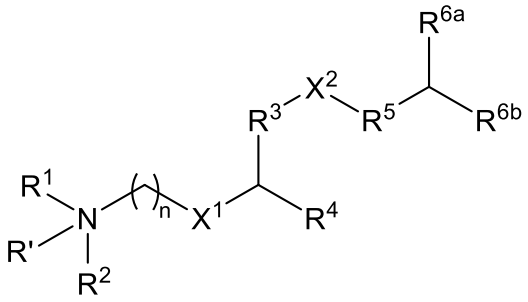
liposome or lipid membrane structure. Thus, uptake into cells is promoted and nucleic acids are delivered into cells.

Some cationic lipids (*e.g.*, DODAP and DOTAP) have two or more structurally identical hydrophobic tails in the hydrophobic domain. Some other cationic lipids have two or more hydrophobic tails that are structurally different from each other. Asymmetrical cationic lipids known in the art, such as CLinDMA, are asymmetrical typically in that either: (i) the hydrophobic tails differ structurally by incorporating different chemical moieties and functional groups (*e.g.*, CLinDMA incorporating cholesterol in one of the hydrophobic tails); or (ii) the hydrophobic tails differ in length. Symmetrical cationic lipids are usually favored because they pose less synthesis challenges.

Some widely used cationic lipids such as CLinDMA, DLinDMA (DODAP), and DOTAP have been employed for ribonucleic acid (siRNA or mRNA) delivery but suffer from sub-optimal delivery efficiency along with toxicity at higher doses. In view of the shortcomings of the current cationic lipids, there is a need in the field to provide lipid scaffolds that not only demonstrate enhanced efficacy along with reduced toxicity, but with improved pharmacokinetics and intracellular kinetics such as cellular uptake and nucleic acid release from the lipid carrier.

SUMMARY

In a first aspect of the present disclosure, there is provided a lipid represented by Formula **I**:



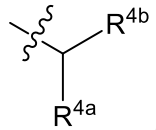
I

or a pharmaceutically acceptable salt thereof, wherein:

R' is absent, hydrogen, or C_1-C_6 alkyl; provided that when **R'** is hydrogen or C_1-C_6 alkyl, the nitrogen atom to which **R'**, **R^1**, and **R^2** are all attached is positively charged;

R^1 and **R^2** are each independently hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^3 is C_1-C_{12} alkylene or C_2-C_{12} alkenylene;

$\mathbf{R^4}$ is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or 

; wherein:

$\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

$\mathbf{R^5}$ is absent, C_1-C_8 alkylene, or C_2-C_8 alkenylene;

$\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_7-C_{16} alkyl or C_7-C_{16} alkenyl; provided that the total number of carbon atoms in $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ as combined is greater than 15;

$\mathbf{X^1}$ and $\mathbf{X^2}$ are the same and are selected from the group consisting of: -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C($\mathbf{R^a}$)=N-, -N=C($\mathbf{R^a}$)-, -C($\mathbf{R^a}$)=NO-, -O-N=C($\mathbf{R^a}$)-, -C(=O)N$\mathbf{R^a}$-, -N$\mathbf{R^a}$C(=O)-, -N$\mathbf{R^a}$C(=O)N$\mathbf{R^a}$-, -OC(=O)O-, -OSi($\mathbf{R^a}$)$_2$O-, -C(=O)(C$\mathbf{R^a}_2$)C(=O)O-, and OC(=O)(C$\mathbf{R^a}_2$)C(=O)-; wherein:

$\mathbf{R^a}$, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6.

In another aspect of the present disclosure, there is provided a lipid nanoparticle (LNP) comprising the lipid as disclosed herein, or a pharmaceutically acceptable salt thereof; and a therapeutic nucleic acid.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the lipid as disclosed herein or the lipid nanoparticle as disclosed herein and a pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a use of the lipid nanoparticle as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease or disorder in a subject.

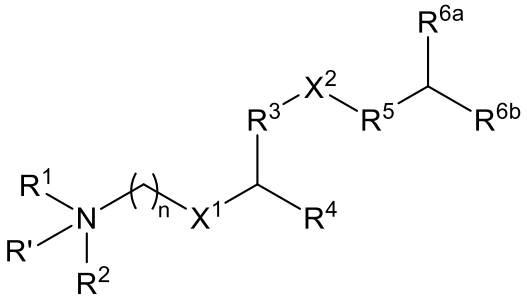
In another aspect of the present disclosure, there is provided the lipid nanoparticle as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in therapy.

The cationic lipids provided in the present disclosure comprise one hydrophobic tail containing a biodegradable group, and a hydrophobic tail that does not contain a biodegradable group. Some of the exemplary lipids provided in this disclosure comprise a hydrophobic tail that bifurcates at the terminal ends to form two branched aliphatic hydrocarbon chains, and a hydrophobic tail that does not bifurcate. The inventors have found that the cationic lipids of the present disclosure can be synthesized at satisfactory yield and purity. The inventors have also found that the cationic lipids of the present disclosure, when formulated as lipid nanoparticles (LNP) for carrying a therapeutic nucleic acid, exhibit sustained excellent and stable *in vivo* expression level of the transgene insert within the

CLAIMS

WHAT IS CLAIMED IS:

1. A lipid represented by Formula **I**:



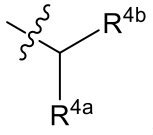
I

or a pharmaceutically acceptable salt thereof, wherein:

R' is absent, hydrogen, or C_1-C_6 alkyl; provided that when **R'** is hydrogen or C_1-C_6 alkyl, the nitrogen atom to which **R'**, **R^1**, and **R^2** are all attached is positively charged;

R^1 and **R^2** are each independently hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl;

R^3 is C_1-C_{12} alkylene or C_2-C_{12} alkenylene;

R^4 is C_1-C_{16} unbranched alkyl, C_2-C_{16} unbranched alkenyl, or  ; wherein:

R^{4a} and **R^{4b}** are each independently C_1-C_{16} unbranched alkyl or C_2-C_{16} unbranched alkenyl;

R^5 is absent, C_1-C_8 alkylene, or C_2-C_8 alkenylene;

R^{6a} and **R^{6b}** are each independently C_7-C_{16} alkyl or C_7-C_{16} alkenyl; provided that the total number of carbon atoms in **R^{6a}** and **R^{6b}** as combined is greater than 15;

X^1 and **X^2** are the same and are selected from the group consisting of: -OC(=O)-, -SC(=O)-, -OC(=S)-, -C(=O)O-, -C(=O)S-, -S-S-, -C(**R^a**)=N-, -N=C(**R^a**)-, -C(**R^a**)=NO-, -O-N=C(**R^a**)-, -C(=O)N**R^a**-, -N**R^a**C(=O)-, -N**R^a**C(=O)N**R^a**-, -OC(=O)O-, -OSi(**R^a**)$_2$O-, -C(=O)(C**R^a**$_2$)C(=O)O-, and OC(=O)(C**R^a**$_2$)C(=O)-; wherein:

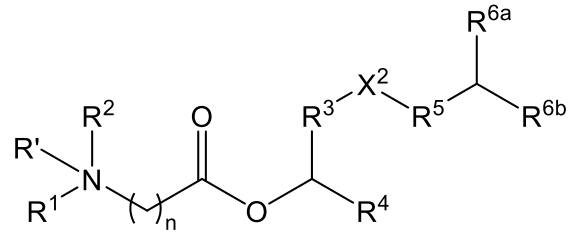
R^a, for each occurrence, is independently hydrogen or C_1-C_6 alkyl; and

n is an integer selected from 1, 2, 3, 4, 5, and 6.

2. The lipid according to claim 1, or a pharmaceutically acceptable salt thereof, wherein **X^1** and **X^2** are each -OC(=O)-, -SC(=O)-, -OC(=S)-,

-C(=O)O-, -C(=O)S-, or -S-S-.

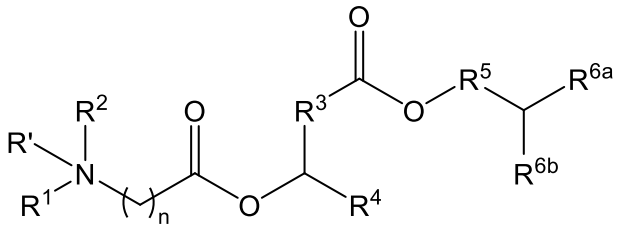
3. The lipid according to claim 1 or 2, wherein the lipid is represented by Formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein **n** is an integer selected from 1, 2, 3, and 4.

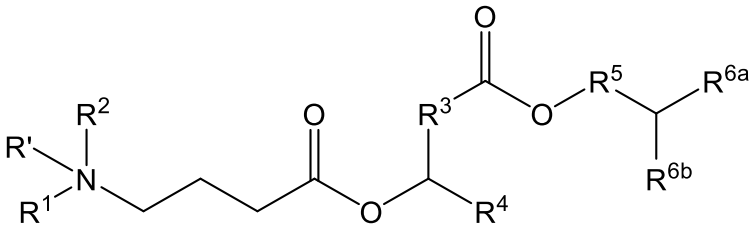
4. The lipid according to any one of claims 1 to 3, wherein the lipid is represented by Formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein **n** is an integer selected from 1, 2, and 3.

5. The lipid according to any one of claims 1 to 4, wherein the lipid is represented by Formula **IV**:



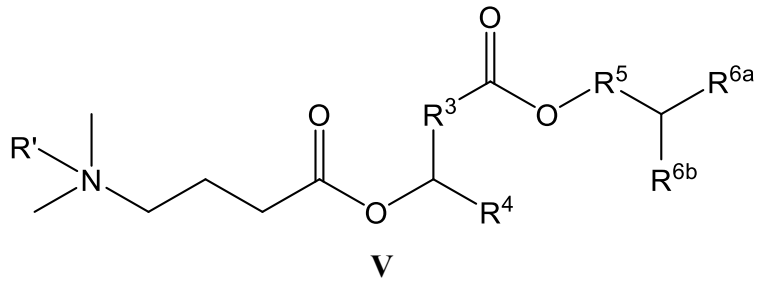
IV

or a pharmaceutically acceptable salt thereof.

6. The lipid according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently hydrogen, C_1-C_3 alkyl, or C_2-C_3 alkenyl.

7. The lipid according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are each independently hydrogen or C_1-C_2 alkyl.

8. The lipid according to any one of claims 1 to 7, wherein the lipid is represented by Formula **V**:



V

or a pharmaceutically acceptable salt thereof.

9. The lipid according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^3}$ is C_1-C_9 alkylene or C_2-C_9 alkenylene.

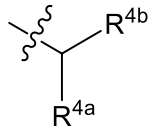
10. The lipid according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^3}$ is C_1-C_7 alkylene.

11. The lipid according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^3}$ is selected from the group consisting of C_7 alkylene, C_6 alkylene, C_5 alkylene, C_4 alkylene and C_3 alkylene.

12. The lipid according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^5}$ is absent, C_1-C_4 alkylene, or C_2-C_4 alkenylene.

13. The lipid according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^5}$ is absent.

14. The lipid according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **R^5** is selected from the group consisting of C_1 alkylene, C_2 alkylene, C_3 alkylene and C_4 alkylene.

15. The lipid according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein **R^4** is C_1-C_{14} unbranched alkyl, C_2-C_{14} unbranched alkenyl, or 

; wherein **R^{4a}** and **R^{4b}** are each independently C_1-C_{12} unbranched alkyl or C_2-C_{12} unbranched alkenyl.

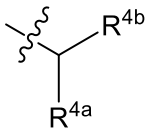
16. The lipid according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein **R^4** is C_2-C_{12} unbranched alkyl or C_2-C_{12} unbranched alkenyl.

17. The lipid according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein **R^4** is C_5-C_{12} unbranched alkyl.

18. The lipid according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein **R^4** is selected from the group consisting of C_6 unbranched alkyl, C_7 unbranched alkyl, C_8 unbranched alkyl and C_9 unbranched alkyl.

19. The lipid according to any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein **R^4** is C_{10}-C_{12} unbranched alkyl.

20. The lipid according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein **R^4** is C_2-C_7 unbranched alkyl or C_2-C_7 unbranched alkenyl.

21. The lipid according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein **R^4** is 

; wherein **R^{4a}** and **R^{4b}** are each independently C_5-C_9 unbranched alkyl.

22. The lipid according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_7-C_{14} alkyl or C_7-C_{14} alkenyl.

23. The lipid according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_8 alkenyl, C_{10} alkenyl, C_{11} alkenyl, or C_{12} alkenyl.

24. The lipid according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, or C_{12} alkyl.

25. The lipid according to any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_{13} alkyl, C_{14} alkyl, C_{15} alkyl, C_{16} alkyl, C_9 alkenyl, C_{10} alkenyl, C_{11} alkenyl, C_{12} alkenyl, C_{13} alkenyl, C_{14} alkenyl, C_{15} alkenyl, or C_{16} alkenyl.

26. The lipid according to claim 25, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are each independently C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_{13} alkyl, C_{14} alkyl, C_{15} alkyl, and C_{16} alkyl.

27. The lipid according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ each contain the same number of carbon atoms.

28. The lipid according to any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are the same.

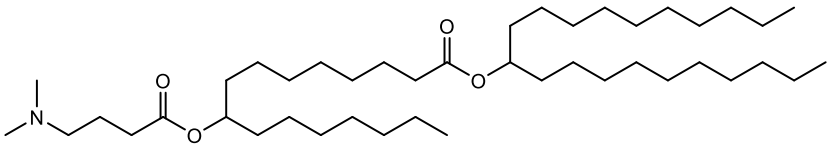
29. The lipid according to any one of claims 1 to 24, 27 and 28, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ are both C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl or C_{12} alkyl.

30. The lipid according to any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ each contain a different number of carbon atoms.

31. The lipid according to any one of claims 1 to 26 and 30, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^{6a}}$ is C_9 alkyl and $\mathbf{R^{6b}}$ is C_8 alkyl; or $\mathbf{R^{6a}}$ is C_8 alkyl and $\mathbf{R^{6b}}$ is C_9 alkyl; or $\mathbf{R^{6a}}$ is C_9 alkyl and $\mathbf{R^{6b}}$ is C_{10} alkyl; or $\mathbf{R^{6a}}$ is C_{10} alkyl and $\mathbf{R^{6b}}$ is C_9 alkyl.

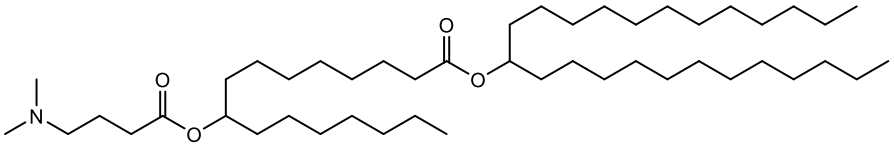
32. The lipid according to any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, wherein **R'** is absent.

33. The lipid according to claim 1, wherein the lipid is selected from the group consisting of:



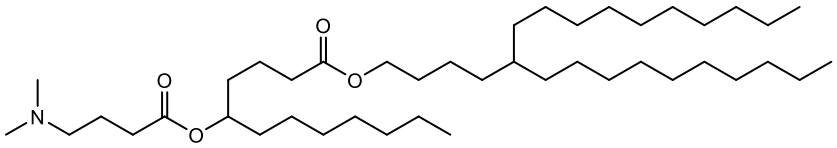
henicosan-11-yl 9-((4-(dimethylamino)butanoyl)oxy)hexadecanoate ;

(**Lipid 1**)



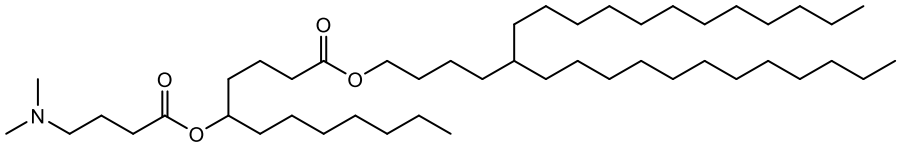
pentacosan-13-yl 9-((4-(dimethylamino)butanoyl)oxy)hexadecanoate ;

(**Lipid 2**)



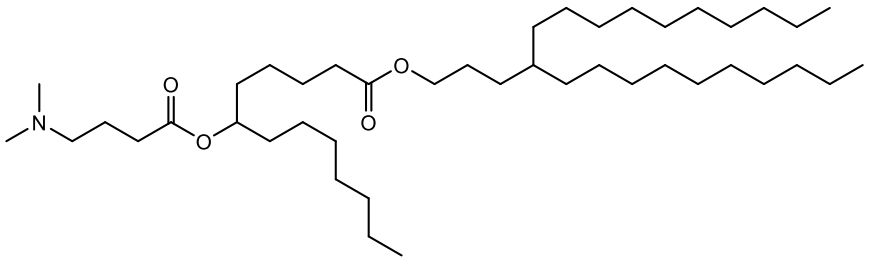
5-decylpentadecyl 5-((4-(dimethylamino)butanoyl)oxy)dodecanoate ;

(**Lipid 3**)



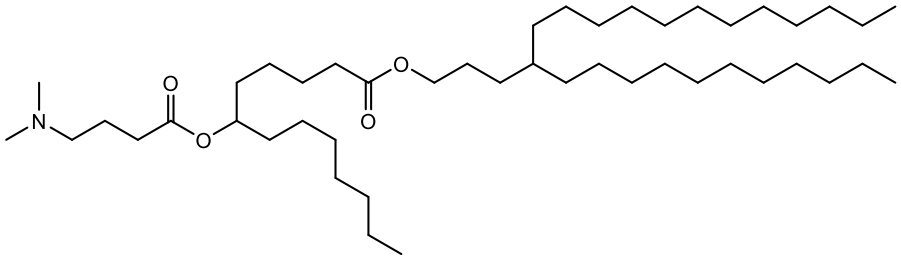
5-dodecylheptadecyl 5-((4-(dimethylamino)butanoyl)oxy)dodecanoate ;

(**Lipid 4**)



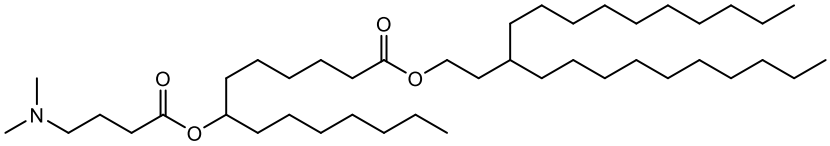
4-decyltetradecyl 6-((4-(dimethylamino)butanoyl)oxy)tridecanoate ;

(**Lipid 5**)



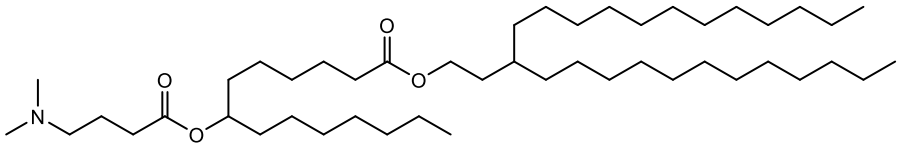
4-dodecylhexadecyl 6-((4-(dimethylamino)butanoyl)oxy)tridecanoate ;

(**Lipid 6**)



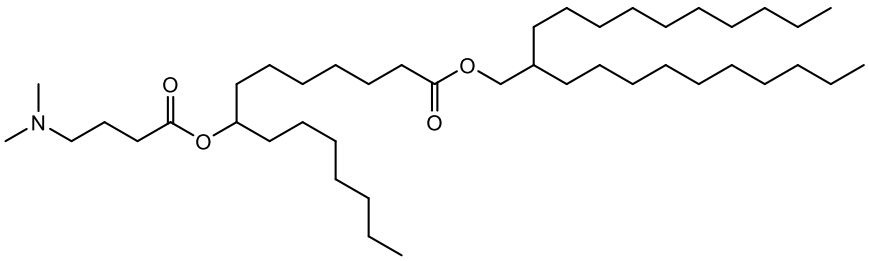
3-decyltridecyl 7-((4-(dimethylamino)butanoyl)oxy)tetradecanoate ;

(**Lipid 7**)



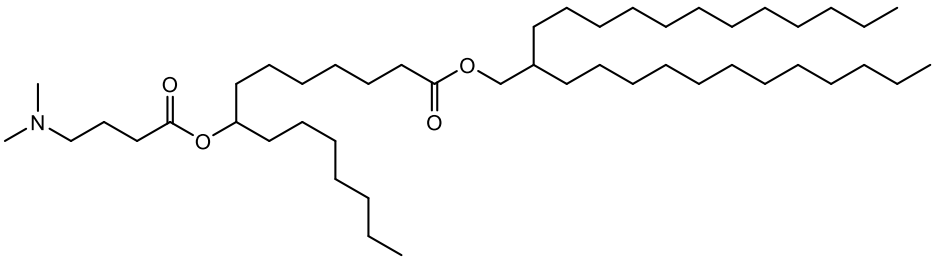
3-dodecylpentadecyl 7-((4-(dimethylamino)butanoyl)oxy)tetradecanoate ;

(**Lipid 8**)



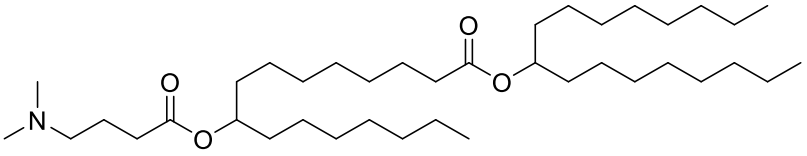
2-decyldodecyl 8-((4-(dimethylamino)butanoyl)oxy)pentadecanoate ;

(**Lipid 9**)



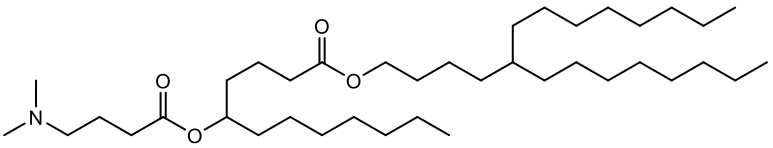
2-dodecyltetradecyl 8-((4-(dimethylamino)butanoyl)oxy)pentadecanoate ;

(**Lipid 10**)



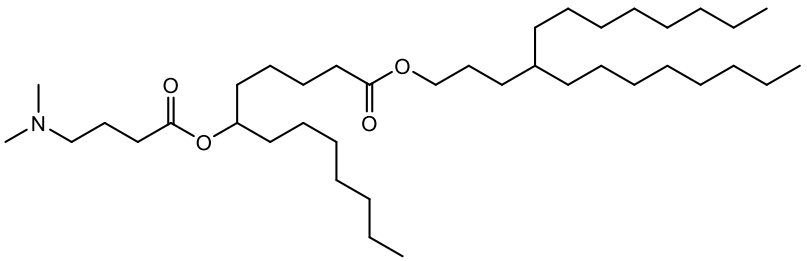
heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)hexadecanoate ;

(**Lipid 11**)



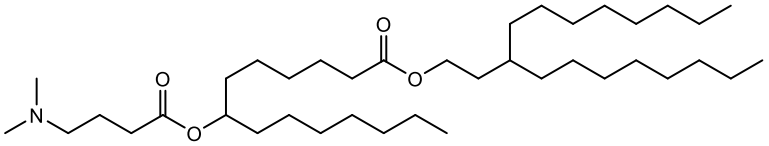
5-octyltridecyl 5-((4-(dimethylamino)butanoyl)oxy)dodecanoate ;

(**Lipid 12**)



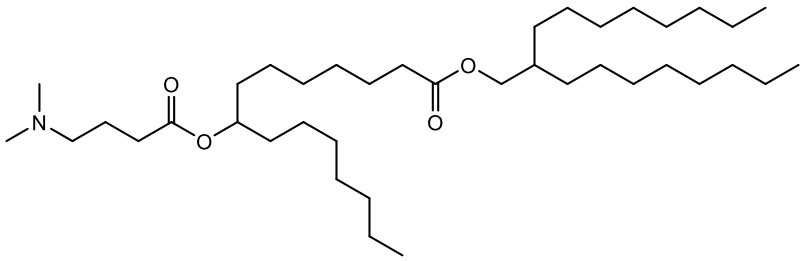
4-octyldodecyl 6-((4-(dimethylamino)butanoyl)oxy)tridecanoate ;

(**Lipid 13**)



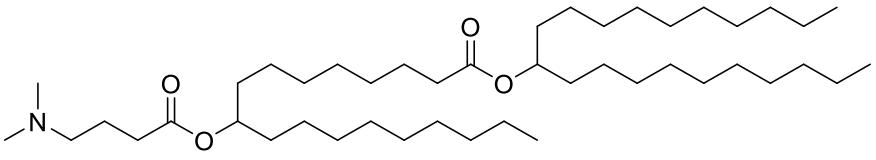
3-octylundecyl 7-((4-(dimethylamino)butanoyl)oxy)tetradecanoate ;

(**Lipid 14**)



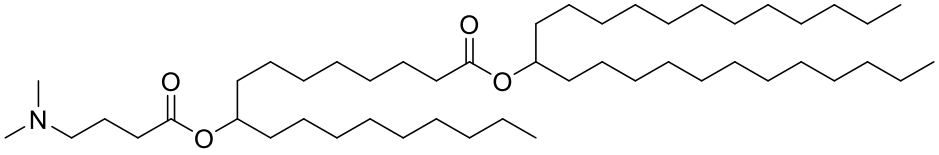
2-octyldecyl 8-((4-(dimethylamino)butanoyl)oxy)pentadecanoate ;

(**Lipid 15**)



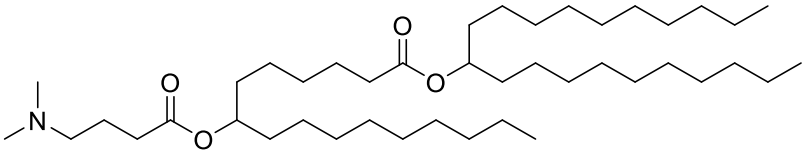
henicosan-11-yl 9-((4-(dimethylamino)butanoyl)oxy)octadecanoate ;

(**Lipid 16**)



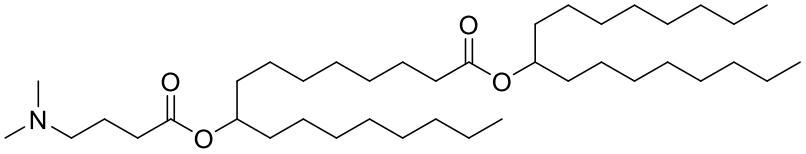
pentacosan-13-yl 9-((4-(dimethylamino)butanoyl)oxy)octadecanoate ;

(**Lipid 17**)



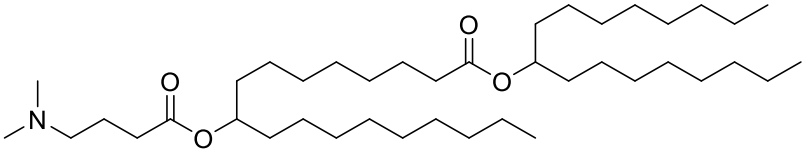
henicosan-11-yl 7-((4-(dimethylamino)butanoyl)oxy)hexadecanoate ;

(**Lipid 18**)



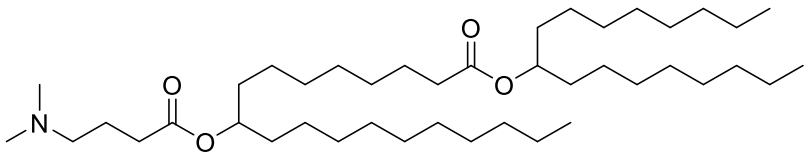
heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)heptadecanoate ;

(**Lipid 19**)



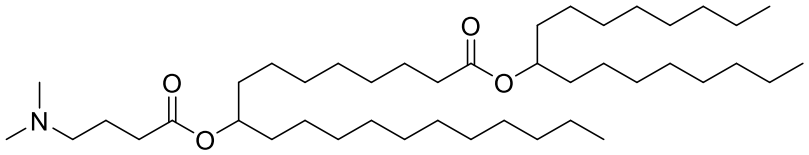
heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)octadecanoate ;

(**Lipid 20**)



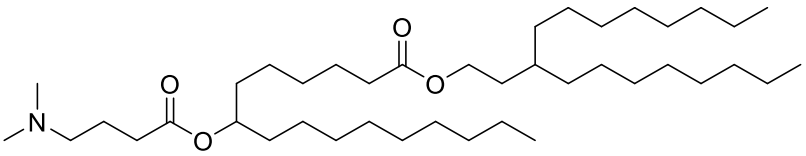
heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)nonadecanoate ;

(**Lipid 21**)



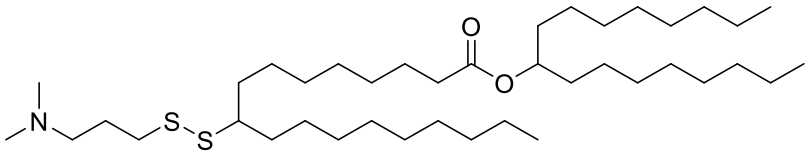
heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)icosanoate ;

(**Lipid 22**)



3-octylundecyl 7-((4-(dimethylamino)butanoyl)oxy)hexadecanoate ; and

(**Lipid 23**)

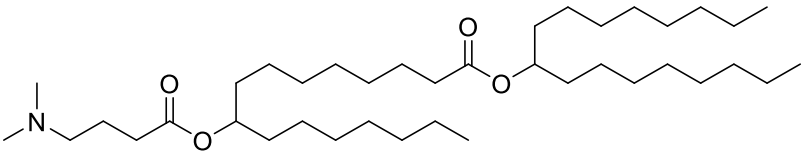


heptadecan-9-yl 9-((3-(dimethylamino)propyl)disulfaneyl)octadecanoate ,

(**Lipid 25**)

or a pharmaceutically acceptable salt thereof.

34. The lipid according to claim 33, wherein the lipid is



heptadecan-9-yl 9-((4-(dimethylamino)butanoyl)oxy)hexadecanoate

(Lipid 11)

or a pharmaceutically acceptable salt thereof.

35. A lipid nanoparticle (LNP) comprising the lipid according to any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof; and a therapeutic nucleic acid.

36. The lipid nanoparticle according to claim 35, wherein the therapeutic nucleic acid is encapsulated in the lipid.

37. The lipid nanoparticle according to claim 35 or 36, wherein the therapeutic nucleic acid is selected from the group consisting of a minigene, a plasmid, a minicircle, a small interfering RNA (siRNA), a microRNA (miRNA), an antisense oligonucleotide (ASO), a ribozyme, a ceDNA, a ministring, a doggybone™, a protelomere closed ended DNA, a dumbbell linear DNA, a dicer-substrate dsRNA, a small hairpin RNA (shRNA), an asymmetrical interfering RNA (aiRNA), an mRNA, a tRNA, an rRNA, a DNA viral vector, a viral RNA vector, a non-viral vector and any combination thereof.

38. The lipid nanoparticle according to any one of claims 35 to 37, wherein the therapeutic nucleic acid is mRNA.

39. The lipid nanoparticle according to any one of claims 35 to 38, further comprising a sterol.

40. The lipid nanoparticle according to claim 39, wherein the sterol is cholesterol or beta-sitosterol.

41. The lipid nanoparticle according to any one of claims 35 to 40, further comprising a non-cationic lipid.

42. The lipid nanoparticle according to claim 41, wherein the non-cationic lipid is selected from the group consisting of distearoyl-sn-glycero-phosphoethanolamine (DSPE), distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoylphosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoylphosphatidylethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoylphosphatidylethanolamine (DSPE), monomethylphosphatidylethanolamine (such as 16-O-monomethyl PE),

dimethylphosphatidylethanolamine (such as 16-O-dimethyl PE), 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoylphosphatidylethanolamine (DEPE), 1,2-dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE); 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPHyPE); lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidic acid, cerebrosides, dicetylphosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, and mixtures thereof.

43. The lipid nanoparticle according to claim 41 or 42, wherein the non-cationic lipid is selected from the group consisting of dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), and dioleoylphosphatidylethanolamine (DOPE).

44. The lipid nanoparticle according to any one of claims 35 to 43, further comprising at least one PEGylated lipid.

45. The lipid nanoparticle according to claim 44, wherein the at least one PEGylated lipid is selected from the group consisting of PEG-dilauryloxypropyl; PEG-dimyristyloxypropyl; PEG-dipalmityloxypropyl, PEG-distearyloxypropyl; l-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (DMG-PEG); PEG-dilaurylglycerol; PEG-dipalmitoylglycerol; PEG-disterylglycerol; PEG-dilaurylglycamide; PEG-dimyristylglycamide; PEG-dipalmitoylglycamide; PEG-disterylglycamide; (l-[8'-(Cholest-5-en-3[beta]-oxy)carboxamido-3',6'-dioxaoctanyl] carbamoyl-[omega]-methyl-poly(ethylene glycol) (PEG-cholesterol); 3,4-ditetradecoxylbenzyl-[omega]- methyl-poly(ethylene glycol) ether (PEG-DMB), and l,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) (DSPE-PEG).

46. The lipid nanoparticle according to any one of claims 35 to 45, further comprising a tissue-specific targeting ligand.

47. The lipid nanoparticle according to claim 46, wherein the tissue-specific targeting ligand is an antibody, or N-acetylgalactosamine (GalNAc).

48. A pharmaceutical composition comprising the lipid according to any one of claims 1 to 34 or the lipid nanoparticle according to any one of claims 35 to 47 and a pharmaceutically acceptable excipient.

49. Use of the lipid nanoparticle according to any one of claims 35 to 47, or the pharmaceutical composition according to claim 48, in the manufacture of a medicament for treating a disease or disorder in a subject.

50. The use according to claim 49, wherein the subject is a human.

51. The use according to claim 49 or 50, wherein the disease or disorder is a genetic disorder.

52. The use according to claim 51, wherein the genetic disorder is selected from the group consisting of melanoma, hemophilia A (clotting factor VIII (FVIII) deficiency), hemophilia B (clotting factor IX (FIX) deficiency), cystic fibrosis (CFTR defect), familial hypercholesterolemia (LDL receptor defect), hepatoblastoma, Wilson disease, phenylketonuria (PKU), congenital hepatic porphyria, an inherited disorder of hepatic metabolism, Lesch-Nyhan syndrome, sickle cell anemia, thalassaemia, xeroderma pigmentosum, Fanconi anemia, retinitis pigmentosa, ataxia telangiectasia, Bloom syndrome, retinoblastoma, a mucopolysaccharide storage disease, Niemann-Pick Disease Type A/B, Niemann-Pick Disease Type C1, Niemann-Pick Disease Type C2, Fabry disease, Schindler disease, GM2-gangliosidosis Type II (Sandhoff Disease), Tay-Sachs disease, Metachromatic Leukodystrophy, Krabbe disease, Mucolipidosis Type I, Mucolipidosis Type II/III, Mucolipidosis Type IV, Sialidosis Type I, Sialidosis Type II, Glycogen Storage disease Type I, Glycogen Storage disease Type II (Pompe disease), Gaucher disease Type I, Gaucher disease Type II, Gaucher disease Type III, cystinosis, Batten disease, Aspartylglucosaminuria, Salla disease, Danon disease (LAMP-2 deficiency), Lysosomal Acid Lipase (LAL) deficiency, neuronal ceroid lipofuscinoses (CLN1-8, INCL, and LINCL), sphingolipidoses, galactosialidosis, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease, spinocerebellar ataxia, spinal muscular atrophy,

Friedreich's ataxia, Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), dystrophic epidermolysis bullosa (DEB), ectonucleotide pyrophosphatase 1 deficiency, generalized arterial calcification of infancy (GACI), Leber Congenital Amaurosis, Stargardt macular dystrophy (ABCA4 deficiency), ornithine transcarbamylase (OTC) deficiency, Usher syndrome, age-related macular degeneration (AMD), alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis (PFIC) type I (ATP8B1 deficiency), progressive familial intrahepatic cholestasis (PFIC) type II (ABCB11 deficiency), progressive familial intrahepatic cholestasis (PFIC) type III (ABCB4 deficiency), progressive familial intrahepatic cholestasis (PFIC) type IV (TJP2 deficiency), and Cathepsin A deficiency.

53. The use according to claim 52, wherein the mucopolysaccharide storage disease is selected from the group consisting of Hurler syndrome (MPS I), Scheie syndrome (MPS I S), Hurler-Scheie syndrome (MPS I H-S), Hunter syndrome (MPS II), Sanfilippo syndrome Types A (MPS IIIA), Sanfilippo syndrome Type B (MPS IIIB), Sanfilippo syndrome Type C (MPS IIIC), Sanfilippo syndrome Type D (MPS Type IIID), Morquio syndrome Type A (MPS IVA), Morquio syndrome Type B (MPS IVB), Maroteaux-Lamy syndrome (MPS VI), Sly syndrome (MPS VII) and hyaluronidase deficiency (MPS IX).

54. The lipid nanoparticle according to any one of claims 35 to 47, or the pharmaceutical composition according to claim 48, for use in therapy.