CLAIMS

1. A double-stranded RNAi agent, wherein the double-stranded RNAi agent comprises an antisense strand and a sense strand complementary to the antisense strand forming a double-stranded region, wherein a nucleotide sequence of the antisense strand is as shown in SEQ ID NO: 8, or a nucleotide sequence of the antisense strand is a modified sequence of a sequence shown in SEQ ID NO: 8;

wherein a nucleotide sequence of the sense strand is as shown in SEQ ID NO: 1, or a nucleotide sequence of the sense strand is a modified sequence of a sequence shown in SEQ ID NO: 1.

2. The double-stranded RNAi agent according to claim 1, wherein the sense strand and the antisense strand comprise at least one modified nucleotide.

3. The double-stranded RNAi agent according to claim 1, wherein the double-stranded RNAi agent has the function of inhibiting HBV gene expression.

4. The double-stranded RNAi agent according to claim 2, wherein at least one of the modified nucleotides is selected from one or more of the group consisting of: deoxy-nucleotide, 3'-terminal deoxy-thymidine nucleotide, 2'-O-methyl-modified nucleotide, 2'-fluoro-modified nucleotide, 2'-deoxy-modified nucleotide, locked nucleotide, unlocked nucleotide, conformationally restricted nucleotide, constrained ethyl nucleotide, abasic nucleotide, 2'-amino-modified nucleotide, 2'-O-allyl-modified nucleotide, 2'-C-alkyl-modified nucleotide, 2'-hydroxy-modified nucleotide, 2'-O-methoxyethyl-modified nucleotide, 2'-O-alkyl-modified nucleotide, morpholino nucleotide, phosphoramidate, nucleotide containing unnatural bases, tetrahydropyran-modified nucleotide, 1,5-anhydrohexitol-modified nucleotide, cyclohexenyl-modified nucleotide, nucleotide containing phosphorothioate groups, nucleotide containing methylphosphonate groups, nucleotide containing 5'-phosphate.

5. The double-stranded RNAi agent according to claim 1, wherein the antisense strand of the double-stranded RNAi agent has a 3' overhang of 2 nucleotides.

6. The double-stranded RNAi agent according to claim 1, wherein the duplex region of the double-stranded RNAi agent is 20 nucleotide pairs in length.

7. The double-stranded RNAi agent according to claim 1, wherein the sense strand of the double-stranded RNAi agent has a length of 20 nucleotides, and the antisense strand has a length of 22 nucleotides.

8. The double-stranded RNAi agent according to claim 1, wherein all modifications on the nucleotides of the sense and antisense strands are chemical modifications at the 2' position of a nucleotide ribose.

9. The double-stranded RNAi agent according to claim 8, wherein the chemical modifications at the 2' position of the nucleotide ribose are selected from one or more of the group consisting of: 2'-methoxy, 2'-O-methoxyethyl, 2'-fluoro, 2'-benzyloxy, 2'-methylcarbonylamino, and 2'-pyridylmethoxy.

10. The double-stranded RNAi agent according to claim 9, wherein the chemical modification at the 2' position of the nucleotide ribose is 2'-methoxy or 2'-fluoro.

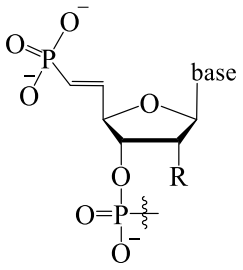
11. The double-stranded RNAi agent according to claim 1, wherein the nucleotides are linked by 3',5'-phosphodiester bonds.

12. The double-stranded RNAi agent according to claim 11, wherein the 3',5'-phosphodiester bond comprises a phosphorothioate modification.

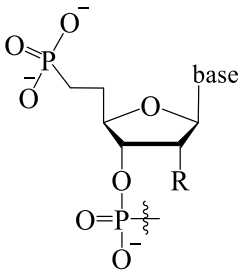
13. The double-stranded RNAi agent according to claim 1, wherein a 5' carbon atom of the 5' terminal nucleotide glycoside of the antisense strand is phosphorylated.

14. The double-stranded RNAi agent according to claim 13, wherein the phosphorylated 5' phosphorylated group includes one or more selected from 5'-vinylphosphonate group, 5'-

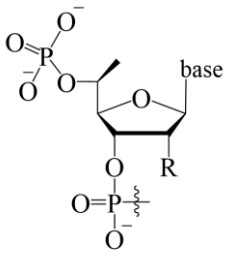
methylphosphonate group, 5'-C-methylphosphate group, 5'-phosphorothioate group, and 5'-phosphate group, with the structure being



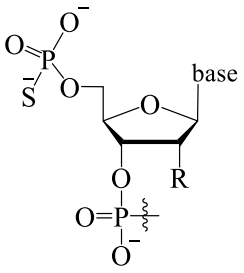
5'-(E)-vinylphosphonate (5'-(E)-VP)



5'-methylphosphonate (5'-MP)

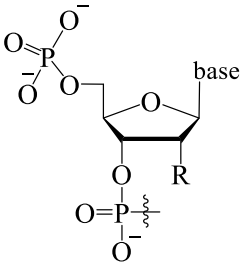


(S)-5'-C-methylphosphate



5'-phosphorothioate (5'-PS)

and



5'-phosphate (5'-P)

;

R is hydrogen, hydroxyl, amino, C_{1-4} alkyl, aryl, C_{1-4} alkoxy, C_{1-4} alkylcarbonylamino, or halogen;

the base is selected from any one of adenine, guanine, cytosine, thymine, and uracil.

15. The double-stranded RNAi agent according to claim 1, wherein terminal nucleotides of the sequence are linked by a 3',5'-phosphodiester bond containing a phosphorothioate modification, forming a chirally pure 3',5'-phosphorothioate bond.

16. The double-stranded RNAi agent according to claim 15, wherein a 5' end of the sense strand and the antisense strand comprises 1 to 3 phosphorothioate linkages, and a 3' end of the antisense strand comprises 1 to 3 phosphorothioate linkages.

17. The double-stranded RNAi agent according to claim 1, wherein the antisense strand adopts one of the modification patterns outlined in the table below:

No.	Antisense strand (AS) 5'-3'																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

A	2'-OMe+PS+EVP	2'-F+PS	2'-OMe	2'-F	2'-F	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe
B	2'-OMe+PS+EVP	2'-F+PS	2'-F	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe
C	2'-OMe+PS+EVP	2'-F+PS	2'-OMe	2'-OMe	2'-F	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe
D	2'-OMe+PS	2'-F+PS	2'-F	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe

	+EVP																					
E	2'-OMe+PS+EVP	2'-F+PS	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe
F	2'-OMe+PS+EVP	2'-F+PS	2'-F	2'-OMe	2'-F	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe+PS	2'-OMe+PS	2'-OMe

and/or, the sense strand adopts one of the modification patterns outlined in the table below:

No.	Sense strand (SS) 5'-3’																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
a	2'-OMe+PS	2'-OMe+PS	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-F	2'-F	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-OMe	2'-F	2'-OMe	2'-OMe	2'-OMe	2'-OMe
b	2'-O	2'-O	2'-O	2'-O	2'-O	2'	2'-O	2'	2'-O	2'	2'-O	2'-O	2'-O	2'-O	2'-O	2'	2'-O	2'-O	2'-O	2'-O

	Me+PS	Me+PS	Me	Me	Me	-F	Me	-F	Me	-F	Me	Me	Me	Me	Me	-F	Me	Me	Me	Me

wherein 2'-OMe is 2'-methoxy; 2'-F is 2'-fluoro; PS is phosphorothioate backbone; EVP is 5'-(E)-vinylphosphonate.

18. The double-stranded RNAi agent according to claim 17, wherein the modification patterns of the double-stranded RNAi agent are as follows:

the antisense strand is modified by pattern A and the sense strand modified by pattern a;

the antisense strand is modified by pattern A and the sense strand modified by pattern b;

the antisense strand is modified by pattern B and the sense strand modified by pattern a;

the antisense strand is modified by pattern B and the sense strand modified by pattern b;

the antisense strand is modified by pattern C and the sense strand modified by pattern b;

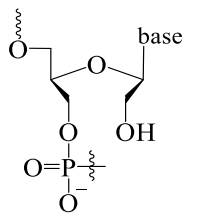
the antisense strand is modified by pattern D and the sense strand modified by pattern b;

the antisense strand is modified by pattern E and the sense strand modified by pattern a;

or

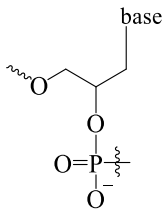
the antisense strand is modified by pattern F and the sense strand modified by pattern b.

19. The double-stranded RNAi agent according to claim 1, wherein the antisense strand is modified with modifying groups from the second to the eighth positions starting from the 5' end, where the modifying groups are selected from one or more of UNA, GNA, and DNA, and the structures of UNA and GNA are



Unlocked nucleic acid (UNA)

and



Glycol nucleic acid (GNA)

;

the base is selected from any one of adenine, guanine, cytosine, thymine, and uracil.

20. The double-stranded RNAi agent according to any one of claims 1 to 19, wherein the

double-stranded RNAi agent comprises an oligonucleotide duplex selected from any one of the following sense and antisense strand pairs:

(1) the sense strand has the sequence as shown in SEQ ID NO: 81, and the antisense strand has the sequence as shown in SEQ ID NO: 179, 180, 181, 182, or 184;

(2) the sense strand has the sequence as shown in SEQ ID NO: 82, and the antisense strand has the sequence as shown in SEQ ID NO: 179, 180, or 183;

(3) the sense strand has the sequence as shown in SEQ ID NO: 83, and the antisense strand has the sequence as shown in SEQ ID NO: 185 or 186;

(4) the sense strand has the sequence as shown in SEQ ID NO: 84, and the antisense strand has the sequence as shown in SEQ ID NO: 186; and

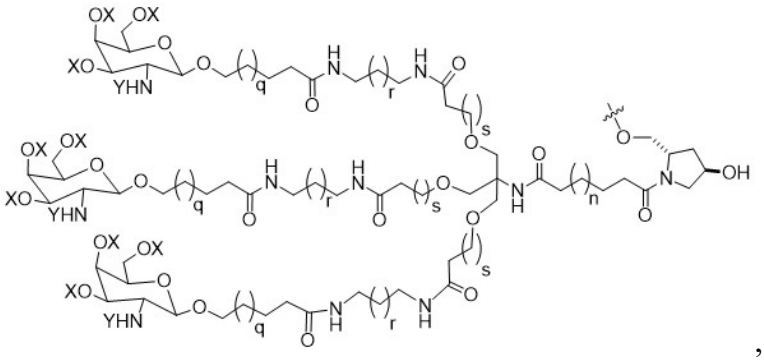
(5) the sense strand has the sequence as shown in SEQ ID NO: 85, and the antisense strand has the sequence as shown in SEQ ID NO: 186.

21. A conjugate, wherein the conjugate comprises the double-stranded RNAi agent according to any one of claims 1 to 20 and a ligand conjugated to the double-stranded RNAi agent.

22. The conjugate according to claim 21, wherein the ligand is conjugated to a 3'-end or a 5'-end of an oligonucleotide sense strand.

23. The conjugate according to claim 21, wherein the ligand is one or more GalNAc derivatives attached via a bivalent or trivalent branched linker, or a GalNAc derivative attached via a monovalent linker.

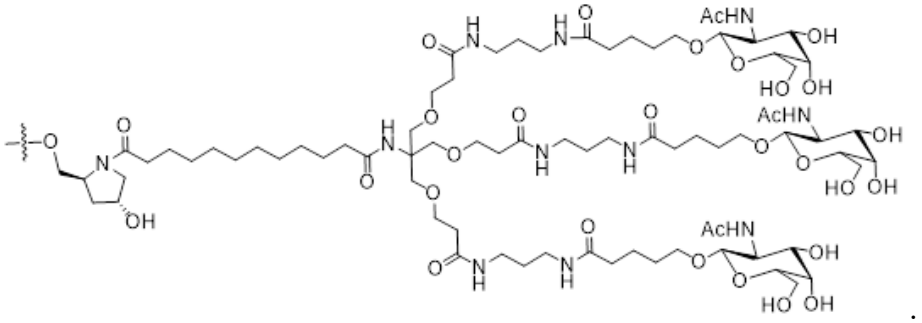
24. The conjugate according to claim 21, wherein the ligand is:



,

wherein X is hydrogen, a hydroxyl protecting group, or H, and the hydroxyl protecting group includes acetyl, benzoyl, or isobutyryl; Y is an amine protecting group or H, and the amine protecting group is formyl, acetyl, propionyl, n-butyryl, or isobutyryl; n is an integer between 0 and 20; q, r, and s are independently integers between 1 and 7.

25. The conjugate according to claim 24, wherein the ligand is:



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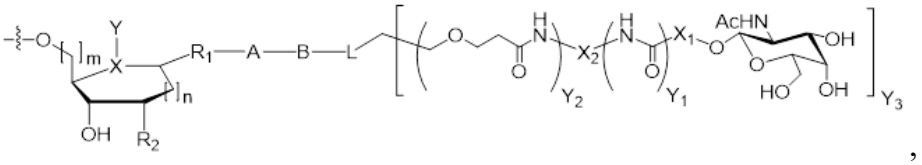
26. The conjugate according to claim 21, wherein the ligand is:



,

wherein X is oxygen, nitrogen, or sulfur;

Y is an alkyl or aromatic group;

R_1 is oxygen or sulfur;

R_2 is hydrogen, an amino group, a C_{1-4} alkyl group, an aromatic group, a C_{1-4} alkoxy group, or a halogen;

A is $-(CH_2)_a-$, $-(CH_2CH_2O)_b-$, $-((CH_2)_cNHCO)_d-$, or $-((CH_2)_cCONH)_d-$, where a is an integer from 1 to 15, b is an integer from 1 to 7, c is an integer from 1 to 7, and d is an integer from 1 to 5;

B is $-(CH_2)_e-$, where e is an integer from 0 to 7;

L is -CONH- or -NHCO-;

X_1 is $-(CH_2)_f-$ or $-(CH_2CH_2O)_fCH_2-$, where f is an integer from 1 to 5;

X_2 is $-(CH_2)_g-$, where g is an integer from 1 to 6;

Y_1 is 0 or 1;

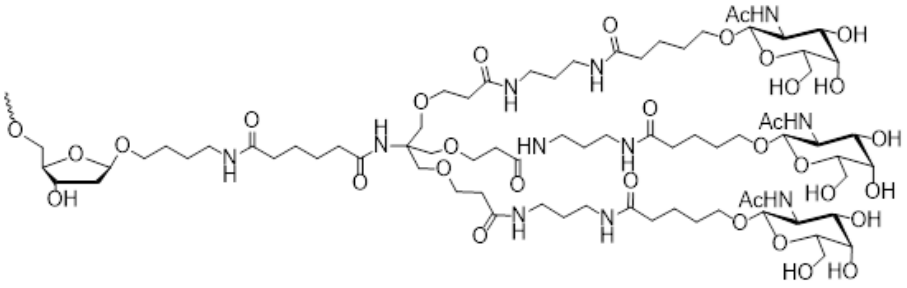
Y_2 is 0, 1, or 2;

Y_3 is 1, 2, or 3;

m is an integer from 0 to 4;

n is an integer from 0 to 4.

27. The conjugate according to claim 26, wherein the ligand is G4, G5, G6, or G7:



G4

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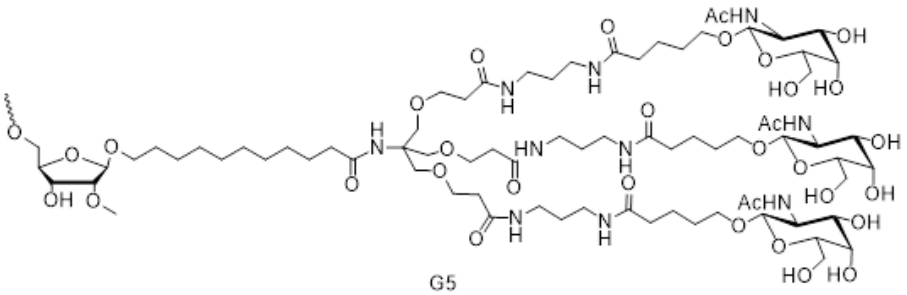

G5

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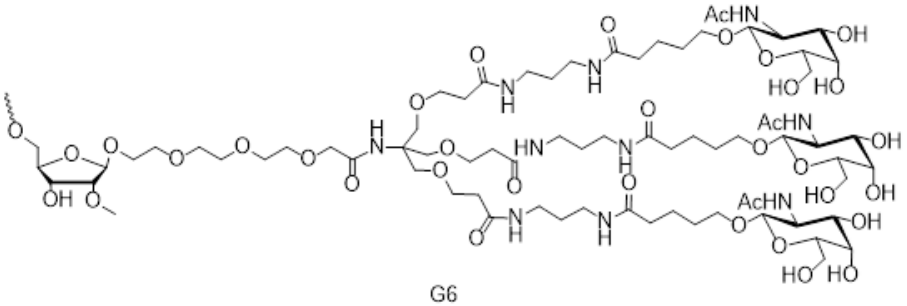
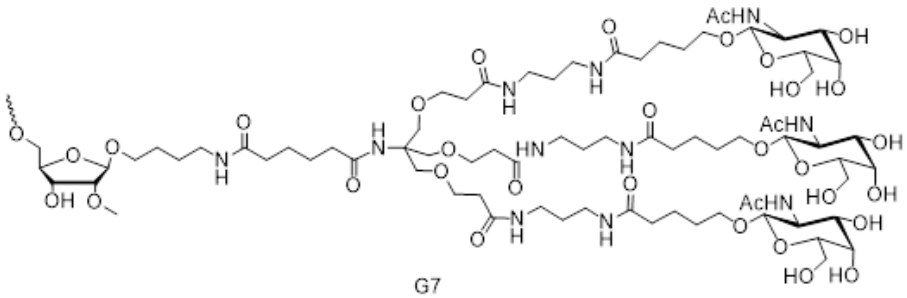


G6

, or



G7

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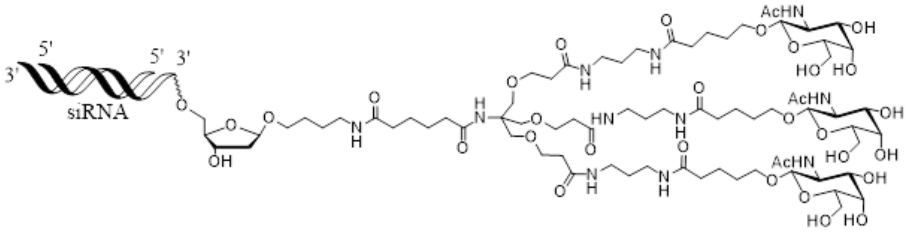
28. The conjugate according to claim 27, wherein the conjugate is represented by the following structures:



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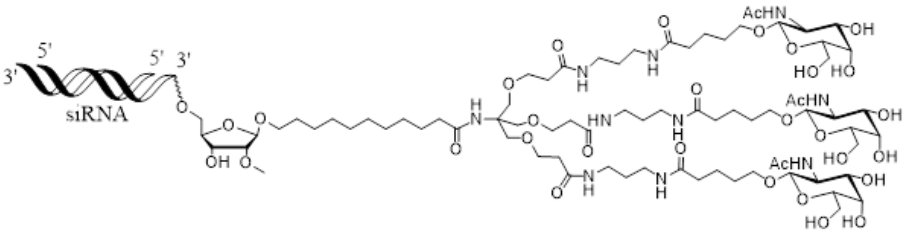

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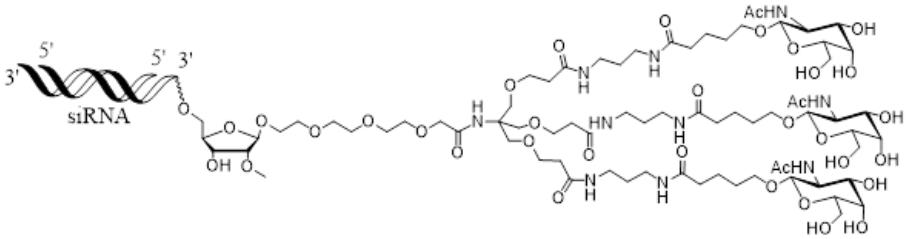

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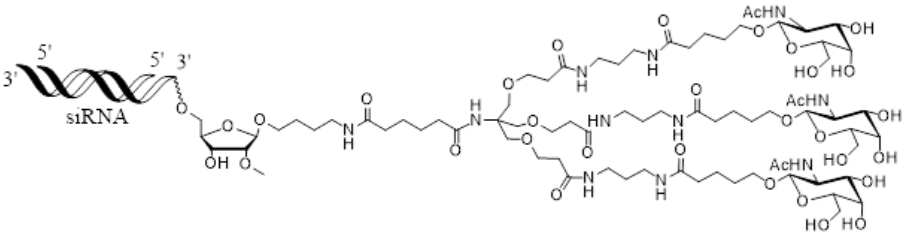
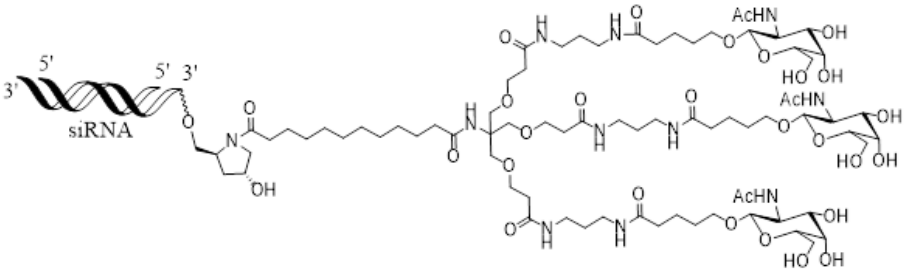


, or



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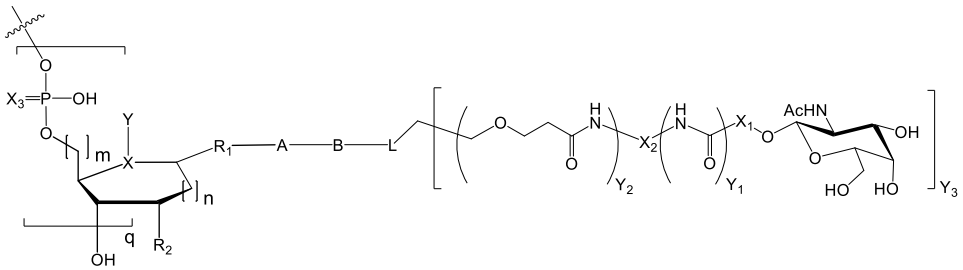
29. The conjugate according to claim 21, wherein the ligand is:



wherein X is oxygen, nitrogen, or sulfur;

Y is an alkyl or aromatic group;

R_1 is oxygen or sulfur;

R_2 is hydrogen, an amino group, a C_{1-4} alkyl group, an aromatic group, a C_{1-4} alkoxy group, or a halogen;

A is $-(CH_2)_a-$, $-(CH_2CH_2O)_b-$, $-((CH_2)_cNHCO)_d-$, or $-((CH_2)_cCONH)_d-$, where a is an integer from 1 to 15, b is an integer from 1 to 7, c is an integer from 1 to 7, and d is an integer from 1 to 5;

B is $-(CH_2)_e-$, where e is an integer from 0 to 7;

L is -CONH- or -NHCO-;

X_1 is $-(CH_2)_f-$ or $-(CH_2CH_2O)_fCH_2-$, where f is an integer from 1 to 5;

X_2 is $-(CH_2)_g-$, where g is an integer from 1 to 6;

Y_1 is 0 or 1;

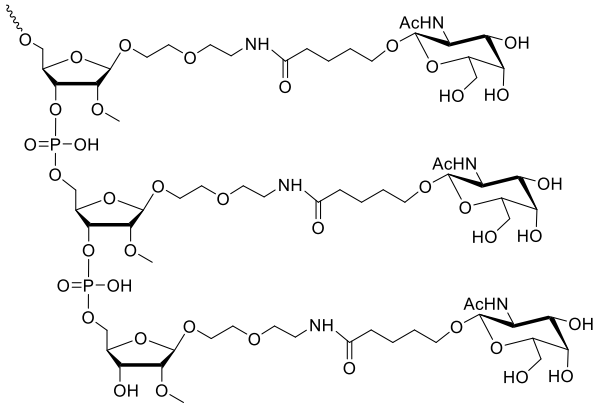
Y_2 is 0, 1, or 2;

Y_3 is 1, 2, or 3;

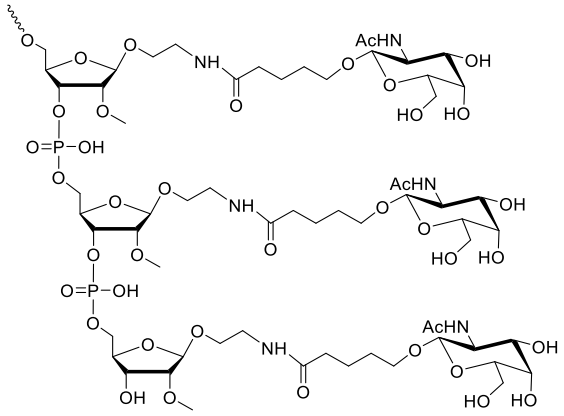
m is an integer from 0 to 4;

n is an integer from 0 to 4.

30. The conjugate according to claim 29, wherein the ligand is G101, G102, G103, G105, or G106:



G101 ,



G102

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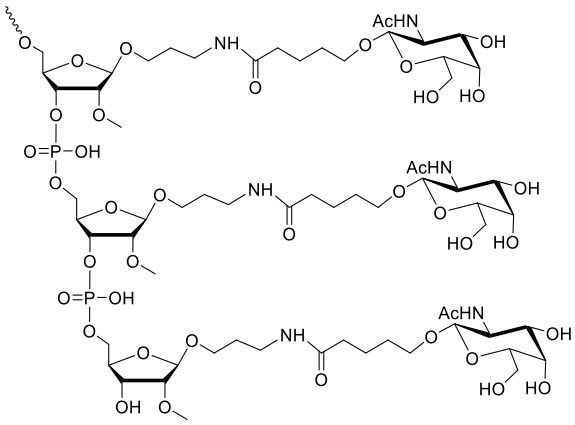

G103

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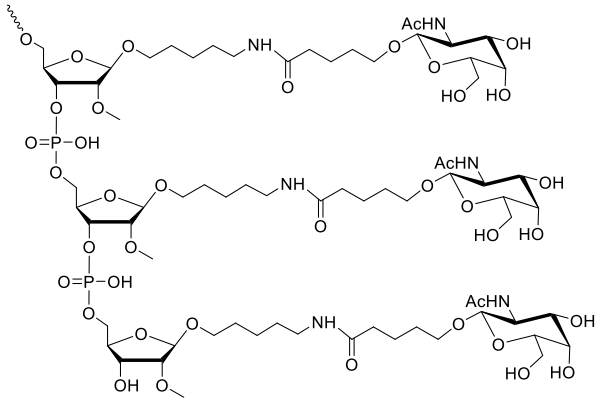
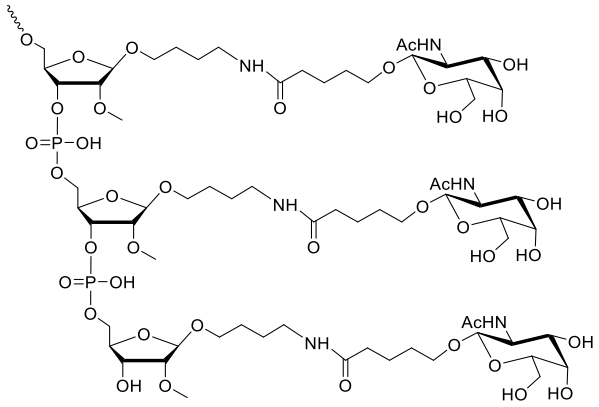


G105

, or



G106

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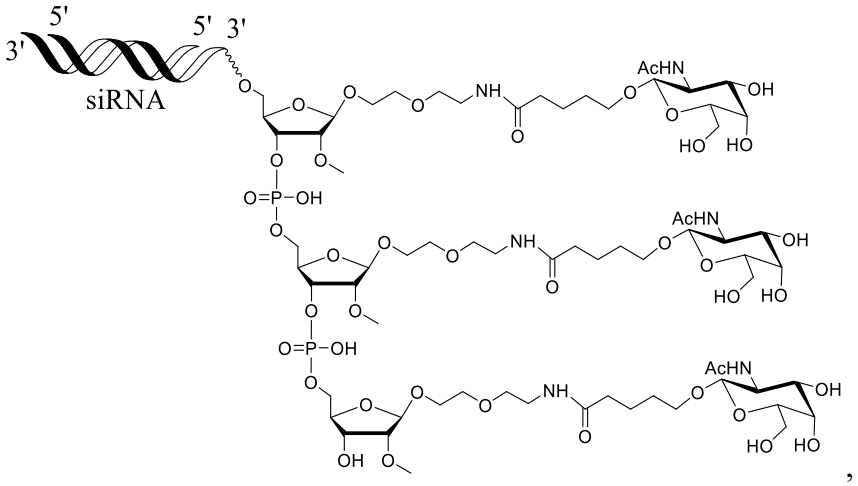
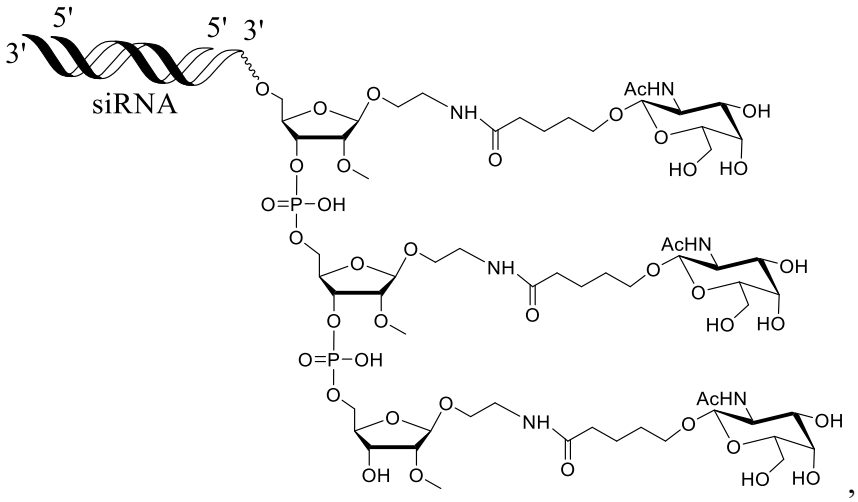
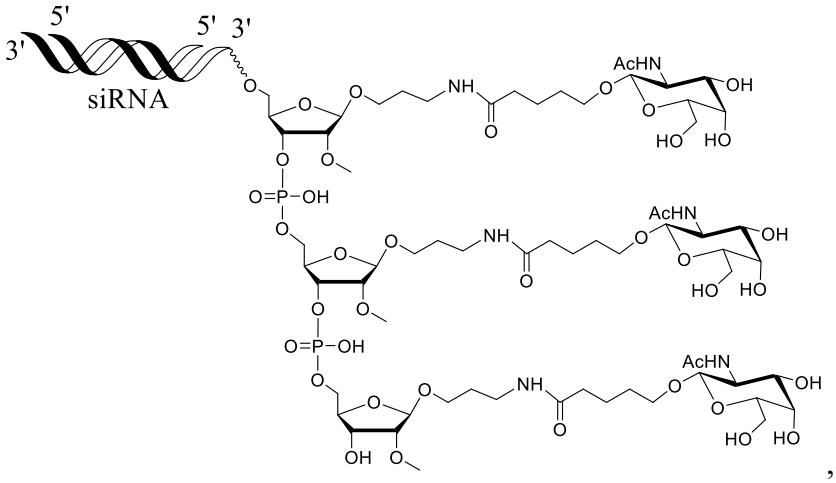
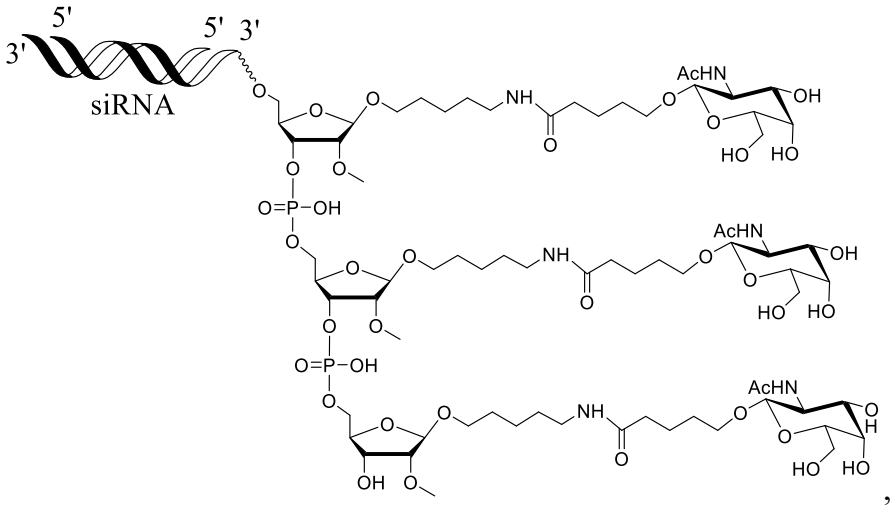
31. The conjugate according to claim 30, wherein the conjugate is represented by the following structures:


5'
3'
5'
3'
siRNA
AcHN
OH
HO
HO
NH
O
O=P–OH
,


5'
3'
5'
3'
siRNA
AcHN
OH
HO
HO
NH
O
O=P–OH
,


5'
3'
5'
3'
siRNA
AcHN
OH
HO
HO
NH
O
O=P–OH
,



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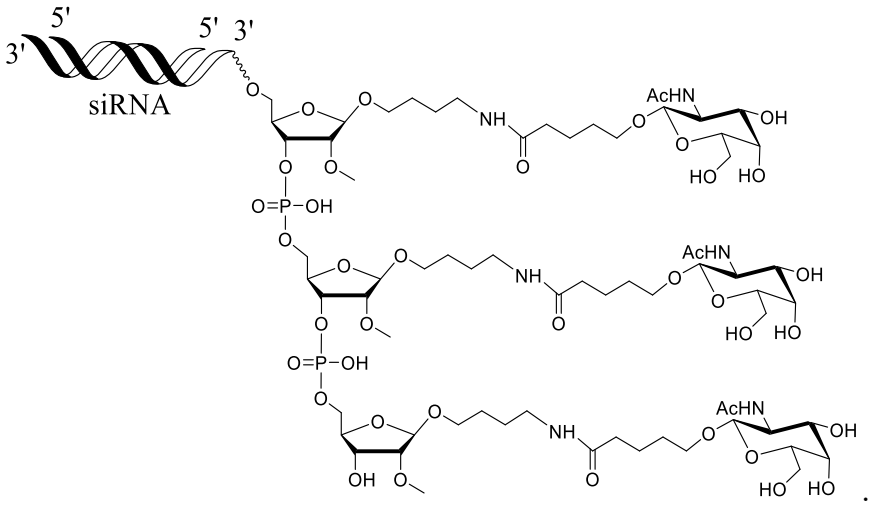

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32. The conjugate according to claim 21, wherein the conjugate comprises an oligonucleotide duplex selected from any one of the following sense and antisense strand pairs:

(1) the sense strand has the sequence as shown in SEQ ID NO: 326, 327 or 328, and the antisense strand has the sequence as shown in SEQ ID NO: 179;

(2) the sense strand has the sequence as shown in SEQ ID NO: 329, 330 or 331, and the antisense strand has the sequence as shown in SEQ ID NO: 181.

33. The conjugate according to any one of claims 21 to 32, wherein the conjugate has the function of inhibiting HBV gene expression.

34. A pharmaceutical composition comprising the double-stranded RNAi agent according to any one of claims 1 to 20 or the conjugate according to any one of claims 21 to 33, along

with a pharmaceutically acceptable carrier.

35. The pharmaceutical composition according to claim 34, wherein the double-stranded RNAi agent or the conjugate is administered in a non-buffered solution.

36. The pharmaceutical composition according to claim 35, wherein the non-buffered solution is saline or water.

37. The pharmaceutical composition according to claim 34, wherein the double-stranded RNAi agent or the conjugate is administered with a buffered solution.

38. The pharmaceutical composition according to claim 37, wherein the buffered solution comprises acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof.

39. The pharmaceutical composition according to claim 38, wherein the buffered solution is phosphate-buffered solution.

40. The pharmaceutical composition according to claim 37, wherein the double-stranded RNAi agent or the conjugate is formulated into a lipid formulation for delivery within membranous molecular assemblies.

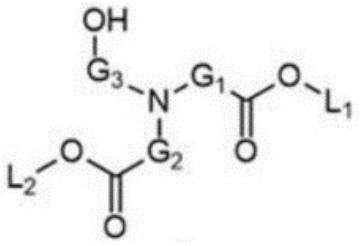
41. The pharmaceutical composition according to claim 40, wherein the lipid formulation is a nucleic acid-lipid particle.

42. The pharmaceutical composition according to claim 41, wherein the lipid formulation is a lipid nanoparticle.

43. The pharmaceutical composition according to claim 40, wherein a mass-to-mass ratio of lipid to the double-stranded RNAi agent or the conjugate is 1:1 to 50:1, 1:1 to 25:1, 3:1 to 15:1, 4:1 to 10:1, 5:1 to 9:1, or 6:1 to 9:1.

44. The pharmaceutical composition according to claim 42, wherein the lipid nanoparticle comprises a cationic lipid, a neutral lipid, a structural lipid, and a polymer-conjugated lipid.

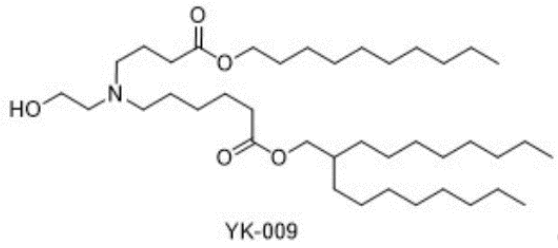
45. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (I), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,



(I),

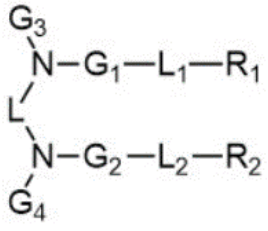
wherein G_1 is a $C_{1–6}$ alkylene group; G_2 is a $C_{2–8}$ alkylene group; G_3 is a $C_{1–3}$ alkylene group; L_1 is a $C_{6–15}$ linear alkyl group; L_2 is a $C_{12–25}$ branched alkyl group.

46. The pharmaceutical composition according to claim 45, wherein the cationic lipid is YK-009 of formula (I-I):



(I-I).

47. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (II), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,

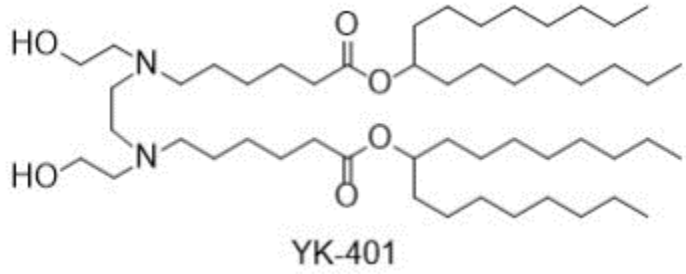


(II),

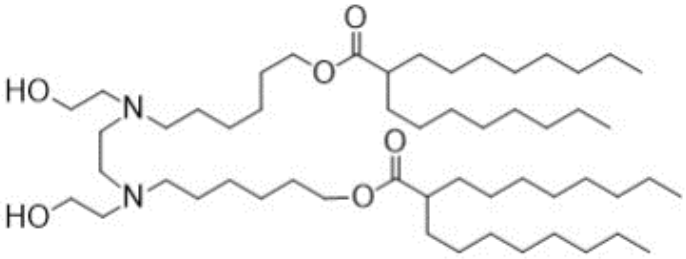
wherein G_1 is a $C_{2–8}$ alkylene group; G_2 is a $C_{2–8}$ alkylene group; L_1 is -C(O)O- or -OC(O)-; L_2 is -C(O)O- or -OC(O)-; R_1 is a $C_{6–25}$ linear or branched alkyl group; R_2 is a $C_{6–25}$ linear or

branched alkyl group; G_3 is $HO(CH_2)_2$- or $HO(CH_2)_3$-; G_4 is $HO(CH_2)_2$- or $HO(CH_2)_3$-; L is -$(CH_2)_2$-, -$(CH_2)_3$-, or -$(CH_2)_4$-.

48. The pharmaceutical composition according to claim 47, wherein the cationic lipid is YK-401 of formula (II-I) or YK-402 of formula (II-II):

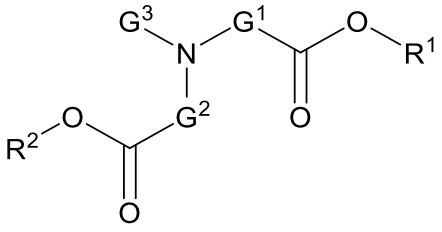


YK-401 (II-I),



YK-402 (II-II).

49. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (III), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,

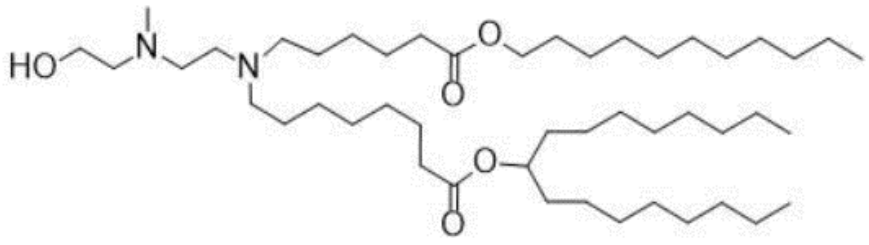


(III),

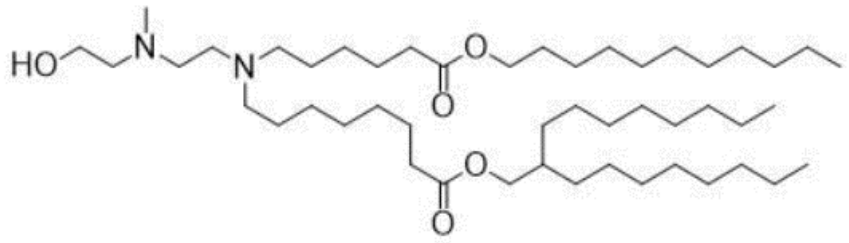
wherein G_1 is a $C_{1–6}$ alkylene group; G_2 is a $C_{2–8}$ alkylene group; R_1 is a $C_{6–20}$ linear or branched alkyl group; R_2 is a $C_{12–25}$ branched alkyl group; G_3 is $HO(CH_2)_2N(CH_3)(CH_2)_2$-, $HO(CH_2)_2N(CH_2CH_3)(CH_2)_2$-, $(HO(CH_2)_2)_2N(CH_2)_2$-, $CH_3O(CH_2)_2N(CH_3)(CH_2)_2$-, $(CH_3)_2N(CH_2)_3SC(O)O(CH_2)_2$-, $(CH_3)_2N(CH_2)_3SC(O)$-,$CH_3NH(CH_2)_2N(CH_3)(CH_2)_2$-, or $CH_3CH_2NH(CH_2)_2$-.

50. The pharmaceutical composition according to claim 49, wherein the cationic lipid is

YK-201 of formula (III-I) or YK-202 of formula (III-II):

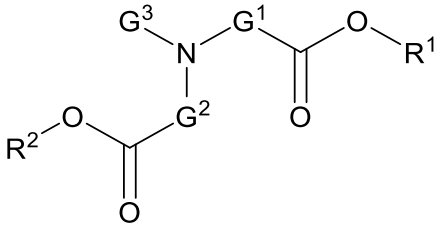


YK-201 (III-I),



YK-202 (III-II).

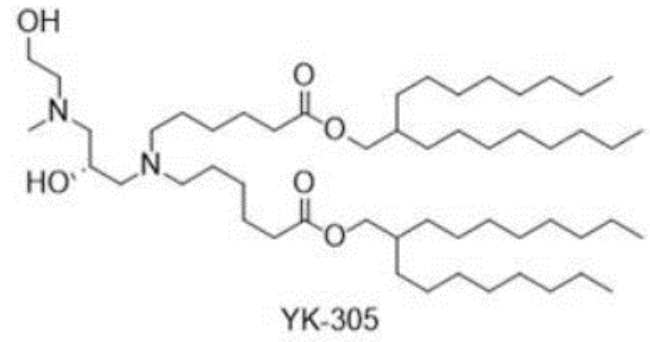
51. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (IV), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,



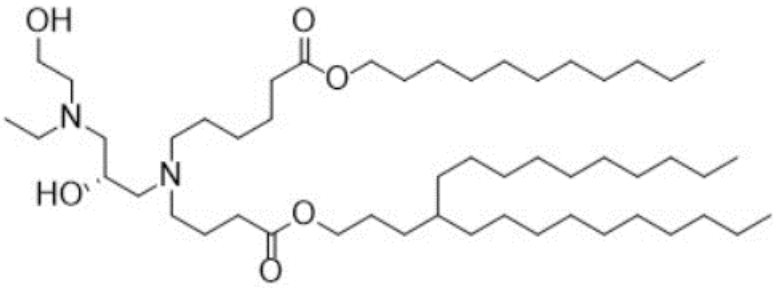
(IV),

wherein G_1 is a $C_{1–8}$ alkylene group; G_2 is a $C_{2–8}$ alkylene group; R_1 is a $C_{6–25}$ linear or branched alkyl group; R_2 is a $C_{12–25}$ linear or branched alkyl group; G_3 is $HO(CH_2)_2N(R_3)CH_2CH(OH)CH_2$-, where R_3 is $-CH_3$, $-CH_2CH_3$, or $-CH_2CH_2OH$.

52. The pharmaceutical composition according to claim 51, wherein the cationic lipid is YK-305 of formula (IV-I) or YK-310 of formula (IV-II):

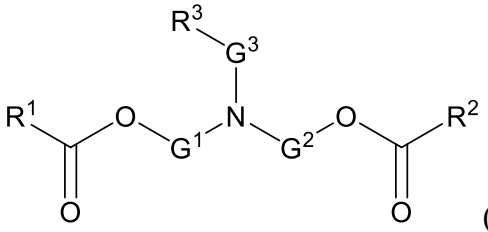


YK-305 (IV-I),



YK-310 (IV-II).

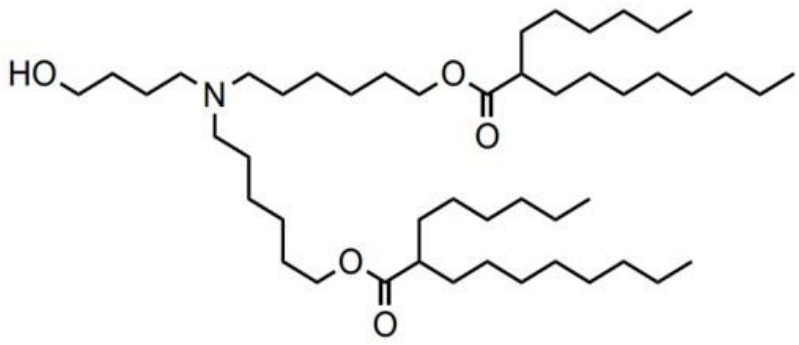
53. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (V), or a N-oxide,pharmaceutically acceptable salt, or stereoisomer thereof,



(V),

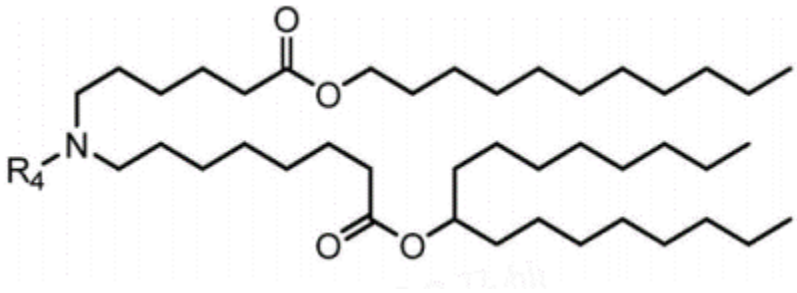
G^1 and G^2 are each independently an unsubstituted C_6–C_{10} alkylene group; G^3 is an unsubstituted C_1–C_{12} alkylene group; R^1 and R^2 are each independently a C_6–C_{24} alkyl group or a C_6–C_{24} alkenyl group; R^3 is OR^5, N, $-C(=O)OR^4$, $-OC(=O)R^4$, or $-NR^5C(=O)R^4$; R^4 is a C_1–C_{12} hydrocarbon group; and R^5 is H or a C_1–C_6 hydrocarbon group.

54. The pharmaceutical composition according to claim 53, wherein the cationic lipid is ALC0315 of formula (V-I):



(V-I).

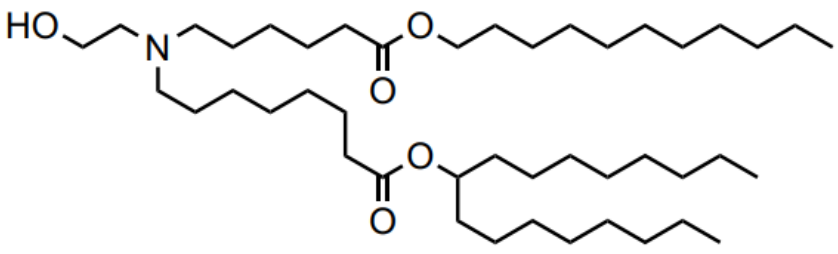
55. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound of formula (VI), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,



(VI),

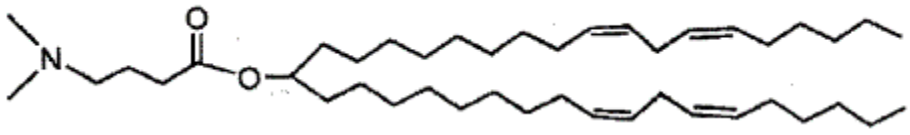
R4 is selected from -$(CH_2)_nQ$ and -$(CH_2)_nCHQR$; Q is selected from the group consisting of -OR, -OH, -$O(CH_2)_nN(R)_2$, -OC(O)R, -CX_3, -CN, -N(R)C(O)R, -N(H)C(O)R, -$N(R)S(O)_2R$, -$N(H)S(O)_2R$, -$N(R)C(O)N(R)_2$, -$N(H)C(O)N(R)_2$, -N(H)C(O)N(H)(R), -$N(R)C(S)N(R)_2$, -$N(H)C(S)N(R)_2$, -N(H)C(S)N(H)(R), -$N(R)S(O)_2R_8$, and a heterocyclic group; n is 1, 2, or 3.

56. The pharmaceutical composition according to claim 55, wherein the cationic lipid is SM102 of formula (VI-I):



(VI-I).

57. The pharmaceutical composition according to claim 44, wherein the cationic lipid is a compound DLIN-MC3-DMA of formula (VII), or a N-oxide, pharmaceutically acceptable salt, or stereoisomer thereof,



(VII).

58. The pharmaceutical composition according to claim 44, wherein the cationic lipid comprises one or more selected from YK-009, YK-401, YK-305, ALC-0315, SM-102, and DLin-MC3-DMA.

59. The pharmaceutical composition according to claim 44, wherein the cationic lipid and the neutral lipid are present in a molar ratio of 1:1 to 10:1.

60. The pharmaceutical composition according to claim 44, wherein the cationic lipid and the structural lipid are present in a molar ratio of 1:1 to 5:1.

61. The pharmaceutical composition according to claim 44, wherein the cationic lipid, the neutral lipid, the structural lipid, and the polymer-conjugated lipid are present in a molar ratio of (25–65):(5–25):(25–70):(0.5–5).

62. The pharmaceutical composition according to claim 61, wherein the cationic lipid, the neutral lipid, the structural lipid, and the polymer-conjugated lipid are present in a molar ratio of (25–65):(5–25):(25–45):(0.5–5).

63. The pharmaceutical composition according to claim 62, wherein the cationic lipid, the neutral lipid, the structural lipid, and the polymer-conjugated lipid are present in a molar ratio of 50:10:38.5:1.5 or 49:10:39.5:1.5.

64. The pharmaceutical composition according to claim 44, wherein the neutral lipid comprises one or more selected from phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, ceramide, and sterols.

65. The pharmaceutical composition according to claim 64, wherein the neutral lipid is

selected from one or more of the following: 1,2-dilinoleoyl-sn-glycero-3-phosphocholine, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-diundecanoyl-sn-glycero-3-phosphocholine, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 1,2-di-O-octadecenyl-sn-glycero-3-phosphocholine, 1-oleoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine, 1-hexadecyl-sn-glycero-3-phosphocholine, 1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine, 1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine, 1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine, 1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine, 1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt, dipalmitoylphosphatidylglycerol, palmitoyloleoylphosphatidylethanolamine, distearoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine, dimyristoylphosphatidylethanolamine, 1-stearoyl-2-oleoyl-stearoylethanolamine, 1-stearoyl-2-oleoyl-phosphatidylcholine, sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyloleoylphosphatidylcholine, lysophosphatidylcholine, lysophosphatidylethanolamine, and mixtures thereof.

66. The pharmaceutical composition according to claim 65, wherein the neutral lipid is 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine and/or 1,2-distearoyl-sn-glycero-3-phosphocholine.

67. The pharmaceutical composition according to claim 44, wherein the structural lipid is selected from one or more of the following: cholesterol, non-sterols, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, ursolic acid, α-tocopherol, and corticosteroids.

68. The pharmaceutical composition according to claim 67, wherein the structural lipid is

cholesterol.

69. The pharmaceutical composition according to claim 44, wherein the polymer-conjugated lipid is selected from one or more of the following: PEG-modified phosphatidylethanolamine, PEG-modified phosphatidic acid, PEG-modified ceramide, PEG-modified dialkylamine, PEG-modified diacylglycerol, and PEG-modified dialkylglycerol.

70. The pharmaceutical composition according to claim 69, wherein the polymer-conjugated lipid is selected from one or more of the following: distearoylphosphatidylethanolamine-polyethylene glycol 2000, dimyristoylglycerol-methoxypolyethylene glycol 2000, and methoxypolyethylene glycol bis(tetradecyl)acetamide.

71. A kit comprising a kit A, wherein the kit A comprises one or more of the double-stranded RNAi agent according to any one of claims 1 to 20, the conjugate according to any one of claims 21 to 33, or the pharmaceutical composition according to any one of claims 34 to 70.

72. The kit according to claim 71, wherein the kit further comprises a kit B, and the kit B comprises one or both of the following:

(1) an additional drug that reduces HBV gene expression or a composition comprising the drug that reduces HBV gene expression;

(2) one or more agents selected from the group consisting of diagnostic agents, oncolytic drugs, inhibitors of inhibitory molecules, and vaccines;

(3) one or both of chemotherapeutic agents and cytotoxic agents.

73. The kit according to claim 71, wherein the kit further comprises a kit B, and the kit B comprises one or both of the following:

one or more agents selected from the group consisting of imaging agents, hormone preparations, targeted small molecule agents, proteasome inhibitors, cytokines, and activators of co-stimulatory molecules.

74. Use of the double-stranded RNAi agent according to any one of claims 1 to 20, the conjugate according to any one of claims 21 to 33, or the pharmaceutical composition according to any one of claims 34 to 70 in the preparation of a medicament for preventing and/or treating chronic hepatitis B, liver fibrosis, liver cirrhosis, liver cancer, acute hepatitis B, and HBV/hepatitis D virus co-infection-associated diseases.