

Claims

1. A double stranded RNA (dsRNA) molecule, wherein the dsRNA molecule 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) (SEQ ID NO:12) or a salt thereof; and

(2) the sense strand comprises (mC)#(mG)#(mG)(fA)(mU)(fC)(mU)(fC)(mC)(fA)(mA)(mA)(mU)(fU)#(mU)#(mA) (SEQ ID NO: 13) or a salt thereof,

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

2. A double stranded RNA (dsRNA) molecule, wherein the dsRNA molecule 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)(fA)(mU)(fG)(mG)(fU)(mA)(fG)(mC)(fU)#(mA)#(fU)#(mG)#(mA)#(mU)#(fG)#(mA) (SEQ ID NO: 16) or a salt thereof; and

(2) the sense strand comprises (mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA) (SEQ ID NO: 15) or a salt thereof,

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

3. The dsRNA molecule of claim 1 or 2, wherein:

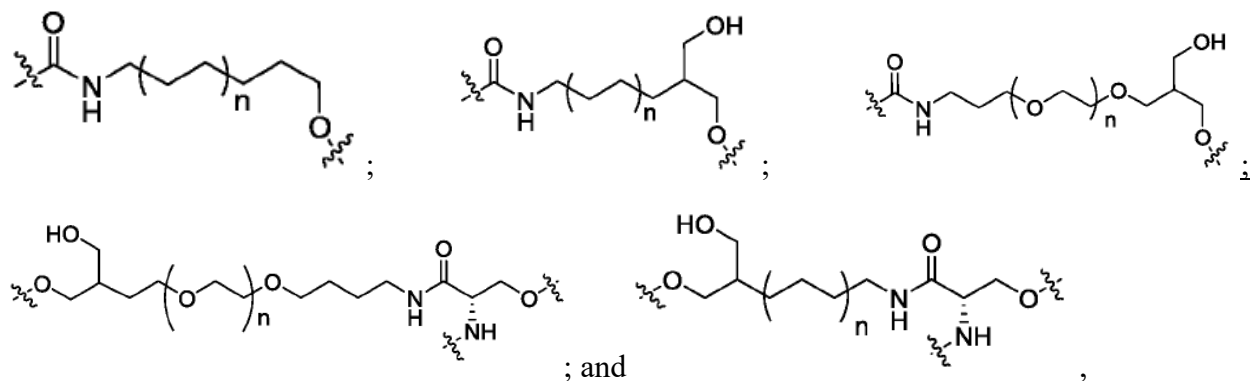
the antisense strand comprises a 5' vinyl phosphonate; and/or

the dsRNA molecule 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.

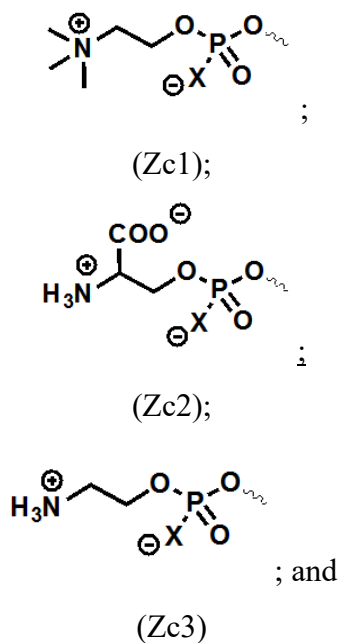
4. The dsRNA molecule of claim 3, wherein the linker comprises a divalent linker or a trivalent linker, optionally wherein:

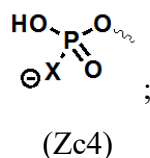
the divalent linker or the trivalent linker is selected from the group consisting of:



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

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





wherein X is O, S or BH₃.

5. A double stranded RNA (dsRNA) molecule, wherein the dsRNA molecule 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) (SEQ ID NO: 17) or a salt thereof; 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 (SEQ ID NO: 18) or a salt thereof,

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.

6. A double stranded RNA (dsRNA) molecule, wherein the dsRNA molecule 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) (SEQ ID NO: 19) or a salt thereof; and

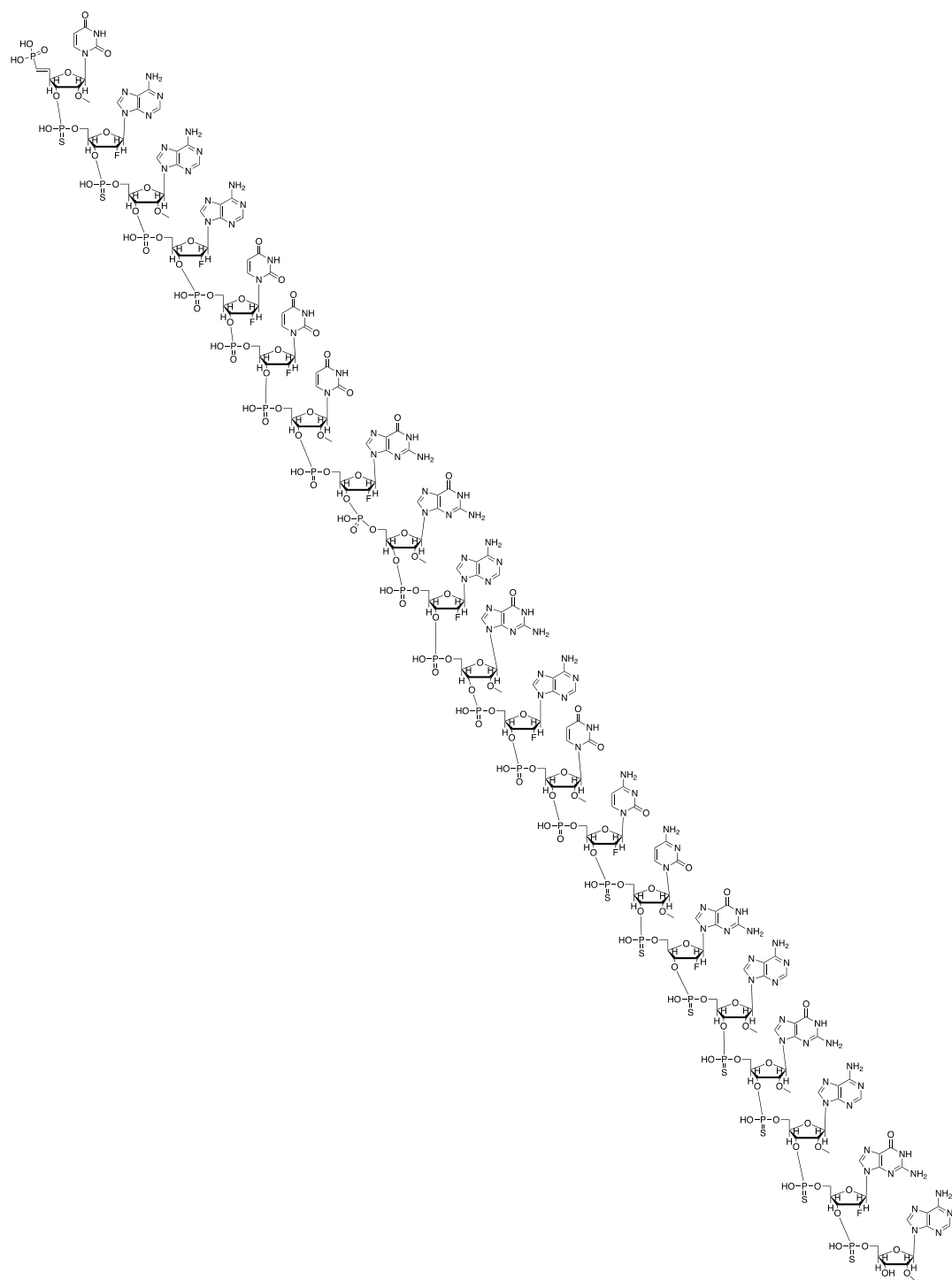
(2) the sense strand comprises (mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA)(T)(T)-PCDCA (SEQ ID NO: 20) or a salt thereof,

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.

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

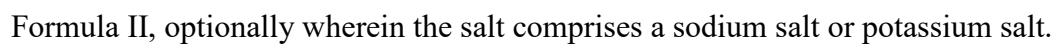
(1) the antisense strand comprises Formula I (SEQ ID NO: 27), or a salt thereof:



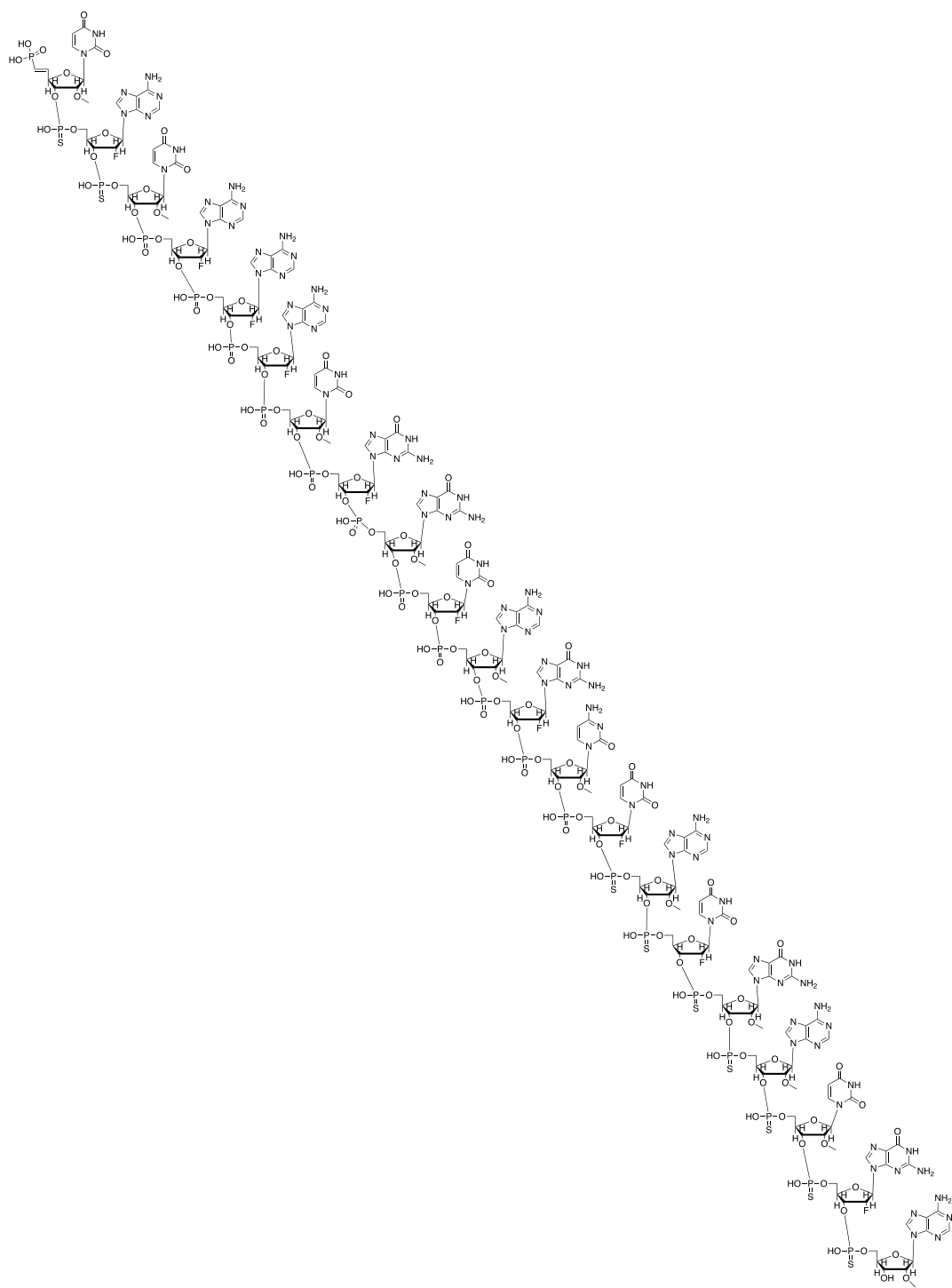
Formula I

; and

(2) the sense strand comprises Formula II (SEQ ID NO: 28), or a salt thereof:



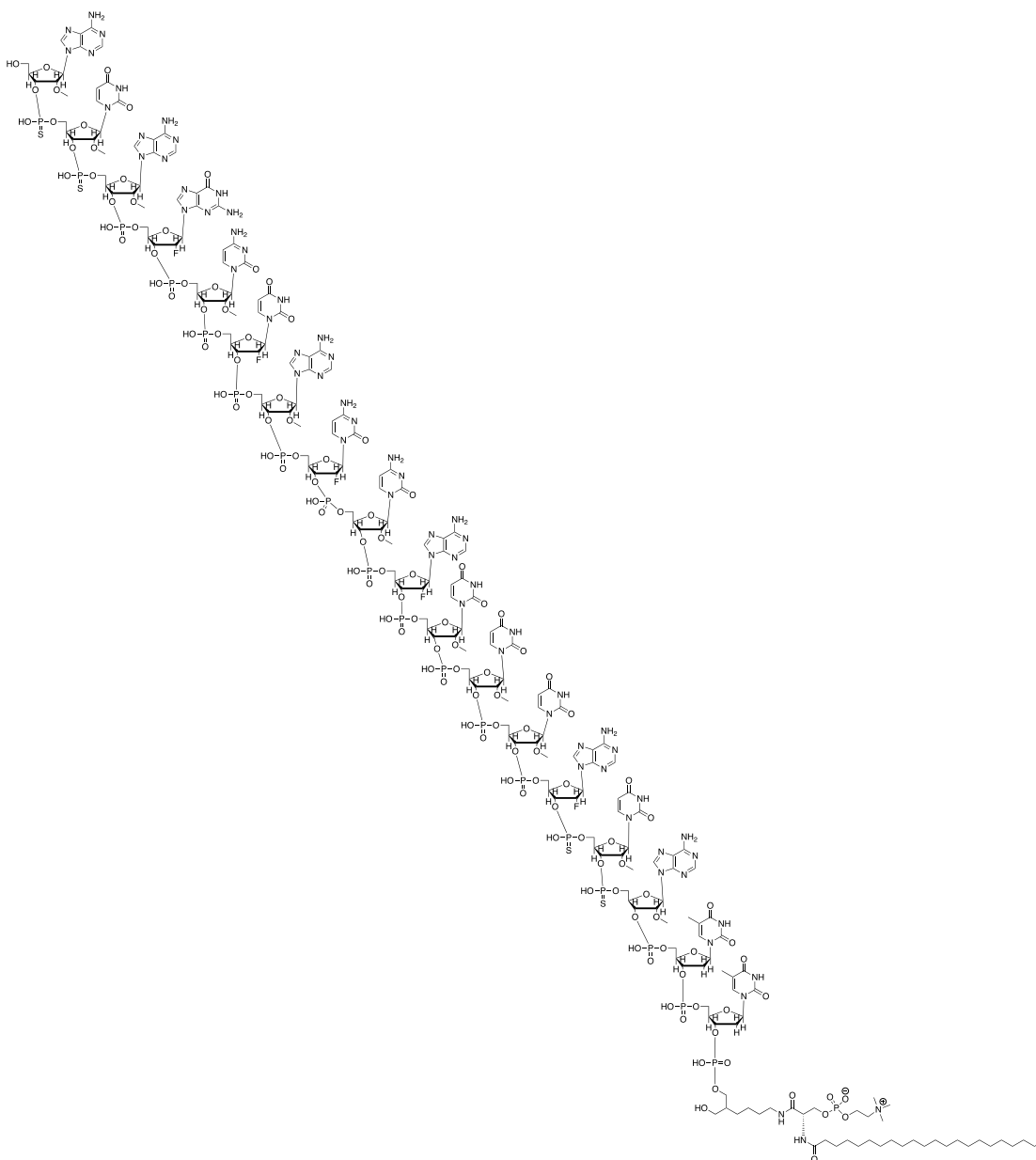
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Formula III

; and

(2) the sense strand comprises Formula IV (SEQ ID NO: 30), or a salt thereof:



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

9. A pharmaceutical composition comprising:

a first double stranded RNA (dsRNA) molecule, wherein the first dsRNA molecule comprises a first antisense strand and a first sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the first 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) (SEQ ID NO: 17) or a salt thereof; and

(2) the first sense strand comprises (mC)#(mG)#(mG)(fA)(mU)(fC)(mU)(fC)(mC)(fA)(mA)(mA)(mU)(fU)#(mU)#(mA)(T)(T)-PCDCA (SEQ ID NO: 18) or a salt thereof; and

a second dsRNA molecule, wherein the second dsRNA molecule comprises a second antisense strand and a second sense strand, each strand with a 5' end and a 3' end, wherein:

(1) the second 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) (SEQ ID NO: 19) or a salt thereof; and

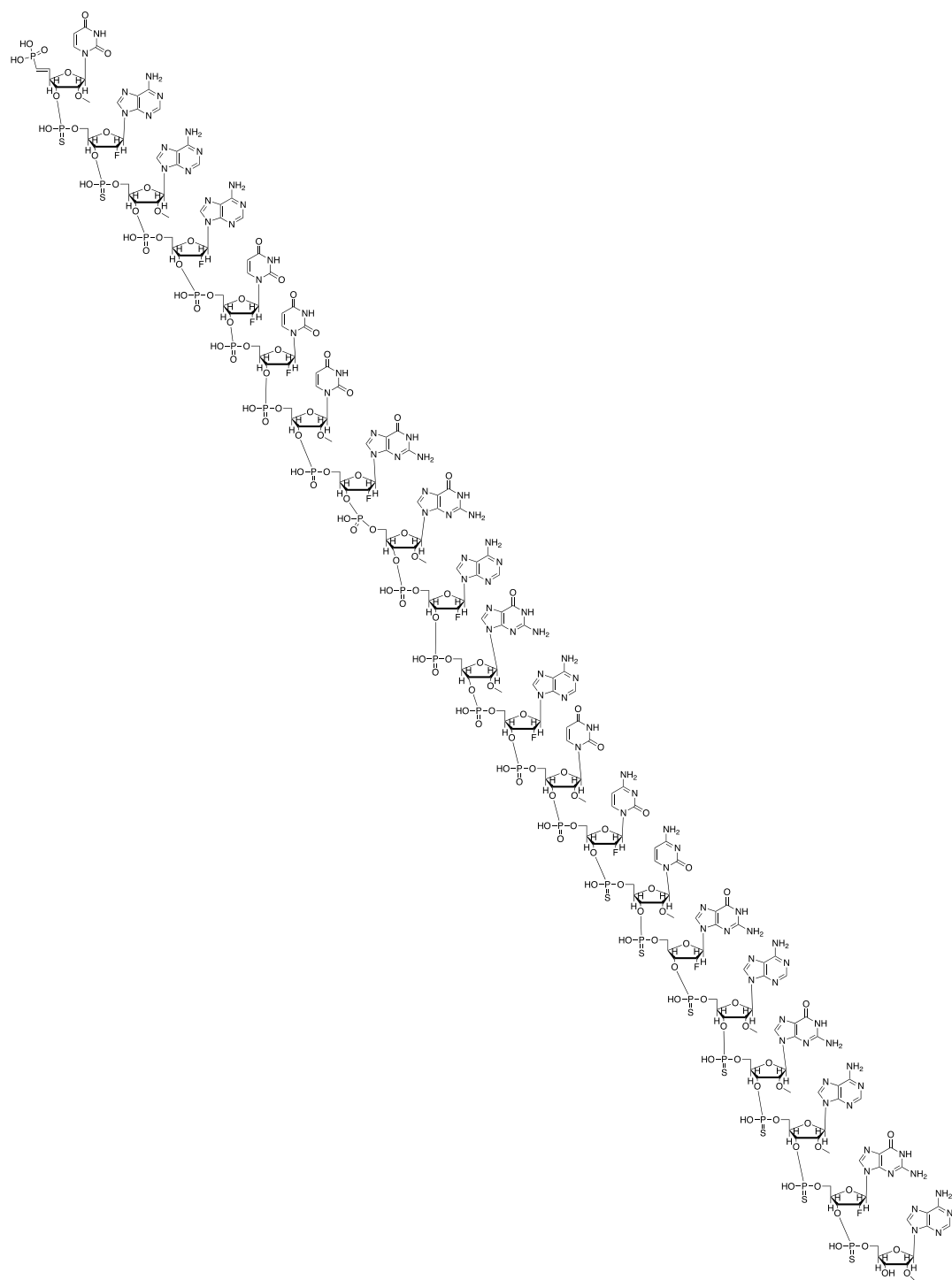
(2) the second sense strand comprises (mA)#(mU)#(mA)(fG)(mC)(fU)(mA)(fC)(mC)(fA)(mU)(mU)(mU)(fA)#(mU)#(mA)(T)(T)-PCDCA (SEQ ID NO: 20) or a salt thereof,

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.

10. A pharmaceutical composition comprising:

a first double stranded RNA (dsRNA) molecule, wherein the first dsRNA molecule comprises a first antisense strand and a first sense strand, each strand with a 5' end and a 3' end, wherein:

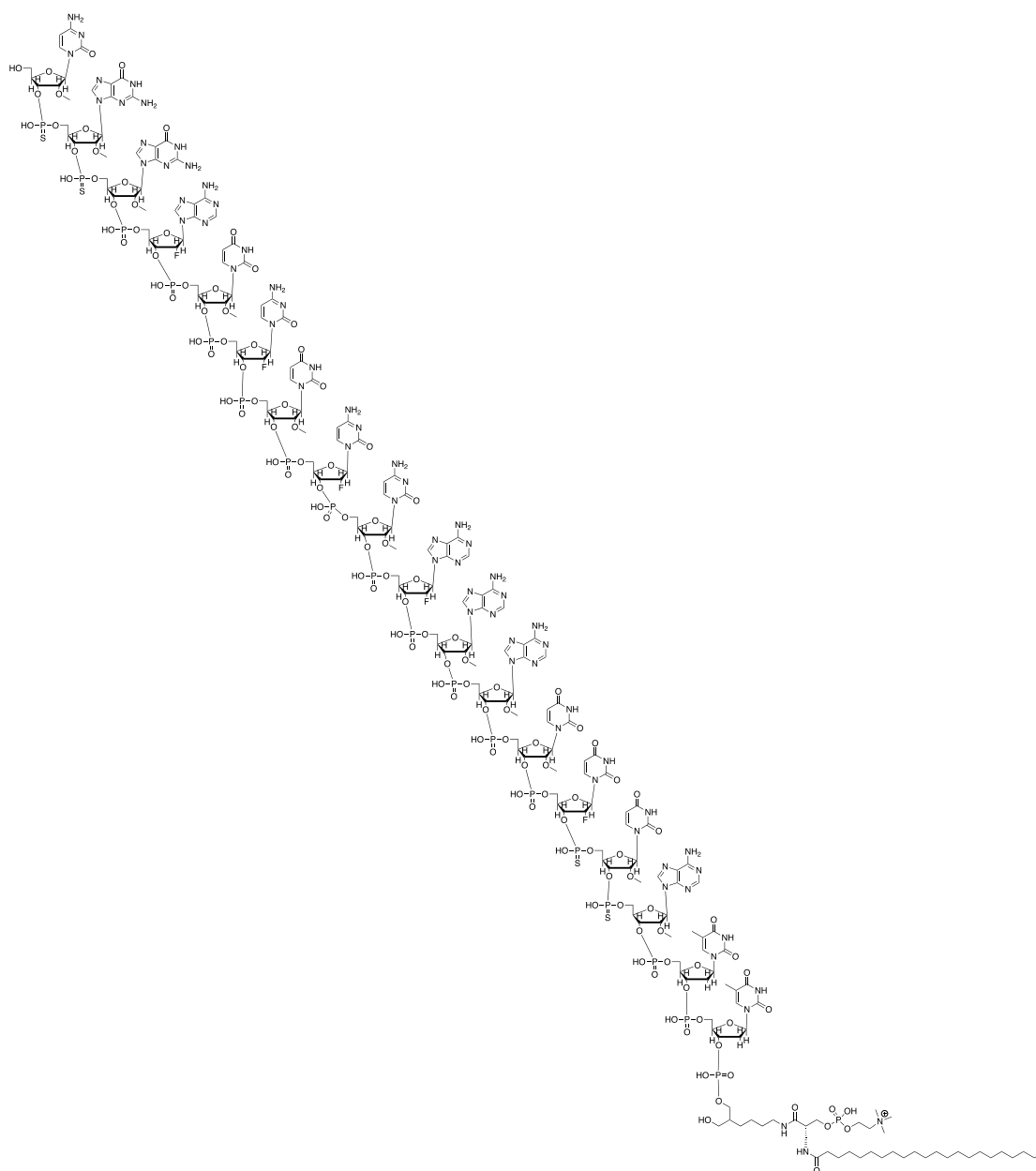
(1) the first antisense strand comprises Formula I (SEQ ID NO: 27), or a salt thereof:



Formula I

; and

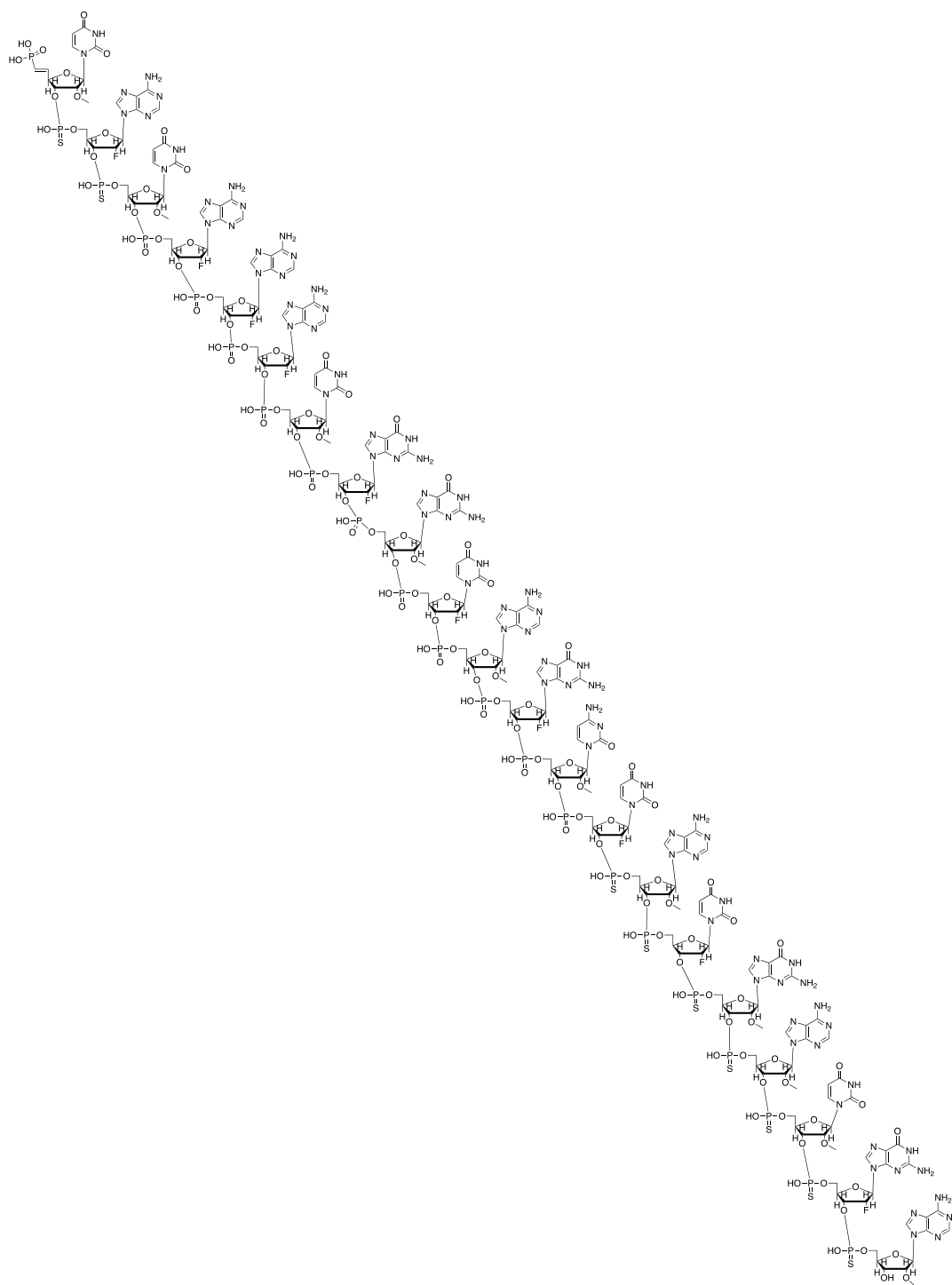
(2) the first sense strand comprises Formula II (SEQ ID NO: 28), or a salt thereof:



Formula II; and

a second dsRNA molecule, wherein the second dsRNA molecule comprises a second antisense strand and a second sense strand, each strand with a 5' end and a 3' end, wherein:

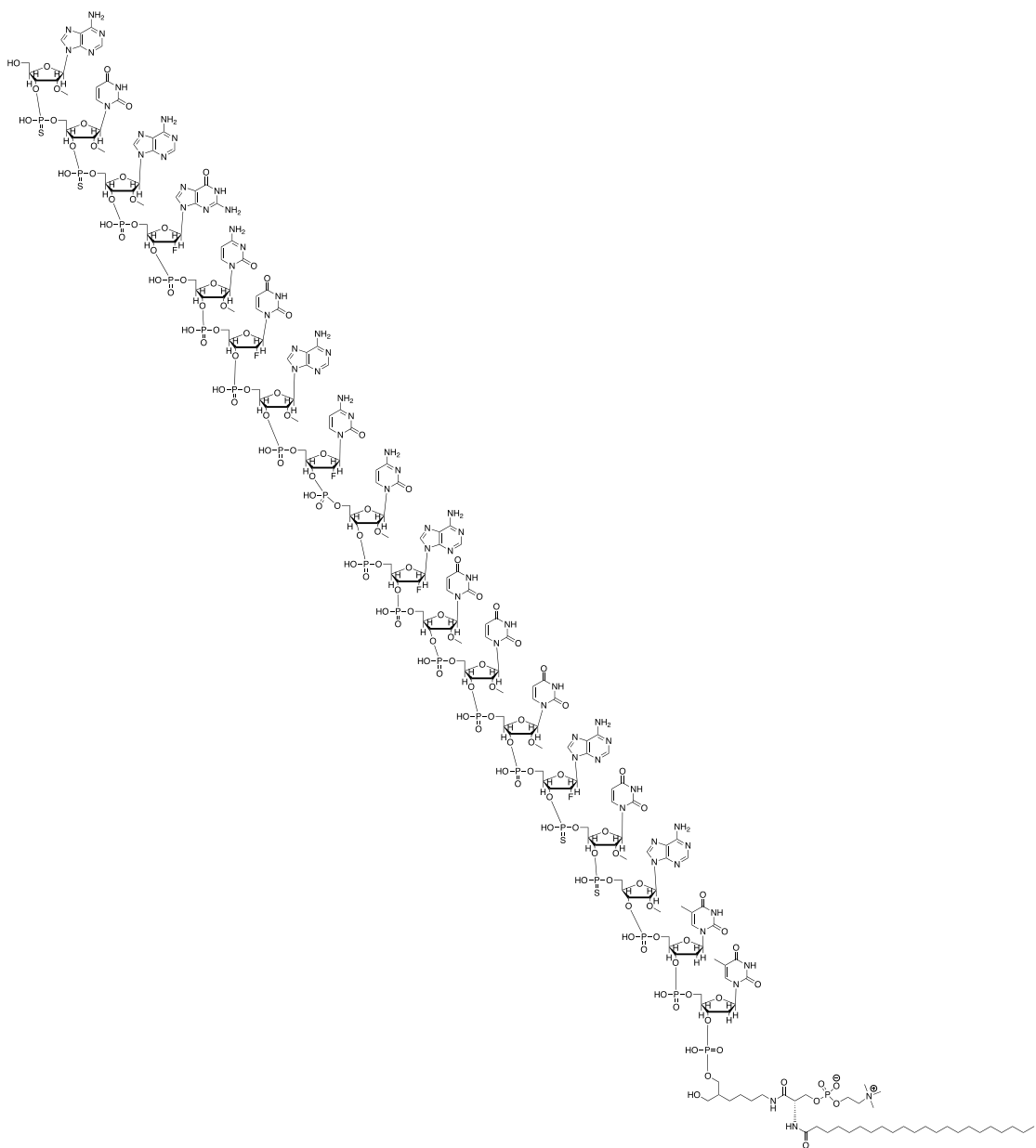
- (1) the second antisense strand comprises Formula III (SEQ ID NO: 29), or a salt thereof:



Formula III

; and

(2) the second sense strand comprises Formula IV (SEQ ID NO: 30), or a salt thereof:



Formula IV.

11. The pharmaceutical composition of claim 10, wherein the salt comprises a sodium salt or a potassium salt.
12. The pharmaceutical composition of any one of claims 9-11 for use in medicine.

13. Use of the pharmaceutical composition of any one of claims 9-11 in the preparation of a medicament for treating or managing pre-eclampsia (PE), postpartum PE, eclampsia, or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome in a subject.

14. Use of the pharmaceutical composition of any one of claims 9-11 in the preparation of a medicament for reducing sFLT1 expression and/or reducing maternal blood pressure in a subject.