CLAIMS

1. An RNAi agent for inhibiting expression of a target gene, wherein the RNAi agent is a double-stranded ribonucleic acid (dsRNA) agent comprising a sense strand and an antisense strand complementary to at least a portion of an mRNA corresponding to the target gene, and the antisense strand has 18-30 nucleotides and comprises a sequence represented by formula (X) in the direction of 3'-5':

3'-$(N_X)_n$ N_X N_X N_X N_X N_F N_X N_X N_X N_X N_X N_X N_X $N_X$$N_X$ N_X N_F N_X-5' formula (X)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

each N_X independently represents a modified or an unmodified nucleotide, wherein no more than three N_X are 2'-fluoro modified nucleotides, or only one N_X is a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7.

2. The dsRNA agent according to claim 1, wherein the antisense strand comprises a sequence represented by formula (I) in the direction of 3'-5':

3'-$(N_X)_n$ N_X N_X N_X N_X N_F N_X N_X N_X N_X N_X N_X N_X $N_X$$N_X$ N_X N_F N_X-5' formula (I)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

each N_X independently represents a modified or an unmodified nucleotide, wherein only three N_X are 2'-fluoro modified nucleotides, or only one N_X is a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7.

3. The dsRNA agent according to claim 1 or 2, wherein the antisense strand comprises:

i) a sequence represented by formula (I-1) in the direction of 3' to 5':

$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_L\ N_{M4}\ N_L\ N_{M5}\ N_{M6}\ N_L\ N_{M7}\ N_{M8}\ N_L\ N_F\ N_L\text{-}5'$ formula (I-1)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, and N_{M8} independently represent a modified or an unmodified nucleotide, wherein only three of N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, and N_{M8} are 2'-fluoro modified nucleotides, or only one of N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, and N_{M8} is a 2'-fluoro modified nucleotide;

each N_L independently represents a modified or an unmodified nucleotide, wherein the modified nucleotide is not a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7;

ii) a sequence represented by formula (II) in the direction of 3'-5':

$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_L\ N_{M4}\ N_L\ N_{M5}\ N_F\ N_L\ N_{M7}\ N_{M8}\ N_L\ N_F\ N_L\text{-}5'$ formula (II)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M7}, and N_{M8} independently represent a modified or an unmodified nucleotide, wherein only two of N_{M1}, N_{M2}, N_{M3}, and N_{M4} are 2'-fluoro modified nucleotides, and N_{M5}, N_{M7} and N_{M8} are not 2'-fluoro modified nucleotides;

each N_L independently represents a modified or an unmodified nucleotide, wherein the modified nucleotide is not a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7;

iii) a sequence represented by formula (III) in the direction of 3'-5':

$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_F\ N_L\ N_{M4}\ N_L\ N_{M5}\ N_{M6}\ N_L\ N_{M7}\ N_{M8}\ N_L\ N_F\ N_L\text{-}5'$ formula (III)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

N_{M1}, N_{M2}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, and N_{M8} independently represent a modified or an unmodified nucleotide, wherein only two of N_{M1}, N_{M2}, N_{M6}, and N_{M7} are 2'-fluoro modified nucleotides, and N_{M4}, N_{M5} and N_{M8} are not 2'-fluoro modified nucleotides;

each N_L independently represents a modified or an unmodified nucleotide, wherein the modified nucleotide is not a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7; or

iv) a sequence represented by the formula (I-2) in the direction of 3' to 5':

$$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M9}\ N_{M4}\ N_{M10}\ N_{M5}\ N_{M6}\ N_L\ N_{M7}\ N_{M8}\ N_L\ N_F\ N_L\text{-}5'$$

formula (I-2)

wherein, each N_F represents a 2'-fluoro modified nucleotide;

N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, N_{M8}, N_{M9} and N_{M10} independently represent a modified or an unmodified nucleotide, wherein only three of N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, N_{M8}, N_{M9} and N_{M10} are 2'-fluoro modified nucleotides;

each N_L independently represents a modified or an unmodified nucleotide, wherein the modified nucleotide is not a 2'-fluoro modified nucleotide; and

n is an integer from 0 to 7.

4. The dsRNA agent according to claim 3, wherein in the antisense strand represented by formula (I-1), only three of N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M6}, N_{M7}, and N_{M8} are 2'-fluoro modified nucleotides, and N_{M5} is not a 2'-F modified nucleotide.

5. The dsRNA agent according to claim 3 or 4, wherein the antisense strand comprises the sequence represented by formula (I-1) and has:

(1) 2’-fluoro modified nucleotides at positions 2, 7, 12, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(2) 2’-fluoro modified nucleotides at positions 2, 7, 12, 14, and 18 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(3) 2’-fluoro modified nucleotides at positions 2, 5, 12, 14, and 18 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(4) 2’-fluoro modified nucleotides at positions 2, 4, 10, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(5) 2’-fluoro modified nucleotides at positions 2, 7, 10, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(6) 2’-fluoro modified nucleotides at positions 2, 5, 12, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end; or

(7) 2’-fluoro modified nucleotides at positions 2, 5, 10, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end.

6. The dsRNA agent according to claim 3, wherein in the antisense strand represented by formula (I-1), only one of N_{M1}, N_{M2}, N_{M3}, N_{M5}, N_{M6}, and N_{M8} is a 2’-fluoro modified nucleotide, and N_{M4} and N_{M7} are not 2’-F modified nucleotides.

7. The dsRNA agent according to claim 6, wherein the antisense strand comprises the sequence represented by formula (I-1) and has::

(1) 2’-fluoro modified nucleotides at positions 2, 4, and 14 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(2) 2’-fluoro modified nucleotides at positions 2, 8, and 14 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(3) 2’-fluoro modified nucleotides at positions 2, 12 and 14 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(4) 2’-fluoro modified nucleotides at positions 2, 14, and 16 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end;

(5) 2’-fluoro modified nucleotides at positions 2, 14, and 18 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end; or

(6) 2’-fluoro modified nucleotides at positions 2, 6, and 14 of the antisense strand represented by formula (I-1) counting from the first paired nucleotide at 5’ end.

8. The dsRNA agent according to claim 3, wherein the antisense strand comprises the sequence represented by formula (I-2) and has:

(1) 2’-fluoro modified nucleotides at positions 2, 7, 11, 14, and 16 of the antisense strand represented by formula (I-2) counting from the first paired nucleotide at 5’ end;

(2) 2’-fluoro modified nucleotides at positions 2, 7, 11, 14, and 18 of the antisense strand represented by formula (I-2) counting from the first paired nucleotide at 5’ end;

(3) 2’-fluoro modified nucleotides at positions 2, 8, 12, 14, and 16 of the antisense strand represented by formula (I-2) counting from the first paired nucleotide at 5’ end; or

(4) 2’-fluoro modified nucleotides at positions 2, 9, 12, 14, and 16 of the antisense strand represented by formula (I-2) counting from the first paired nucleotide at 5’ end.

9. The dsRNA agent according to claim 3, wherein in the antisense strand represented by

formula (I-1), formula (I-2), formula (II), or formula (III), the dsRNA agent comprises one or more features selected from the group consisting of:

(i) one or more of N_L are modified nucleotides independently selected from the group consisting of 2'-O-methyl modified nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide (LNA), unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), bicyclo nucleic acid (BNA), 2'-F-arabino nucleotide, 2'-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide (Invab), inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, 2'-amino modified nucleotide, 2'-alkyl modified nucleotide, morpholino nucleotide, 3'-OMe nucleotide, phosphorothioate modified nucleotide, terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, 2'-amino modified nucleotide, phosphoramidate, and non-natural base comprising nucleotide; and(ii) N_L in the dsRNA agent is a modified nucleotide selected from the group consisting of 2'-O-methyl modified nucleotide, UNA, and Invab.

10. The dsRNA agent according to claim 1, wherein in the antisense strand represented by formula (X), one or more of N_X are modified nucleotides independently selected from the group consisting of 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide (LNA), unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), bicyclo nucleic acid (BNA), 2'-F-arabino nucleotide, 2'-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide (Invab), inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, 2'-amino modified nucleotide, 2'-alkyl modified nucleotide, morpholino nucleotide, 3'-OMe nucleotide, phosphorothioate modified nucleotide, terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, 2'-amino modified nucleotide, phosphoramidate, and non-natural base comprising nucleotide.

11. The dsRNA agent according to any one of claims 1-10, wherein the antisense strand has an E-vinylphosphonate nucleotide at 5’ end of the antisense strand.

12. The dsRNA agent according to any one of claims 3-11, wherein in the antisense strand represented by formula (I-1), formula (I-2), formula (II), or formula (III), N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, N_{M8}, N_{M9} and/or N_{M10} are modified nucleotides independently selected from the group consisting of 2’-fluoro modified nucleotide, 2’-O-methyl modified nucleotide, 2’-deoxy nucleotide, 2’,3’-seco nucleotide mimic, locked nucleotide (LNA), unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), bicyclo nucleic acid (BNA), 2’-F-arabino nucleotide, 2’-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide (Invab), inverted 2’-OMe nucleotide, inverted 2’-deoxy nucleotide, 2’-amino modified nucleotide, 2’-alkyl modified nucleotide, morpholino nucleotide, 3’-OMe nucleotide, phosphorothioate modified nucleotide, terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, 2’-amino modified nucleotide, phosphoramidate, and non-natural base comprising nucleotide.

13. The dsRNA agent according to claim 12, wherein in the antisense strand represented by formula (I-1), N_{M1}, N_{M2}, N_{M3}, N_{M4}, N_{M5}, N_{M6}, N_{M7}, and N_{M8} are independently 2’-O methyl modified nucleotides in case of not being 2’-fluoro modified nucleotides.

14. The dsRNA agent according to any one of claims 1-13, wherein the dsRNA agent comprises one or more features selected from the group consisting of:

(1) the dsRNA agent has the sense strand complementary or substantially complementary to the antisense strand, and the complementary region is 18-25 nucleotides in length;

(2) the dsRNA agent has the sense strand complementary or substantially complementary to the antisense strand, and the complementary region is 18-23 nucleotides in length;

(3) the dsRNA agent has the sense strand complementary or substantially complementary to the antisense strand, and the complementary region is 19-21 nucleotides in length;

(4) the dsRNA agent has the sense strand complementary or substantially complementary to the antisense strand, and the complementary region is 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length;

(5) the dsRNA agent has the sense strand fully complementary to the antisense strand;

(6) wherein n is 0, 1, 2, 3, 4, 5, 6, or 7;

(7) the sense strand is no more than 40 nucleotides in length;

(8) each strand of the dsRNA agent is no more than 30 nucleotides in length;

(9) each strand of the dsRNA agent is no more than 25 nucleotides in length;

(10) each strand of the dsRNA agent is no more than 23 nucleotides in length;

(11) each strand of the dsRNA agent is 19, 20, or 21 nucleotides in length;

(12) either strand of the dsRNA agent comprises one or more of an overhang at the 3' or 5' end or both ends, and the overhang is 1-5 nucleotides in length;

(13) the antisense strand of the dsRNA agent has a blunt end at 3' end;

(14) the antisense strand of the dsRNA agent has an overhang of 1, 2, 3, 4, or 5 unpaired nucleotides at 3' end, and/or the sense strand of the dsRNA agent has an overhang of 1, 2, 3, 4, or 5 unpaired nucleotides at 5' end;

(15) the sense strand of the dsRNA agent has a blunt end at 3' end;

(16) the antisense strand of the dsRNA agent has a blunt end at 5' end;

(17) the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(18) the sense strand of the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(19) the antisense strand of the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(20) the sense strand of the dsRNA agent comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;

(21) the antisense strand of the dsRNA agent comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;

(22) the dsRNA agent comprises 1 or 2 phosphorothioate internucleoside linkages at 3' end and/or 5' end of the sense strand and/or the antisense strand;

(23) the dsRNA agent further comprises one or more targeting groups or linking groups;

(24) the antisense strand of the dsRNA agent comprises an inverted abasic residue at 3' end; and

(25) the sense strand of the dsRNA agent comprises one or two inverted abasic residues at 3' end or/and 5' end.

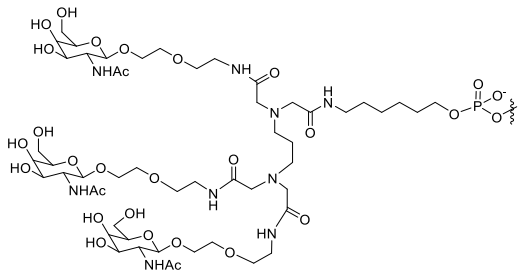
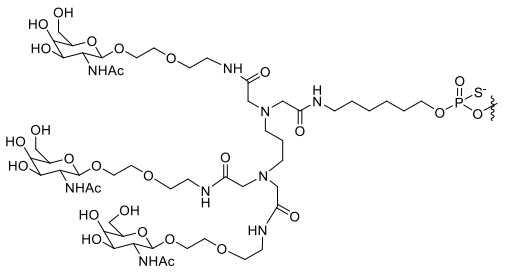
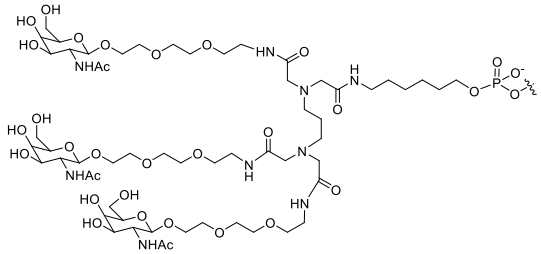
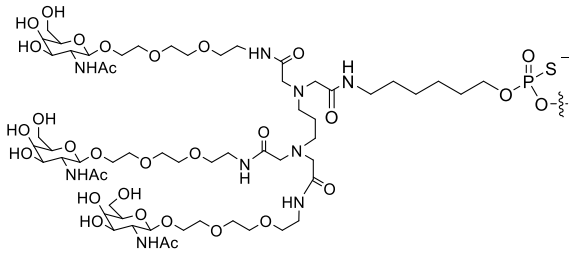
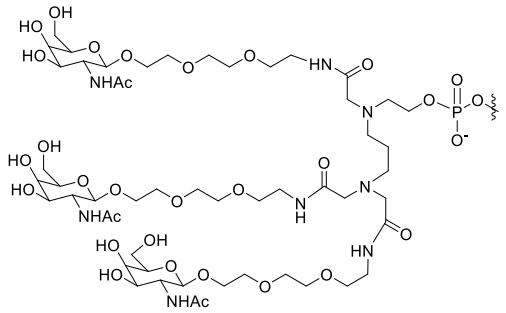
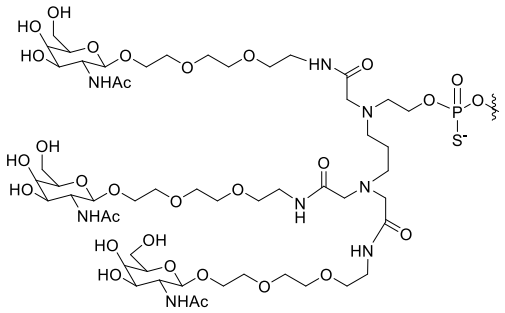
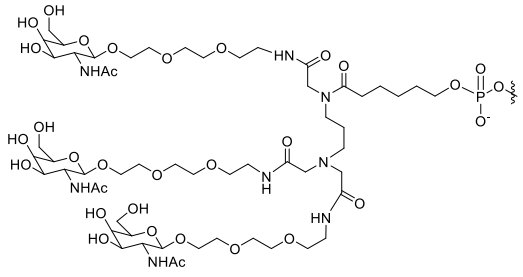
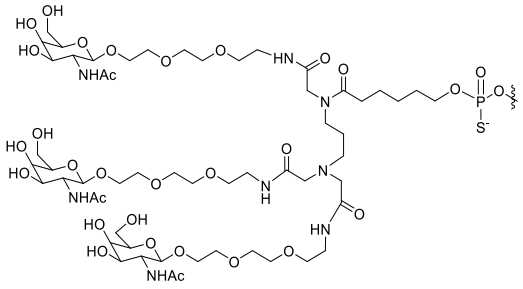
15. The dsRNA agent according to claim 14, wherein the one or more targeting groups or linking groups comprise one or more features selected from the group consisting of:

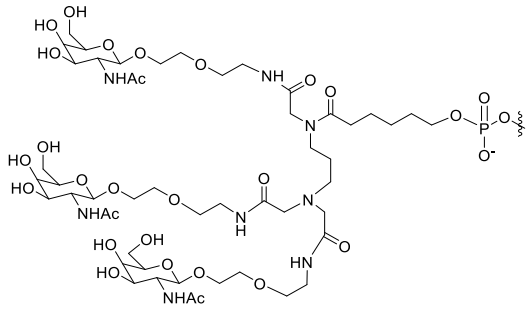
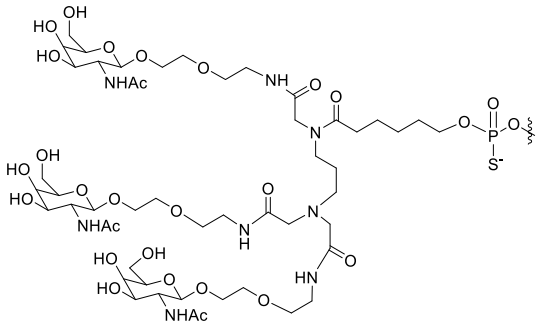
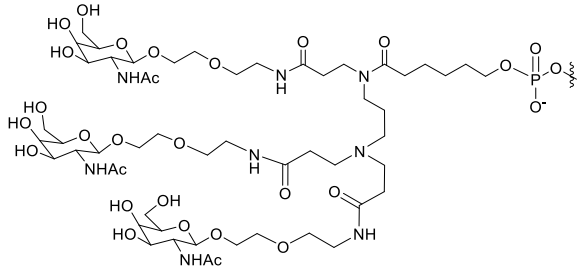
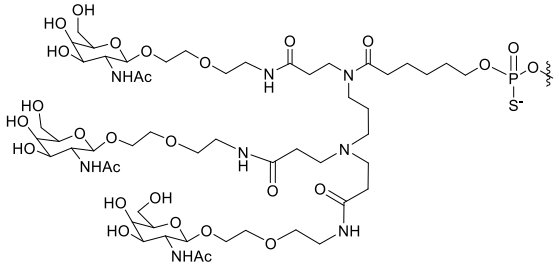
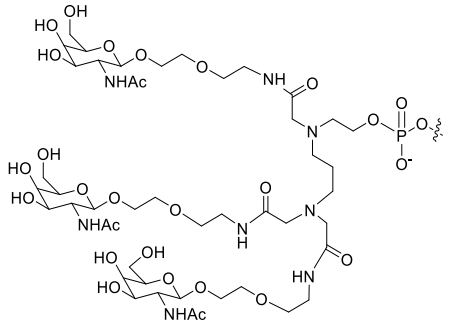
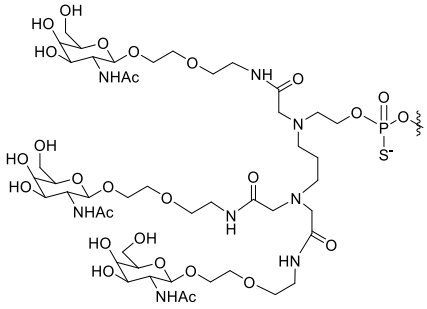
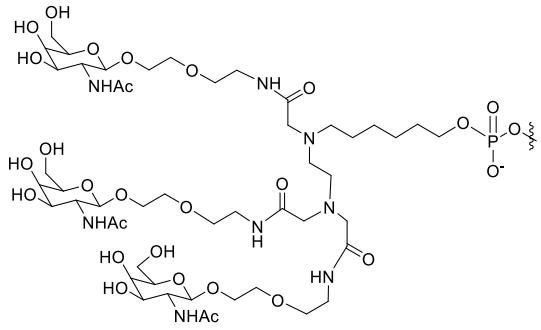
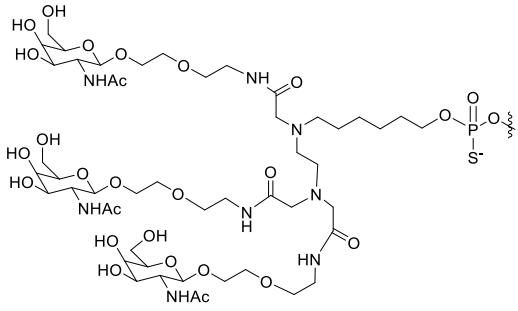
(1) the one or more targeting groups or linking groups are conjugated to the sense strand;

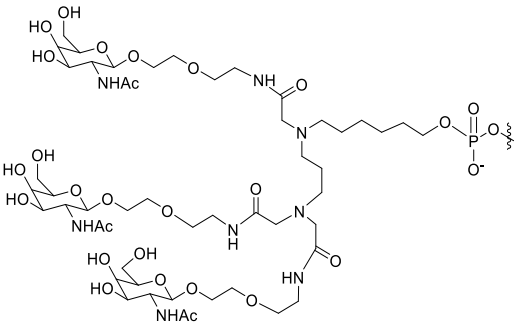
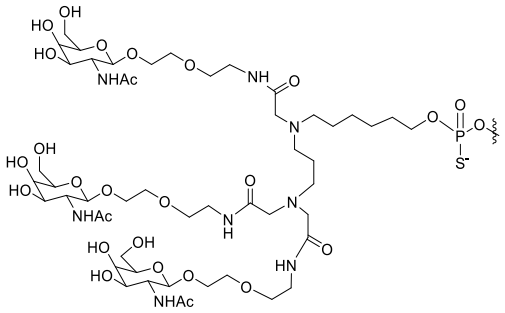
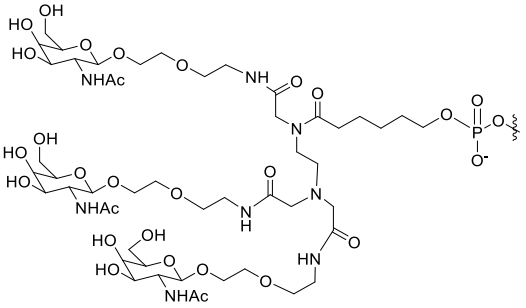
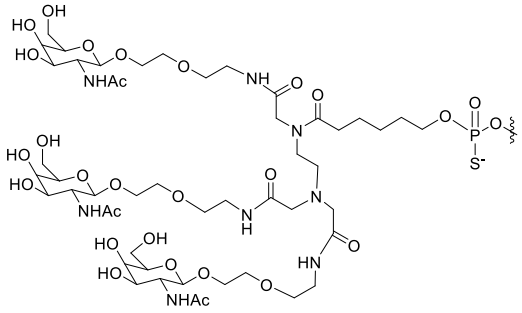
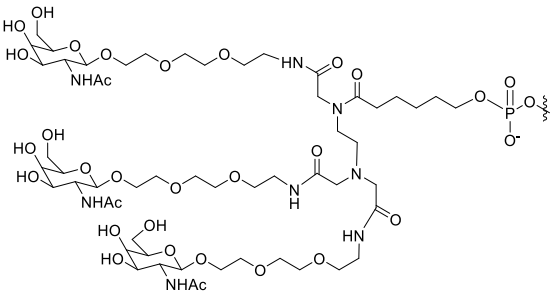
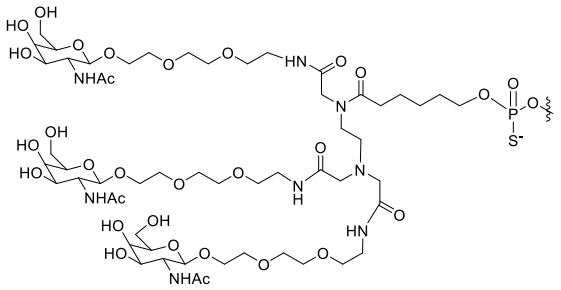
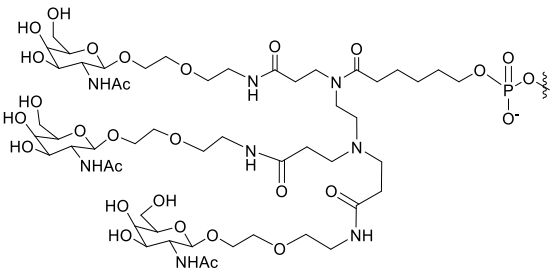
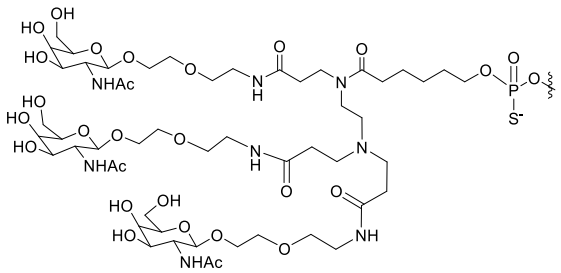
(2) the one or more targeting groups or linking groups are independently selected from the group consisting of N-acetyl-galactosamine (GalNAc) and a lipophilic molecule; and

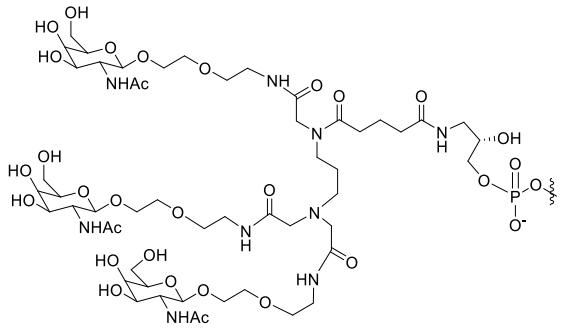
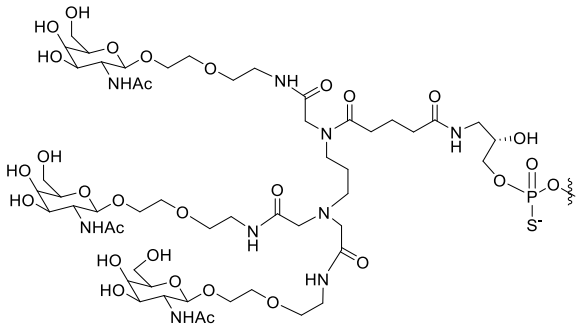
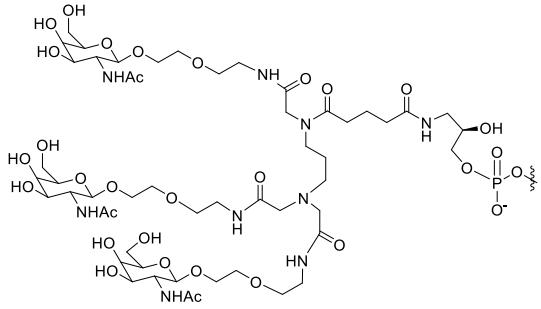
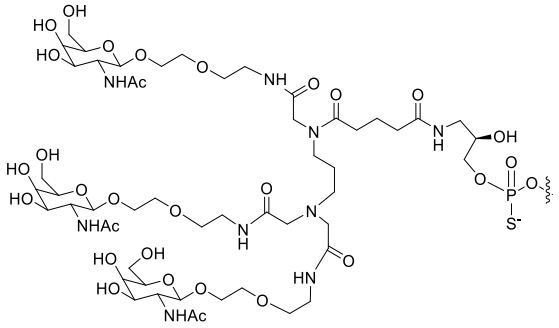
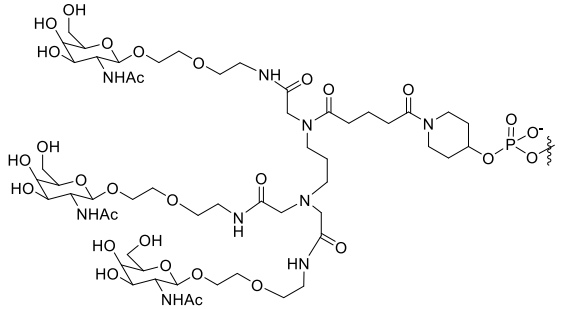
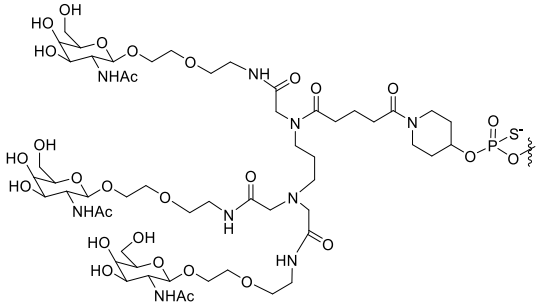
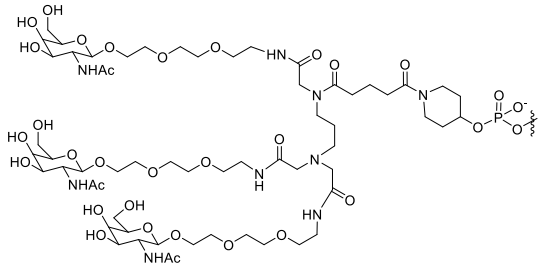
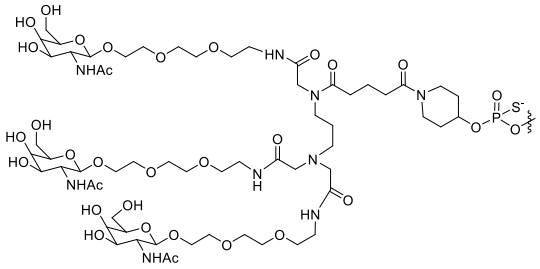
(3) the one or more targeting groups or linking groups are conjugated to 5' end of the sense

strand, and the targeting group has a structure selected from the group consisting of:

 GLO-1	 GLS-1
 GLO-2	 GLS-2
 GLO-3	 GLS-3
 GLO-4	 GLS-4

 GLO-5	 GLS-5
 GLO-6	 GLS-6
 GLO-7	 GLS-7
 GLO-8	 GLS-8

 GLO-9	 GLS-9
 GLO-10	 GLS-10
 GLO-11	 GLS-11
 GLO-12	 GLS-12

 GLO-13	 GLS-13
 GLO-14	 GLS-14
 GLO-15	 GLS-15
 GLO-16	 GLS-16

.

16. An RNAi agent for inhibiting expression of a target gene, wherein the RNAi agent is a

double-stranded ribonucleic acid (dsRNA) agent comprising a sense strand and an antisense strand complementary to at least a portion of an mRNA corresponding to the target gene, and the sense strand has 18-40 nucleotides and the sense strand comprises:

(i) a sequence represented by formula (V) in the direction of 5'-3':

$$5'\text{-}(N'_L)_{n'}\ N'_L\,N'_L\,N'_L\,N'_{N1}\,N'_{N2}\,N'_{N3}\,N'_{N4}\,N'_F\,N'_L\,N'_{N5}N'_{N6}\,N'_L\ N'_L\,N'_L\,N'_L\,N'_L\,N'_L\,N'_L\text{-}3'$$

formula (V)

wherein, each N'_F represents a 2'-fluoro modified nucleotide;

N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} independently represent a modified or an unmodified nucleotide, wherein at least two of N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} are 2'-fluoro modified nucleotides;

formula (V) has no motif of three or more contiguous 2'-fluoro modified nucleotides and has no more than six 2'-fluoro modified nucleotides;

each N'_L independently represents a modified or an unmodified nucleotide; and

n' is an integer from 0 to 7;

(ii) a sequence represented by formula (IX) in the direction of 5'-3':

$$5'\text{-}(N'_L)_{n'}\ N'_L\,N'_L\,N'_L\,N'_{N1}\,N'_{N2}\,N'_{N3}\,N'_{N4}\,N'_F\,N'_L\,N'_{N5}N'_{N6}\,N'_{N7}\,N'_L\,N'_L\,N'_L\,N'_L\,N'_L\,N'_L\text{-}3'$$

formula (IX)

wherein, each N'_F represents a 2'-fluoro modified nucleotide;

N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, N'_{N6}, and N'_{N7} independently represent a modified or an unmodified nucleotide, wherein at least two of N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, N'_{N6}, and N'_{N7} are 2'-fluoro modified nucleotides;

formula (IX) has no motif of three or more contiguous 2'-fluoro modified nucleotides and has no more than six 2'-fluoro modified nucleotides;

each N'_L independently represents a modified or an unmodified nucleotide; and

n' is an integer from 0 to 7.

17. The dsRNA agent according to claim 16, wherein the sense strand comprises a sequense represented by formula (V') in the direction of 5'-3':

$$5'\text{-}(N'_L)_{n'}\ N'_L\,N'_L\,N'_L\,N'_{N1}\,N'_{N2}\,N'_{N3}\,N'_{N4}\,N'_F\,N'_L\,N'_{N5}N'_{N6}\,N'_L\ N'_L\,N'_L\,N'_L\,N'_L\,N'_L\,N'_L\text{-}3'$$

formula (V')

wherein, each N'_F represents a 2'-fluoro modified nucleotide;

N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} independently represent a modified or an unmodified nucleotide, wherein only two of N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, and N'_{N6} are 2'-fluoro modified nucleotides.

each N'_L independently represents a modified or an unmodified nucleotide, wherein the modified nucleotide is not a 2'-fluoro modified nucleotide; and

n' is an integer from 0 to 7.

18. The dsRNA agent according to claim 17, wherein the sense strand comprises the sequence represented by formula (V') and has:

(1) 2'-fluoro modified nucleotides at positions 9, 11, and 13 of the sense strand represented by formula (V') counting from the first paired nucleotide at 3' end of the sense strand;

(2) 2'-fluoro modified nucleotides at positions 9, 11 and 12 of the sense strand represented by formula (V') counting from the first paired nucleotide at 3' end of the sense strand;

(3) 2'-fluoro modified nucleotides at positions 8, 11 and 13 of the sense strand represented by formula (V') counting from the first paired nucleotide at 3' end of the sense strand;

(4) 2’-fluoro modified nucleotides at positions 11, 12 and 14 of the sense strand represented by formula (V’) counting from the first paired nucleotide at 3’ end of the sense strand; and

(5) 2’-fluoro modified nucleotides at positions 11, 12 and 15 of the sense strand represented by formula (V’) counting from the first paired nucleotide at 3’ end of the sense strand.

19. The dsRNA agent according to claim 16, wherein the dsRNA agent has 2’-fluoro modified nucleotides at positions 7, 9, 11 and 13 of the sense strand represented by formula (IX) counting from the first paired nucleotide at 3’ end of the sense strand.

20. The dsRNA agent according to any one of claims 16-19, the dsRNA agent comprises one or more features selected from the group consisting of:

(1) the sense strand represented by formula (V) or formula (IX), one or more of N'_L are modified nucleotides independently selected from the group consisting of 2’-fluoro modified nucleotide, 2’-O-methyl modified nucleotide, 2’-deoxy nucleotide, 2’,3’-seco nucleotide mimic, locked nucleotide (LNA), unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), bicyclo nucleic acid (BNA), 2’-F-arabino nucleotide, 2’-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide (Invab), inverted 2’-OMe nucleotide, inverted 2’-deoxy nucleotide, 2’-amino modified nucleotide, 2’-alkyl modified nucleotide, morpholino nucleotide, 3’-OMe nucleotide, phosphorothioate modified nucleotide, terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, 2’-amino modified nucleotide, phosphoramidate, and non-natural base comprising nucleotide;

(2) N'_L in formula (V) is a modified nucleotide selected from the group consisting of 2’-O-methyl modified nucleotide, UNA, and Invab;

(3) the dsRNA agent has an E-vinylphosphonate nucleotide at 5’ end of the antisense strand;

(4) in the sense strand represented by formula (V) or formula (IX), N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, N'_{N6}, and N'_{N7} are modified nucleotides independently selected from the group consisting of 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, 2'-deoxy nucleotide, 2',3'-seco nucleotide mimic, locked nucleotide (LNA), unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), bicyclo nucleic acid (BNA), 2'-F-arabino nucleotide, 2'-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide (Invab), inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, 2'-amino modified nucleotide, 2'-alkyl modified nucleotide, morpholino nucleotide, 3'-OMe nucleotide, phosphorothioate modified nucleotide, terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, 2'-amino modified nucleotide, phosphoramidate, and non-natural base comprising nucleotide;

(5) in the sense strand represented by formula (V) or formula (IX), N'_{N1}, N'_{N2}, N'_{N3}, N'_{N4}, N'_{N5}, N'_{N6}, and N'_{N7} are independently 2'-O methyl modified nucleotides in case of not being 2'-fluoro modified nucleotides;

(6) the dsRNA agent has an antisense strand complementary or substantially complementary to the sense strand, and the complementary region is 18-25 nucleotides in length;

(7) the dsRNA agent has an antisense strand complementary or substantially complementary to the sense strand, and the complementary region is 18-23 nucleotides in length;

(8) the dsRNA agent has an antisense strand complementary or substantially complementary to the sense strand, and the complementary region is 19-21 nucleotides in length;

(9) the dsRNA agent has an antisense strand complementary or substantially complementary to the sense strand, and the complementary region is 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length;

(10) the dsRNA agent has an antisense strand fully complementary to the sense strand;

(11) n' is 0, 1, 2, 3, 4, 5, 6, or 7;

(12) the antisense strand is no more than 30 nucleotides in length;

(13) each strand of the dsRNA agent is no more than 30 nucleotides in length;

(14) each strand of the dsRNA agent is no more than 25 nucleotides in length;

(15) each strand of the dsRNA agent is no more than 23 nucleotides in length;

(16) each strand of the dsRNA agent is 19, 20, or 21 nucleotides in length;

(17) the sense strand represented by formula (V) or formula (IX) has an overhang with unpaired nucleotide at one or two positions at 5’ end;

(18) the sense strand represented by formula (V) or formula (IX) has a blunt end at 5’ end;

(19) the antisense strand of the dsRNA agent has an overhang of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 unpaired nucleotides at 3’ end;

(20) the antisense strand of the dsRNA has a blunt end at 5’ end, and/or the sense strand of the dsRNA has a blunt end at 3’ end;

(21) the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(22) the sense strand of the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(23) the antisense strand of the dsRNA agent comprises at least one phosphorothioate internucleoside linkage;

(24) the sense strand and/or antisense strand of the dsRNA agent comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;

(25) the dsRNA agent comprises 1 or 2 phosphorothioate internucleoside linkages at 3’ end and/or 5’ end of the sense strand and/or the antisense strand;

(26) the dsRNA agent further comprises one or more targeting groups or linking groups,

(27) the sense strand of the dsRNA agent comprises an inverted abasic residue at 3’ end; and

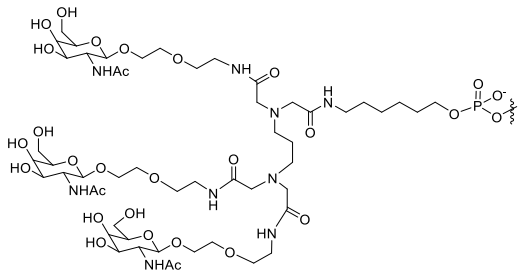
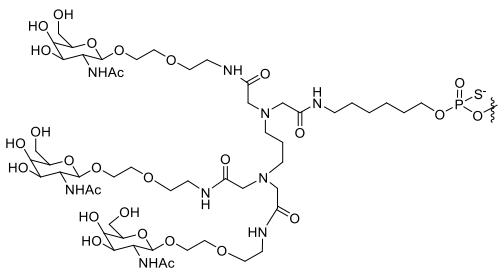
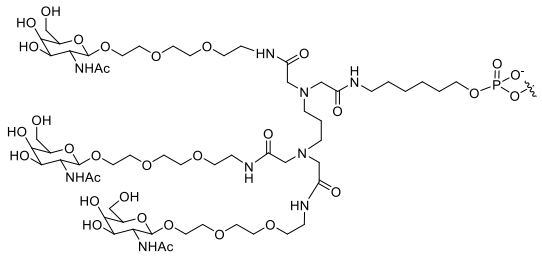
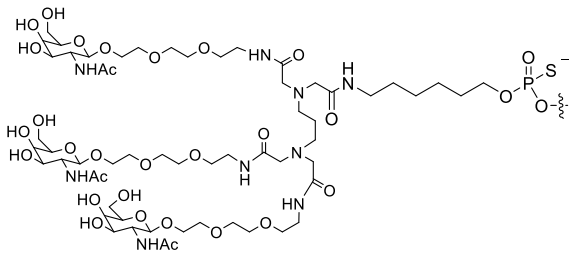
(28) the sense strand of the dsRNA agent comprises one or two inverted abasic residues 3’ end or/and 5’ end.

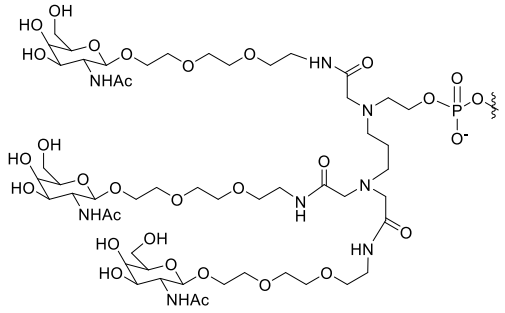
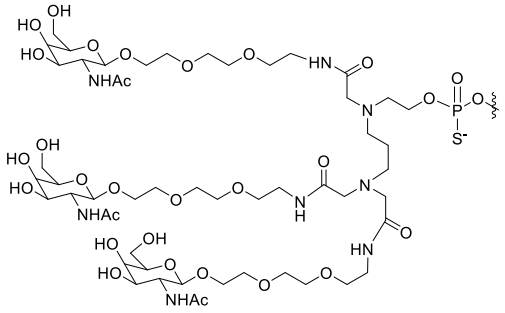
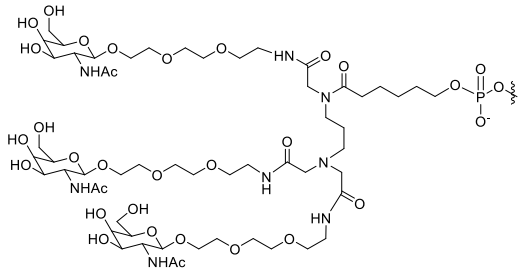
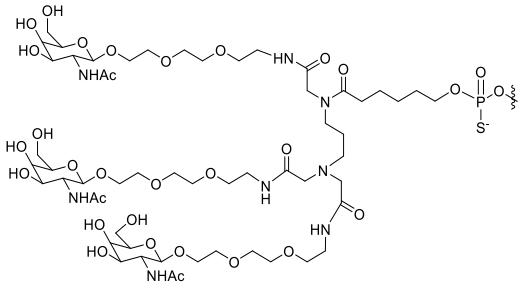
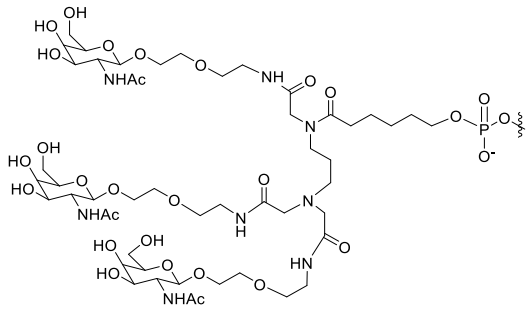
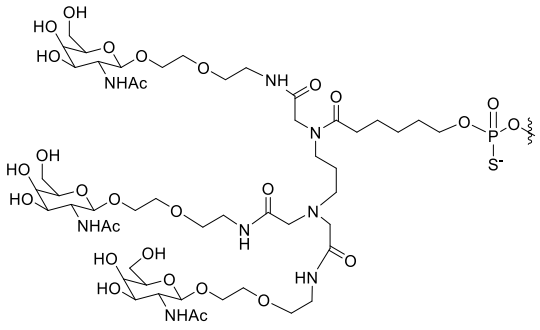
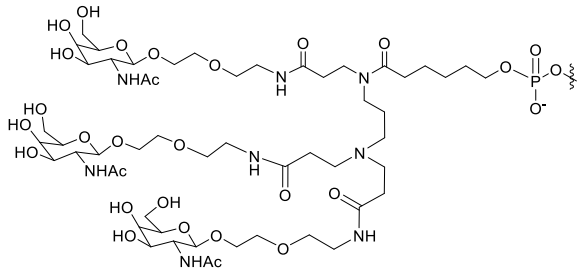
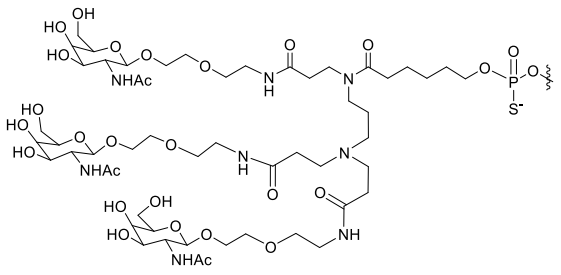
21. The dsRNA agent according to claim 20, wherein the one or more targeting groups or linking groups comprise one or more features selected from the group consisting of:

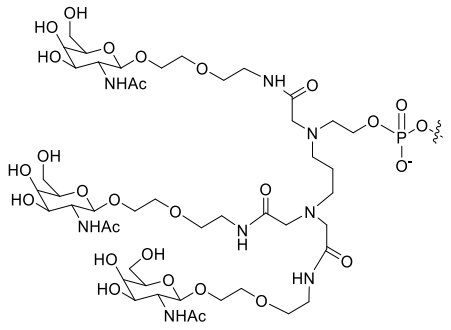
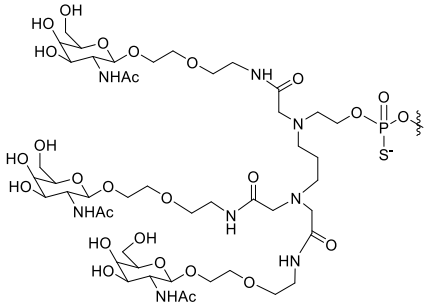
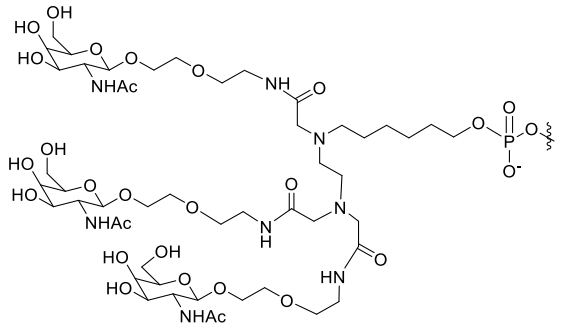
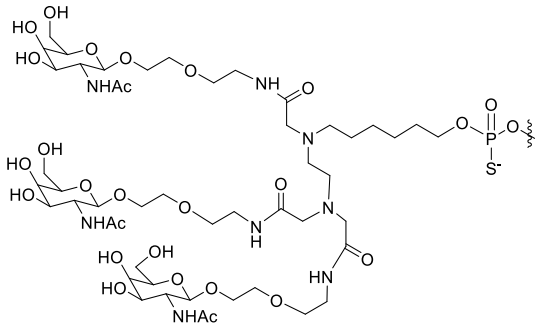
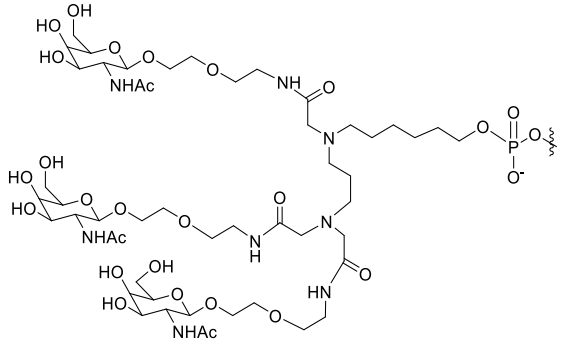
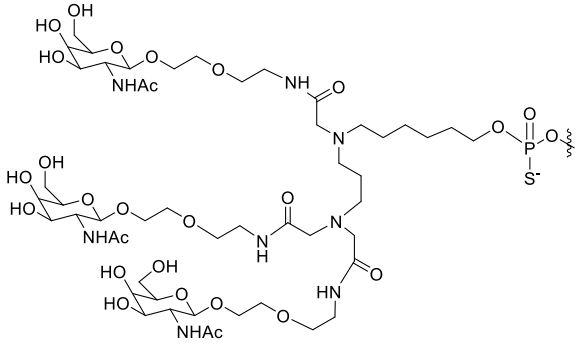
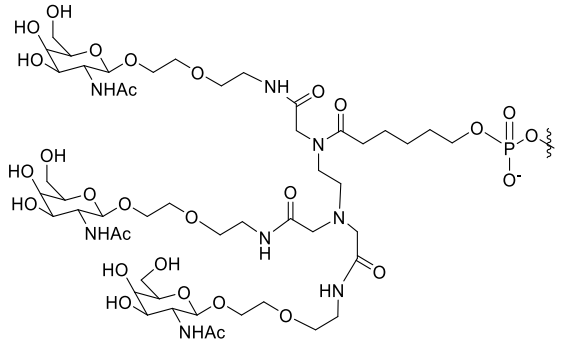
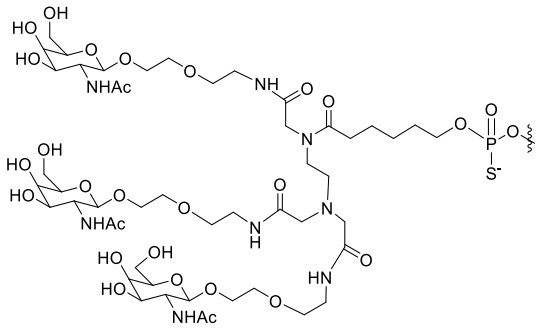
(1) the one or more targeting groups or linking groups are selected from the group consisting of N-acetyl-galactosamine (GalNAc) and a lipophilic molecule,

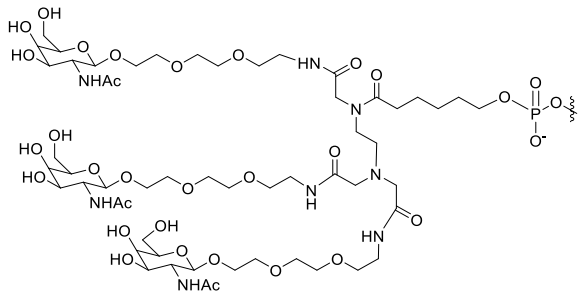
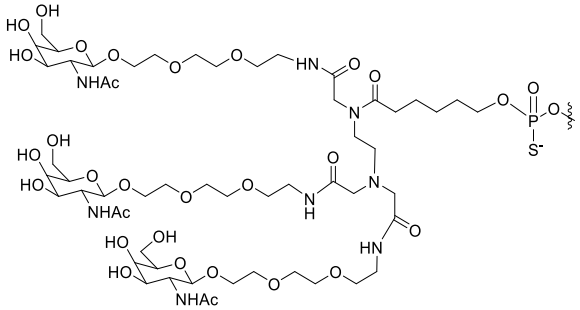
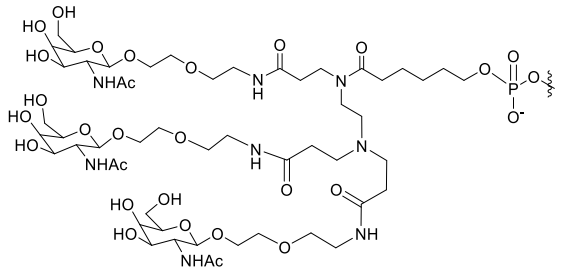
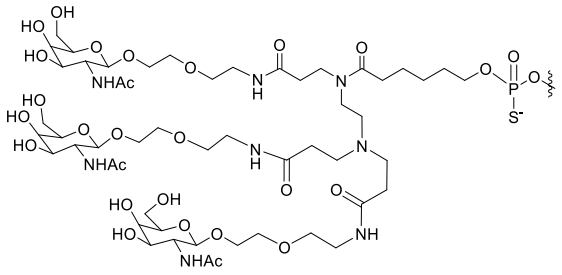
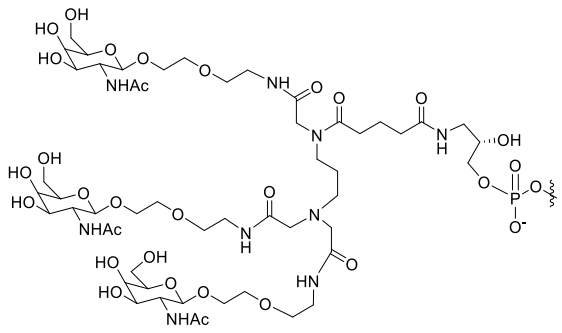
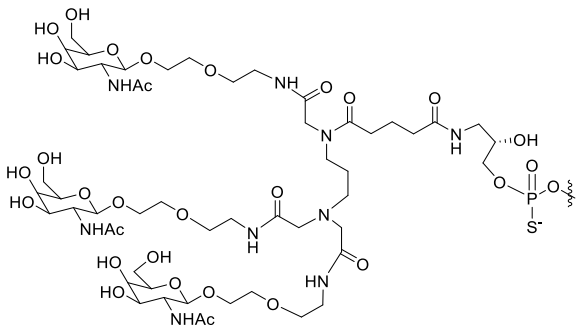
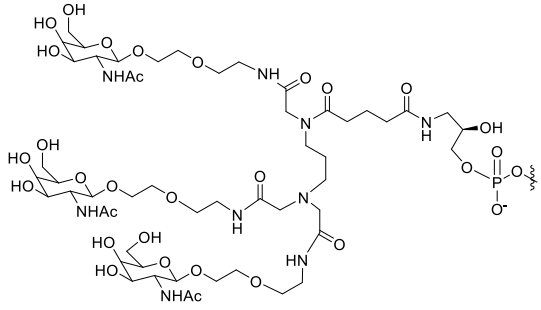
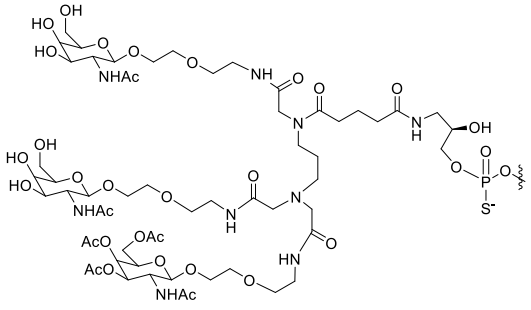
(2) the one or more targeting groups or linking groups are conjugated to 5’ end of the sense strand; and

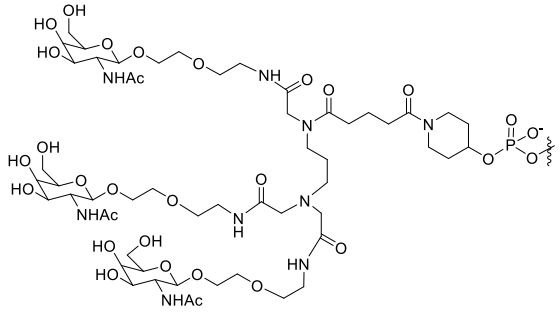
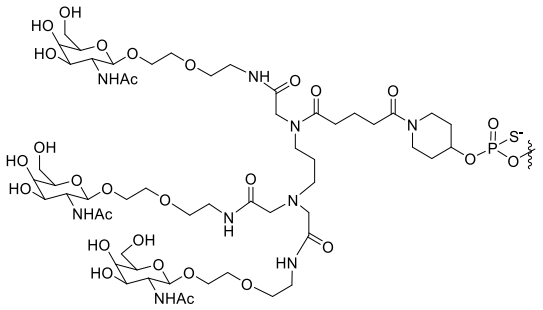
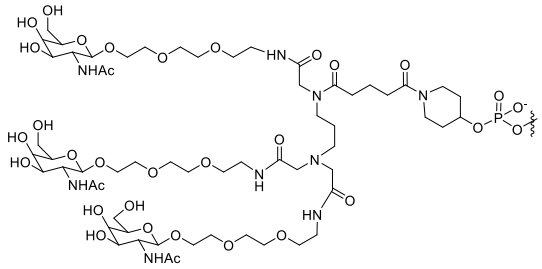
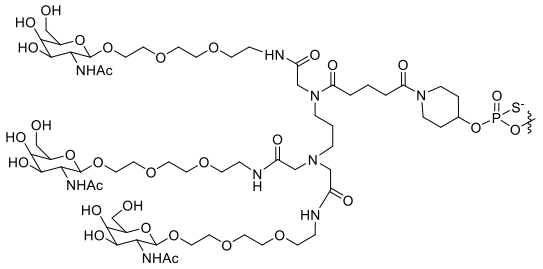
(3) the targeting group has a structure selected from the group consisting of:

 GLO-1	 GLS-1
 GLO-2	 GLS-2

 GLO-3	 GLS-3
 GLO-4	 GLS-4
 GLO-5	 GLS-5
 GLO-6	 GLS-6

 GLO-7	 GLS-7
 GLO-8	 GLS-8
 GLO-9	 GLS-9
 GLO-10	 GLS-10

 GLO-11	 GLS-11
 GLO-12	 GLS-12
 GLO-13	 GLS-13
 GLO-14	 GLS-14

 GLO-15	 GLS-15
 GLO-16	 GLS-16

22. The dsRNA agent according to any one of claims 1-21, wherein the dsRNA agent is siRNA.

23. An RNAi agent for inhibiting expression of a target gene, wherein the RNAi agent is a double-stranded ribonucleic acid (dsRNA) agent, comprising an antisense strand of the dsRNA agent according to any one of claims 1-15 and a sense strand of the dsRNA agent according to any one of claims 16-21.

24.A composition comprising the dsRNA agent according to any one of claims 1-23.

25. The composition according to claim 24, further comprising a pharmaceutically acceptable carrier.

26. The composition according to claim 25, further comprising one or more additional therapeutic agents.

27. The composition according to claim 25, wherein the composition is packaged in a kit, container, pack, dispenser, pre-filled syringe, or vial.

28. The composition according to claim 25, wherein the composition is formulated for ophthalmic, vaginal, rectal, intranasal, transdermal, subcutaneous, intravenous, intraarterial, intralymphatic, intrabronchial, intrapleural, intraperitoneal, intracerobrospinal, intramuscular, pulmonary, intrathecal, or intraventricular administration.

29. A cell comprising the dsRNA agent according to any one of claims 1-23.

30. Use of the dsRNA agent according to any one of claims 1-23 in the manufacture of a medicament for inhibiting expression of a target gene in a cell, wherein the dsRNA agent is to be delivered to a specific target in a subject.

31. The use according to claim 30, wherein the dsRNA agent is to be administered to the subject by ophthalmic, vaginal, rectal, intranasal, transdermal, subcutaneous, intravenous, intraarterial, intralymphatic, intrabronchial, intrapleural, intraperitoneal, intracerobrospinal, intramuscular, pulmonary, intrathecal, or intraventricular administration.

32. The use according to claim 30, wherein the target gene is selected from the group

consisting of LPA, PNPLA3, ASGR1, F7, F12, FXI, APOCIII, APOB, APOL1, TTR, PCSK9, SCAP, KRAS, CD274, PDCD1, C5, ALAS1, HAO1, LDHA, ANGPTL3, SERPINA1, AGT, HAMP, LECT2, EGFR, VEGF, KIF11, AT3, CTNNB1, HMGB1, HIF1A, APP, ATXN2, C9orf72, TARDBP, MAPT (Tau), HTT, SNCA, FUS, ATXN3, SCN9A, SCN10A, CACNA1B, ATXNl, SCAl, SCA7, SCA8, MeCP2, PRNP, SODl, DMPK and STAT3.

33. Use of the dsRNA agent according to any one of claims 1-28 in the manufacture of a medicament for treating a viral disease, neuromuscular disease, bacterial infection, inflammation, immune disease, metabolic disease, liver disease, kidney disease, cardiovascular disease, ophthalmic disease, lung disease, or a rare disease.