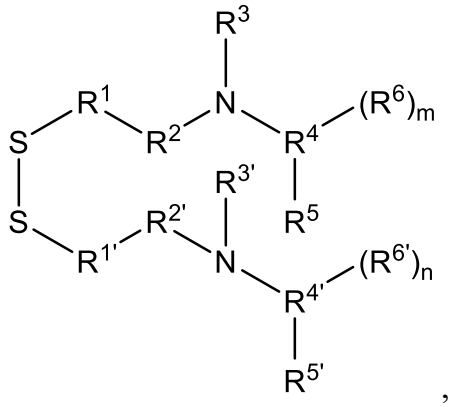
with reduced toxicity, but with improved pharmacokinetics and intracellular kinetics such as cell uptake and nucleic acid release from the lipid carrier.

SUMMARY

In one aspect of the present disclosure, there is provided an ionizable lipid represented by Formula (I):



,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently linear or branched C_{1-3} alkylene;

R^2 and $R^{2'}$ are each independently linear or branched C_{1-6} alkylene;

R^3 and $R^{3'}$ are each independently linear or branched C_{1-6} alkyl;

or alternatively, when R^2 is branched C_{1-6} alkylene, R^2 and R^3, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{2'}$ is branched C_{1-6} alkylene, $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^4 and $R^{4'}$ are each independently $–CR^a$, $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$;

each R^a, for each occurrence, is independently H or C_{1-3} alkyl;

or alternatively, when R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, R^3 and R^4, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

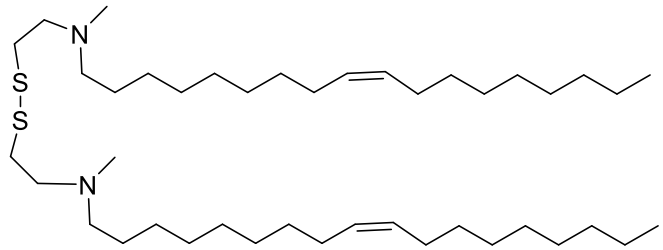
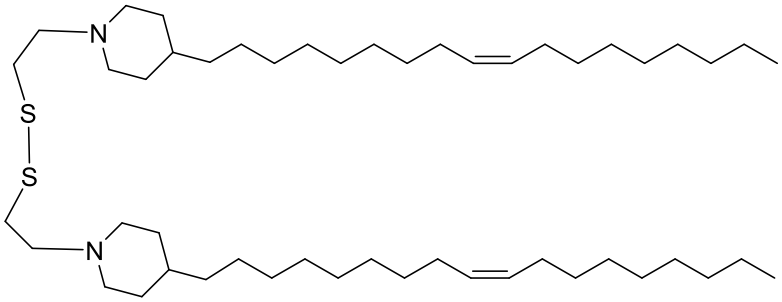
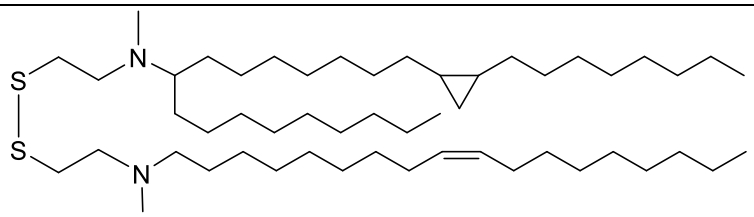
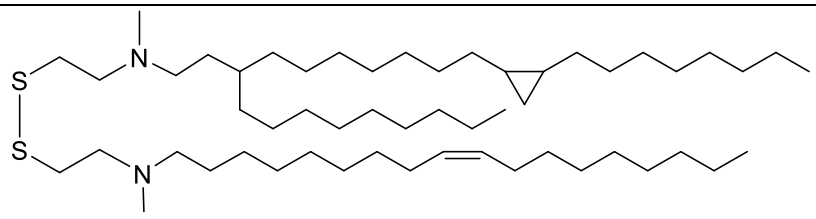
or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

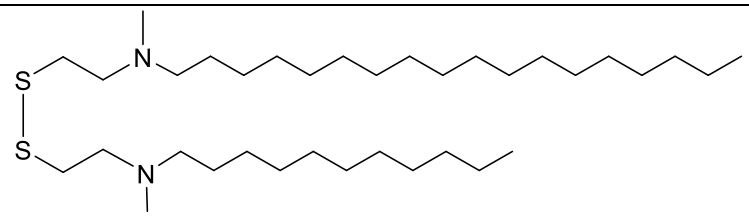
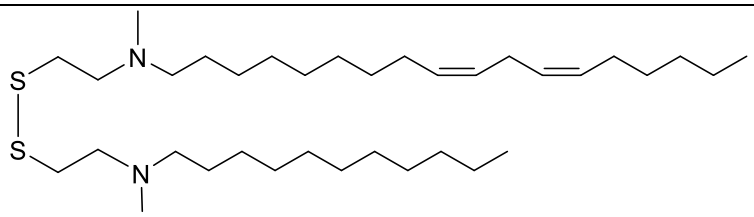
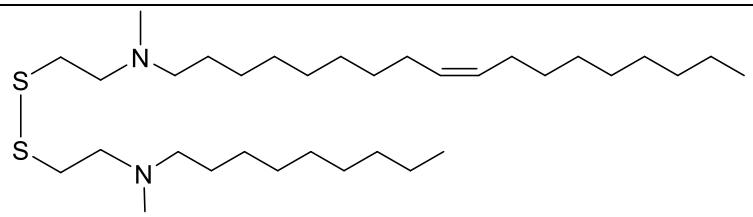
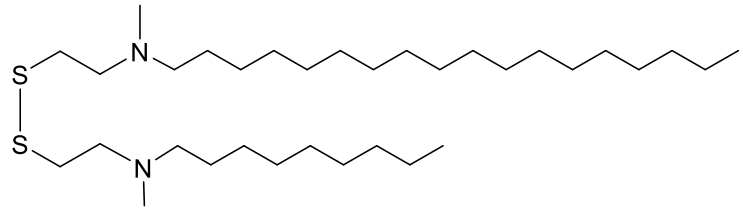
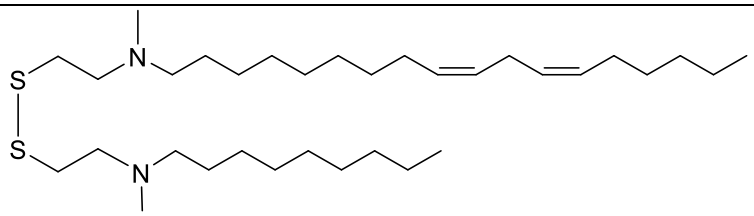
R^5 and $R^{5'}$ are each independently C_{4-20} alkylene or C_{4-20} alkenylene;

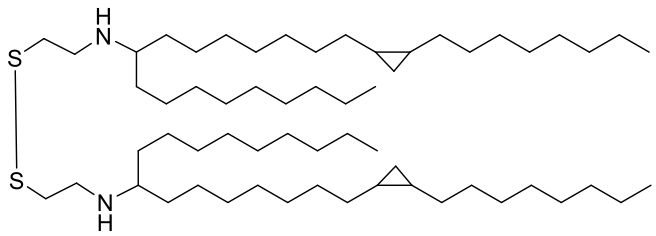
R^6 and $R^{6'}$, for each occurrence, are independently C_{1-20} alkylene, C_{3-20} cycloalkylene, or C_{2-20} alkenylene; and

m and n are each independently an integer selected from the group consisting of 1, 2, 3, 4, and 5.

In another aspect of the present disclosure, there is provided an ionizable lipid selected from the group consisting of:

 (9Z,9'Z)-N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyloctadec-9-en-1-amine);
 1,2-bis(2-(4-((Z)-octadec-9-en-1-yl)piperidin-1-yl)ethyl)disulfane;
 (Z)-N-methyl-N-(2-((2-(methyl(1-(2-octylcyclopropyl)heptadecan-8-yl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl(3-(7-(2-octylcyclopropyl)heptyl)dodecyl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;

 N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)octadecan-1-amine;
 (9Z,12Z)-N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)octadeca-9,12-dien-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadecan-1-amine;
 (9Z,12Z)-N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadeca-9,12-dien-1-amine; and



N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(1-(2-octylcyclopropyl)heptadecan-8-amine).

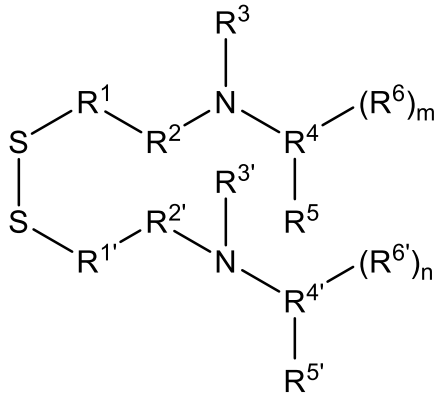
In a further aspect of the present disclosure, there is provided a lipid nanoparticle (LNP) comprising the ionizable lipid disclosed herein and a nucleic acid.

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

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

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

Provided herein is an ionizable lipid represented by Formula (I):



,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently optionally substituted linear or branched C_{1-3} alkylene;

R^2 and $R^{2'}$ are each independently optionally substituted linear or branched C_{1-6} alkylene;

R^3 and $R^{3'}$ are each independently optionally substituted linear or branched C_{1-6} alkyl;

or alternatively, when R^2 is optionally substituted branched C_{1-6} alkylene, R^2 and R^3, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{2'}$ is optionally substituted branched C_{1-6} alkylene, $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^4 and $R^{4'}$ are each independently $–CR^a$, $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$;

R^a, for each occurrence, is independently H or C_{1-3} alkyl;

or alternatively, when R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, R^3 and R^4, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

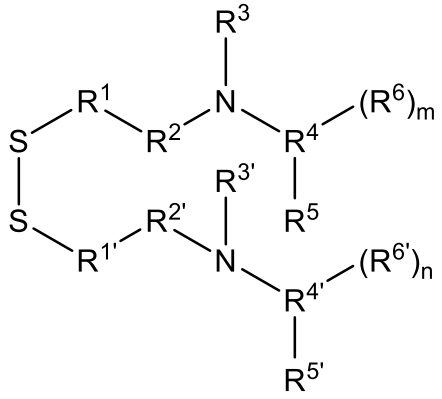
R^5 and $R^{5'}$ are each independently C_{1-20} alkylene or C_{2-20} alkenylene;

R^6 and $R^{6'}$, for each occurrence, are independently C_{1-20} alkylene, C_{3-20} cycloalkylene, or C_{2-20} alkenylene; and

CLAIMS

What is Claimed is:

1. An ionizable lipid represented by Formula (I):



,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and $R^{1'}$ are each independently linear or branched C_{1-3} alkylene;

R^2 and $R^{2'}$ are each independently linear or branched C_{1-6} alkylene;

R^3 and $R^{3'}$ are each independently linear or branched C_{1-6} alkyl;

or alternatively, when R^2 is branched C_{1-6} alkylene, R^2 and R^3, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{2'}$ is branched C_{1-6} alkylene, $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^4 and $R^{4'}$ are each independently $–CR^a$, $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$;

each R^a, for each occurrence, is independently H or C_{1-3} alkyl;

or alternatively, when R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, R^3 and R^4, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

or alternatively, when $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and when R^a is C_{1-3} alkyl, $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 4- to 8-membered heterocyclyl;

R^5 and $R^{5'}$ are each independently C_{4-20} alkylene or C_{4-20} alkenylene;

R^6 and $R^{6'}$, for each occurrence, are independently C_{1-20} alkylene, C_{3-20} cycloalkylene, or C_{2-20} alkenylene; and

m and n are each independently an integer selected from the group consisting of 1, 2, 3, 4, and 5.

2. The ionizable lipid according to claim 1, wherein R^2 and $R^{2'}$ are each independently C_{1-3} alkylene; or R^1 and R^2 taken together are C_{1-3} alkylene and $R^{1'}$ and $R^{2'}$ taken together are C_{1-3} alkylene.

3. The ionizable lipid according to claim 2, wherein R^3 and $R^{3'}$ are each methyl.

4. The ionizable lipid according to claim 1, wherein R^4 and $R^{4'}$ are each –CH.

5. The ionizable lipid according to claim 1, wherein R^2 is branched C_{1-6} alkylene; and wherein R^2 and R^3, taken together with their intervening N atom, form a 5- or 6-membered heterocyclyl.

6. The ionizable lipid according to claim 1, wherein $R^{2'}$ is branched C_{1-6} alkylene; and wherein $R^{2'}$ and $R^{3'}$, taken together with their intervening N atom, form a 5- or 6-membered heterocyclyl.

7. The ionizable lipid according to claim 1, wherein R^4 is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and R^a is C_{1-3} alkyl; and wherein R^3 and R^4, taken together with their intervening N atom, form a 5- or 6-membered heterocyclyl.

8. The ionizable lipid according to claim 1, wherein $R^{4'}$ is $–C(R^a)_2CR^a$, or $–[C(R^a)_2]_2CR^a$ and R^a is C_{1-3} alkyl; and wherein $R^{3'}$ and $R^{4'}$, taken together with their intervening N atom, form a 5- or 6-membered heterocyclyl.

9. The ionizable lipid according to any one of claims 5-8, wherein the 5- or 6-membered heterocyclyl is pyrrolidinyl or piperidinyl.

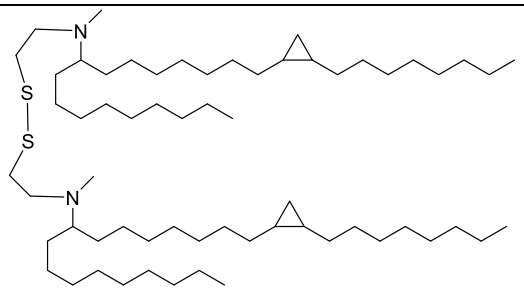
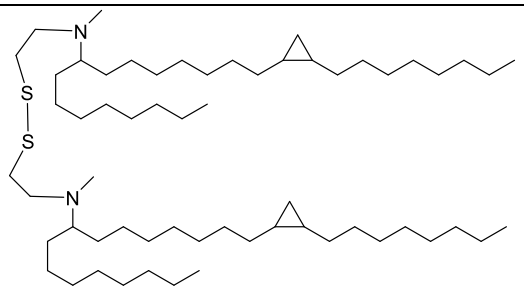
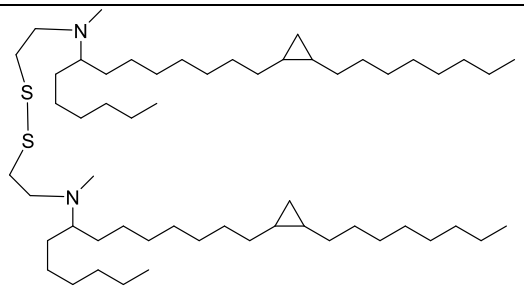
10. The ionizable lipid according to any one of claims 1-9, wherein R^5 and $R^{5'}$ are each independently C_{4-9} alkylene or C_{4-9} alkenylene.

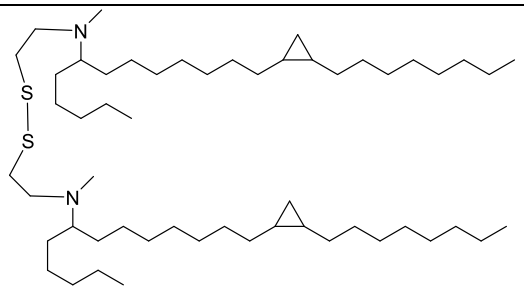
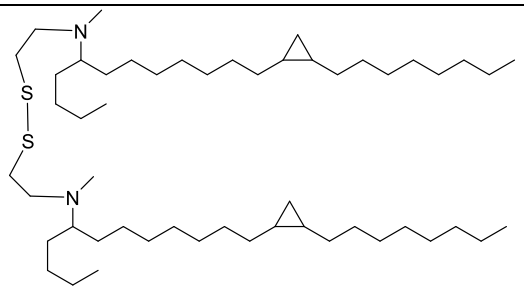
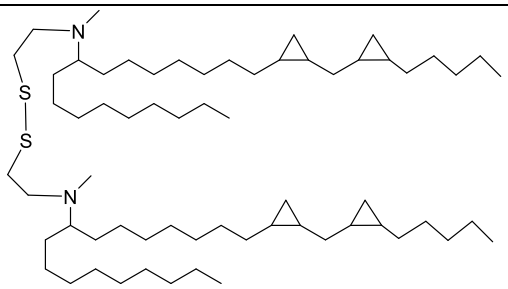
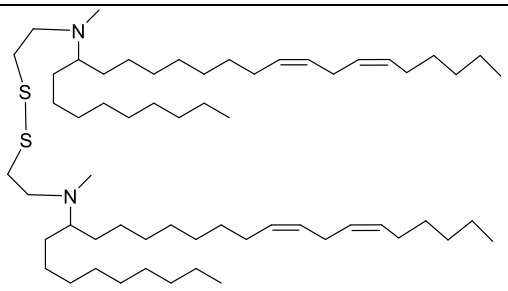
11. The ionizable lipid according to any one of claims 1-10, wherein R^6 and $R^{6'}$, for each occurrence, are independently C_{1-10} alkylene, C_{3-10} cycloalkylene, or C_{2-10} alkenylene.

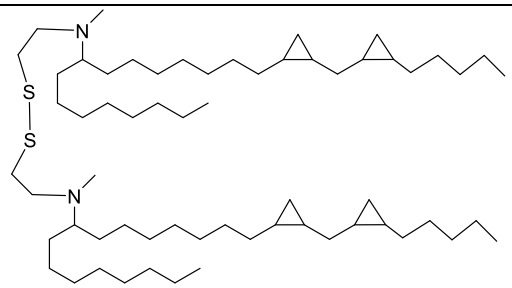
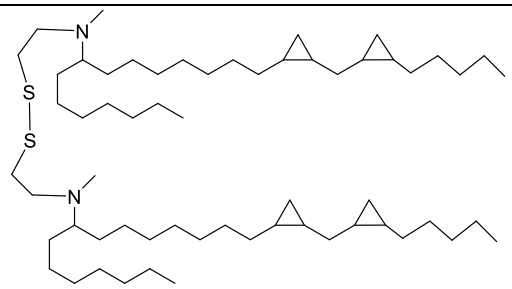
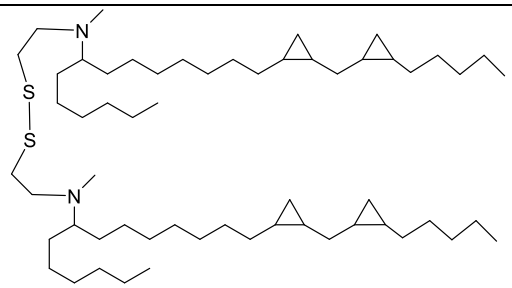
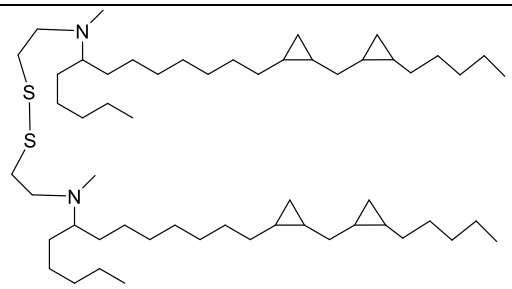
12. The ionizable lipid according to claim 11, wherein the C_{3-10} cycloalkylene is cyclopropylene.

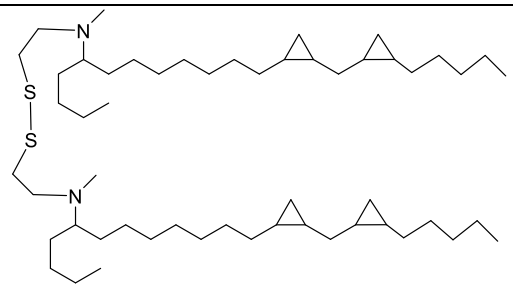
13. The ionizable lipid according to claim 11 or claim 12, wherein m and n are each 3 or 5.

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

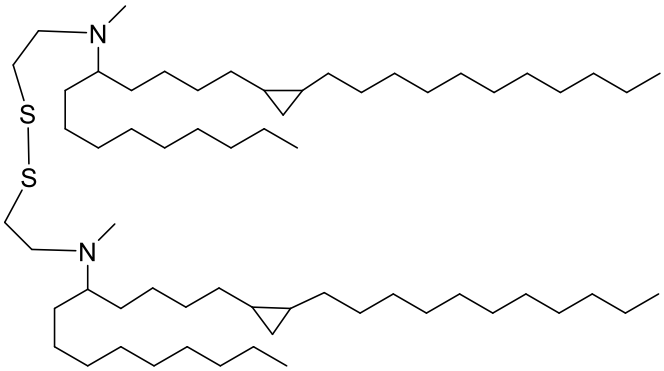
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-octylcyclopropyl)heptadecan-8-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-octylcyclopropyl)hexadecan-8-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-14-(2-octylcyclopropyl)tetradecan-7-amine);

 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-13-(2-octylcyclopropyl)tridecan-6-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-12-(2-octylcyclopropyl)dodecan-5-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)heptadecan-8-amine);
 (18Z,18'Z,21Z,21'Z)-N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methylheptacosa-18,21-dien-10-amine);

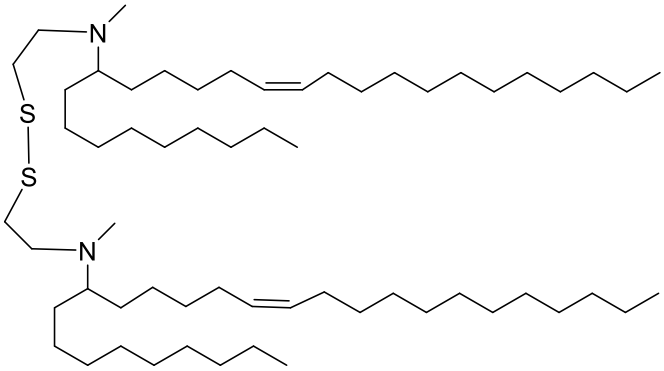
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)hexadecan-8-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)pentadecan-8-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-14-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)tetradecan-7-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-13-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)tridecan-6-amine);



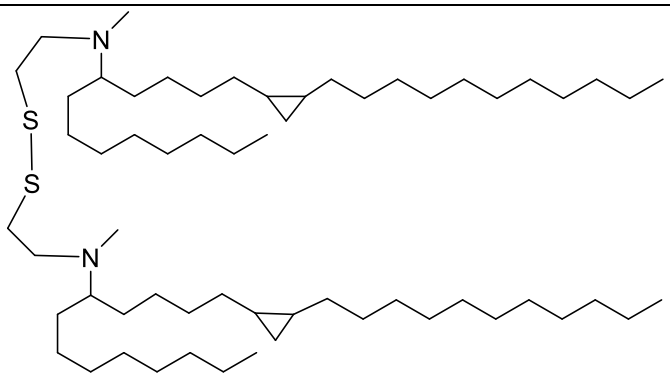
N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-12-(2-((2-pentylcyclopropyl)methyl)cyclopropyl)dodecan-5-amine);

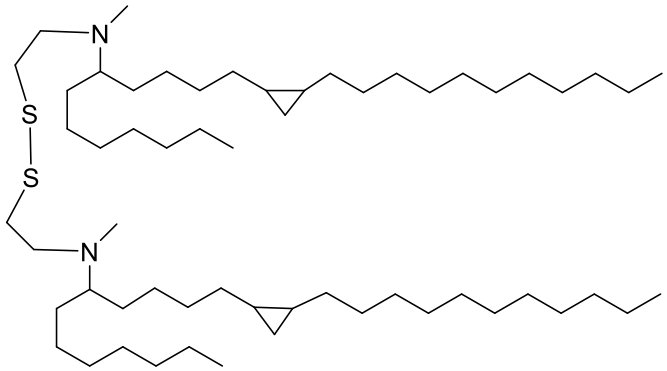
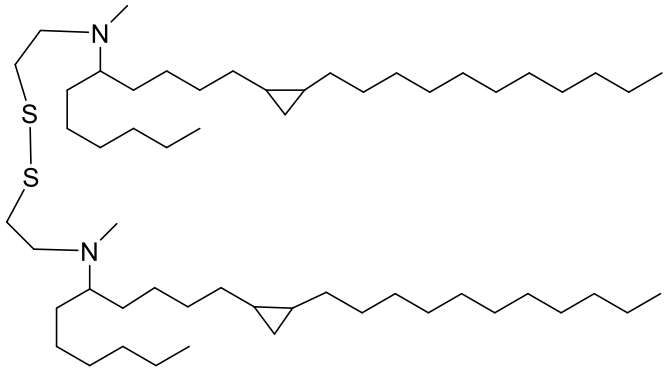
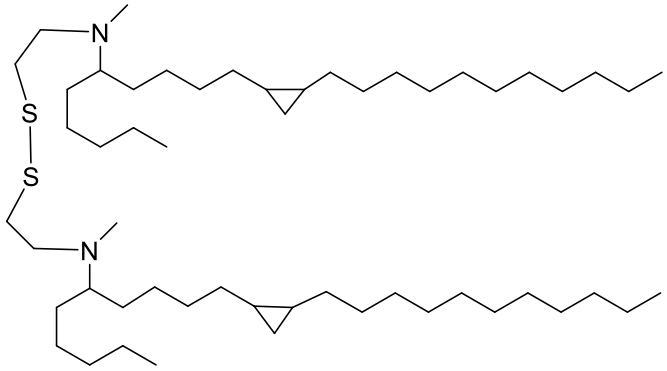


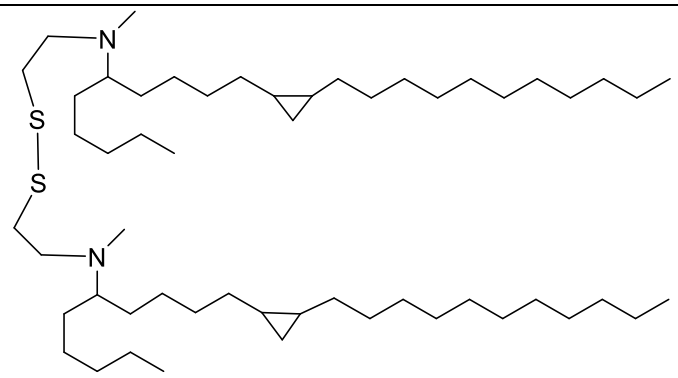
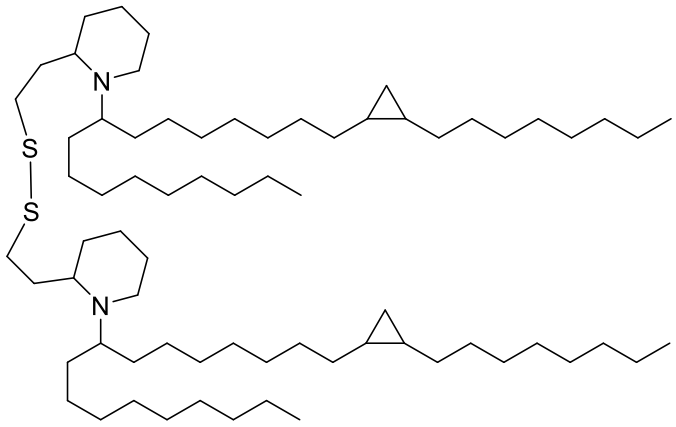
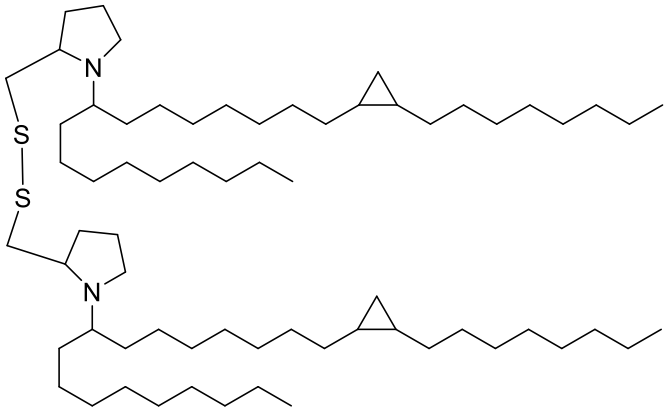
N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)tetradecan-5-amine);

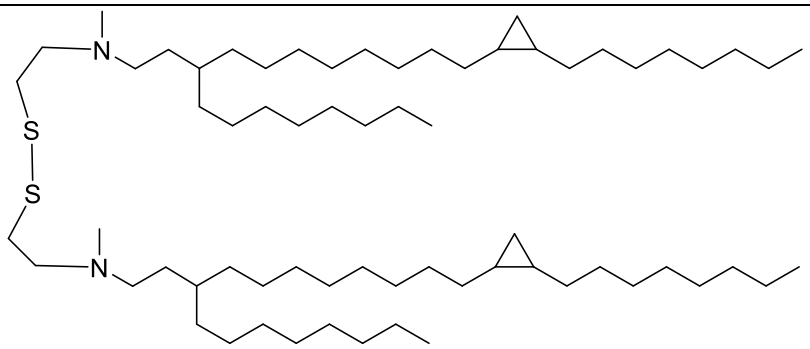


(15Z,15'Z)-N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methylheptacos-15-en-10-amine);

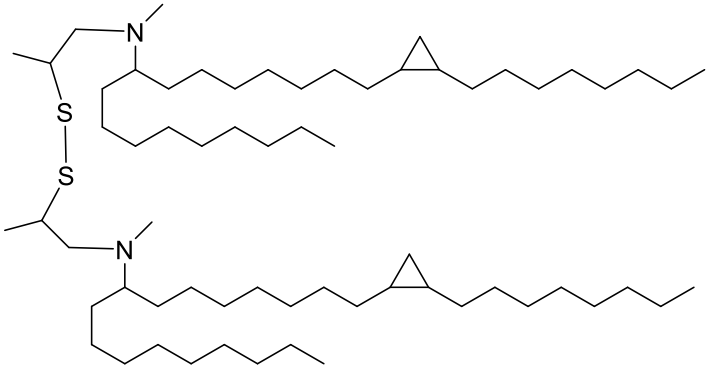


N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)tridecan-5-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)dodecan-5-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)undecan-5-amine);
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)decan-5-amine);

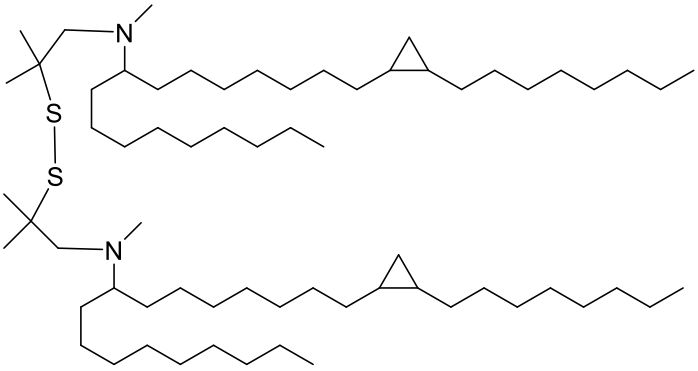
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-1-(2-undecylcyclopropyl)decan-5-amine);
 1,2-bis(2-(1-(1-(2-octylcyclopropyl)heptadecan-8-yl)piperidin-2-yl)ethyl)disulfane;
 1,2-bis((1-(1-(2-octylcyclopropyl)heptadecan-8-yl)pyrrolidin-2-yl)methyl)disulfane;



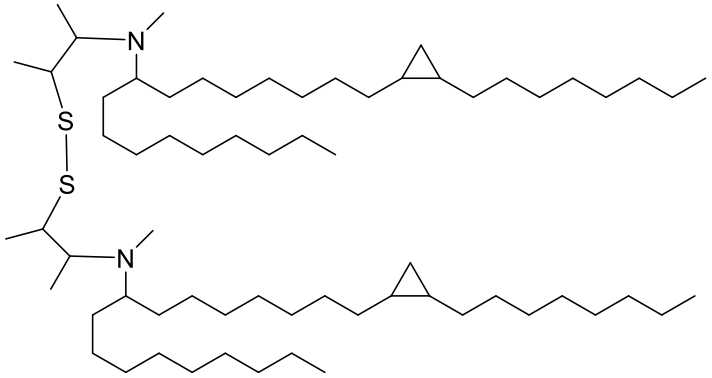
N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-3-octyl-11-(2-octylcyclopropyl)undecan-1-amine);



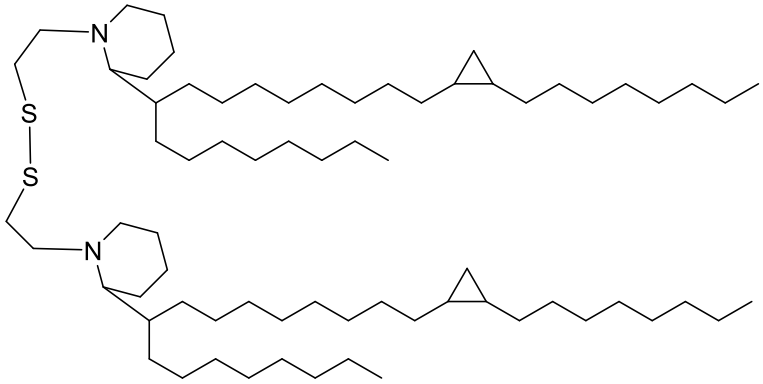
N,N'-(disulfanediylbis(propane-2,1-diyl))bis(N-methyl-1-(2-octylcyclopropyl)heptadecan-9-amine);



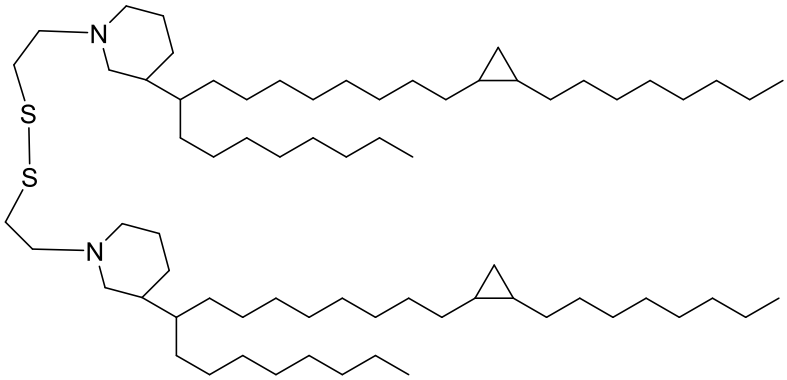
N,N'-(disulfanediylbis(2-methylpropane-2,1-diyl))bis(N-methyl-1-(2-octylcyclopropyl)heptadecan-8-amine);



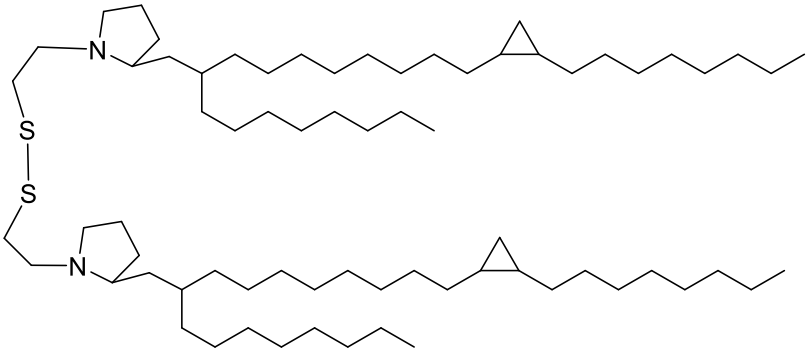
N,N'-(disulfanediylbis(butane-3,2-diyl))bis(N-methyl-1-(2-octylcyclopropyl)heptadecan-8-amine);



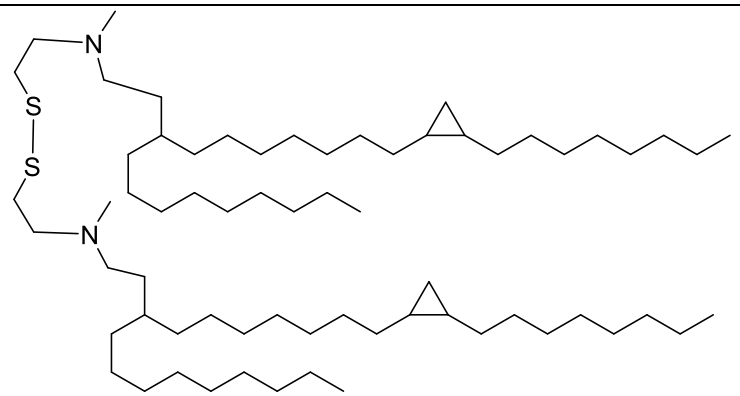
1,2-bis(2-(2-(1-(2-octylcyclopropyl)heptadecan-9-yl)piperidin-1-yl)ethyl)disulfane;



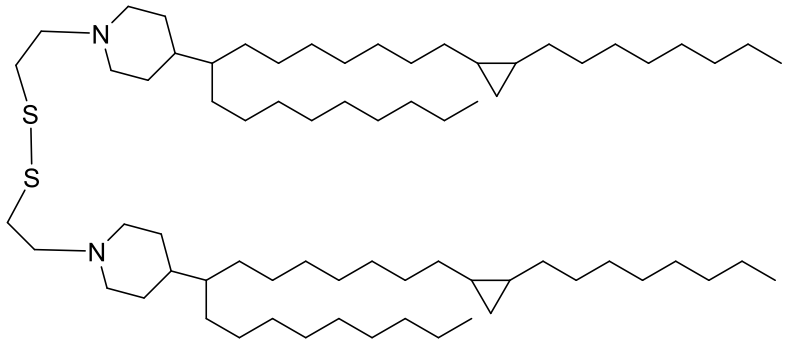
1,2-bis(2-(3-(1-(2-octylcyclopropyl)heptadecan-9-yl)piperidin-1-yl)ethyl)disulfane;



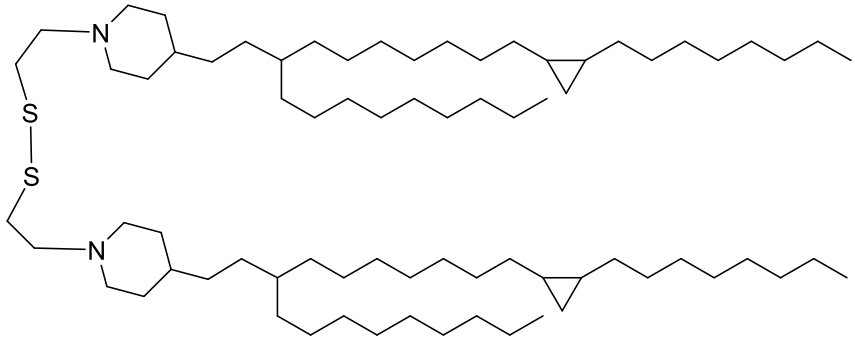
1,2-bis(2-(2-(2-octyl-10-(2-octylcyclopropyl)decyl)pyrrolidin-1-yl)ethyl)disulfane;



N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyl-3-(7-(2-octylcyclopropyl)heptyl)dodecan-1-amine);



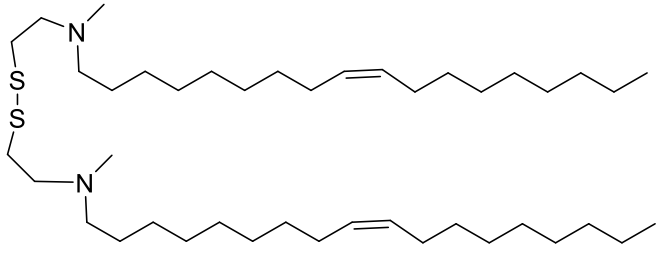
1,2-bis(2-(4-(1-(2-octylcyclopropyl)heptadecan-8-yl)piperidin-1-yl)ethyl)disulfane; and

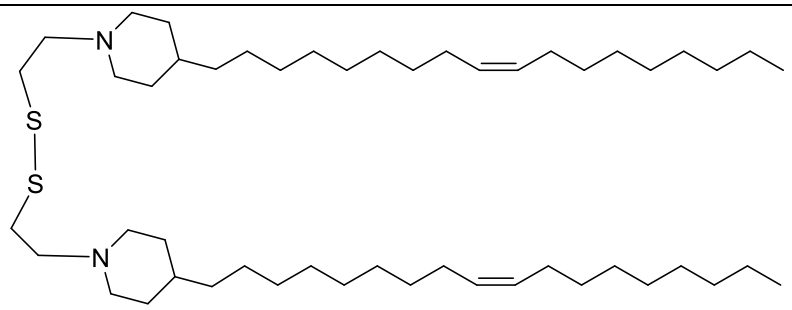
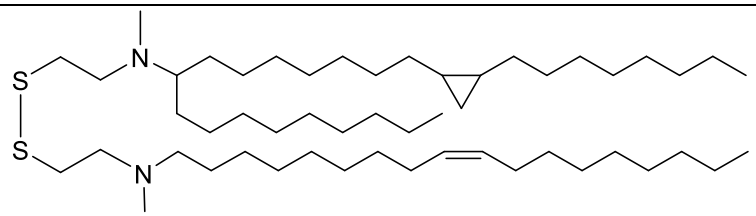
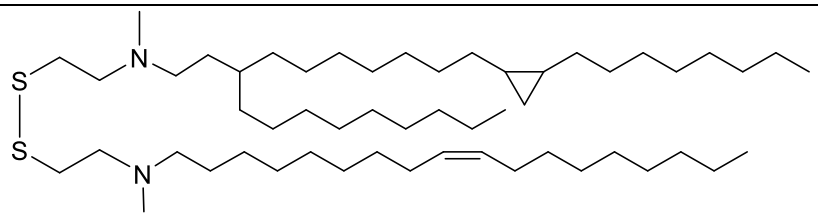
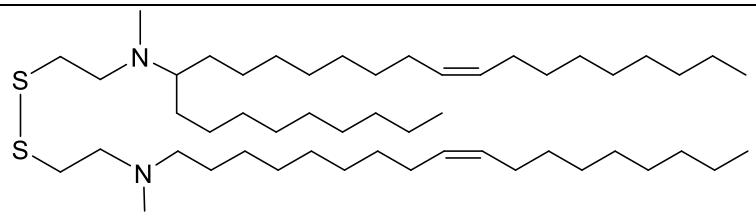
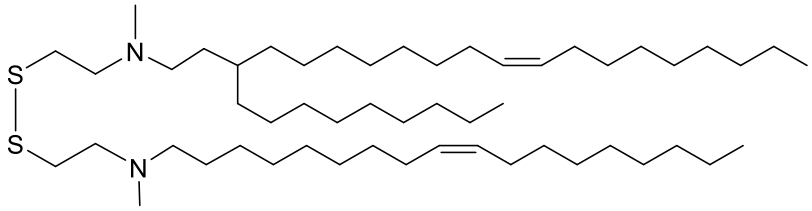


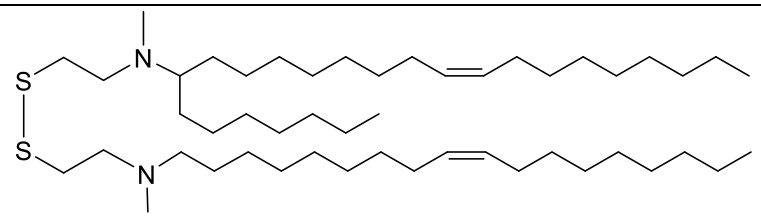
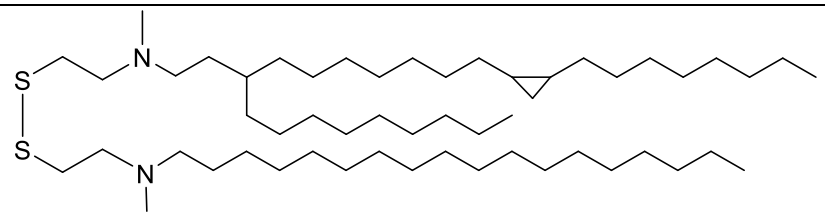
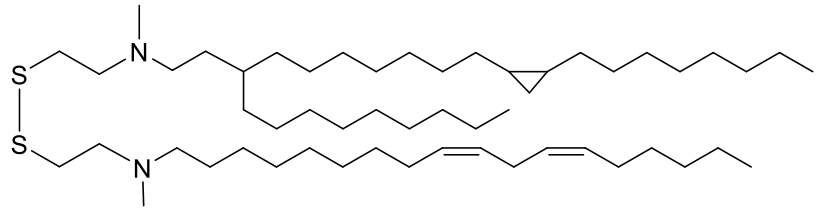
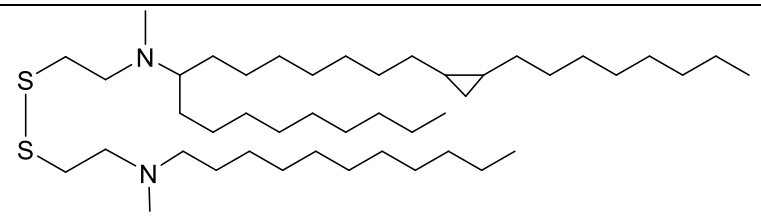
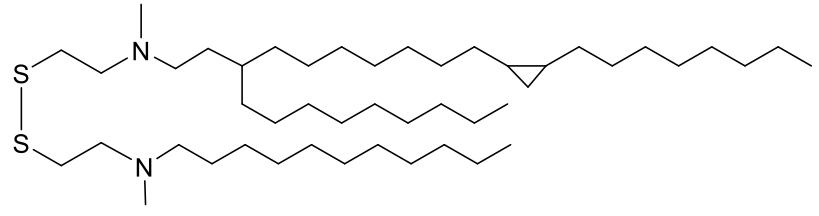
1,2-bis(2-(4-(3-(7-(2-octylcyclopropyl)heptyl)dodecyl)piperidin-1-yl)ethyl)disulfane;

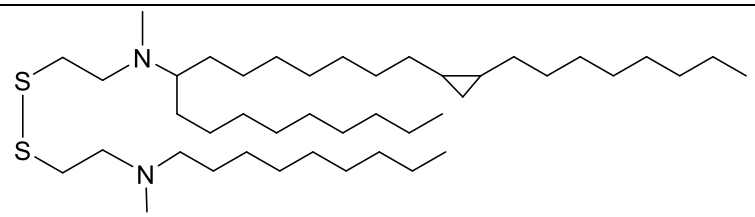
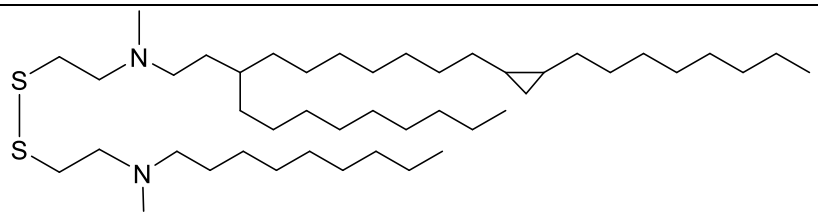
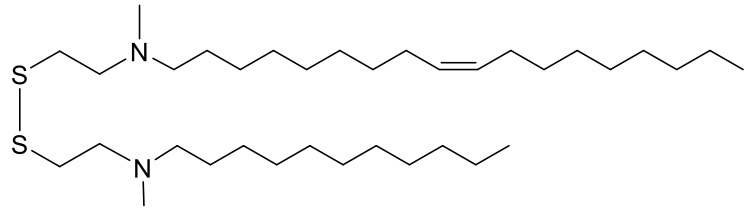
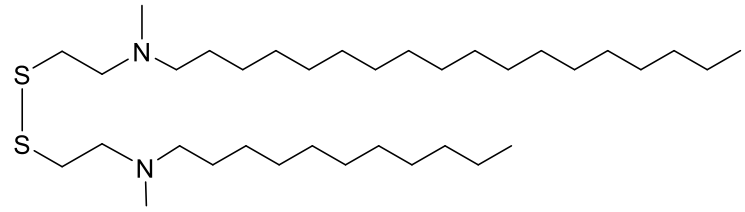
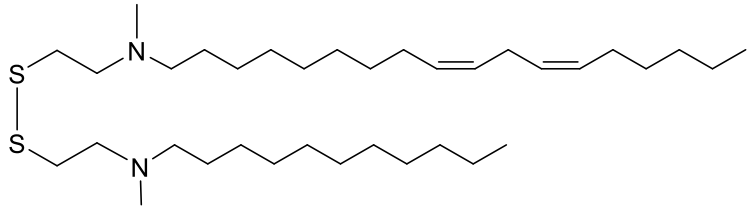
or a pharmaceutically acceptable salt of any of the foregoing.

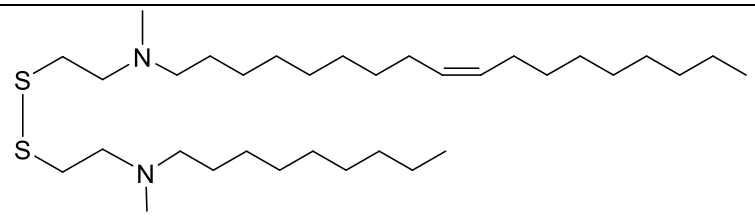
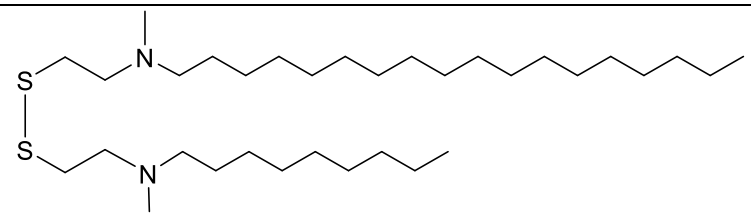
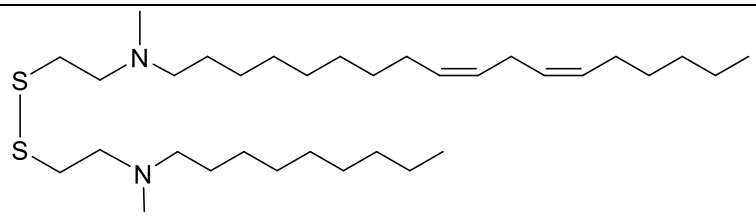
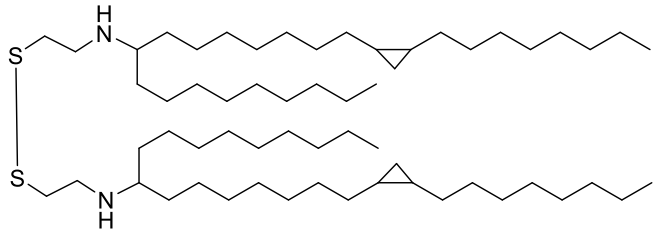
15. An ionizable lipid is selected from the group consisting of:



(9Z,9'Z)-N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(N-methyloctadec-9-en-1-amine);
 1,2-bis(2-(4-((Z)-octadec-9-en-1-yl)piperidin-1-yl)ethyl)disulfane;
 (Z)-N-methyl-N-(2-((2-(methyl(1-(2-octylcyclopropyl)heptadecan-8-yl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl(3-(7-(2-octylcyclopropyl)heptyl)dodecyl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl((Z)-octadec-9-en-1-yl)amino)ethyl)disulfaneyl)ethyl)heptacos-18-en-10-amine;
 (Z)-N-methyl-N-(2-((2-(methyl((Z)-octadec-9-en-1-

yl)amino)ethyl)disulfaneyl)ethyl)-3-nonylicos-11-en-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl((Z)-octadec-9-en-1-yl)amino)ethyl)disulfaneyl)ethyl)pentacos-16-en-8-amine;
 N-methyl-N-(2-((2-(methyl(3-(7-(2-octylcyclopropyl)heptyl)dodecyl)amino)ethyl)disulfaneyl)ethyl)octadecan-1-amine;
 (9Z,12Z)-N-methyl-N-(2-((2-(methyl(3-(7-(2-octylcyclopropyl)heptyl)dodecyl)amino)ethyl)disulfaneyl)ethyl)octadeca-9,12-dien-1-amine;
 N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)-1-(2-octylcyclopropyl)heptadecan-8-amine;
 N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)-3-(7-(2-

octylcyclopropyl)heptyl)dodecan-1-amine;
 N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)-1-(2-octylcyclopropyl)heptadecan-8-amine;
 N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)-3-(7-(2-octylcyclopropyl)heptyl)dodecan-1-amine;
 (Z)-N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)octadecan-1-amine;
 (9Z,12Z)-N-methyl-N-(2-((2-(methyl(undecyl)amino)ethyl)disulfaneyl)ethyl)octadeca-9,12-dien-1-amine;

 (Z)-N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadec-9-en-1-amine;
 N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadecan-1-amine;
 (9Z,12Z)-N-methyl-N-(2-((2-(methyl(nonyl)amino)ethyl)disulfaneyl)ethyl)octadeca-9,12-dien-1-amine; and
 N,N'-(disulfanediylbis(ethane-2,1-diyl))bis(1-(2-octylcyclopropyl)heptadecan-8-amine).

16. A lipid nanoparticle (LNP) comprising the ionizable lipid of any one of claims 1-15 and a nucleic acid.

17. The lipid nanoparticle according to claim 16, wherein the nucleic acid is encapsulated in the ionizable lipid.

18. The lipid nanoparticle according to claim 16 or claim 17, wherein the 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 closed-ended DNA (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.

19. The lipid nanoparticle according to claim 18, wherein the nucleic acid is a ceDNA, an mRNA or an siRNA.

20. The lipid nanoparticle according to claim 16, wherein the lipid nanoparticle comprises one or more of:

a sterol;

a polyethylene glycol (PEG) or a PEG-lipid conjugate; and

a non-cationic lipid.

21. The lipid nanoparticle according to claim 20, wherein the sterol is cholesterol;

the PEG-lipid conjugate is 1-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (PEG-DMG);

the non-cationic lipid is selected from the group consisting of distearoyl-sn-glycerophosphoethanolamine, 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-oleoylphosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC),

dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (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.

22. The lipid nanoparticle according to claim 20, wherein the PEG or PEG-lipid conjugate is present in the lipid nanoparticle at a molar percentage of 2% to 4%, 2% to 3.5%, 2.5 to 3%, or about 3%;

wherein the cholesterol is present in the lipid nanoparticle at a molar percentage of 20% to 40%; and/or

the ionizable lipid is present in the lipid nanoparticle at a molar percentage of 80% to 60%.

23. The lipid nanoparticle according to claim 22, wherein the cholesterol is present in the lipid nanoparticle at a molar percentage of about 40%, and wherein the ionizable lipid is present in the lipid nanoparticle at a molar percentage of about 50%.

24. The lipid nanoparticle according to claim 23, wherein:

the ionizable lipid is present in the lipid nanoparticle at a molar percentage of 42.5% to 62.5%; and/or

the non-cationic lipid is present in the lipid nanoparticle at a molar percentage of 2.5% to 12.5%.

25. The lipid nanoparticle according to claim 16, further comprising dexamethasone palmitate.

26. The lipid nanoparticle according to claim 16, wherein the lipid nanoparticle has a mean diameter of 50 nm to 110 nm; less than about 100 nm; or about 70 nm.

27. The lipid nanoparticle according to claim 18, wherein the nanoparticle has a total lipid to nucleic acid ratio of about 10:1; or about 20:1; or about 30:1; or about 40:1.

28. The lipid nanoparticle according to claim 16, further comprising a tissue specific targeting moiety.

29. The lipid nanoparticle according to claim 28, wherein the tissue specific targeting moiety is a peptide or an N-acetylgalactosamine (GalNAc) containing moiety.

30. The lipid nanoparticle according to claim 29, wherein the GalNAc containing moiety is GalNAC-PEG-lipid conjugate.

31. The lipid nanoparticle according to claim 30, wherein the GalNAc-PEG-lipid-conjugate is present in the lipid nanoparticle at a molar percentage of about 1.5%, about 1.4%, about 1.3%, about 1.2%, about 1.1%, about 1.0%, about 0.9%, about 0.8%, about 0.7%, about 0.6%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, or about 0.1% of the total lipid.

32. The lipid nanoparticle according to claim 19, wherein the ceDNA is a closed-ended linear duplex DNA.

33. The lipid nanoparticle according to claim 19, wherein the ceDNA is a CELiD, DNA-based minicircle, a MIDGE, a ministring DNA, a dumbbell shaped linear duplex closed-ended DNA comprising two hairpin structures of ITRs in the 5’ and 3’ ends of an expression cassette, or a doggybone™ DNA.

34. A pharmaceutical composition comprising the lipid nanoparticle according to claim 16 and a pharmaceutically acceptable excipient.

35. Use of a lipid nanoparticle according to any one of claims 16-33, or an effective amount of the pharmaceutical composition according to claim 34, in the manufacture of a medicament for treating a genetic disorder in a subject.

36. The use of claim 35, 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, inherited disorders 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, Fabry disease, 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, 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.

37. The use of claim 36, 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 Type 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).

38. The lipid nanoparticle according to any one of claims 16-33, or an effective amount of the pharmaceutical composition according to claim 34, for use in therapy.