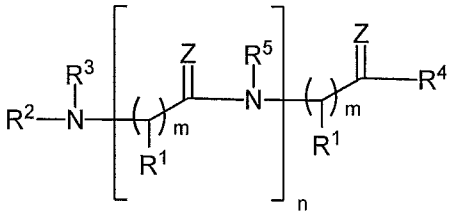
the clinical use of siRNA continues to require development of safer and more effective delivery systems. Toward this end, numerous lipid-like molecules have been developed including poly β-amino esters and amino alcohol lipids. See, *e.g.*, PCT Application Publication Nos. WO 2002/031025; WO 2004/106411; WO 2008/011561; WO 2007/143659; WO 2006/138380; and WO 2010/053572. Amino acid, peptide, polypeptide-lipids (APPL) have also been studied for a variety of applications, including use as therapeutics, biosurfactants, and nucleotide delivery systems. See, *e.g.,* Giuliani *et al., Cellular and Molecular Life Sciences* (2011) 68:2255-2266; Ikeda *et al., Current Medicinal Chemistry* (2007) 14: 111263-1275; Sen, *Advances in Experimental Medicine and Biology* (2010) 672:316-323; and Damen *et al., Journal of Controlled Release* (2010) 145:33-39. However, there continues to remain a need to investigate and develop new APPL systems with improved properties, such as new and improved APPL nucleotide delivery systems.

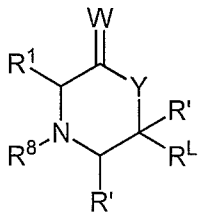
Summary

[0005] Described herein are inventive compounds and compositions characterized, in certain embodiments, by conjugation of various groups, such as lipophilic groups, to an amino or amide group of an amino acid, a linear or cyclic peptide, a linear or cyclic polypeptide, or structural isomer thereof, to provide compounds of the present invention, collectively referred to herein as "APPLs". Such APPLs are deemed useful for a variety of applications, such as, for example, improved nucleotide delivery. The subject matter is as defined in the independent claims 1, 17, 35, 37, and 38, and their dependent claims.

[0006] Exemplary APPLs include, but are not limited to, compounds of Formula (I), (II), (III), (IV), (V), and (VI), and salts thereof, as described herein:



(I)

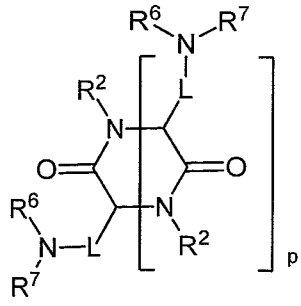


(II)

Claims

What is claimed is:

1. A compound of Formula (III):



(III-c)

or salt thereof;

wherein:

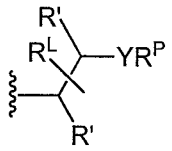
p is 1;

wherein L is an optionally substituted C_{1-50} alkylene, and

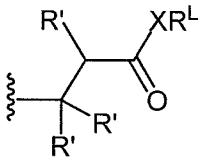
R^6 and R^7 are each independently a group of the formula (i) or (ii);

each instance of R^2 is independently hydrogen, or a group of the formula (i) or (ii); and

Formulae (i) and (ii) are:

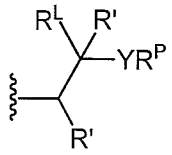


(i)

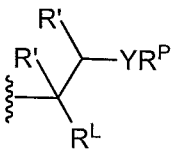


(ii)

wherein each instance of formula (i) is independently formula (i-a) or formula (i-b):



(i-a)



(i-b);

wherein:

each instance of R′ is independently hydrogen or optionally substituted alkyl;

X is O, S, NR^X, wherein R^X is hydrogen, optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted 3–14 membered heterocyclyl, optionally substituted C_{6-14} aryl, optionally substituted 5-10 membered heteroaryl, or a nitrogen protecting group;

Y is O, S, NR^Y, wherein R^Y is hydrogen, optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted 3–14 membered heterocyclyl, optionally substituted C_{6-14} aryl, optionally substituted 5-10 membered heteroaryl, or a nitrogen protecting group;

R^P is hydrogen, optionally substituted C_{1-50} alkyl, optionally substituted C_{2-50} alkenyl, optionally substituted C_{2-50} alkynyl, optionally substituted C_{3-10} carbocyclyl, optionally substituted 3–14 membered heterocyclyl, optionally substituted C_{6-14} aryl, optionally substituted 5-10 membered heteroaryl, an oxygen protecting group when attached to an oxygen atom, a sulfur protecting group when attached to a sulfur atom, or a nitrogen protecting group when attached to a nitrogen atom; and

R^L is optionally substituted C_{6-20} alkyl, optionally substituted C_{6-20} alkenyl, optionally substituted C_{6-20} alkynyl, optionally substituted heteroC_{6-20} alkyl, optionally substituted heteroC_{6-20} alkenyl, optionally substituted heteroC_{6-20} alkynyl, or a polymer;

wherein:

heteroalkyl refers to an alkyl group which further includes at least one heteroatom selected from oxygen, sulfur, nitrogen, boron, silicon, and phosphorus;

polymer refers to a cellulose polymer, dextran polymer, polymaleic acid polymer, poly(acrylic acid) polymer, poly(vinylalcohol) polymer, polyvinylpyrrolidone (PVP) polymer, or a polyethyleneglycol (PEG) polymer;

optionally substituted refers to a carbon atom of a group which is unsubstituted or independently substituted with halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, -SeH, $-SeR^{aa}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-50} alkyl, C_{2-50} alkenyl, C_{2-50} alkynyl, C_{3-14} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$; or

refers to a nitrogen atom of a group which is unsubstituted or independently substituted with OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-50} alkyl, C_{2-50} alkenyl, C_{2-50} alkynyl, C_{3-10} carbocyclyl, 3–14 membered

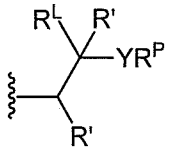
heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

$Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$.

2. The compound of claim 1, wherein at least one instance of R^2 is H.

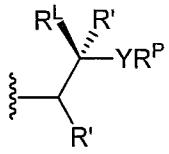
3. The compound of claim 1, wherein L is an unsubstituted C_{1-50} alkylene.

4. The compound of claim 1, wherein the group of formula (i) represents a group of formula (i-a):



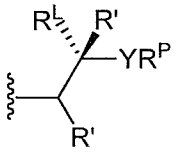
(i-a) .

5. The compound of claim 4, wherein the group of formula (i-a) is a group of formula (i-a1):



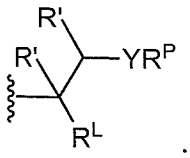
(i-a1) .

6. The compound of claim 4, or salt thereof, wherein the group of formula (i-a) is a group of formula (i-a2):



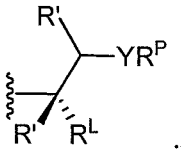
(i-a2)

7. The compound of claim 1, or salt thereof, wherein the group of formula (i) is a group of formula (i-b):



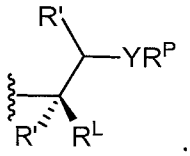
(i-b)

8. The compound of claim 7, wherein the group of formula (i-b) is a group of formula (i-b1):



(i-b1)

9. The compound of claim 7, or salt thereof, wherein the group of formula (i-b) is a group of formula (i-b2):

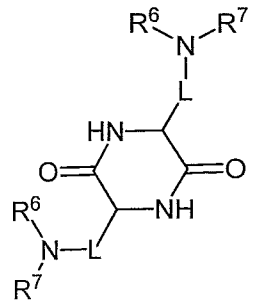


(i-b2)

10. The compound of any one of claims 1-9, or salt thereof, wherein R^L is optionally substituted C_{6-20} alkyl.

11. The compound of claim 10, or salt thereof, wherein R^L is unsubstituted C_{6-20}alkyl.

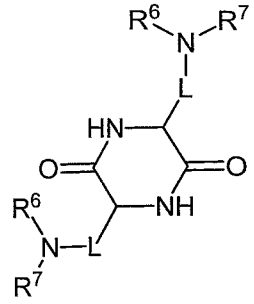
12. The compound of any one of claims 1-11, wherein the compound is of formula (III-c2):



(III-c2)

wherein R^6 is a group of formula (i) and R^7 is a group of formula (i).

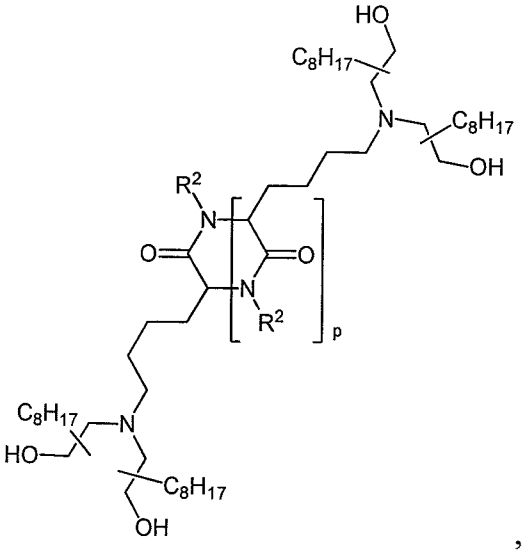
13. The compound of any one of claims 1-12, wherein the compound is of formula:



(III-c2)

wherein R^6 is a group of formula (ii) and R^7 is a group of formula (ii).

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



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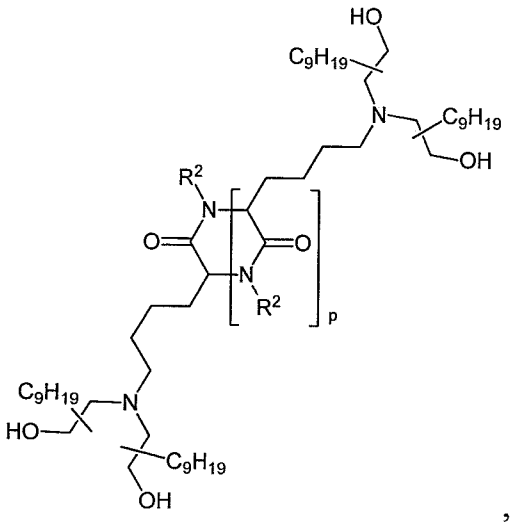

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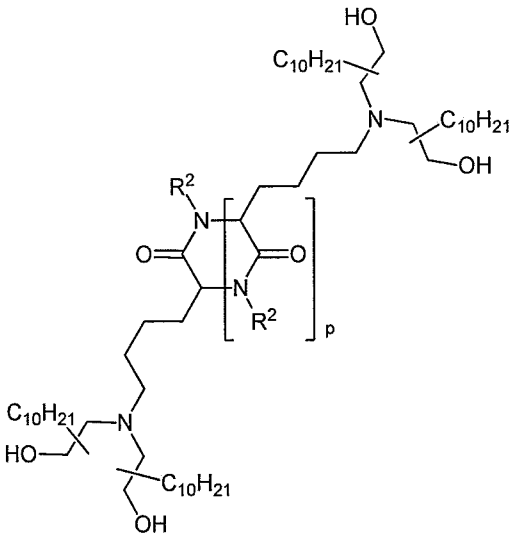
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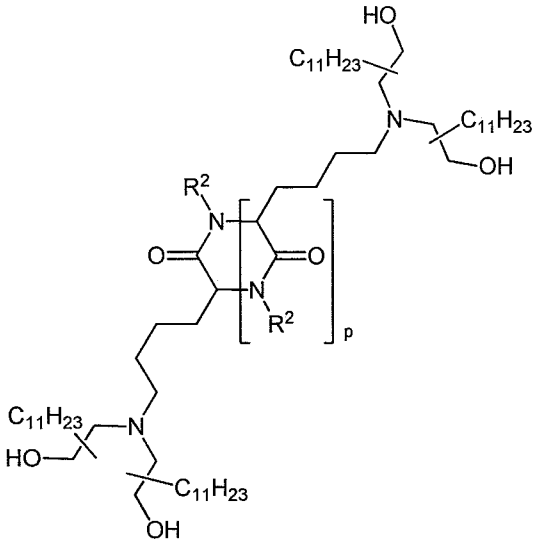
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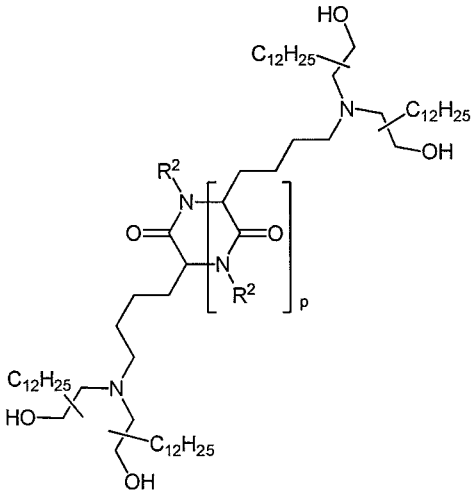
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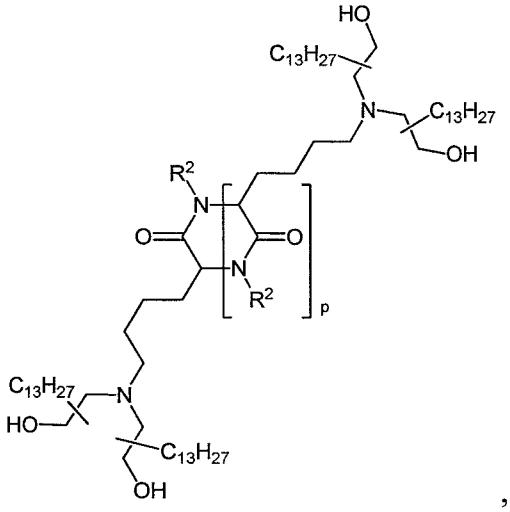
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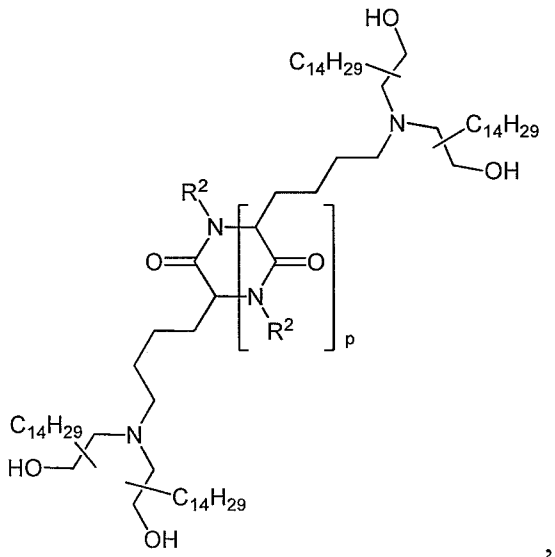
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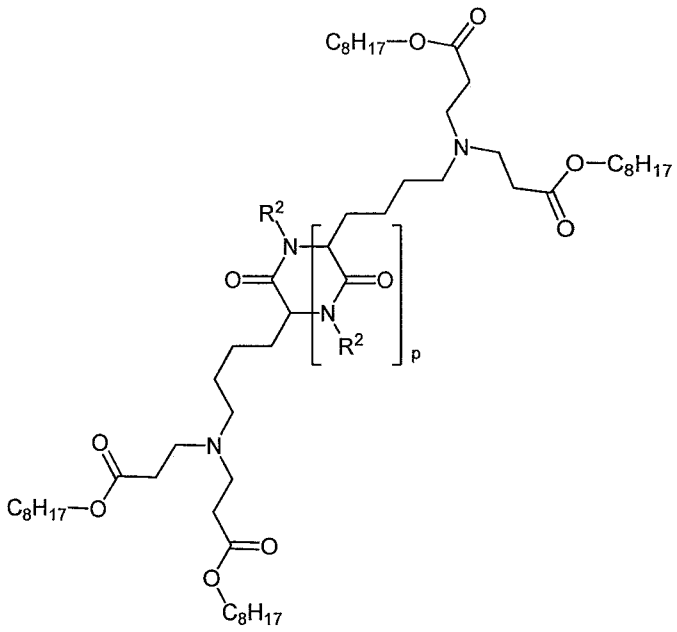

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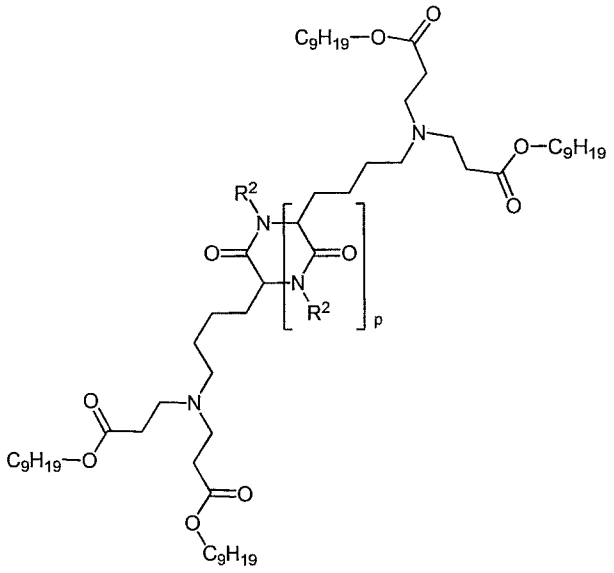

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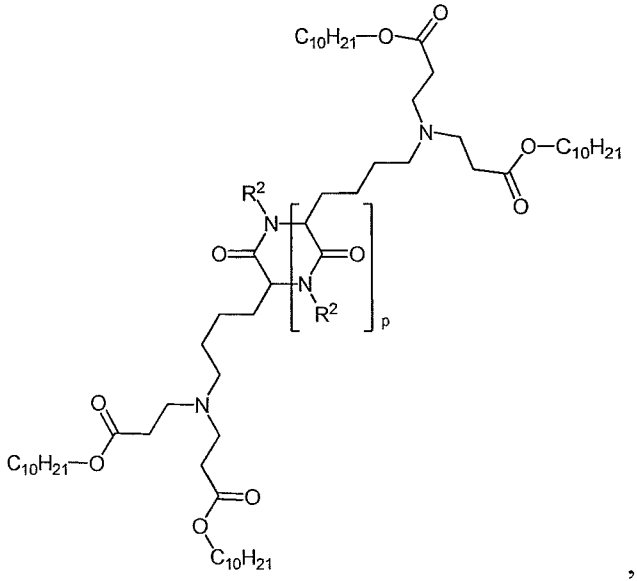

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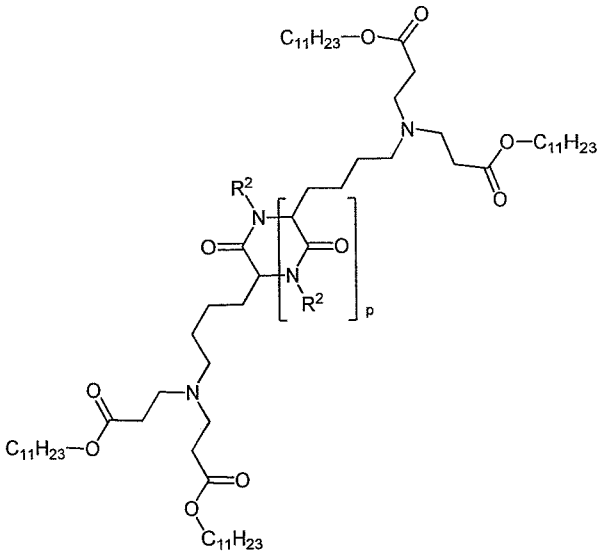

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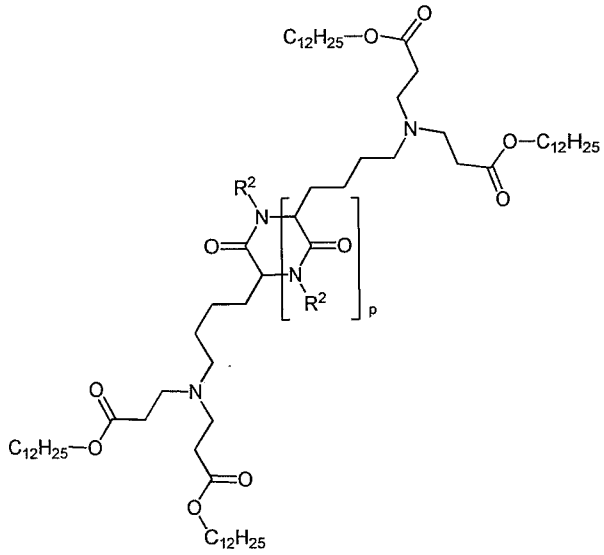

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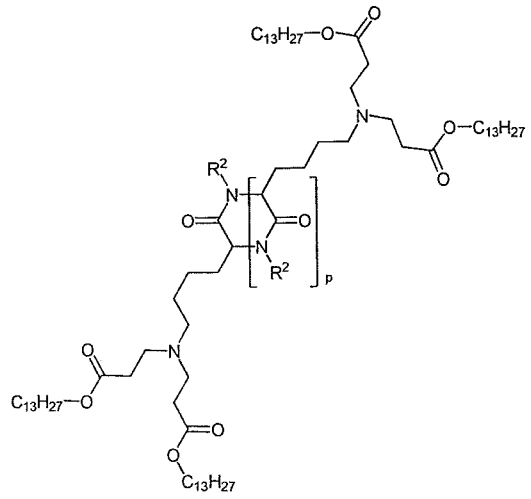

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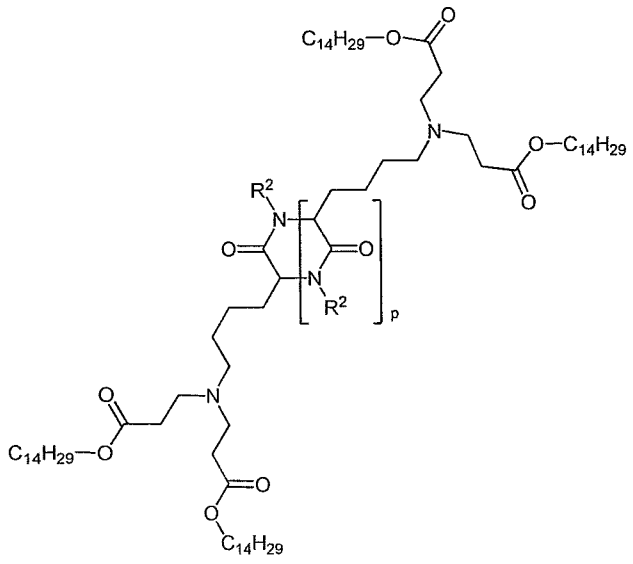

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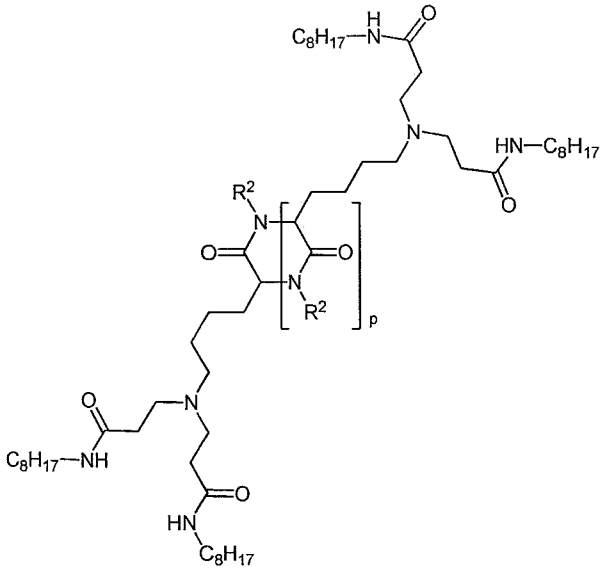

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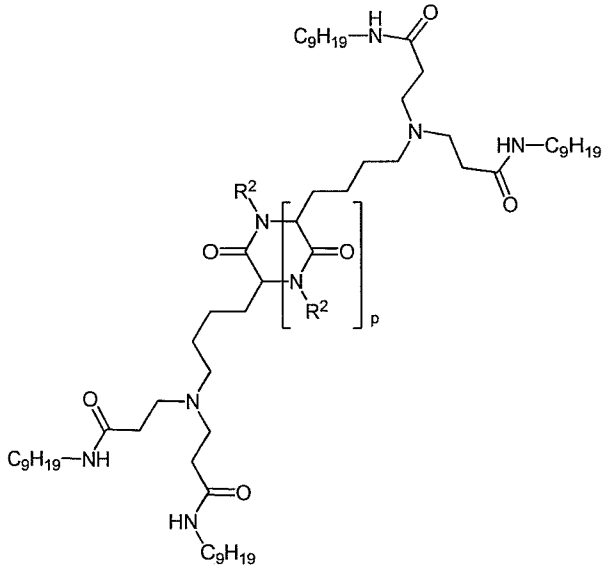

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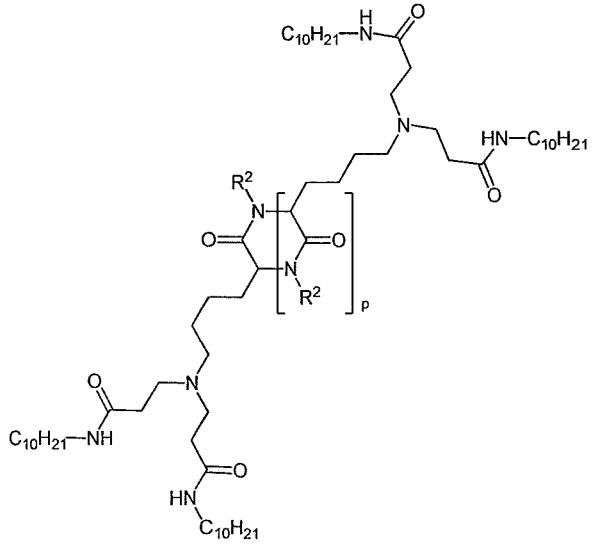

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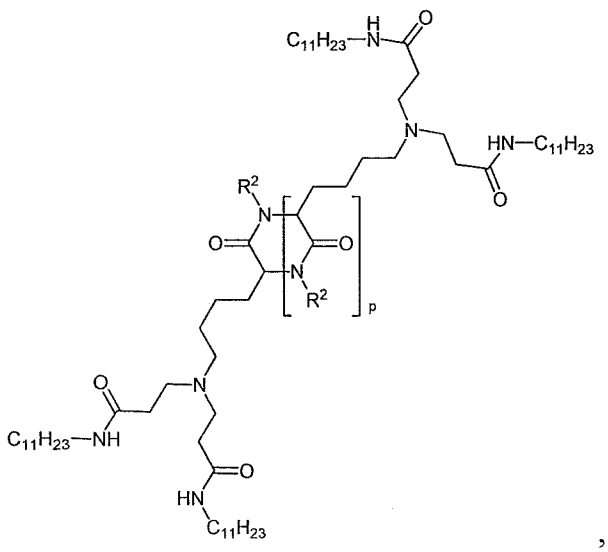

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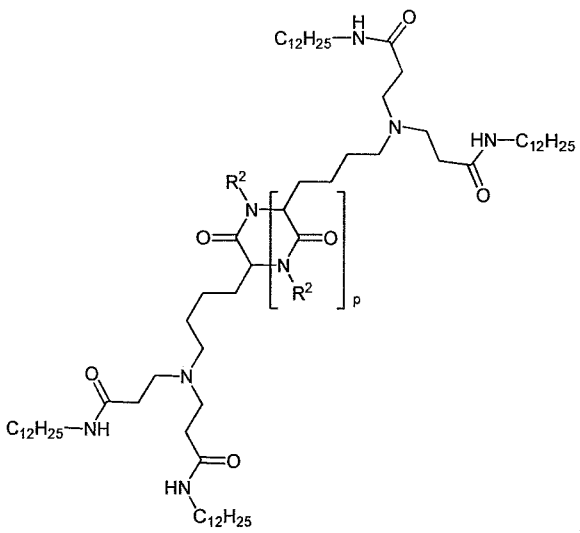
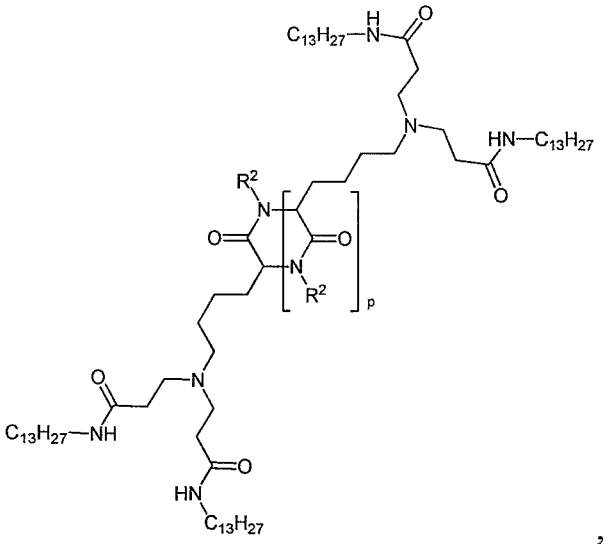
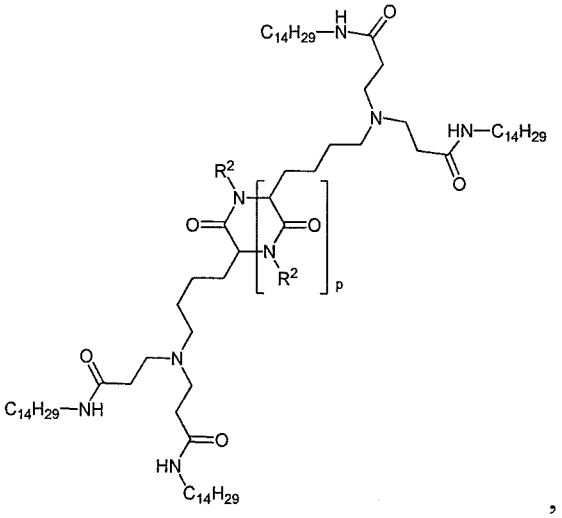
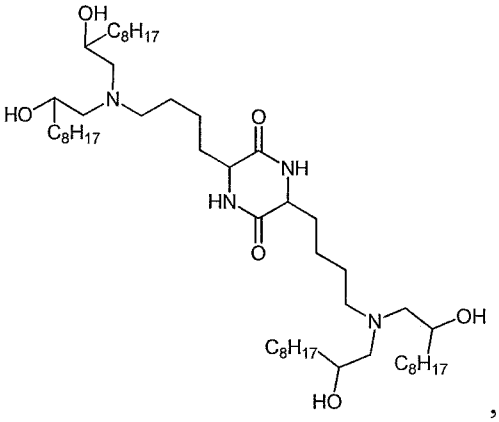
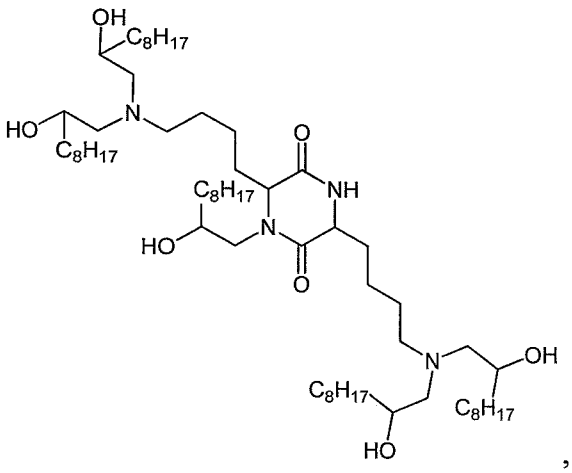
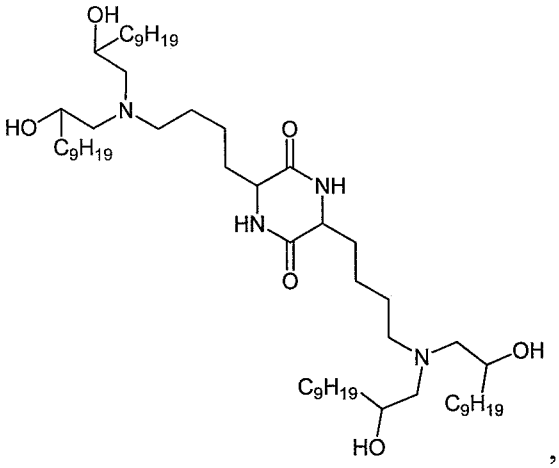




and salts thereof, wherein p is 1.

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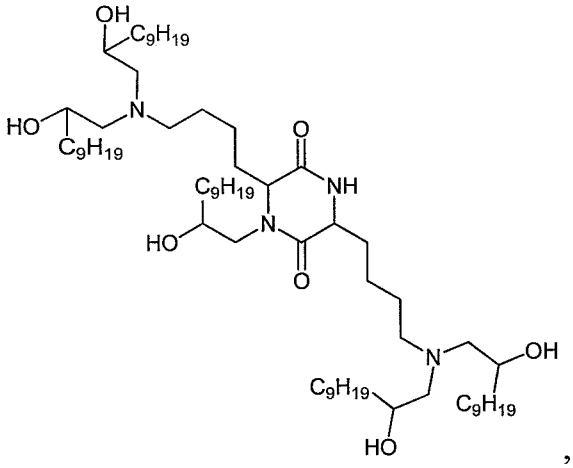
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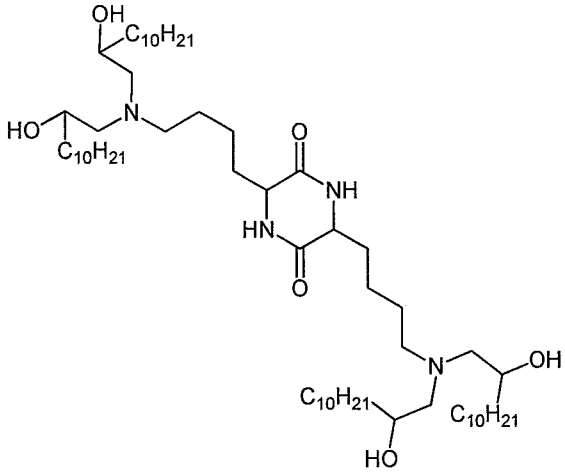
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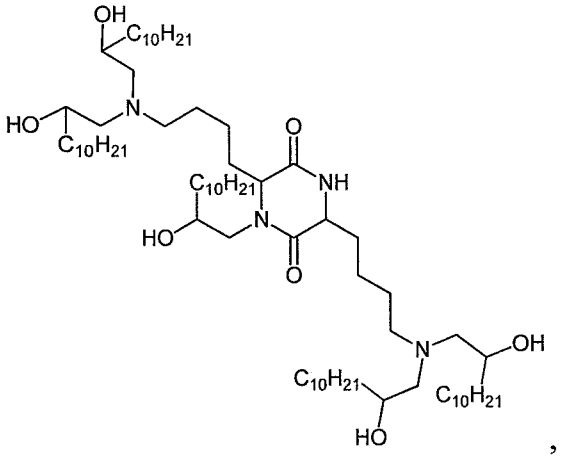
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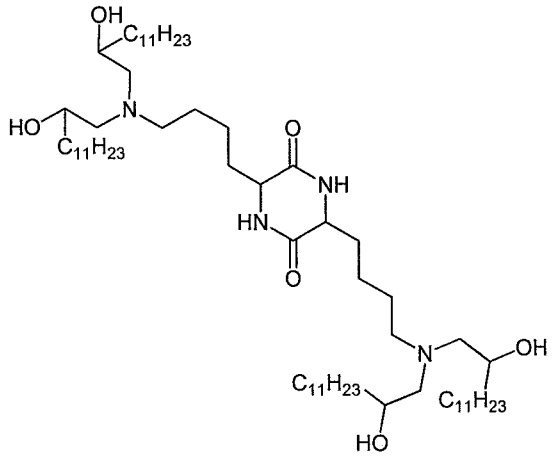
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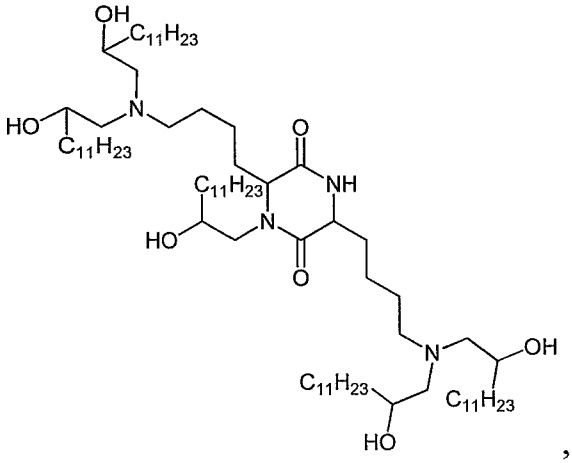
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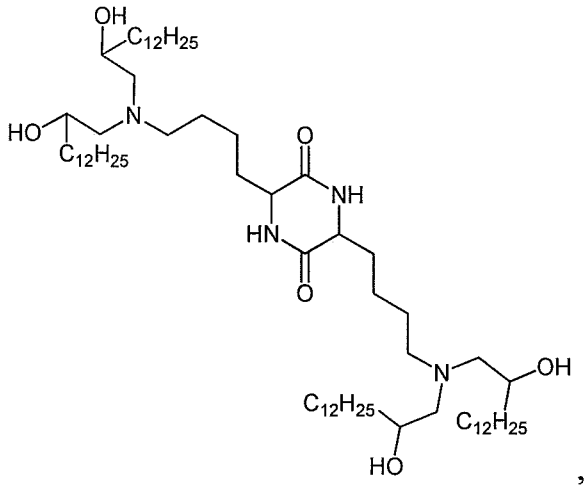
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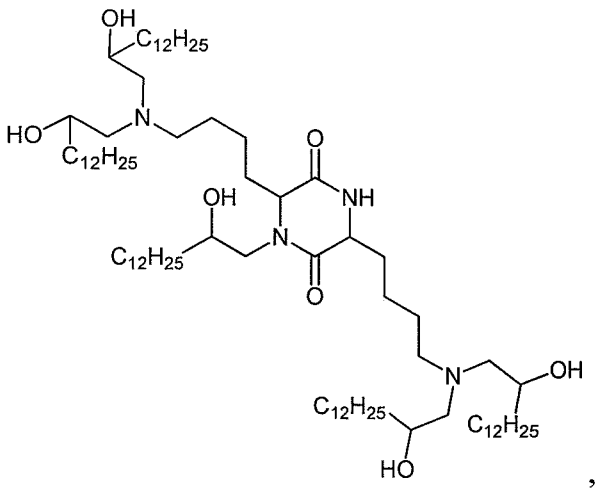
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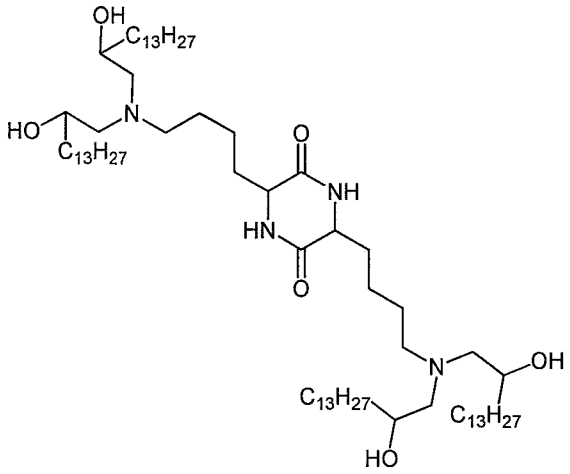
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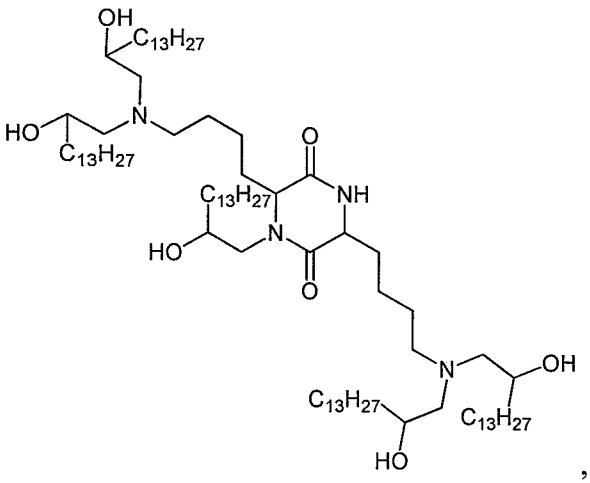
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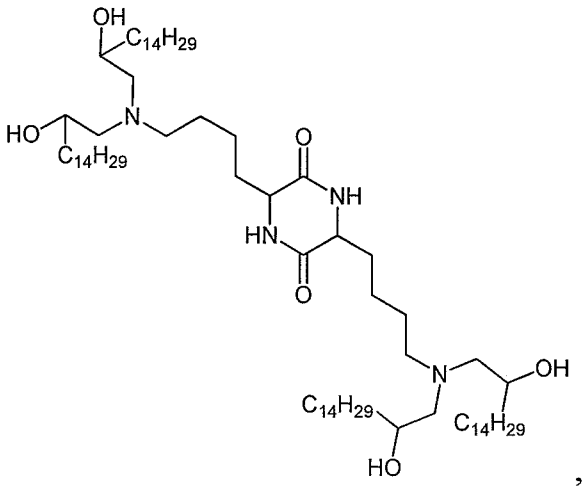
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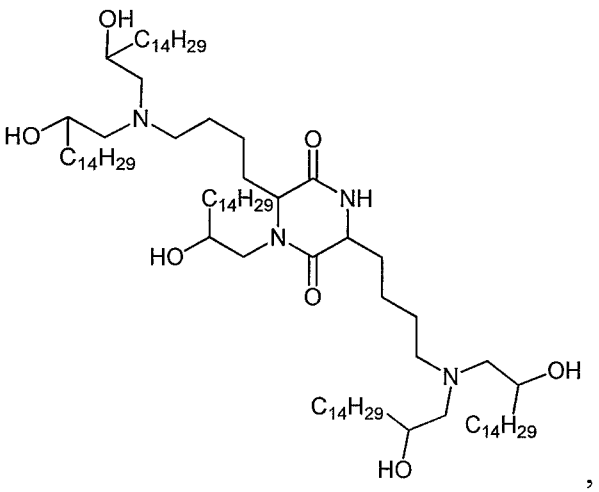
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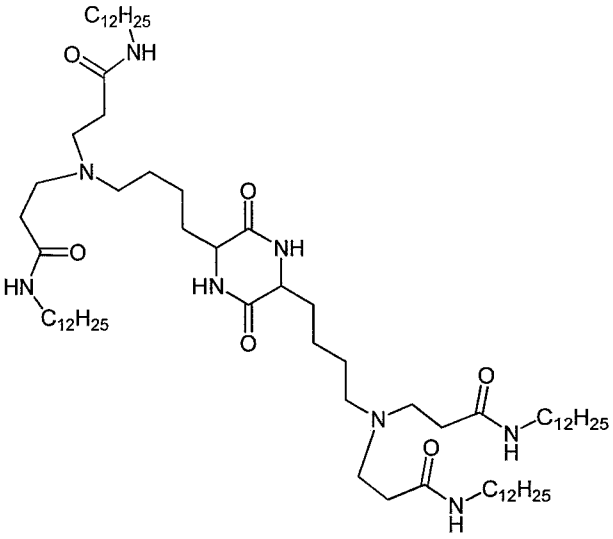
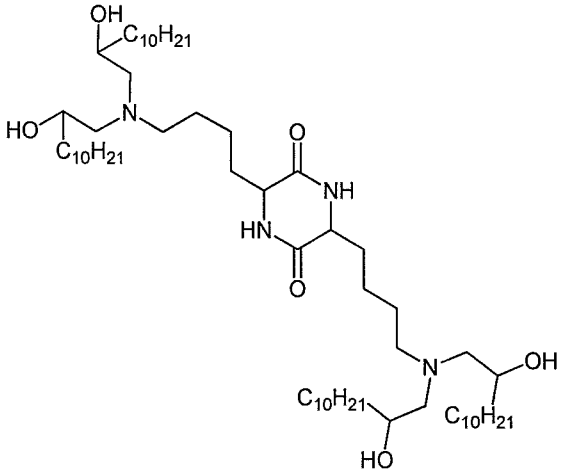


and salts thereof.

16. The compound of claim 15, wherein the compound is:



or salt thereof.

17. A composition comprising a compound of any one of claims 1-16, or salt thereof, and an excipient.

18. The composition of claim 17, wherein the composition is a pharmaceutical composition, a cosmetic composition, a nutraceutical composition, or a composition with non-medical application.

19. The composition of claim 18, wherein the composition with non-medical application is an emulsion or emulsifier useful as a food component, for extinguishing fires, for disinfecting surfaces, or for oil cleanup.

20. The composition of claim 18, wherein the composition is a pharmaceutical composition.

21. The composition of claim 17, wherein the composition further comprises cholesterol.

22. The composition of claim 17, wherein the composition further comprises a PEGylated lipid.

23. The composition of claim 17, wherein the composition further comprises a phospholipid.

24. The composition of claim 17, wherein the composition further comprises an apolipoprotein.

25. The composition of claim 17, wherein the composition further comprises an agent, wherein the agent is an organic molecule, inorganic molecule, nucleic acid, protein, peptide, polynucleotide, targeting agent, an isotopically labeled chemical compound, vaccine, an immunological agent, or an agent useful in bioprocessing; wherein:

a targeting agent is an agent that targets a particular cell, and is selected from the group consisting of glycoproteins, lipids, antibodies, fragments of antibodies, low-density lipoproteins, transferrin, gp120 envelope protein of the human immunodeficiency virus, carbohydrates, receptor ligands, sialic acid, and aptamers;

an immunological agent is an agent useful in the treatment of cancer and/or autoimmune disorders; and

an agent useful in bioprocessing is an agent useful in maintaining a cell's health and/or growth, and/or in the cell's bioprocessing of a commercially useful chemical or fuel.

26. The composition of claim 25, wherein the agent is a polynucleotide, and the polynucleotide is DNA.

27. The composition of claim 25, wherein the agent is a polynucleotide, and the polynucleotide is RNA.

28. The composition of claim 27, wherein the RNA is RNA*i*, dsRNA, siRNA, shRNA, miRNA, or antisense RNA.

29. The composition of claim 25, wherein the agent is a polynucleotide, and the polynucleotide encodes a protein or peptide.

30. The composition of claim 25, wherein the agent and the compound are not covalently attached.

31. The composition of any one of claims 17 to 30, wherein the composition is in the form of a particle.

32. The composition of claim 31, wherein the particle is a nanoparticle or microparticle.

33. The composition of claim 31, wherein the particle is a micelle, liposome, or lipoplex.

34. The composition of claim 31, wherein the particle encapsulates an agent, wherein the agent is an organic molecule, inorganic molecule, nucleic acid, protein, peptide, polynucleotide, targeting agent, an isotopically labeled chemical compound, vaccine, an immunological agent, or an agent useful in bioprocessing; wherein:

a targeting agent is an agent that targets a particular cell, and is selected from the group consisting of glycoproteins, lipids, antibodies, fragments of antibodies, low-density lipoproteins, transferrin, gp120 envelope protein of the human immunodeficiency virus, carbohydrates, receptor ligands, sialic acid, and aptamers;

an immunological agent is an agent useful in the treatment of cancer and/or autoimmune disorders; and

an agent useful in bioprocessing is an agent useful in maintaining a cell's health and/or growth, and/or in the cell's bioprocessing of a commercially useful chemical or fuel.

35. A method of screening a compound library, the method comprising:

providing a plurality of different compounds of any one of claims 1-16, or salts thereof; and

performing at least one assay with the compound library to determine the presence or absence of a desired property.

36. The method of claim 35, wherein the desired property is solubility in water, solubility at different pH, ability to bind polynucleotides, ability to bind heparin, ability to bind small molecules, ability to bind protein, ability to form microparticles, ability to increase tranfection efficiency, ability to support cell growth, ability to support cell attachment, ability to support tissue growth, and/or intracellular delivery of the compound and/or an agent complexed or attached thereto to aid in bioprocessing.

37. Use of a composition of any one of claims 17-34 or a compound of any one of claims 1 to 16 in the manufacture of a medicament for treating a disease, disorder, or condition from which a subject suffers, wherein the disease, disorder, or condition is selected from the group consisting of proliferative disorders, inflammatory disorders, autoimmune disorders, painful conditions, liver diseases, and familial amyloid neuropathies.

38. An *in vitro* method of delivering a polynucleotide to a biological cell, comprising:

providing a composition of any one of claims 17-34 and a polynucleotide; and

exposing the composition to the biological cell under conditions sufficient to facilitate delivery of the polynucleotide into the interior of the biological cell.

39. The method of claim 38, wherein the polynucleotide is DNA.

40. The method of claim 38, wherein the polynucleotide is RNA.

41. The method of claim 40, wherein the RNA is RNA*i*, dsRNA, siRNA, shRNA, miRNA, or antisense RNA.

42. The method of claim 41, wherein upon delivery of the RNA into the cell, the RNA is able to interfere with the expression of a specific gene in the biological cell.