

Claims

1. A double stranded RNA (dsRNA) molecule, said dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises a sequence substantially complementary to a nucleic acid sequence of 5' CTCTCGGATCTCCAAATTTA 3' (SEQ ID NO:1) or 5' CATCATAGCTACCATTATT 3' (SEQ ID NO:2);

(2) the antisense strand is at least 20 nucleotides in length;

(3) the antisense strand comprises at least 50% 2'-O-methyl modifications;

(4) the nucleotides at any one or more of positions 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, and 20 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;

(5) the nucleotides at positions 1-2 to 1-8 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;

(6) a portion of the antisense strand is complementary to a portion of the sense strand;

(7) the sense strand is at least 15 nucleotides in length;

(8) the sense strand comprises at least 65% 2'-O-methyl modifications;

(9) the nucleotides at any one of more of positions 4, 6, 8, 10, and 14 from the 5' end of the sense strand are not 2'-methoxy-ribonucleotides, or the nucleotides at any one of more of positions 7, 9, and 11 from the 5' end of the sense strand are not 2'-methoxy-ribonucleotides, or all nucleotides are 2'-methoxy-ribonucleotides; and

(10) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

2. The dsRNA of claim 1, wherein: the antisense strand is 20, 21, or 22 nucleotides in length; the sense strand is 15, 16, 18, or 20 nucleotides in length;

the dsRNA comprises a double-stranded region of 15 base pairs to 20 base pairs

the dsRNA comprises a blunt-end;

the dsRNA comprises at least one single stranded nucleotide overhang, optionally wherein the dsRNA comprises about a 2-nucleotide to 5-nucleotide single stranded nucleotide overhang;

the dsRNA comprises 4-16 or 8-13 phosphorothioate internucleotide linkages;

the sense strand comprises one or more nucleotide mismatches between the antisense strand and the sense strand;

the nucleotides at positions 1 and 2 from the 3' end of sense strand, and the nucleotides at positions 1 and 2 from the 5' end of antisense strand, are connected to adjacent ribonucleotides via phosphorothioate linkages;

said region of complementarity is complementary to at least 15, 16, 17 or 18 contiguous nucleotides of SEQ ID NO: 1 or SEQ ID NO: 2;

said region of complementarity contains no more than 3 mismatches with SEQ ID NO: 1 or SEQ ID NO: 2 or is fully complementary to SEQ ID NO: 1 or SEQ ID NO: 2; and/or expression of a sFLT1 protein in a cell or organism is reduced by at least about 20%.

3. The dsRNA of claim 1 or 2, wherein the antisense strand comprises a 5' phosphate, a 5'-alkyl phosphonate, a 5' alkylene phosphonate, or a 5' alkenyl phosphonate, optionally wherein the antisense strand comprises a 5' vinyl phosphonate.

4. The dsRNA of any one of claims 1-3, wherein a functional moiety is linked to the 3' end of the sense strand, optionally wherein the functional moiety comprises a hydrophobic moiety, optionally wherein the hydrophobic moiety is selected from the group consisting of fatty acids, steroids, secosteroids, lipids, gangliosides, nucleoside analogs, endocannabinoids, vitamins, and a mixture thereof, optionally wherein:

the steroid selected from the group consisting of cholesterol and Lithocholic acid (LCA);

the fatty acid is selected from the group consisting of Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA) and Docosanoic acid (DCA); and/or

the vitamin is selected from the group consisting of choline, vitamin A, vitamin E, and derivatives or metabolites thereof.

5. The dsRNA of claim 4, wherein the functional moiety comprises Docosahexaenoic acid (DHA) or Docosanoic acid (DCA).

6. The dsRNA of claim 4 or 5, wherein the functional moiety is linked to the sense strand by

a linker, optionally wherein:

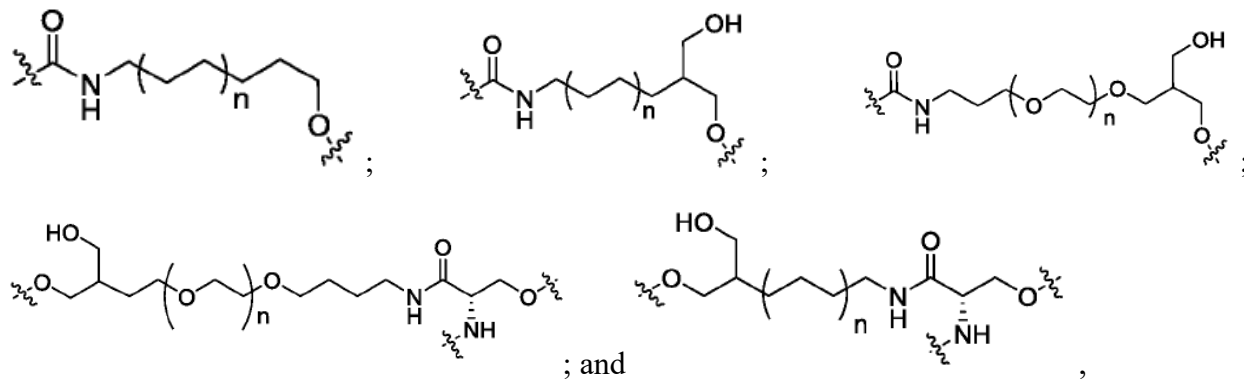
the linker comprises an ethylene glycol chain, an alkyl chain, a peptide, an RNA, a DNA, a phosphodiester, a phosphorothioate, a phosphoramidate, an amide, a carbamate, or a combination thereof; and/or

the linker is a cleavable linker, optionally wherein the cleavable linker comprises a phosphodiester linkage, a disulfide linkage, an acid-labile linkage, or a photocleavable linkage, optionally wherein acid-labile linkage comprises a β -thiopropionate linkage or a carboxydimethylmaleic anhydride (CDM) linkage.

7. The dsRNA of claim 6, wherein the cleavable linker comprises a dTdT dinucleotide with phosphodiester internucleotide linkages.

8. The dsRNA of claim 6 or 7, wherein the linker comprises a divalent or trivalent linker.

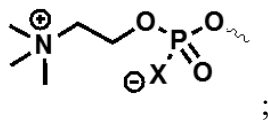
9. The dsRNA of claim 8, wherein the divalent or trivalent linker is selected from the group consisting of:



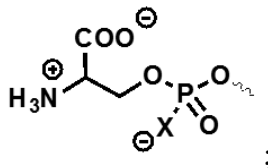
wherein n is 1, 2, 3, 4, or 5.

10. The dsRNA of claim 8 or 9, wherein when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative.

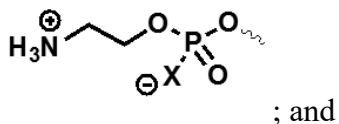
11. The dsRNA of claim 10, wherein the phosphodiester or phosphodiester derivative is selected from the group consisting of:



(Zc1);

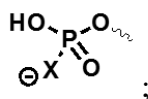


(Zc2);



; and

(Zc3)



(Zc4)

wherein X is O, S or BH₃.

12. The dsRNA of any one of claims 1-11, wherein the antisense strand comprises the nucleic acid sequence of 5' UAAAUUUGGAGAUCCGAGAGA 3' and the sense strand comprises the nucleic acid sequence of 5' CGGAUCUCCAAAUUUA 3'.

13. The dsRNA of any one of claims 1-11, wherein the antisense strand comprises the nucleic acid sequence of 5' UAUAAAUGGUAGCUAUGAUGA 3' and the sense strand comprises the nucleic acid sequence of 5' AUAGCUACCAUUUAUA 3'.

14. A pharmaceutical composition comprising the dsRNA according to any one of claims 1-13.

15. The dsRNA according to any one of claims 1-13 or the pharmaceutical composition of claim 14 for use in medicine.

16. Use of the dsRNA of any one of claims 1-13 or the pharmaceutical composition of claim 14 in the preparation of a medicament for the treating or managing PE, postpartum PE, eclampsia or HELLP syndrome in a subject, optionally wherein:

wherein the dsRNA or the pharmaceutical composition is to be administered intravenously or subcutaneously; and/or

sFLT1 protein expression is reduced in the subject by at least about 20%.

17. Use of the dsRNA of any one of claims 1-13 or the pharmaceutical composition of claim 14 in the preparation of a medicament for treating one or more symptoms of an angiogenic disorder in a subject, optionally wherein the angiogenic disorder is selected from the group consisting of PE, postpartum PE, eclampsia and HELLP syndrome.

18. A pharmaceutical composition comprising:

a first dsRNA comprising a first sense strand and a first antisense strand, wherein the first antisense strand comprises a region of complementarity which is substantially complementary to SEQ ID NO: 1, wherein the first dsRNA comprises the dsRNA of any one of claims 1-11;

a second dsRNA comprising a second sense strand and a second antisense strand, wherein the second antisense strand comprises a region of complementarity which is substantially complementary to SEQ ID NO: 2, wherein the second dsRNA comprises the dsRNA of any one of claims 1-11; and

a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising:

a first dsRNA comprising a first sense strand and a first antisense strand, each strand with a 5' end and a 3' end, wherein the first antisense strand comprises a region of complementarity which is substantially complementary to SEQ ID NO: 1;

a second dsRNA comprising a second sense strand and a second antisense strand, each strand with a 5' end and a 3' end, wherein the second antisense strand comprises a region of complementarity which is substantially complementary to SEQ ID NO: 2; and

a pharmaceutically acceptable carrier, wherein for each of the first dsRNA and second dsRNA:

- (1) the antisense strand is at least 20 nucleotides in length;
- (3) the antisense strand comprises at least 50% 2'-O-methyl modifications;
- (4) the nucleotides at any one or more of positions 2, 4, 5, 6, 8, 10, 12, 14, 16, and 20 from the 5' end of the antisense strand are not 2'-methoxy-ribonucleotides;
- (5) the nucleotides at positions 1-2 to 1-8 from the 3' end of the antisense strand are connected to each other via phosphorothioate internucleotide linkages;
- (6) a portion of the antisense strand is complementary to a portion of the sense strand;
- (7) the sense strand is at least 15 nucleotides in length;
- (8) the sense strand comprises at least 65% 2'-O-methyl modifications;
- (9) the nucleotides at any one of more of positions 4, 6, 8, 10, and 14 from the 5' end of the sense strand are not 2'-methoxy-ribonucleotides; and
- (10) the nucleotides at positions 1-2 from the 5' end of the sense strand are connected to each other via phosphorothioate internucleotide linkages.

20. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises (mU)#(fA)#(mA)(fA)(fU)(fU)(mU)(fG)(mG)(fA)(mG)(fA)(mU)(fC)#(mC)#(fG)#(mA)#(mG)#(mA)#(fG)#(mA); and

(2) the sense strand comprises (mC)#(mG)#(mG)(fA)(mU)(fC)(mU)(fC)(mC)(fA)(mA)(mA)(mU)(fU)#(mU)#(mA),

wherein "m" corresponds to a 2'-O-methyl modification, "f" corresponds to a 2'-fluoro modification, "#" corresponds to a phosphorothioate internucleotide linkage.

21. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense

strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises (mU)#(fA)#(mU)(fA)(fA)(mU)(fG)(mG)(fU)(mA)(fG)(mC)(fU)#(mA)#(fU)#(mG)#(mA)#(mU)#(fG)#(mA); and

(2) the sense strand comprises (mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA),

wherein “m” corresponds to a 2'-O-methyl modification, “f” corresponds to a 2'-fluoro modification, “#” corresponds to a phosphorothioate internucleotide linkage.

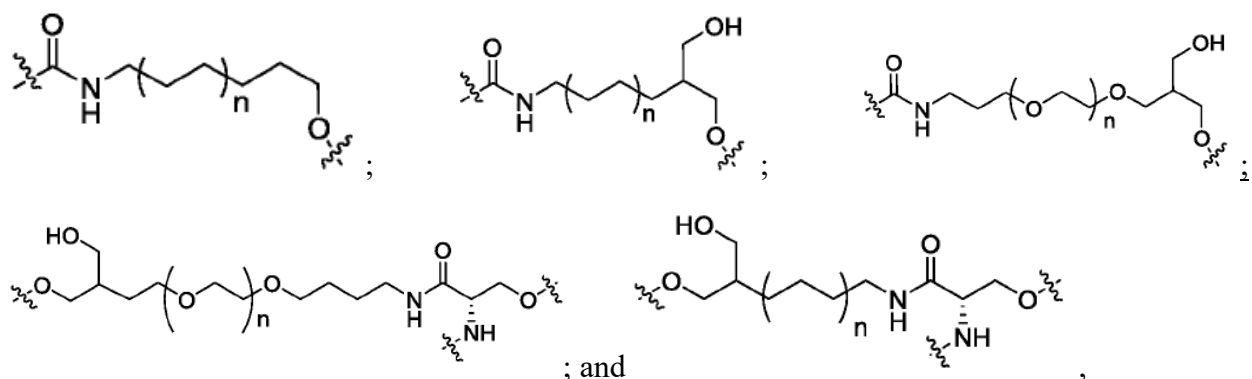
22. The dsRNA of claim 20 or 21, wherein:

the antisense strand comprises a 5' vinyl phosphonate; and/or

the dsRNA comprises a docosanoic acid (DCA) conjugate linked to the 3' end of the sense strand, optionally wherein the DCA is linked to the sense strand by a linker, optionally wherein the linker is a cleavable linker, optionally wherein the cleavable linker comprises a phosphodiester linkage, a disulfide linkage, an acid-labile linkage, or a photocleavable linkage, or optionally, the cleavable linker comprises a dTdT dinucleotide with phosphodiester internucleotide linkages.

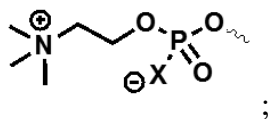
23. The dsRNA of claim 22, wherein the linker comprises a divalent or trivalent linker, optionally wherein:

the divalent or trivalent linker is selected from the group consisting of:

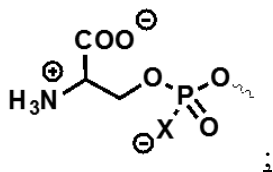


wherein n is 1, 2, 3, 4, or 5; and/or

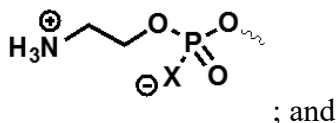
when the linker is a trivalent linker, the linker further links a phosphodiester or phosphodiester derivative, optionally wherein the phosphodiester or phosphodiester derivative is selected from the group consisting of:



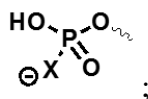
(Zc1);



(Zc2);



(Zc3)



(Zc4)

wherein X is O, S or BH₃.

24. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises V(mU)#(fA)#(mA)(fA)(fU)(fU)(mU)(fG)(mG)(fA)(mG)(fA)(mU)(fC)#(mC)#(fG)#(mA)#(mG)#(mA)#(fG)#(mA); and

(2) the sense strand comprises (mC)#(mG)#(mG)(fA)(mU)(fC)(mU)(fC)(mC)(fA)(mA)(mA)(mU)(fU)#(mU)#(mA)(T)(T)-PCDCA,

wherein “m” corresponds to a 2'-O-methyl modification, “f” corresponds to a 2'-fluoro

modification, “T” corresponds to a thymidine DNA nucleotide, “#” corresponds to a phosphorothioate internucleotide linkage, “V” corresponds to a 5'-vinylphosphonate, and “PCDCA” corresponds to a 3'-C7-phosphocholine-docosanoic acid conjugate through a phosphate linker.

25. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

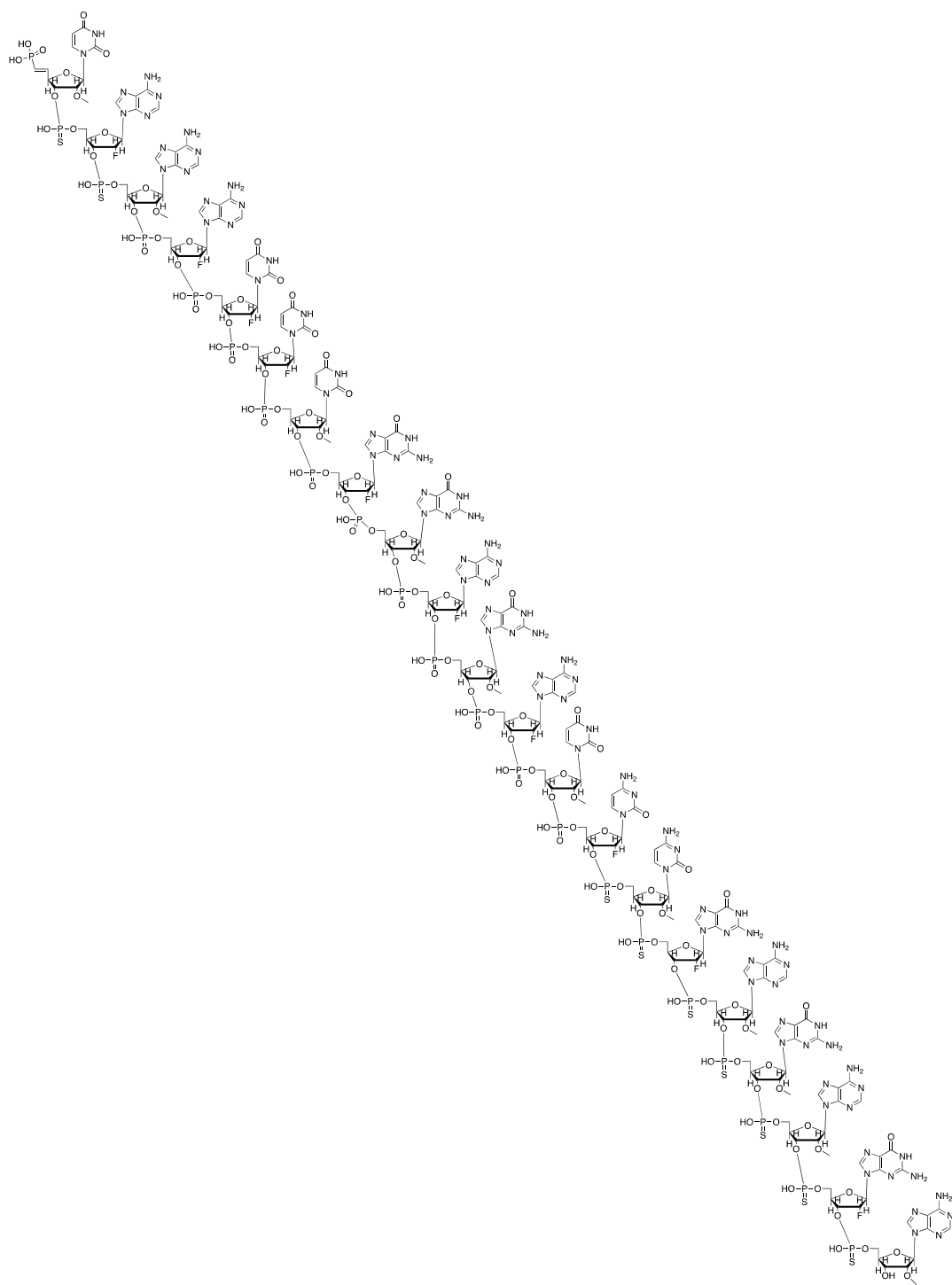
(1) the antisense strand comprises
V(mU)#(fA)#(mU)(fA)(fA)(fA)(mU)(fG)(mG)(fU)(mA)(fG)(mC)(fU)#(mA)#(fU)#(mG)#(mA)
#(mU)#(fG)#(mA); and

(2) the sense strand comprises
(mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA)(T)(T)-
PCDCA,

wherein “m” corresponds to a 2'-O-methyl modification, “f” corresponds to a 2'-fluoro modification, “T” corresponds to a thymidine DNA nucleotide, “#” corresponds to a phosphorothioate internucleotide linkage, “V” corresponds to a 5'-vinylphosphonate, and “PCDCA” corresponds to a 3'-C7-phosphocholine-docosanoic acid conjugate through a phosphate linker.

26. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

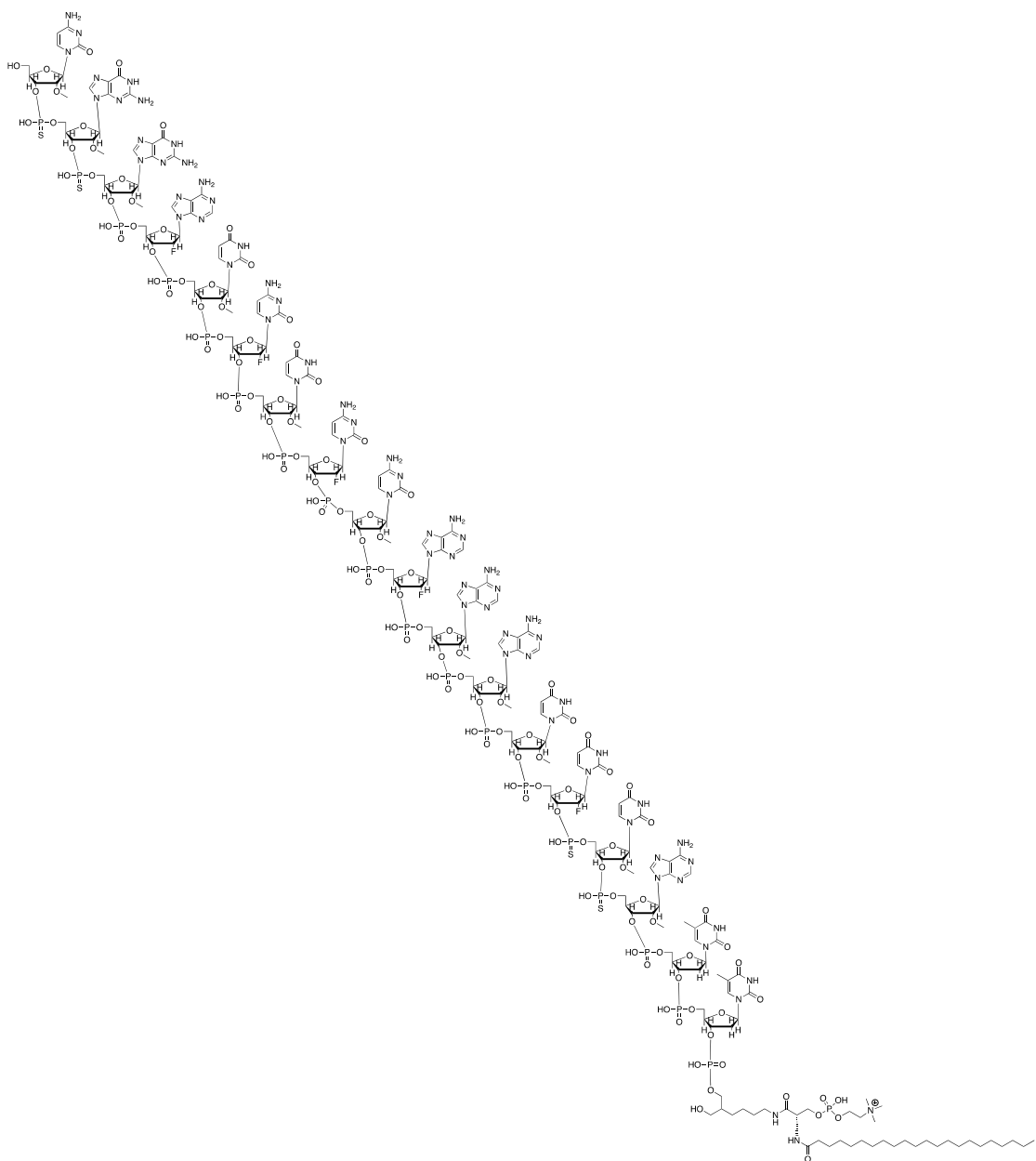
(1) the antisense strand comprises Formula I, or a salt thereof:



Formula I

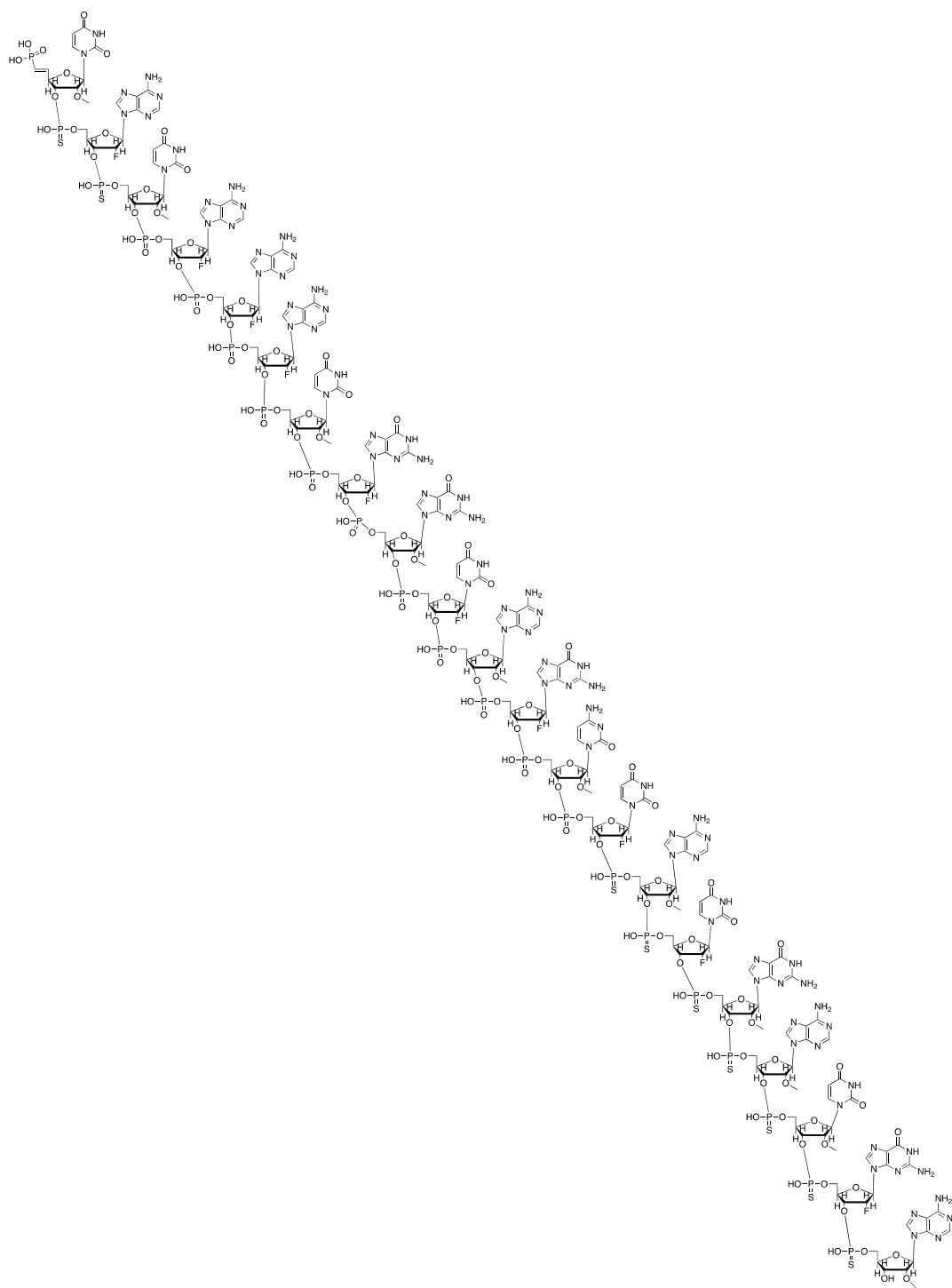
; and

(2) the sense strand comprises Formula II, or a salt thereof:



Formula II, optionally wherein the salt comprises a sodium salt or potassium salt.

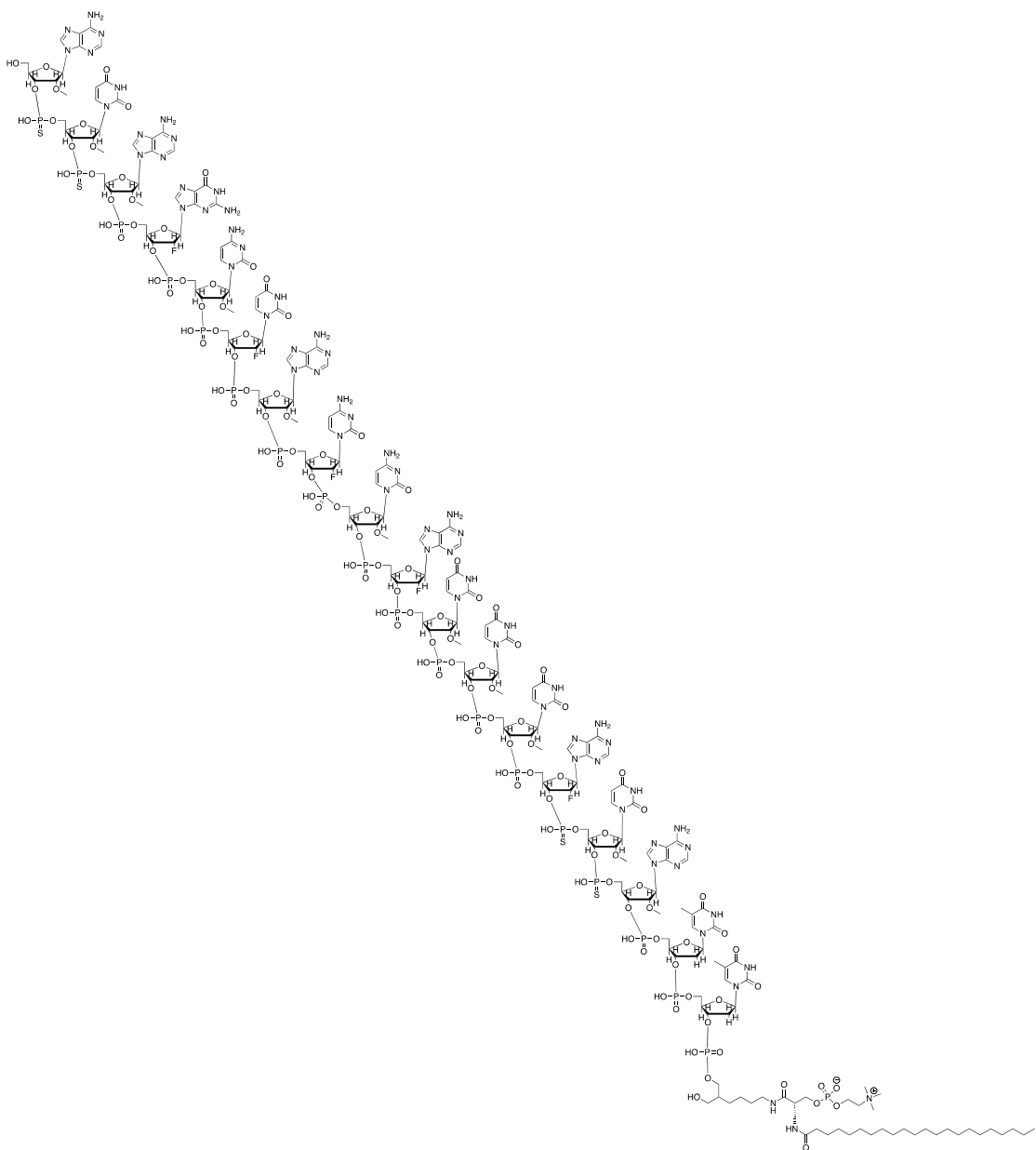
27. A double stranded RNA (dsRNA) molecule, wherein said dsRNA comprises an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:
- (1) the antisense strand comprises Formula III, or a salt thereof:



Formula III, or a salt thereof

; and

(2) the sense strand comprises Formula IV, or a salt thereof:



Formula IV, optionally wherein the salt comprises a sodium salt or potassium salt.

28. A pharmaceutical composition comprising:

a first dsRNA, said first dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises
V(mU)#(fA)#(mA)(fA)(fU)(fU)(mU)(fG)(mG)(fA)(mG)(fA)(mU)(fC)#(mC)#(fG)#(mA)#(mG)
#(mA)#(fG)#(mA); and

(2) the sense strand comprises (mC)#(mG)#(mG)(fA)(mU)(fC)(mU)(fC)(mC)(fA)(mA)(mA)(mU)(fU)#(mU)#(mA)(T)(T)-PCDCA; and

a second dsRNA, said second dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the antisense strand comprises V(mU)#(fA)#(mU)(fA)(fA)(fA)(mU)(fG)(mG)(fU)(mA)(fG)(mC)(fU)#(mA)#(fU)#(mG)#(mA)#(mU)#(fG)#(mA); and

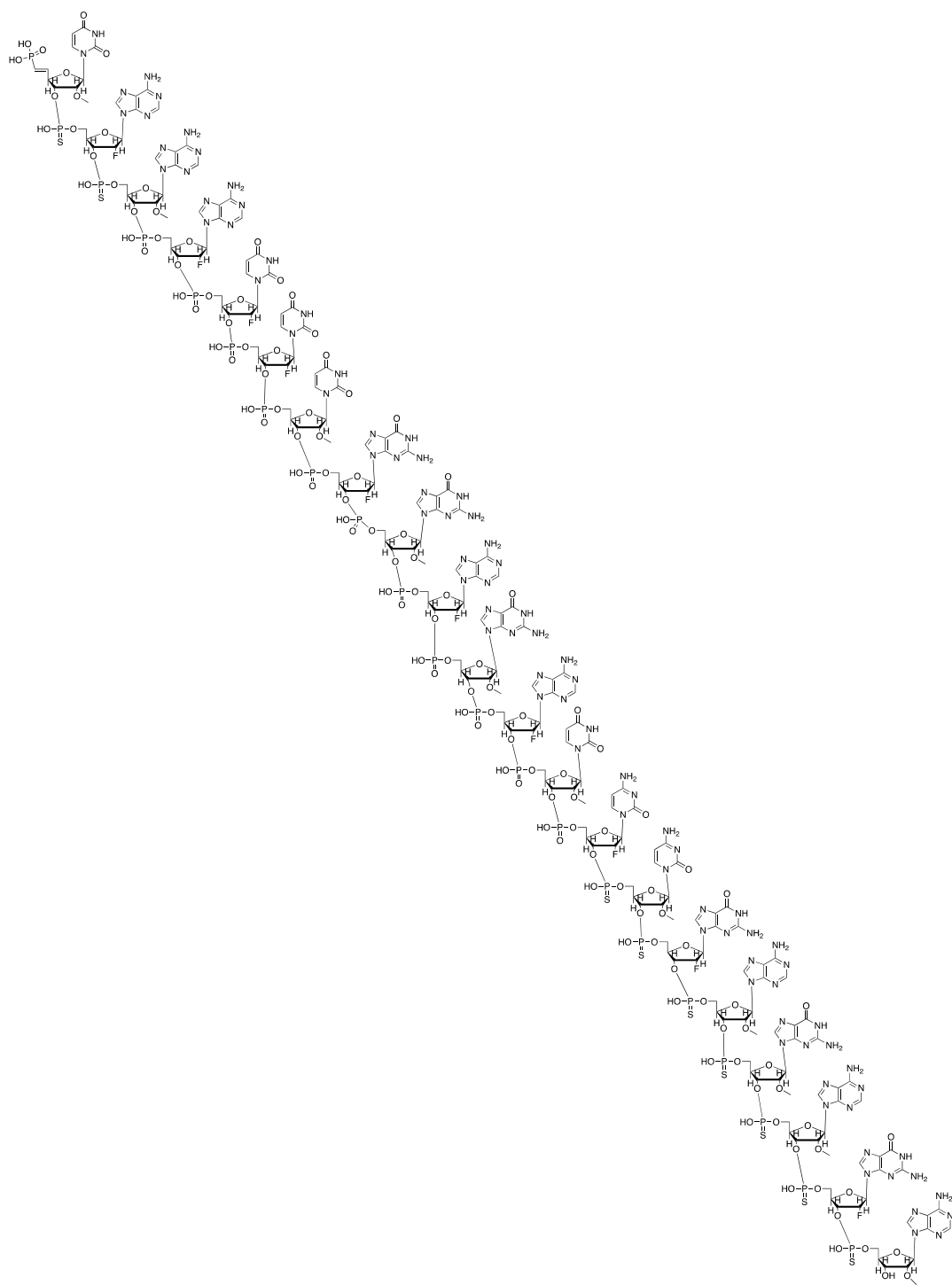
(2) the sense strand comprises (mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA)(T)(T)-PCDCA,

wherein “m” corresponds to a 2'-O-methyl modification, “f” corresponds to a 2'-fluoro modification, “T” corresponds to a thymidine DNA nucleotide, “#” corresponds to a phosphorothioate internucleotide linkage, “V” corresponds to a 5'-vinylphosphonate, and “PCDCA” corresponds to a 3'-C7-phosphocholine-docosanoic acid conjugate through a phosphate linker.

29. A pharmaceutical composition comprising:

a first dsRNA, said first dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

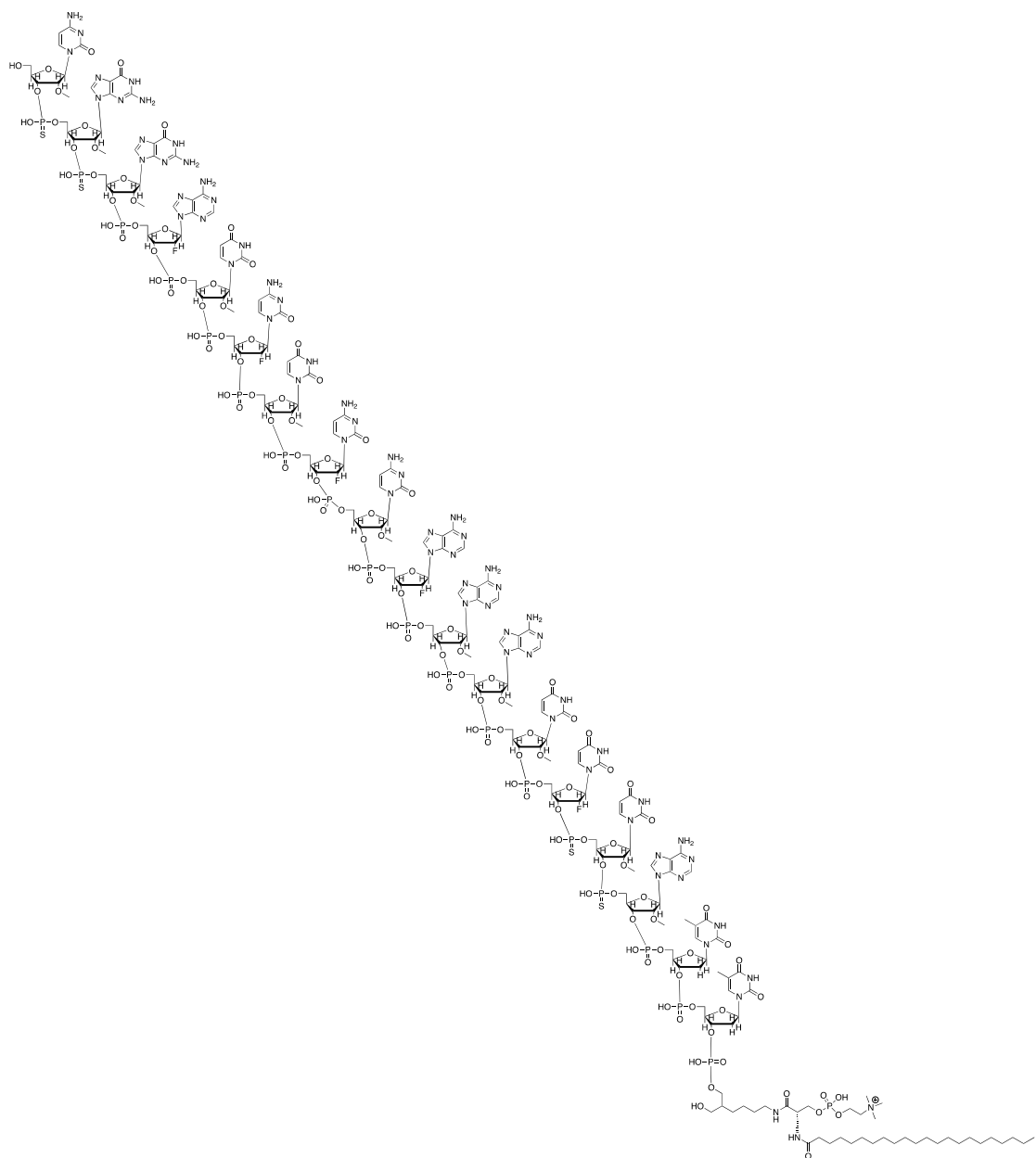
(1) the antisense strand comprises Formula I, or a salt thereof:



Formula I

; and

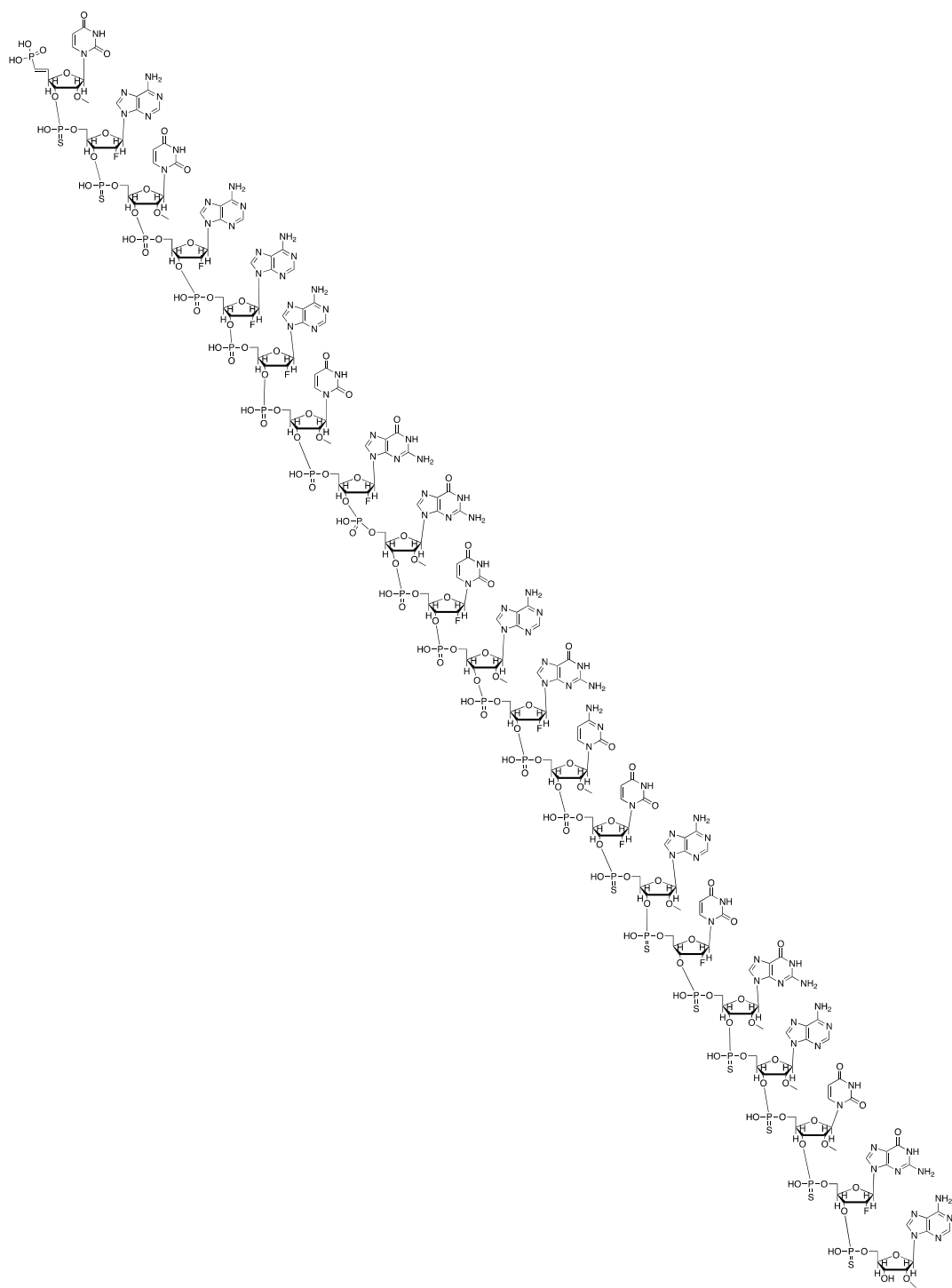
(2) the sense strand comprises Formula II, or a salt thereof:



Formula II; and

a second dsRNA, said second dsRNA comprising an antisense strand and a sense strand, each strand with a 5' end and a 3' end, wherein:

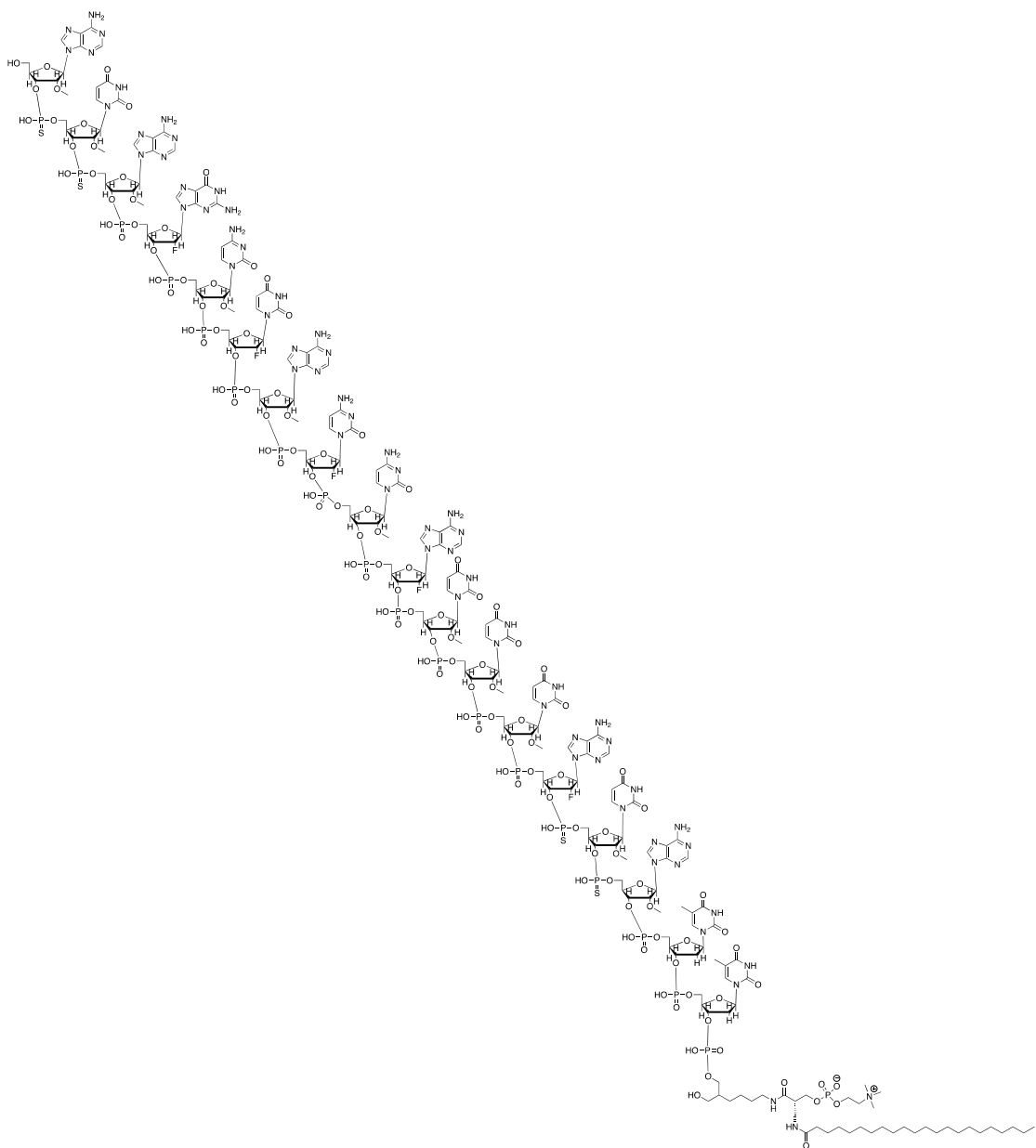
- (1) the antisense strand comprises Formula III, or a salt thereof:



Formula III

; and

(2) the sense strand comprises Formula IV, or a salt thereof:



Formula IV.

30. The pharmaceutical composition of claim 29, wherein the salt comprises a sodium salt or potassium salt.
31. The pharmaceutical composition of any one of claims 28-30 for use in medicine.

32. Use of the pharmaceutical composition of any one of claims 28-30 in the preparation of a medicament for treating or managing PE, postpartum PE, eclampsia or HELLP syndrome in a subject

33. Use of the pharmaceutical composition of any one of claims 28-30 in the preparation of a medicament for treating one or more symptoms of an angiogenic disorder in a subject.