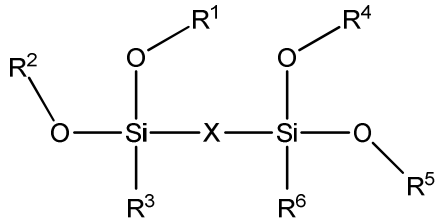
CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R^1 is a ~~C_2~~C_5-C_{30} hydrocarbyl;

R^2 is a C_2-C_{30} hydrocarbyl;

R^3 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl;

R^4 is a C_2-C_{30} hydrocarbyl;

R^5 is a C_2-C_{30} hydrocarbyl;

R^6 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl; and

X is a divalent linking group.

~~2. The compound of claim 1, wherein R^1 is C_2-C_{20} hydrocarbyl.~~

~~3. The compound of claim 1, wherein R^1 is C_2-C_{15} hydrocarbyl.~~

~~4. The compound of claim 1, wherein R^1 is C_2-C_{10} hydrocarbyl.~~

~~5. The compound of claim 1, wherein R^1 is C_5-C_{20} hydrocarbyl.~~

~~6~~2. The compound of claim 1, wherein R^1 is (~~C_2~~C_7-C_{20})alkyl, (~~C_2~~C_7-C_{20})alkenyl, or (~~C_2~~C_7-C_{20})alkynyl~~.~~, preferably,

~~7. The compound of claim 1, wherein R^1 is (C_7-C_{15})alkyl.~~

~~8. The compound of claim 1, wherein R^1 is (C_7-C_{15})alkenyl.~~

~~9. The compound of claim 1, wherein R^1 is (C_7-C_{15})alkynyl.~~

~~10. The compound of claim 1, wherein~~ R^1 is (C_7-C_{15})alkenyl, having only one double bond~~.~~, and/or

~~11. The compound of claim 1, wherein R^1 is (Z)-4-decen-1-yl, 1-tridecyl, (Z)-3-hept-1-yl, or (Z)-5-dodecen-1-yl.~~

~~12. The compound of any one of claims 1-11, wherein R^2 is C_2-C_{20} hydrocarbyl.~~

~~13. The compound of any one of claims 1-11, wherein R^2 is C_2-C_{15} hydrocarbyl.~~

~~14. The compound of any one of claims 1-11, wherein R^2 is C_2-C_{10} hydrocarbyl.~~

~~15. The compound of any one of claims 1-11, wherein R^2 is C_5-C_{20} hydrocarbyl.~~

~~16. The compound of any one of claims 1-11,~~ wherein R^2 is (C_2-C_{20})alkyl, (C_2-C_{20})alkenyl, or (C_2-C_{20})alkynyl~~.~~, preferably,

~~17. The compound of any one of claims 1-11, wherein R^2 is a (C_7-C_{15})alkyl.~~

~~18. The compound of any one of claims 1-11, wherein R^2 is a (C_7-C_{15})alkenyl.~~

~~19. The compound of any one of claims 1-11, wherein R^2 is a (C_7-C_{15})alkynyl.~~

~~20. The compound of any one of claims 1-11, wherein~~ R^2 is a (C_7-C_{15})alkenyl, having only one double bond~~.~~, and/or

~~21. The compound of any one of claims 1-11, wherein R^2 is (Z)-4-decen-1-yl, 1-tridecyl, (Z)-3-hept-1-yl, or (Z)-5-dodecen-1-yl.~~

~~22. The compound of any one of claims 1-21, wherein R^3 is C_1-C_4 alkyl.~~

~~23. The compound of any one of claims 1-21,~~ wherein R^3 is methyl~~.~~, and/or

~~24. The compound of any one of claims 1-21, wherein R^3 is -O-C_2-C_{20} hydrocarbyl.~~

~~25. The compound of any one of claims 1-21, wherein R^3 is -O-C_2-C_{15} hydrocarbyl.~~

~~26. The compound of any one of claims 1-21, wherein R^3 is -O-C_2-C_{10} hydrocarbyl.~~

~~27. The compound of any one of claims 1-21, wherein R^3 is -O-C_5-C_{20} hydrocarbyl.~~

~~28. The compound of any one of claims 1-21, wherein R^3 is -O-(C_2-C_{20})alkyl, -O-(C_2-C_{20})alkenyl, or -O-(C_2-C_{20})alkynyl.~~

~~29. The compound of any one of claims 1-21, wherein R^3 is a -O-(C_7-C_{15})alkyl.~~

~~30. The compound of any one of claims 1-21, wherein R^3 is a -O-(C_7-C_{15})alkenyl.~~

~~31. The compound of any one of claims 1-21, wherein R^3 is a -O-(C_7-C_{15})alkynyl.~~

~~32. The compound of any one of claims 1-21, wherein R^3 is a -O-(C_7-C_{15})alkenyl, having only one double bond.~~

~~33. The compound of any one of claims 1-21, wherein R^3 is (Z)-4-decen-1-yloxy, 1-tridecyloxy, (Z)-3-hept-1-yloxy, or (Z)-5-dodecen-1-yloxy.~~

~~34. The compound of any one of claims 1-33, wherein R^4 is C_2-C_{20} hydrocarbyl.~~

~~35. The compound of any one of claims 1-33, wherein R^4 is C_2-C_{15} hydrocarbyl.~~

~~36. The compound of any one of claims 1-33, wherein R^4 is C_2-C_{10} hydrocarbyl.~~

~~37. The compound of any one of claims 1-33, wherein R^4 is C_5-C_{20} hydrocarbyl.~~

~~38. The compound of any one of claims 1-33,~~ wherein R^4 is (C_2-C_{20})alkyl, (C_2-C_{20})alkenyl, or (C_2-C_{20})alkynyl~~.~~, preferably,

~~39. The compound of any one of claims 1-33, wherein R^4 is (C_7-C_{15})alkyl.~~

~~40. The compound of any one of claims 1-33, wherein R^4 is (C_7-C_{15})alkenyl.~~

~~41. The compound of any one of claims 1-33, wherein R^4 is (C_7-C_{15})alkynyl.~~

~~42. The compound of any one of claims 1-33, wherein~~ R^4 is (C_7-C_{15})alkenyl, having only one double bond~~.~~, and/or

~~43. The compound of any one of claims 1-33, wherein R^4 is (Z)-4-decen-1-yl, 1-tridecyl, (Z)-3-hept-1-yl, or (Z)-5-dodecen-1-yl.~~

~~44. The compound of any one of claims 1-43, wherein R^5 is C_2-C_{20} hydrocarbyl.~~

~~45. The compound of any one of claims 1-43, wherein R^5 is C_2-C_{15} hydrocarbyl.~~

~~46. The compound of any one of claims 1-43, wherein R^5 is C_2-C_{10} hydrocarbyl.~~

~~47. The compound of any one of claims 1-43, wherein R^5 is C_5-C_{20} hydrocarbyl.~~

~~48. The compound of any one of claims 1-43,~~ wherein R^5 is (C_2-C_{20})alkyl, (C_2-C_{20})alkenyl, or (C_2-C_{20})alkynyl~~.~~, preferably,

~~49. The compound of any one of claims 1-43, wherein R^5 is a (C_7-C_{15})alkyl.~~

~~50. The compound of any one of claims 1-43, wherein R^5 is a (C_7-C_{15})alkenyl.~~

~~51. The compound of any one of claims 1-43, wherein R^5 is a (C_7-C_{15})alkynyl.~~

~~52. The compound of any one of claims 1-43, wherein~~ R^5 is a (C_7-C_{15})alkenyl, having only one double bond~~.~~, and/or

~~53. The compound of any one of claims 1-43, wherein R^5 is (Z)-4-decen-1-yl, 1-tridecyl, (Z)-3-hept-1-yl, or (Z)-5-dodecen-1-yl.~~

~~54. The compound of any one of claims 1-53, wherein R^6 is C_1-C_4 alkyl.~~

~~55. The compound of any one of claims 1-53,~~ wherein R^6 is methyl.

~~56. The compound of any one of claims 1-53, wherein R^6 is -O-C_2-C_{20} hydrocarbyl.~~

~~57. The compound of any one of claims 1-53, wherein R^6 is -O-C_2-C_{15} hydrocarbyl.~~

~~58. The compound of any one of claims 1-53, wherein R^6 is -O-C_2-C_{10} hydrocarbyl.~~

~~59. The compound of any one of claims 1-53, wherein R^6 is -O-C_5-C_{20} hydrocarbyl.~~

~~60. The compound of any one of claims 1-53, wherein R^6 is -O-(C_2-C_{20})alkyl, -O-(C_2-C_{20})alkenyl, or -O-(C_2-C_{20})alkynyl.~~

~~61. The compound of any one of claims 1-53, wherein R^6 is a -O-(C_7-C_{15})alkyl.~~

~~62. The compound of any one of claims 1-53, wherein R^6 is a -O-(C_7-C_{15})alkenyl.~~

~~63. The compound of any one of claims 1-53, wherein R^6 is a -O-(C_7-C_{15})alkynyl.~~

~~64. The compound of any one of claims 1-53, wherein R^6 is a -O-(C_7-C_{15})alkenyl, having only one double bond.~~

~~65. The compound of any one of claims 1-53, wherein R^6 is (Z)-4-decen-1-yloxy, 1-tridecyloxy, (Z)-3-hept-1-yloxy, or (Z)-5-dodecen-1-yloxy.~~

663. The compound of ~~any one of claims 1-65~~claim 1 or 2, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more ~~(e.g. 1, 2, 3, or 4)~~ of the carbon atoms is optionally replaced by (-O-), (-NR^a-), (a divalent (C_3-C_8)cycloalkyl), or (a divalent 3-12 membered heterocycle), and wherein the chain, the divalent (C_3-C_8)cycloalkyl, or the divalent 3-12 membered heterocycle is optionally substituted with one or more ~~(e.g. 1, 2, 3, or 4)~~ substituents independently selected from the group consisting of (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, nitro, halo, hydroxy, oxo (=O), and carboxy; and wherein each R^a is independently selected from H and (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

~~67. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-), (-NR^a-), (a divalent (C_3-C_8)cycloalkyl), or (a divalent 3-8 membered heterocycle), and wherein the chain, the divalent (C_3-C_8)cycloalkyl, or the divalent 3-8 membered heterocycle is optionally substituted with one or more (e.g. 1, 2, 3, or 4) substituents independently selected from the group consisting of (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, cyano, nitro, halo, hydroxy, oxo (=O), and carboxy; and wherein each R^a is independently selected from H and (C_1-C_6)alkyl.~~

~~68. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-NR^a-) or (a divalent 3-12 membered heterocycle); and wherein each R^a is independently selected from (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.~~

~~69. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-NR^a-) or (a divalent 3-8 membered heterocycle); and wherein each R^a is independently selected from (C_1-~~

~~C_6)alkyl.~~

~~70. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is replaced by (-NR^a-); and wherein each R^a is independently selected from (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.~~

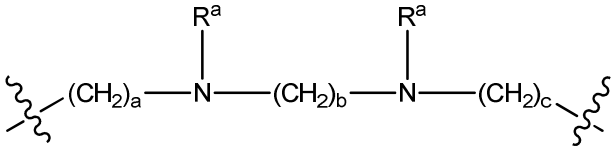
~~71. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is replaced by (-NR^a-); and wherein each R^a is independently selected from (C_1-C_6)alkyl.~~

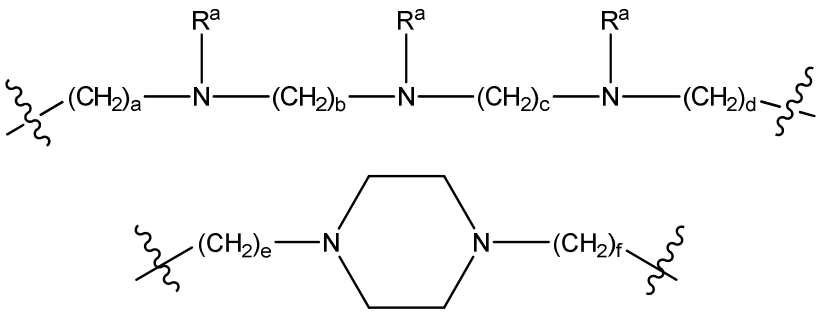
~~72. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by a divalent 3-12 membered heterocycle.~~

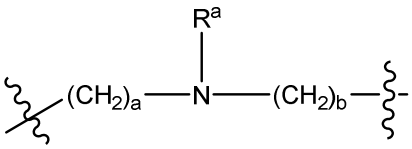
~~73. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by a divalent 3-8 membered heterocycle.~~

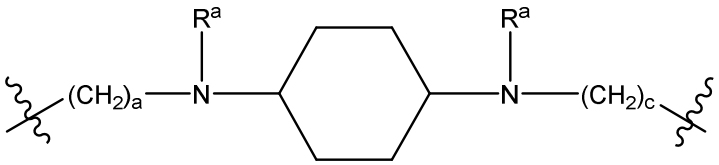
~~74. The compound of any one of claims 1-65, wherein X is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 6 to 12 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by a piperrazin-1,4-diyl.~~

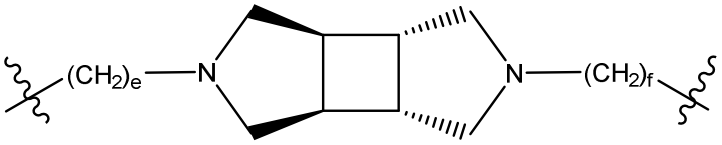
~~75~~4. The compound of any one of claims 1-~~65~~3, wherein X is selected from the group consisting of:

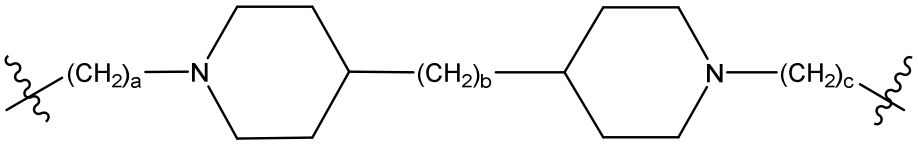


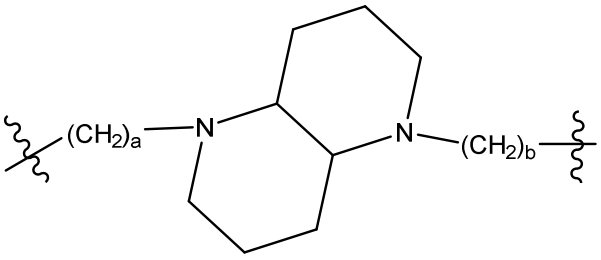


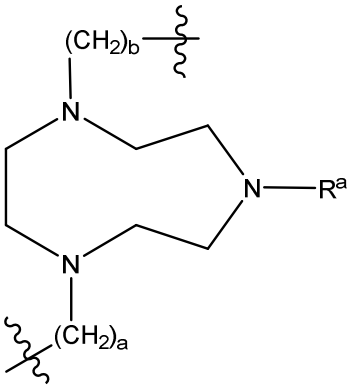


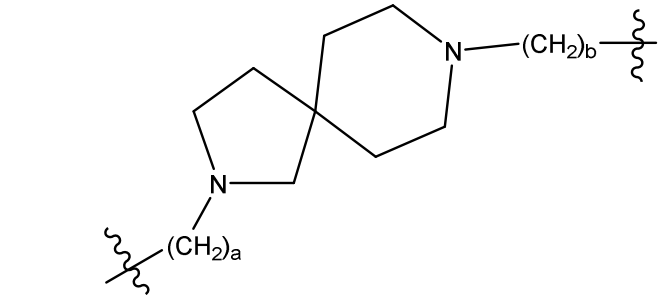


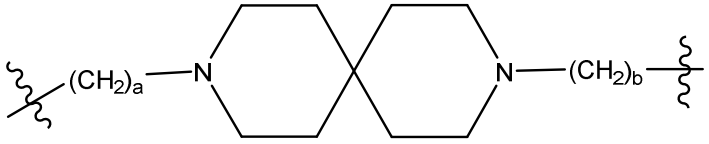




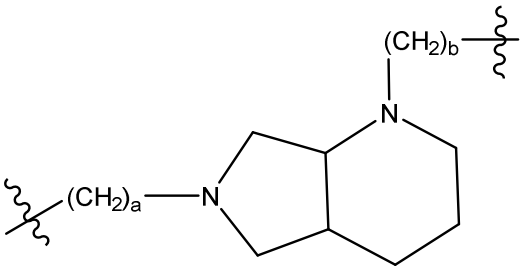








and



wherein:

a is 2, 3, 4, or 5;

b is 2, 3, 4, or 5;

c is 2, 3, 4, or 5;

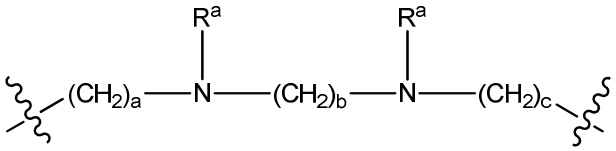
d is 2, 3, 4, or 5;

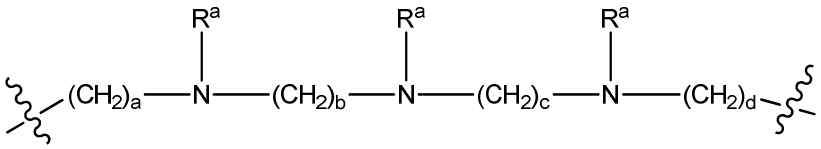
e is 2, 3, 4, 5, 6, 7, or 8;

f is 2, 3, 4, 5, 6, 7, or 8; and

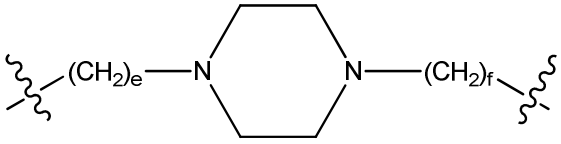
each R^a is independently selected from H and (C_1-C_6)alkyl that is optionally substituted with one of more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy~~.~~, preferably,

~~76. The compound of any one of claims 1-65, wherein~~ X is selected from the group consisting of:





and



wherein:

a is 2, 3, 4, or 5;

b is 2, 3, 4, or 5;

c is 2, 3, 4, or 5;

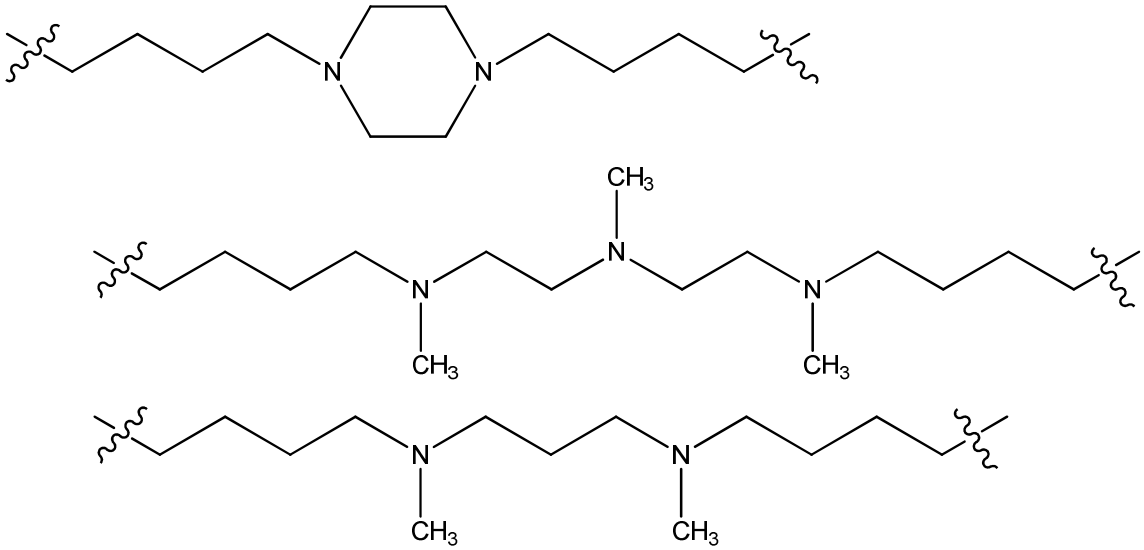
d is 2, 3, 4, or 5;

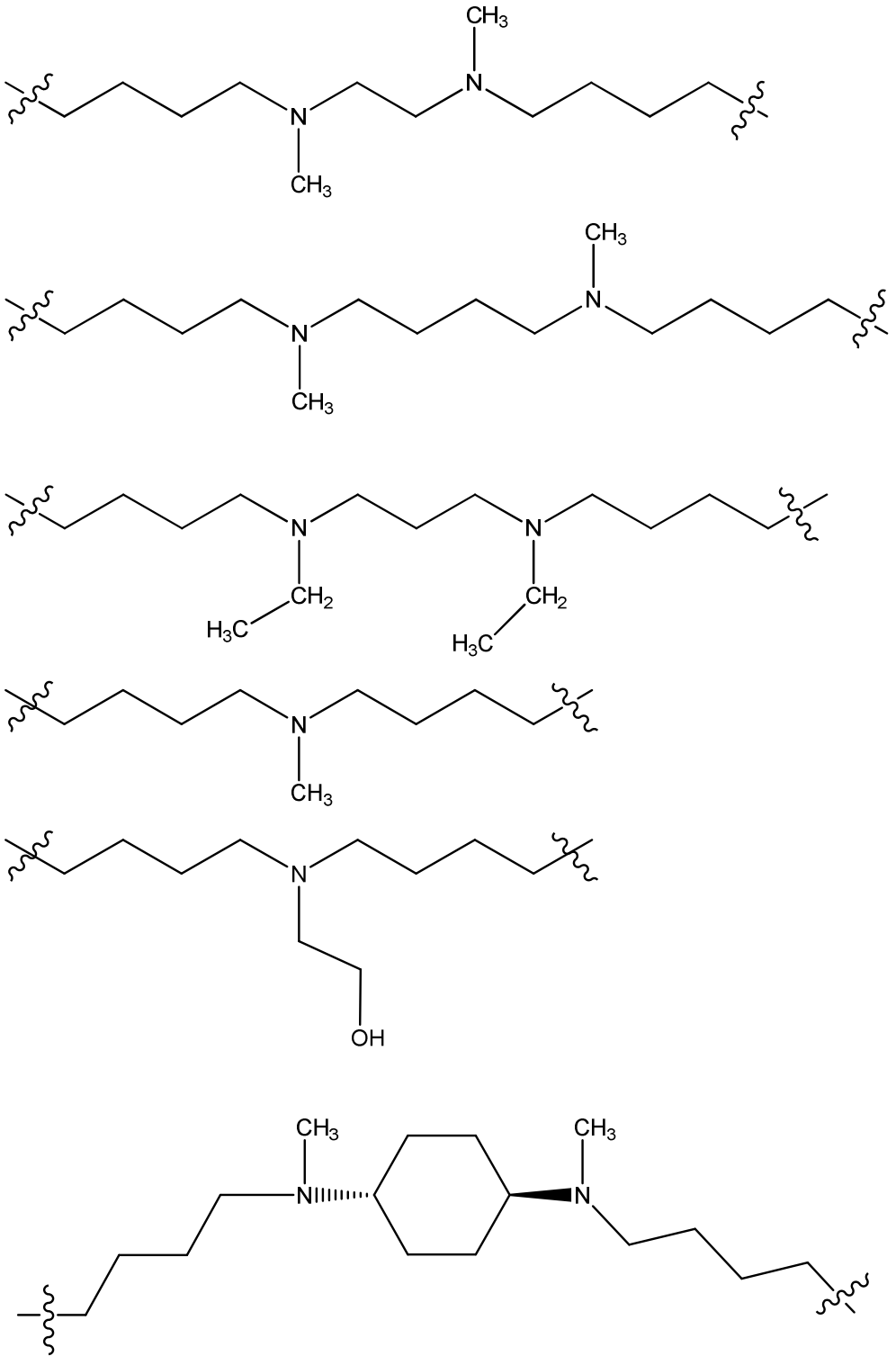
e is 2, 3, 4, 5, 6, 7, or 8;

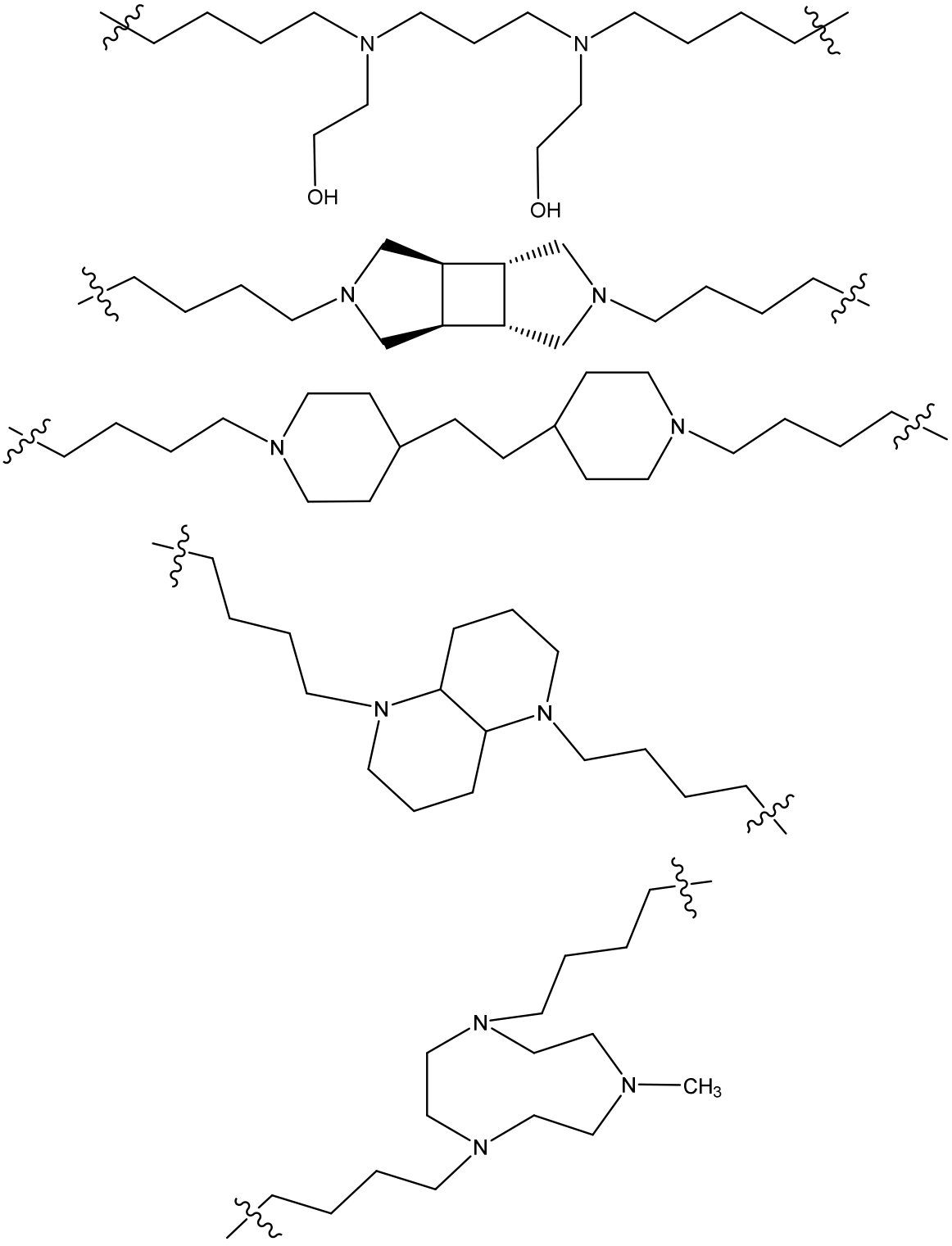
f is 2, 3, 4, 5, 6, 7, or 8; and

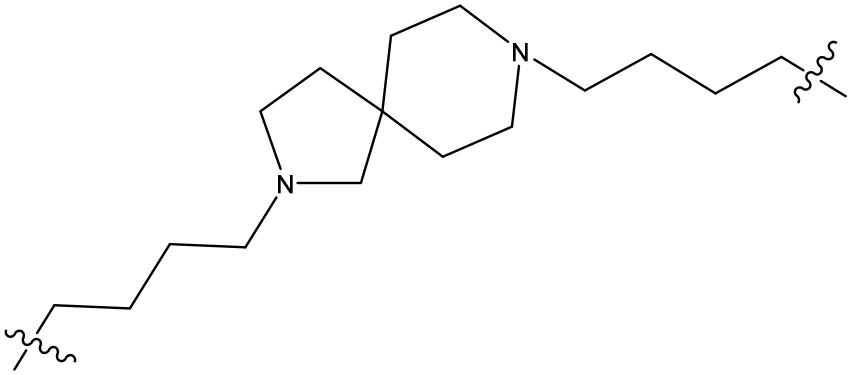
each R^a is independently selected from H and (C_1-C_6)alkyl~~.~~, further preferably,

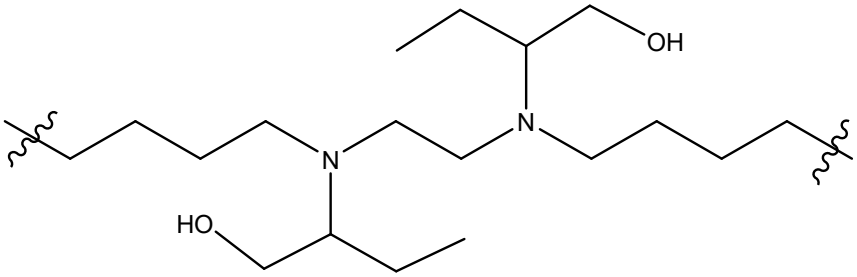
~~77. The compound of any one of claims 1-65, wherein~~ X is selected from the group consisting of:

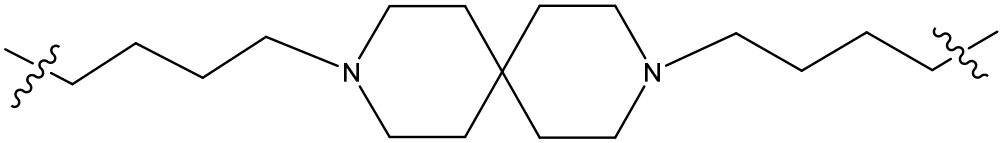




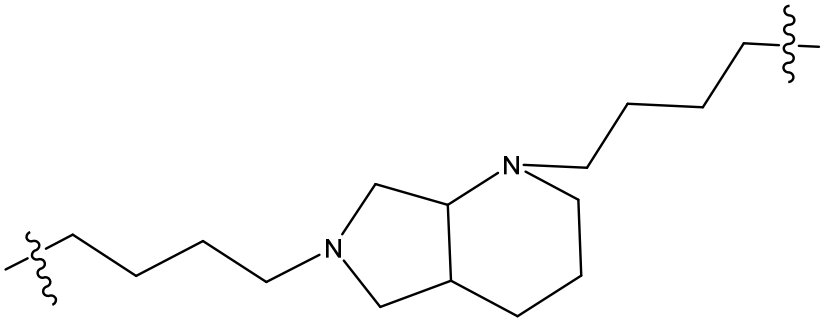

N
N
OH
OH
N
N
N
N
N
N
N
N
CH3





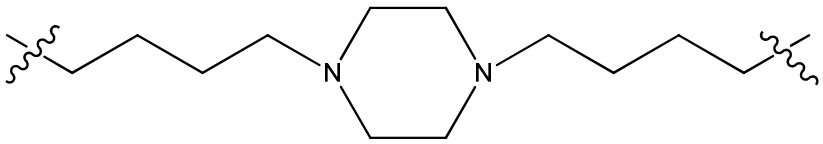


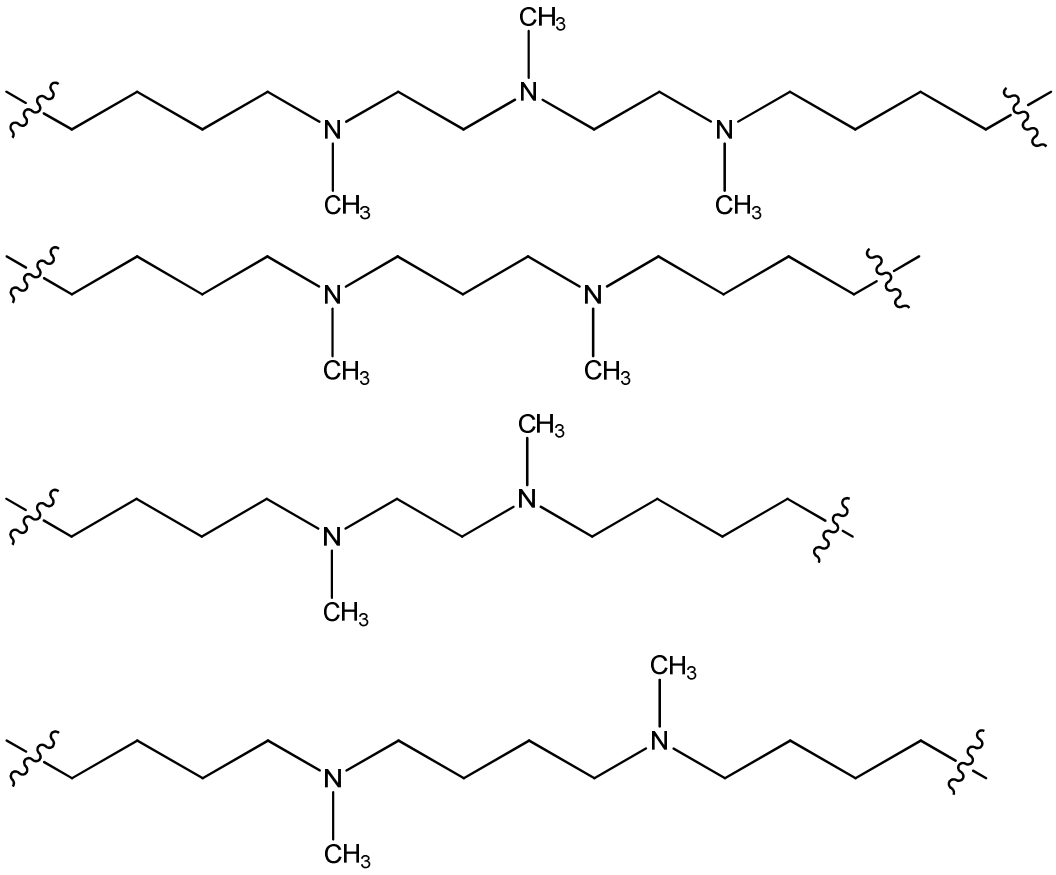
and



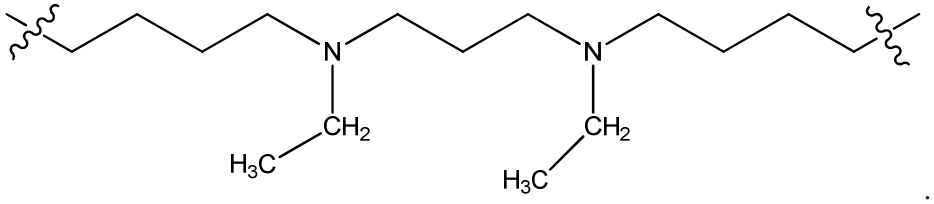
-, further preferably,

~~78. The compound of any one of claims 1-65, wherein~~ X is selected from the group consisting of:





and



795. The compound of claim 1, which is selected from a compound of formula 12-43 as described in the Examples, or a salt thereof.

806. A lipid particle comprising the compound of any one of claims 1-795.

~~81. The lipid particle of claim 80, wherein the lipid particle further comprises a non-cationic lipid.~~

~~82. The lipid particle of claim 80 or 81, wherein the lipid particle further comprises a conjugated lipid that inhibits aggregation of particles.~~

~~83~~7. The lipid particle of ~~any one of claims 80-82~~claim 6, wherein the lipid particle further comprises a therapeutic agent.

~~84~~8. The lipid particle of claim ~~83~~7, wherein the therapeutic agent is a nucleic acid therapeutic agent~~.~~,

~~85. The lipid particle of claim 83, wherein the therapeutic agent is~~ an interfering RNA agent, or mRNA, preferably the interfering RNA being siRNA.

~~86. The lipid particle of claim 85, wherein the therapeutic agent is siRNA.~~

~~87. The lipid particle of claim 83, wherein the therapeutic agent is mRNA.~~

~~88. The lipid particle of any one of claims 84-87, wherein the nucleic acid therapeutic agent comprises at least one modified nucleotide.~~

~~89. The lipid particle of claim 88, wherein the nucleic acid therapeutic agent comprises at least one 2'-O-methyl (2'OMe) nucleotide.~~

~~90. The lipid particle of any one of claims 81-89, wherein the non-cationic lipid is cholesterol or a derivative thereof.~~

~~91. The lipid particle of any one of claims 81-90, wherein the non-cationic lipid is cholesterol.~~

~~92. The lipid particle of any one of claims 81-89, wherein the non-cationic lipid comprises a phospholipid.~~

~~93. The lipid particle of any one of claims 81-90, wherein the non-cationic lipid comprises a mixture of a phospholipid and cholesterol.~~

~~94. The lipid particle of any one of claims 92-93, wherein the phospholipid is distearoylphosphatidylcholine (DSPC).~~

~~95. The lipid particle of any one of claims 82-90, wherein the conjugated lipid is a polyethyleneglycol (PEG) lipid conjugate.~~

~~96. The lipid particle of claim 95, wherein the PEG lipid conjugate is a PEG dimyristyloxypropyl (PEG-DMA) conjugate.~~

~~97~~9. A composition comprising a compound of any one of claims 1-~~79~~5.

~~98~~10. A pharmaceutical composition comprising a lipid particle of any one of claims ~~80-96~~6 to 8, and a pharmaceutically acceptable carrier.

~~99~~11. The lipid particle of claim 7 or 8 for use in ~~A method for~~ the *in vivo* delivery of a therapeutic agent~~, the method comprising: administering~~ to a mammalian subject ~~a lipid particle of any one of claims 83-96~~.

~~100. A lipid particle of any one of claims 83-96 for use in the *in vivo* delivery of a therapeutic agent to a mammal.~~

~~101. The use of a lipid particle of any one of claims 83-96 to prepare a medicament for the *in vivo* delivery of a therapeutic agent to a mammal.~~

12. Use of the lipid particle of claim 7 or 8 in the manufacture of a medicament for the *in vivo* delivery of a therapeutic agent to a mammalian subject.

~~102~~13. The lipid particle of claim 7 or 8 for use in ~~A method for~~ treating a disease or disorder in a mammalian subject in need thereof.~~, the method comprising:~~

~~administering to the mammalian subject a therapeutically effective amount of a lipid particle of any one of claims 83-96.~~

~~103~~14. The lipid particle for use of claim 13~~The method of claim 102~~, wherein the disease or disorder is liver fibrosis~~.~~

~~104. The method of claim 102, wherein the disease or disorder is non-alcoholic steatohepatitis (NASH).~~

~~105. The method of claim 102, wherein the disease or disorder is alcoholic steatohepatitis (ASH).~~

~~106. The method of claim 102, wherein the disease or disorder is~~ or liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

15. Use of the lipid particle of claim 7 or 8 in the manufacture of a medicament for treating a disease or disorder in a mammalian subject in need thereof, wherein the disease or disorder is liver fibrosis or liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

~~107~~16. A method of delivering a therapeutic agent to a hepatic stellate cell (HSC), ~~*in vivo* or~~ *in vitro*, comprising contacting the HSC with the lipid particle of ~~any one of claims 83-96~~claim 7 or 8.

17. The lipid particle of claim 7 or 8 for use in delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle of claim 7 or 8.

18. Use of the lipid particle of claim 7 or 8 in the manufacture of a medicament for delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle of claim 7 or 8.