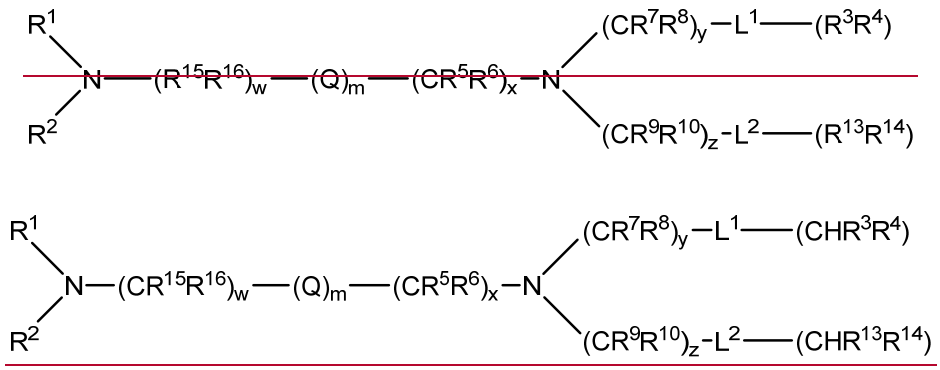
CLAIMS

What is claimed is:

1. A compound of the formula V:



Formula V

wherein each R^1 and each R^2 is independently selected from the group consisting of H, an optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_4-C_6 heterocycloalkyl, optionally substituted C_4-C_6 alkylcycloalkyl, optionally substituted C_4-C_6 aryl, optionally substituted C_3-C^6 heteroaryl, optionally substituted C_4-C_8 aryloxy, optionally substituted C_7-C_{10} arylalkyl; optionally substituted C_5-C_{10} heteroarylalkyl group, optionally substituted amine; or R^1 and R^2 can together form cycloalkyl or heterocycloalkyl ring;

wherein each R^3, R^4, R^{13}, and R^{14} is independently selected from the group consisting of an -H, optionally substituted C_1-C_{22} alkyl, optionally substituted C_2-C_{22} alkenyl, optionally substituted C_2-C_{22} alkynyl;

wherein each R^5, R^6, R^7, R^8, R^9, R^{10}, R^{15}, and R^{16} is independently selected from the group consisting of H, OH, halo, phenyl, benzyl, optionally substituted C_1-C_{22} alkyl, optionally substituted C_2-C_{22} alkenyl, optionally substituted C_2-C_{22} alkynyl,

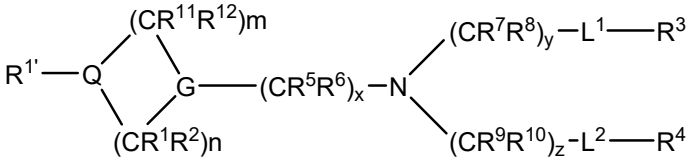
wherein each of w, y, and z is independently an integer from 0-10;

wherein each Q is independently an atom selected from O, NH, NR^1, S, or a disulfide bond;

wherein each of m is an integer from 0-20, and

wherein each of L^1 and L^2 is independently selected from the group consisting of -C(=O)-; OC(=O)-; -OC(=O)O-; -C(=O)O-; -C(=O)O(CR^6R^7)$_m$-; -NH-C(=O)-; -C(=O)NH-; -SO-; -SO_2-; -SO_3-; -NSO_2-; -SO_2N-; -NH((C_1-C_8)alkyl); -N((C_1-C_8)alkyl)$_2$; -NH((C_6)aryl); -N((C_6)aryl)$_2$; -NHC(=O)NH-; -NHC(=O)O-; -OC(=O)NH-; -NHC(=O)NR^1-; -NHC(=O)O-; -OC(=O)NR^1-; -C(=O)R^1-; -CO((C_1-C_8)alkyl); -CO((C_6)aryl); -CO_2((C_1-C_8)alkyl); -CO_2((C_6)aryl); -SO_2((C_1-C_8)alkyl); and -SO_2((C_6)aryl).

2. A compound of Formula III:



Formula III

wherein each $R^{1'}$, R^1, R^2, R^{11}, and R^{12} is independently selected from the group consisting of H, an optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_4-C_6 heterocycloalkyl, optionally substituted C_4-C_6 alkylcycloalkyl, optionally substituted C_4-C_6 aryl, optionally substituted C_3-C_6 heteroaryl, optionally substituted C_4-C_8 aryloxy,

optionally substituted C_7-C_{10} arylalkyl; optionally substituted C_5-C_{10} heteroarylalkyl group, optionally substituted amine; or R^1 and R^2 can together form cycloalkyl or heterocycloalkyl ring, wherein if Q is S or O the R^1 attached to the S or O is an electron pair;

wherein each R^3 and R^4 is independently selected from the group consisting of an optionally substituted C_1-C_{22} alkyl, optionally substituted C_2-C_{22} alkenyl, optionally substituted C_2-C_{22} alkynyl;

wherein each R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from the group consisting of H, OH, halo, phenyl, benzyl, optionally substituted C_1-C_{22} alkyl, optionally substituted C_2-C_{22} alkenyl, optionally substituted C_2-C_{22} alkynyl,

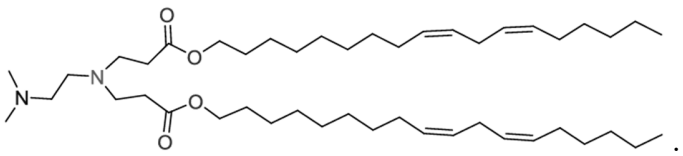
wherein each of x, y, and z is independently an integer from 0-10;

wherein G and Q are each independently an atom selected from CH, O, N, and S;

wherein each of m and n is an integer from 0-20; and

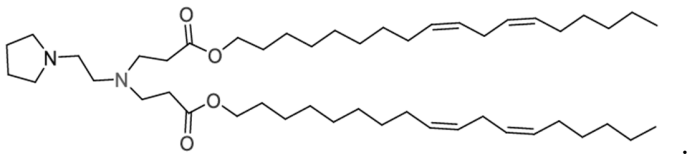
wherein each of L^1 and L^2 is independently selected from the group consisting of -C(=O)-; OC(=O)-; -OC(=O)O-; -C(=O)O-; -C(=O)O(CR^6R^7)$_m$-; -NH-C(=O)-; -C(=O)NH-; -SO-; -SO_2-; -SO_3-; -NSO_2-; -SO_2N-; -NH((C_1-C_8)alkyl); -N((C_1-C_8)alkyl)$_2$; -NH((C_6)aryl); -N((C_6)aryl)$_2$; -NHC(=O)NH-; -NHC(=O)O-; -OC(=O)NH-; -NHC(=O)NR^1-; -NHC(=O)O-; -OC(=O)NR^1-; -C(=O)R^1-; -CO((C_1-C_8)alkyl); -CO((C_6)aryl); -CO_2((C_1-C_8)alkyl); -CO_2((C_6)aryl); -SO_2((C_1-C_8)alkyl); and -SO_2((C_6)aryl).

3. The compound of claim 1, wherein the compound has the following structure:

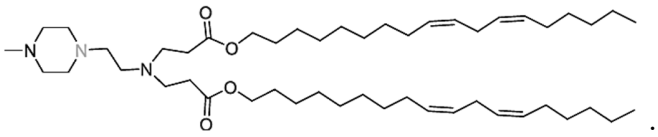


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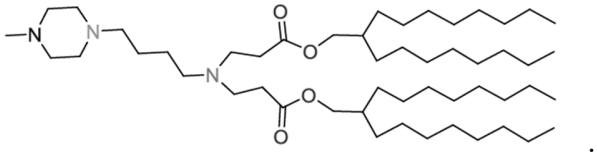
4. The compound of claim 2, wherein the compound has the following structure:



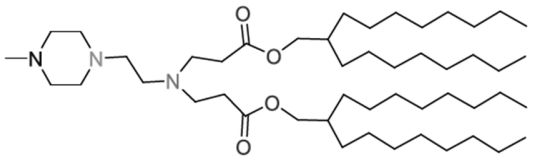
5. The compound of claim 2, wherein the compound has the following structure:



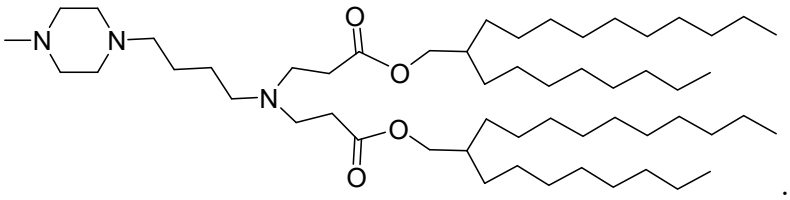
6. The compound of claim 2, wherein the compound has the following structure:



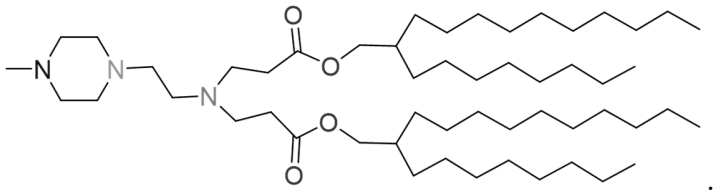
7. The compound of claim 2, wherein the compound has the following structure:



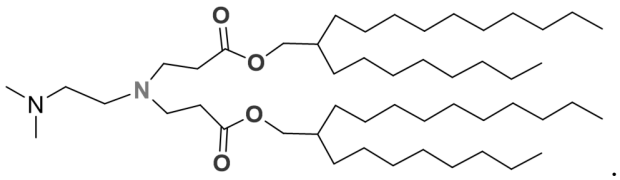
8. The compound of claim 2, wherein the compound has the following structure:



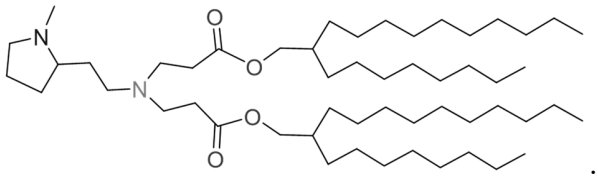
9. The compound of claim 2, wherein the compound has the following structure:



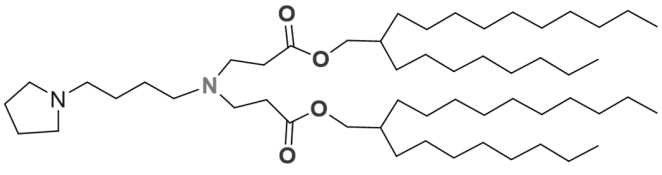
10. The compound of claim 2, wherein the compound has the following structure:



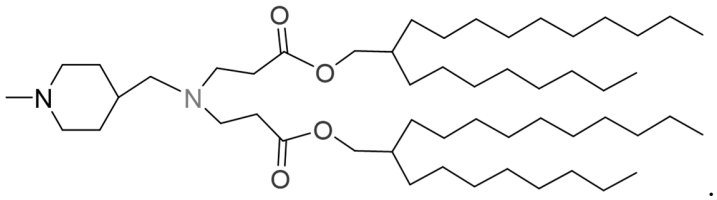
11. The compound of claim 2, wherein the compound has the following structure:



12. The compound of claim 2, wherein the compound has the following structure:



13. The compound of claim 2, wherein the compound has the following structure:



14. A Lipid Nanoparticle comprising:

i) a compound of claim 1;

ii) a second lipid, for example, a neutral or zwitterionic lipid;

iii) a steroid;

iv) a polymer conjugated lipid; and

v) a therapeutic or prophylactic agent, or a pharmaceutically acceptable salt thereof, encapsulated within or associated with the lipid nanoparticle.

15. A Lipid Nanoparticle comprising:

i) a compound of claim 2;

ii) a second lipid, for example, a neutral or zwitterionic lipid;

iii) a steroid;

iv) a polymer conjugated lipid; and

v) a therapeutic or prophylactic agent, or a pharmaceutically acceptable salt thereof, encapsulated within or associated with the lipid nanoparticle.

~~16. A method of delivering a nucleic acid to a subject comprising administering to said subject a lipid nanoparticle comprising:~~

~~i) a compound of claim 1;~~

~~ii) a second lipid, for example, a neutral or zwitterionic lipid;~~

~~iii) a steroid;~~

~~iv) a polymer conjugated lipid; and~~

~~v) a nucleic acid, or a pharmaceutically acceptable salt thereof, encapsulated within or associated with the lipid nanoparticle.~~

~~17. A method of delivering a nucleic acid to a subject comprising administering to said subject a lipid nanoparticle comprising:~~

~~i) a compound of claim 2;~~

~~ii) a second lipid, for example, a neutral or zwitterionic lipid;~~

~~iii) a steroid;~~

~~iv) a polymer conjugated lipid; and~~

~~v) a nucleic acid, or a pharmaceutically acceptable salt thereof, encapsulated within or associated with the lipid nanoparticle.~~

~~18. A method of delivering a therapeutic agent comprising a therapeutic protein, a vaccine, a gene editing RNA to a subject comprising administering to said subject a lipid nanoparticle comprising:~~

~~i) a compound of claim 1;~~

~~ii) a second lipid, for example, a neutral or zwitterionic lipid;~~

~~iii) a steroid;~~

~~iv) a polymer conjugated lipid; and~~

~~v) a therapeutic agent, or a pharmaceutically acceptable salt thereof, encapsulated within or associated with the lipid nanoparticle.~~

16. The lipid nanoparticle of claim 14 or 15 for use in therapy.

17. Use of the lipid nanoparticle of claim 14 or 15 in the manufacture of a medicament for treating or preventing a disease or disorder selected from the group consisting of cancer, an infectious disease, an allergic disease, and an autoimmune disease.

18. The lipid nanoparticle for use according to claim 16 or the use of the lipid nanoparticle according to claim 17, wherein the therapeutic or prophylactic agent comprises a nucleic acid.

19. A method of ~~*in vivo*~~*ex vivo* targeted delivery of a lipid nanoparticle (LNP) to a cell or tissue sample comprising a therapeutic or prophylactic agent comprising:

1.) predict molecular pKa of an ionizable lipid, synthesize the ionizable lipid, measure pKa with analytical methods such as NMR;

2.) measure LNP pKa using analytical methods including TNS and zeta potential;

3.) assess cell ~~and organ~~ or tissue sample targeting ~~in vivo~~ex vivo using reporter genes selected from the group consisting of luciferase, mCherry, Cre reporter;

4.) adjust ionizable lipid structure to find optimal molecular pKa for cell or tissue sample targeting;

5.) selecting a headgroup, spacer group, and tail group possessing the desired pKa associated with targeting the desired cell or tissue sample; and

6.) repeat steps 1-4 until optimal cell ~~and~~ or tissue sample targeting is achieved.