CLAIMS:

1. An RNAi agent for inhibiting expression of a double homeobox 4 (*DUX4*) gene, comprising:
    i. an antisense strand comprising at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2, Table 3, or Table 5.4; and
    ii. a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.

2. The RNAi agent of claim 1, wherein the antisense strand comprises nucleotides 2-18 of any one of the sequences provided in Table 2, Table 3, or Table 5.4.

3. The RNAi agent of claim 1 or claim 2, wherein the sense strand comprises a nucleotide sequence of at least 17 contiguous nucleotides differing by 0 or 1 nucleotides from any one of the sequences provided in Table 2, Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, Table 4.6, or Table 5.4, and wherein the sense strand has a region of at least 85% complementarity over the 17 contiguous nucleotides to the antisense strand.

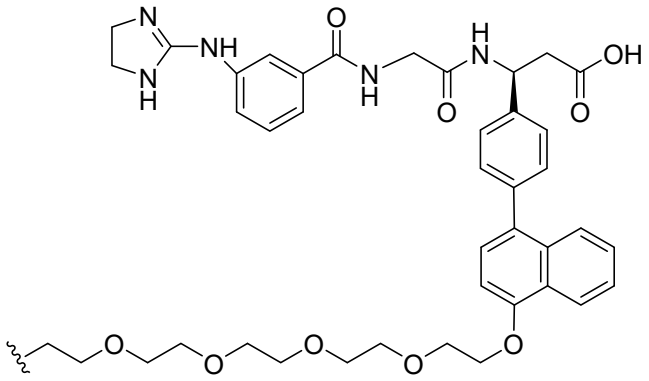
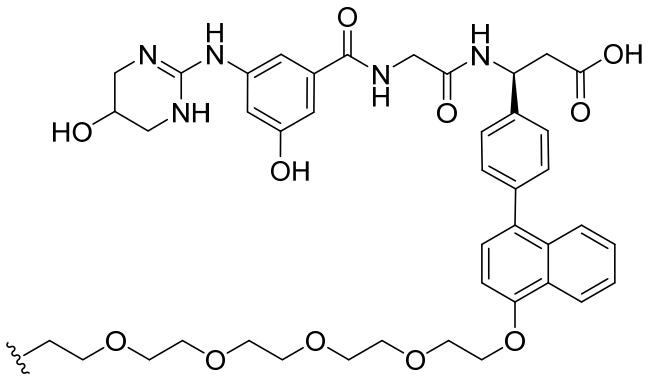
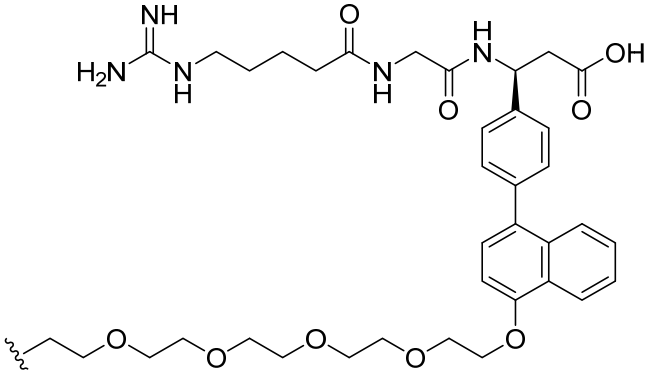
4. The RNAi agent of any one of claims 1-3, wherein the antisense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 3.

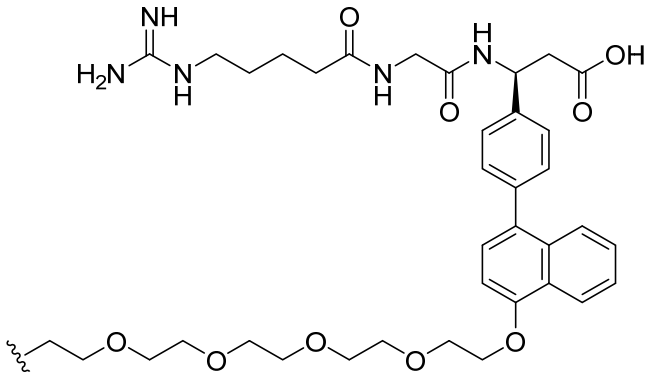
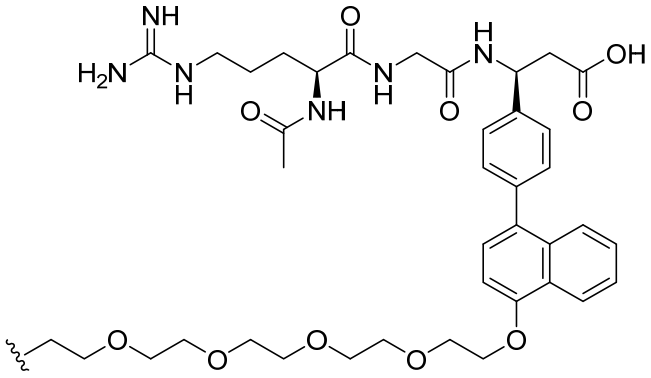
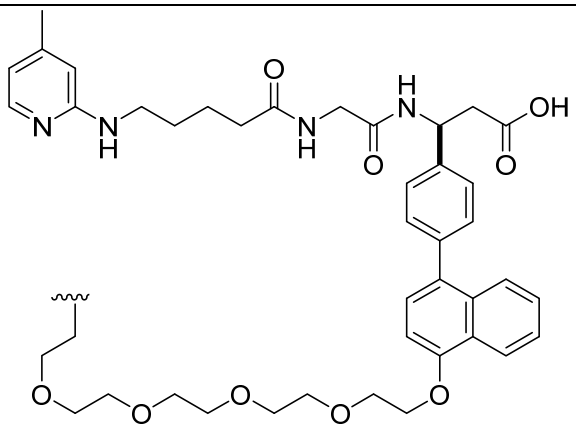
5. The RNAi agent of any one of claims 1-4, wherein the sense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, Table 4.6, or Table 5.4.

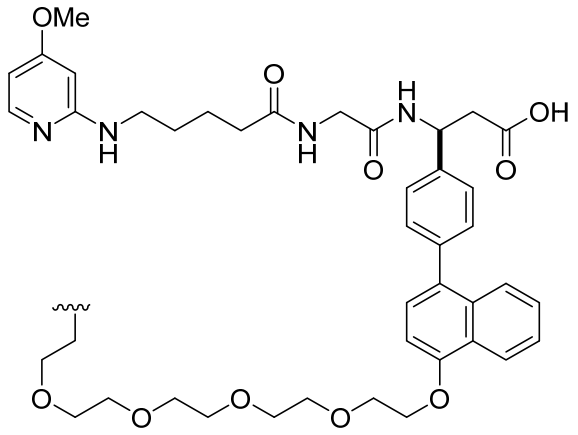
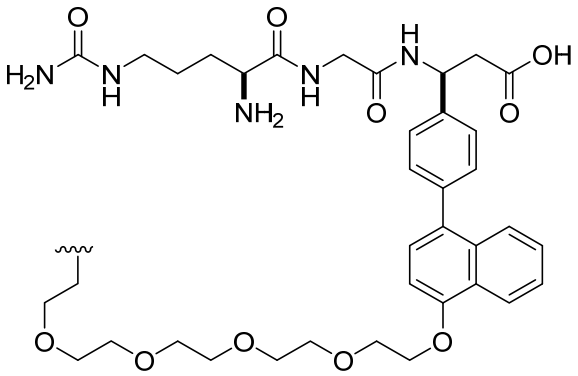
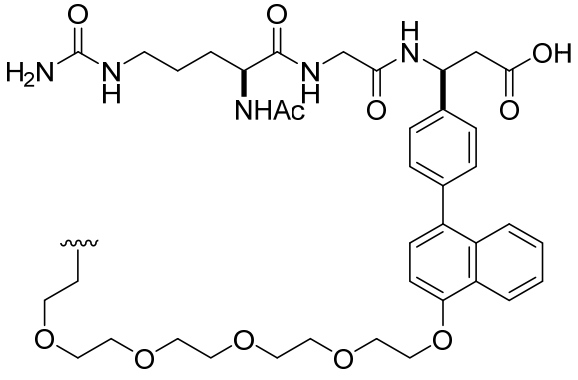
6. The RNAi agent of claim 1, wherein the antisense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 3 and the sense strand comprises the nucleotide sequence of any one of the modified sequences provided in Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, Table 4.6, or Table 5.4.

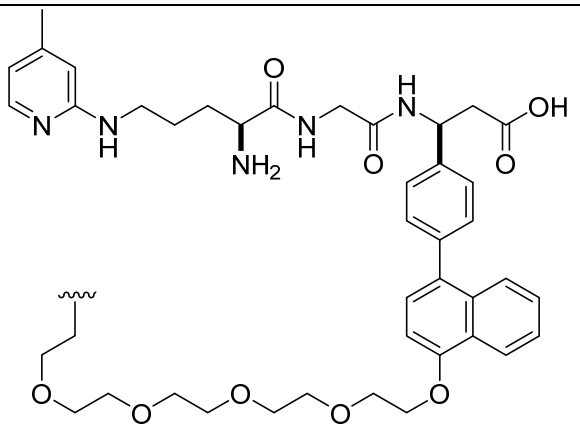
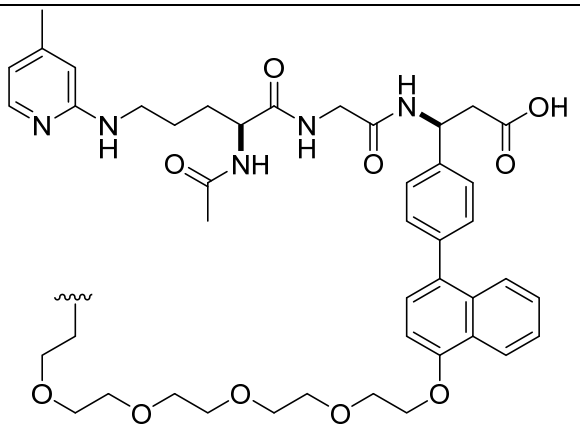
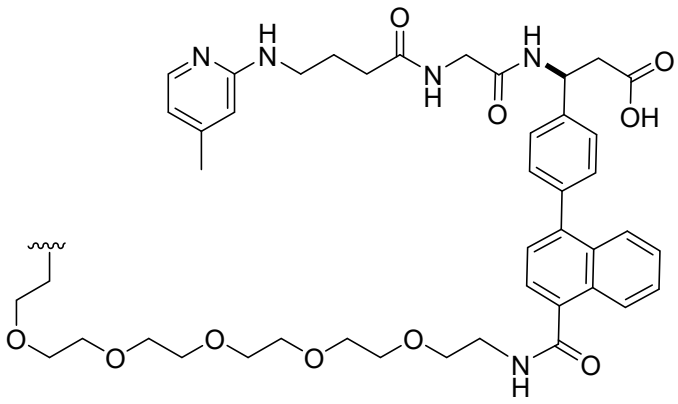
7. The RNAi agent of any one of claims 1-6, wherein the RNAi agent is linked to a targeting ligand.

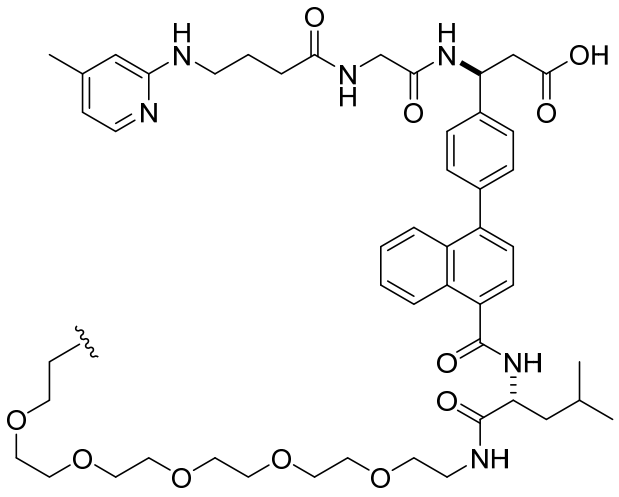
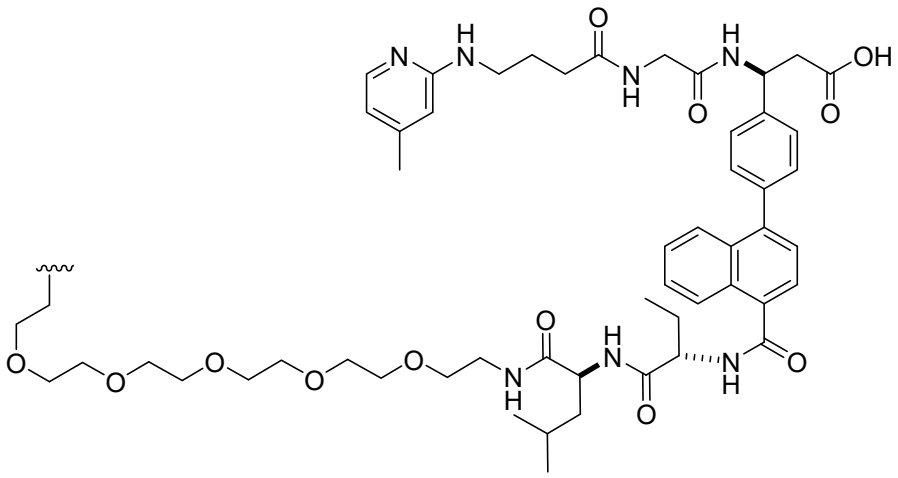
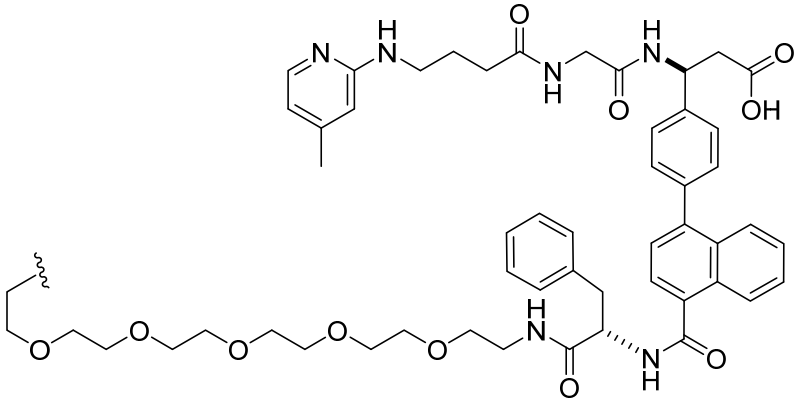
8. The RNAi agent of claim 7, wherein the targeting ligand is selected from the group consisting of:

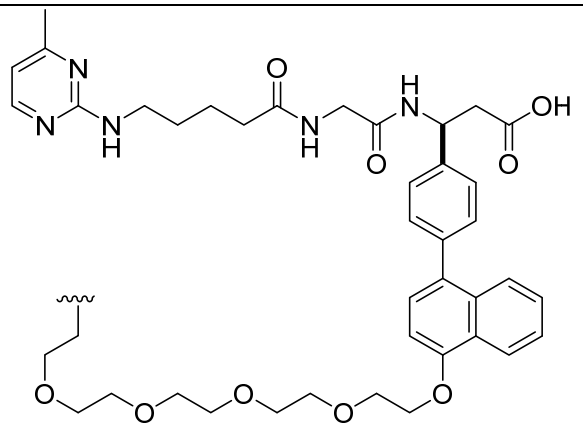
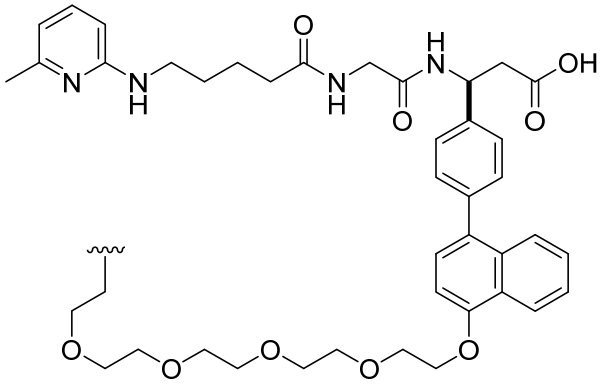
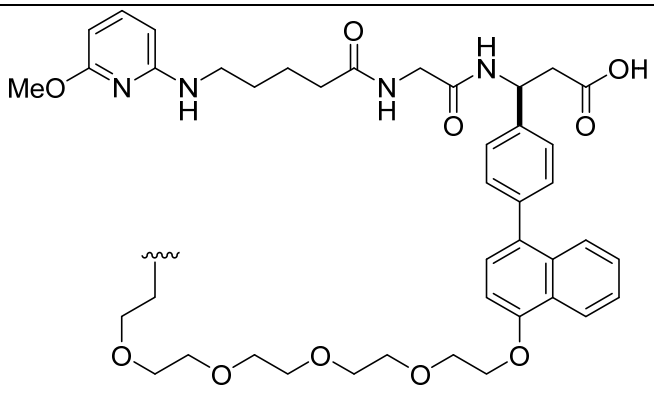
Compound Number	Formula
40b	
41b	
42b	

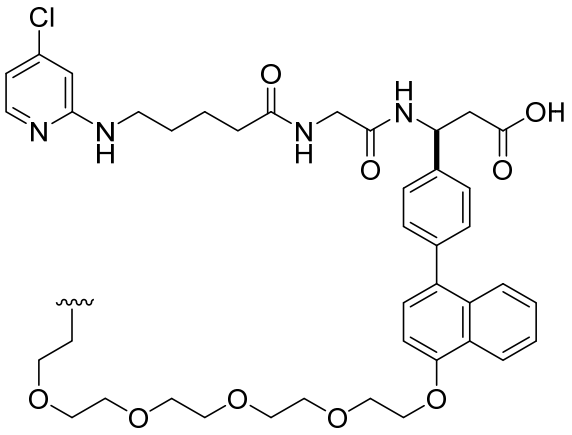
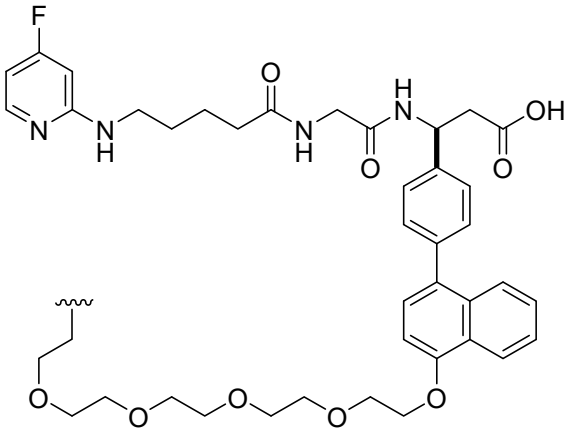
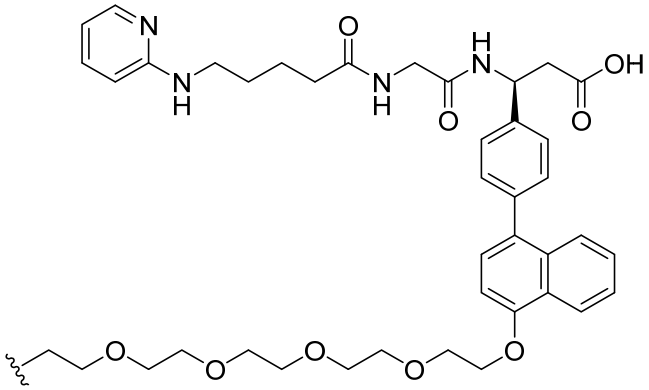
43b	
44b	
45b	

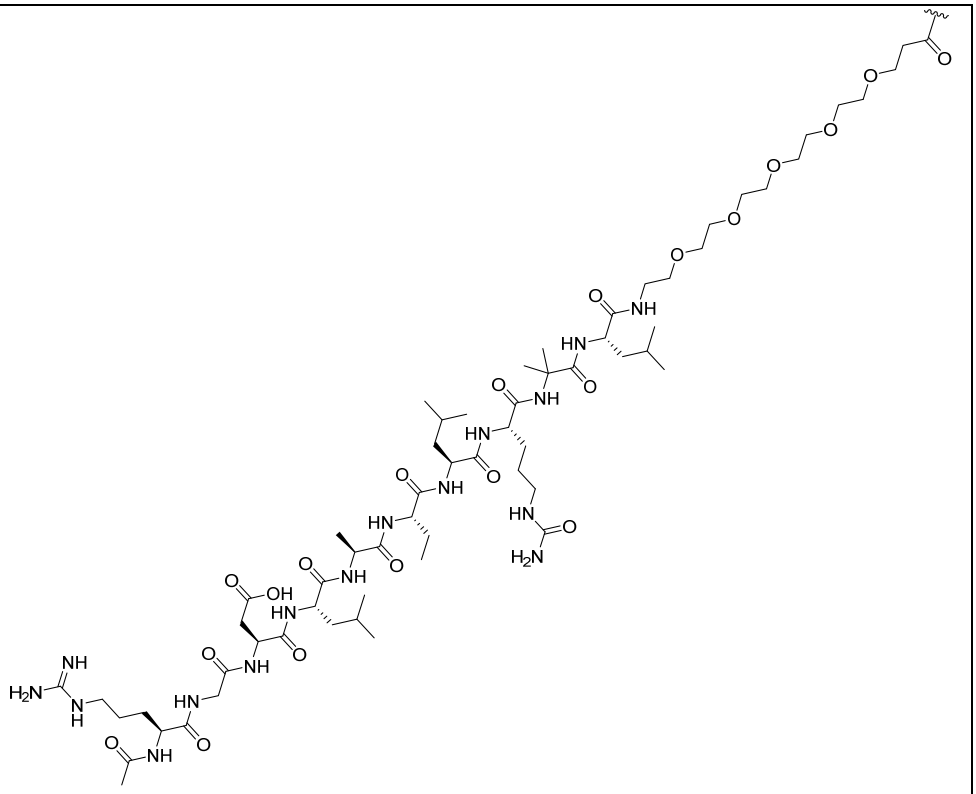
46b	
47b	
48b	

49b	
50b	
51b	

52b	
53b	
54b	

55b	
56b	
57b	

58b	
59b	
60b	

αvβ6 Peptide 1	

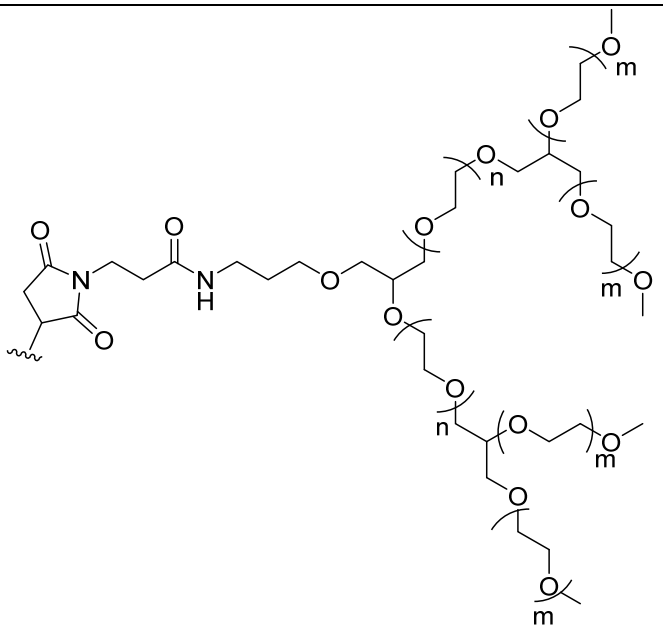
or a pharmaceutically acceptable salt thereof, wherein ≀ indicates the point of connection to the RNAi agent.

9. The RNAi agent of any one of claims 1-8, wherein the RNAi agent is further linked to a pharmacokinetic/pharmacodynamic (PK/PD) modulator.

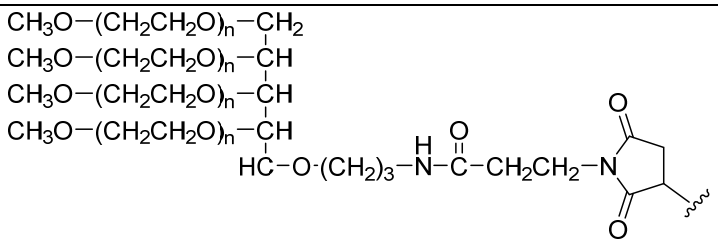
10. The RNAi agent of claim 9, wherein the PK/PD modulator is linked to the sense strand.

11. The RNAi agent of claim 10, wherein the PK/PD modulator is linked to the 3' terminal end of the sense strand.

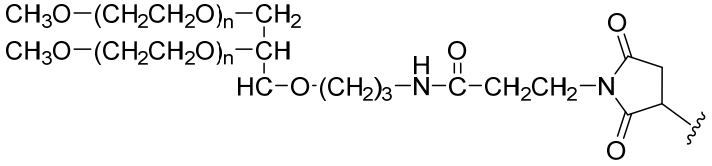
12. The RNAi agent of any one of claims 9-11, wherein the PK/PD modulator is selected from the group consisting of:



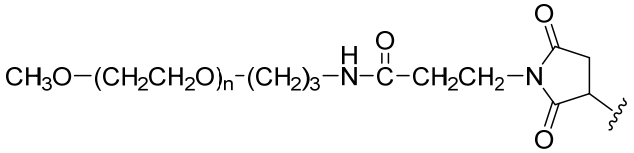
PEG40K (2x2-arm),
wherein n and m are integers, and the molecular weight of the PEG groups is about 40 kilodaltons



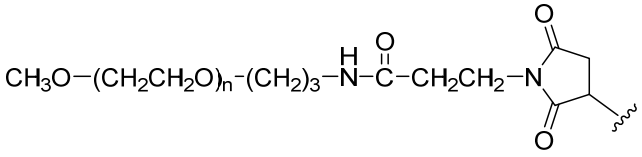
PEG40K (4-arm),
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



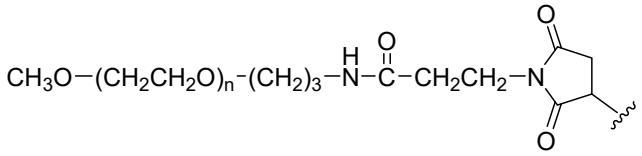
PEG40K (2-arm),
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



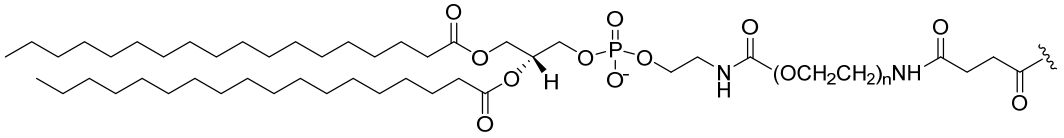
PEG40K,
wherein n is an integer, and the molecular weight of the PEG groups is about 40 kilodaltons



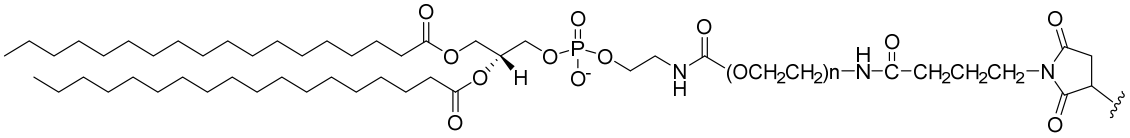
PEG10K,
wherein n is an integer, and the molecular weight of the PEG groups is about 10 kilodaltons



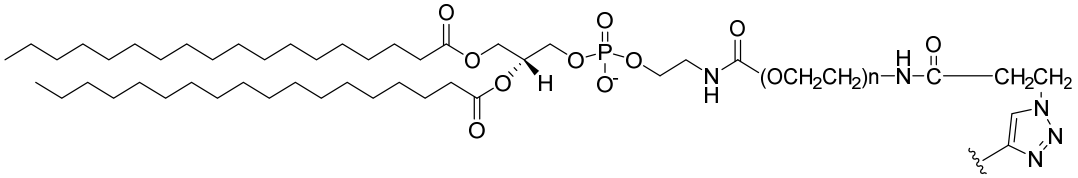
PEG5K,
wherein n is an integer, and the molecular weight of the PEG groups is about 5 kilodaltons



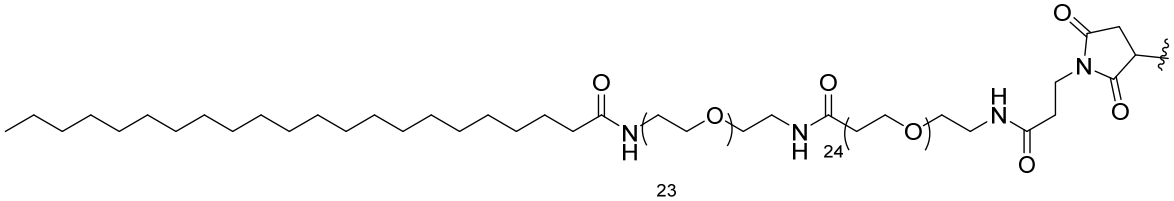
DSPE-PEG5K-NHS
wherein n is an integer and the molecular weight of the PEG groups is about 5 kilodaltons



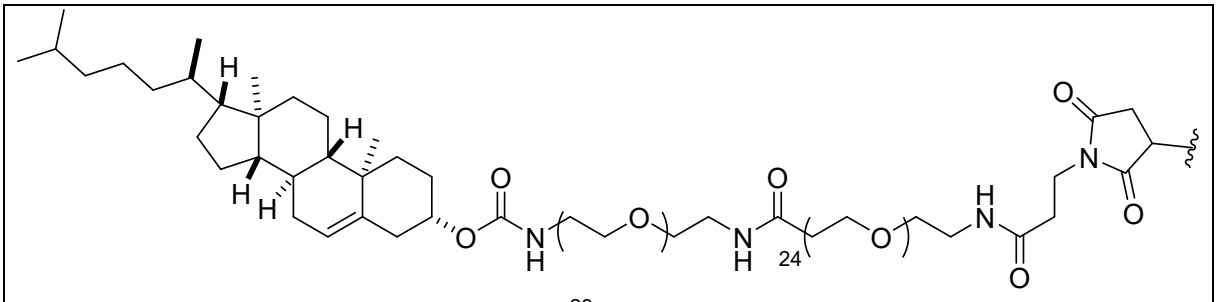
DSPE-PEG5K-MAL
Wherein n is an integer and the molecular weight of the PEG groups is about 5 kilodaltons



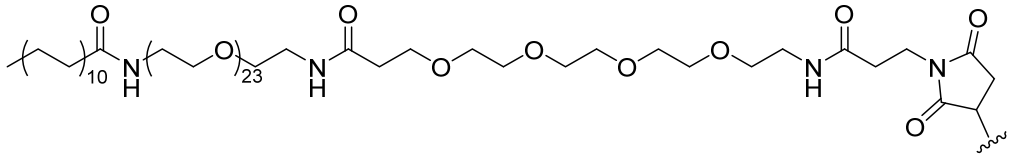
DSPE-PEG5K-N3
wherein n is an integer and the molecular weight of the PEG groups is about 5 kilodaltons



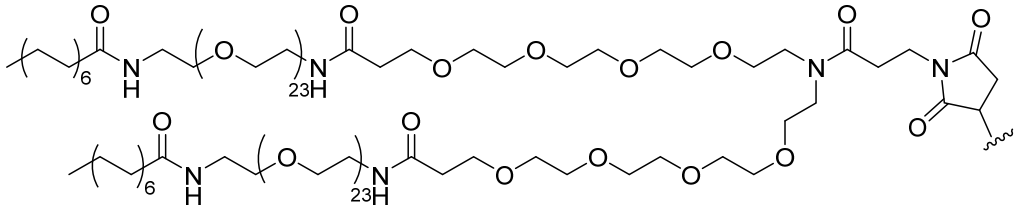
PEG47+C22



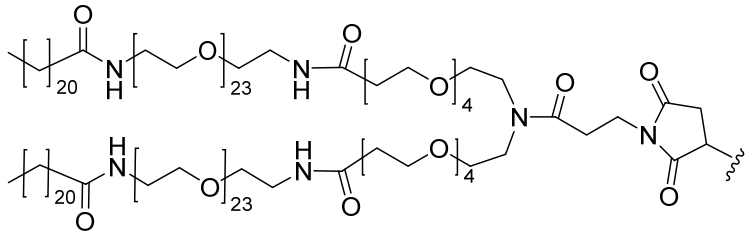
PEG47+CLS (cholesterol)



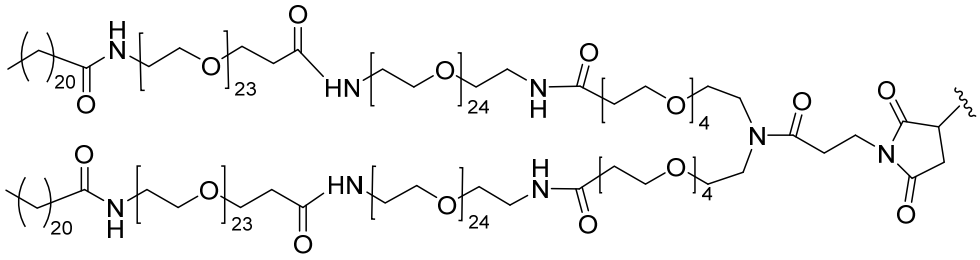
PEG23+C22



Bis(PEG23+C14)



Bis(PEG23+C22)



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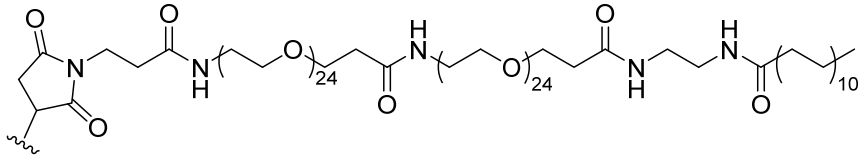
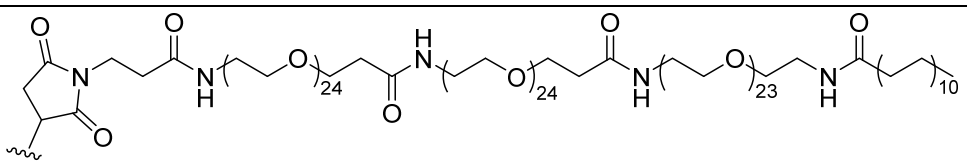
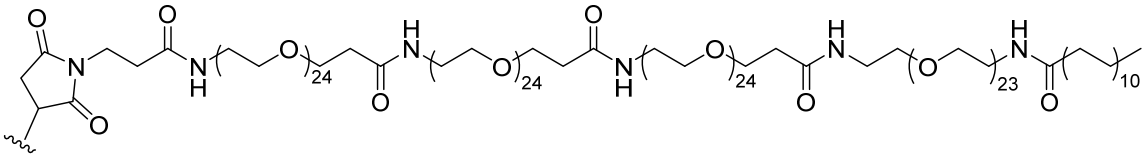


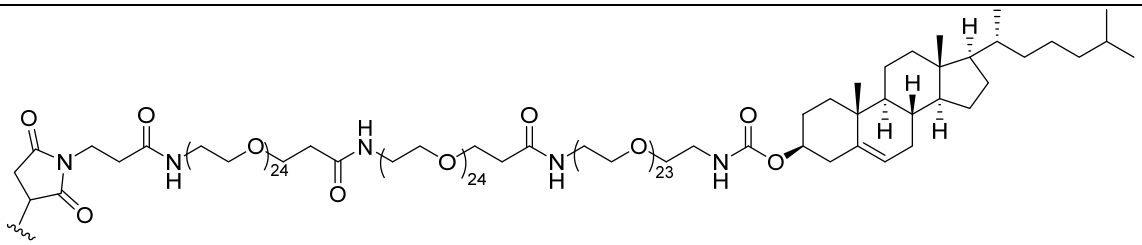
PEG48+C22



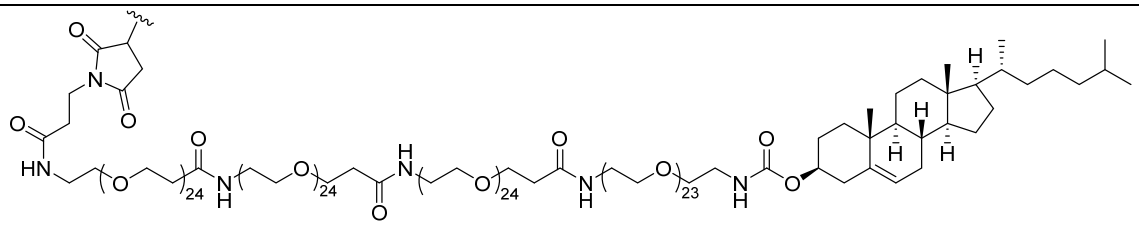
PEG71+C22



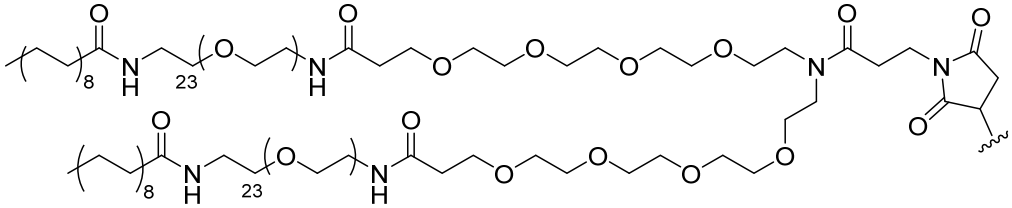
PEG95+C22



PEG71+CLS



PEG95+CLS



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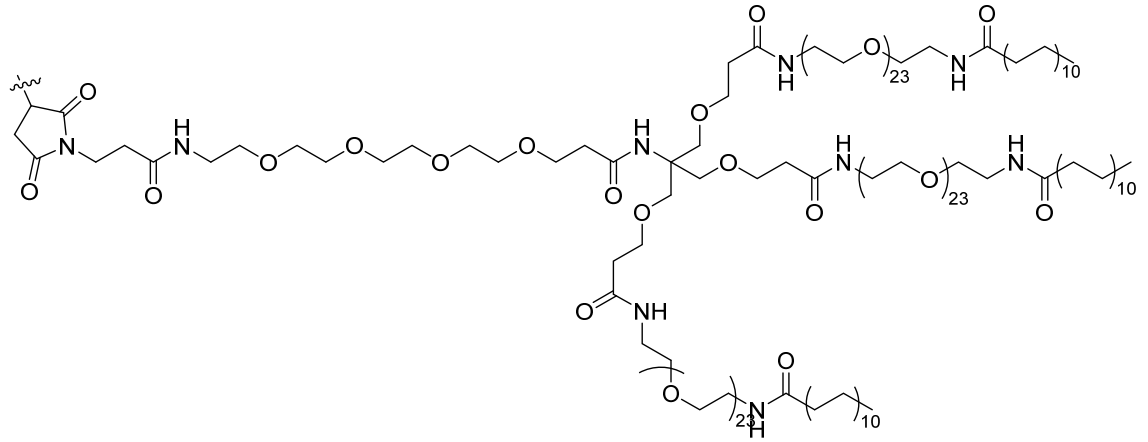

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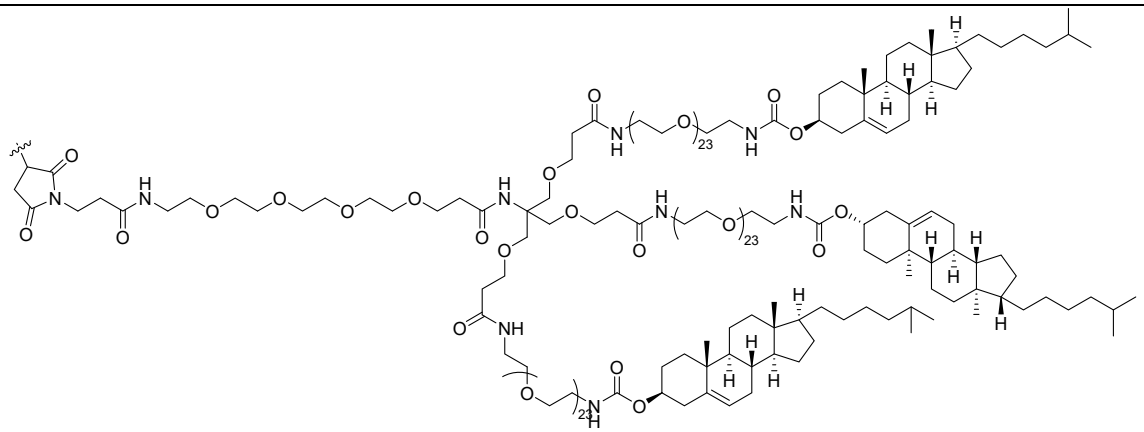
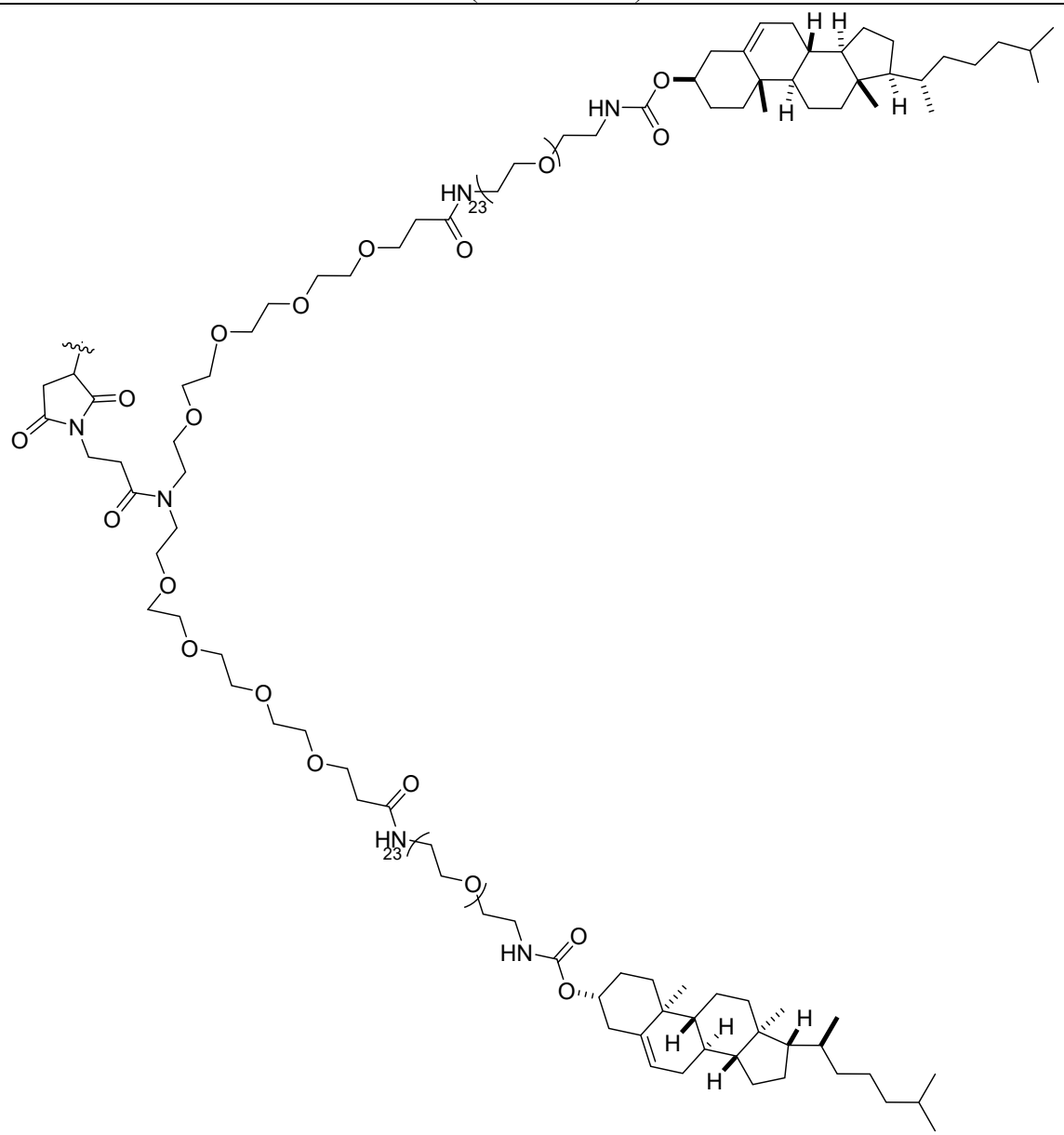


Tris(PEG23+CLS)



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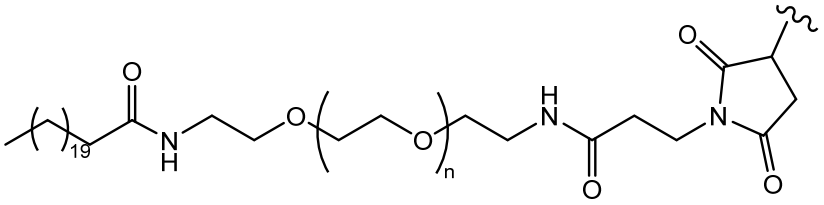
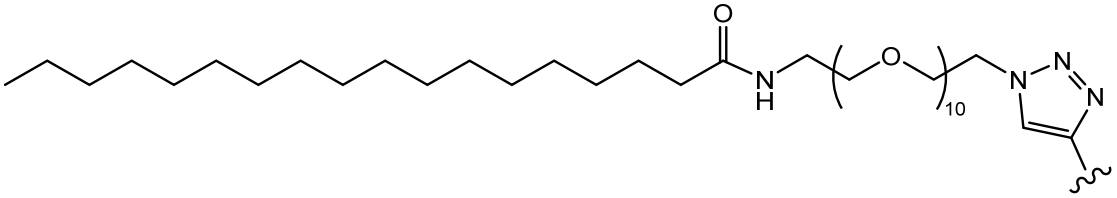
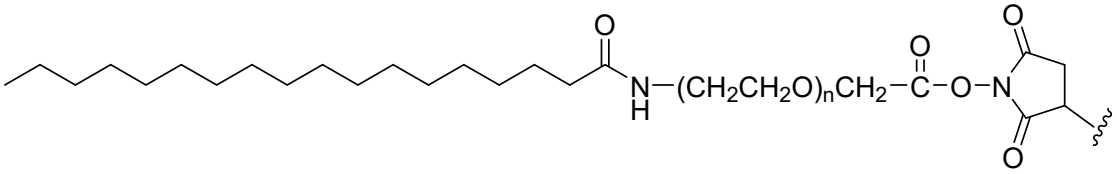


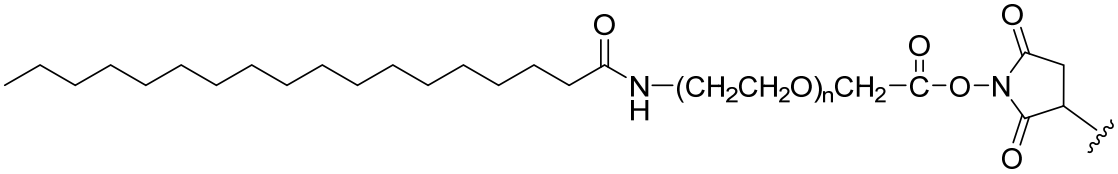
PEG5K+C22
wherein n is an integer and the molecular weight of the PEG units is about 5 kilodaltons



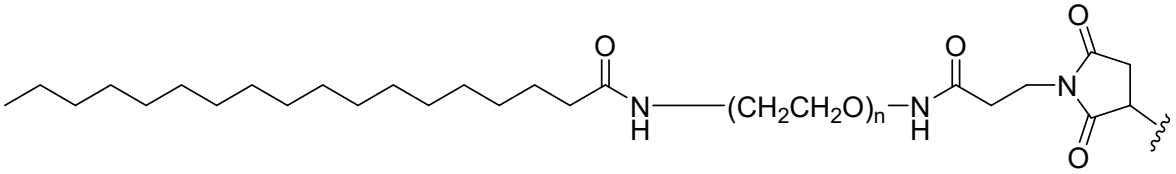
C18



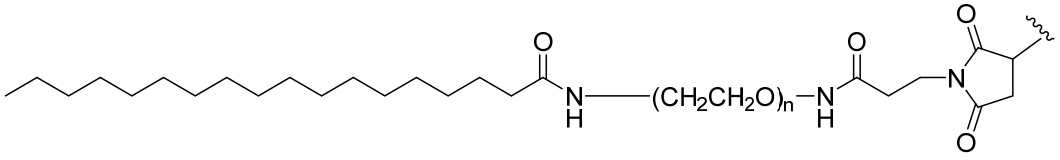
(NHS)-PEG1K+C18
wherein n is an integer and the molecular weight of the PEG units is about 1 kilodalton



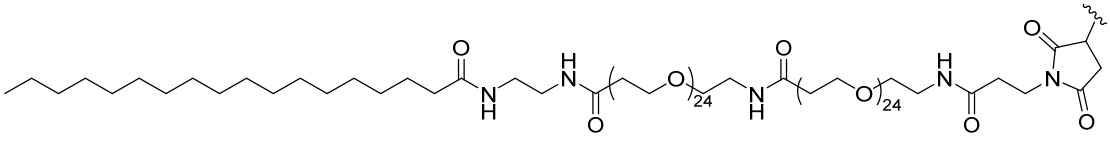
(NHS)-PEG2K+C18
wherein n is an integer and the molecular weight of the PEG units is about 2 kilodaltons



(NHS)-PEG5K+C18
wherein n is an integer and the molecular weight of the PEG units is about 5 kilodaltons



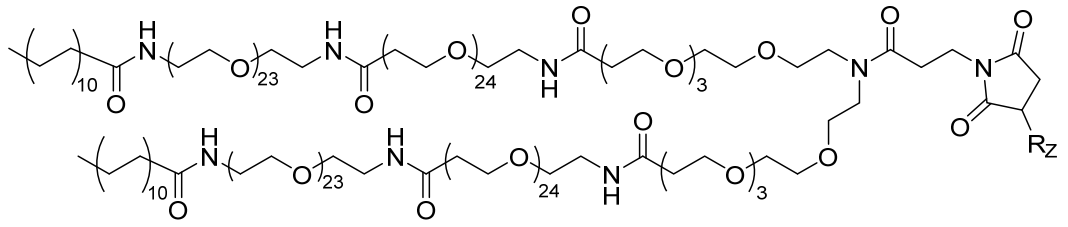
(MAL)-PEG5K+C18
wherein n is an integer and the molecular weight of the PEG units is about 5 kilodaltons



PEG48+C18

or a pharmaceutically acceptable salt thereof, wherein ≀ indicates the point of connection to the RNAi agent.

13. The RNAi agent of any one of claims 9-11, wherein the PK/PD modulator is selected from the group consisting of:

LP 1b

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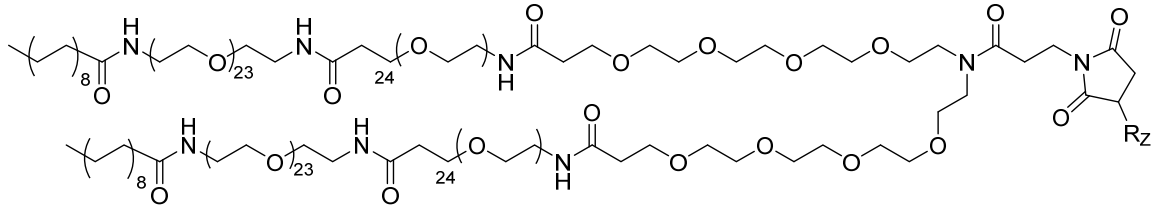
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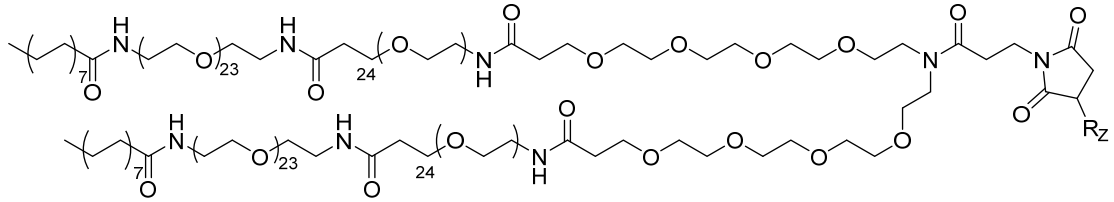
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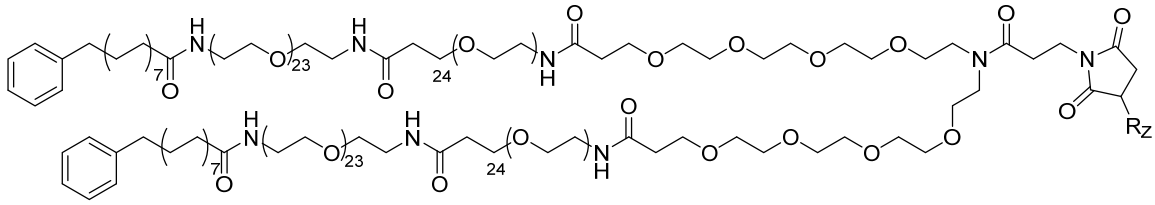
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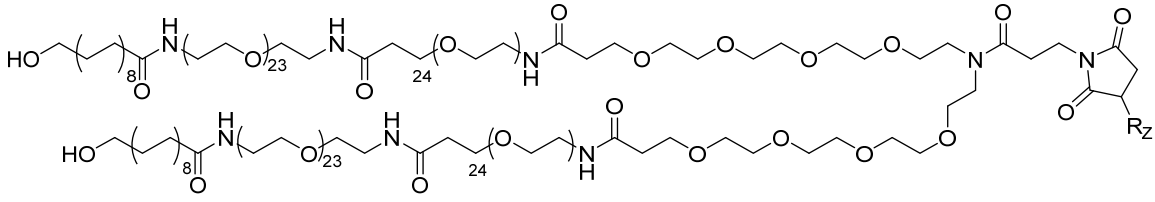

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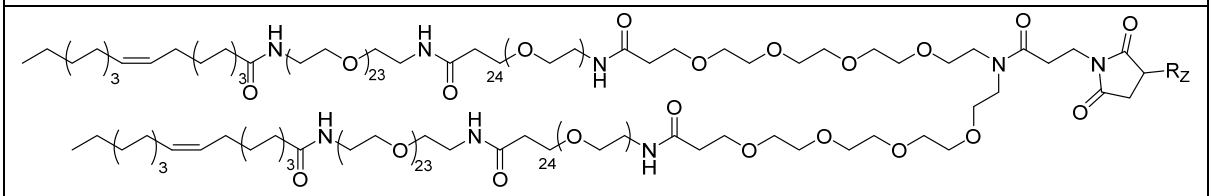
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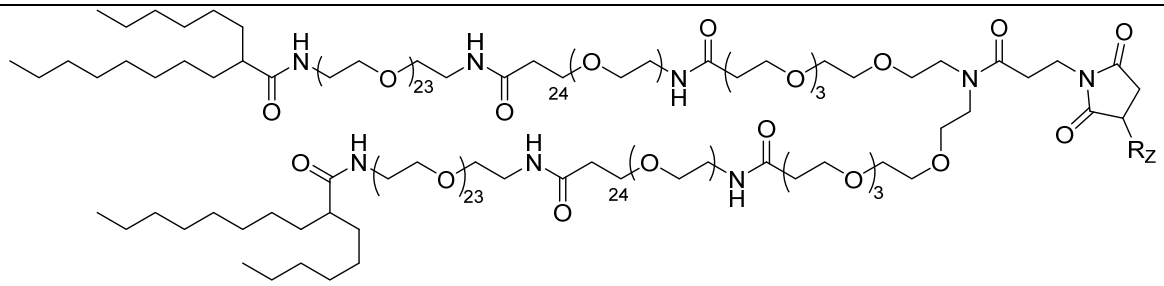
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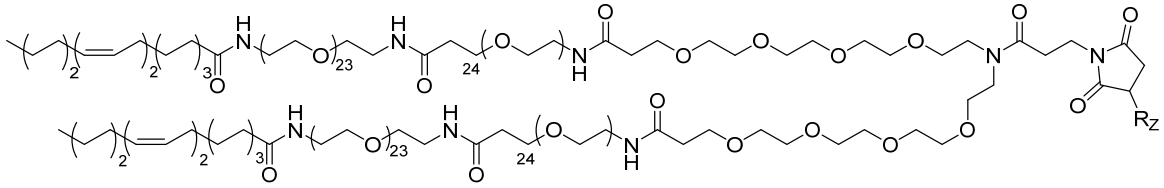
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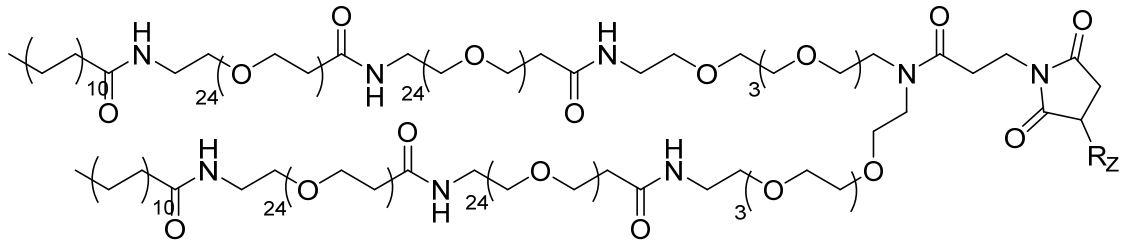
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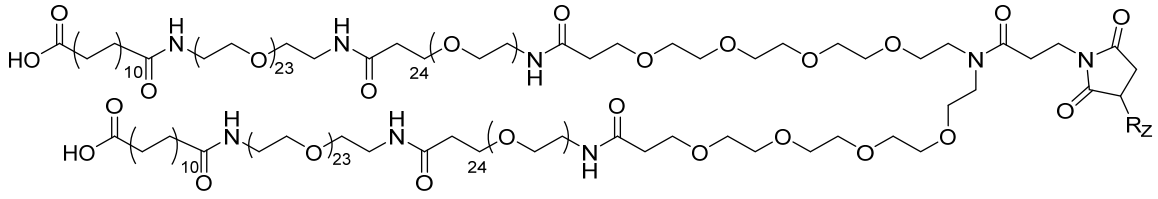
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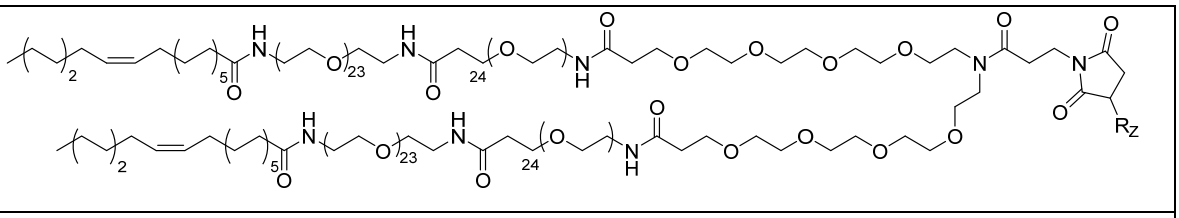

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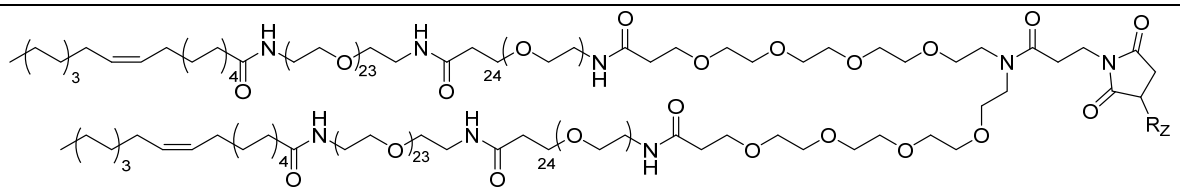

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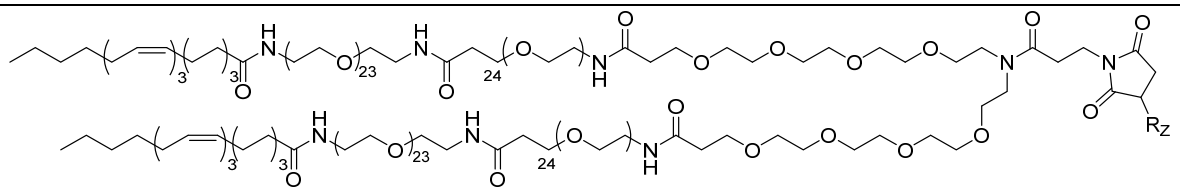

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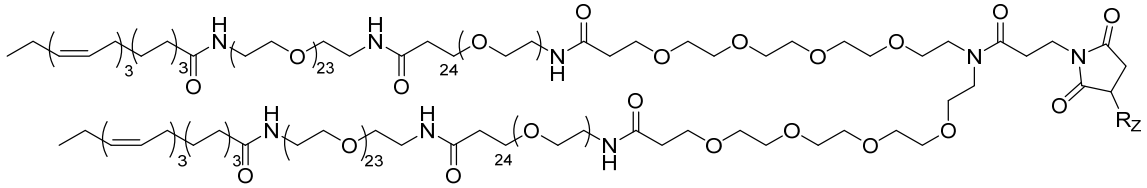

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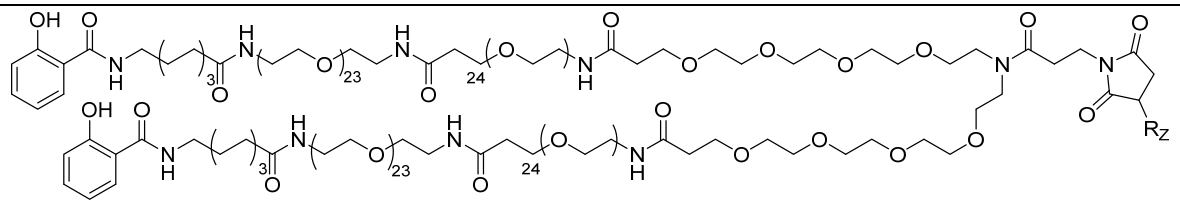

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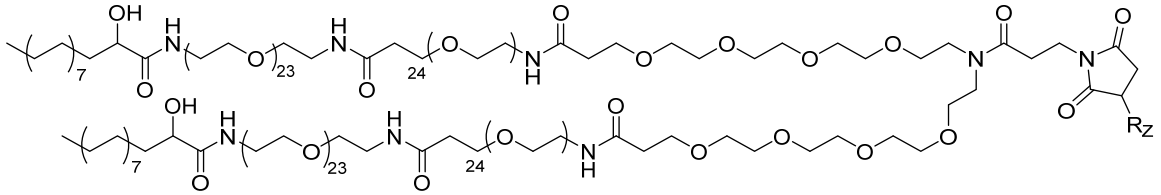

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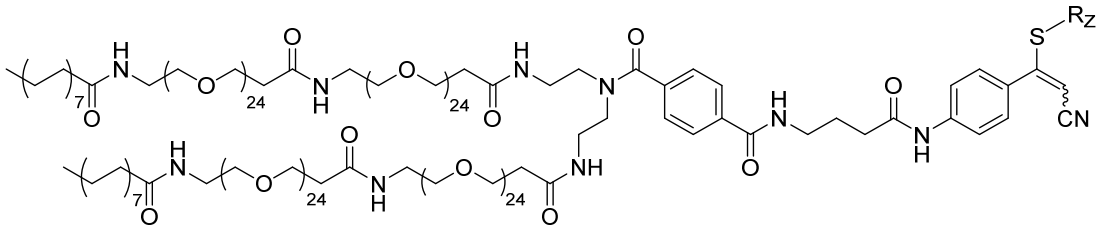

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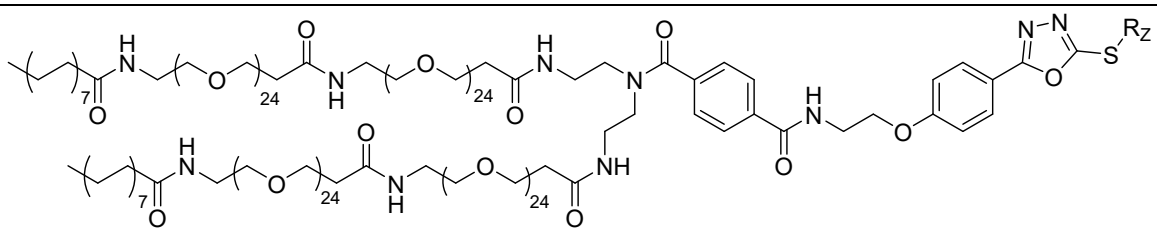

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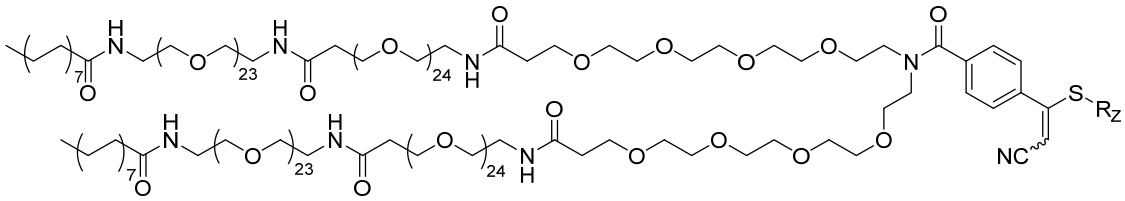
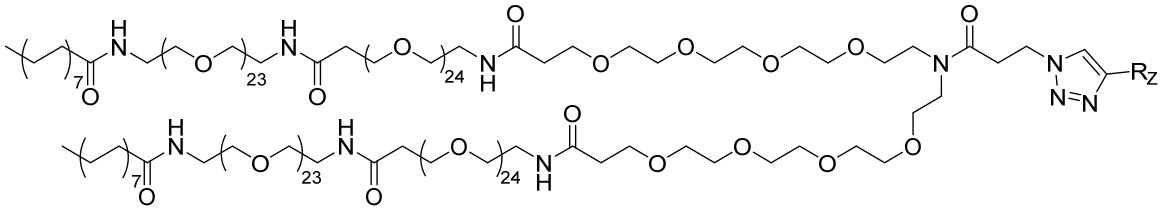
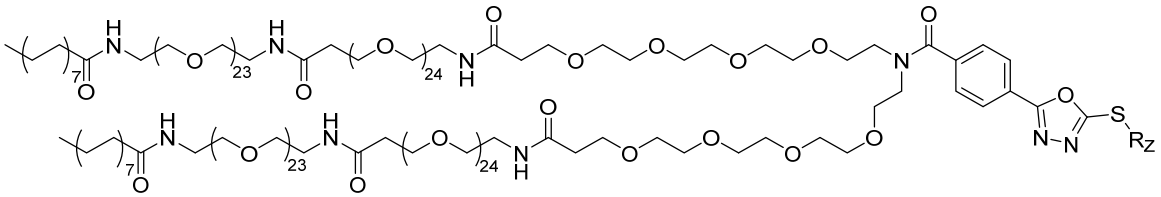


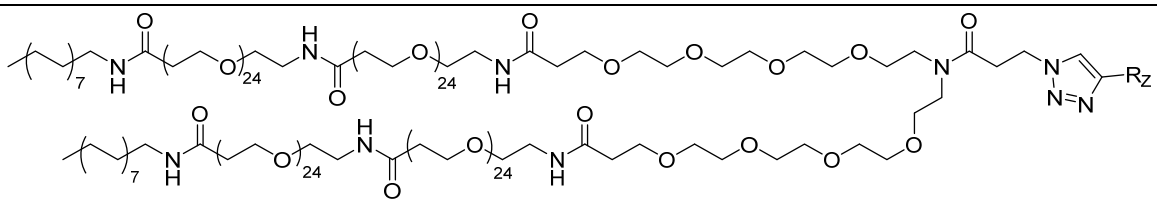
LP 226b



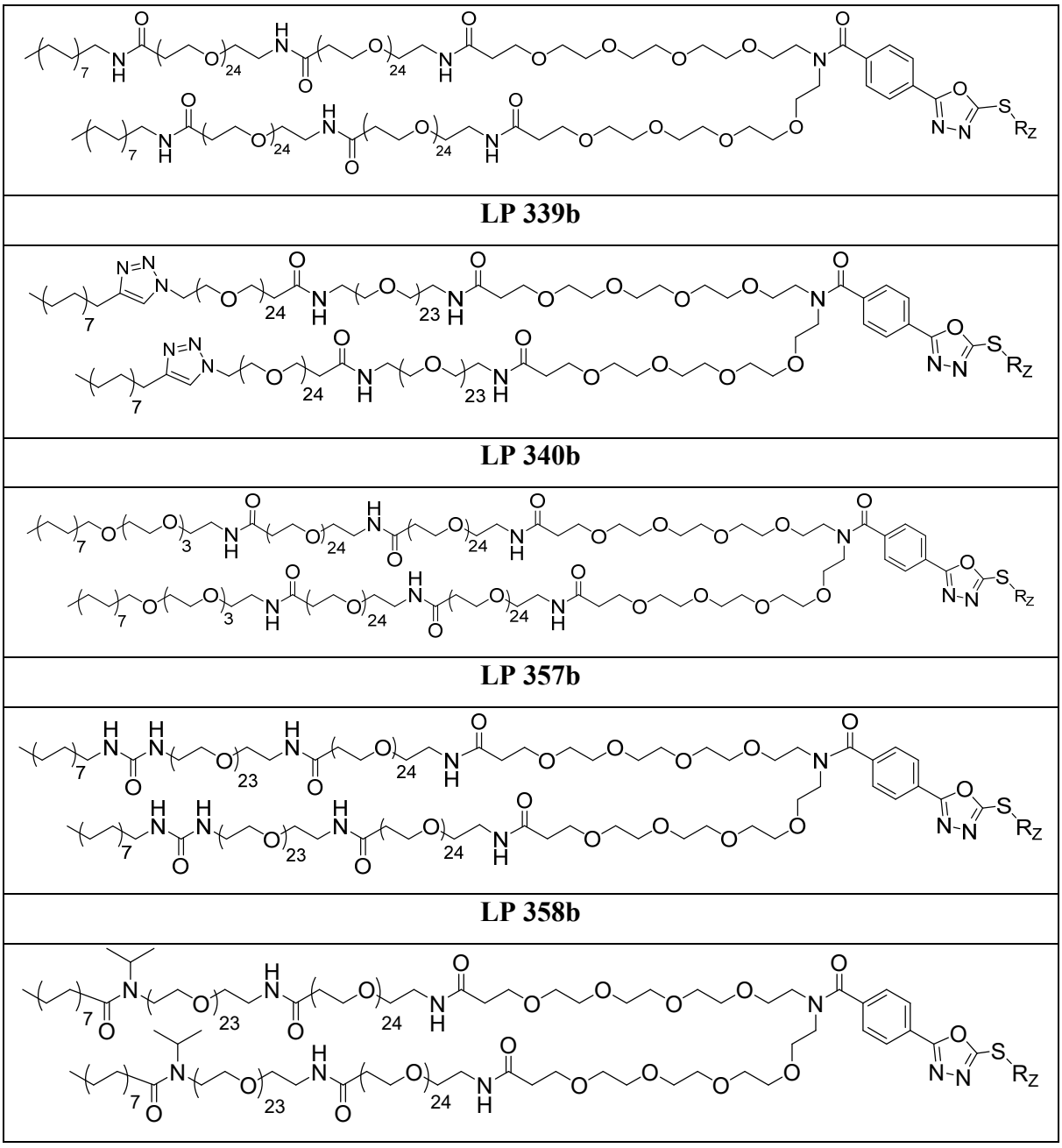
LP 238b



LP 246b



LP 247b



LP 339b

LP 340b

LP 357b

LP 358b

wherein Rz comprises the RNAi agent.

14. The RNAi agent of any one of claims 1-13, comprising an antisense strand that consists of, consists essentially of, or comprises a nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

UAGAAUUUCACGGAAGAAC (SEQ ID NO:22);

UGAAACCAGAUCUGAAUCC (SEQ ID NO:10);
UUGAAACCAGAUCUGAAUC (SEQ ID NO:14);
UAGAAUUUCACGGAAGAACAG (SEQ ID NO:164);
UGAAACCAGAUCUGAAUCCUG (SEQ ID NO:162);
UUGAAACCAGAUCUGAAUCCU (SEQ ID NO:163); and
UUGAAACCAGAUCUGAAUCCC (SEQ ID NO:169).

15. The RNAi agent of claim 14, wherein all or substantially all of the nucleotides are modified nucleotides.

16. The RNAi agent of any one of claims 1-15, comprising an antisense strand that comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):

usAfsGfsAfauuucacGfgAfaGfaacasg (SEQ ID NO:82);
cPrpusAfsGfsAfauuucacGfgAfaGfaacasg (SEQ ID NO:84);
cPrpusAfsgsAfauuucacGfgAfaGfaacasg (SEQ ID NO:100);
cPrpusAfsGfsaauuucacGfgAfaGfaacasg (SEQ ID NO:101);
cPrpusGfsasaaccagauCfuGfaAfuccusg (SEQ ID NO:97);
cPrpusGfsasAfaccagauCfuGfaAfuccusg (SEQ ID NO:99);
cPrpusGfsasAfaCfcAfgAfuCfuGfaAfuCfcUfsg (SEQ ID NO:75);
usGfsasaaccagauCfuGfaAfuccusg (SEQ ID NO:96);
cPrpusUfsgsAfaAfcCfaGfaUfcUfgAfaUfcCfsu (SEQ ID NO:76);
cPrpusUfsgsaaaccagaUfcUfgAfauccsc (SEQ ID NO:89); and
cPrpusUfsgsAfaAfcCfaGfaUfcUfgAfaUfcCfsc (SEQ ID NO:87);

wherein a, c, g, and u represent 2′-O-methyl adenosine, 2′-O-methyl cytidine, 2′-O-methyl guanosine, and 2′-O-methyl uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, 2′-fluoro cytidine, 2′-fluoro guanosine, and 2′-fluoro uridine, respectively; cPrpu represents a 5’-cyclopropyl phosphonate-2’-O-methyl uridine; s represents a phosphorothioate

linkage; and wherein all or substantially all of the nucleotides on the sense strand are modified nucleotides.

17. The RNAi agent of claim 16, wherein the sense strand comprises, consists of, or consists essentially of a modified nucleotide sequence that differs by 0 or 1 nucleotides from one of the following nucleotide sequences (5′ → 3′):
caggauucAfGfAfucugguuuca (SEQ ID NO:147);
aggauucaGfAfUfcugguuucaa (SEQ ID NO:148)
cuguucuuCfCfGfugaaauucua (SEQ ID NO:149);
gggauucaGfAfUfcugguuucaa (SEQ ID NO:156); and
gggauucaGfaUfCfugguuucaa (SEQ ID NO:159);

wherein a, c, g, and u represent 2′-O-methyl adenosine, 2′-O-methyl cytidine, 2′-O-methyl guanosine, and 2′-O-methyl uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, 2′-fluoro cytidine, 2′-fluoro guanosine, and 2′-fluoro uridine, respectively; and wherein all or substantially all of the nucleotides on the antisense strand are modified nucleotides.

18. An RNAi agent of any one of claims 1-17, comprising:
(i) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usAfsGfsAfauuucacGfgAfaGfaacasg (SEQ ID NO:82), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cuguucuuCfCfGfugaaauucua (SEQ ID NO:149);
(ii) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusAfsGfsAfauuucacGfgAfaGfaacasg (SEQ ID NO:84), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cuguucuuCfCfGfugaaauucua (SEQ ID NO:149);
(iii) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusAfsgsAfauuucacGfgAfaGfaacasg (SEQ ID NO:100), and a sense strand that consists of, consists essentially of, or

comprises the modified nucleotide sequence (5′ → 3′) cuguucuuCfCfGfugaaauucua (SEQ ID NO:149);

(iv) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusAfsGfsaauuucacGfgAfaGfaacasg (SEQ ID NO:101), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cuguucuuCfCfGfugaaauucua (SEQ ID NO:149);

(v) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusGfsasaaccagauCfuGfaAfuccusg (SEQ ID NO:97), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) caggauucAfGfAfucugguuuca (SEQ ID NO:147);

(vi) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusGfsasAfaccagauCfuGfaAfuccusg (SEQ ID NO:99), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) caggauucAfGfAfucugguuuca (SEQ ID NO:147);

(vii) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusGfsasAfaCfcAfgAfuCfuGfaAfuCfcUfsg (SEQ ID NO:75), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) caggauucAfGfAfucugguuuca (SEQ ID NO:147);

(viii) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) usGfsasaaccagauCfuGfaAfuccusg (SEQ ID NO:96), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) caggauucAfGfAfucugguuuca (SEQ ID NO:147);

(ix) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusUfsgsAfaAfcCfaGfaUfcUfgAfaUfcCfsu (SEQ ID NO:76), and a sense

strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) aggauucaGfAfUfcugguuucaa (SEQ ID NO:148);

(x) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusUfsgsaaaccagaUfcUfgAfauccsc (SEQ ID NO:89), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gggauucaGfAfUfcugguuucaa (SEQ ID NO:156); or

(xi) an antisense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) cPrpusUfsgsAfaAfcCfaGfaUfcUfgAfaUfcCfsc (SEQ ID NO:87), and a sense strand that consists of, consists essentially of, or comprises the modified nucleotide sequence (5′ → 3′) gggauucaGfaUfCfugguuucaa (SEQ ID NO:159);

wherein a, c, g, and u represent 2′-O-methyl adenosine, 2′-O-methyl cytidine, 2′-O-methyl guanosine, and 2′-O-methyl uridine, respectively; Af, Cf, Gf, and Uf represent 2′-fluoro adenosine, 2′-fluoro cytidine, 2′-fluoro guanosine, and 2′-fluoro uridine, respectively; cPrpu represents a 5’-cyclopropyl phosphonate-2’-O-methyl uridine; s represents a phosphorothioate linkage; and wherein the respective sense strand further optionally includes an inverted abasic residue at the 3’ terminal end of the nucleotide sequence and at the 5’ terminal end of the nucleotide sequence; and the sense strand also optionally includes a targeting ligand that is covalently linked to the inverted abasic residue at the 5’ terminal end of the sense strand, wherein the targeting ligand has affinity for skeletal muscle cells and/or a receptor present on skeletal muscle cells, and wherein the sense strand further optionally includes a PK/PD modulator that is covalently linked to the inverted abasic residue at the 3’ terminal end of the sense strand.

19. The RNAi agent of claim 1, wherein the RNAi agent is comprised of a sense strand and an antisense strand that form a duplex having the structure of any one of the duplexes in Table 5.1, Table 5.2, Table 5.3, or Table 5.4.

20. The RNAi agent of claim 19, wherein the sense strand of the RNAi agent is linked to a targeting ligand.

21. The RNAi agent of claim 20, wherein the targeting ligand comprises a compound having the structure set forth in Table 6.2 or Table 6.3.

22. The RNAi agent of any one of claims 1-21, wherein the RNAi agent is a pharmaceutically acceptable salt.

23. The RNAi agent of claim 22, wherein the RNAi agent is in the sodium salt form.

24. A pharmaceutical composition comprising the RNAi agent of any one of claims 1-23, wherein the composition further comprises a pharmaceutically acceptable excipient.

25. A method for inhibiting expression of a *DUX4* gene in a cell *in vitro*, the method comprising introducing into a cell an effective amount of an RNAi agent of any one of claims 1-23 or the composition of claim 24.

26. A composition comprising the RNAi agent of any one of claims 1-23, for use in treating one or more symptoms or diseases that can be ameliorated at least in part by a reduction in DUX4 protein levels or a reduction in DUX4 mRNA levels.

27. The pharmaceutical composition of claim 26, wherein the disease is FSHD.

28. The pharmaceutical composition of any one of claims 25-27, wherein the DUX4 gene expression is reduced in one or more of paraspinal, facial, torso, abdominal, and limb muscle tissues of a subject.

29. The pharmaceutical composition of any one of claims 25-28, wherein the DUX4 gene expression is reduced in one or more of the triceps, biceps, quadriceps, gastrocnemius, soleus, EDL (extensor digitorum longus), TA (Tibialis anterior), or diaphragm of a subject.

30. The pharmaceutical composition of any one of claims 25-29, wherein the RNAi agent is administered at a dose of about 0.5 mg/kg to about 10.0 mg/kg of body weight.

31. The pharmaceutical composition of claim 30, wherein the RNAi agent is administered by subcutaneous (SQ) injection.

32. Use of the pharmaceutical composition according to claim 24, for the manufacture of a medicament for treatment of a disease, disorder, or symptom that is mediated at least in part by a reduction in DUX4 protein levels or a reduction in DUX4 mRNA levels, or both.

33. A composition for inhibiting expression of a double homeobox 4 (*DUX4*) gene, the composition comprising:

    i. an RNAi agent comprising an antisense strand 18 to 49 nucleotides in length that is at least partially complementary to a portion of SEQ ID NO:1 or SEQ ID NO:2;
    ii. a targeting ligand linked to the RNAi agent, wherein the targeting ligand has affinity for skeletal muscle cells; and
    iii. a PK/PD modulator linked to the RNAi agent.

34. An RNAi agent for inhibiting expression of a double homeobox 4 (*DUX4*) gene, comprising:
    i. a sense strand comprising a nucleotide sequence that comprises at least 15 contiguous nucleotides differing by 0, 1, 2, or 3 nucleotides from a stretch of 15 contiguous nucleotides of SEQ ID NO:1; and
    ii. an antisense strand comprising a nucleotide sequence that is at least partially complementary to the sense strand.

35. An RNAi agent for inhibiting expression of a double homeobox 4 (*DUX4*) gene, comprising:

i. an antisense strand comprising a nucleotide sequence that comprises at least 15 contiguous nucleotides that are at least partially complementary to a stretch of 15 contiguous nucleotides of SEQ ID NO:1; and
ii. a sense strand comprising a nucleotide sequence that is at least partially complementary to the antisense strand.