CLAIMS

1. An RNAi agent comprising a sense strand comprising a nucleobase sequence according to SEQ ID NO: 302, and an antisense strand comprising a nucleobase sequence according to SEQ ID NO: 171, wherein at least one nucleotide of the sense strand and/or at least one nucleotide of the antisense strand of the RNAi agent is a modified nucleotide and/or has a modified internucleoside linkage.

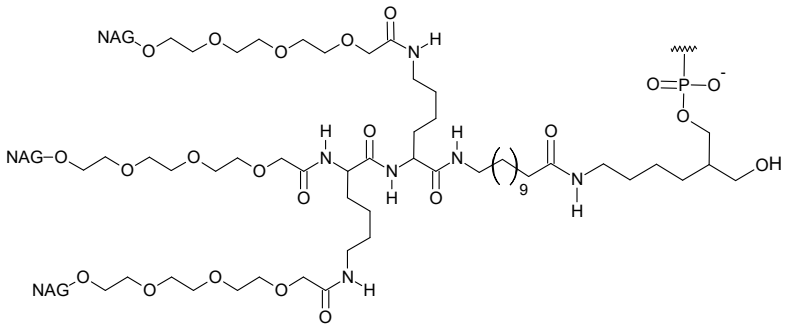
2. The RNAi agent of claim 1, wherein 0, 1, 2, 3 or 4 nucleotides in both the sense strand and the antisense strand are unmodified ribonucleotides.

3. The RNAi agent of claim 1 or 2, wherein both the sense strand and the antisense strand independently comprise 1, 2, 3, 4, 5 or 6 phosphorothioate linkages.

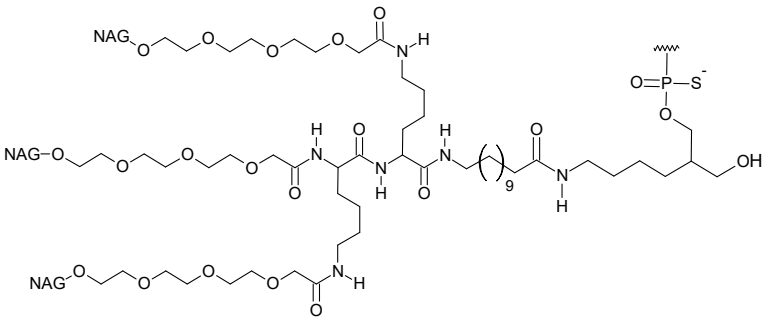
4. The RNAi agent of any of claims 1-3, wherein the RNAi agent comprises a targeting ligand.

5. The RNAi agent of claim 4, wherein the targeting ligand comprises N-acetyl-galactosamine.

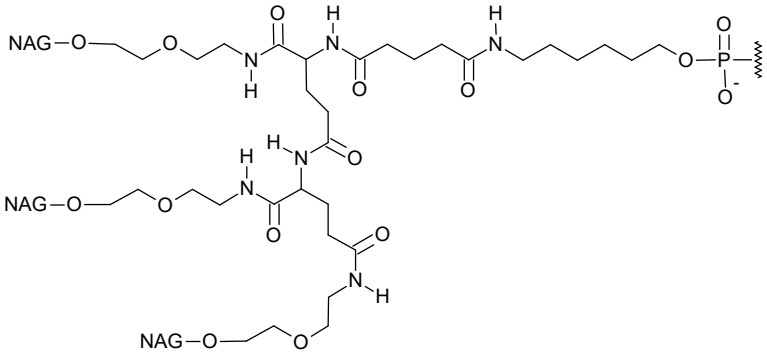
6. The RNAi agent of claim 5, wherein the targeting ligand is selected from a group consisting of:



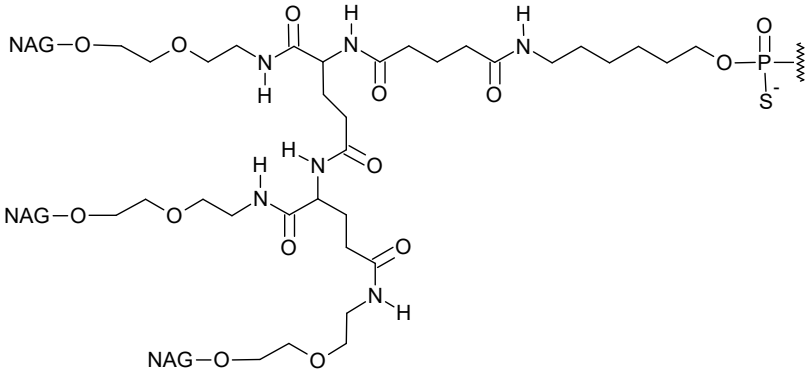
(NAG13),



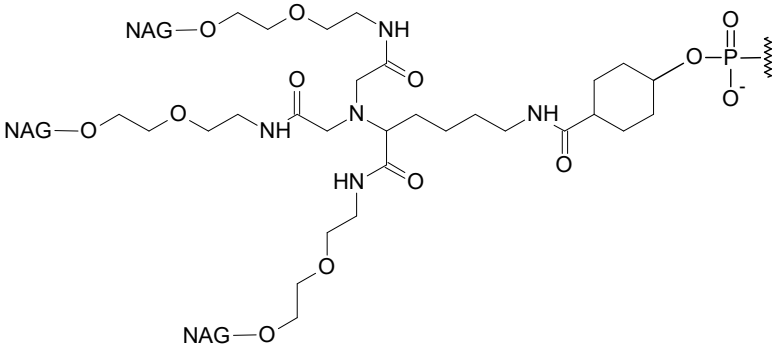
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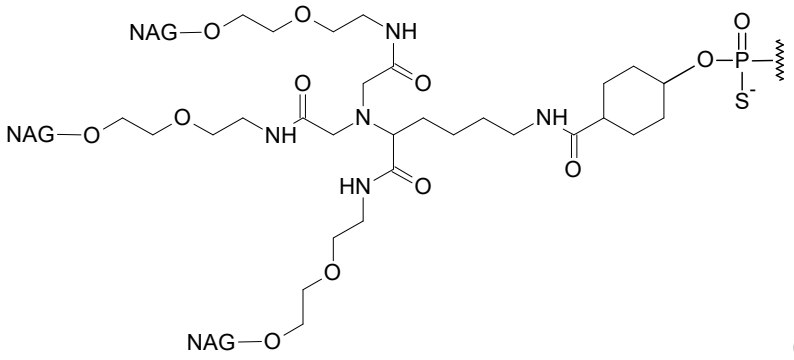
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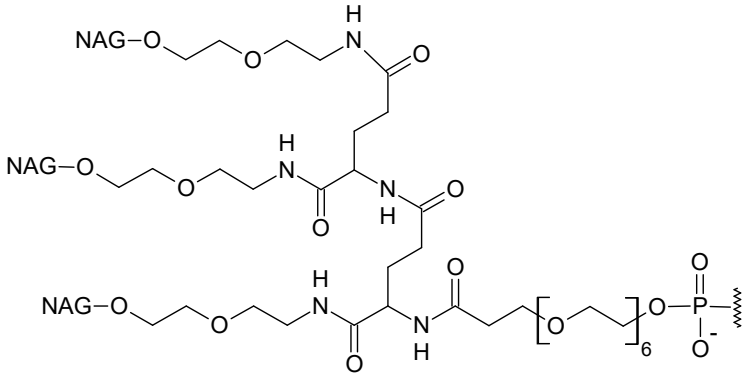
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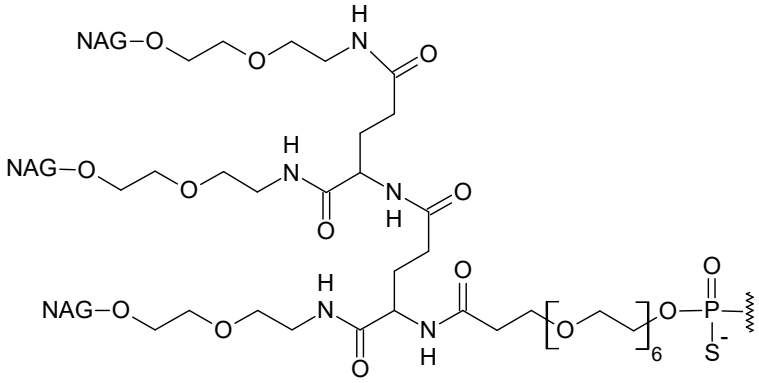
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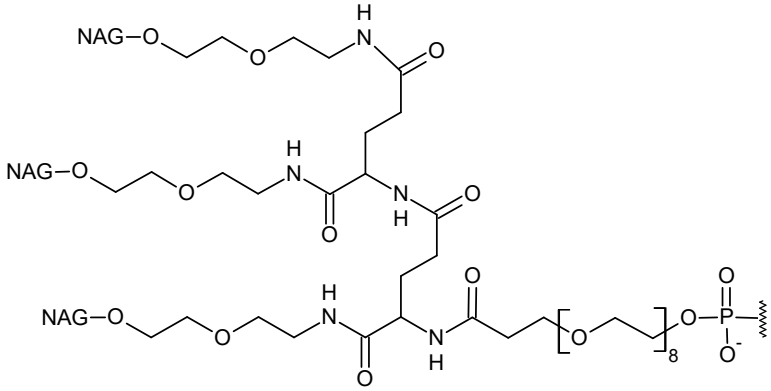
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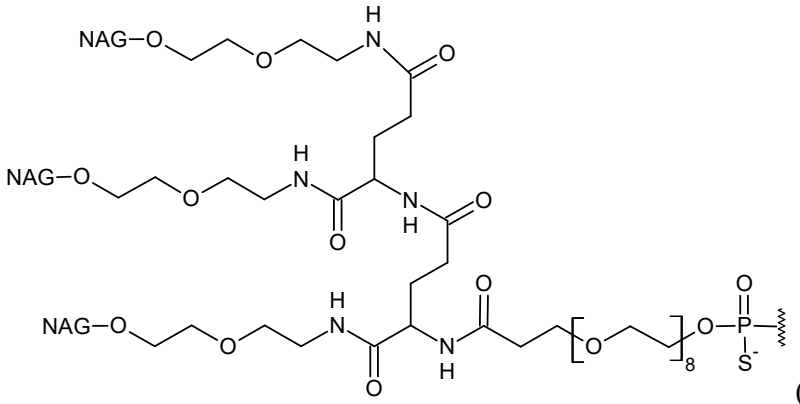
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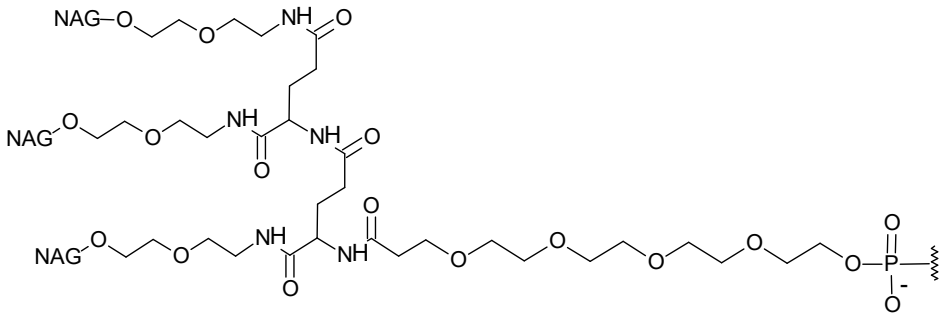
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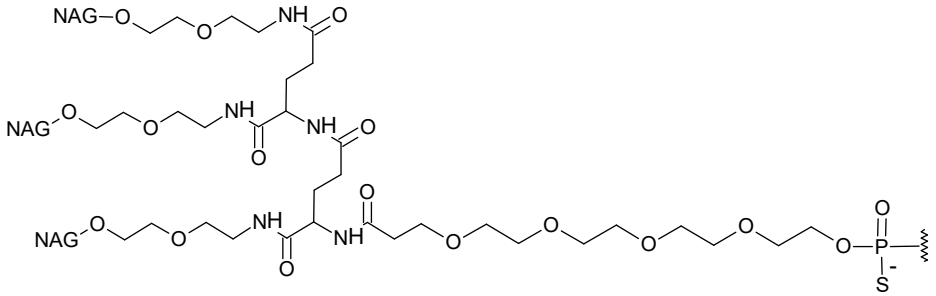
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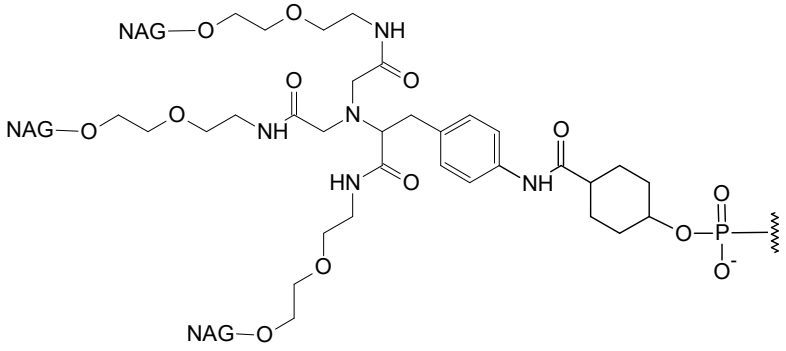
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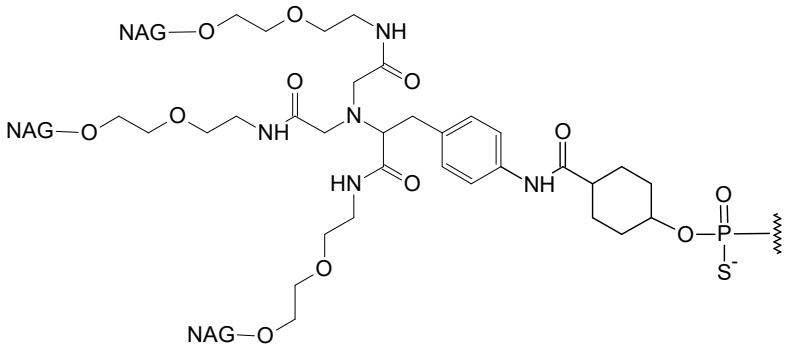
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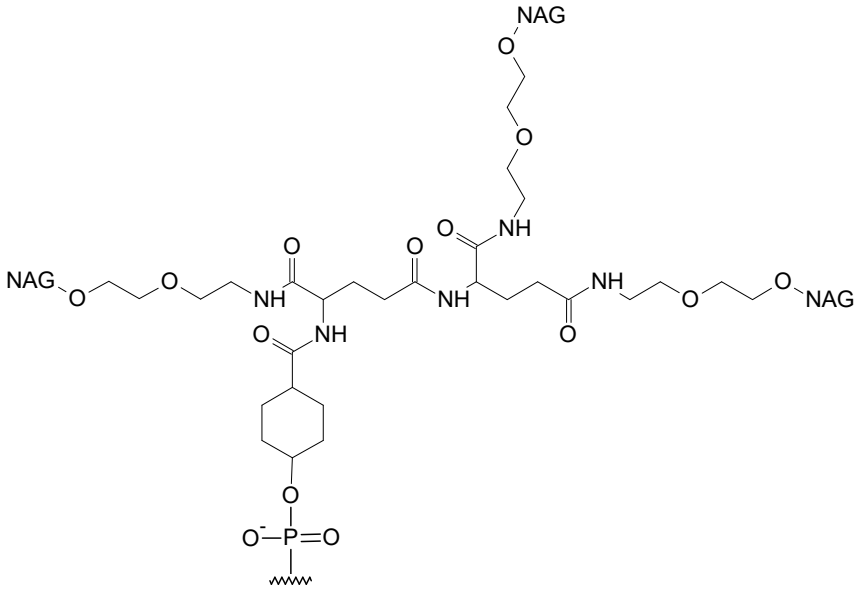
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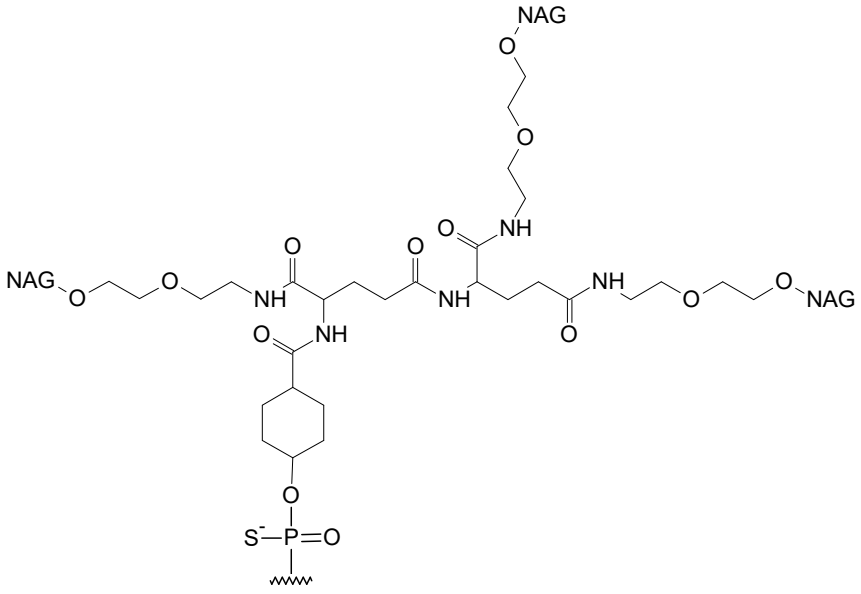
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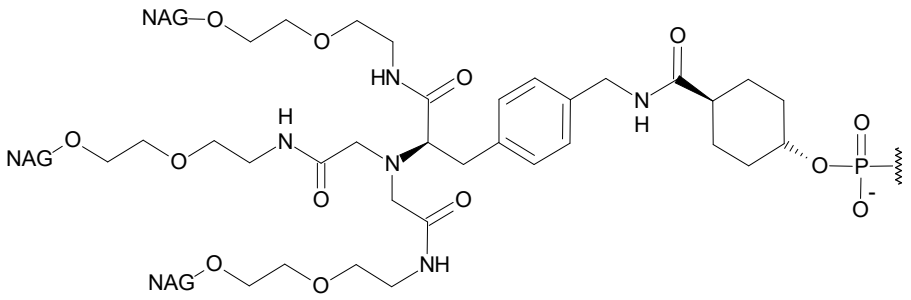
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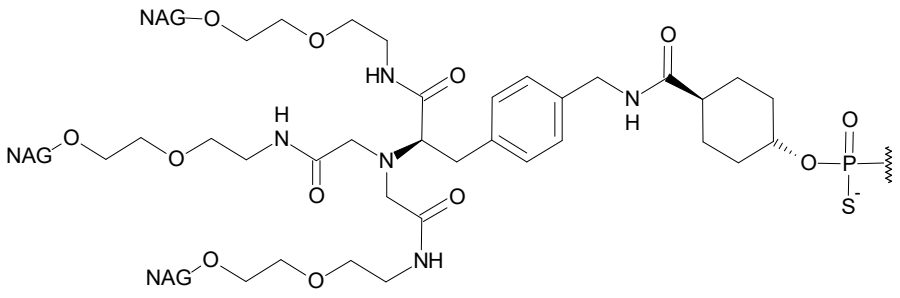
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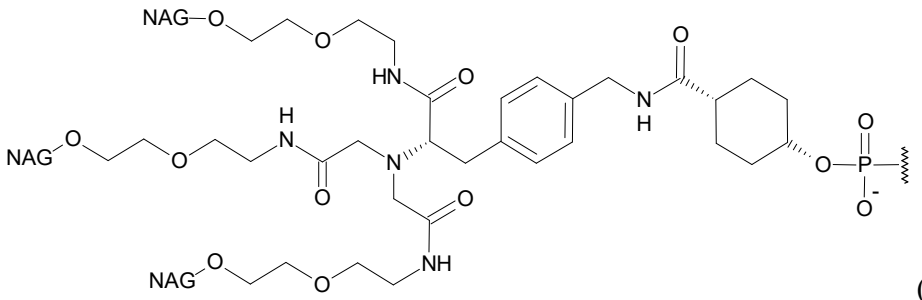
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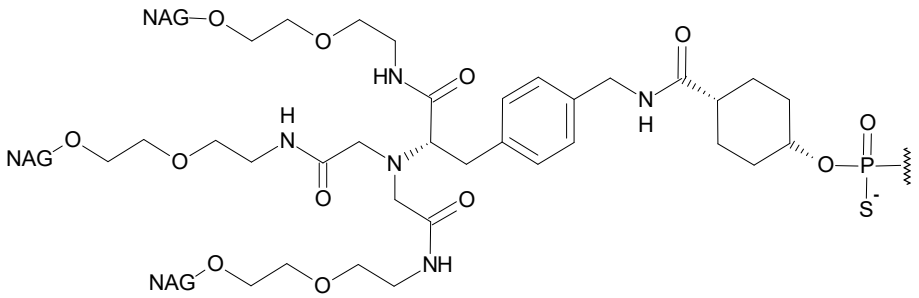
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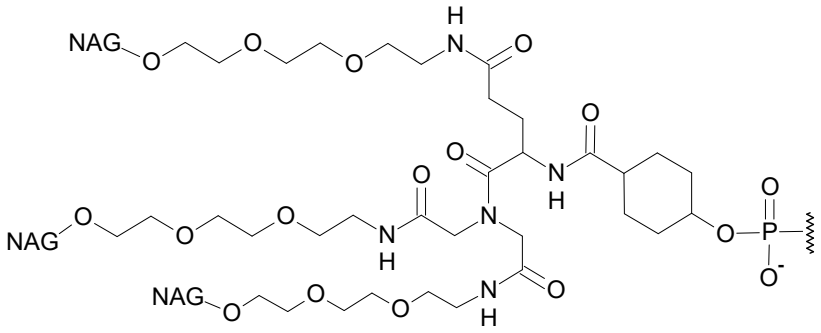
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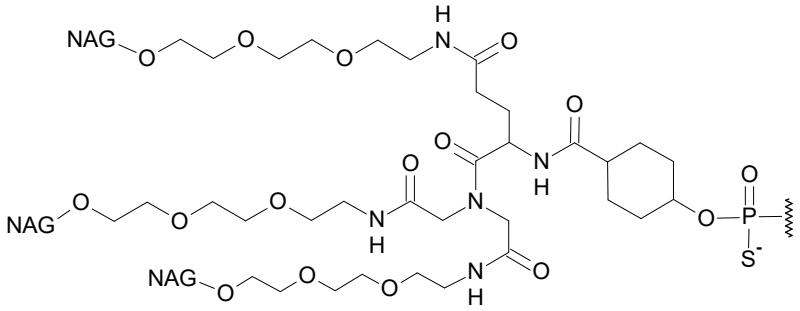
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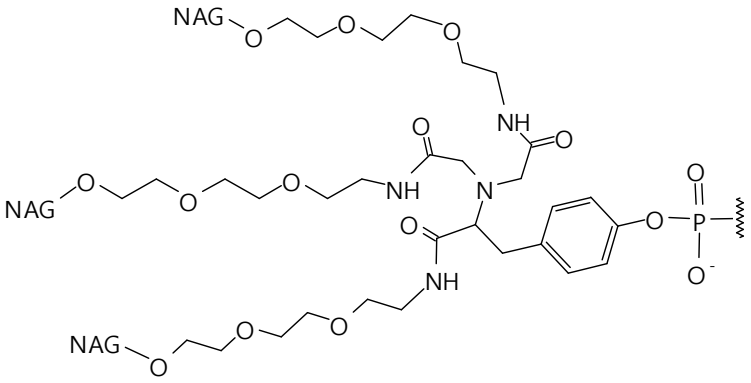
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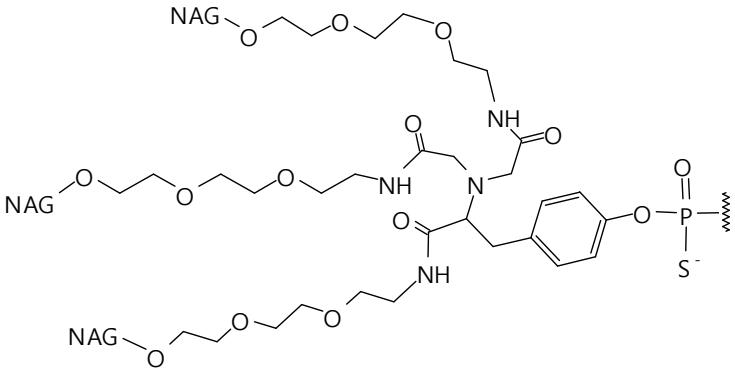
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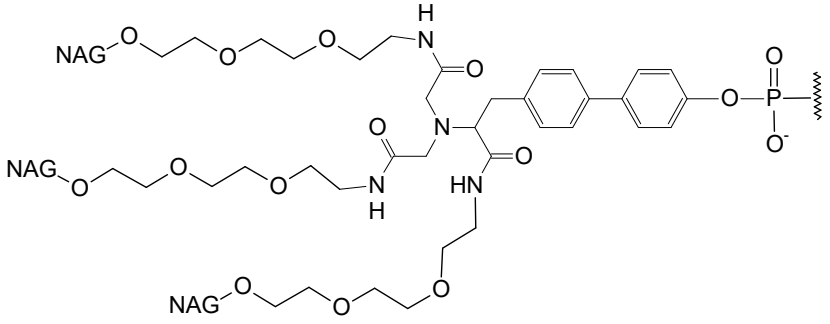
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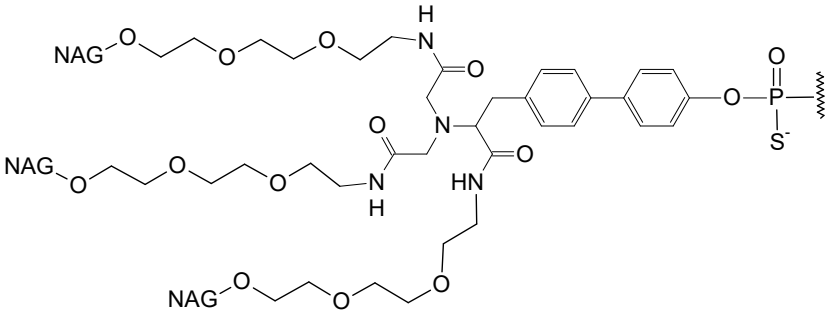
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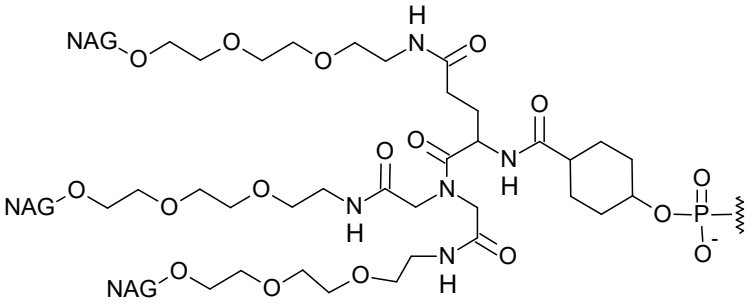
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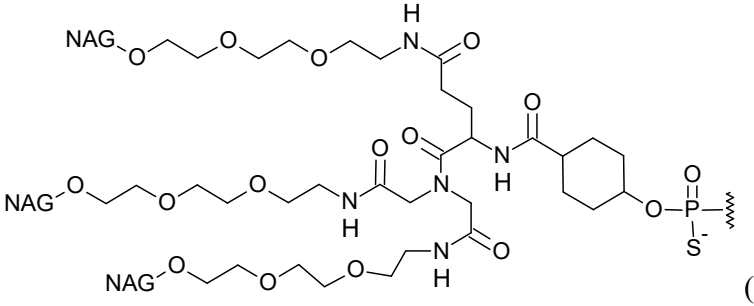
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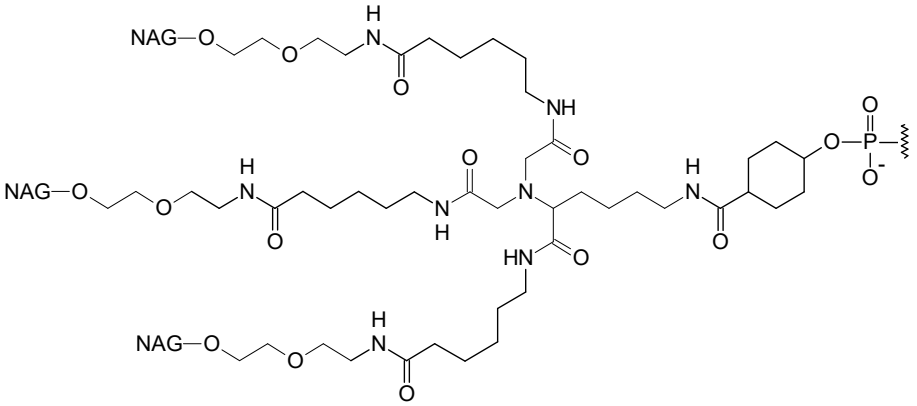
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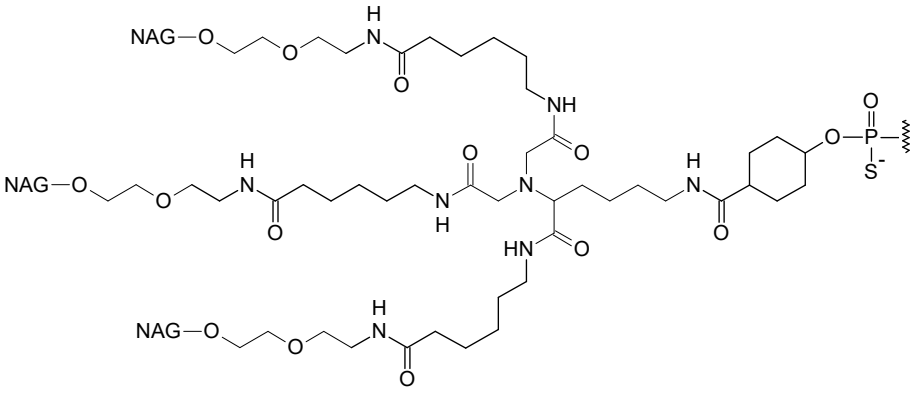
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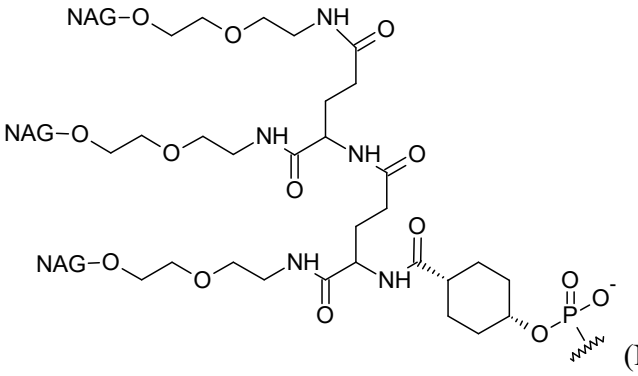
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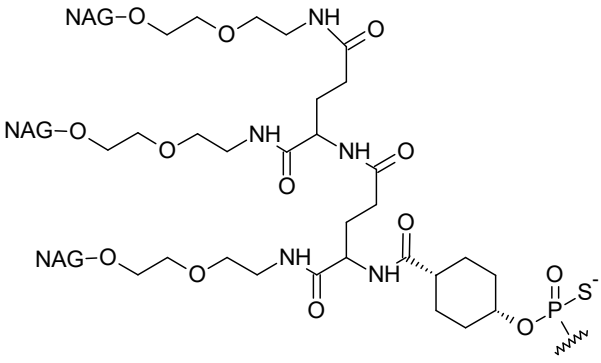
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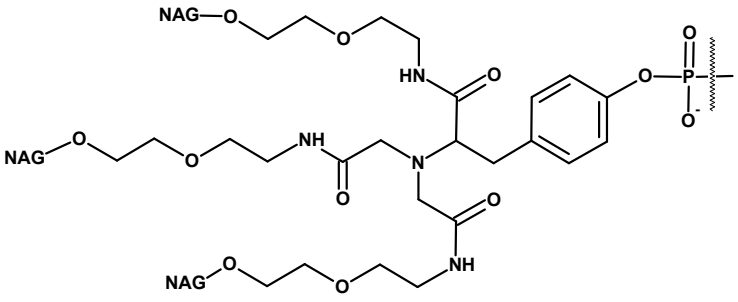
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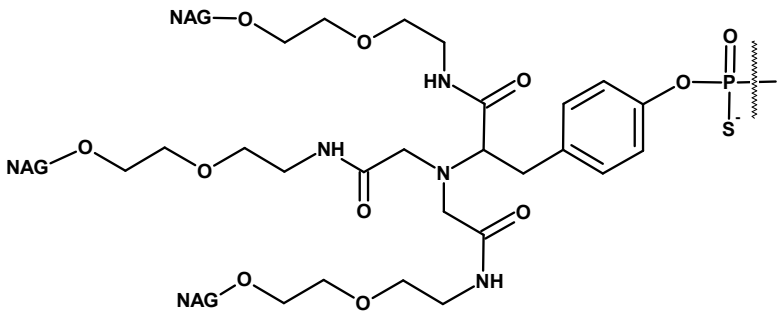
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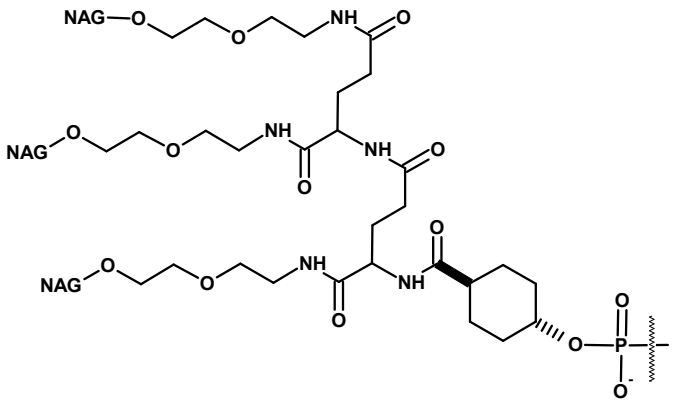
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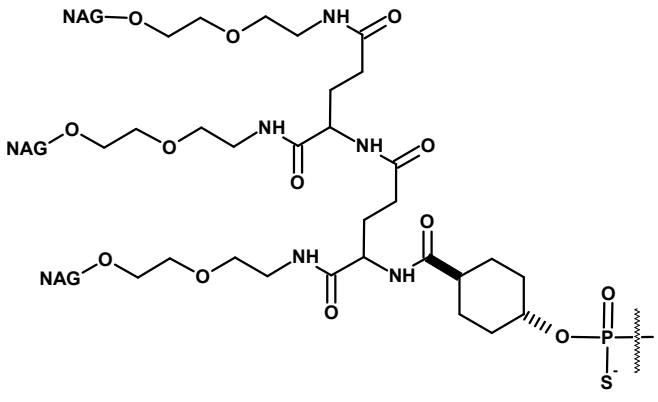
(NAG38),



(NAG38)s,



(NAG39), or



(NAG39)s;

wherein NAG is N-acetyl-galactosamine.

7. The RNAi agent of any one of claims 4-6, wherein the targeting ligand is linked to the 3′ or 5′ end of the sense strand of the RNAi agent.

8. The RNAi agent of any one of claims 4-6, wherein the targeting ligand is linked to the 3′ or 5′ end of the antisense strand of the RNAi agent.

9. The RNAi agent of any one of claims 4-7, wherein the sense strand has a structure of:

(NAG25)sgsuggacuuCfUfCfucaauuuucus(invAb) (SEQ ID NO: 229);

(NAG37)s(invAb)sguggacuuCfUfCfucaauuuucus(invAb) (SEQ ID NO: 252); or

(NAG25)s(invAb)sguggacuuCfUfCfucaauuuucus(invAb) (SEQ ID NO: 273);

wherein a, g, c and u are 2'-O-methyl modified nucleotides;

Af, Cf, Gf, and Uf are 2'-fluoro modified nucleotides;

s is a phosphorothioate internucleoside linkage;

(invAb)s is an inverted (3'-3' linked) abasic deoxyribonucleotide-5'-phosphorothioate; and

(invAb) is an inverted (3'-3' linked) abasic deoxyribonucleotide.

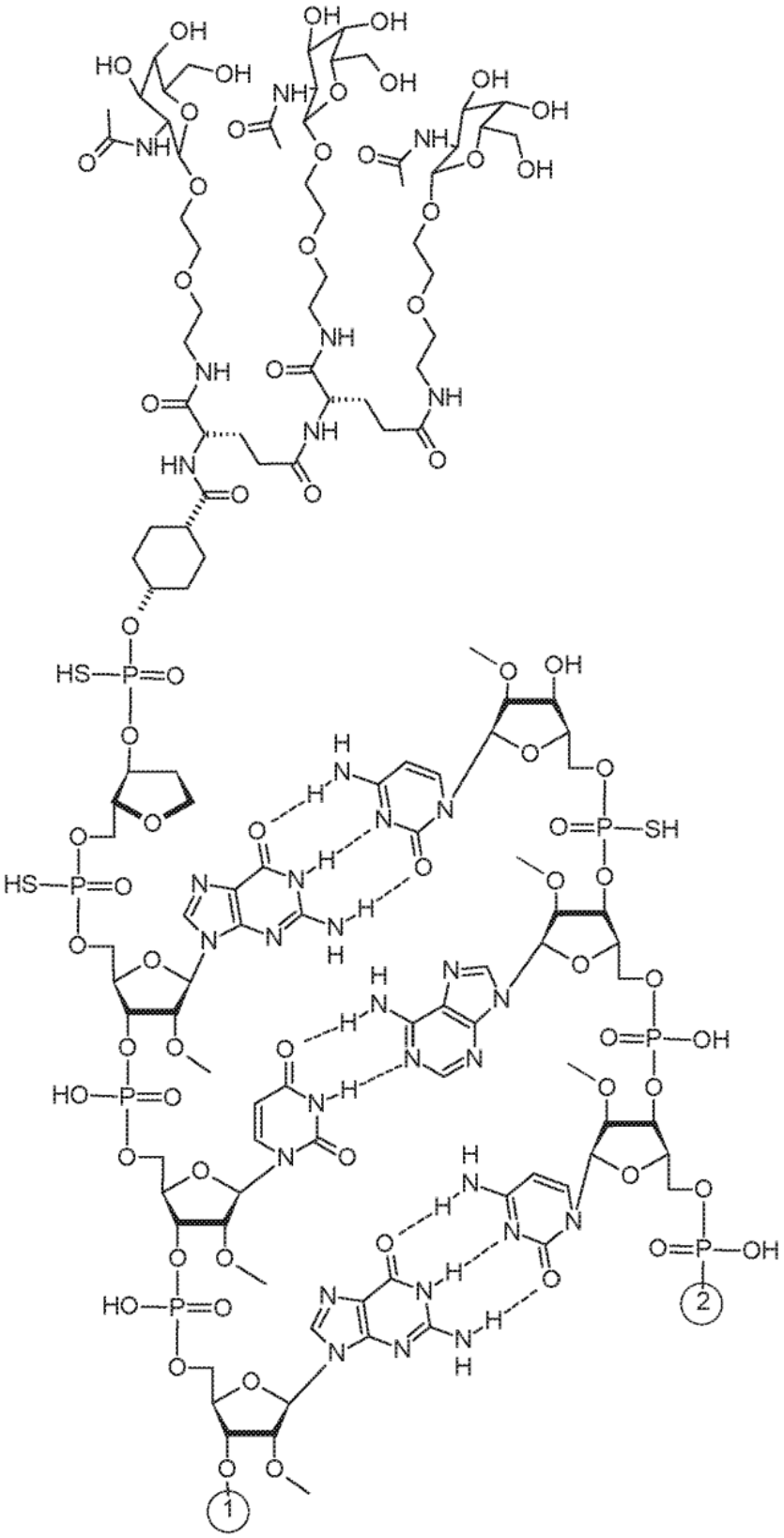
10. The RNAi agent of any one of claims 1-9, wherein the antisense strand has a structure of:

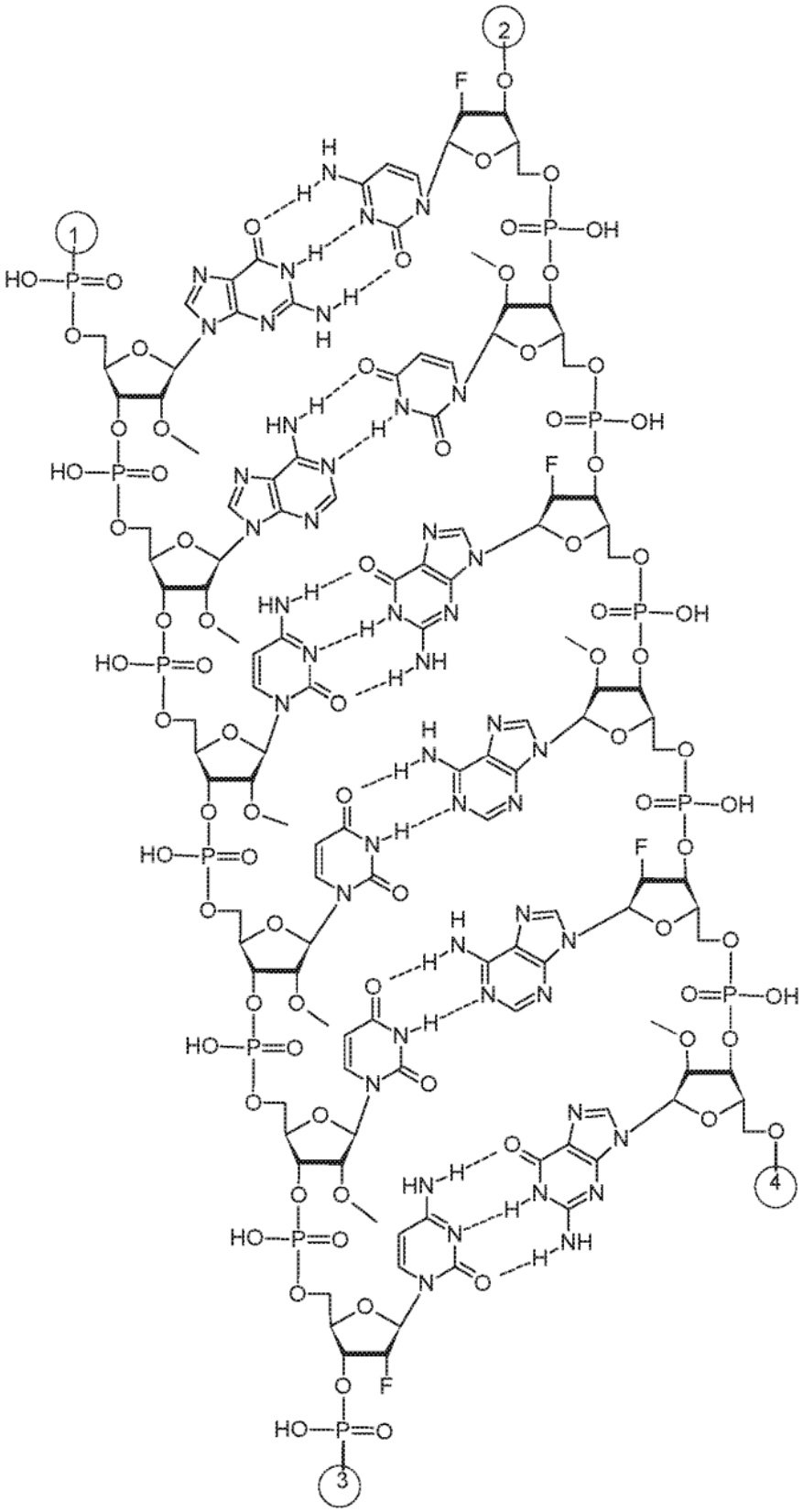
asGfsasAfaAfuugagAfgAfaGfuCfcAfsc (SEQ ID NO: 100); or

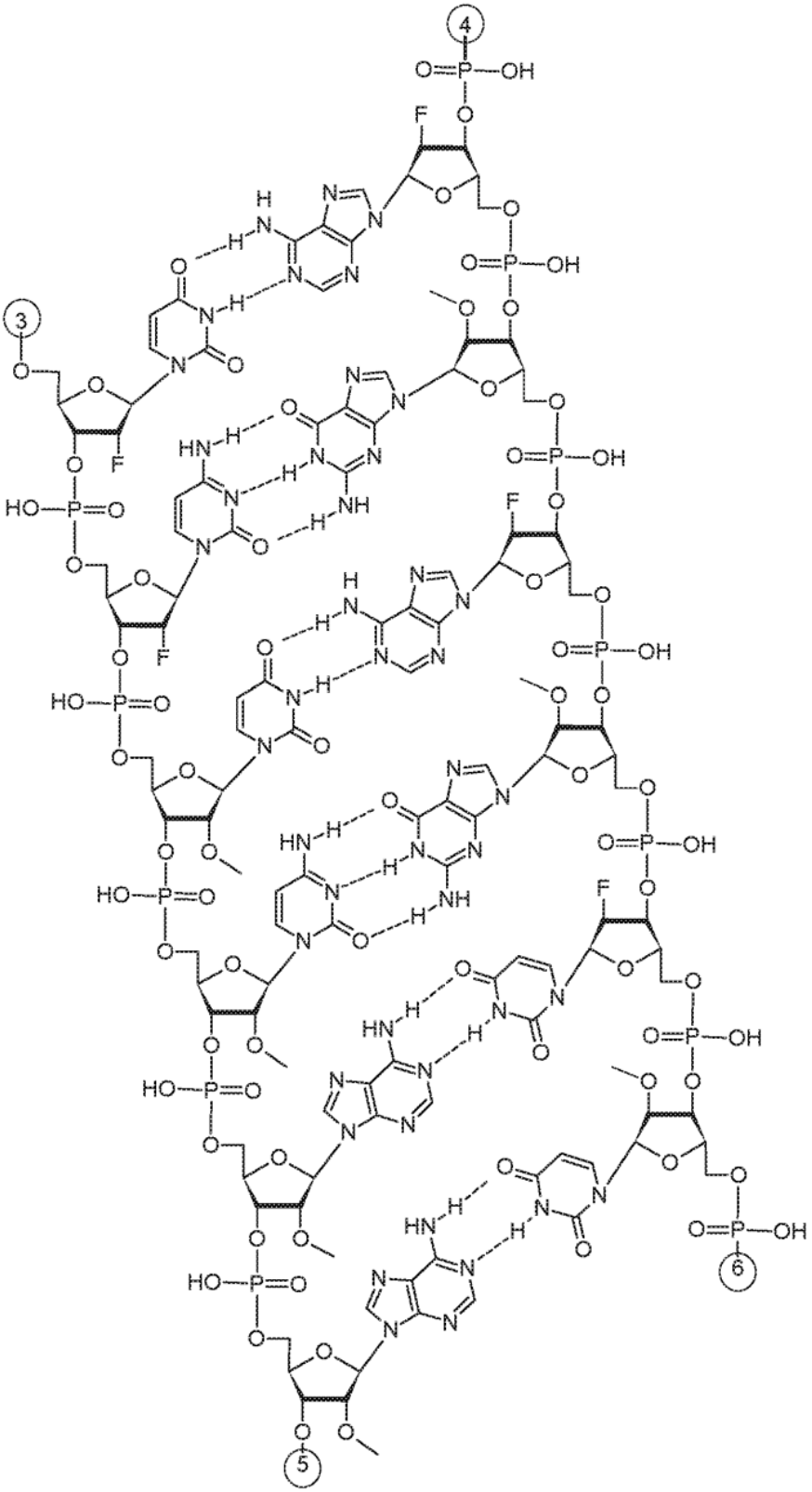
asGfsasAfaAfuUfgAfgAfgAfaGfuCfcasc (SEQ ID NO: 126).

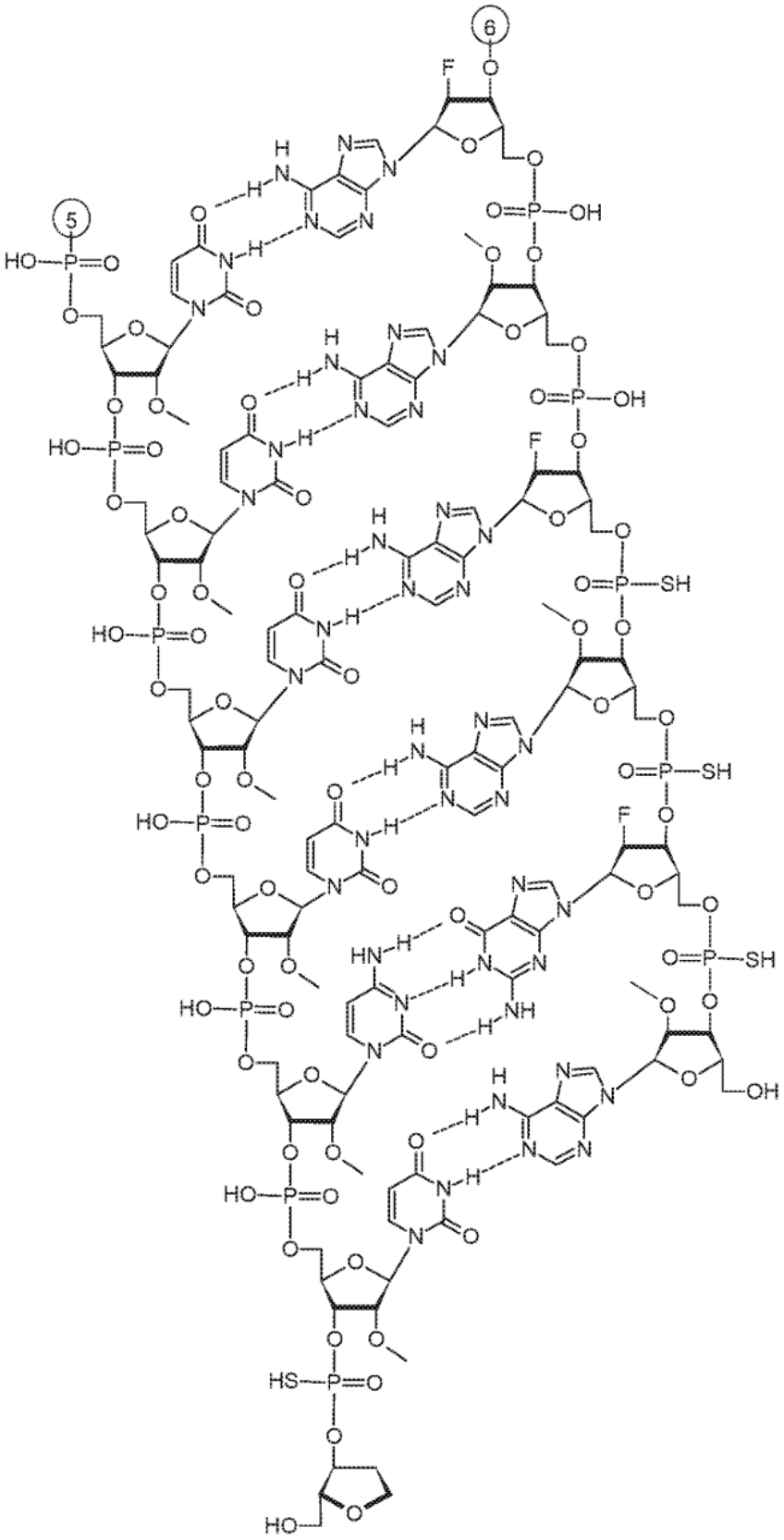
11. The RNAi agent of any one of claims 1-10, wherein the RNAi agent comprises a sense strand linked at the 5' terminal end to NAG37s having the structure (NAG37)s-(invAb)sguggacuuCfUfCfucaauuuucus(invAb) (SEQ ID NO: 252) and an antisense strand having the structure asGfsasAfaAfuUfgAfgAfgAfaGfuCfcasc (SEQ ID NO: 126).

12. The RNAi agent of claim 11, which has the structure:



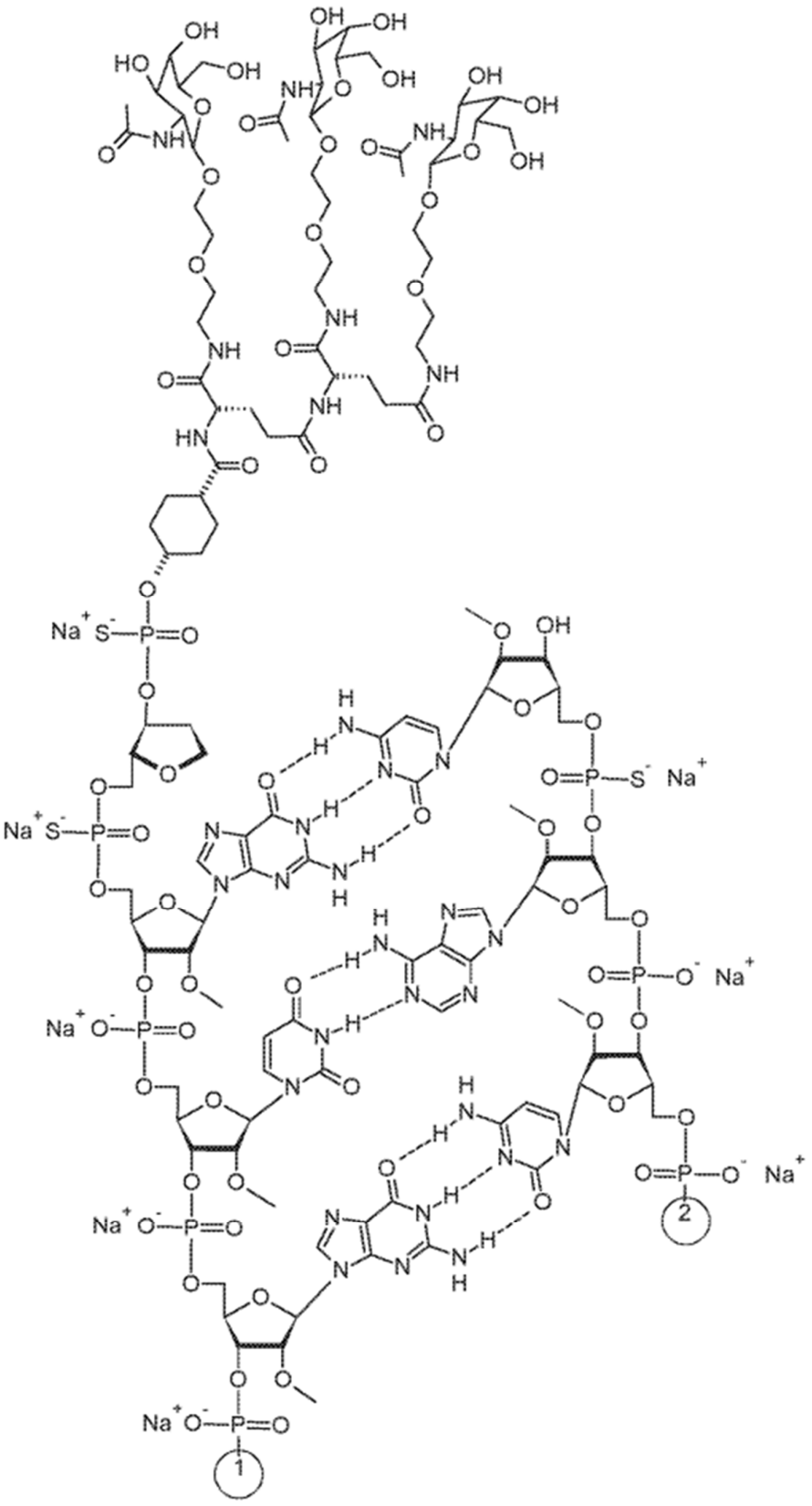


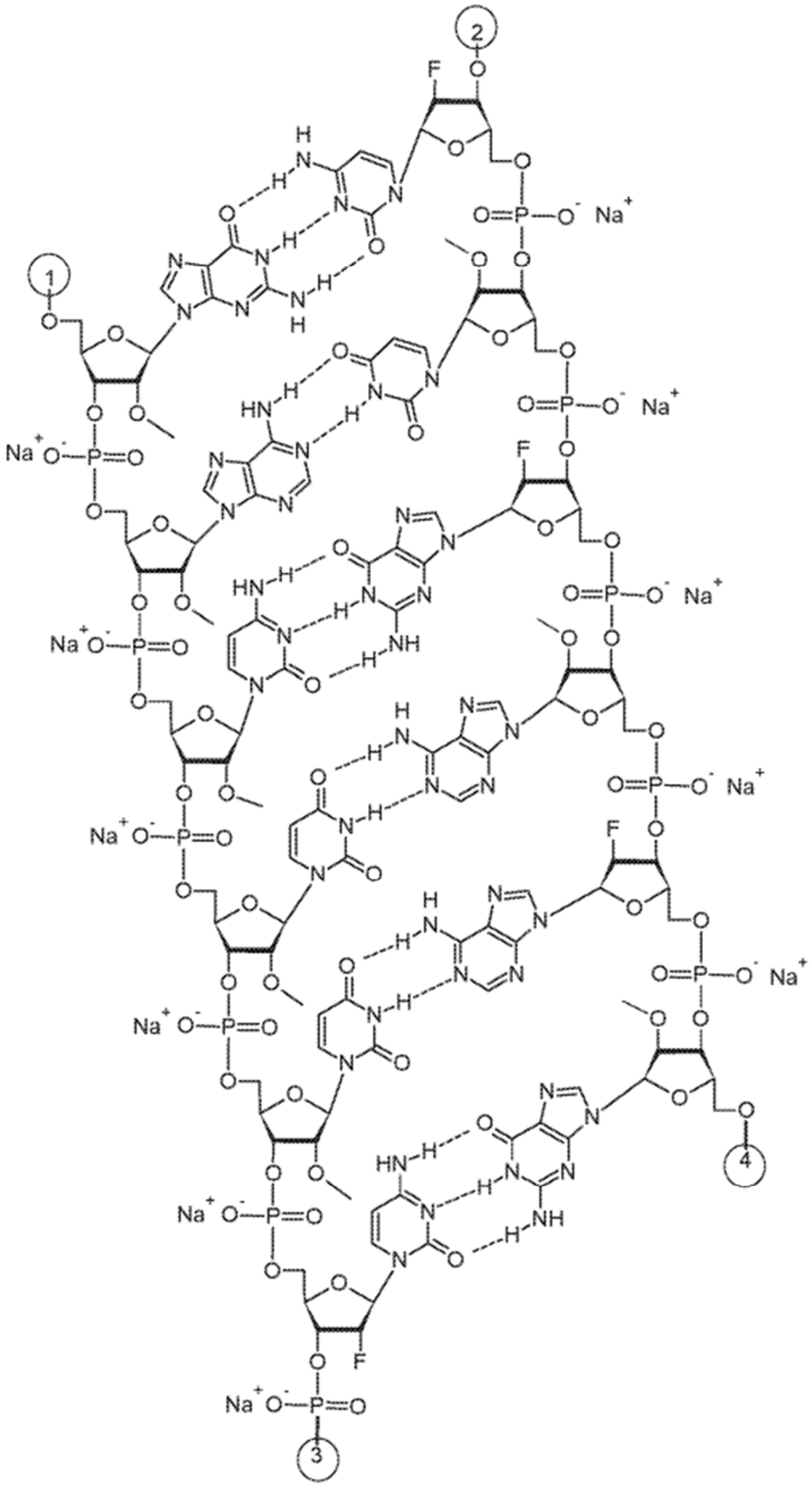


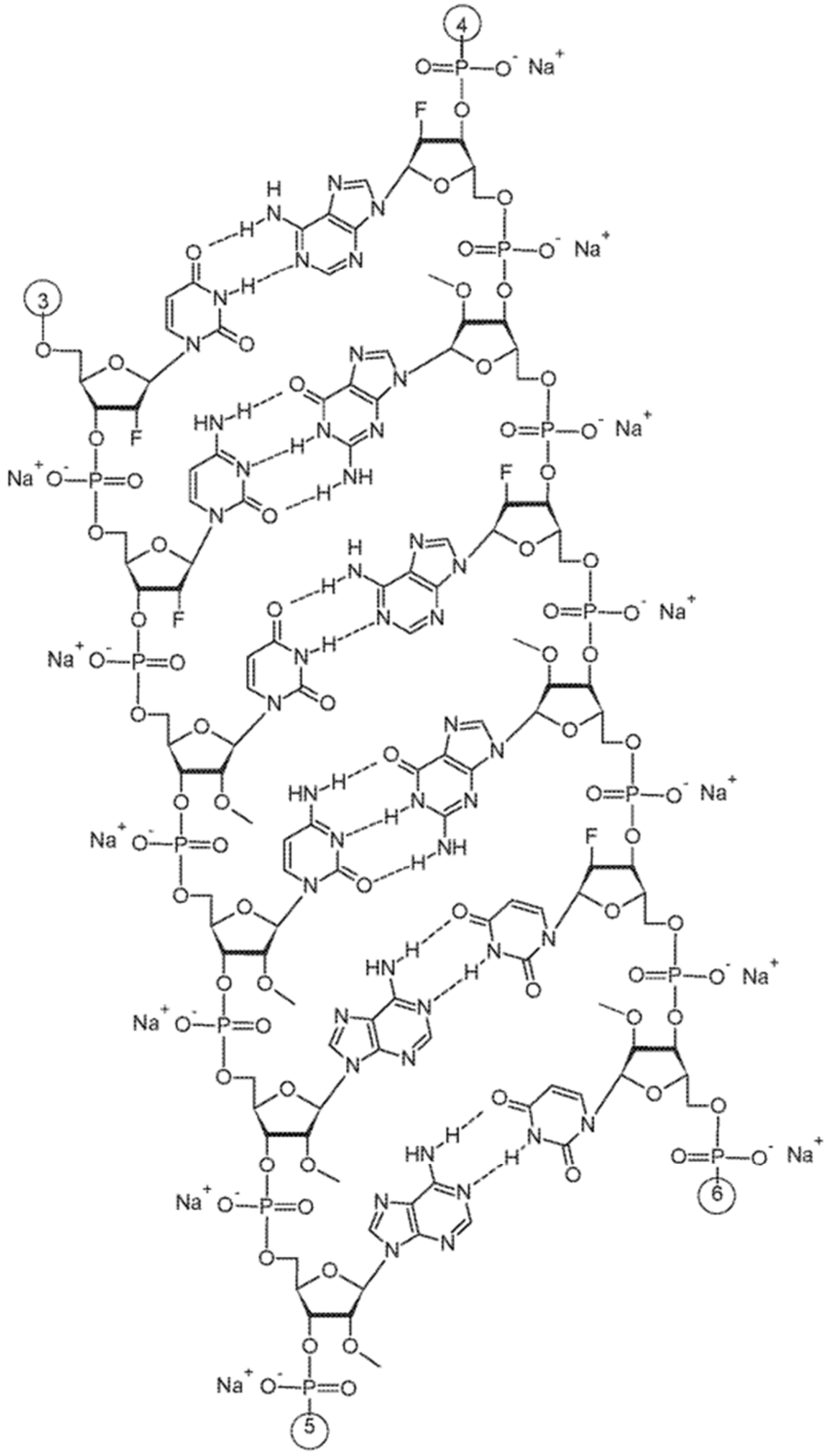


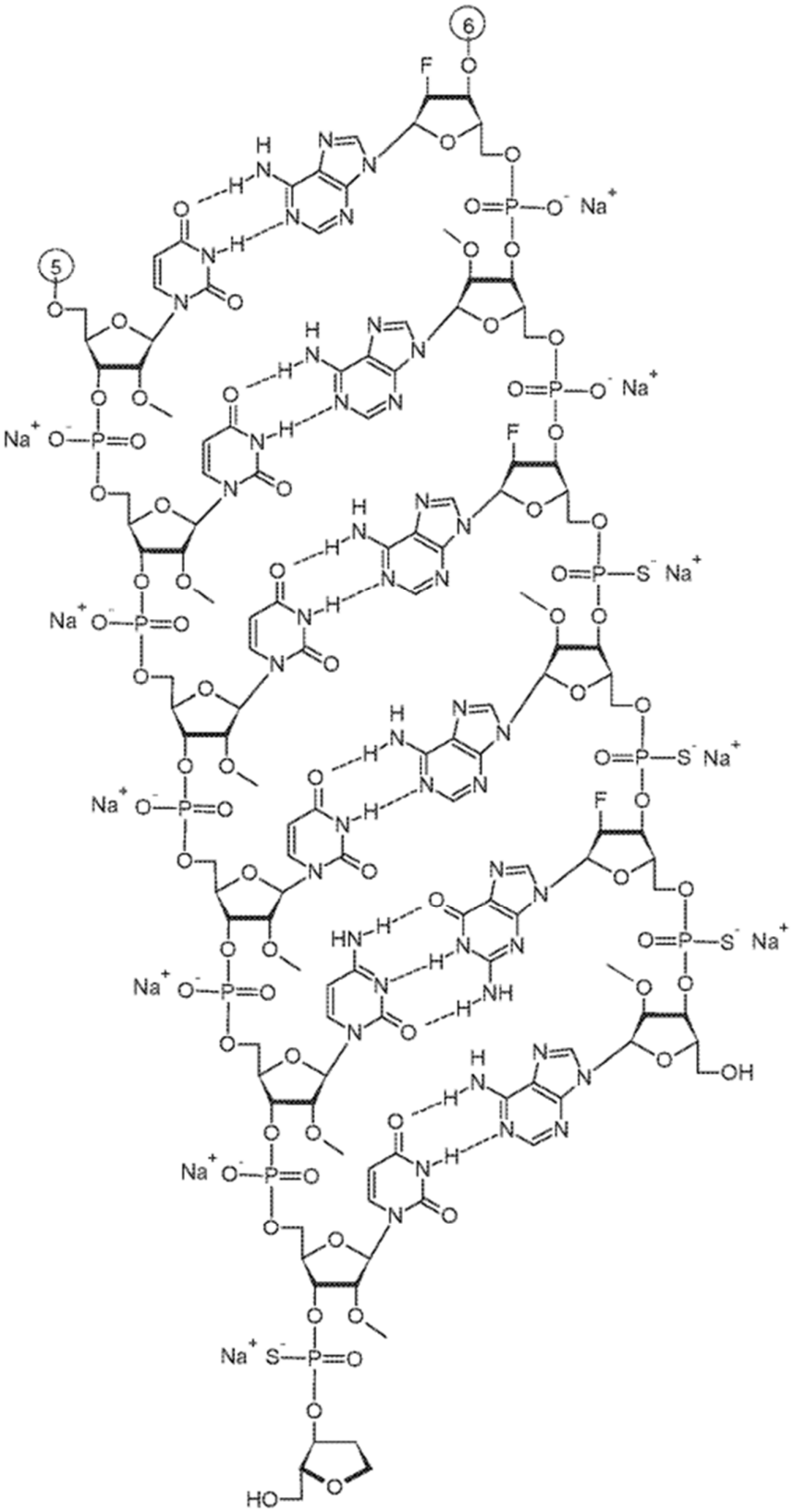
and is provided as a salt, mixed salt, or a free-acid.

13. The RNAi agent of claim 12, wherein the RNAi agent is a sodium salt and has the structure:





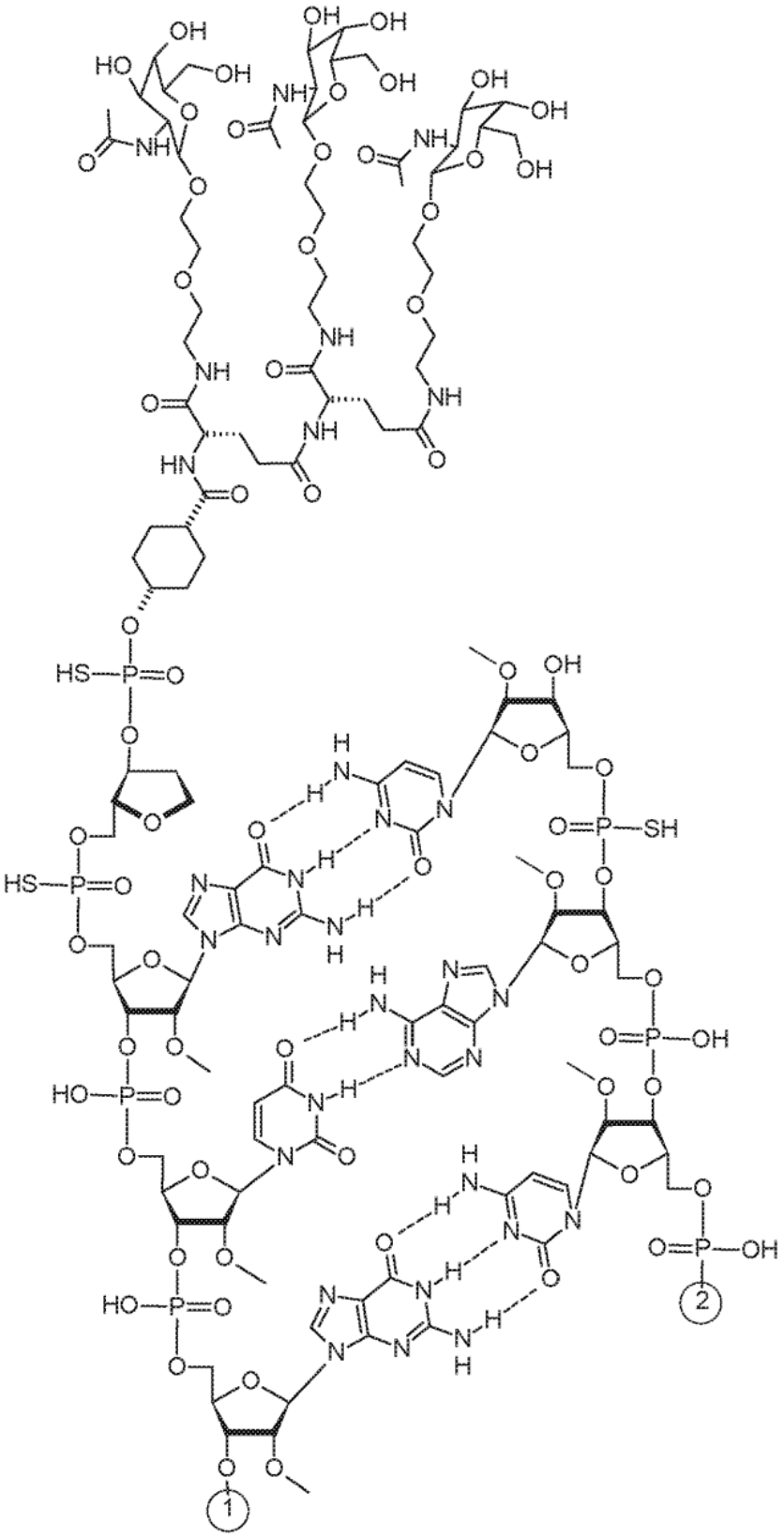


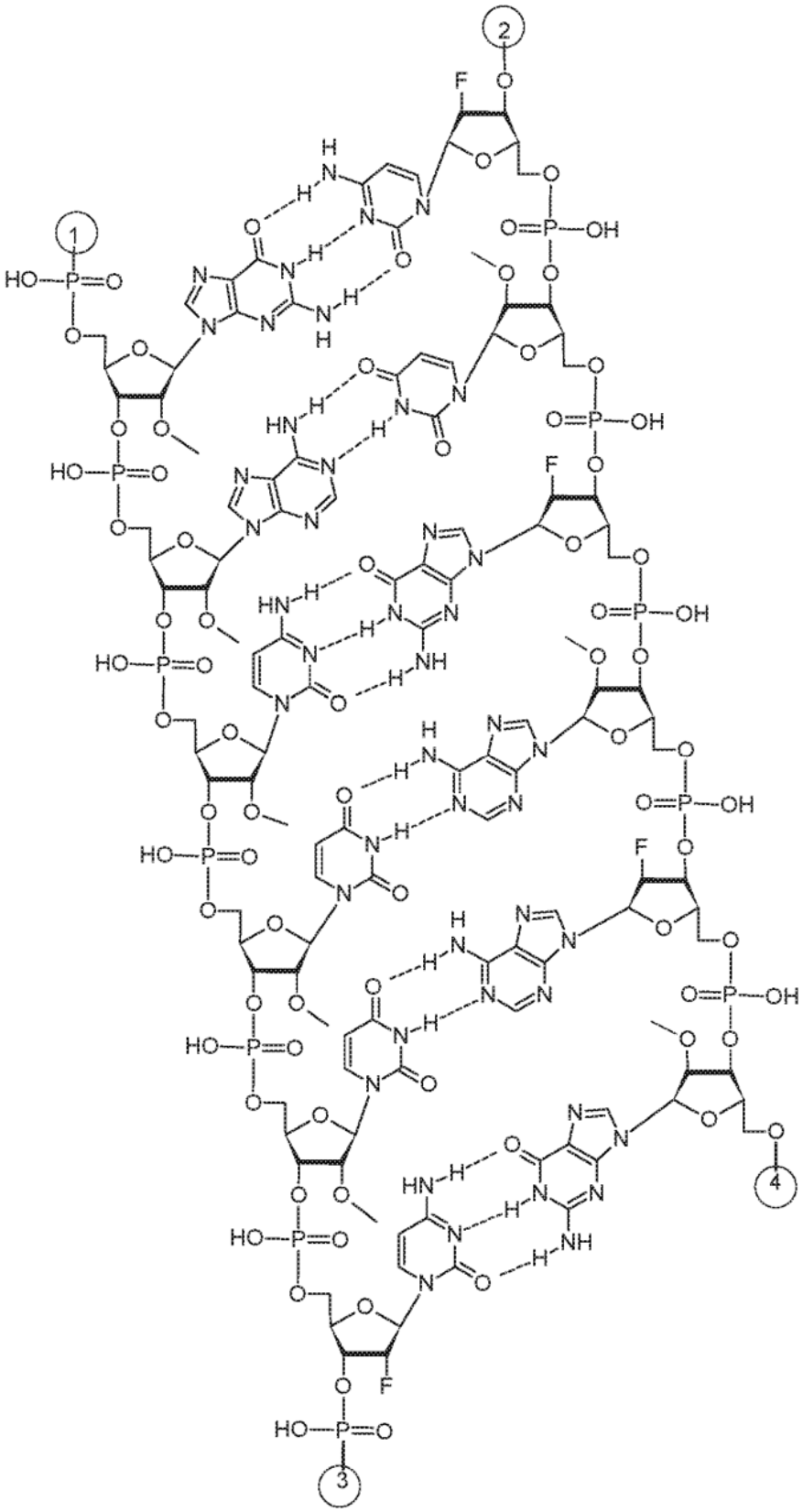


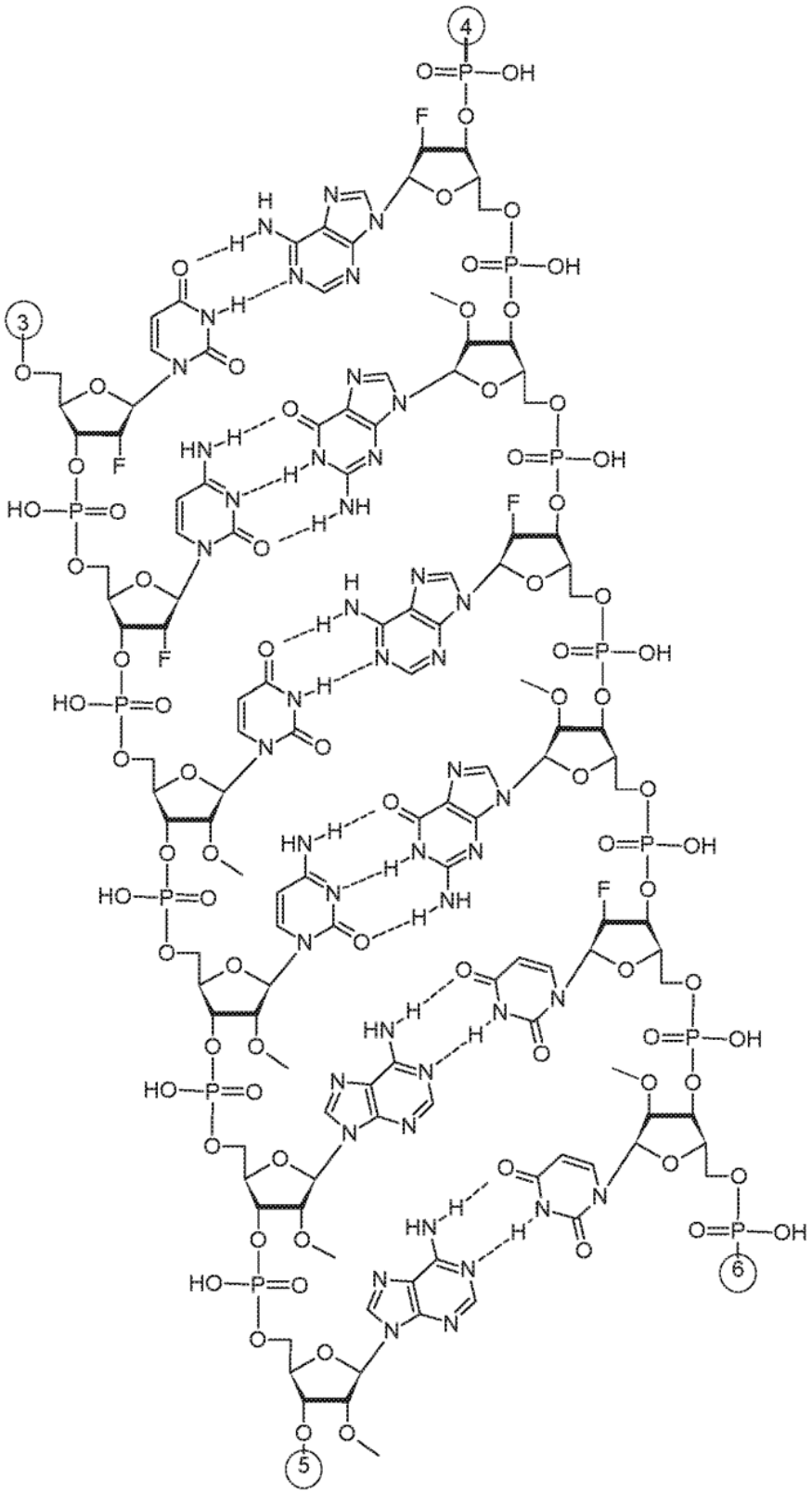
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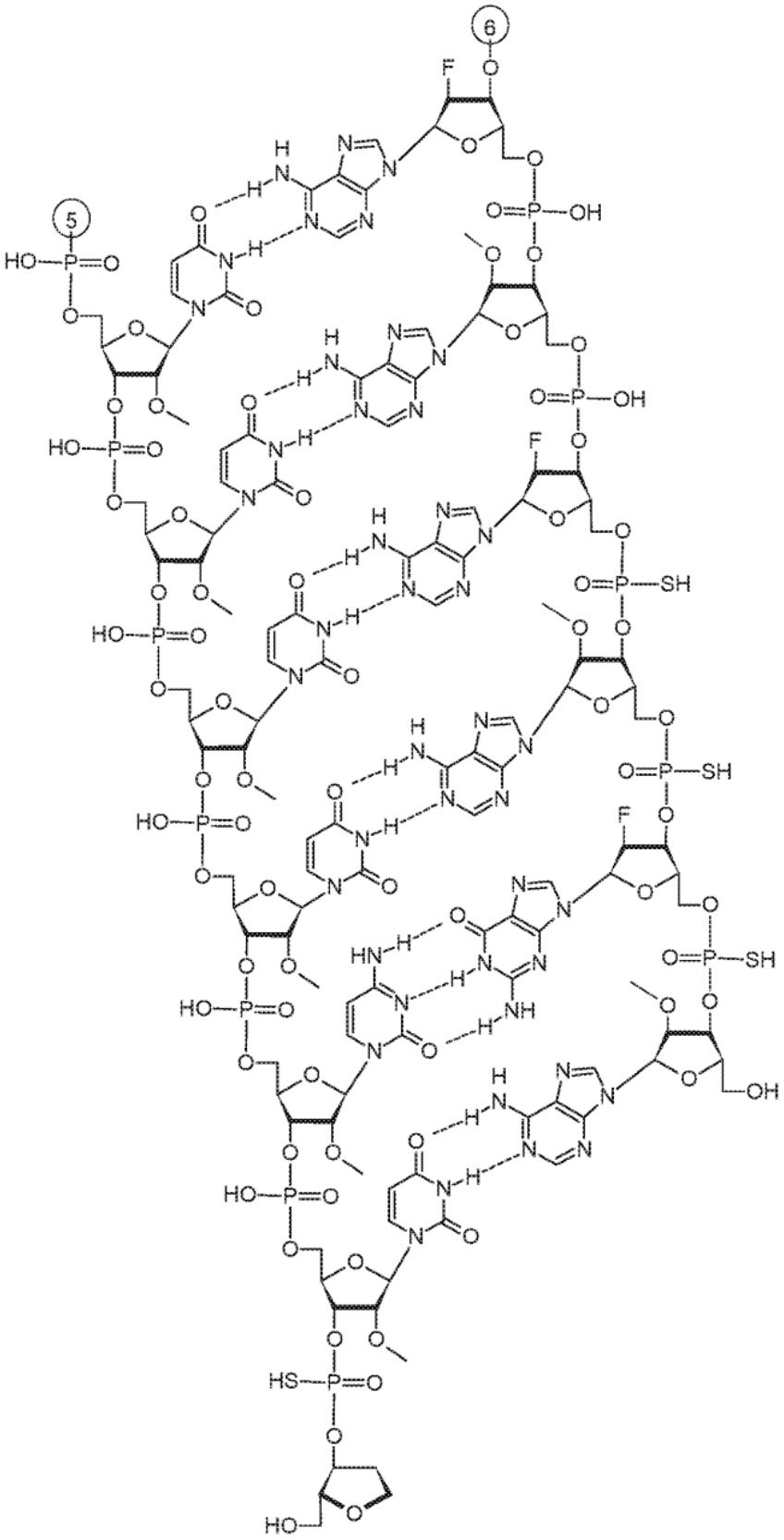
14. A combination comprising a first RNAi agent according to claim 11, and a second RNAi agent comprising a sense strand linked at the 5' terminal end to NAG37s which has the structure (NAG37)s-(invAb)scgcuguagGfCfAfuaaauugguas(invAb) (SEQ ID NO: 262) and an antisense strand having the structure usAfscsCfaAfuUfuAfuGfcCfuAfcAfgcsg (SEQ ID NO: 140), wherein the ratio of the first RNAi agent to the second RNAi agent is about 2:1.

15. The combination of claim 14, wherein the first RNAi agent has the structure represented by the following:



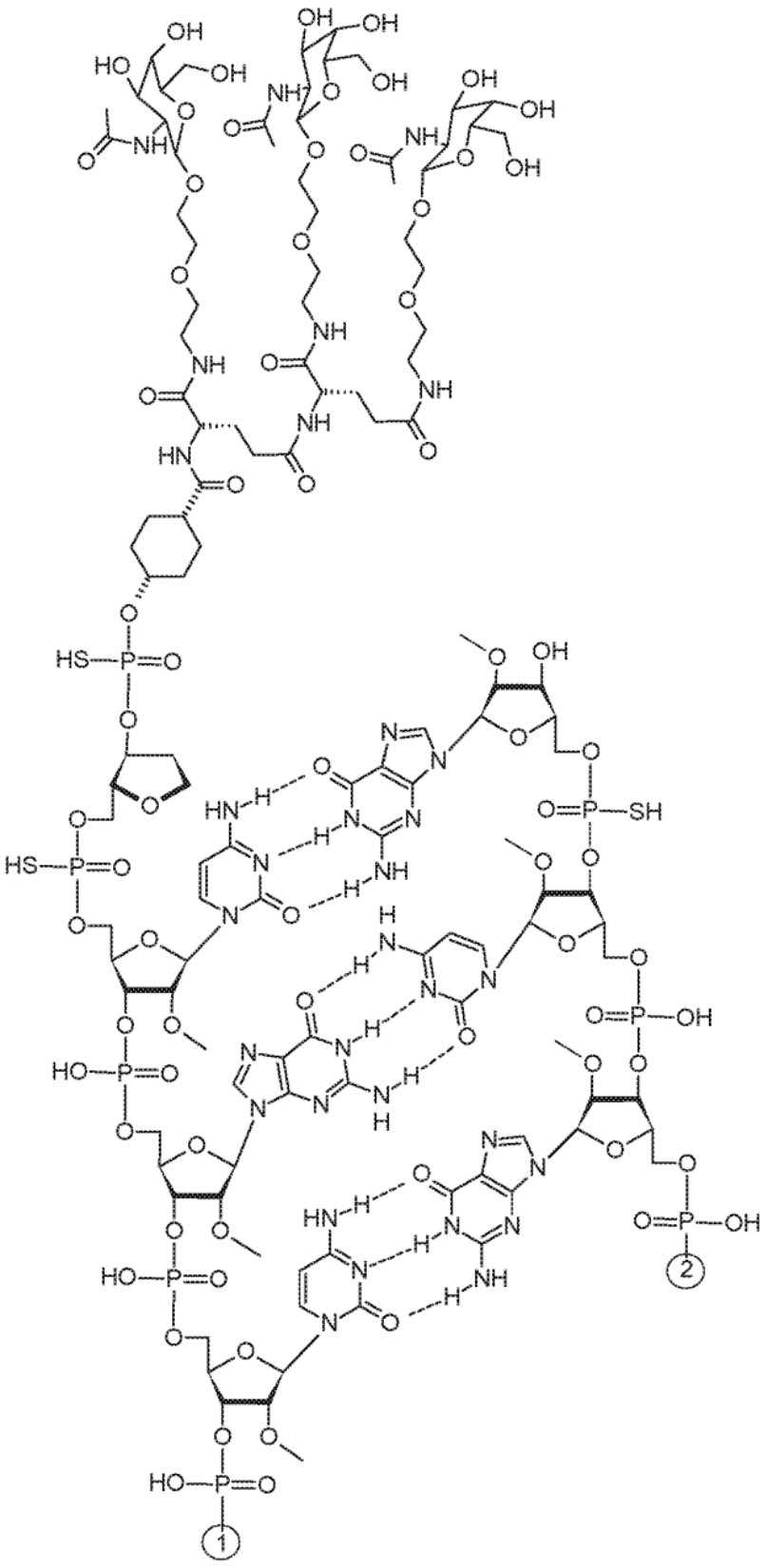


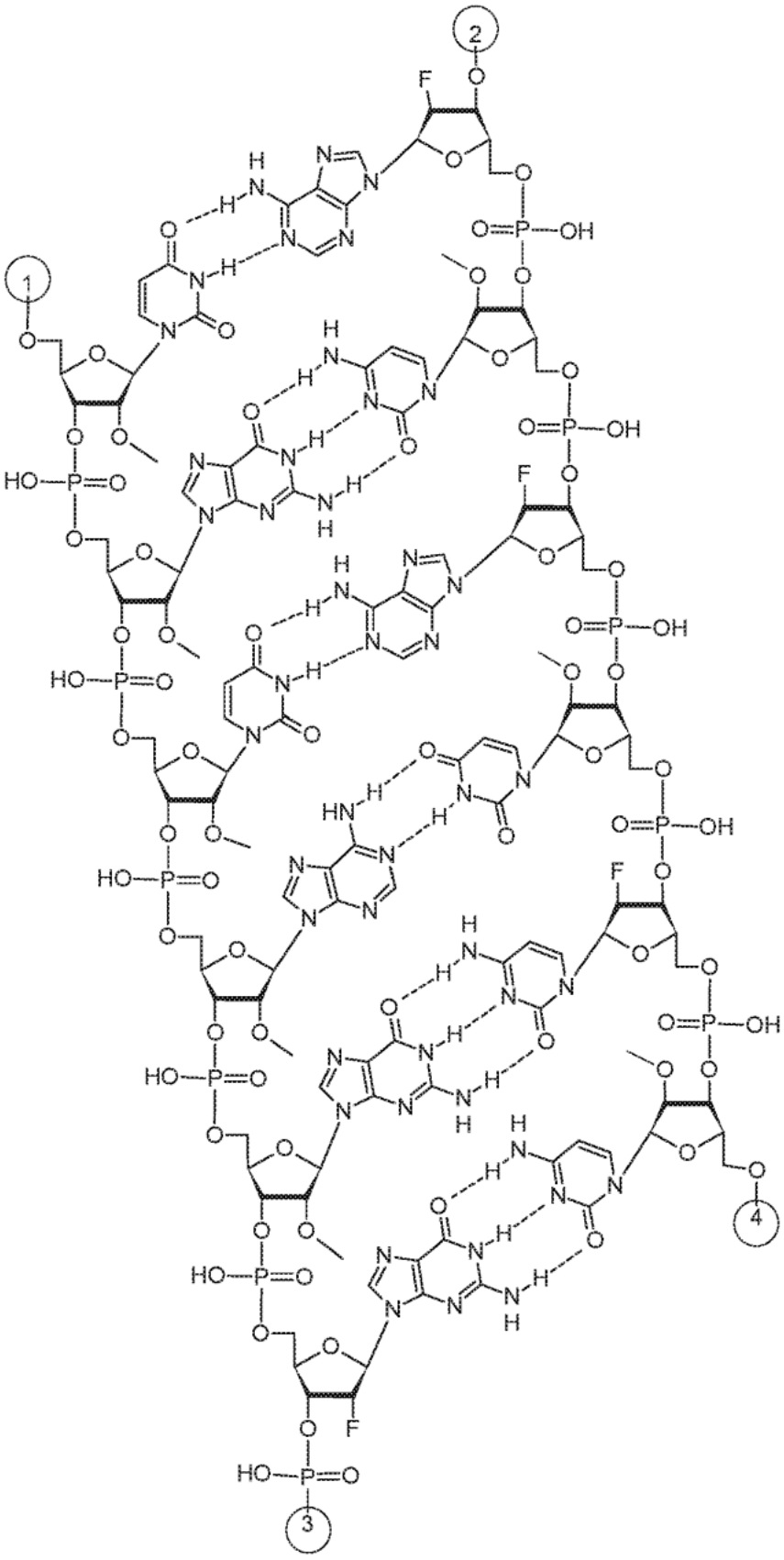


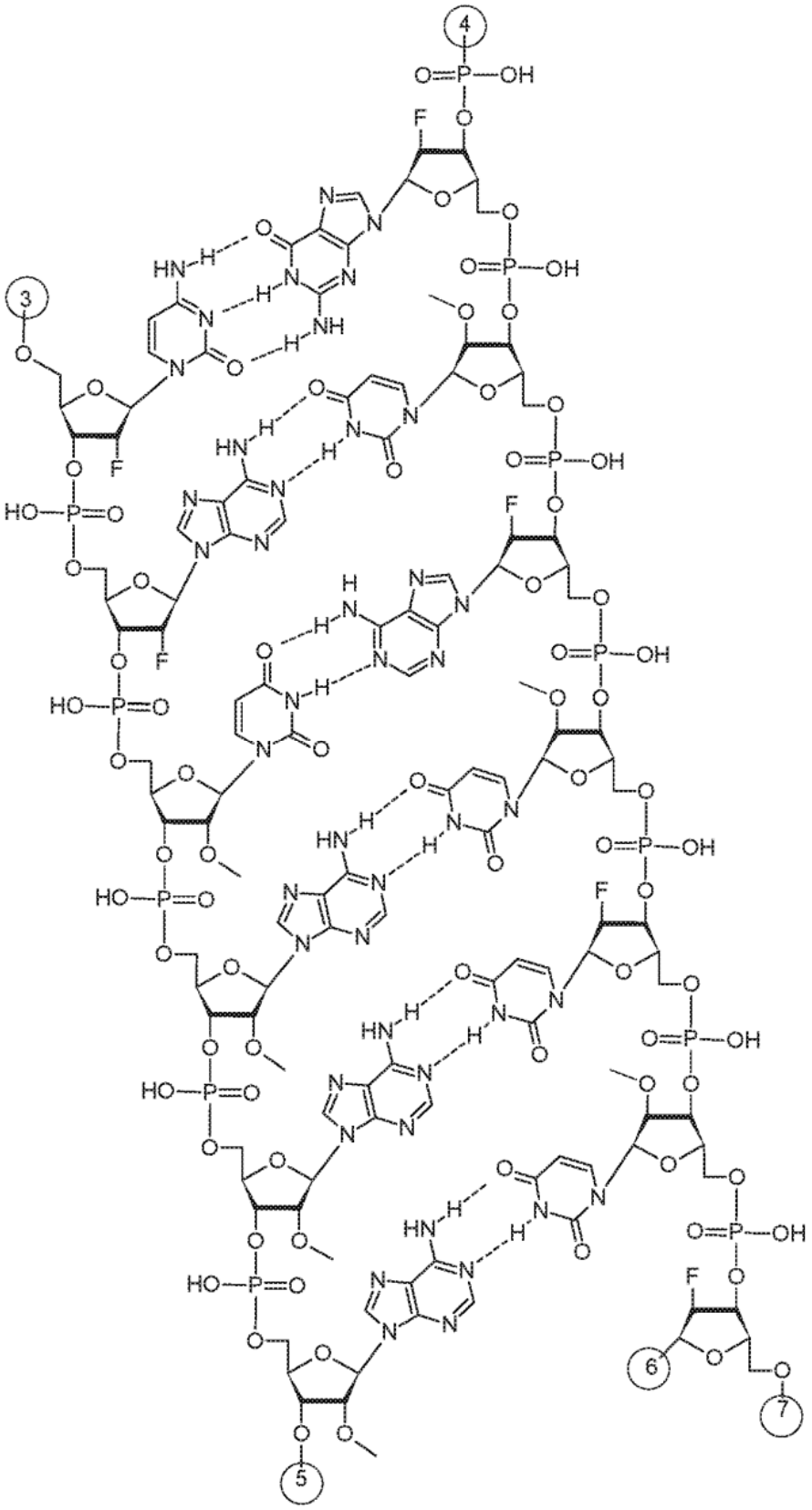


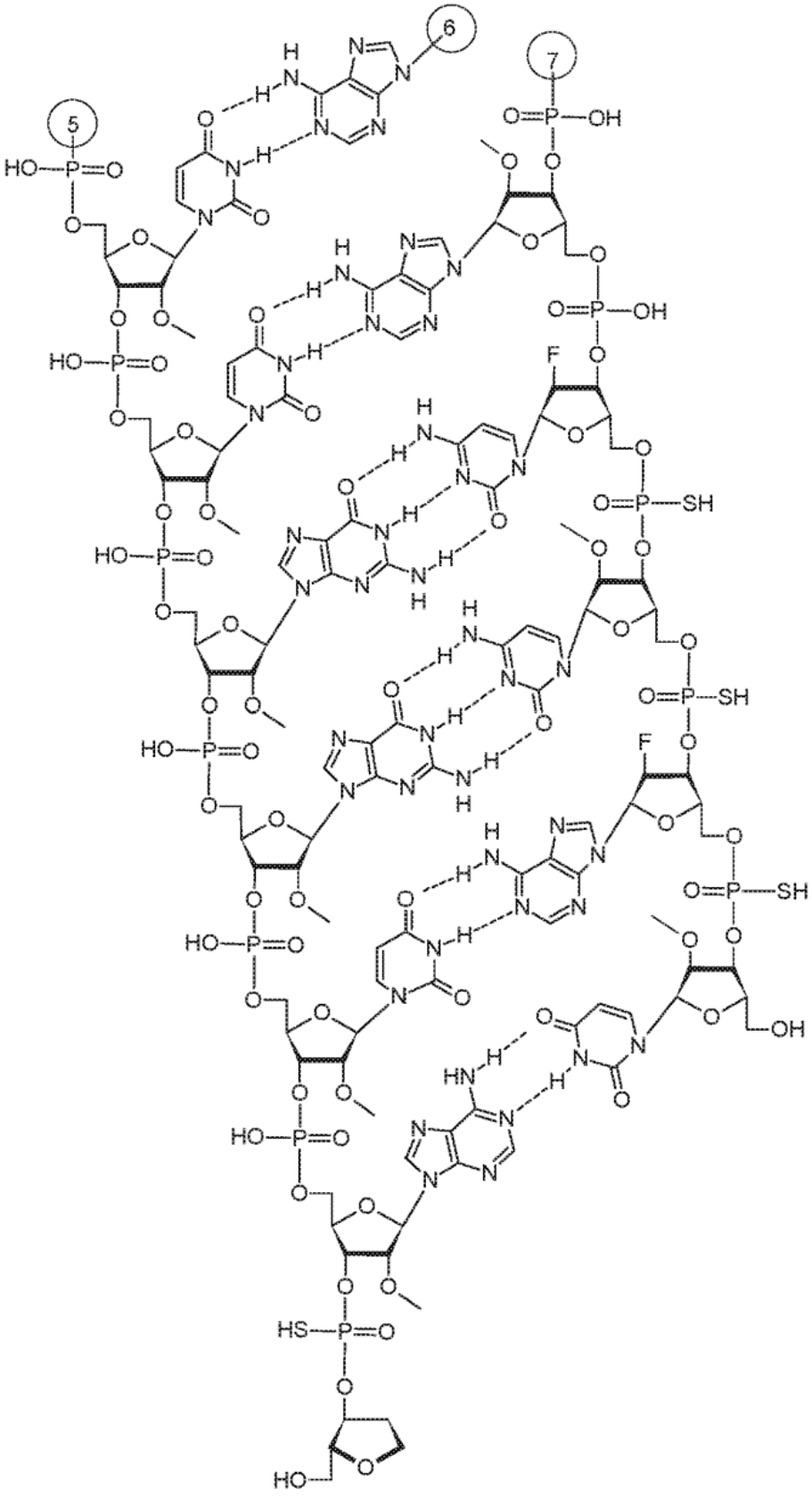
and is provided as a salt, mixed salt, or a free-acid;

and wherein the second RNAi agent has the structure represented by the following:




1
2
3
4
F
HO—P=O
O=P—OH

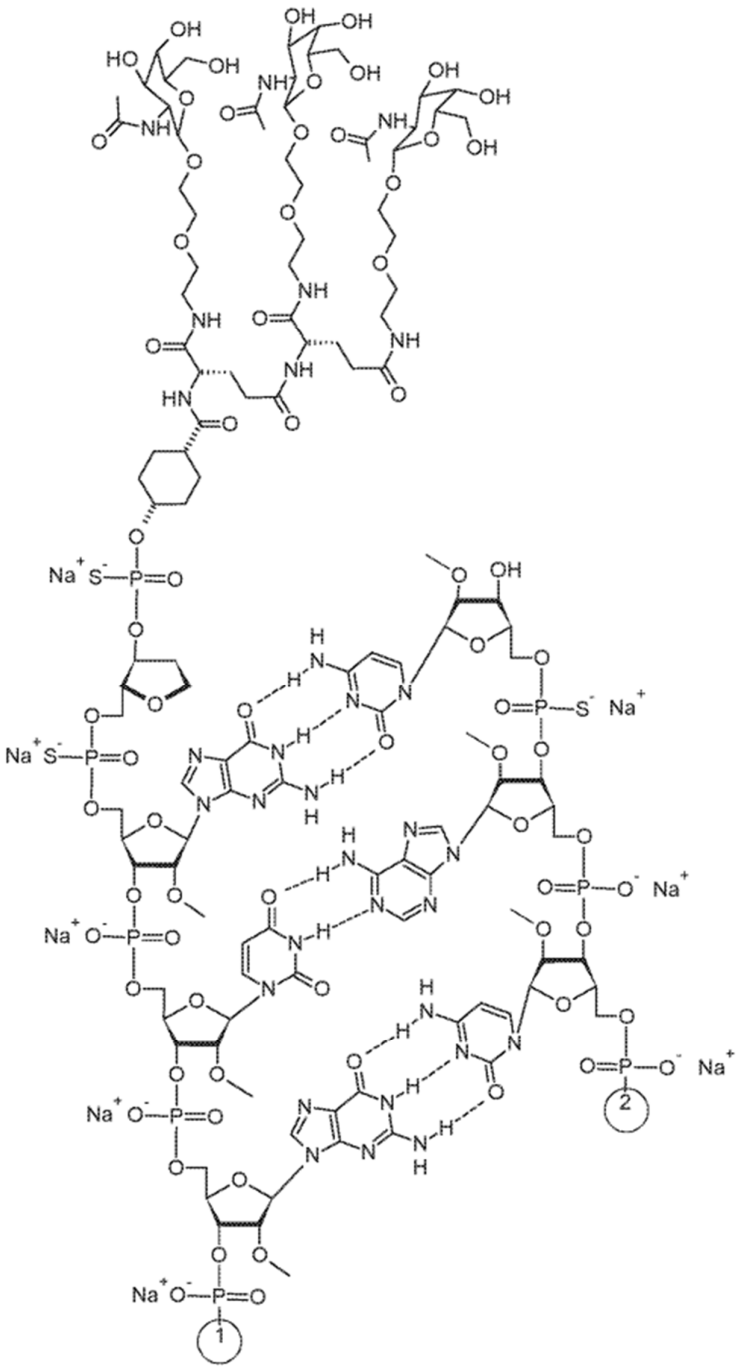


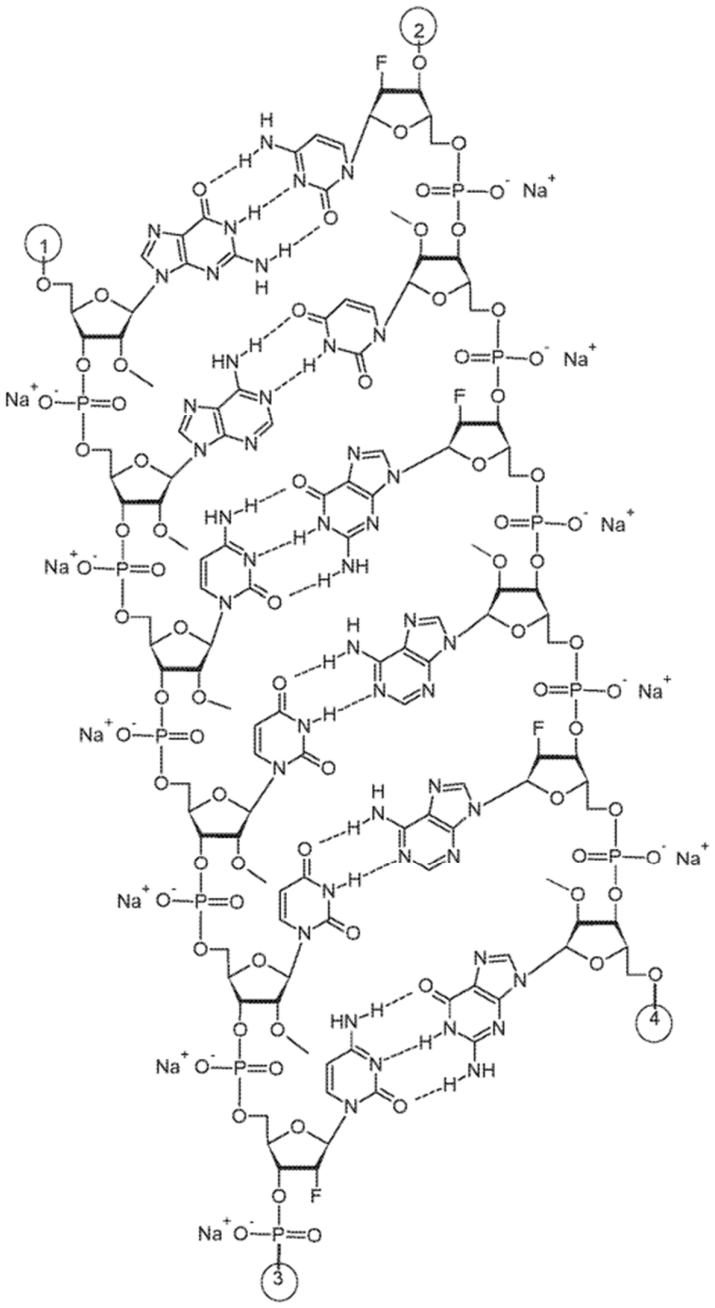


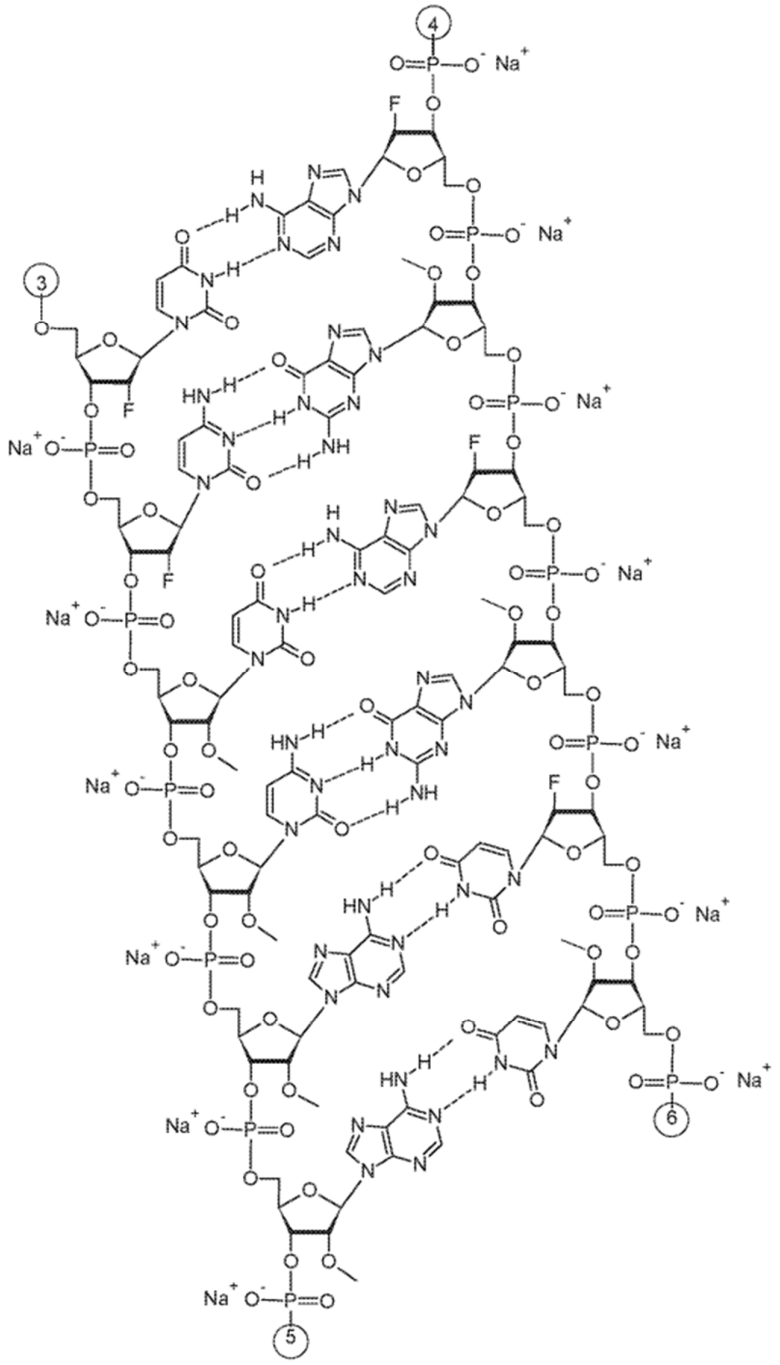
and is provided as a salt, mixed salt, or a free-acid.

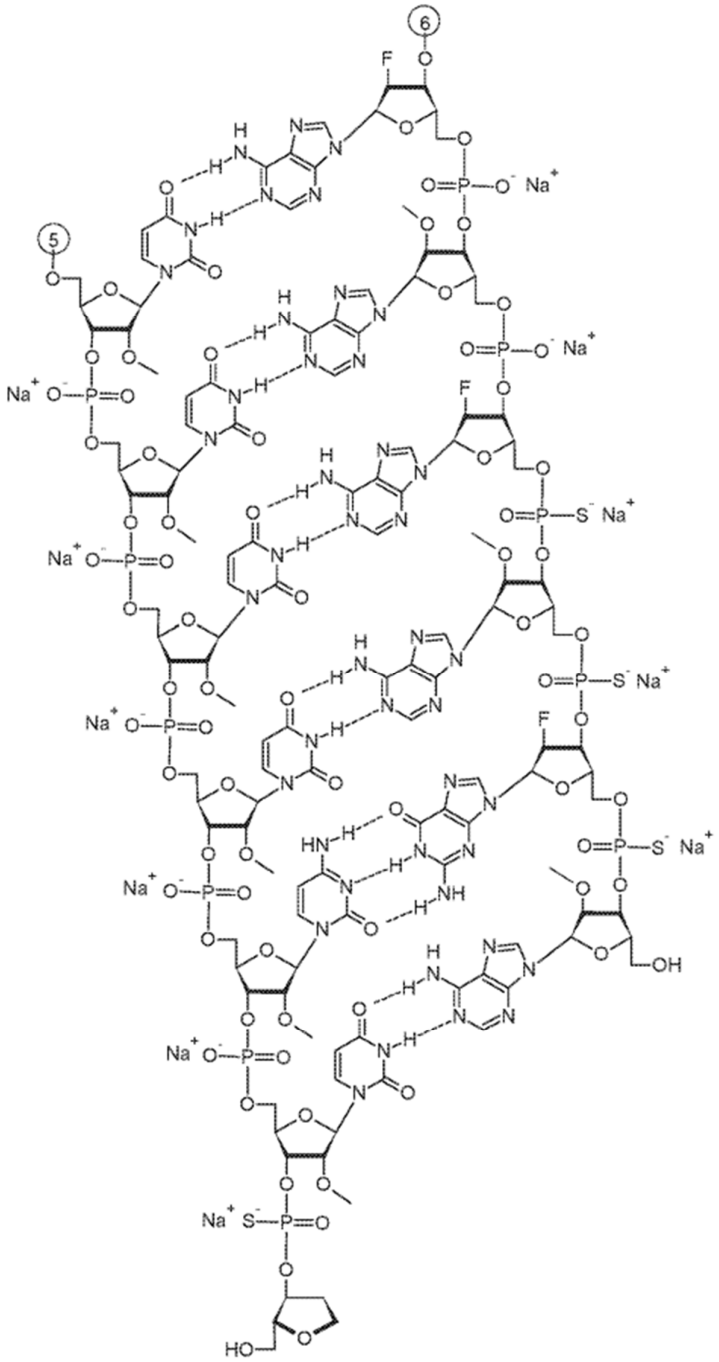
16. The combination of claim 15, wherein the first RNAi agent and/or the second RNAi agent are in a sodium salt form.

17. The combination of claim 16, wherein the first RNAi agent is in a sodium salt form and has the following structure:

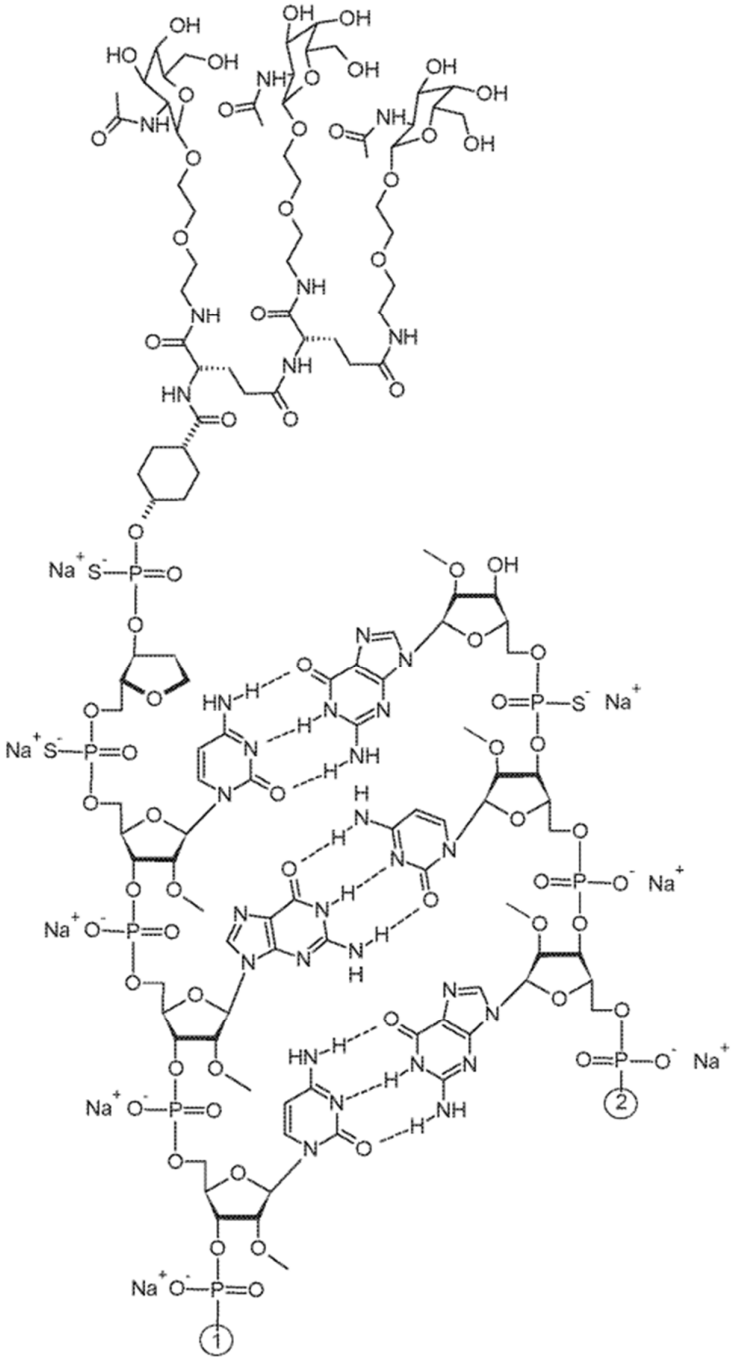


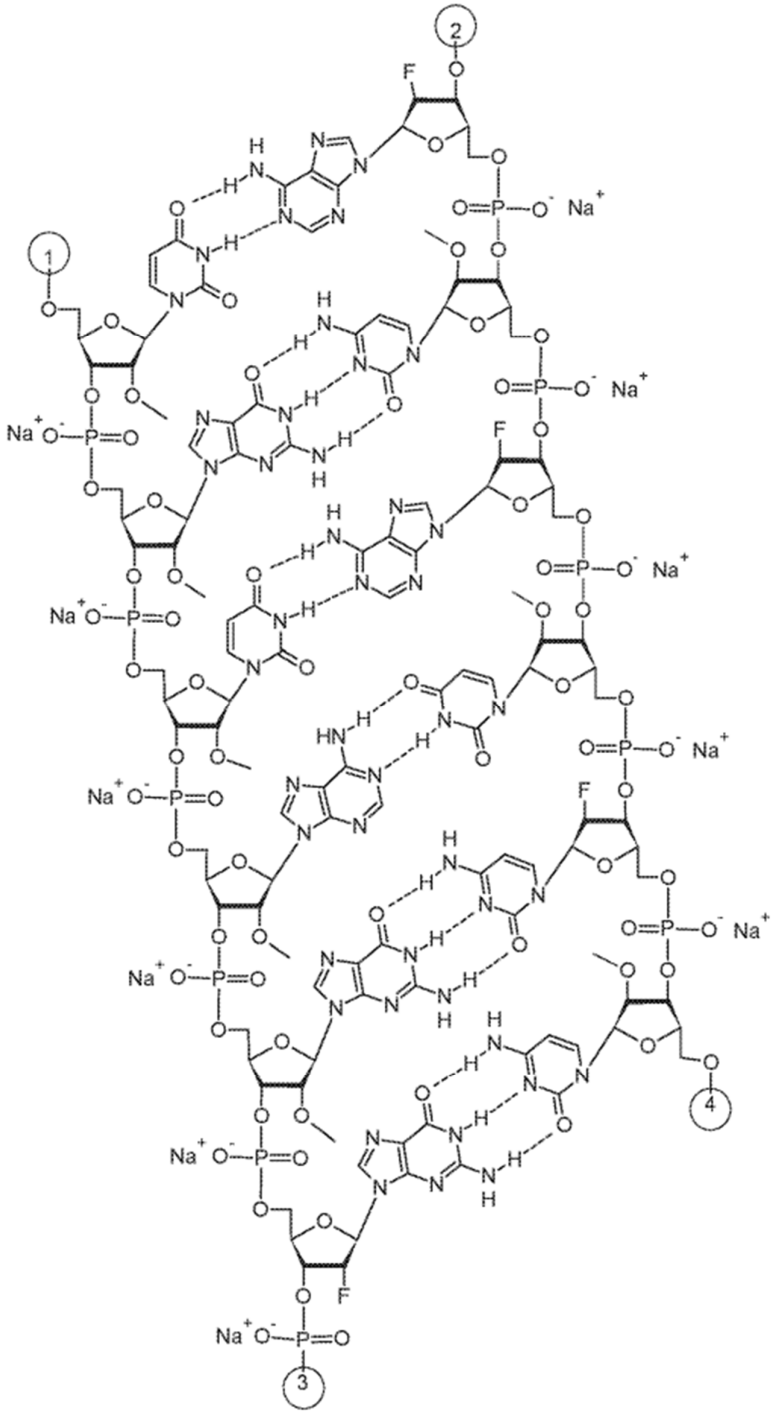


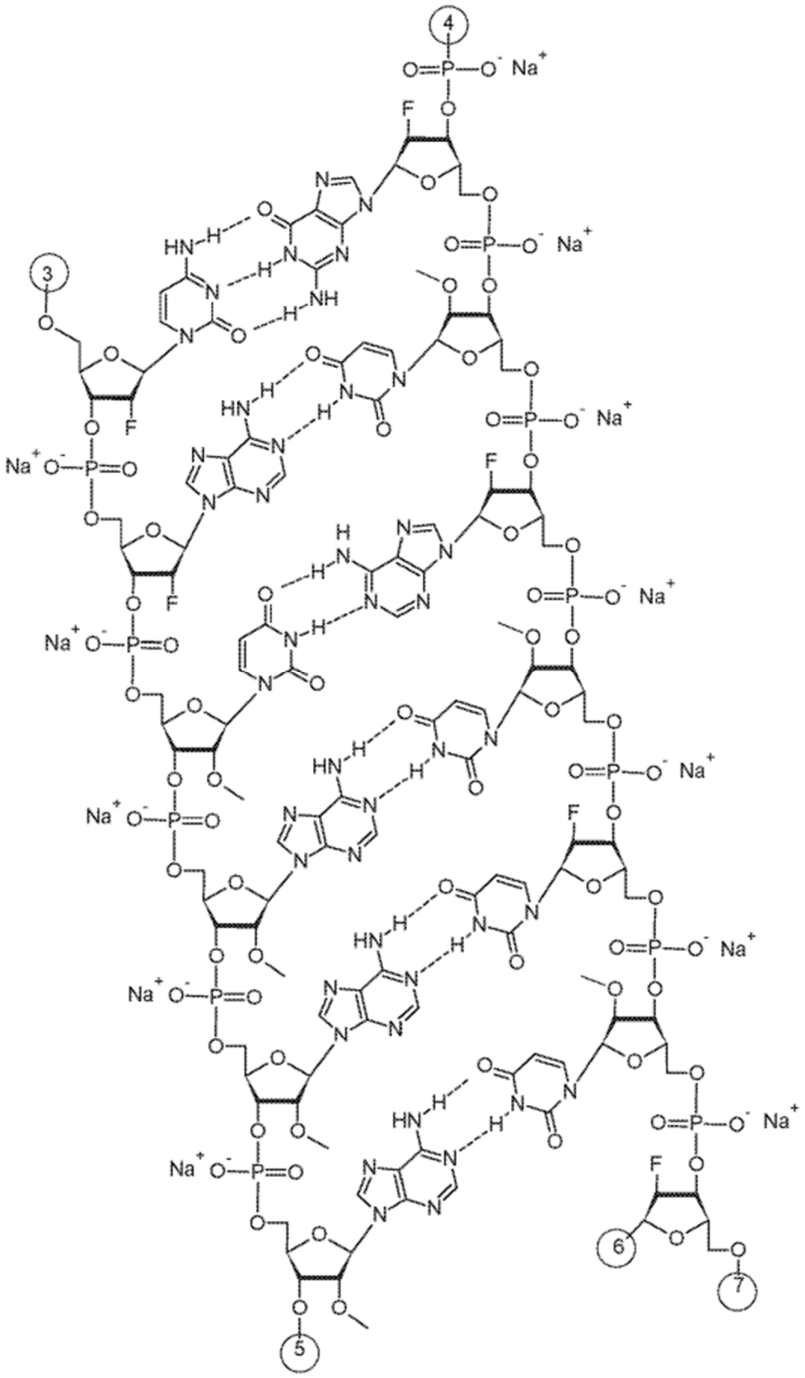


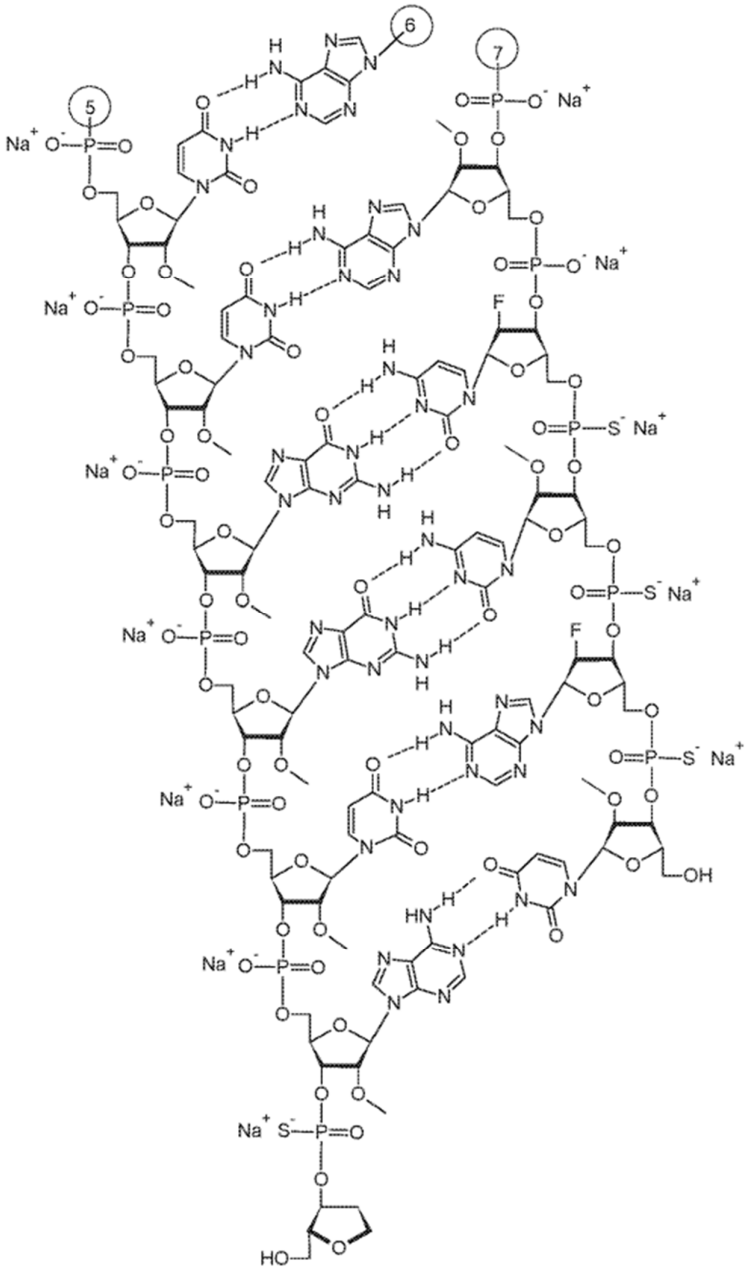


and wherein the second RNAi agent is in sodium salt form and has the following structure:









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18. A composition comprising the RNAi agent of any one of claims 1-13, or the combination of any of claims 14-17, and a pharmaceutically acceptable excipient.

19. The composition of claim 18, which is formulated for subcutaneous injection.

20. The composition of claim 18 or claim 19, which is a sterile injectable solution.

21. The composition of claim 18, which is a sterile powder for the preparation of a sterile injectable solution.

22. The composition of any one of claims 19-21, which is packaged in a pre-filled syringe or vial.

23. The composition of any one of claims 18-22, for use in the therapeutic treatment of chronic HBV infection.

24. The composition of any one of claims 18-22 and a further therapeutic for use in the treatment of chronic HBV infection, wherein the composition and further therapeutic are to be administered separately.

25. The composition and further therapeutic for use according to claim 24, wherein the additional therapeutic is a nucleoside inhibitor or nucleotide inhibitor.