4, 5, or 6; alternatively c= 2, 4, 5, or 6;

d=0, 1, 2, 3, or 4; alternatively d=0, 1, 2, or 4;

c+d=5 or 6, alternatively c+d=6;

one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O- or -OC(O)-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₉₋₁₁ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl; alternatively H or C₄₋₁₀ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene, alternatively C₃₋₄ cycloalkylene.

42. The compound of formula (II) of claim 40 or 41, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2, 3, or 4;

b=4, 5, 6, or 7, alternatively b=5 or 6, alternatively b=6;

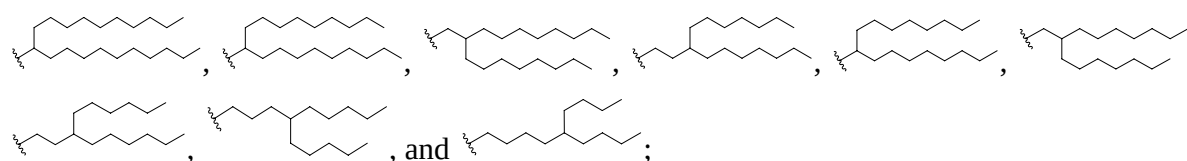
c= 2, 3, 4, 5, or 6; alternatively c= 2, 4, 5, or 6;

d=0, 1, 2, 3, or 4; alternatively d=0, 1, 2, or 4;

c+d=5 or 6, alternatively c+d=6;

one of M₁ and M₂ is -OC(O)O-, and the other is -C(O)O- or -OC(O)-;

R₁ and R₂ are independently selected from -(CH₂)₈CH₃, -(CH₂)₉CH₃, -(CH₂)₁₀CH₃, ,



R₄ and R₅ are methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene;

alternatively, only one of R₁ and R₂ is substituted;

alternatively, M₁ is -C(O)O- or -OC(O)-, alternatively -C(O)O-, and M₂ is -OC(O)O-;

alternatively, M₁ is -OC(O)O-, and M₂ is -OC(O)-.

43. The compound of formula (II) of claim 40, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2;

b=5 or 6, alternatively b=6;

c=4, 5, or 6; alternatively c=4 or 6; alternatively c=6;

d=0, 1, or 2; alternatively d=0 or 2;

c+d=6;

M₁ is -C(O)O-, and M₂ is -OC(O)O-;

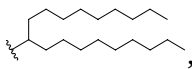
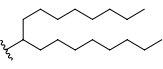
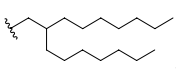
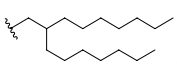
R₁ is C₈₋₁₁ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is C₇₋₉ alkyl, alternatively C₇ alkyl;

R₂ is C₈₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring;

alternatively, R₁ is , , or , alternatively .

44. The compound of formula (II) of claim 40, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2;

b=6;

c=4, 5, or 6; alternatively c=5 or 6; alternatively c=6;

d=0, 1, or 2; alternatively d=0 or 1;

c+d=6;

M₁ is -C(O)O-, and M₂ is -OC(O)O-;

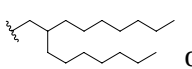
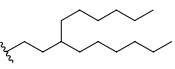
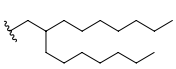
R₁ is C₈₋₁₀ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₈₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is C₆₋₇ alkyl, alternatively C₇ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring;

alternatively, R₂ is  or , alternatively .

45. The compound of formula (II) of claim 40, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2;

b=5 or 6; alternatively b=6;

c=5;

d=1;

M₁ is -OC(O)-, and M₂ is -OC(O)O-;

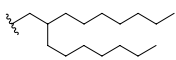
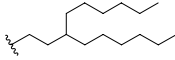
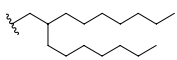
R₁ is C₈₋₁₀ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is C₆₋₈ alkyl, alternatively C₆₋₇ alkyl;

R₂ is C₈₋₁₂ linear alkyl, alternatively C₁₀₋₁₁ linear alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring;

alternatively, R₁ is  or , alternatively .

46. The compound of formula (II) of claim 40, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein,

a=2, 3 or 4; alternatively a=2;

b=5, 6, 7, or 8; alternatively b=6 or 7; alternatively b=7;

c=4, 5, or 6; alternatively c=4;

d=0, 1, or 2; alternatively d=1;

c+d=5 or 6; alternatively c+d=5;

M₁ is -OC(O)O-, M₂ is -OC(O)-;

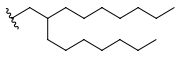
R₁ is C₈₋₁₂ alkyl, alternatively C₈₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is C₆₋₁₀ alkyl, alternatively C₆₋₈ alkyl;

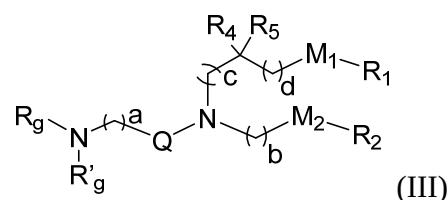
R₂ is C₈₋₁₂ linear alkyl, alternatively C₈₋₁₀ linear alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively not to form a ring;

alternatively, R₁ is .

47. The compound of formula (III) of claim 20 or 21, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein,

Q is -SC(O)- or -OC(O)-;

R_g and R'_g are independently C₁₋₆ alkyl;

a = 2, 3, 4, 5, or 6; alternatively a = 2, 3, or 4;

b = 4, 5, 6, 7, 8, or 9; alternatively b = 5, 6, or 7;

c = 2, 3, 4, 5, or 6;

d = 0, 1, 2, 3, or 4;

c+d=5 or 6;

M₁ and M₂ are independently selected from -C(O)O-, -C(O)S-, -OC(O)-, -SC(O)-, and -OC(O)O-;

R₁ and R₂ are independently C₆₋₁₄ alkyl, which is optionally substituted with 1, 2, 3, or 4 R_{1s};

R_{1s} is independently H, C₁₋₁₄ alkyl, -L_c-OR_c, or -L_c-NR_cR'_c; alternatively H or C₁₋₁₄ alkyl;

L_c is independently a chemical bond or C₁₋₁₄ alkylene;

R_c and R'_c are independently H or C₁₋₁₄ alkyl;

R₄ and R₅ are independently C₁₋₆ alkyl,

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene or 3- to 6-membered heterocyclylene.

48. The compound of formula (III) of claim 47, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

Q is -SC(O)- or -OC(O)-;

R_g and R'_g are independently C₁₋₃ alkyl;

a = 3 or 4;

b = 6 or 7;

c = 2, 3, 4, or 5; alternatively 2 or 5;

d = 1, 2, 3, or 4; alternatively 1 or 4;

c+d=5 or 6;

M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, and -OC(O)O-; alternatively, M₁ and M₂ are not simultaneously -OC(O)O-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₈₋₁₀ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl; alternatively H or C₁₋₉ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl,

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene.

49. The compound of formula (III) of claim 47 or 48, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein

Q is -SC(O)-;

R_g and R'_g are methyl;

a = 3 or 4;

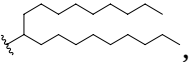
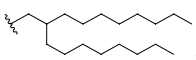
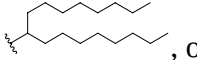
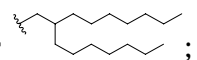
b = 6 or 7;

c = 2, 4, or 5; alternatively 2 or 5;

d = 1, 2, or 4; alternatively 1 or 4;

c+d=6;

M₁ and M₂ are independently selected from -C(O)O-, -OC(O)-, and -OC(O)O-; alternatively, M₁ and M₂ are not simultaneously -OC(O)O-;

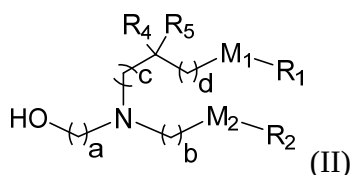
R₁ and R₂ are independently -(CH₂)₇CH₃, -(CH₂)₈CH₃, -(CH₂)₉CH₃, , , , or  ;

R₄ and R₅ are methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form cyclopropylene, alternatively not to form a ring;

alternatively, only one of R₁ and R₂ is substituted; alternatively, R₁ is unsubstituted, and R₂ is substituted.

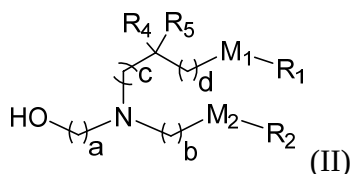
50. The compound of formula (II) of claim 20 or 21, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein, M₁ and M₂ are independently -C(O)O- or -C(O)S-, alternatively -C(O)O-;

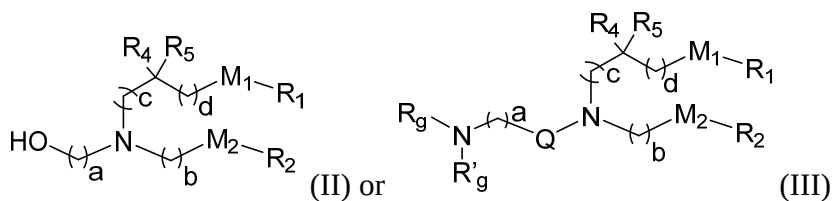
the other groups are as defined in any one of claims 21-27 and 29-33.

51. The compound of formula (II) of claim 20 or 21, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof,



wherein, one of M₁ and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-, and the other is -OC(O)- or -SC(O)-, alternatively -OC(O)-;
the other groups are as defined in any one of claims 21-24, 29-31 and 34-39;
alternatively, R_{1s} is independently H or C₁₋₆ alkyl; alternatively H or C₁₋₄ alkyl;
alternatively, R_{1s} is independently C₁₋₈ alkyl, alternatively C₄₋₈ alkyl, alternatively C₆₋₈ alkyl, alternatively C₇₋₈ alkyl, alternatively C₈ alkyl;
alternatively M₁ is -OC(O)- or -SC(O)-, alternatively -OC(O)-; and M₂ is -C(O)O- or -C(O)S-, alternatively -C(O)O-.

52. A compound of formula (II) or formula (III), or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof:



wherein

Q is a chemical bond, -SC(O)- or -OC(O)-;

R_g and R'_g are independently C₁₋₆ alkyl;

a = 2, 3, 4, 5, or 6;

b = 6 or 7;

c = 5 or 6;

d = 0 or 1;

c + d = 5 or 6;

M₁ is -OC(O)- or -SC(O)-; and M₂ is -C(O)O- or -C(O)S-;

R₁ and R₂ are independently C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, which is optionally substituted with 1 R_{1s};

R_{1s} is independently H or C₁₋₁₀ alkyl;

R₄ and R₅ are independently C₁₋₆ alkyl,

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₆ cycloalkylene;

alternatively, only one of R₁ and R₂ is substituted; alternatively, R₁ is unsubstituted, and R₂ is substituted.

53. The compound of formula (II) or formula (III) of claim 52, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof:

wherein

Q is -SC(O)- or -OC(O)-, alternatively -SC(O)- ;

R_g and R'_g are independently C₁₋₃ alkyl, alternatively methyl;

a = 2, 3, or 4; alternatively a = 2 or 4; alternatively a = 4;

b = 6 or 7; alternatively b = 7;

c = 5 or 6; alternatively c = 5;

d = 0 or 1; alternatively d = 1;

c + d = 5 or 6; alternatively c + d = 6;

M₁ is -OC(O)-; M₂ is -C(O)O-;

R₁ is C₇₋₁₁ linear alkyl, alternatively C₉₋₁₀ linear alkyl, alternatively C₉ linear alkyl;

R₂ is C₇₋₁₂ alkyl, alternatively C₈₋₁₂ alkyl, alternatively C₉₋₁₀ alkyl, alternatively C₉ alkyl, which is optionally substituted with 1 R_{1s};

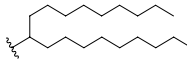
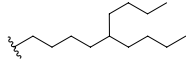
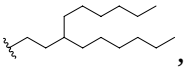
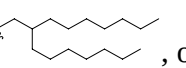
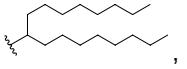
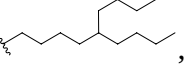
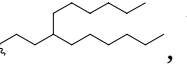
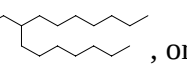
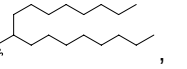
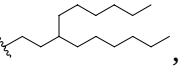
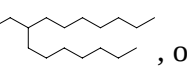
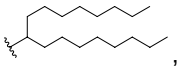
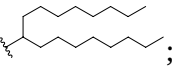
R_{1s} is independently C₁₋₉ alkyl, alternatively C₁₋₈ alkyl, alternatively C₄₋₉ alkyl, alternatively C₄₋₈ alkyl;

R₄ and R₅ are independently C₁₋₃ alkyl, alternatively methyl;

or, R₄ and R₅ are taken together with the carbon atom to which they are attached to form C₃₋₄ cycloalkylene, alternatively cyclopropylene;

alternatively, the substitution site of R_{1s} on R₁ or R₂ is separated from M₁ or M₂ by 0-10 carbon atoms, alternatively 0-6 carbon atoms, alternatively 0-4 carbon atoms, alternatively 0-2 carbon atoms, alternatively 0 carbon atom;

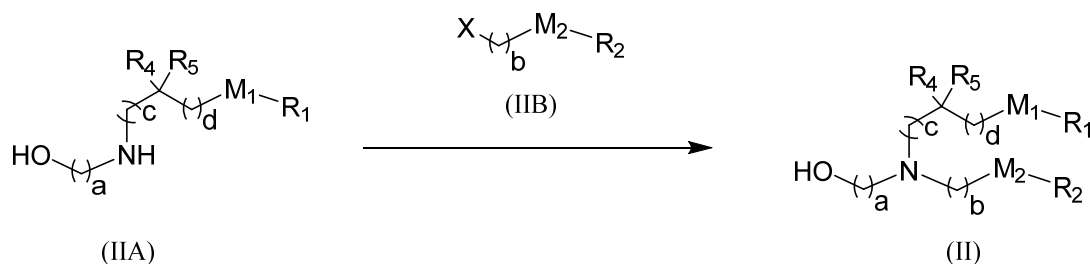
alternatively, R₁ is not substituted with R_{1s}, and the substitution site of R_{1s} on R₂ is separated from M₂ by 0-10 carbon atoms, alternatively 1-10 carbon atoms, alternatively 1-6 carbon atoms, alternatively 1-4 carbon atoms, alternatively 1-2 carbon atoms; alternatively 2-10 carbon atoms, alternatively 2-6 carbon atoms, alternatively 2-4 carbon atoms ;

alternatively, R₂ is , , , , or , alternatively , , , or , alternatively , , or , alternatively ;

alternatively, R₄ and R₅ are not taken together with the carbon atom to which they are attached to form a ring.

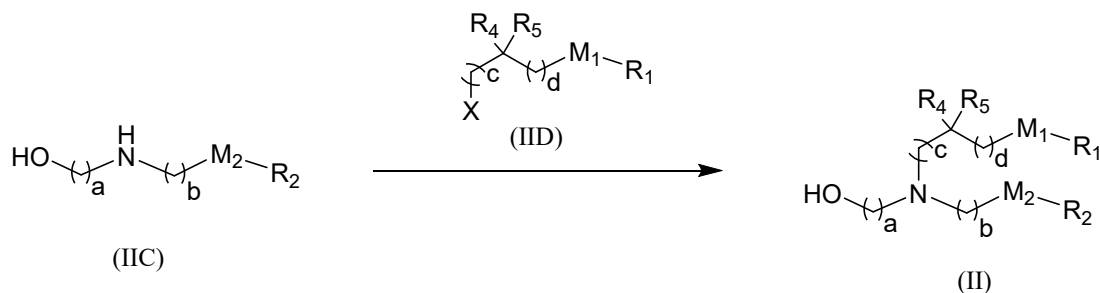
54. The compound of formula (I) of claim 1, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, wherein the compound is selected from the compounds in Table (I).
55. A pharmaceutical composition, comprising the compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof and a pharmaceutically acceptable excipient(s).
56. A nanoparticle composition, comprising a lipid component, and optionally a load, wherein the lipid component comprises the compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, and the load is selected from one or more of therapeutic, prophylactic, and diagnostic agents.
57. Use of the compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, or the pharmaceutical composition of claim 55, or the nanoparticle composition of claim 56 in the manufacture of a medicament for treating, diagnosing, or preventing a disease; alternatively, the medicament for treating, diagnosing, or preventing a disease is a therapeutic or prophylactic mRNA vaccine.
58. Use of the compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, or the pharmaceutical composition of claim 55, or the nanoparticle composition of claim 56 in the manufacture of a medicament for delivering a load, wherein the load is selected from one or more of therapeutic, prophylactic, and diagnostic agents.
59. A method for treating, diagnosing, or preventing a disease in a subject, comprising administering to the subject the pharmaceutical composition of claim 55 or the nanoparticle composition of claim 56.
60. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, or the pharmaceutical composition of claim 55, or the nanoparticle composition of claim 56, for use in treating, diagnosing, or preventing a disease.
61. A method for delivering a load in a subject, comprising administering to the subject the pharmaceutical composition of claim 55 or the nanoparticle composition of claim 56; wherein the load is selected from one or more of therapeutic, prophylactic, and diagnostic agents.

62. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, isotopic variant, tautomer, or stereoisomer thereof, or the pharmaceutical composition of claim 55, or the nanoparticle composition of claim 56, for use in delivering a load; wherein the load is selected from one or more of therapeutic, prophylactic, and diagnostic agents.
63. The nanoparticle composition of claim 56, or the use of claim 58 or 62, or the method of claim 61, wherein the therapeutic, prophylactic, or diagnostic agents is a nucleic acid; alternatively, the nucleic acid is selected from one or more of ASO, RNA, and DNA; alternatively, the RNA is selected from one or more of small interfering RNA (siRNA), short hairpin RNA (shRNA), antisense RNA (aRNA), messenger RNA (mRNA), long non-coding RNA (lncRNA), microRNA (miRNA), small activating RNA (saRNA), multimeric coding nucleic acid (MCNA), polymeric coding nucleic acid (PCNA), guide RNA (gRNA), CRISPRRNA (crRNA), and nucleases, alternatively mRNA, more alternatively modified mRNA.
64. A method for preparing a compound of formula (II), comprising:
reacting a compound of formula (IIA) with a compound of formula (IIB) to give the compound of formula (II),



wherein X is halogen, and the other variables are as defined in any one of claims 20-46.

65. A method for preparing a compound of formula (II), comprising:
reacting a compound of formula (IIC) with a compound of formula (IID), to give the compound of formula (II),



wherein X is halogen, and the other variables are as defined in any one of claims 20-46.