CLAIMS:

1. A delivery vehicle for inhibiting expression of a gene expressed in skeletal muscle cells comprising:

(a) an RNAi agent comprising:

(i) an antisense strand comprising 17-49 nucleotides wherein at least 15 nucleotides are complementary to the mRNA sequence of a gene that is expressed in skeletal muscle cells

(ii) a sense strand that is 16-49 nucleotides in length that is at least partially complementary to the antisense strand;

(b) a targeting ligand with affinity for a receptor present on the surface of a skeletal muscle cell, wherein the targeting ligand is a polypeptide; and

(c) a PK/PD modulator;

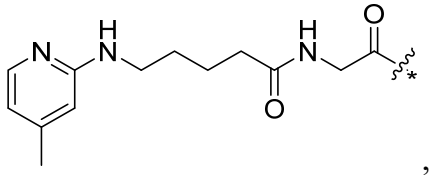
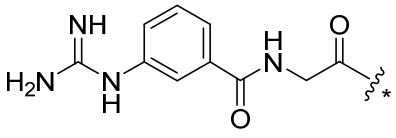
wherein the RNAi agent is covalently linked to the targeting ligand and to the PK/PD modulator.

2. The delivery vehicle of claim 1, wherein the polypeptide of the targeting ligand is a polypeptide of Formula (**P**):

$$Xaa^1G'DLXaa^2Xaa^3L\text{-}Xaa^4Xaa^5L—\{$$

(**P**)

or a pharmaceutically acceptable salt thereof, wherein

Xaa^1 is L-arginine optionally having an N-terminal cap, , or , wherein each $\{^*$ indicates a point of connection to G';

G' is L-glycine or N-methyl-L-glycine;

D is L-aspartic acid (L-aspartate);

L is L-leucine;

Xaa^2 is an L-α amino acid, an L-β amino acid, or an α,α-disubstituted amino acid;

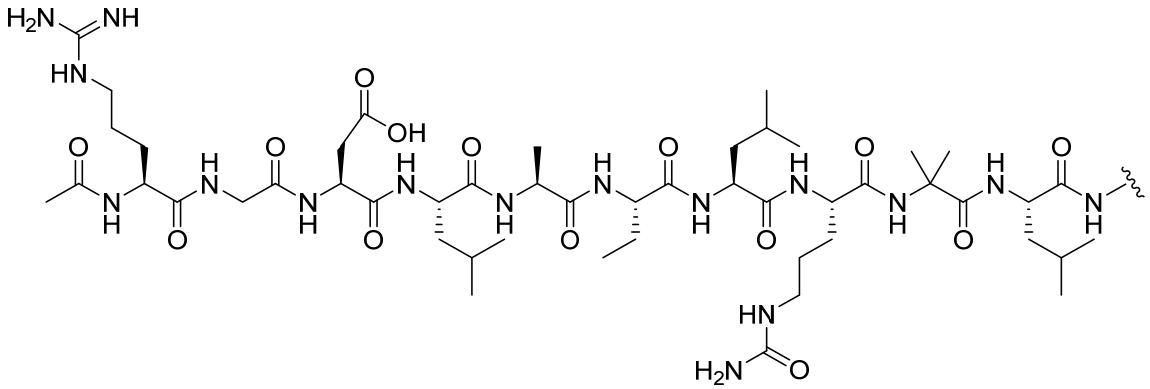
Xaa^3 is an L-α amino acid, an L-β amino acid, or an α,α-disubstituted amino acid;

Xaa^4 is an L-α amino acid, an L-β amino acid, or an α,α-disubstituted amino acid;

Xaa^5 is an L-α amino acid, an L-β amino acid, or an α,α-disubstituted amino acid; and

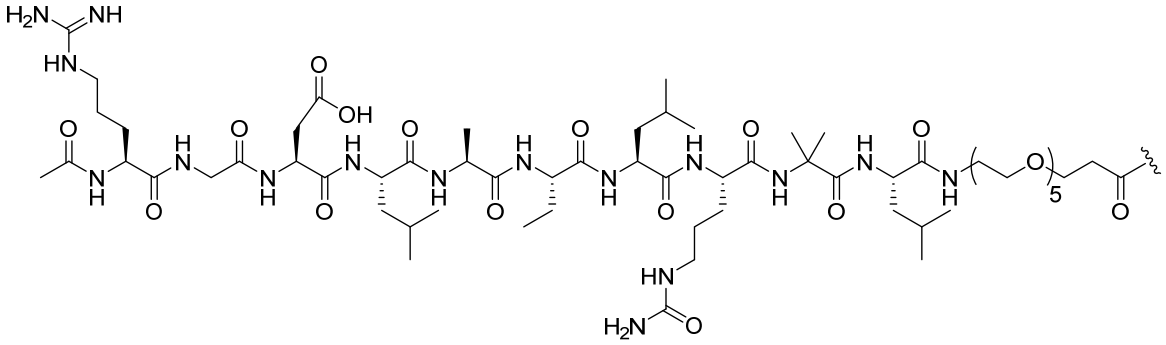
≈ indicates a point of connection to the RNAi agent.

3. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



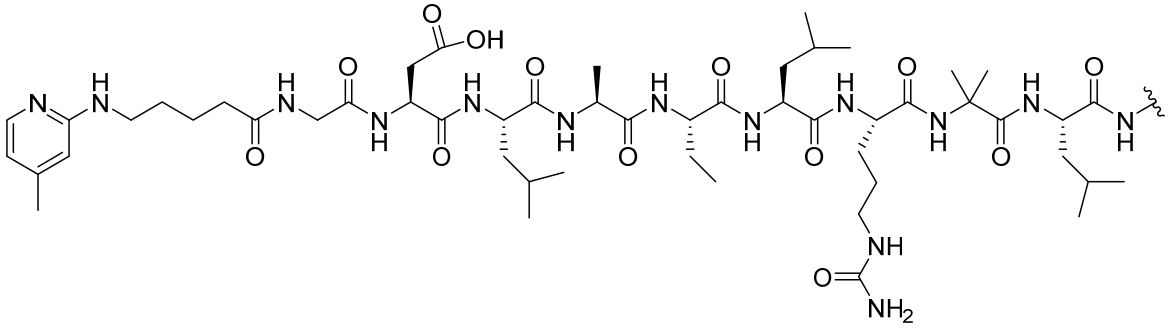
or a pharmaceutically acceptable salt thereof, wherein ≈ indicates a point of connection to the remainder of the delivery vehicle.

4. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



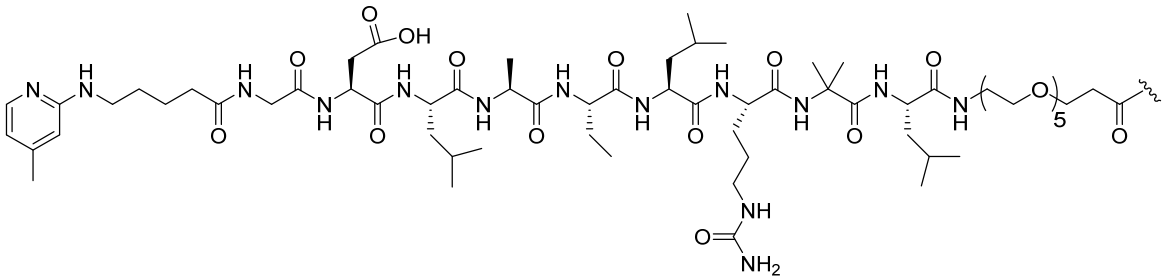
or a pharmaceutically acceptable salt thereof, wherein ≈ indicates a point of connection to the remainder of the delivery vehicle.

5. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



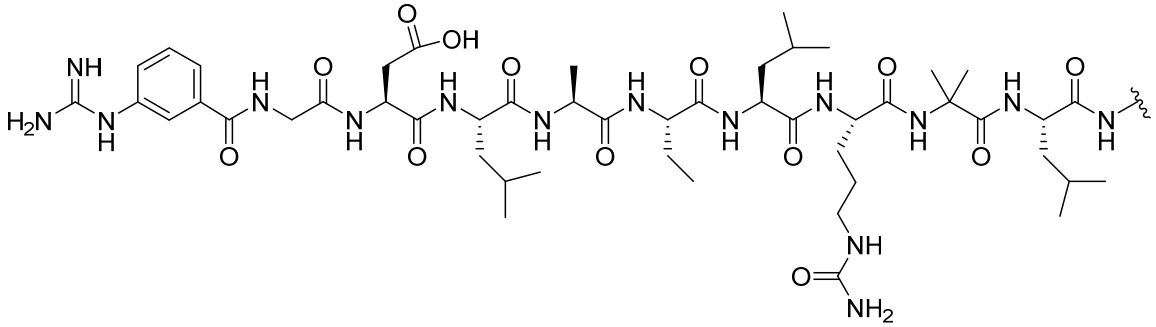
or a pharmaceutically acceptable salt thereof, wherein ≀ indicates a point of connection to the remainder of the delivery vehicle.

6. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



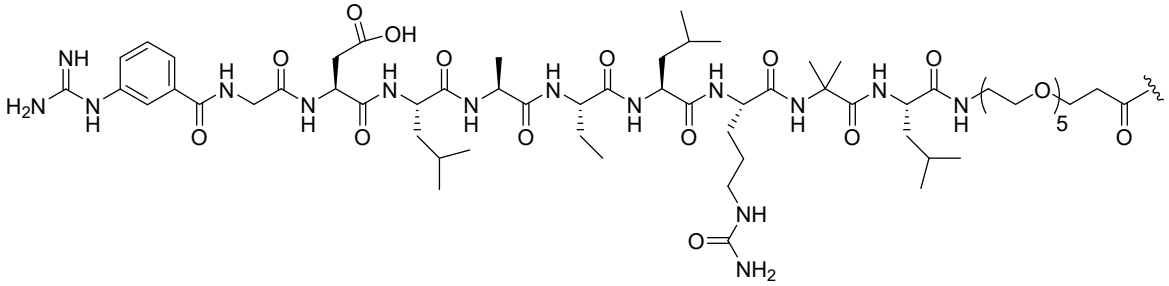
or a pharmaceutically acceptable salt thereof, wherein ≀ indicates a point of connection to the remainder of the delivery vehicle.

7. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



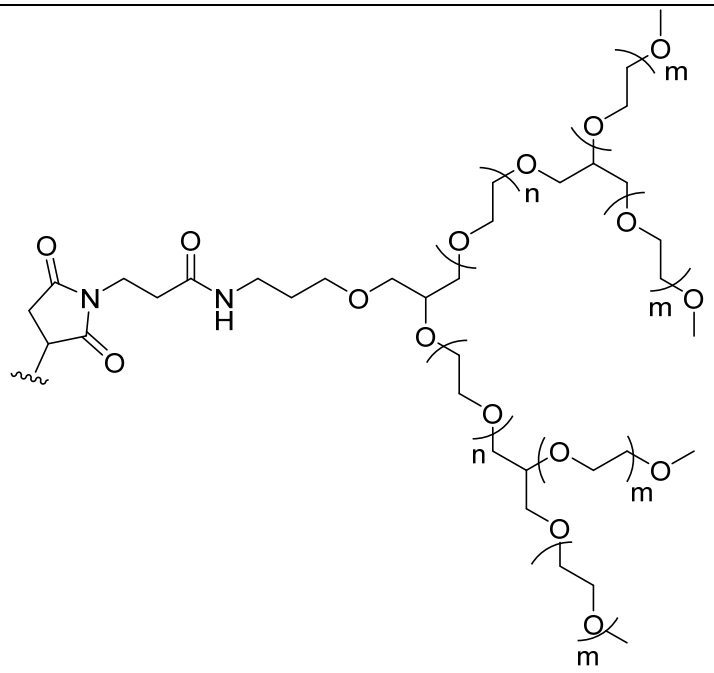
or a pharmaceutically acceptable salt thereof, wherein ≀ indicates a point of connection to the remainder of the delivery vehicle.

8. The delivery vehicle of claim 1, wherein the targeting ligand has the formula:



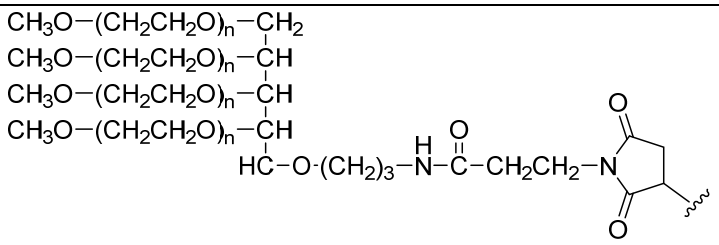
or a pharmaceutically acceptable salt thereof, wherein ≀ indicates a point of connection to the remainder of the delivery vehicle.

9. The delivery vehicle of any one of claims 1-8, wherein the PK/PD modulator is:



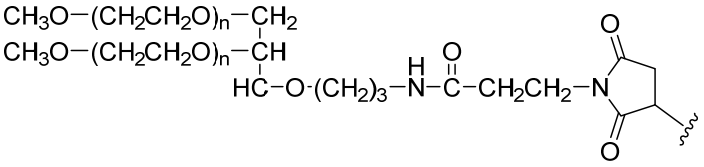
PEG40K (2x2-arm),

wherein n and m are each independently integers, and the molecular weight of the sum of all PEG units is about 40 kilodaltons



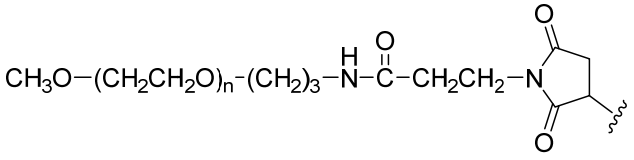
PEG40K (4-arm),

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 40 kilodaltons



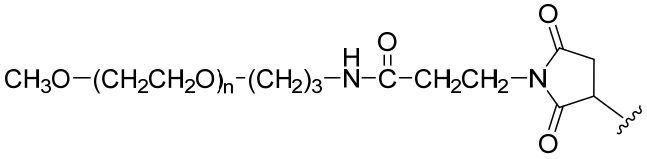
PEG40K (2-arm),

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 40 kilodaltons



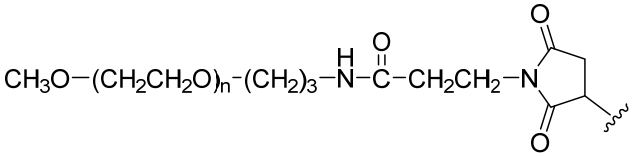
PEG40K,

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 40 kilodaltons



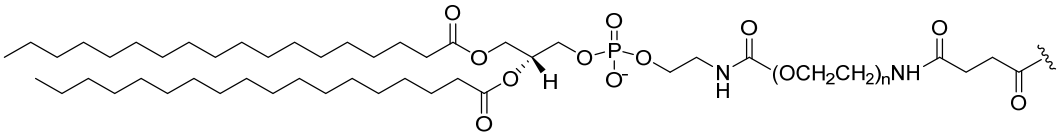
PEG10K,

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 10 kilodaltons



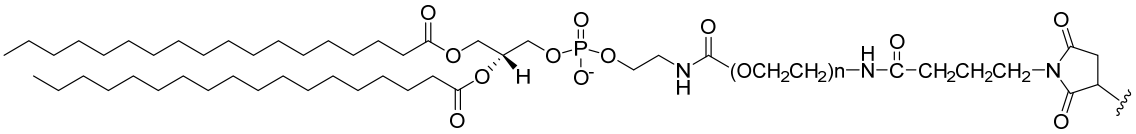
PEG5K,

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons



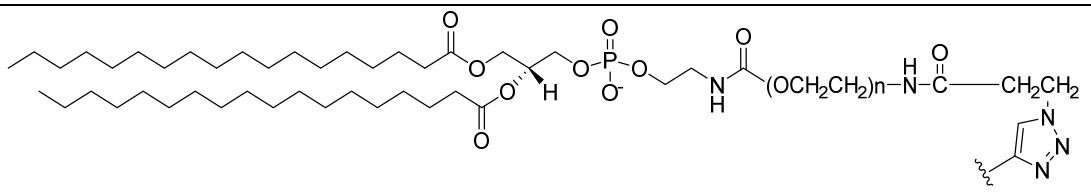
DSPE-PEG5K-NHS

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons



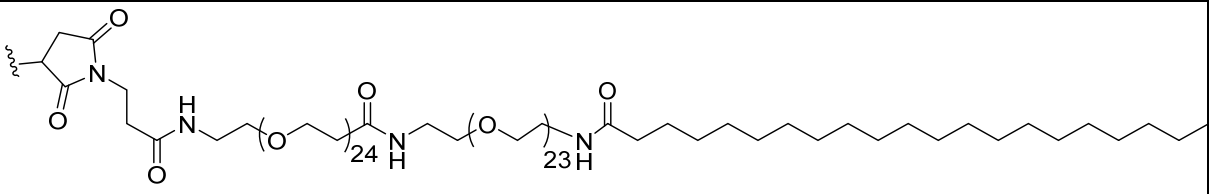
DSPE-PEG5K-MAL

Wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons

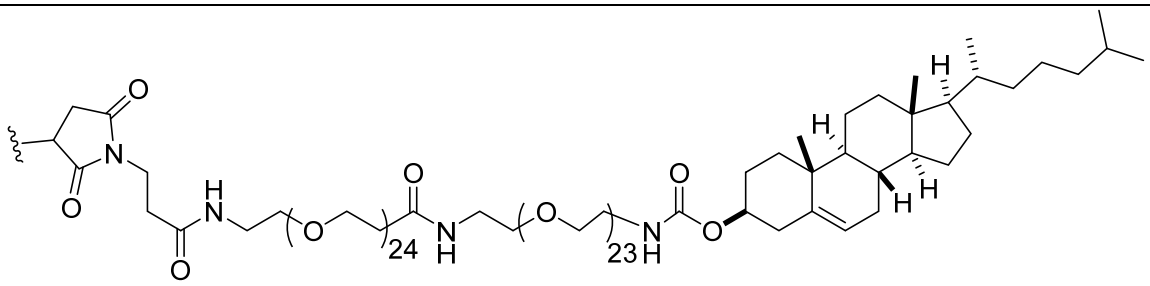


DSPE-PEG5K-N3

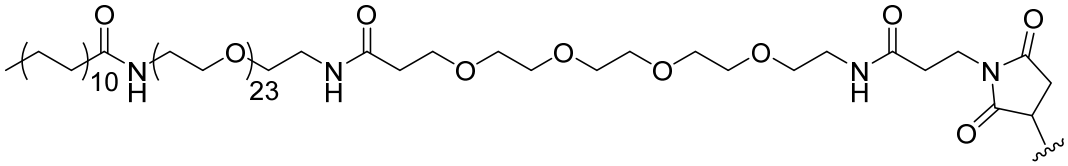
wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons



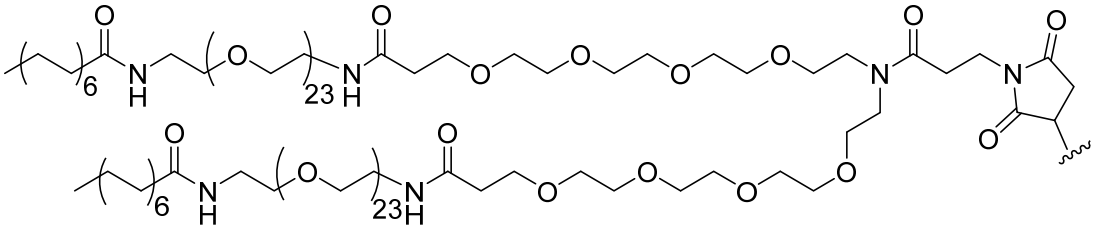
PEG47+C22



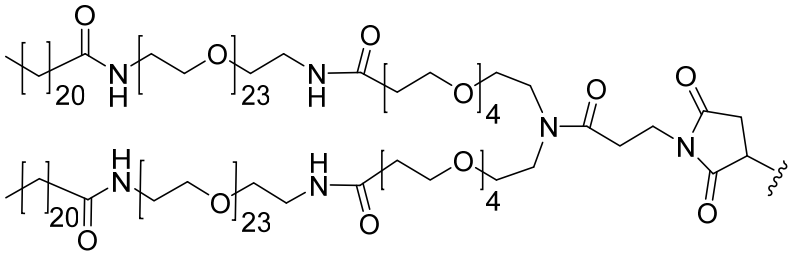
PEG47+CLS (cholesterol)



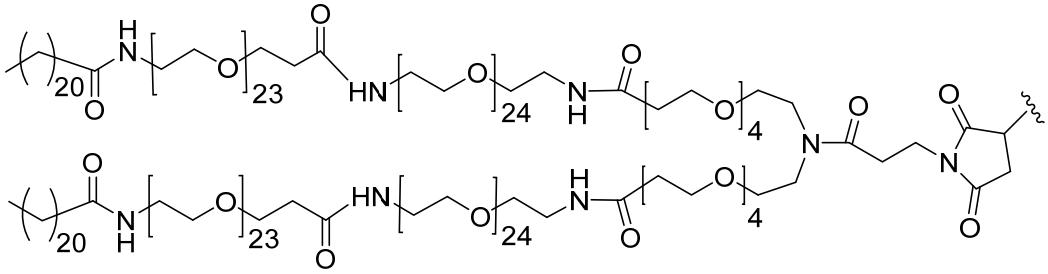
PEG23+C22



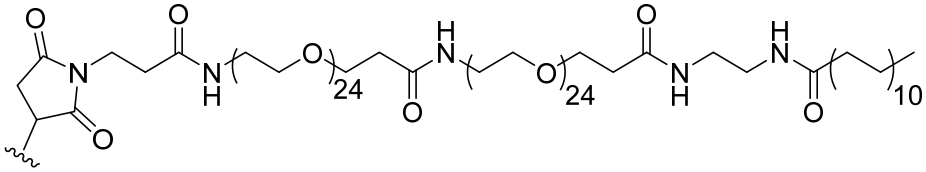
Bis(PEG23+C14)



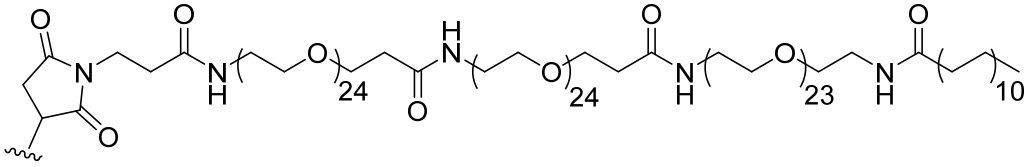
Bis(PEG23+C22)



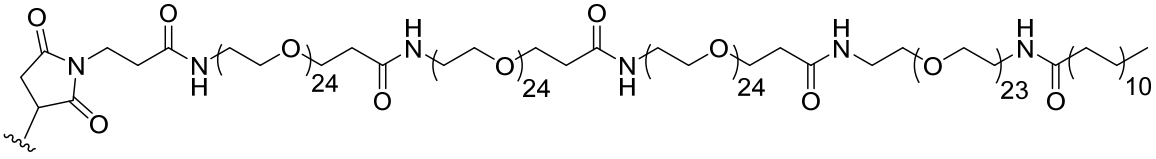
Bis(PEG47+C22)



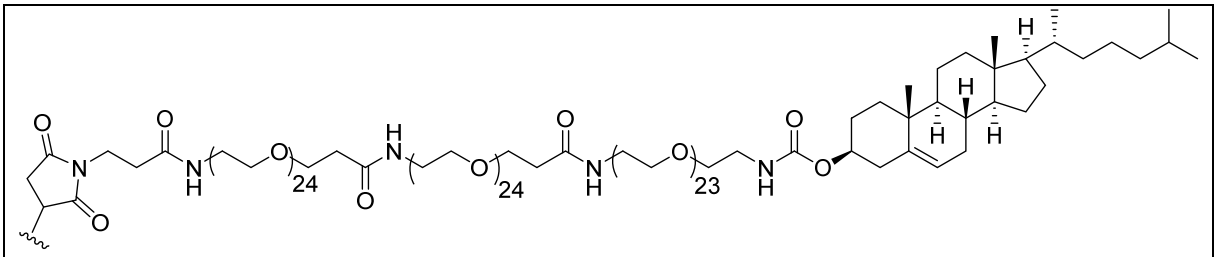
PEG48+C22



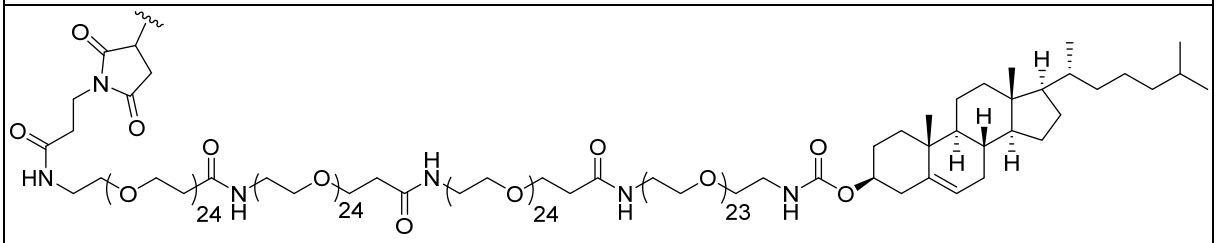
PEG71+C22



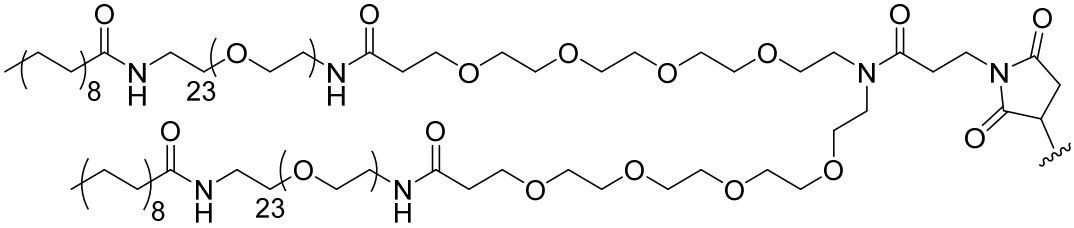
PEG95+C22



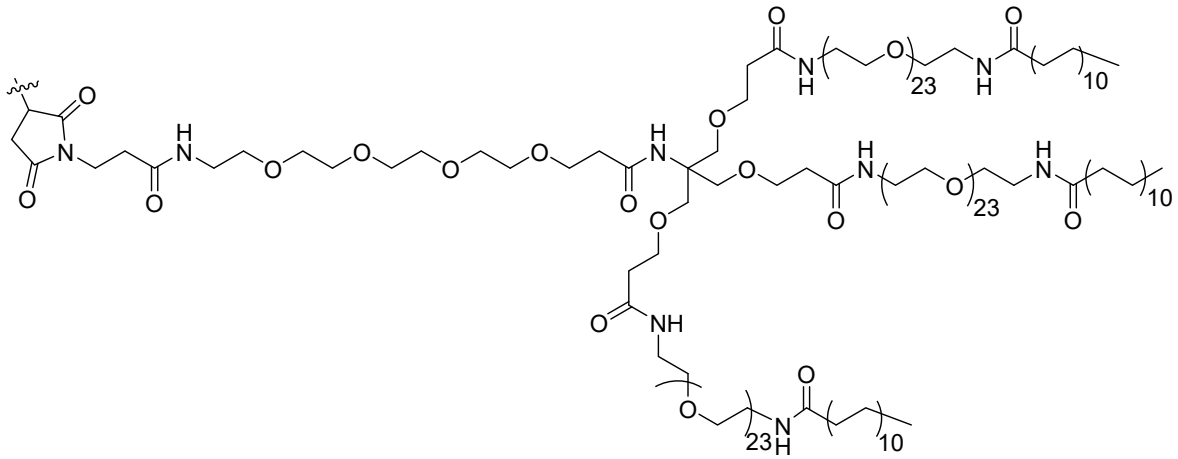
PEG71+CLS



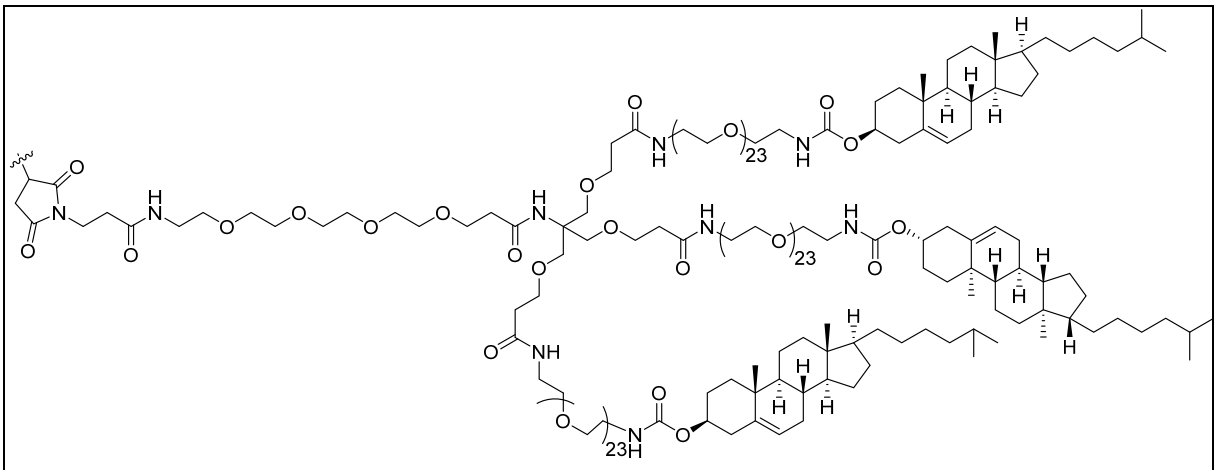
PEG95+CLS



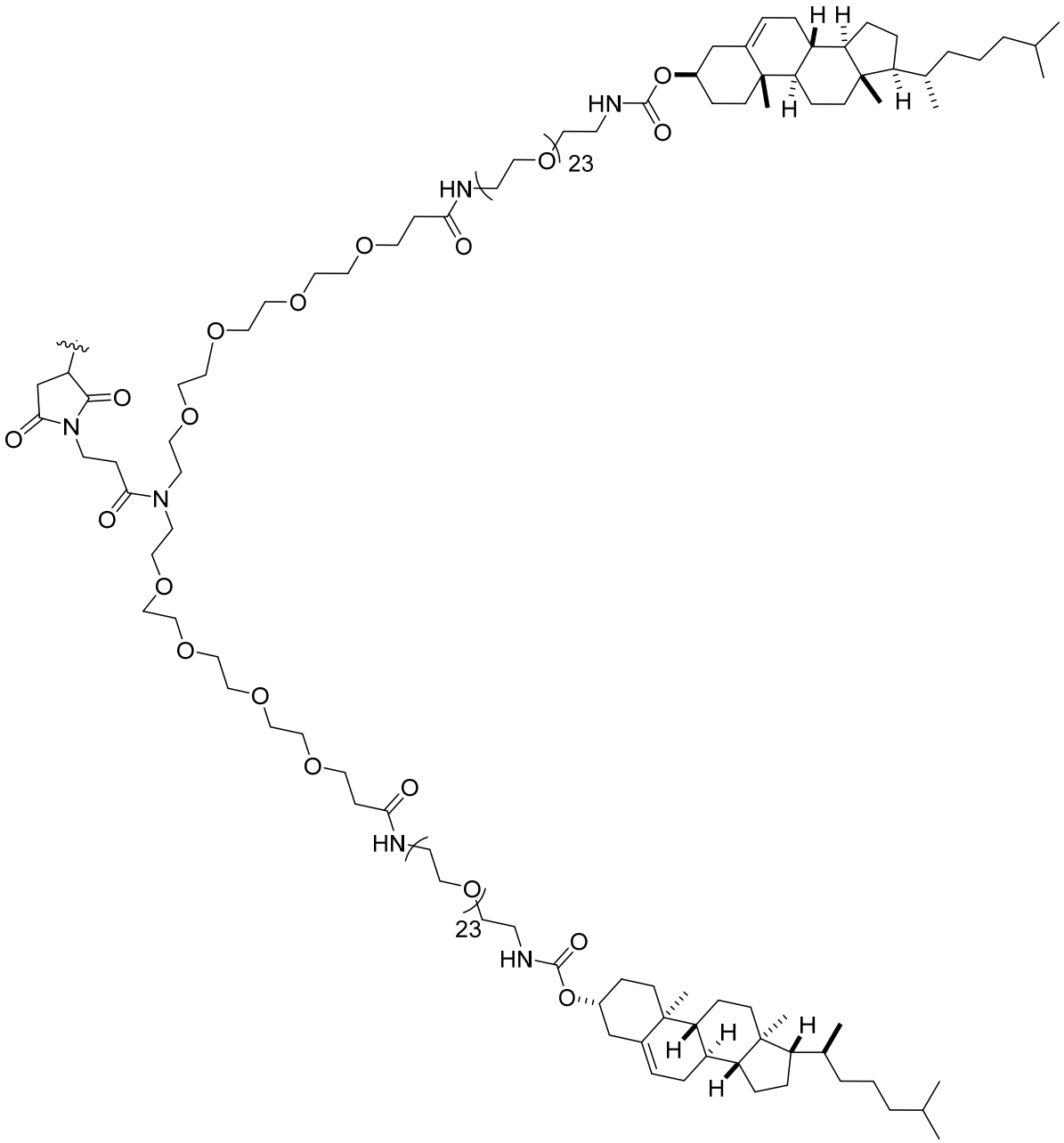
Bis(PEG23+C18)



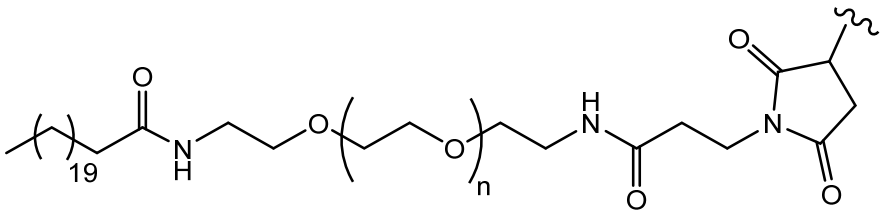
Tris(PEG23+C22)



Tris(PEG23+CLS)

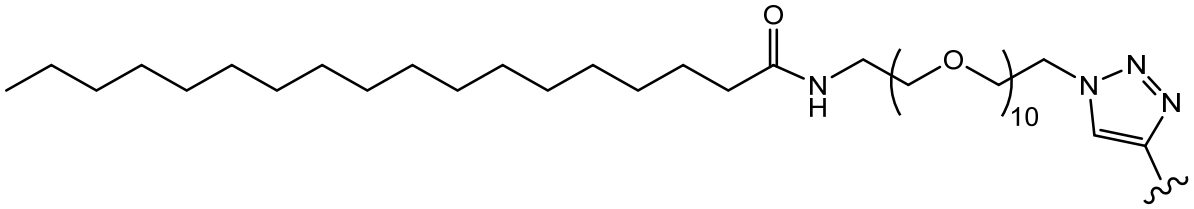


Bis(PEG23+CLS)

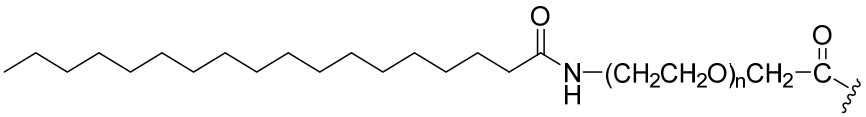


PEG5K+C22

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons

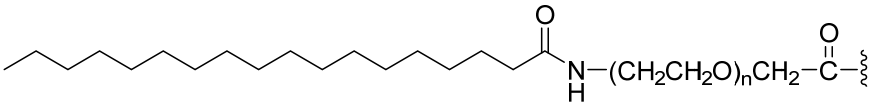


C18



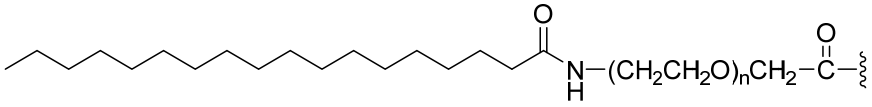
(NHS)-PEG1K+C18

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 1 kilodalton



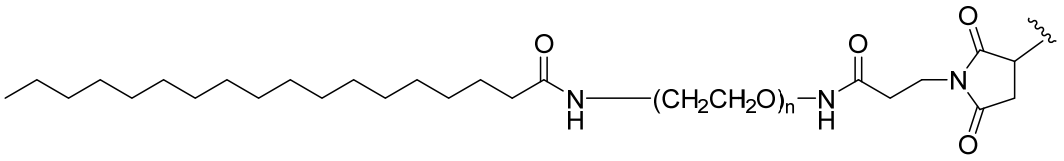
(NHS)-PEG2K+C18

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 2 kilodaltons



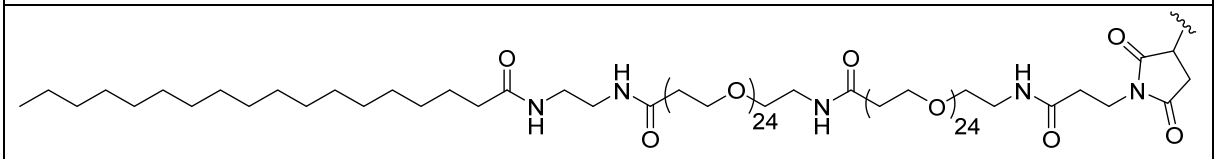
(NHS)-PEG5K+C18

wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons



(MAL)-PEG5K+C18

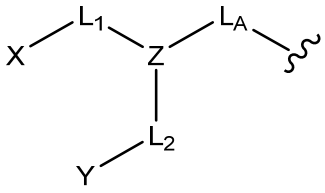
wherein n is an integer, and the molecular weight of the sum of all PEG units is about 5 kilodaltons



PEG48+C18

or a pharmaceutically acceptable salt of any of these PK/PD modulators, wherein ≀ indicates a point of connection to the RNAi agent.

10. The delivery vehicle of any one of claims 1-9, wherein the PK/PD modulator is a PK/PD modulator of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof, wherein

L_A is a bond or a bivalent moiety connecting Z to the RNAi agent;

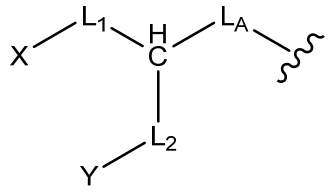
Z is CH, phenyl, or N;

L_1 and L_2 are each independently linkers comprising at least about 5 PEG units;

X and Y are each independently lipids comprising from about 10 to about 50 carbon atoms; and

≀ indicates a point of connection to the RNAi agent.

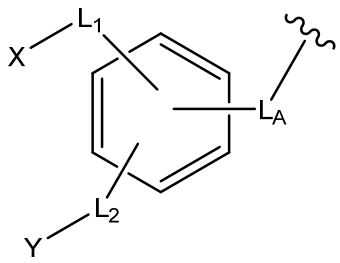
11. The delivery vehicle of claim 10, wherein the PK/PD modulator of Formula (**I**) is a PK/PD modulator of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt thereof.

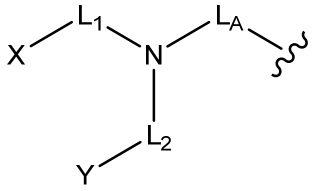
12. The delivery vehicle of claim 10, wherein the PK/PD modulator of Formula (**I**) is a PK/PD modulator of Formula (**Ib**):



(**Ib**)

or a pharmaceutically acceptable salt thereof.

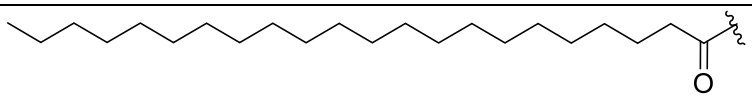
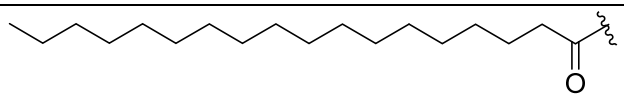
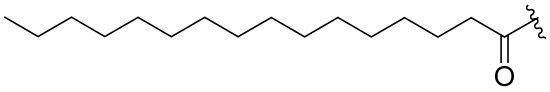
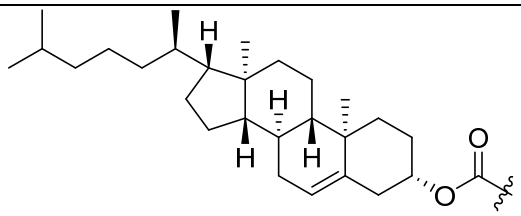
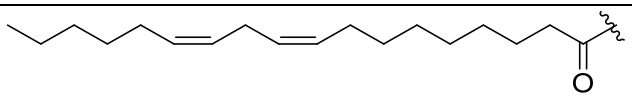
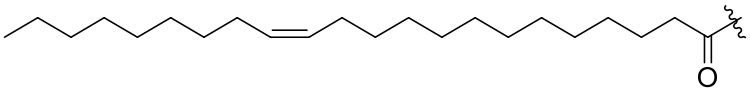
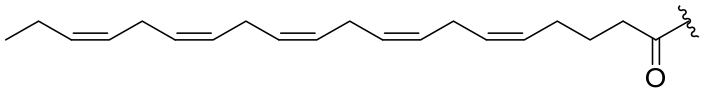
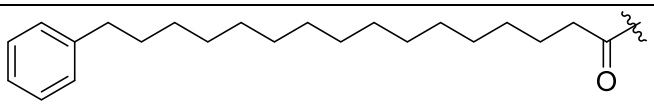
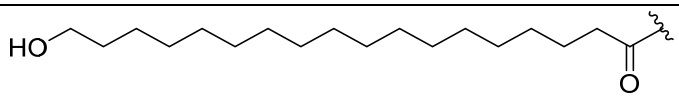
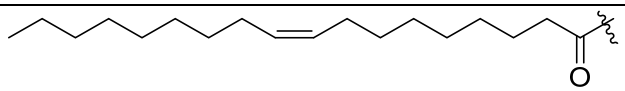
13. The delivery vehicle of claim 10, wherein the PK/PD modulator of Formula (**I**) is a PK/PD modulator of Formula (**Ic**):

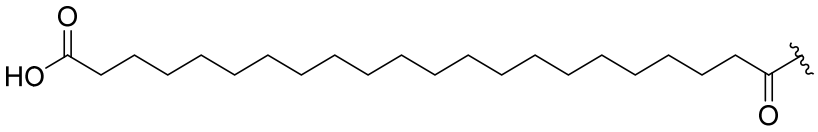
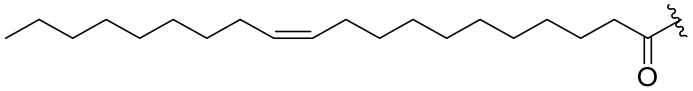
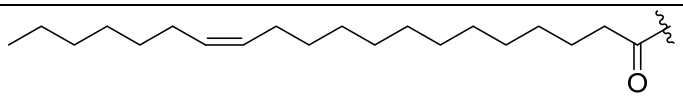
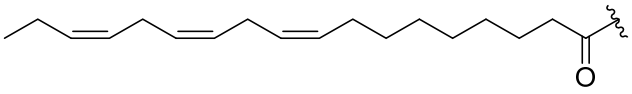
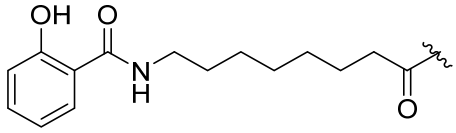
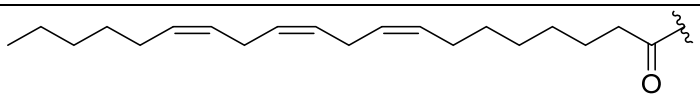
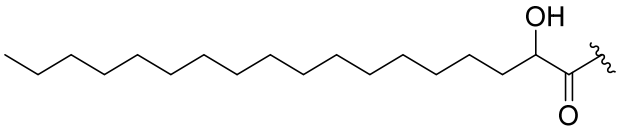
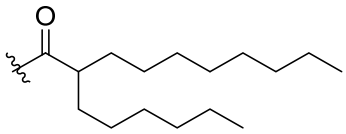
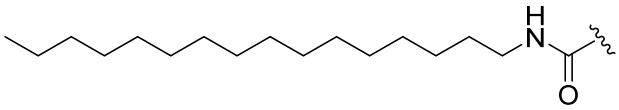
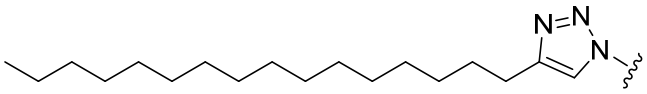


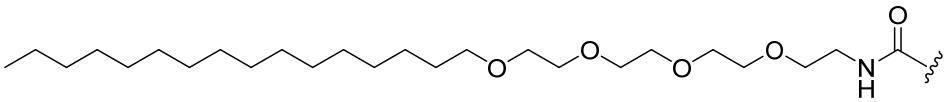
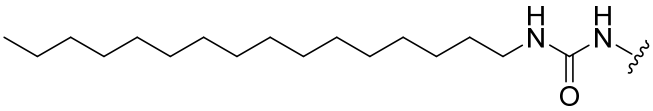
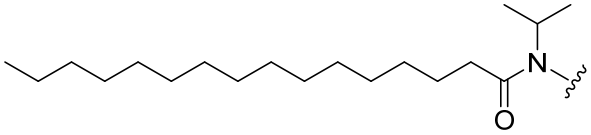
(**Ic**)

or a pharmaceutically acceptable salt thereof.

14. The delivery vehicle of any one of claims 10-13, wherein at least one of X and Y is selected from the group consisting of:

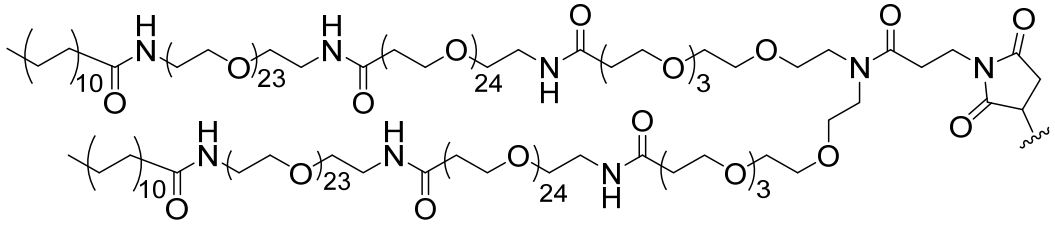
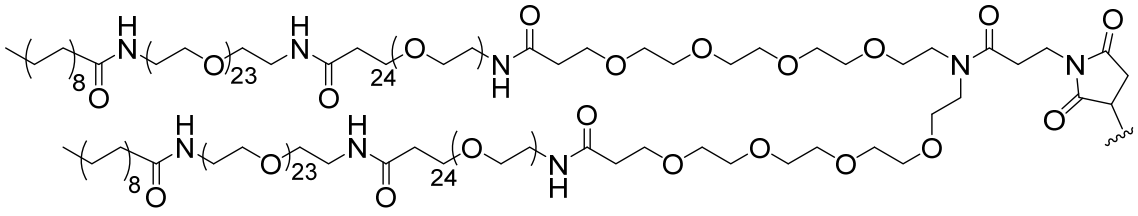
Name	Structure
Lipid 1	
Lipid 2	
Lipid 3	
Lipid 4	
Lipid 5	
Lipid 6	
Lipid 7	
Lipid 8	
Lipid 9	
Lipid 10	

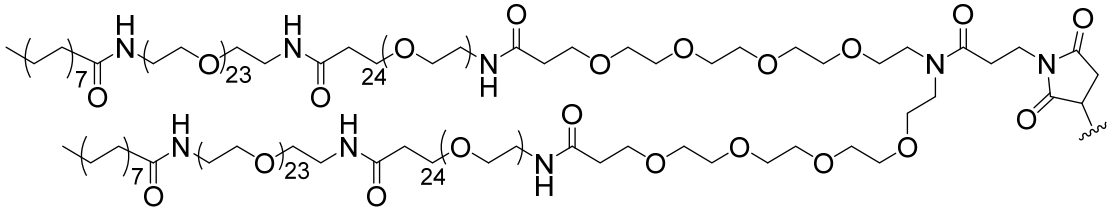
Name	Structure
Lipid 11	
Lipid 12	
Lipid 14	
Lipid 15	
Lipid 16	
Lipid 17	
Lipid 18	
Lipid 19	
Lipid 20	
Lipid 21	

Name	Structure
Lipid 22	
Lipid 23	
Lipid 24	

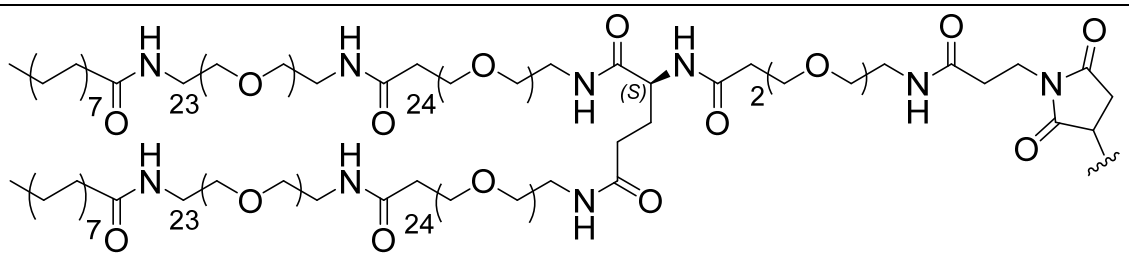
wherein  indicates a point of connection to L_1 or L_2.

15. The delivery vehicle of claims 1-8, wherein the PK/PD modulator is selected from the group consisting of:

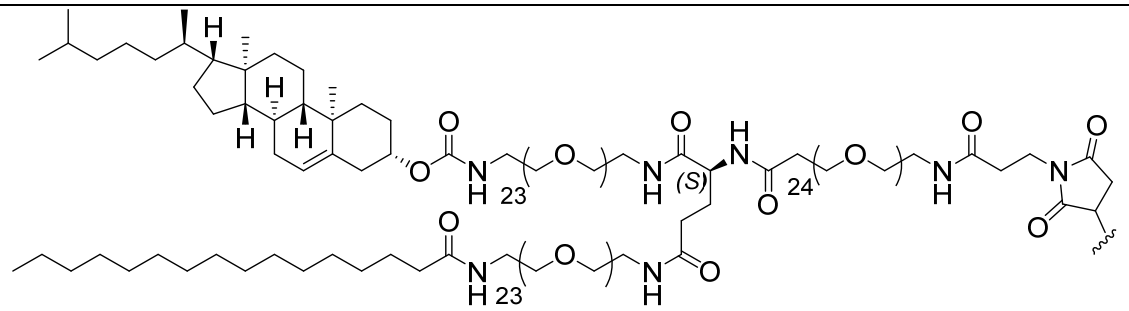
LP 1b

LP 28b

LP 29b



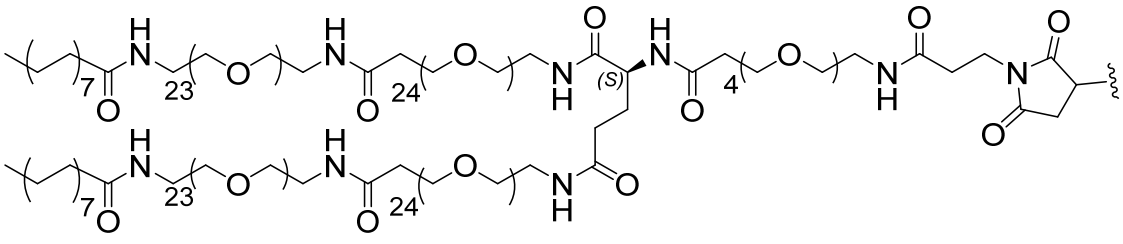
LP 38b



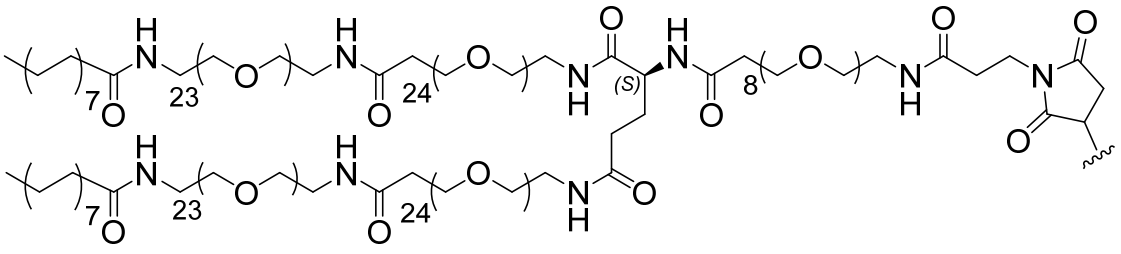
LP 39b



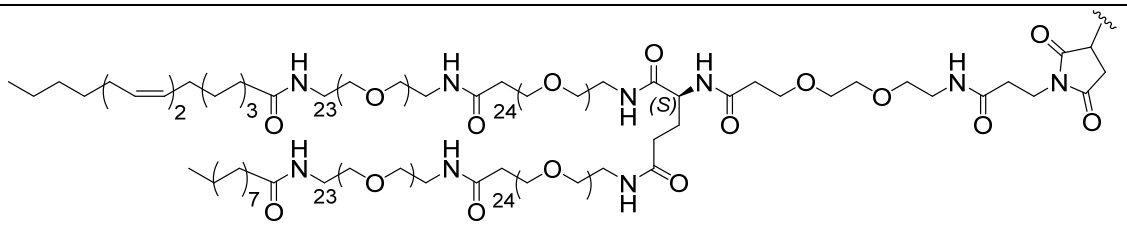
LP 41b



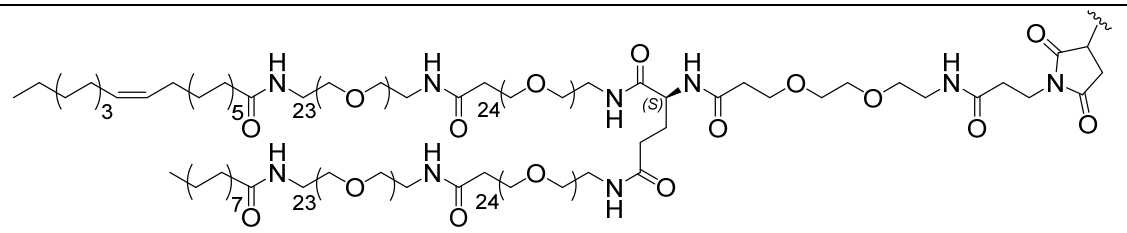
LP 42b



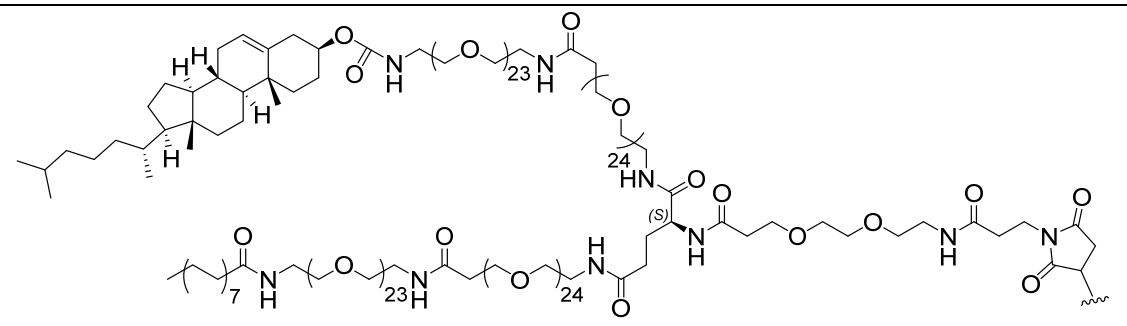
LP 43b



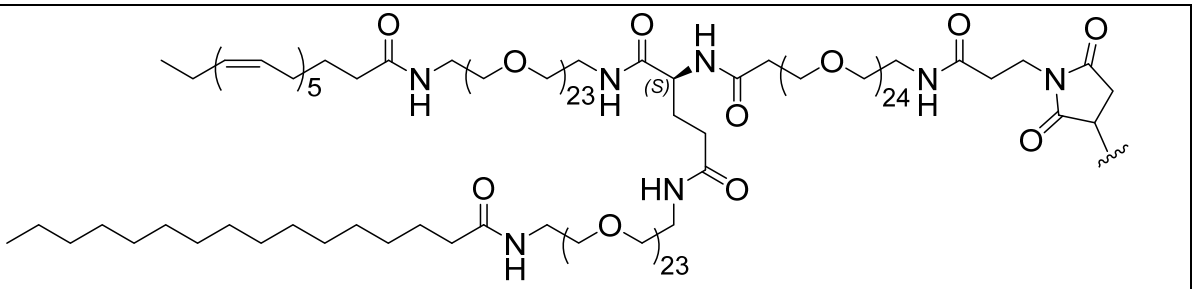
LP 44b



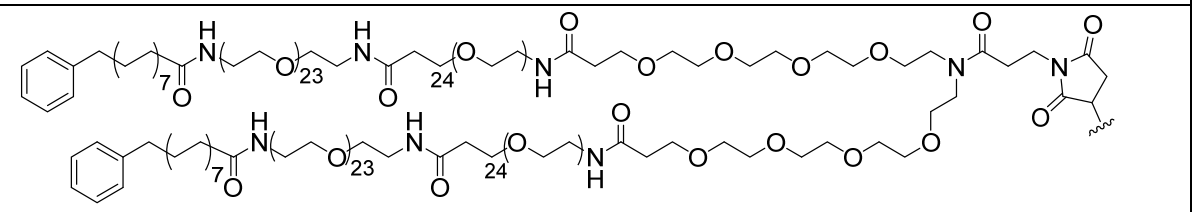
LP 45b



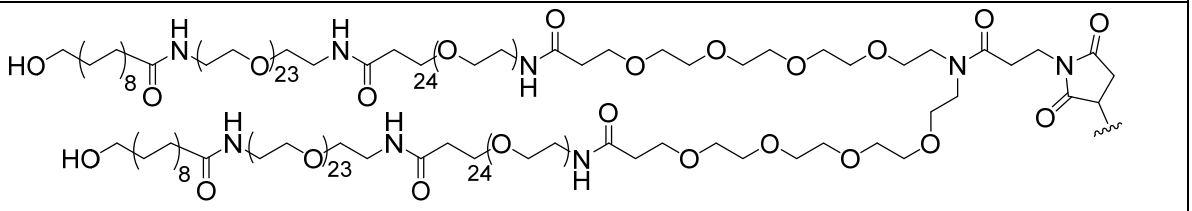
LP 47b



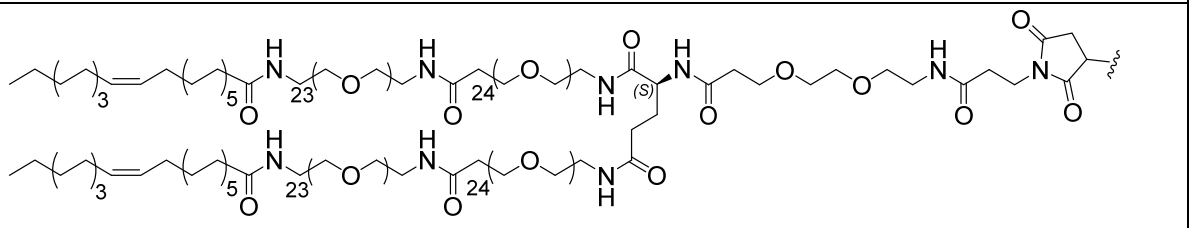
LP 48b



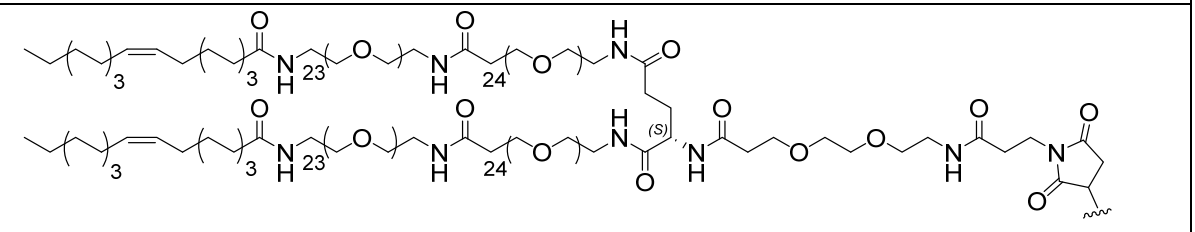
LP 49b



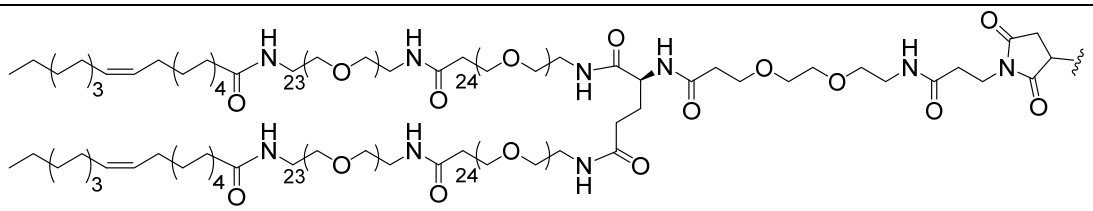
LP 53b



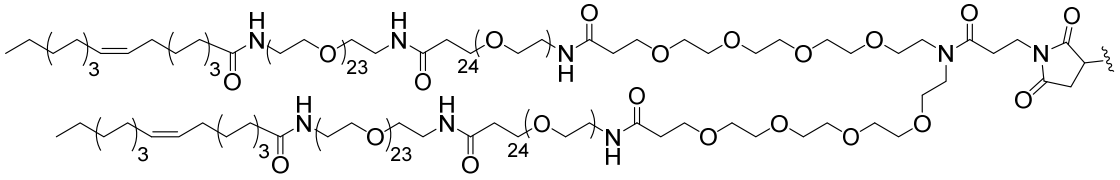
LP 54b



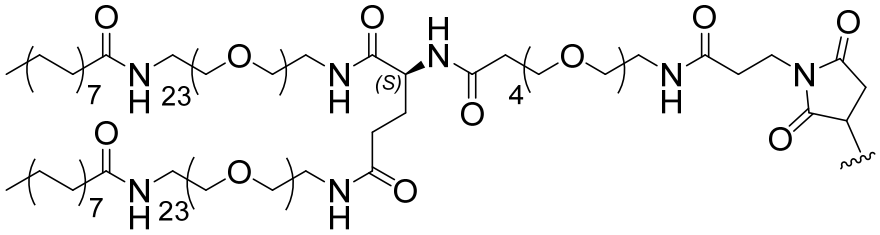
LP 55b



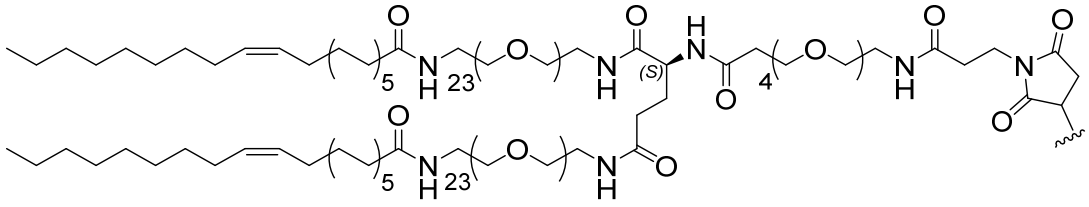
LP 56b



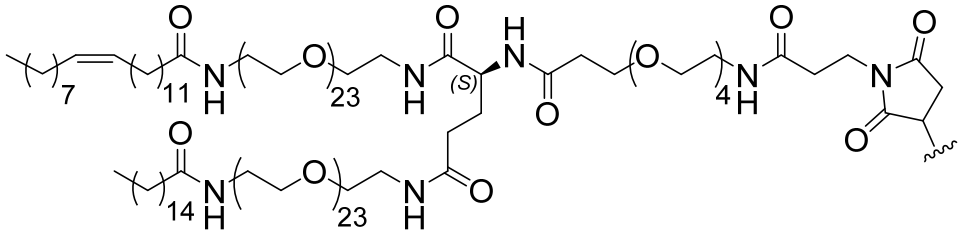
LP 57b

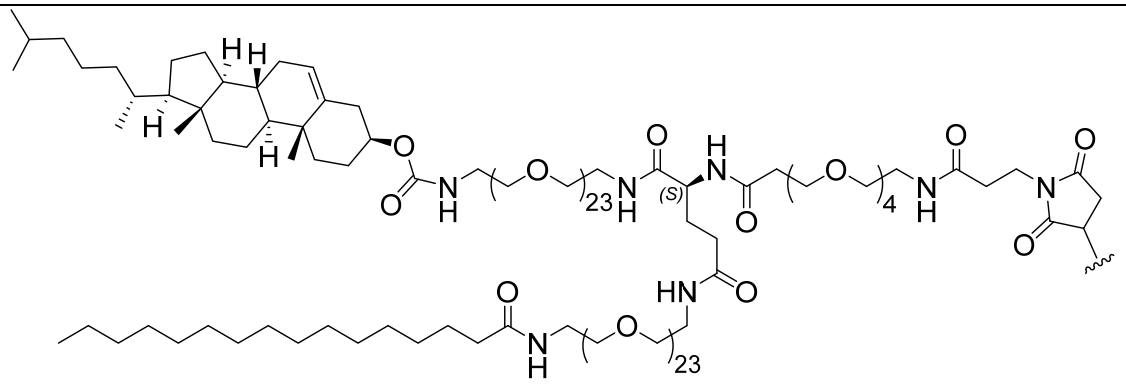
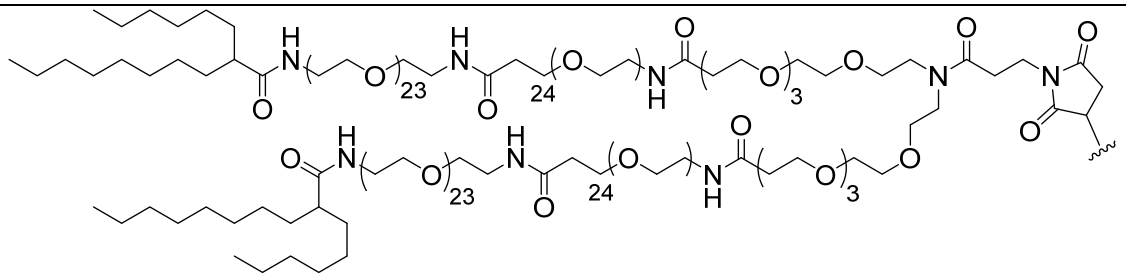
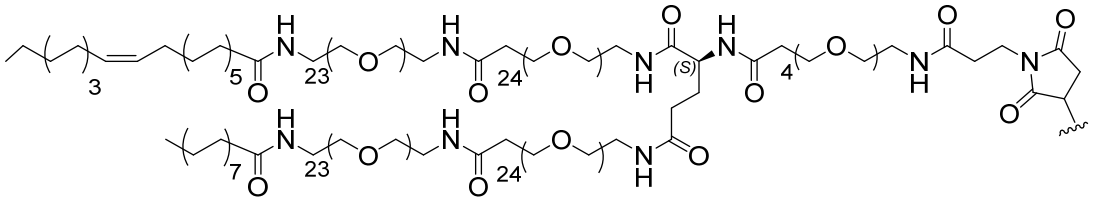
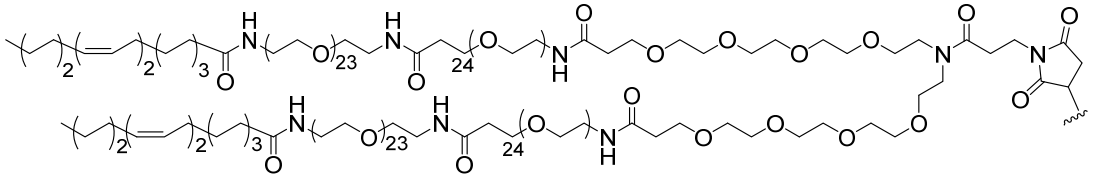


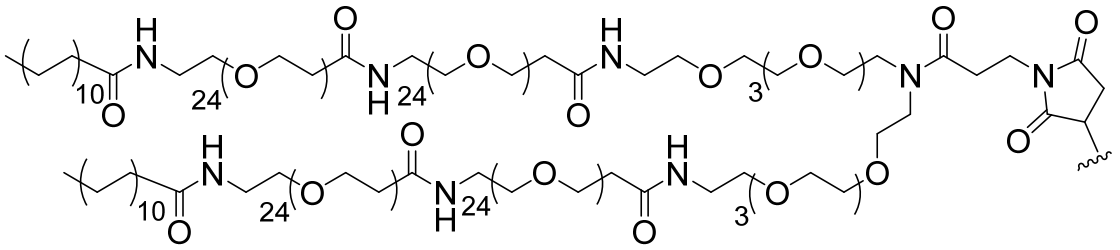
LP 58b



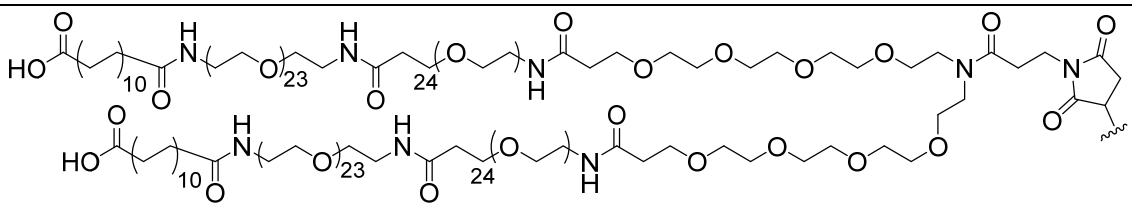
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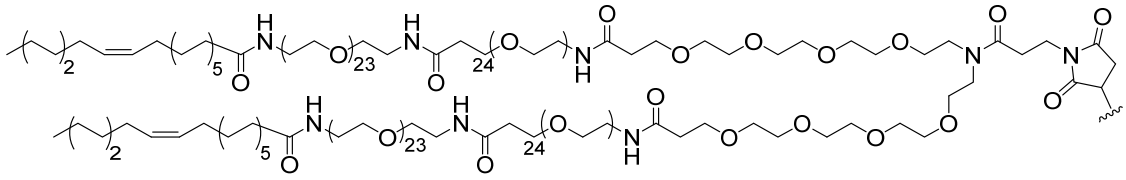
LP 60b

LP 61b

LP 62b

LP 87b

LP 89b



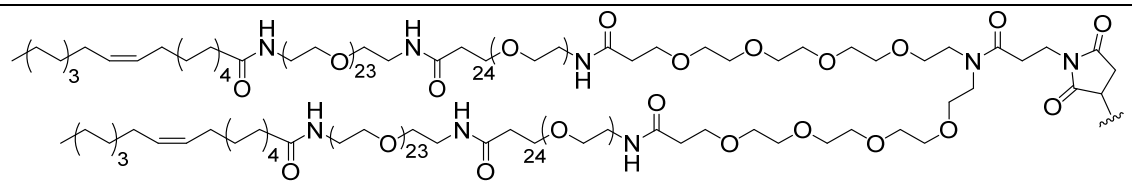
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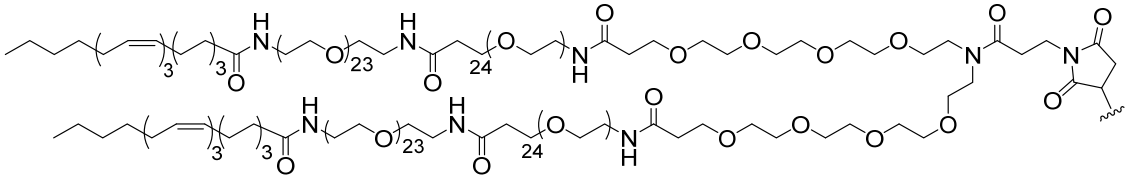
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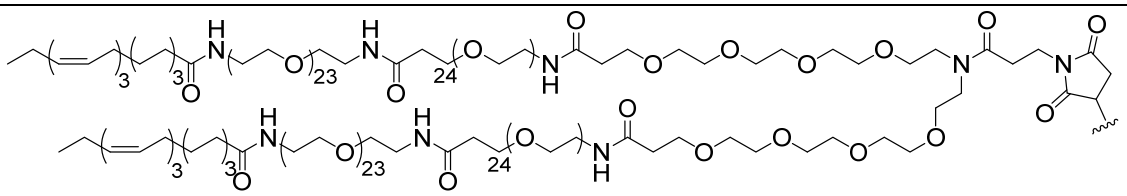
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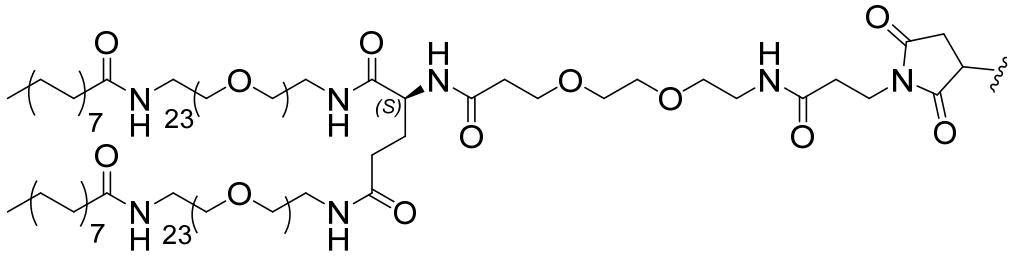
LP 94b



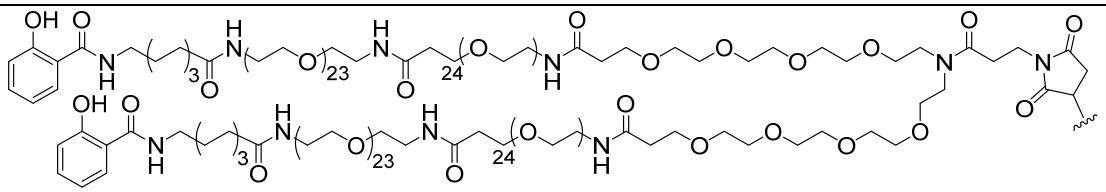
LP 95b



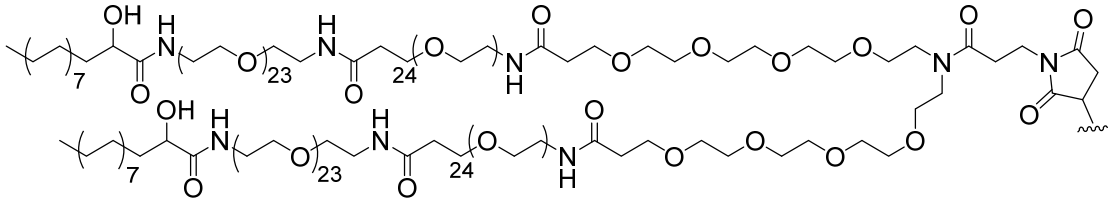
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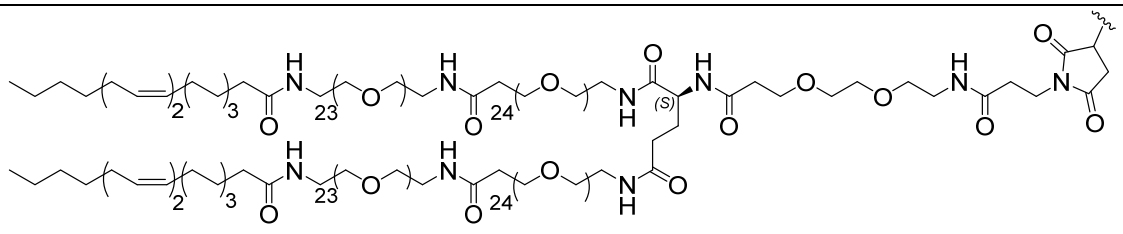
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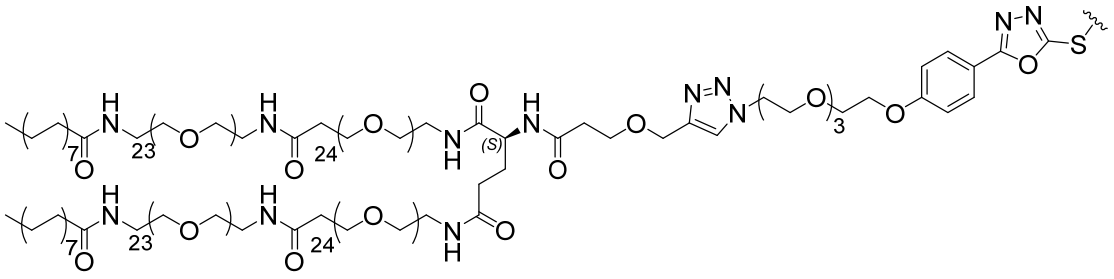
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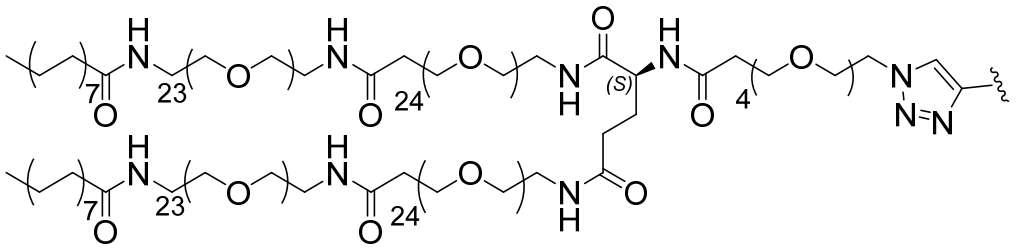
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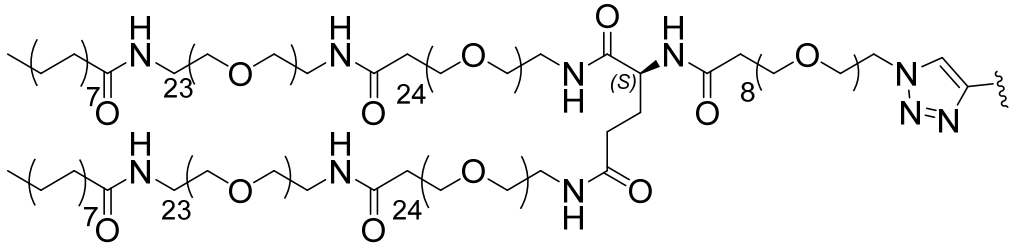
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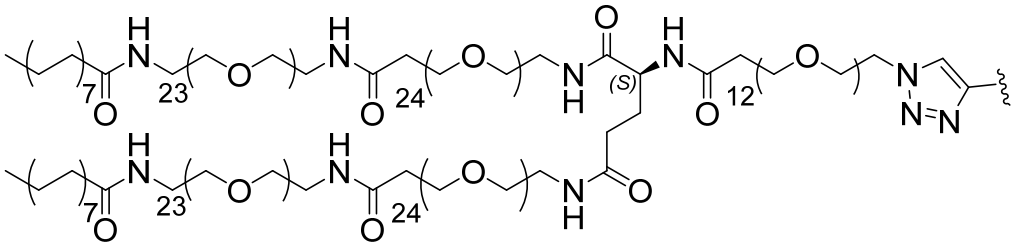
LP 107b



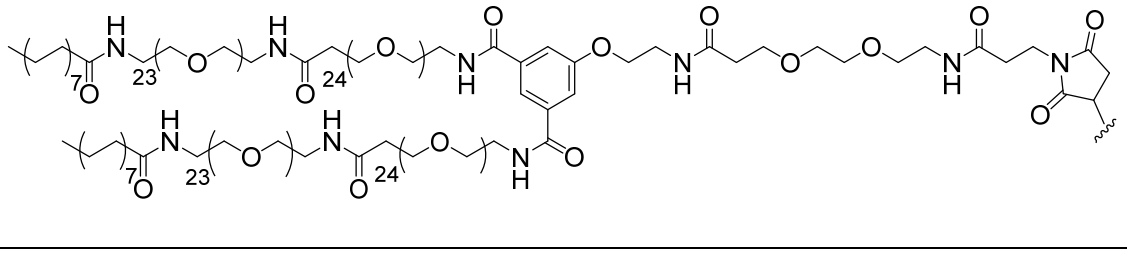
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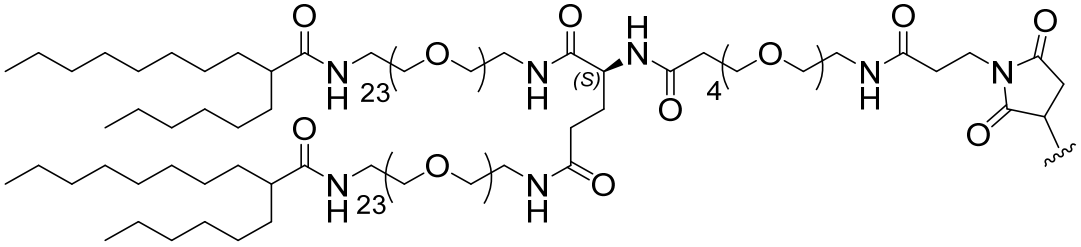
LP 109b



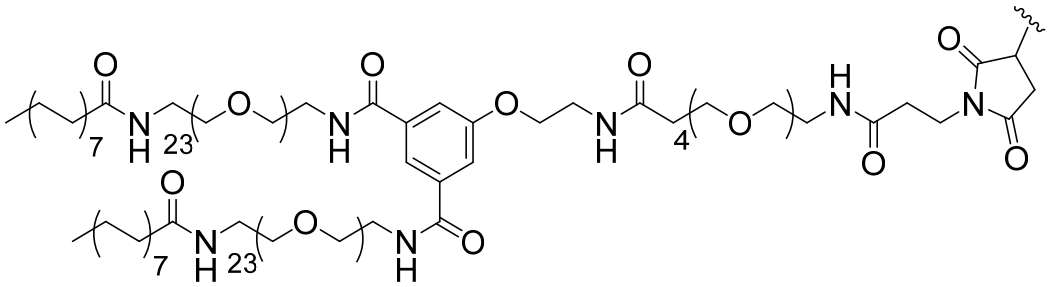
LP 110b



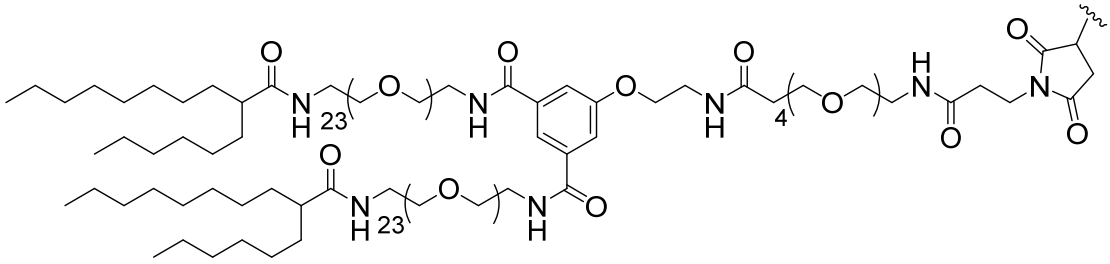
LP 111b



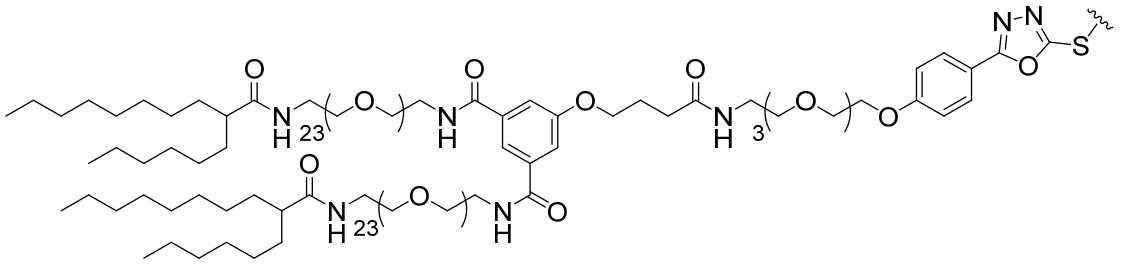
LP 124b



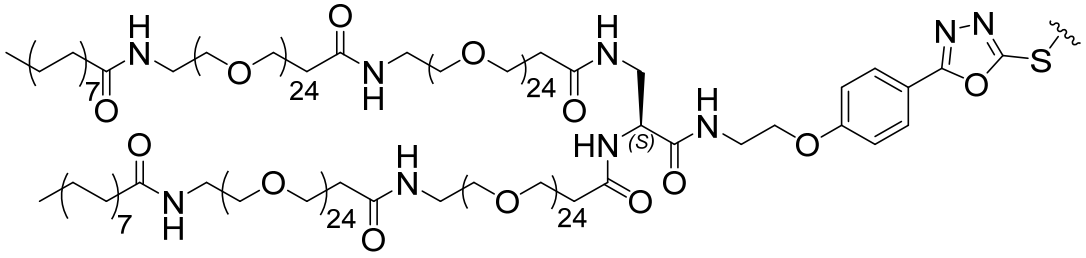
LP 130b



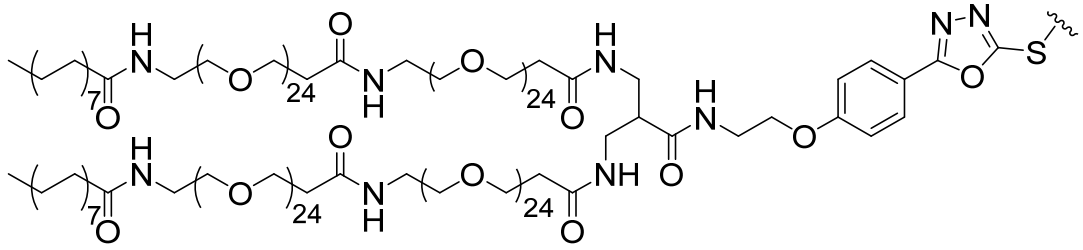
LP 143b



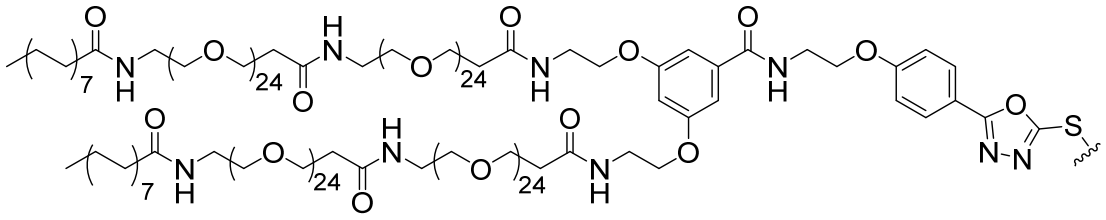
LP 210b



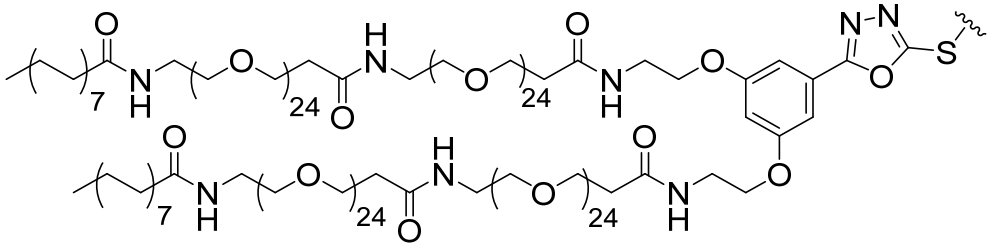
LP 217b



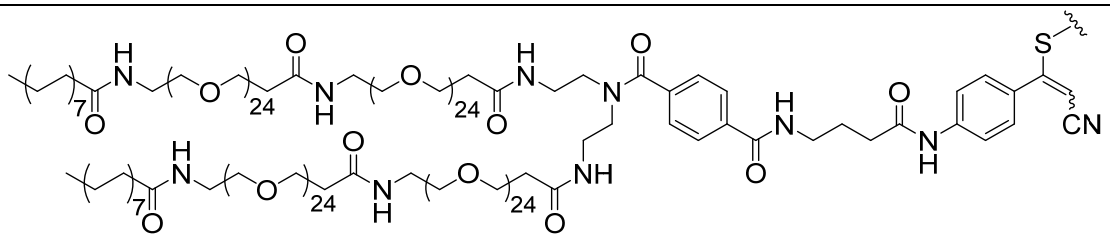
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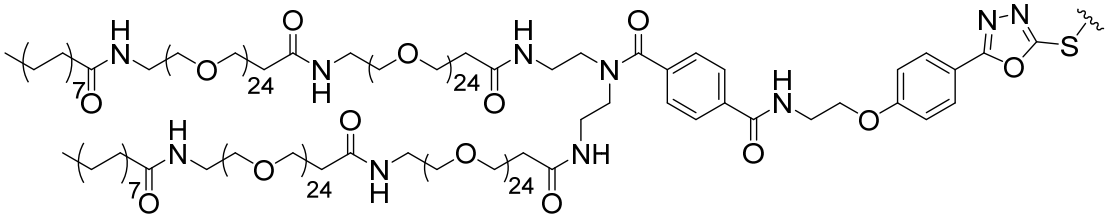
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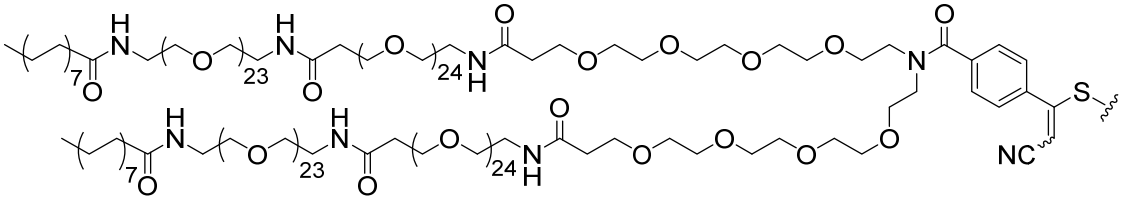
LP 223b



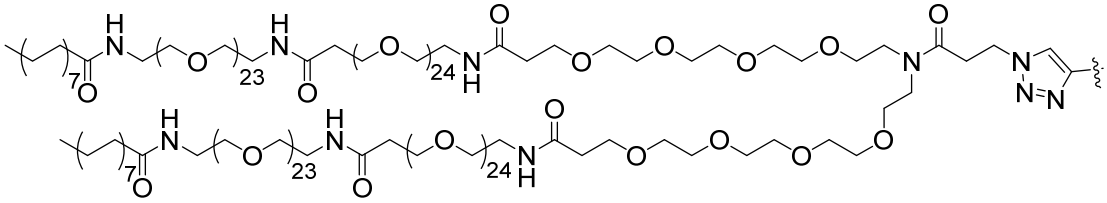
LP 224b



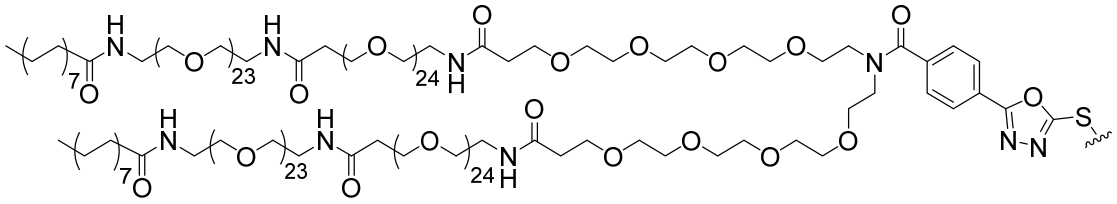
LP 225b



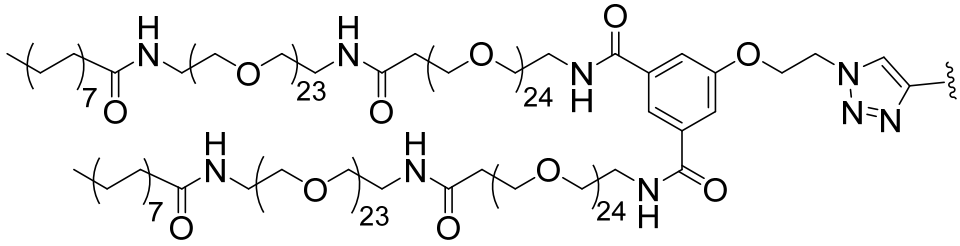
LP 226b



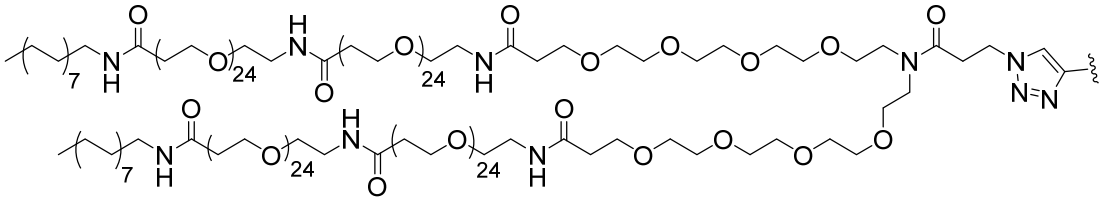
LP 238b



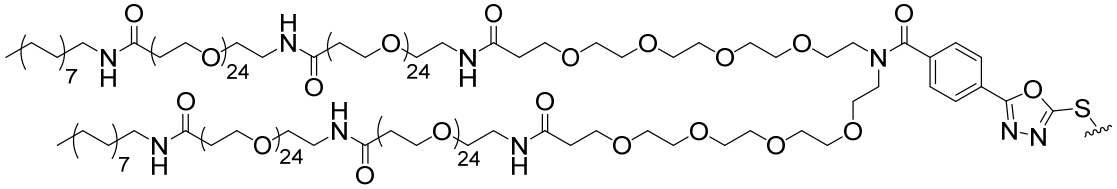
LP 240b



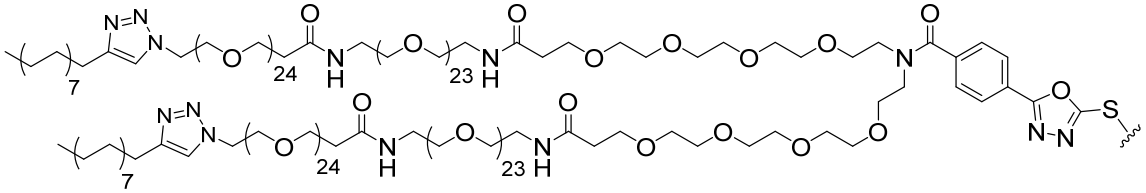
LP 246b

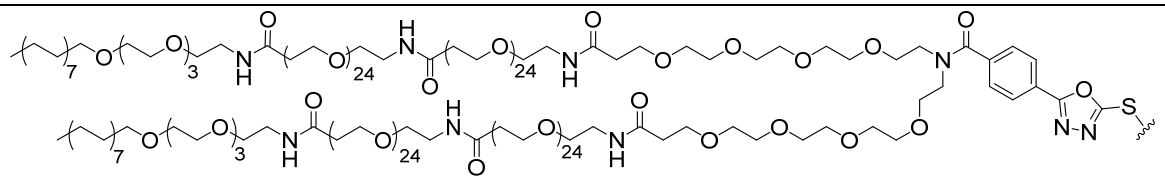
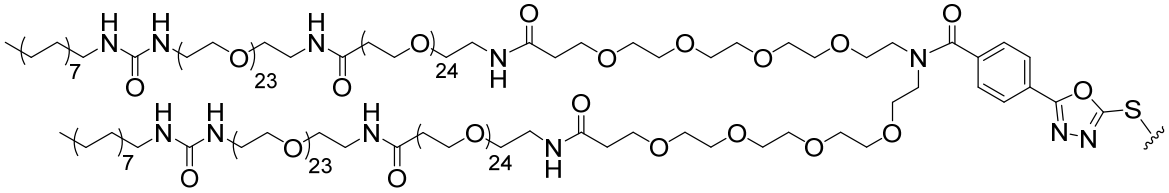
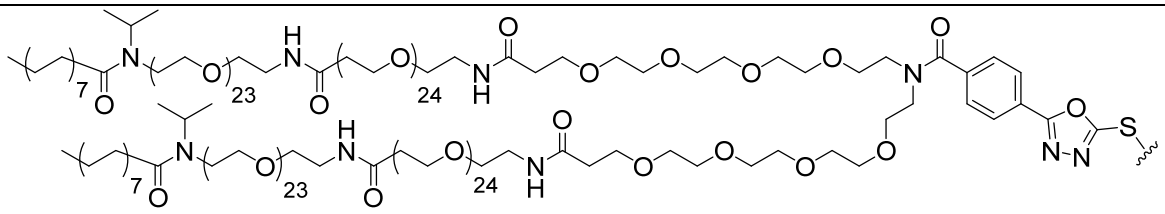


LP 247b



LP 339b



LP 340b

LP 357b

LP 358b


or a pharmaceutically acceptable salt of any of these PK/PD modulators, wherein each  indicates a point of connection to the RNAi agent.

16. The delivery vehicle of any one of claims 1-15, wherein the RNAi agent inhibits expression of the mRNA of a human gene in a skeletal muscle cell.

17. The delivery vehicle of any one of claims 2-16, wherein the pharmaceutically acceptable salt is a sodium salt.

18. A composition comprising the delivery vehicle of any one of claims 1-17.

19. A pharmaceutical composition comprising the composition of claim 18 and a pharmaceutical excipient.

20. The pharmaceutical composition of claim 19, wherein the pharmaceutical excipient is selected form water for injection and saline solution.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical excipient is saline solution.

22. A composition comprising the delivery vehicle of any one of claims 1-17 for use in treating a disease or disorder of a skeletal muscle cell.

23. The composition of claim 22, wherein the disease or disorder is muscular dystrophy.

24. The composition of claim 23, wherein the muscular dystrophy is selected from the group consisting of: Duchenne muscular dystrophy, myotonic muscular dystrophy, Becker muscular dystrophy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy, and Emery-Dreifuss muscular dystrophy.

25. Use of the delivery vehicle of any one of claims 1-17, the composition of claim 51, or the pharmaceutical composition of any one of claims 52-54, for the preparation of a medicament for the treatment of a disease or disorder.

26. The use of claim 25, wherein the disease or disorder is a muscular dystrophy.

27. The use of claim 26, wherein the muscular dystrophy is selected from the group consisting of: Duchenne muscular dystrophy, myotonic muscular dystrophy, Becker muscular dystrophy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy, and Emery-Dreifuss muscular dystrophy.

28. A method of making the delivery vehicle of any one of claims 1-17, the method comprising:

(i) synthesizing the sense strand;

(ii) synthesizing the antisense strand;

(iii) annealing the sense strand and the antisense strand;

(iv) before or after annealing the sense strand and the antisense strand, conjugating the targeting ligand to the sense strand or the antisense strand; and

(v) before or after annealing the sense strand and the antisense strand, and before or after conjugating the targeting ligand to the sense strand or the antisense strand, conjugating the PK/PD modulator to the sense strand or the antisense strand.