[0016] n4 is an integer between zero and 4.

[0017] There is also provided a lipid nanoparticle composition comprising: an ionizable lipid as described herein; a phospholipid; a polyethylene glycol-lipid; a cholesterol; and optionally a nucleic acid. Another aspect described herein relates to a lipid nanoparticle composition comprising: an ionizable lipid that comprises a compound as described herein, optionally wherein the amount of the ionizable lipid is present in a range of about 35 to 65 mole percent, based on total moles; a phospholipid, optionally wherein the phospholipid is DSPC or DMPC; a polyethylene glycol-lipid; a cholesterol; and optionally a nucleic acid. Further examples are directed toward a method of delivering a nucleic acid to a subject in need thereof, comprising administering to the subject in need the lipid nanoparticle composition. Another aspect described herein relates to a use of the lipid nanoparticle composition as described herein in the manufacture of a medicament for the treatment of cancer, autoimmune disease, infectious disease, organ transplant, organ failure, protein deficiency, or a combination thereof.

[0018] These and other examples are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] **FIG. 1** illustrates a reaction scheme for preparing compounds of the Formula (I).

[0020] **FIG. 2** summarizes the structures of the compounds of Examples 1-148.

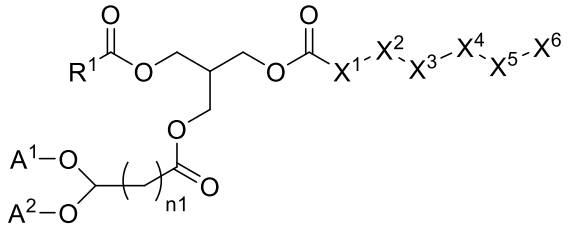
DETAILED DESCRIPTION

Definitions

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

wherein:

R^1 is C_9-C_{20} alkyl or C_9-C_{20} alkenyl with 1-3 units of unsaturation;

X^1 and X^2 are each independently absent or selected from –O–, –NR^2– and $-(CH)_a-$ (X^7), wherein each R^2 is independently hydrogen or C_1-C_6 alkyl;

each a is independently an integer between 1 and 6;

X^3 and X^4 are each independently absent or selected from the group consisting of: 4- to 8-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 5- to 6-membered heteroaryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 5- to 6-membered aryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 4- to 7-membered cycloalkyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, –O– and –NR^3–, wherein each R^3 is independently a hydrogen atom or C_1-C_6 alkyl and wherein X^1-X^2-X^3-X^4 does not contain any oxygen-oxygen, oxygen-nitrogen or nitrogen-nitrogen bonds;

X^5 is –$(CH_2)_b$–, wherein b is an integer between 0 and 6;

X^6 is hydrogen, C_1-C_6 alkyl, 5- to 6-membered heteroaryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, or –NR^4R^5, wherein R^4 and R^5 are each independently hydrogen or C_1-C_6 alkyl; or alternatively R^4 and R^5 join together with the nitrogen to which they are bound to form a 4- to 7-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, wherein the heterocyclyl optionally includes an additional heteroatom selected from oxygen, sulfur, and nitrogen;

each X^7 is independently hydrogen, hydroxyl or –NR^6R^7, wherein R^6 and R^7 are each independently hydrogen or C_1-C_6 alkyl; or alternatively R^6 and R^7 join together with the nitrogen to which they are bound to form a 4- to 7-membered

heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, wherein the heterocyclyl optionally includes an additional heteroatom selected from oxygen, sulfur, and nitrogen;

at least one of X^1, X^2, X^3, X^4, and X^5 is present;

A^1 and A^2 are each independently selected from the group consisting of: C_5-C_{12} haloalkyl, C_5-C_{12} alkenyl, C_5-C_{12} alkynyl, (C_5-C_{12} alkoxy)-$(CH_2)_{n2}$–, (C_5-C_{10} aryl)-$(CH_2)_{n3}$– optionally ring substituted with one or two halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy groups, and (C_3-C_8 cycloalkyl)-$(CH_2)_{n4}$– optionally ring substituted with 1 or 2 C_1-C_6 alkyl groups; or alternatively A^1 and A^2 join together with the atoms to which they are bound to form a 5- to 6-membered cyclic acetal substituted with 1 or 2 C_4-C_{10} alkyl groups;

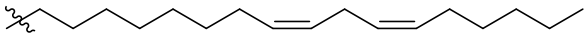
n1, n2 and n3 are each individually an integer between 1 and 4; and

n4 is an integer between zero and 4.

2. The compound of claim 1, wherein A^1 and A^2 are each independently C_5-C_{12} alkenyl, or wherein A^1 and A^2 are each independently C_5-C_{12} haloalkyl.

3. The compound of claim 1, wherein A^1 and A^2 are each independently (C_5-C_{10} aryl)-$(CH_2)_{n3}$– optionally ring substituted with one or two halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy groups, or wherein A^1 and A^2 are each independently (C_3-C_8 cycloalkyl)-$(CH_2)_{n4}$– optionally ring substituted with 1 or 2 C_1-C_6 alkyl groups.

4. The compound of claim 1, wherein A^1 and A^2 are each independently C_5-C_{12} alkynyl, A^1 and A^2 are each independently (C_5-C_{12} alkoxy)-$(CH_2)_{n2}$–, or A^1 and A^2 join together with the oxygen atoms to which they are bound to form a 5- to 6-membered cyclic acetal substituted with 1 or 2 C_4-C_{10} alkyl groups.

5. The compound of any one of claims 1-4, wherein R^1 is C_9-C_{20} alkenyl with 2 units of unsaturation, optionally wherein R^1 is .

6. The compound of any one of claims 1-3, wherein

X^1 is absent, and X^2 is , wherein X^7 is optionally: hydrogen, hydroxyl and a is 1, or –NR^6R^7 and a is 1;

X^1 is –O–, and X^2 is , wherein X^7 is optionally: hydrogen, hydroxyl and a is 1, or –

NR^6R^7 and a is 1; or

X^1 is , and X^2 is , wherein X^7 is optionally: hydrogen, hydroxyl and a is 1, or – NR^6R^7 and a is 1.

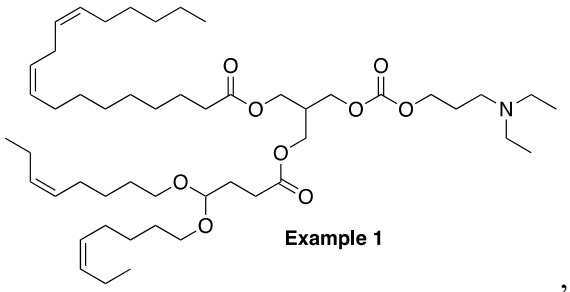
7. The compound of any one of claims 1-6, wherein X^3 is absent or X^3 is 4- to 8-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups.

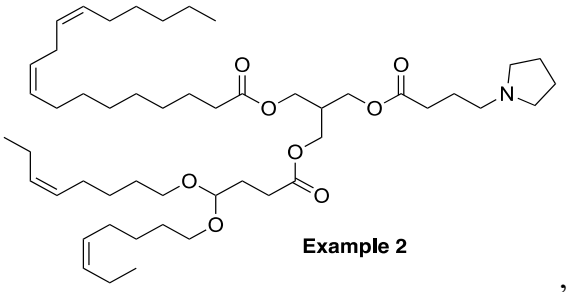
8. The compound of any one of claims 1-7, wherein X^4 is absent.

9. The compound of any one of claims 1-8, wherein b is an integer between 1 and 6 and X^6 is hydrogen or NR^4R^5,

optionally wherein R^4 and R^5 join together with the nitrogen to which they are bound to form a 4- to 7-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups.

10. The compound of claim 1, wherein the compound is selected from a group consisting of:


Example 1 ,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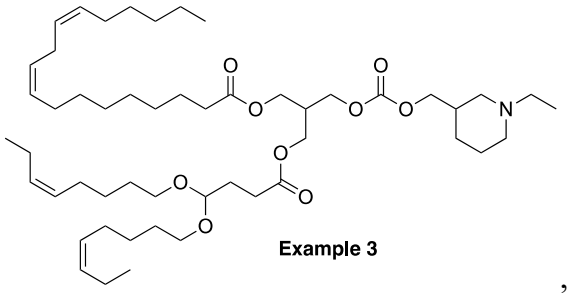
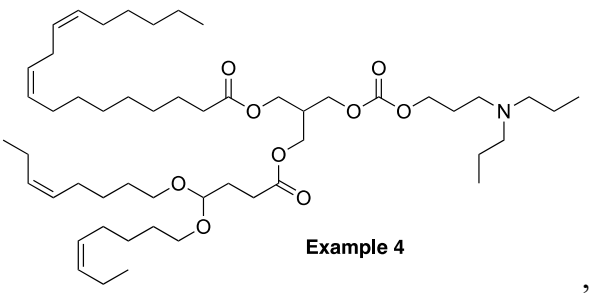

Example 3 ,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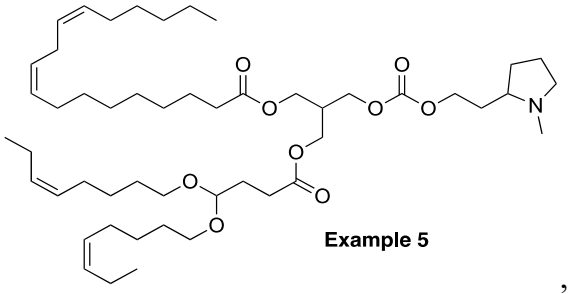
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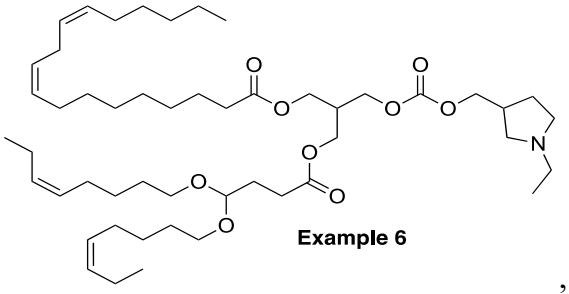
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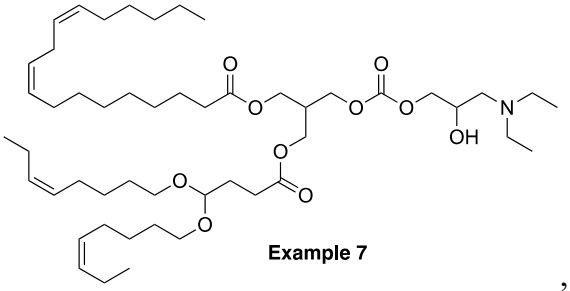

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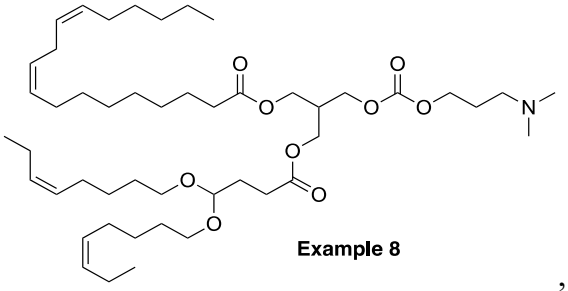

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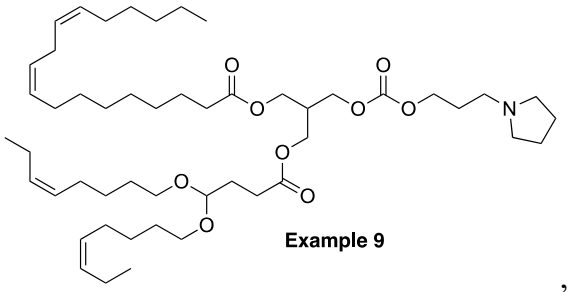

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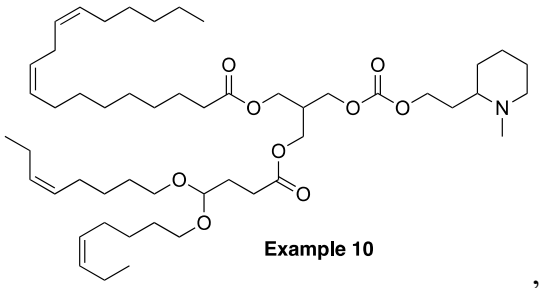

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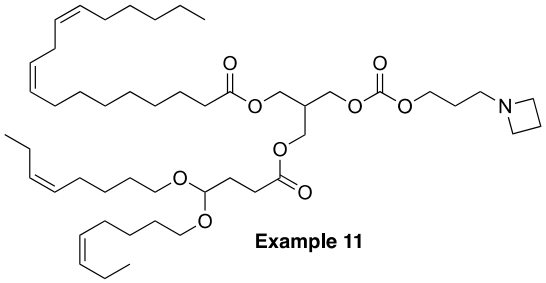

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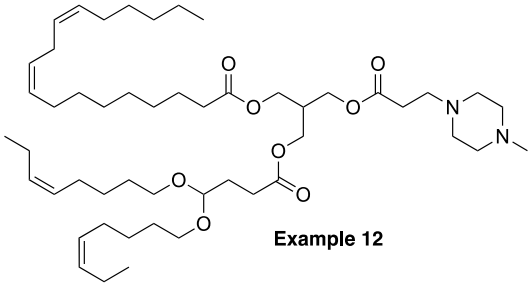

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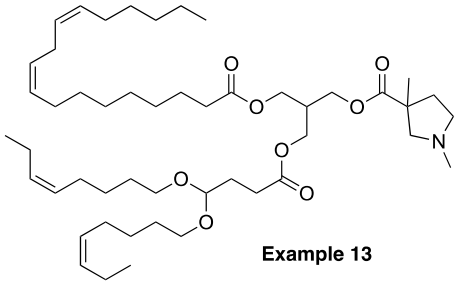

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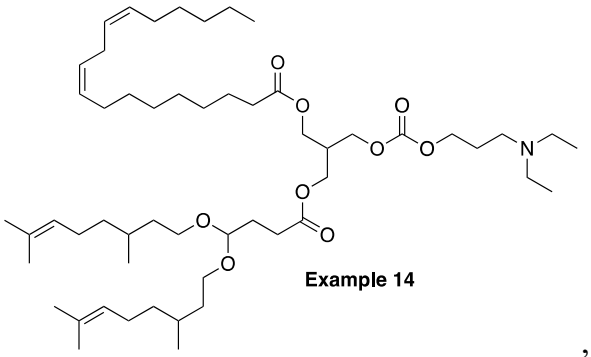

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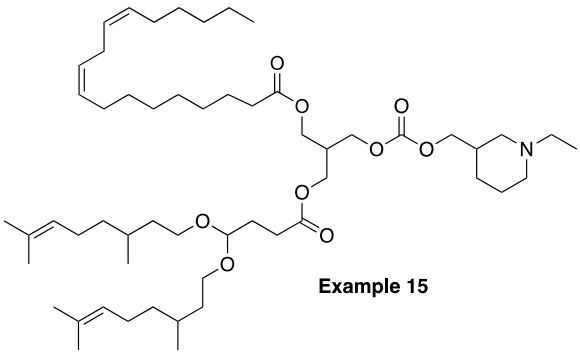

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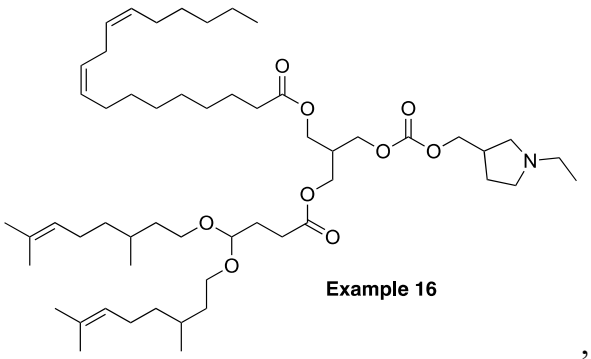

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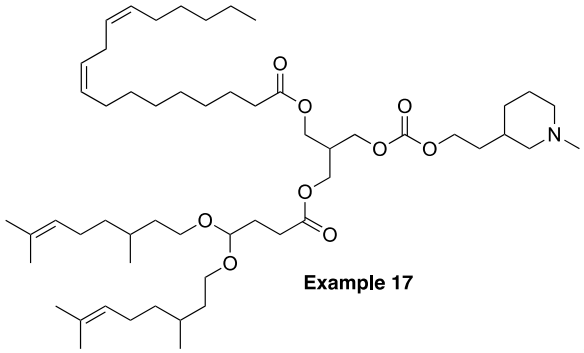

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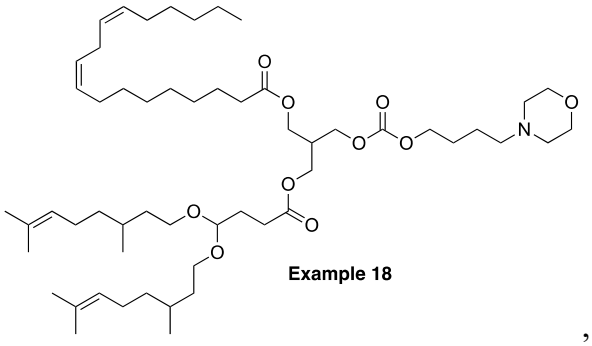

Example 18

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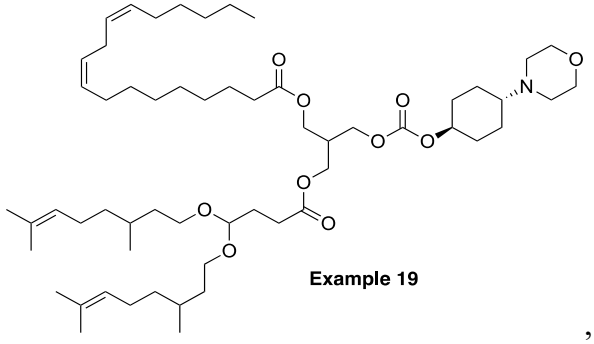

Example 19

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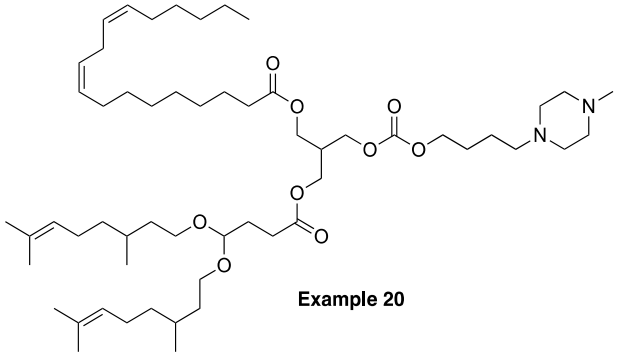

Example 20

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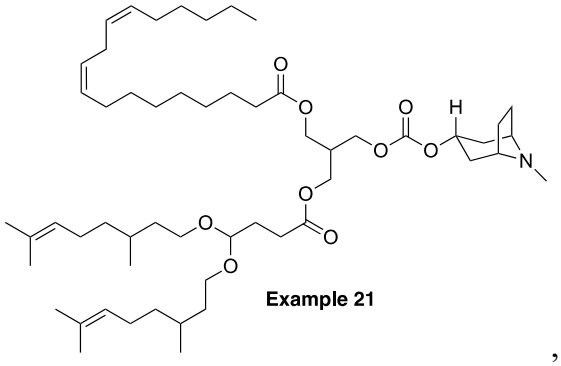

Example 21

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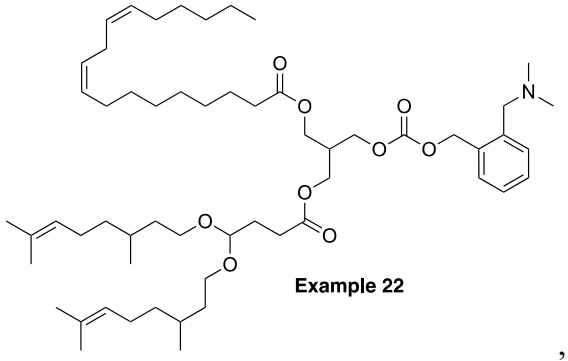

Example 22

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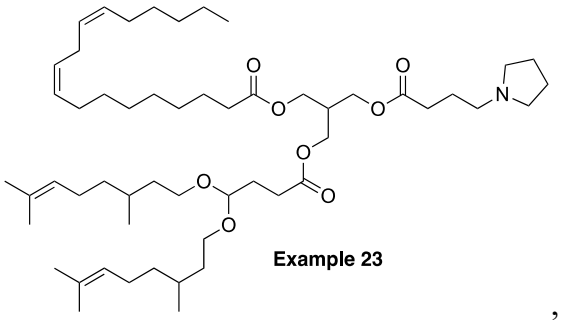

Example 23

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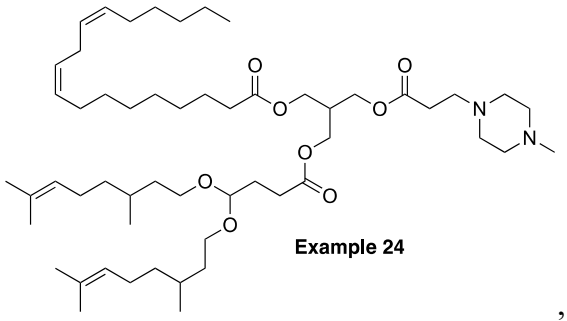

Example 24

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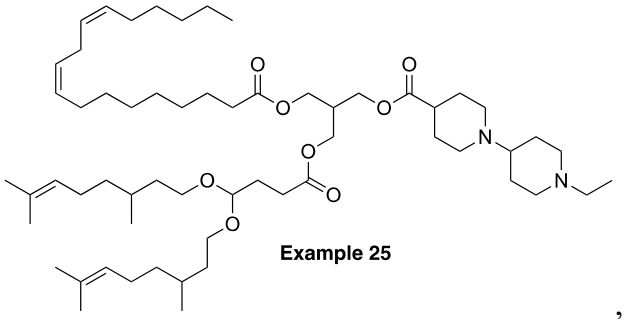

Example 25

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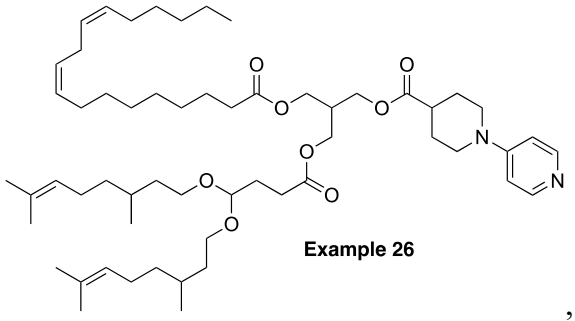

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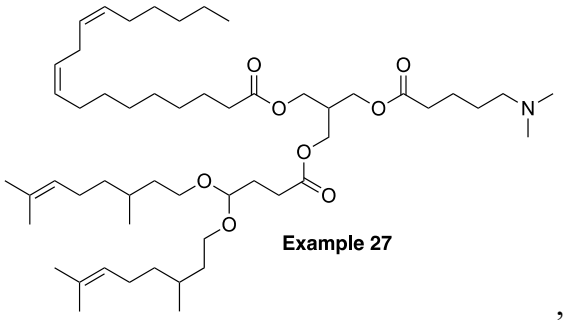

Example 27

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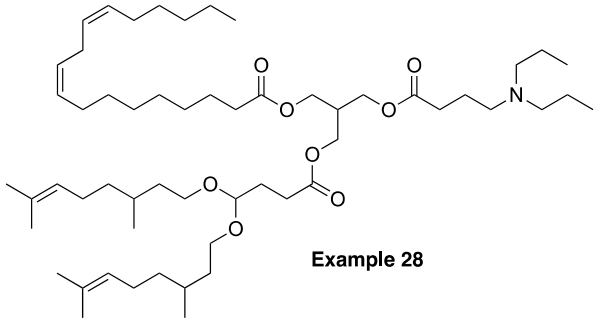

Example 28

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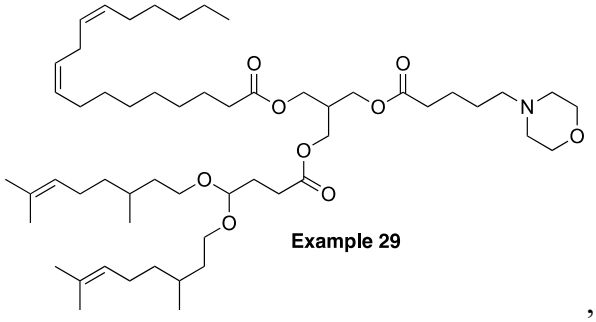

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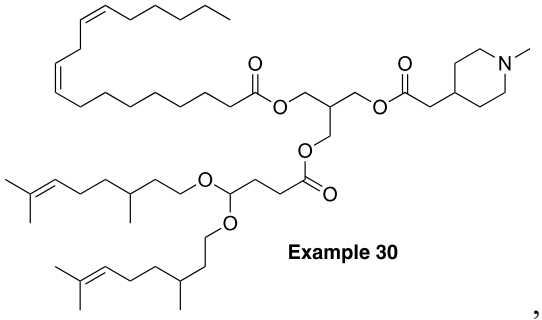

Example 30

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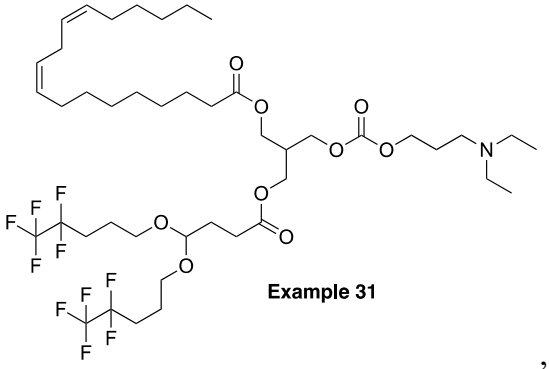

Example 31

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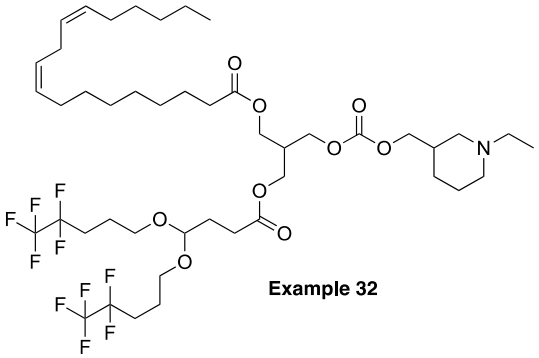

Example 32

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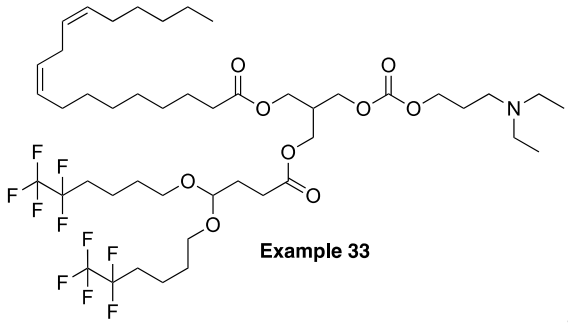

Example 33

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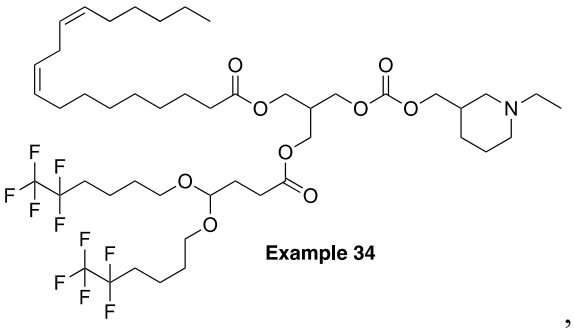

Example 34

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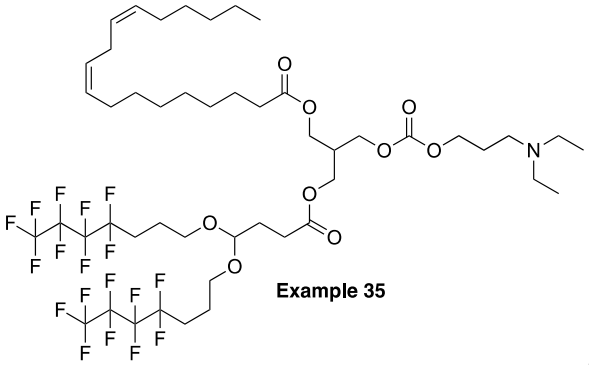

Example 35

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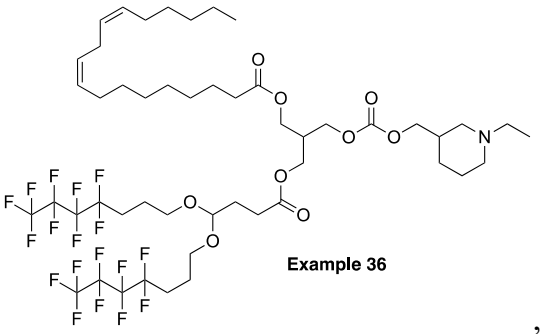

Example 36

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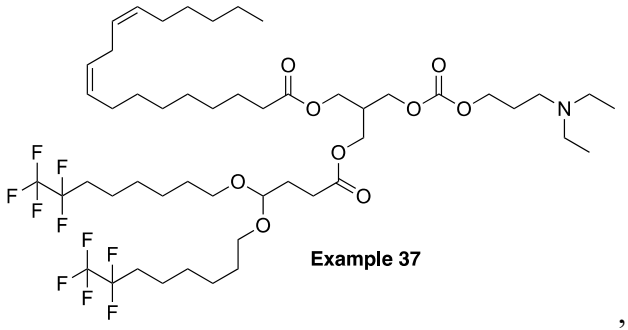

Example 37

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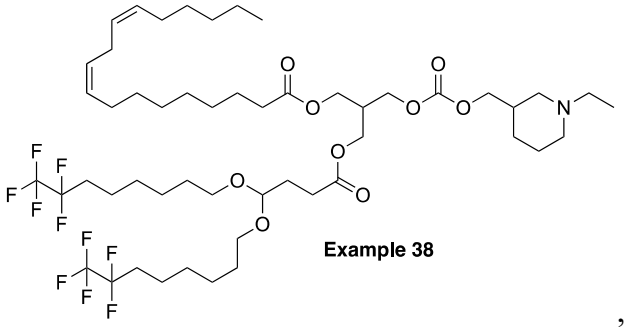

Example 38

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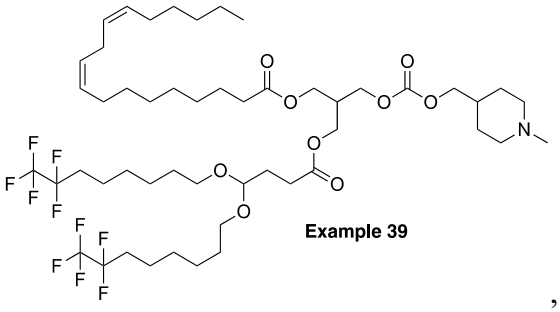

Example 39

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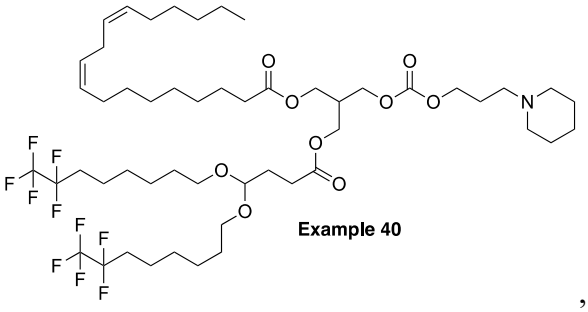

Example 40

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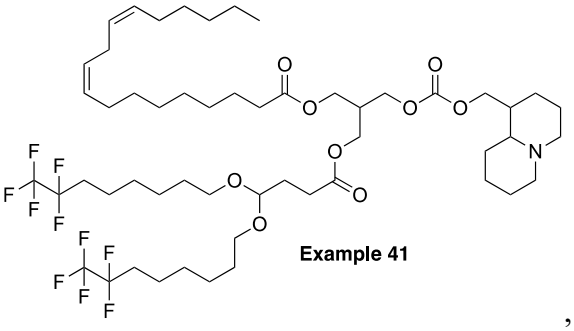

Example 41

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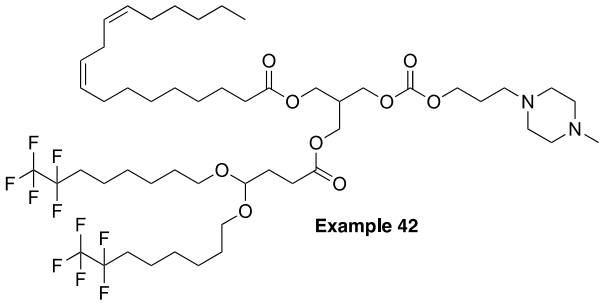

Example 42

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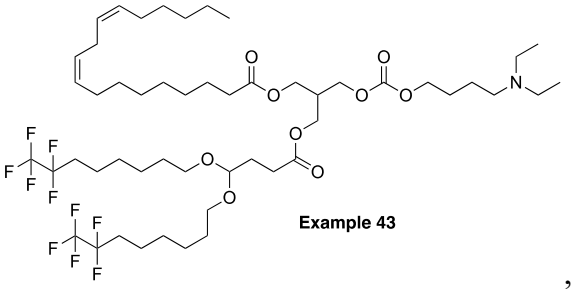

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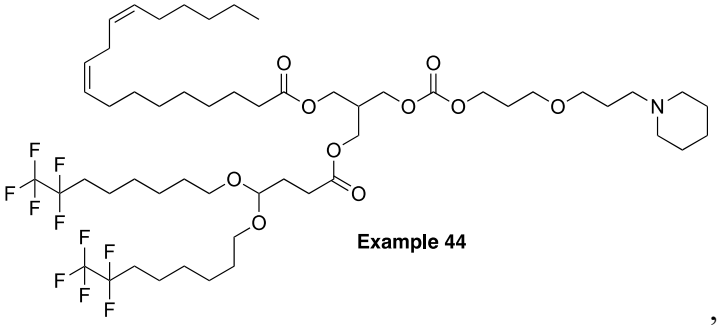

Example 44

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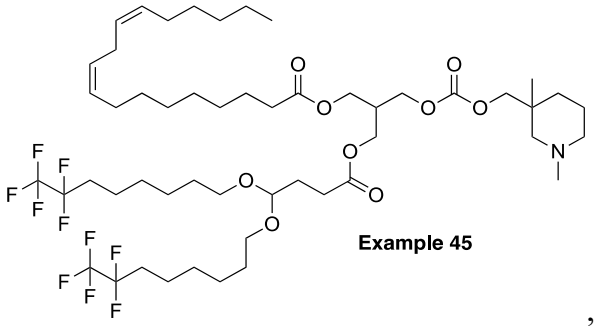

Example 45

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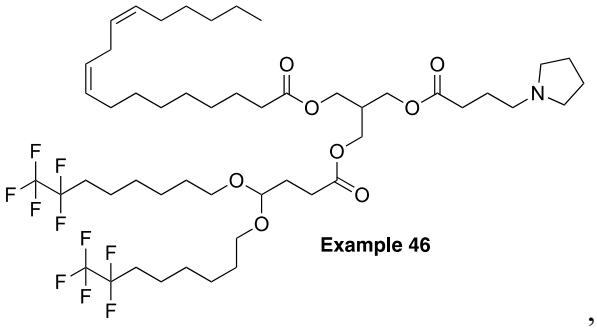

Example 46

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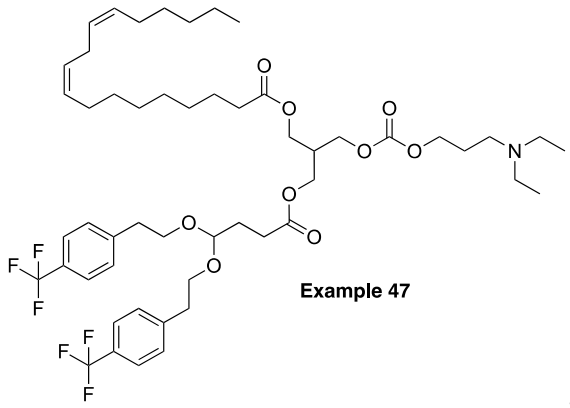

Example 47

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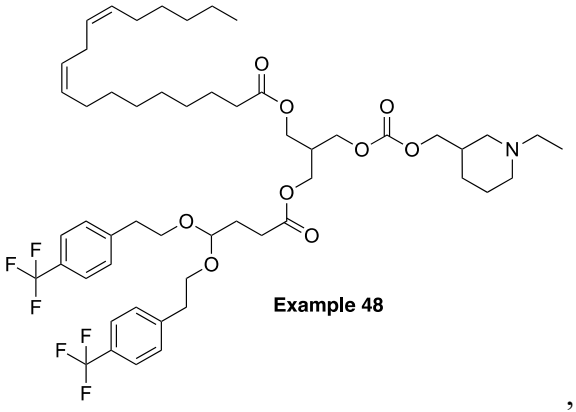

Example 48

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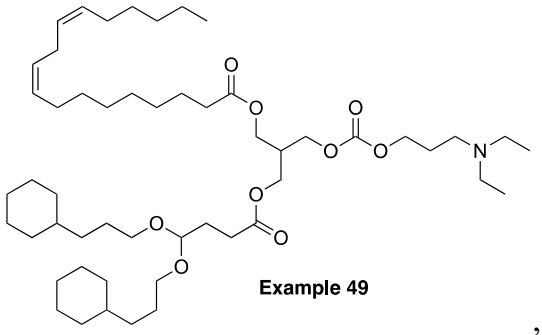

Example 49

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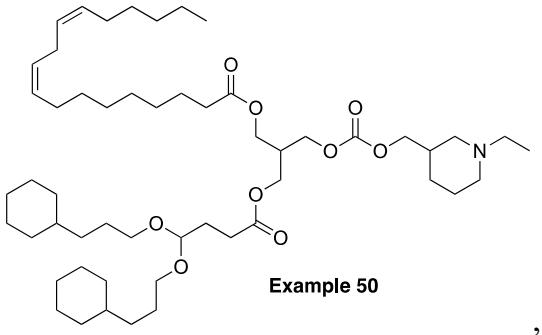

Example 50

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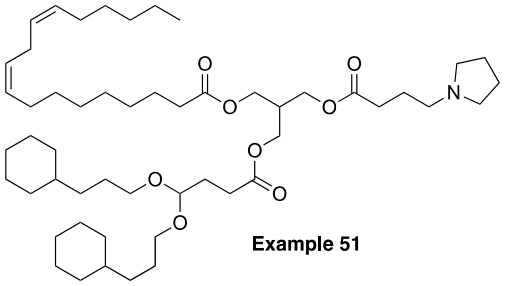

Example 51

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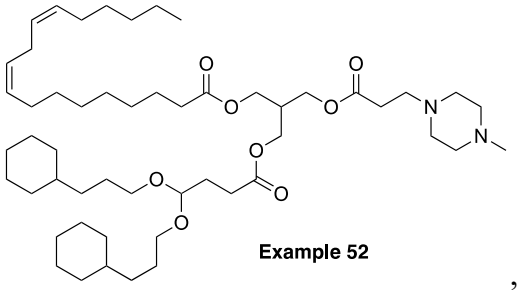

Example 52

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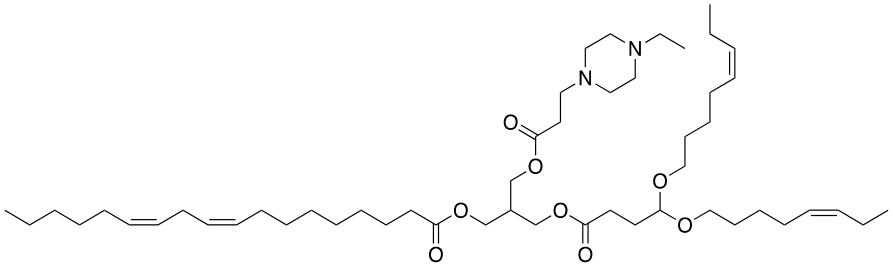

Example 75

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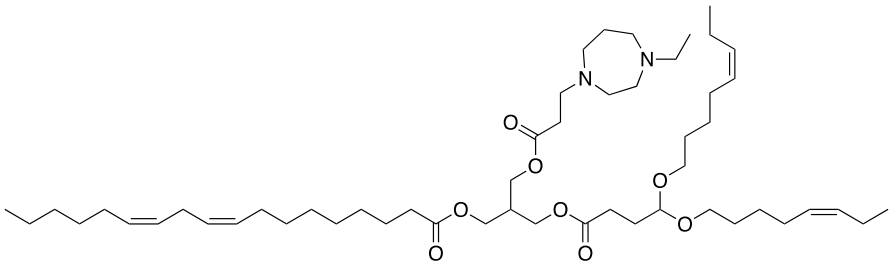

Example 76

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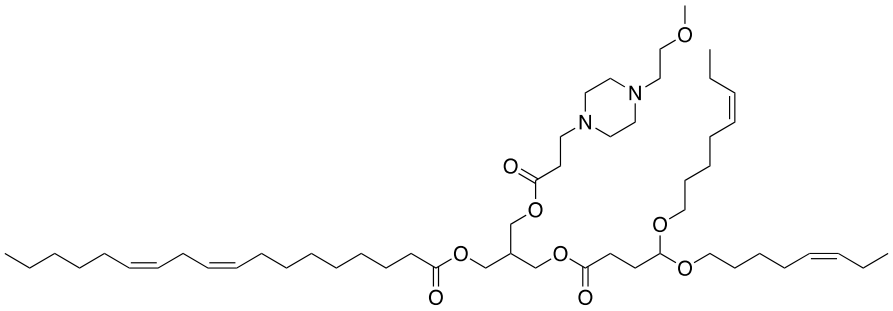

Example 77

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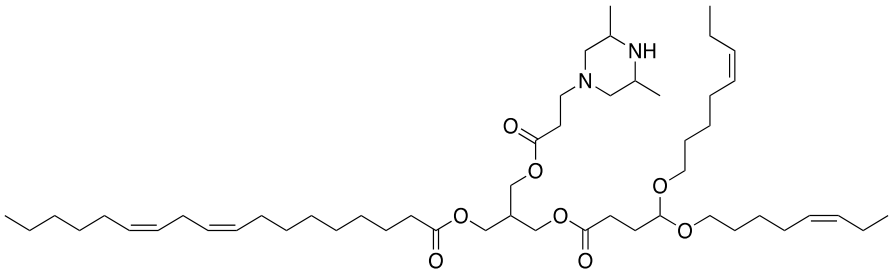

Example 78

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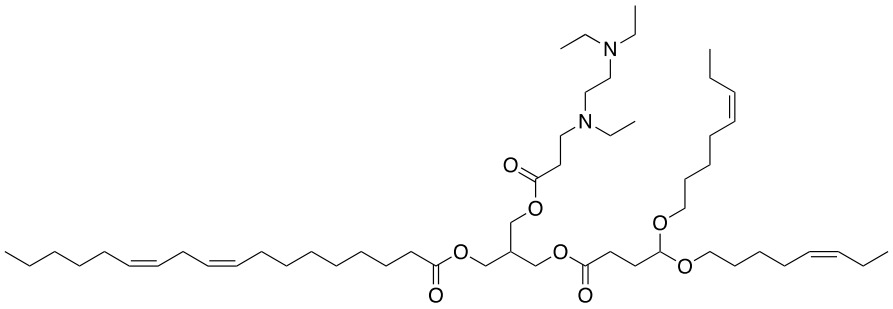

Example 79

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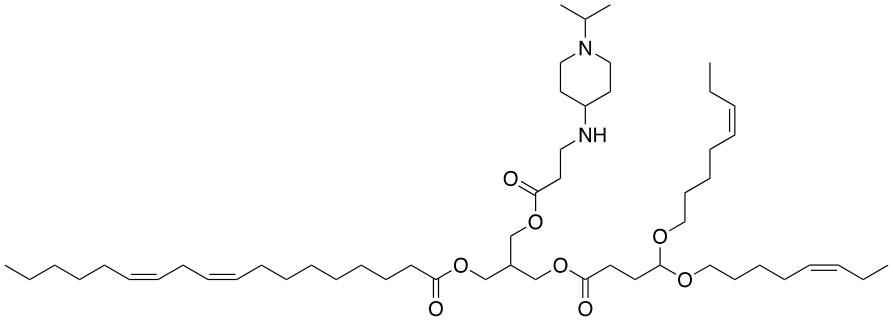

Example 80

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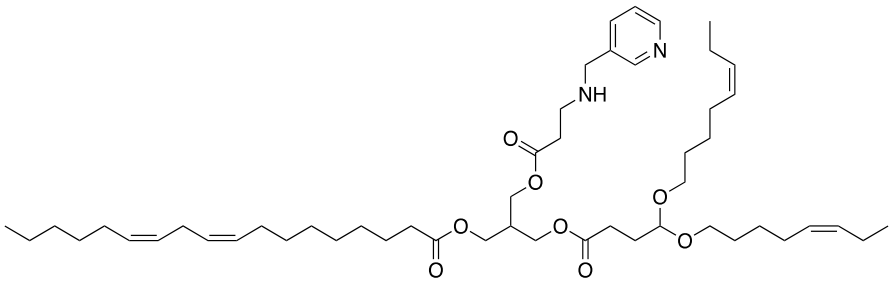

Example 81

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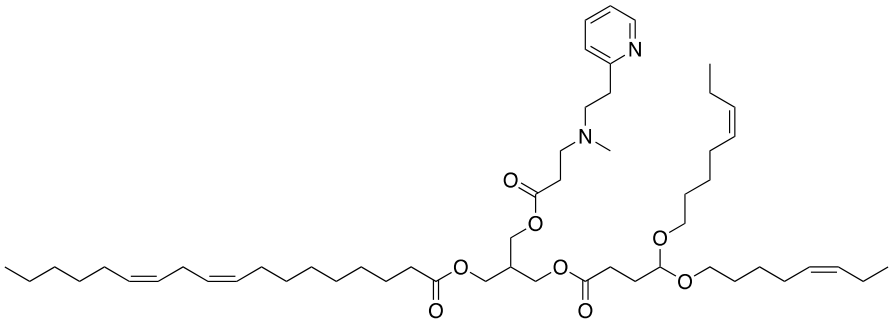

Example 82

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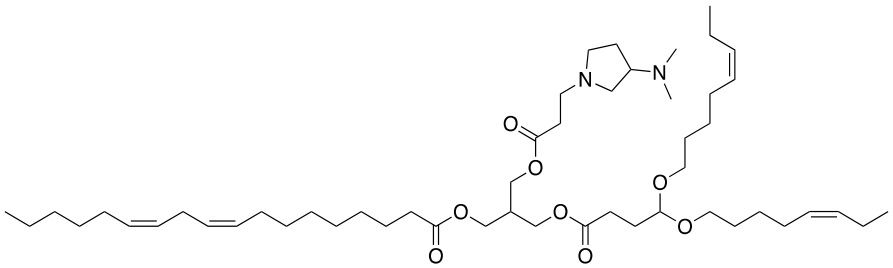

Example 83

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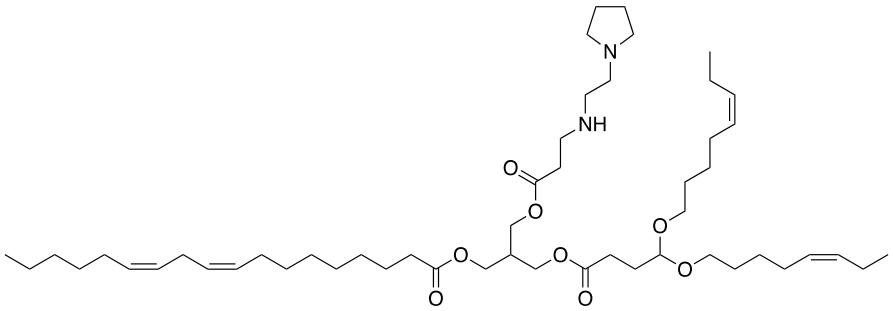

Example 84

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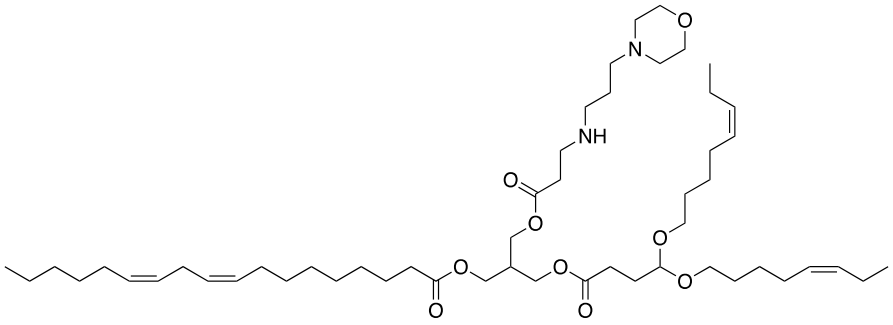

Example 85

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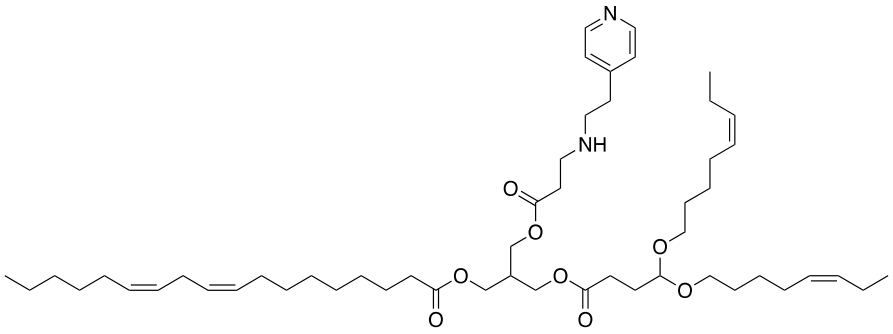

Example 86

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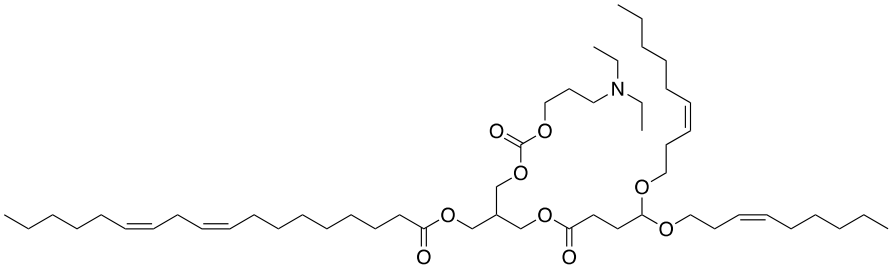

Example 88

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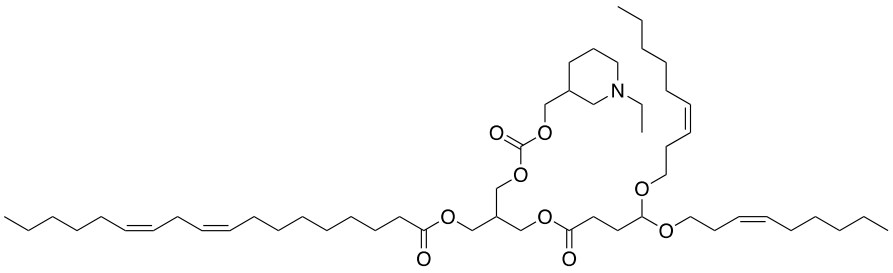

Example 89

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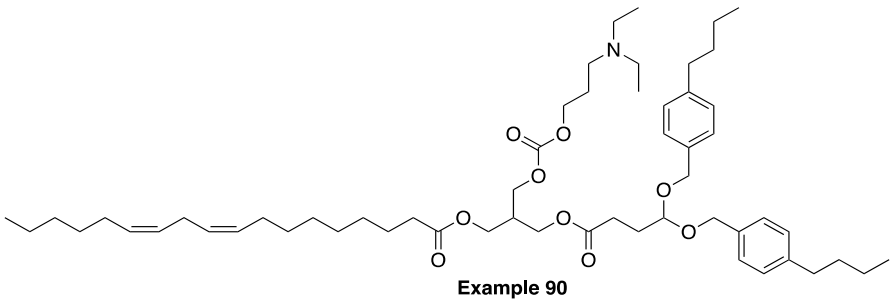

Example 90

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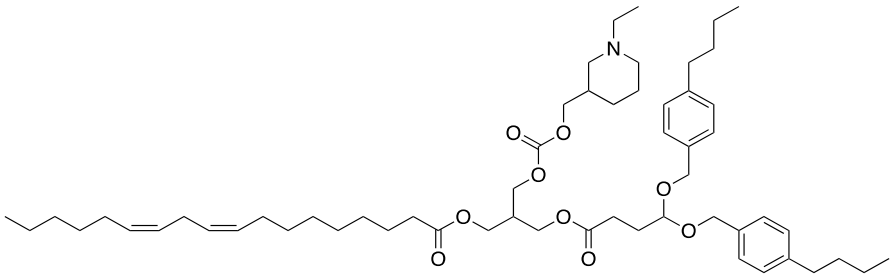

Example 91

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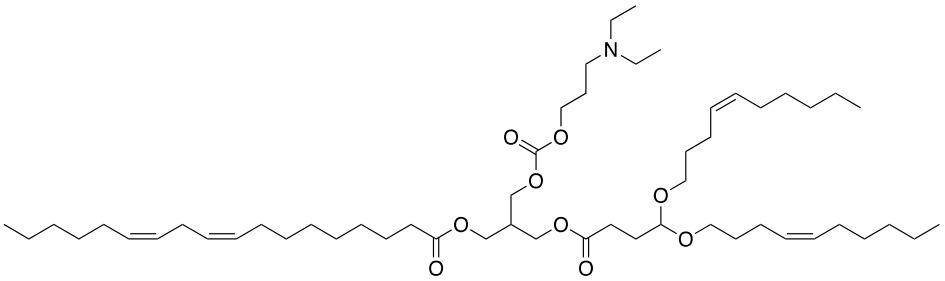

Example 92

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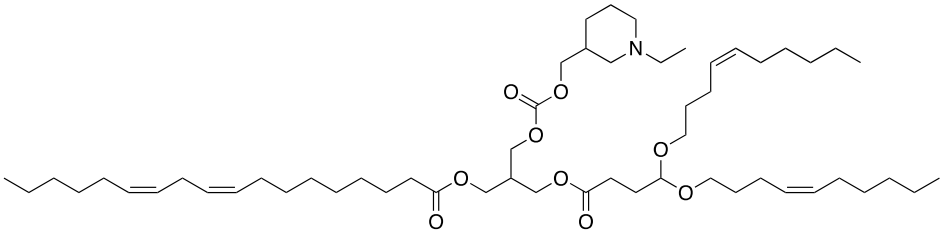

Example 93

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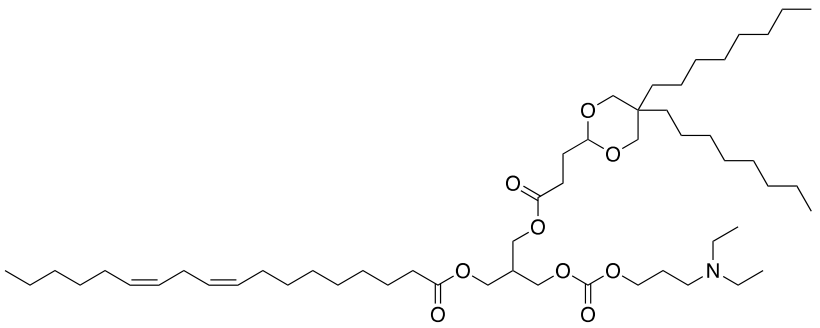

Example 94

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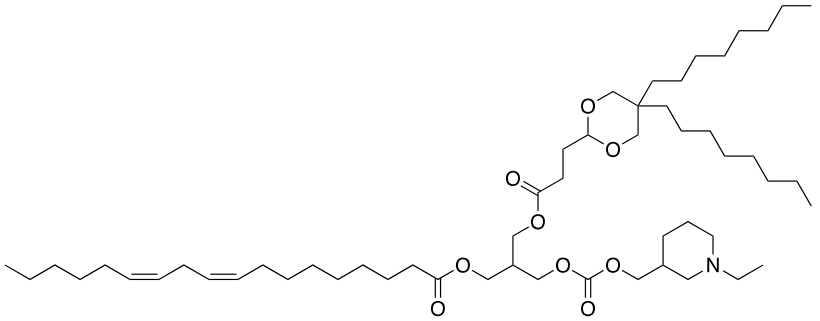

Example 95

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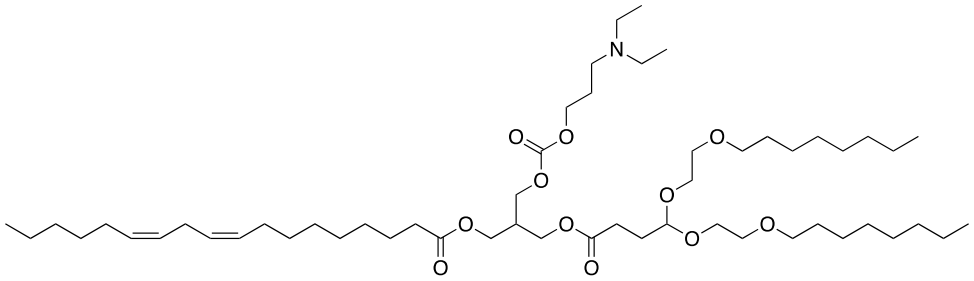

Example 96

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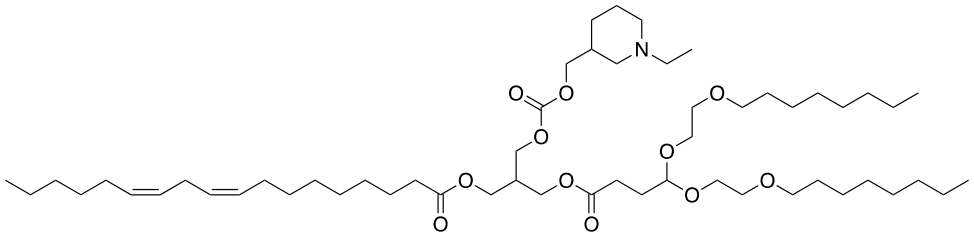

Example 97

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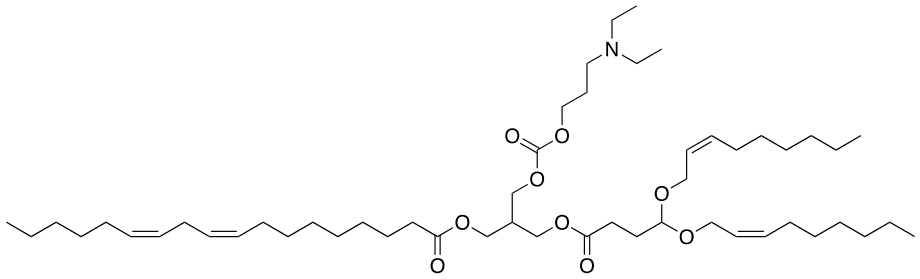

Example 98

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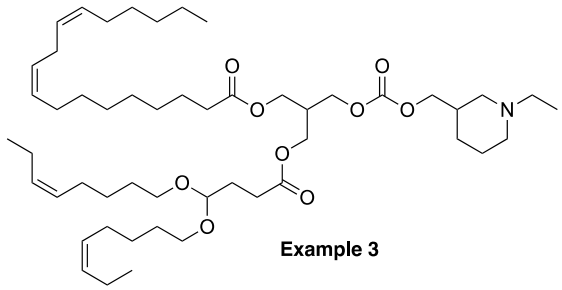
11. The compound of claim 1, wherein the compound is selected from the group consisting of:



Example 3

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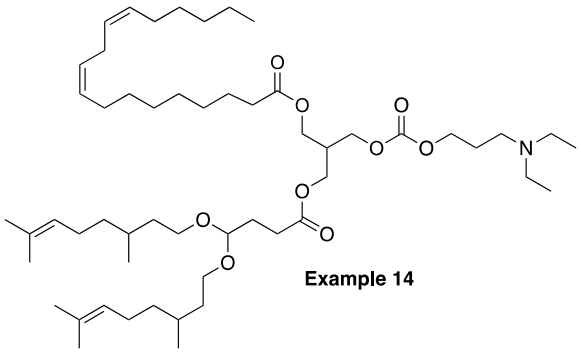

Example 14

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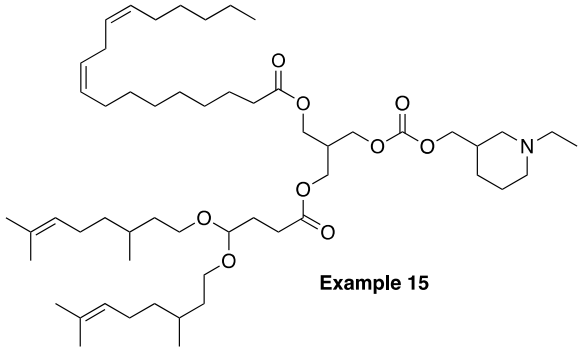

Example 15

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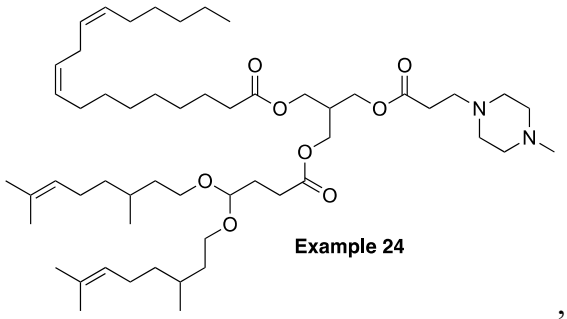

Example 24

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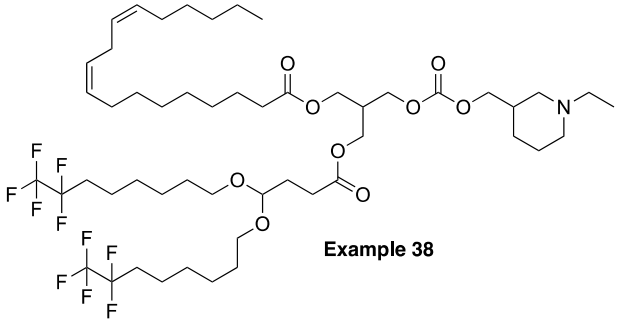

Example 38

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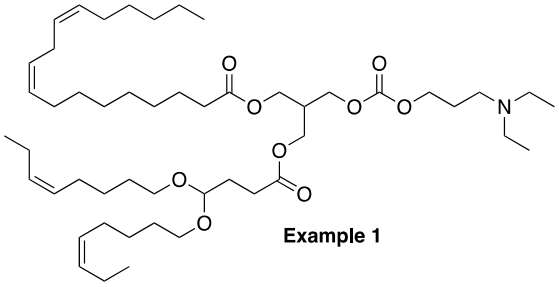

Example 1

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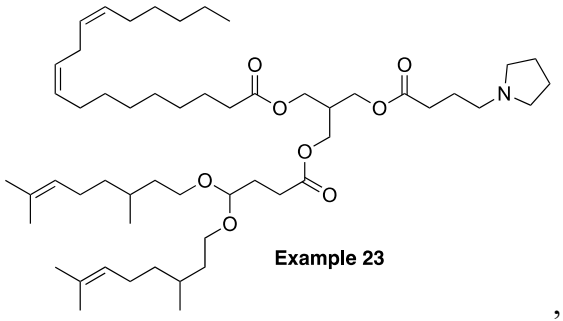

Example 23

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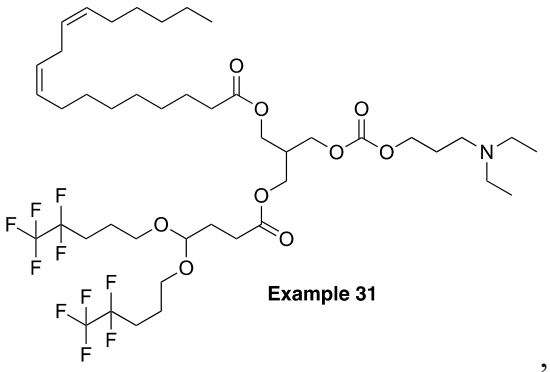

Example 31

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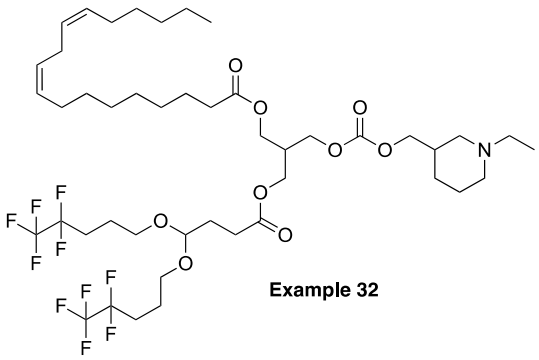

Example 32

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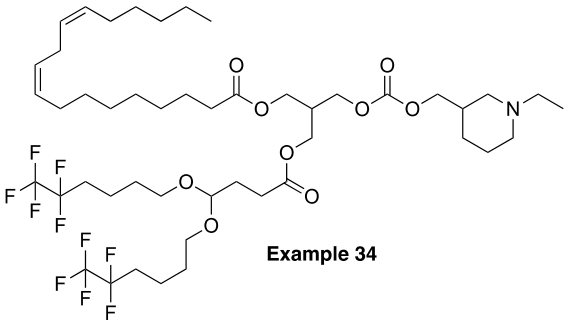

Example 34

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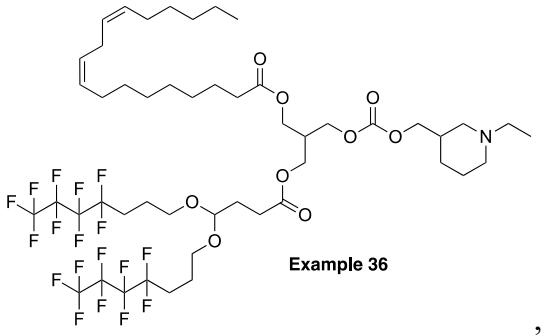

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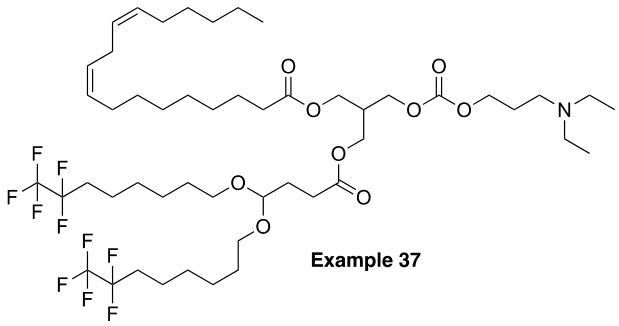

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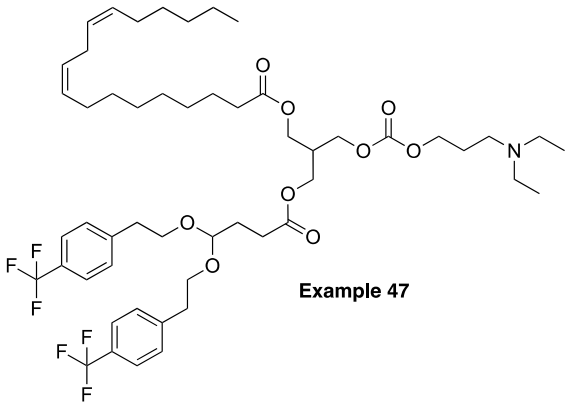

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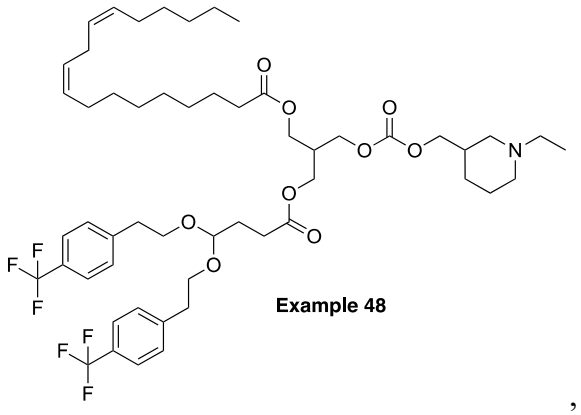

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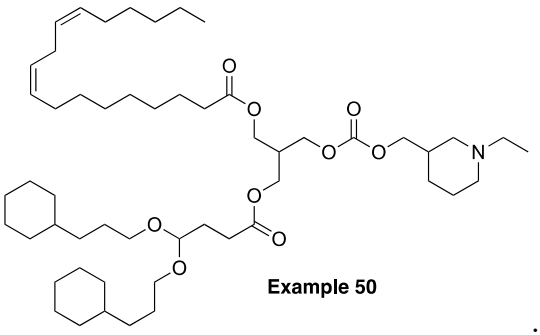

and .

12. A lipid nanoparticle composition comprising:

An ionizable lipid that comprises a compound of any one of claims 1-11, optionally wherein the amount of the ionizable lipid is present in a range of about 35 to 65 mole percent, based on total moles;

a phospholipid, optionally wherein the phospholipid is DSPC or DMPC;

a polyethylene glycol-lipid;

a cholesterol; and optionally

a nucleic acid.

13. The lipid nanoparticle composition of claim 12, wherein the nucleic acid is siRNA, miRNA, mRNA, expressing DNA, anti-sense oligonucleotide, or immunostimulatory oligonucleotide.

14. The lipid nanoparticle composition of claim 12, wherein the nucleic acid is guide RNA.

15. Use of the lipid nanoparticle composition of any one of claims 12-14 in the manufacture of a medicament for the treatment of cancer, autoimmune disease, infectious disease, organ transplant, organ failure, protein deficiency, or a combination thereof.