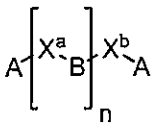
WHAT IS CLAIMED IS:

1. A composition, the composition comprising a sterol; a neutral lipid; a PEG or a PEG-modified lipid; and a lipid of formula (I)



wherein,

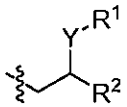
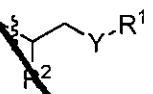
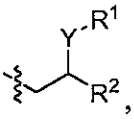
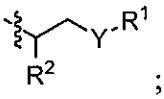
formula (I)

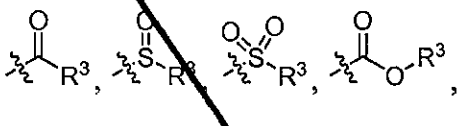
each X^a and X^b, for each occurrence, is independently C_{1-6} alkylene;

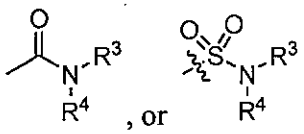
n is 0, 1, 2, 3, 4, or 5;

A for each occurrence is NR_2 or a cyclic moiety optionally substituted with 1-3 R;

B is NR or a cyclic moiety optionally substituted with 1-2 R;

each R is independently H, alkyl, , or ; provided that at least one R is , or ;

R^1, for each occurrence, is independently H, R^3, ,

;

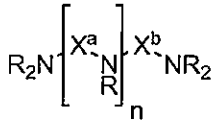
R^2, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

R^3, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent (e.g., a hydrophilic substituent);

Y, for each occurrence, is independently O, NR^4, or S;

R^4, for each occurrence is independently H alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent.

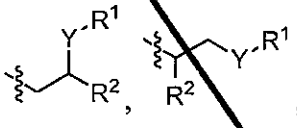
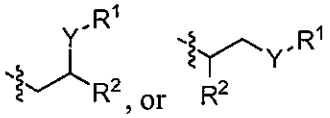
2. The composition of claim 1, comprising a sterol; a PEG or a PEG-modified lipid, a neutral lipid and a lipid of formula (II):

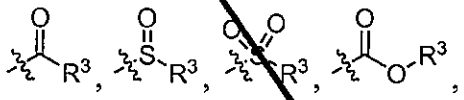
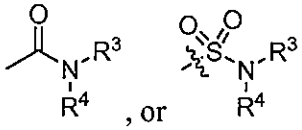


formula (II)

each X^a and X^b, for each occurrence, is independently C_{1-6} alkylene;

n is 0, 1, 2, 3, 4, or 5;

each R is independently H, alkyl, , or two Rs, together with the nitrogen to which they are attached form a ring; provided that at least one R is ;

R^1, for each occurrence, is independently H, R^3, , , or ; wherein R^3 is optionally substituted with one or more substituent;

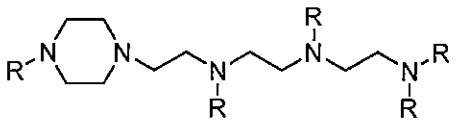
R^2, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

R^3, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

Y, for each occurrence, is independently O, NR^4, or S;

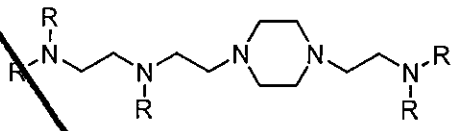
R^4, for each occurrence is independently H alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent.

3. A composition, the composition comprising a sterol; a neutral lipid; a PEG or a PEG-modified lipid; and a compound of formula (III), (IV) or a mixture thereof,

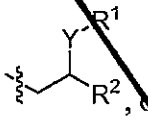
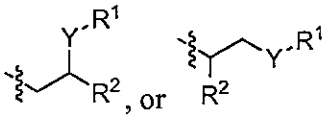
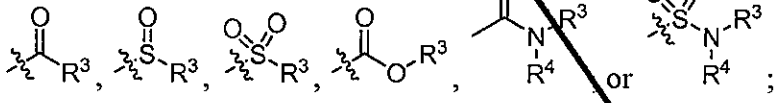


formula (III)

or



formula (IV),

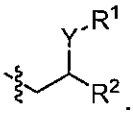
wherein each R is independently H, alkyl, ; provided that at least one R is ; wherein R^1, for each occurrence, is independently H, R^3,  or ; wherein R^3 is optionally substituted with one or more substituent;

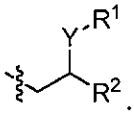
R^2, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

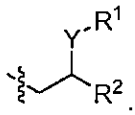
R^3, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

Y, for each occurrence, is independently O, NR^4, or S;

R^4, for each occurrence is independently H alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent; and

4. The composition of claim 3, wherein R, for at least 3 occurrences, is .

5. The composition of claim 3, wherein n is 2 or 3 and wherein R, for at least 3 occurrences, is .

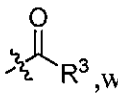
6. The composition of claim 3, wherein n is 3 and wherein R, for 5 occurrences, is .

7. The composition of claim 3, wherein Y is O or NR^4.

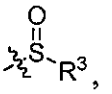
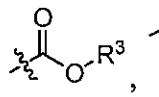
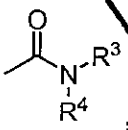
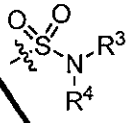
8. The composition of claim 3, wherein Y is O.

9. The composition of claim 3, wherein Y is O for each occurrence.

10. The composition of claim 3, wherein R^1 is H.

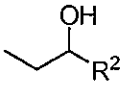
11. The composition of claim 3, wherein R^1 is ,wherein R^3 alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl, each of which is optionally substituted with one or more substituent (e.g., a hydrophilic substituent).

12. The composition of claim 3, wherein R^1 is , and R^3 alkyl optionally substituted with one or more substituent (e.g., a hydrophilic substituent).

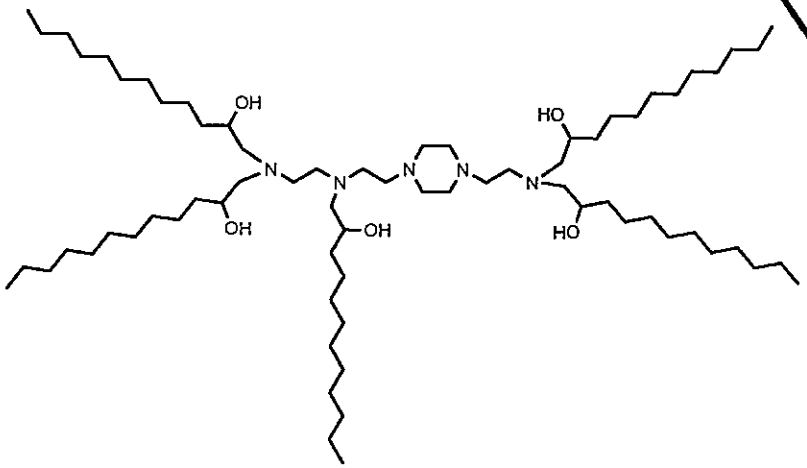
13. The composition of claim 3, wherein R^1 is R^3, , , , , , or ; wherein R^3 alkyl is optionally substituted with one or more substituent.

14. The composition of claim 3, wherein R^2 is alkyl, alkenyl, or alkynyl.

15. The composition of claim 3, wherein R^2 is alkyl (e.g., C_6-C_{18} alkyl, e.g., C_8-C_{12} alkyl, e.g., C_{10} alkyl).

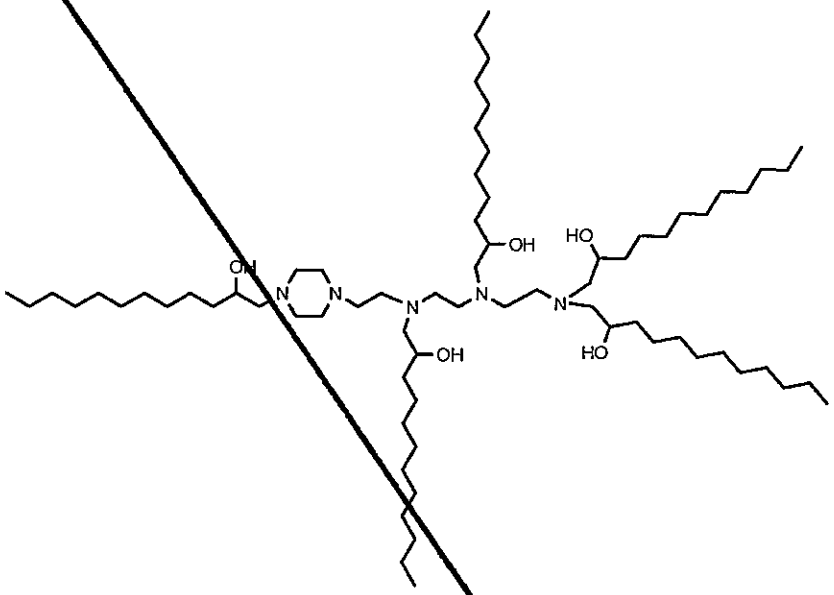
16. The composition of claim 3, wherein R for at least 3 (e.g., at least 4 or 5) occurrences is .

17. The composition of claim 3, comprising a compound of formula (V)



formula (V).

18. The composition of claim 3, comprising a compound of formula (VI)



formula (VI).

19. The composition of claim 1, 2, 3, 17, or 18, wherein the compound of formula (I), (II), (III), (IV), (V), or (VI) is an inorganic or organic salt thereof, e.g., a hydrohalide salt thereof, such as a hydrochloride salt thereof.

20. The composition of claim 1, 2, 3, 17, or 18, wherein the compound of formula (I), (II), (III), (IV), (V), or (VI) is salt of an organic acid, e.g., an acetate or formate.

21. The composition of claim 1, 2, 3, 17, or 18, wherein the compound of formula (I), (II), (III), (IV), (V), or (VI) is in the form of a hydrate.

22. The composition of claim 1, 2, or 3, wherein the sterol is cholesterol.

23. The composition of claim 1, 2, or 3, wherein the lipid is a PEG-modified lipid.

24. The composition of claim 23, wherein the PEG-modified lipid is PEG-DMG.

25. The composition of claim 1, 2 or 3 wherein the neutral lipid is DSPC.

26. The composition of claim 1, 2, 3, 17, or 18, wherein the composition comprises about 25-75% of the compound of formula (I), (II), (III), (IV), (V), (VI) or mixture thereof, about 5-50% of the sterol, about 0.5-20% of the PEG or PEG-modified lipid and about 0.1-15% of the neutral lipid.

27. The composition of claim 1, 2, 3, 17, or 18, wherein the composition comprises about 35-65% formula (I), (II), (III), (IV), (V), (VI) or mixture thereof, about 15-45% of the sterol, and about 0.5-10% of the PEG or PEG-modified lipid and about 3-15% of the neutral lipid.

28. The composition of claim 1, 2, 3, 17, or 18, wherein the composition comprises about 40-65% of the compound of formula (I), (II), (III), (IV), (V), (VI) or mixture thereof about 25-40% of the sterol, and about 0.5-5% of the PEG or PEG-modified lipid, and about 5-10% of the neutral lipid.

29. The composition of claim 1, 2, 3, 17, or 18, wherein the composition comprises about 50% of the compound of formula (I), (II), (III), (IV), (V), (VI) or mixture thereof about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid, and about 10% of the neutral lipid.

30. The composition of claim 29, wherein the composition comprises about 50% of the compound of formula (V) or mixture thereof about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid, and about 10% of the neutral lipid.

31. The composition of claim 29, wherein the composition comprises about 50% of the compound of formula (VI) or mixture thereof about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid, and about 10% of the neutral lipid.

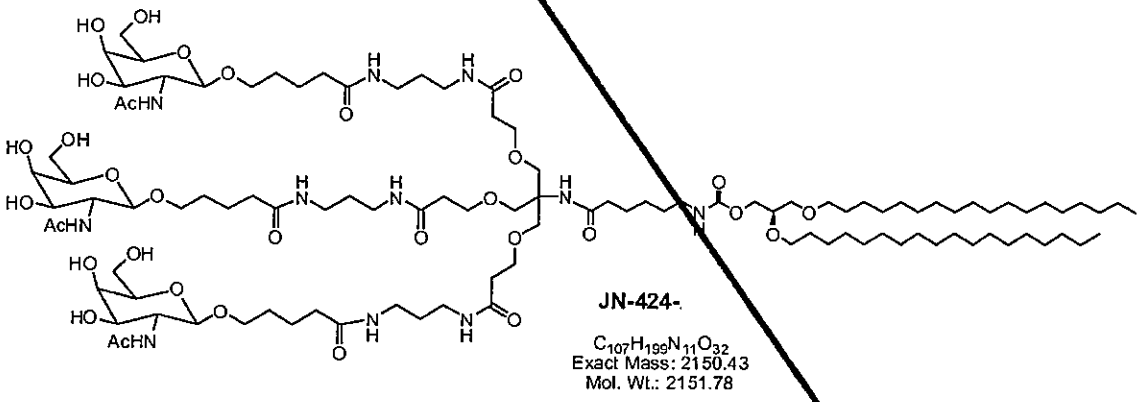
32. The lipid formulation of claim 1, 2, 3, 17, or 18, further comprising a targeting lipid comprising N-acetyl galactosamine as a targeting moiety.

33. The formulation of claim 32, wherein the targeting lipid comprises a plurality of N-acetyl galactosamine moieties.

34. The formulation of claim 32, wherein said targeting lipid is present in the formulation in a molar amount of from about 0.001% to about 5%.

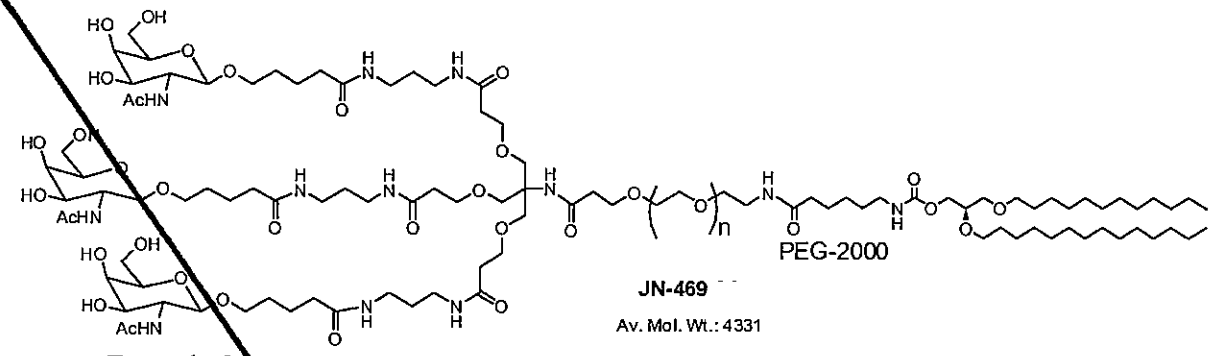
35. The formulation of claim 32, wherein said targeting lipid is present in the formulation in a molar amount of from about 0.005% to about 1.5% (e.g., about 0.3%).

36. The formulation of claim 32, wherein said targeting lipid is the compound selected from the group consisting of formula 2, formula 3, formula 6 and formula 7:



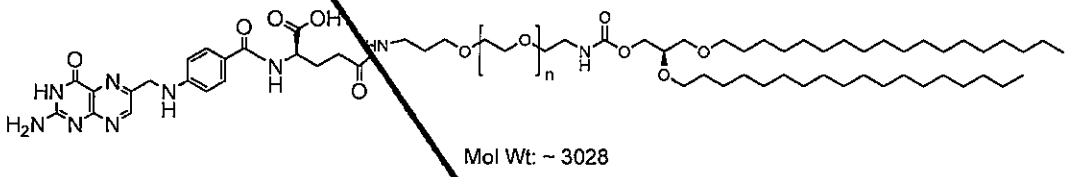
Formula **2**

GalNAc3-DSG



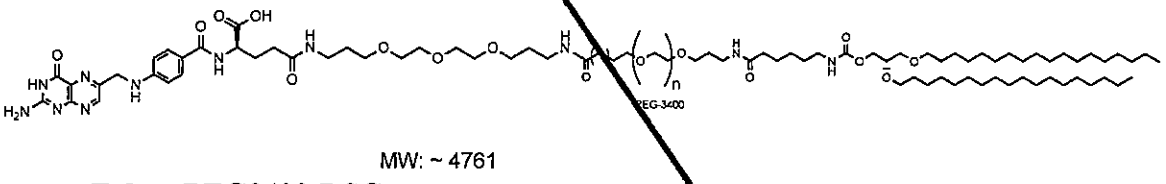
Formula **3**

GalNAc3-PEG-DSG



Folate-PEG2000-DSG

Formula **6**



Folate-PEG3400-DSG

Formula **7**.

37. The composition of claim 1, 2, or 3 wherein the composition is an association complex.

38. The composition of claim 1, 2, or 3, wherein the composition is a liposome.

39. The composition of claim 1, 2, or 3, further comprising a nucleic acid agent.

40. The composition of claim 39, further comprising one or more nucleic acid agents.

41. The composition of claim 40, further comprising five or more nucleic acid agents.

42. The composition of claim 41, further comprising ten or more nucleic acid agents.

43. The composition of claim 1, 2, or 3, further comprising an RNA agent.

44, The composition of claim 1, 2, or 3, further comprising single stranded RNA agent.

45, The composition of claim 1, 2, or 3, further comprising a double stranded RNA agent.

46. A method of producing the composition of claim 1, 2, or 3, the method comprising an extrusion method or an in-line mixing method.

47. The composition of claim 46, wherein the ratio of lipid:nucleic acid is about 3 to about 15.

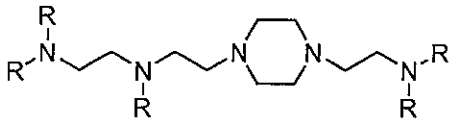
48. The composition of claim 46, wherein the ratio of lipid:nucleic acid about 5 to about 13.

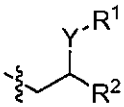
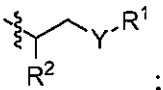
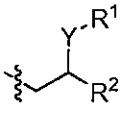
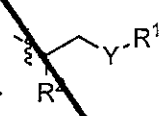
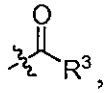
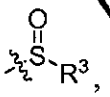
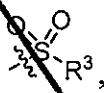
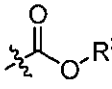
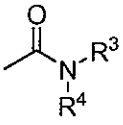
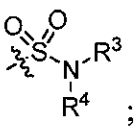
49. The composition of claim 1, 2, or 3 further comprising at least one apolipoprotein.

50. The composition of claim 49, wherein the apolipotprotein is selected from the group consisting of ApoA-I, ApoA-II, ApoA-IV, ApoA-V and ApoE, active polymorphic forms, isoforms, variants and mutants, and fragments or truncated forms thereof.

51. The composition of claim 49, wherein the apolipotprotein is ApoE, active polymorphic forms, isoforms, variants and mutants, and fragments or truncated forms thereof.

52. A method of making a compound of formula (IV)


(IV),

wherein each R is independently H, alkyl, , or  ; provided that at least one R is , or  ; wherein R^1, for each occurrence, is independently H, R^3, , , , , , or  ; wherein R^3 is optionally substituted with one or more substituent;

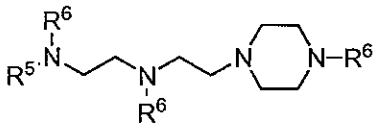
R^2, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

R^3, for each occurrence, is independently, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

Y, for each occurrence, is independently, O, NR^4, or S;

R^4, for each occurrence, is independently, H alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, or heteroalkynyl; each of which is optionally substituted with one or more substituent;

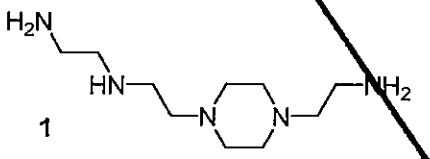
the method comprising contacting an enantiomerically enriched β-hydroxyalkyl synthetic equivalent, the β-hydroxyalkyl group being optionally substituted with one or more substituent, with a compound of formula (VIII)



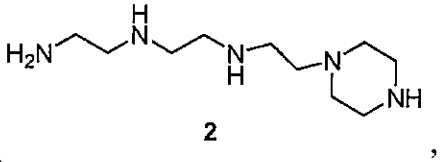
(VIII)

wherein R^5, for each occurrence, is independently, H, alkyl, or an amine protecting group, wherein alkyl is optionally substituted with one or more substituent; and R^6, for each occurrence, is independently, H, $-(CH_2)_2N(R^5)_2$, or an amine protecting group.

53. The method of claim 52, wherein the compound of formula (VIII) is

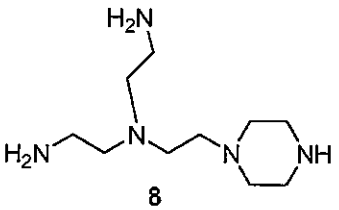


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2

,



8

, or a mixture thereof.

54. The method of claim 53, wherein the enantiomerically enriched β-hydroxyalkyl synthetic equivalent includes an enantiomerically enriched 1,2-epoxyalkane.

55. The method of claim 54, wherein the enantiomerically enriched 1,2-epoxyalkane is *(R)*-1,2-epoxydodecane.

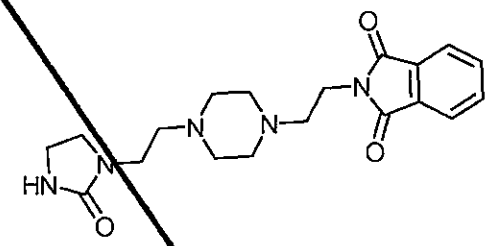
56. The method of claim 52, wherein the enantiomerically enriched β-hydroxyalkyl synthetic equivalent includes a protected α-hydroxyaldehyde.

57. The method of claim 56, wherein the protected α-hydroxyaldehyde includes 2-(O-Pg)-dodecanal, wherein O-Pg represents a protected hydroxyl group.

58. The method of claim 52, further comprising contacting a primary alcohol trapping reagent with a product of a reaction between the enantiomerically enriched β-hydroxyalkyl synthetic equivalent and the compound of formula (VIII).

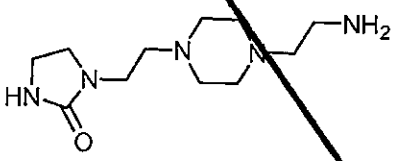
59. A method of making a compound comprising contacting 1-(2-(phthalimido)ethyl)-piperazine with 1-(2-chloroethyl)imidazolidin-2-one.

60. The compound having the formula:



and salts thereof.

61. The compound having the formula:



and salts thereof.

62. A method of making a compound, comprising contacting 1-cyanomethyl-4-(2-((cyanomethyl)amino)ethyl)piperazine with a reducing agent.

63. The method of claim 62, wherein the reducing agent is other than H_2.

64. The method of claim 63, wherein the reducing agent includes $NaBH_4$.

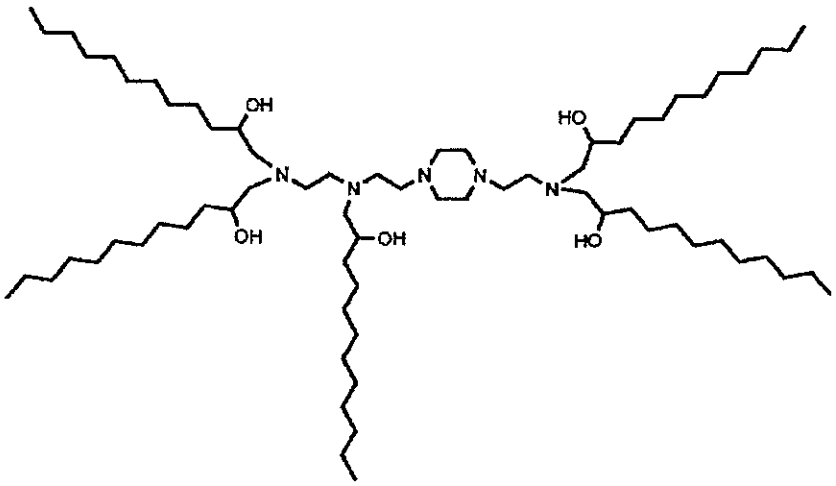
65. The method of claim 62, further comprising simultaneously contacting cyanomethyl-4-(2-((cyanomethyl)amino)ethyl)piperazine with a reducing agent and an amino group protecting reagent.

66. The method of claim 65, wherein the reducing agent includes $NaBH_4$.

67. The method of claim 66, wherein the amino group protecting reagent includes $(Boc)_2O$.

WHAT IS CLAIMED IS:

1. A composition, the composition comprising a sterol; a neutral lipid; a PEG or a PEG-modified lipid; and a lipid formula (V)



2. The composition of claim 1 wherein the compound of formula (V) is an inorganic or organic salt thereof.

3. The composition of claim 2, wherein the salt is a hydrohalide salt.

4. The composition of claim 3, wherein the hydrohalide salt is a hydrochloride salt.

5. The composition of claim 1 wherein the compound of formula (V) is salt of an organic acid.

6. The composition of claim 5, wherein the salt of an organic acid is an acetate or formate.

7. The composition of claim 1 wherein the compound of formula (V) is in the form of a hydrate.

8. The composition of claim 1 wherein the sterol is cholesterol.

9. The composition of claim 1 wherein the lipid is a PEG-modified lipid.

10. The composition of claim 9, wherein the PEG-modified lipid is PEG-DMG.

11. The composition of claim 1 wherein the neutral lipid is DSPC.

12. The composition of claim 1 wherein the composition comprises about 25-75% of the compound of formula (V)or mixture thereof, about 5-50% of the sterol, about 0.5-20% of the PEG or PEG-modified lipid and about 0.1-15% of the neutral lipid.

13. The composition of claim 1 wherein the composition comprises about 35-65% formula (V)or mixture thereof, about 15-45% of the sterol, and about 0.5-10% of the PEG or PEG-modified lipid and about 3-15% of the neutral lipid.

14. The composition of claim 1 wherein the composition comprises about 40-65% of the compound of formula (V)or mixture thereof about 25-40% of the sterol, and about 0.5-5% of the PEG or PEG-modified lipid, and about 5-10% of the neutral lipid.

15. The composition of claim 1 wherein the composition comprises about 50% of the compound of formula (V)or mixture thereof about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid, and about 10% of the neutral lipid.

16. The composition of claim 15, wherein the composition comprises about 50% of the compound of formula (V) or mixture thereof about 38.5% of the sterol, and about 1.5% of the PEG or PEG-modified lipid, and about 10% of the neutral lipid.

17. The lipid formulation of claim 1further comprising a targeting lipid comprising N-acetyl galactosamine as a targeting moiety.

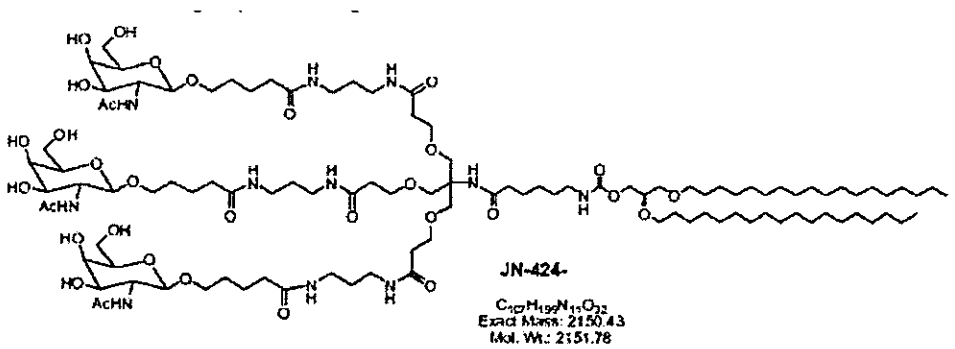
18. The formulation of claim 17, wherein the targeting lipid comprises a plurality of N-acetyl galactosamine moieties.

19. The formulation of claim 17, wherein said targeting lipid is present in the formulation in a molar amount of from about 0.001% to about 5%.

20. The formulation of claim 17, wherein said targeting lipid is present in the formulation in a molar amount of from about 0.005% to about 1.5%.

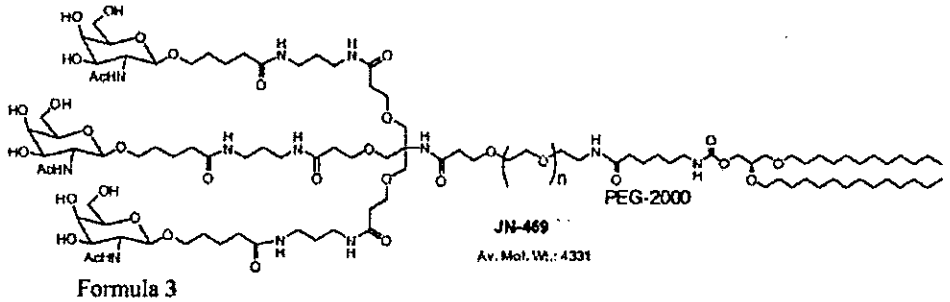
21. The formulation of claim 17, wherein the targeting lipid is present in the formulation in a molar amount of about 0.3%.

22. The lipid formulation of claim 1, further comprising a targeting lipid selected from the group consisting of formula 2, formula 3, formula 6 and formula 7:



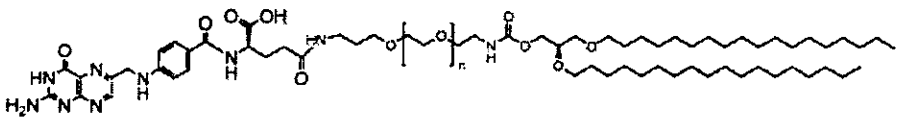
Formula 2

GalNAc3-DSG



Formula 3

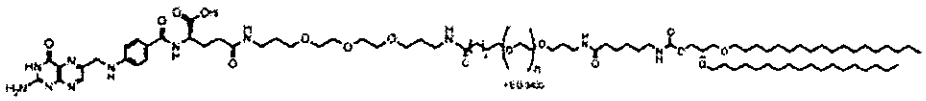
GalNAc3-PEG-DSG



Mol Wt: ~ 3028

Folate-PEG2000-DSG

Formula **6**



MW: ~ 4761

Folate-PEG3400-DSG

Formula 7.

23. The composition of claim 1 wherein the composition is an association complex.

24. The composition of claim 1 wherein the composition is a liposome.

25. The composition of claim 1 further comprising a nucleic acid agent.

26. The composition of claim 25, further comprising one or more nucleic acid agents.

27. The composition of claim 26, further comprising five or more nucleic acid agents.

28. The composition of claim 27, further comprising ten or more nucleic acid agents.

29. The composition of claim 1 further comprising an RNA agent.

30. The composition of claim 1 further comprising single stranded RNA agent.

31. The composition of claim 1 further comprising a double stranded RNA agent.

32. A method of producing the composition of claim 1 the method comprising an extrusion method or an in-line mixing method.

33. The composition of claim 28, wherein the ratio of lipid:nucleic acid is about 3 to about 15.

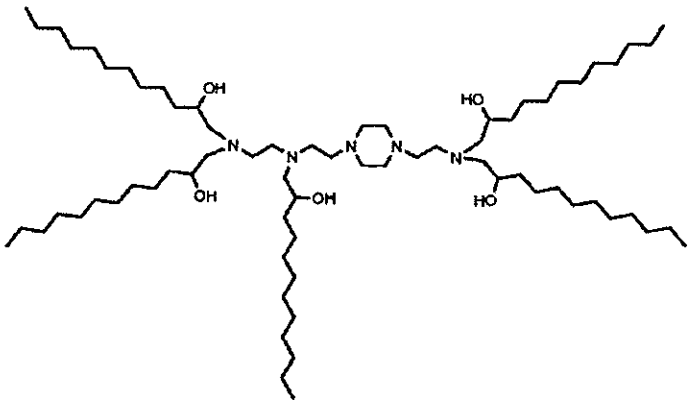
34. The composition of claim 28, wherein the ratio of lipid:nucleic acid about 5 to about 13.

35. The composition of claim 1 further comprising at least one apolipoprotein.

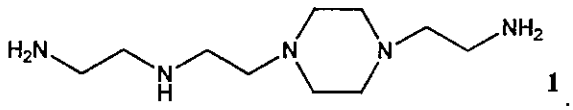
36. The composition of claim 35, wherein the apolipotprotein is selected from the group consisting of ApoA-I, ApoA-II, ApoA-IV, ApoA-V and ApoE, active polymorphic forms, isoforms, variants and mutants, and fragments or truncated forms thereof.

37. The composition of claim 35, wherein the apolipotprotein is ApoE, active polymorphic forms, isoforms, variants and mutants, and fragments or truncated forms thereof.

38. A method of making a compound of formula (V)



the method comprising contacting an enantiomerically enriched β-hydroxyalkyl synthetic equivalent, the β-hydroxyalkyl group being optionally substituted with one or more substituent, with a compound of formula (1)



1

39. The method of claim 38, wherein the enantiomerically enriched β-hydroxyalkyl synthetic equivalent includes an enantiomerically enriched 1,2-epoxyalkane.

40. The method of claim 39, wherein the enantiomerically enriched 1,2-epoxyalkane is (*R*)-1,2-epoxydodecane.

41. The method of claim 38, wherein the enantiomerically enriched β-hydroxy alkyl synthetic equivalent includes a protected α-hydroxy aldehyde.

42. The method of claim 41, wherein the protected α-hydroxyaldehyde includes 2- (O-Pg)-dodecanal, wherein O-Pg represents a protected hydroxyl group.

43. The method of claim 38, further comprising contacting a primary alcohol trapping reagent with a product of a reaction between the enantiomerically enriched β-hydroxyalkyl synthetic equivalent and the compound of formula (1).

44. The composition of any one of claims 1 to 31 or 33 to 37, substantially as herein described.

45. The method of claim 32, substantially as herein described.

46. The method of any one of claims 38 to 43, substantially as herein described.