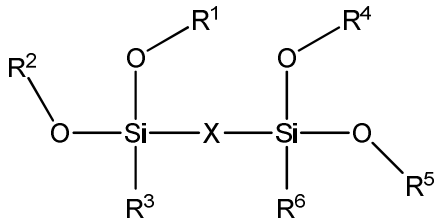
R^5 is a C_2-C_{30} hydrocarbyl;

R^6 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl; and

X is a divalent linking group.

In one aspect, the present disclosure refers to a compound of formula (I):



(I)

wherein:

R^1 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

R^2 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

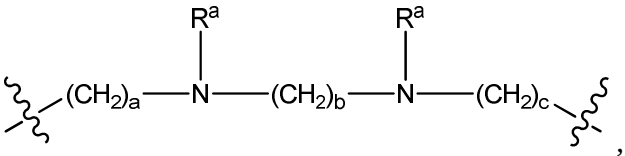
R^3 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl;

R^4 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

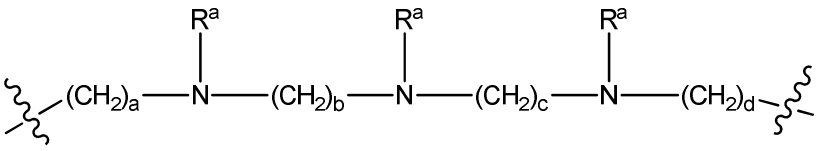
R^5 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

R^6 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl; and

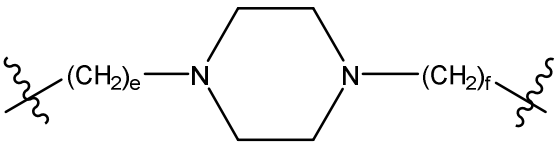
X is selected from the group consisting of:



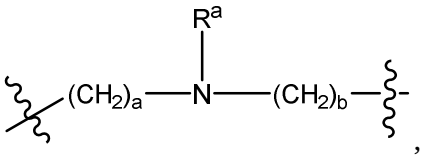
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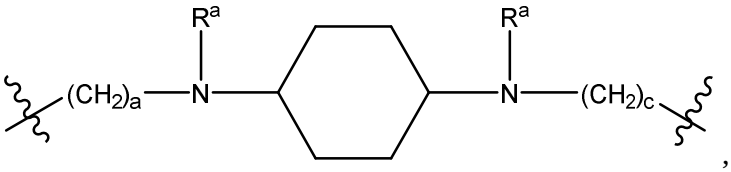
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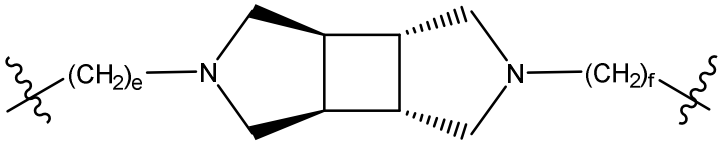
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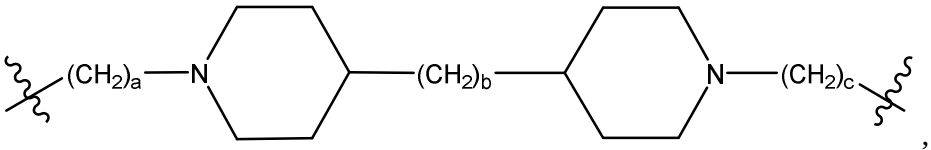


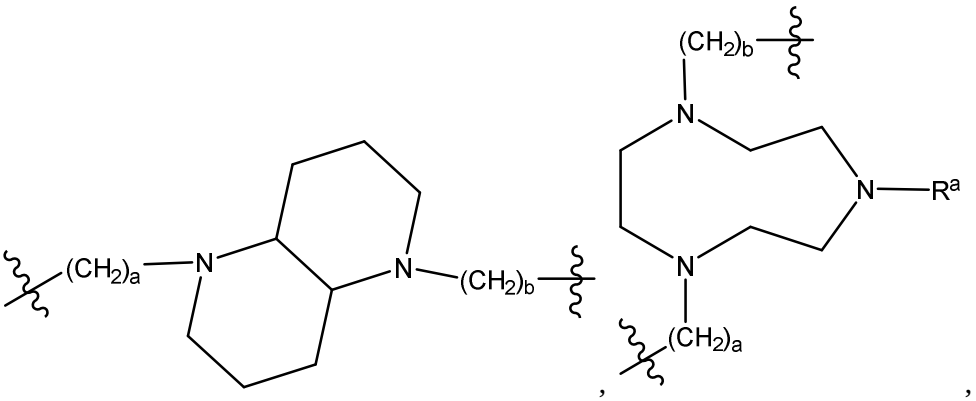
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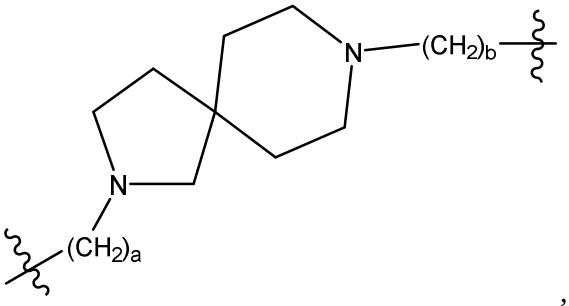


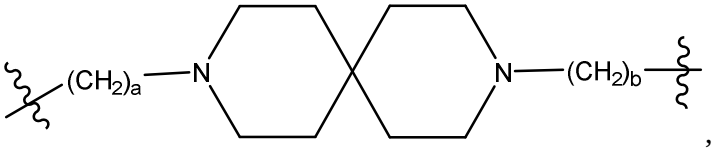
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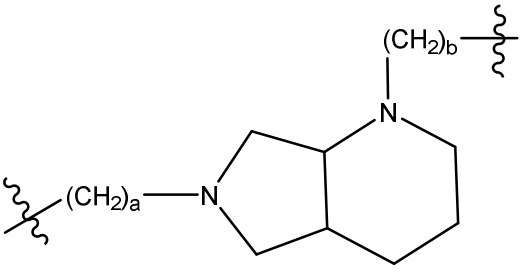

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wherein:

a is 2, 3, 4, or 5;

b is 2, 3, 4, or 5;

c is 2, 3, 4, or 5;

d is 2, 3, 4, or 5;

e is 2, 3, 4, 5, 6, 7, or 8;

f is 2, 3, 4, 5, 6, 7, or 8; and

each R^a is independently selected from H and (C_1-C_6)alkyl that is optionally substituted with one of more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

In one aspect, the present disclosure refers to a composition comprising any one of the compounds disclosed herein.

Also provided are lipid particled comprising such compounds, and for methods of using the lipid particles, *e.g.*, to deliver therapeutics specifically to hepatic stellate cells to treat diseases.

In one aspect, the present disclosure refers to a lipid particle comprising any one of the compounds disclosed herein.

In one aspect, the present disclosure refers to a lipid particle disclosed herein for use in the *in vivo* delivery of a therapeutic agent to a mammalian subject.

In one aspect, the present disclosure refers to use of the lipid particle disclosed herein in the manufacture of a medicament for the *in vivo* delivery of a therapeutic agent to a mammalian subject.

In one aspect, the present disclosure refers to the lipid particle disclosed herein for use in treating a disease or disorder in a mammalian subject in need thereof.

In one aspect, the present disclosure refers to use of the lipid particle disclosed herein in the manufacture of a medicament for treating a disease or disorder in a mammalian subject in need thereof, wherein the disease or disorder is liver fibrosis or liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

In one aspect, the present disclosure refers to a method of delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vitro*, comprising contacting the HSC with the lipid particle disclosed herein.

In one aspect, the present disclosure refers to a lipid particle disclosed herein for use in delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle disclosed herein.

In one aspect, the present disclosure refers to use of the lipid particle disclosed herein in the manufacture of a medicament for delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle disclosed herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Figure 1 depicts reelin mRNA knock-down 48 hours following IV administration of the LNP formulations in Balb/C Mice (n=4). LNP with a representative compound of the invention (presented in columns 3 and 4) has equivalent potency to a benchmark compound (**100**; presented in column 2), but at 4-times lower dose (0.025 mg/kg instead of 0.1 mg/kg).

Figure 2. Figure 2 depicts reelin mRNA knock-down 48 hours following IV administration of the LNP formulations in Balb/C Mice (n=4). An LNP with a representative compound of the invention (presented in column 3) has high specificity for HSCs, whereas an LNP with a benchmark compound (**101**; presented in column 2) designed for delivery to hepatocytes demonstrates no knock-down in HSCs. This comparative data demonstrates that lipids of the invention possess the desired quality of enabling LNP-delivery of therapeutic agents to HSCs.

Figure 3. Figure 3 depicts reelin mRNA knock-down 24 hours following IV administration of the LNP formulations in Balb/C Mice (n=4). LNP with a representative compound of the invention demonstrate that at about 0.03 mg/kg, maximum knock-down in HSCs is achieved.

Figure 4. Figure 4 depicts reelin mRNA knock-down 24 hours following IV administration of the LNP formulations in Balb/C Mice (n=4). A benchmark LNP (with compound **100**; presented in columns 2-4) requires higher doses (~1 mg/kg) to achieve equivalent knock-down to a representative lipid of the invention (presented in columns 5-7) (0.03 mg/kg).

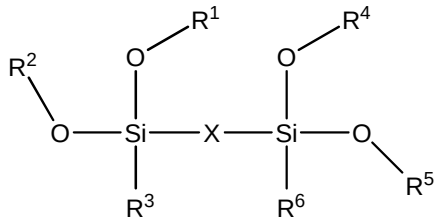
Figure 5A-5B. Figures 5A-5B demonstrate that LNP formulated with a representative lipid of the invention (presented in columns 5-7) demonstrate tolerability as no significant increases in liver enzyme levels over a dose range, up to 3 mg/kg in this study, were evident. LNP with compound **100** are also included as the first set of data in Figure 5A (presented in columns 2-4).

Figure 6. Figure 6 demonstrates that LNP formulated with a representative lipid of the invention and with minimally modified siRNA show good duration of action (presented in the

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R^1 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

R^2 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

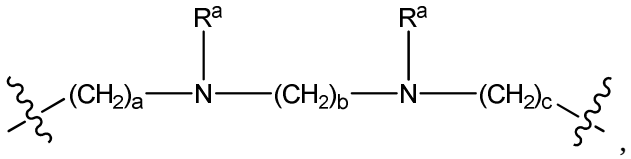
R^3 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl;

R^4 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

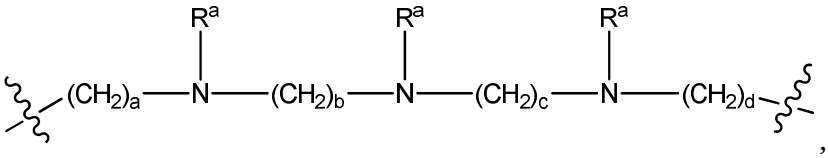
R^5 is (C_7-C_{20})alkyl or (C_7-C_{20})alkenyl;

R^6 is C_1-C_4 alkyl or –O-C_2-C_{30} hydrocarbyl; and

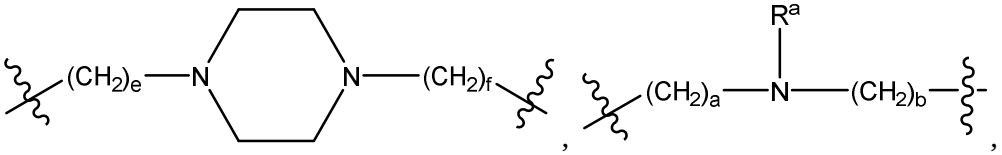
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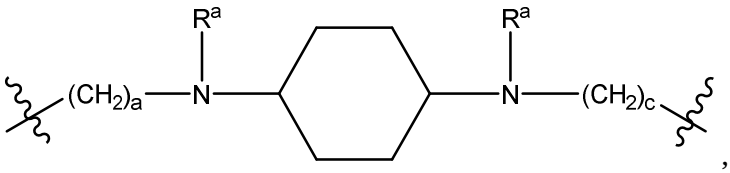
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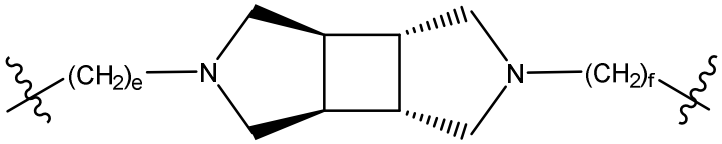
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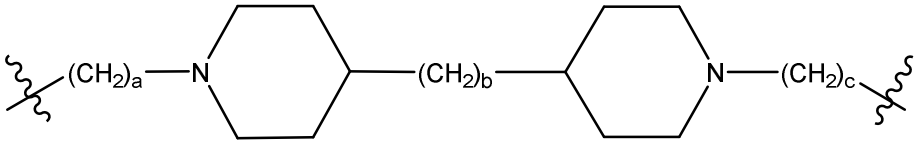
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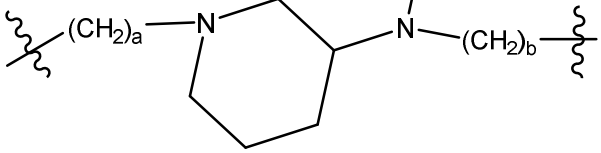
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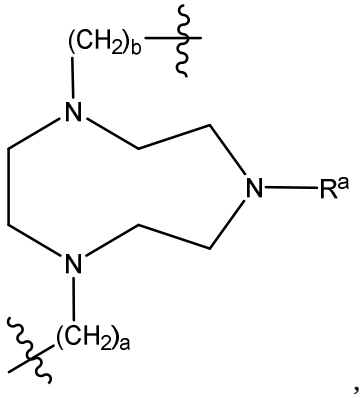
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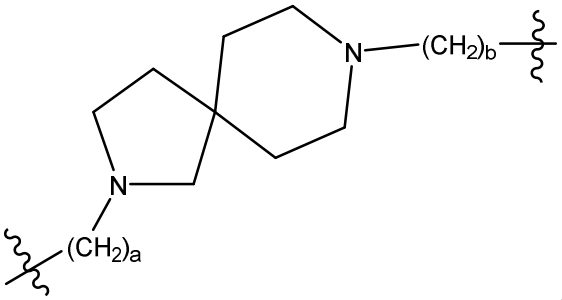
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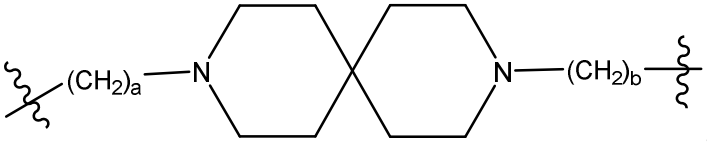
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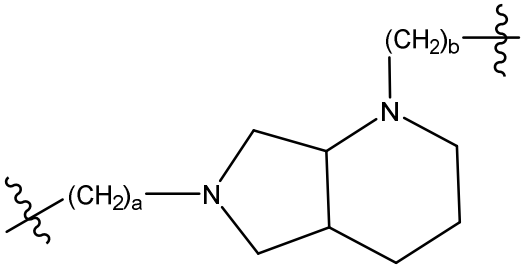
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, and



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wherein:

a is 2, 3, 4, or 5;

b is 2, 3, 4, or 5;

c is 2, 3, 4, or 5;

d is 2, 3, 4, or 5;

e is 2, 3, 4, 5, 6, 7, or 8;

f is 2, 3, 4, 5, 6, 7, or 8; and

each R^a is independently selected from H and (C_1-C_6)alkyl that is optionally substituted with one of more groups independently selected from halo, hydroxy, and (C_1-C_6)alkoxy.

2. The compound of claim 1, wherein R^1 is (C_7-C_{15})alkenyl, having only one double bond, and/or

wherein R^2 is (C_7-C_{15})alkenyl, having only one double bond, and/or

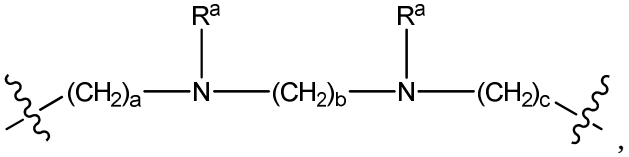
wherein R^3 is methyl, and/or

wherein R^4 is (C_7-C_{15})alkenyl, having only one double bond, and/or

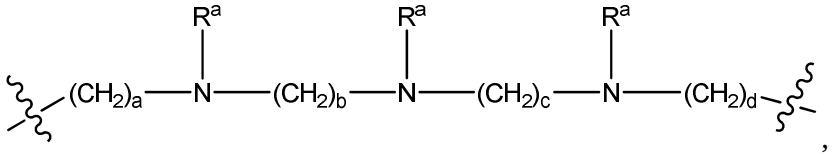
wherein R^5 is (C_7-C_{15})alkenyl, having only one double bond, and/or

wherein R^6 is methyl.

3. The compound of claim 1 or 2, wherein X is selected from the group consisting of:

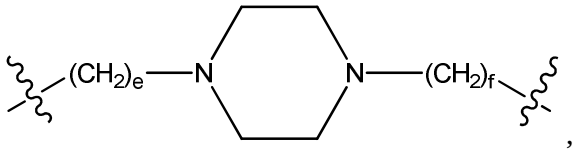


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wherein:

a is 2, 3, 4, or 5;

b is 2, 3, 4, or 5;

c is 2, 3, 4, or 5;

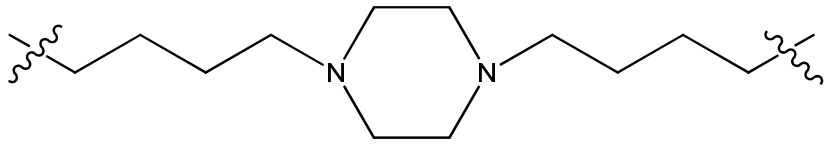
d is 2, 3, 4, or 5;

e is 2, 3, 4, 5, 6, 7, or 8;

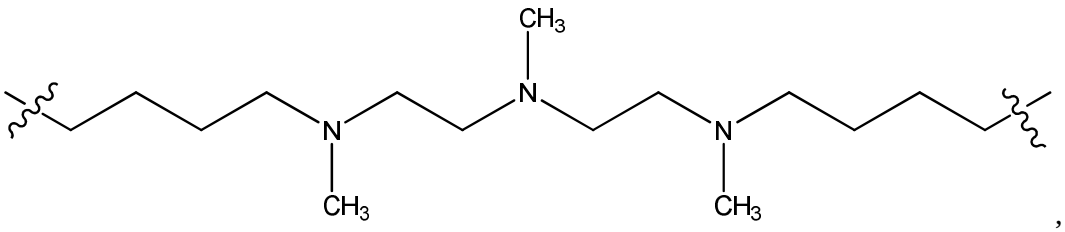
f is 2, 3, 4, 5, 6, 7, or 8; and

each R^a is independently selected from H and (C_1-C_6)alkyl, preferably,

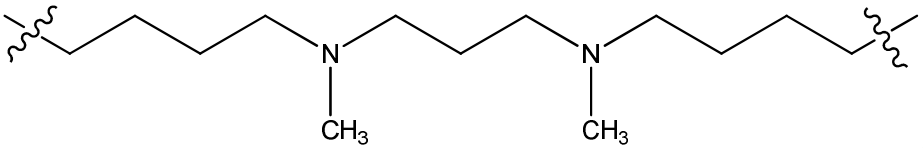
X is selected from the group consisting of:



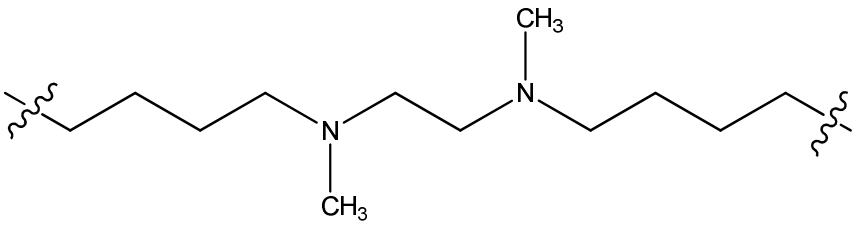
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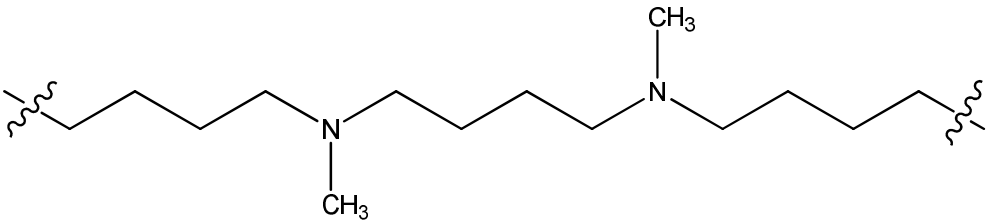
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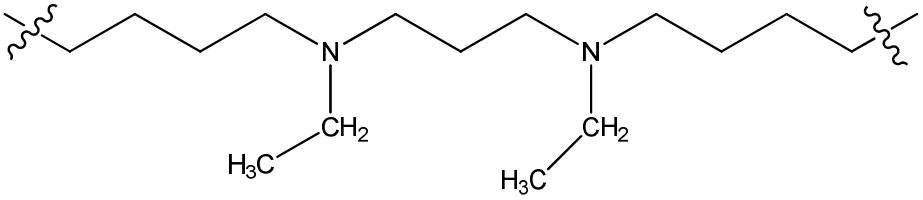
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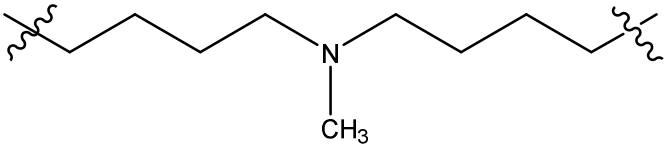
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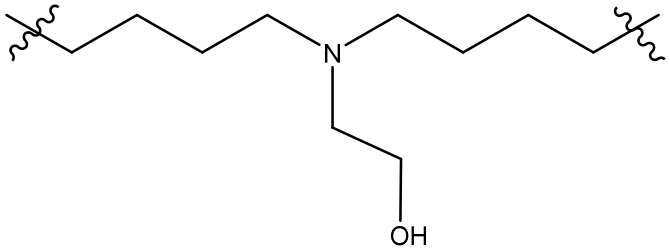
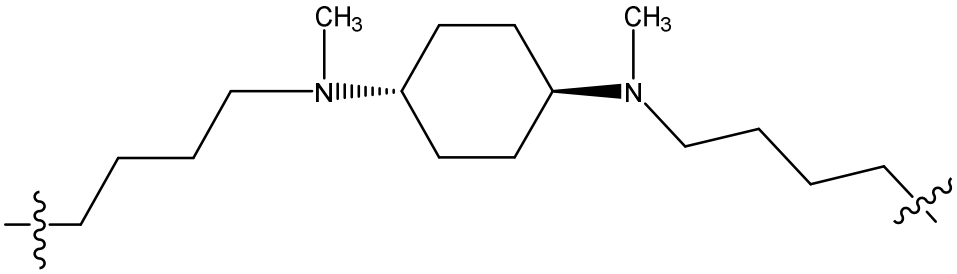
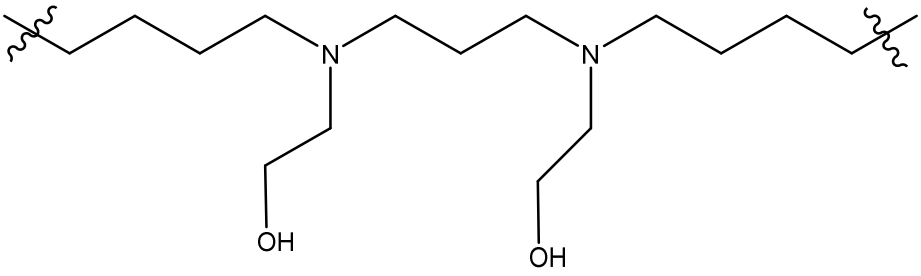
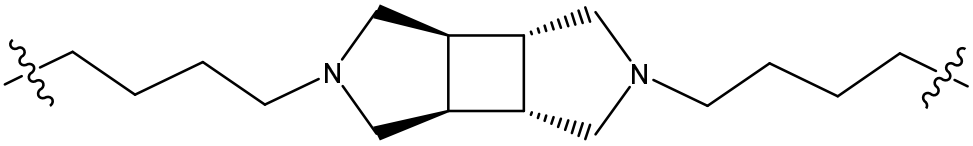
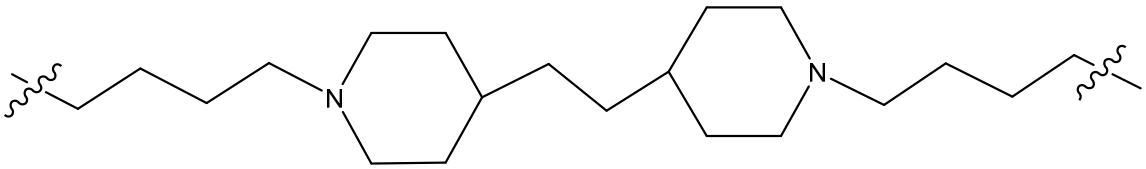
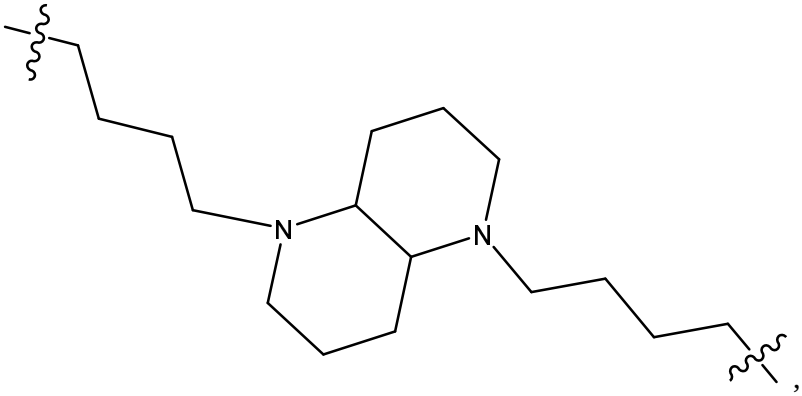
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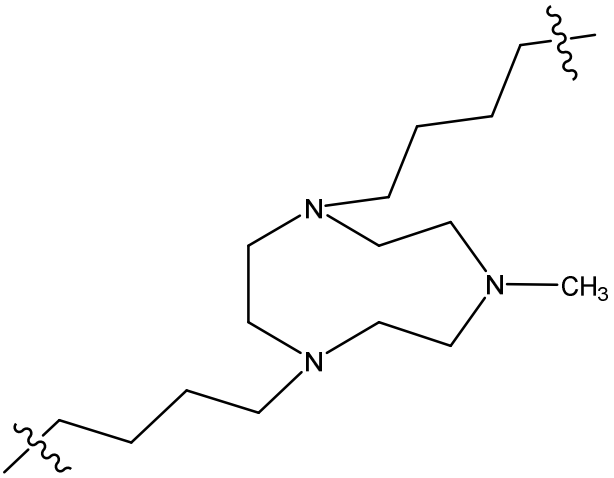


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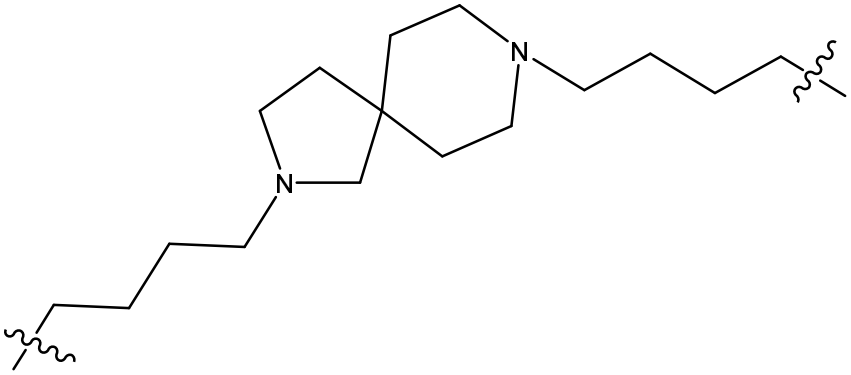


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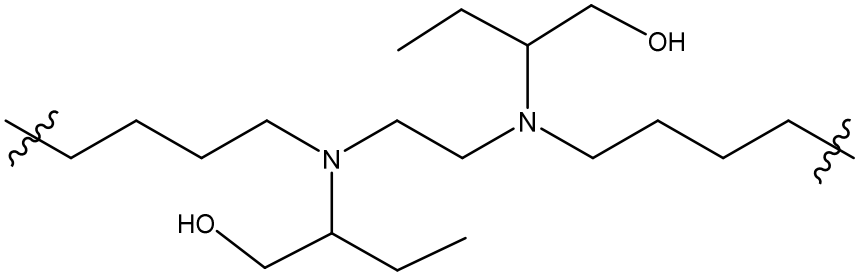

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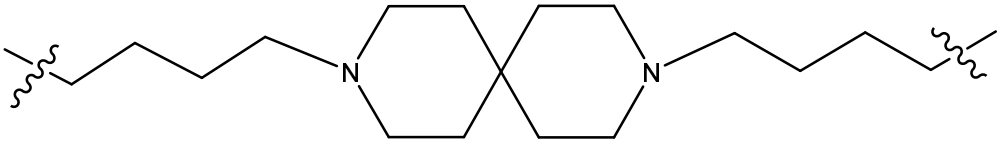
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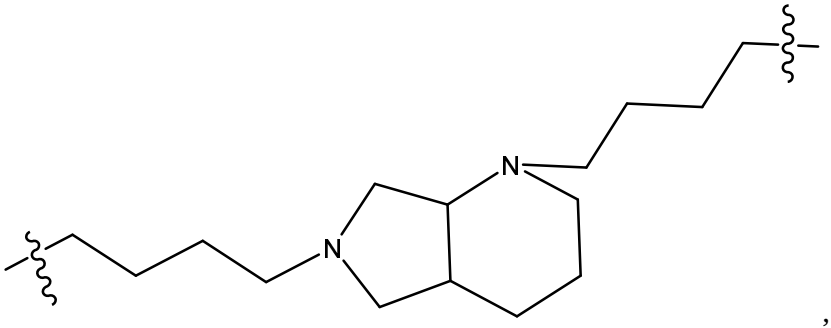
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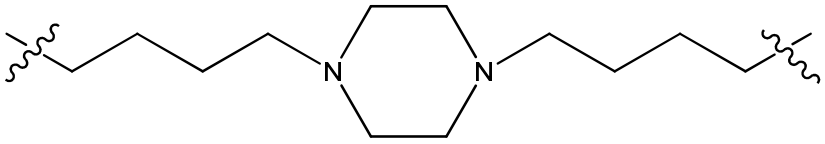


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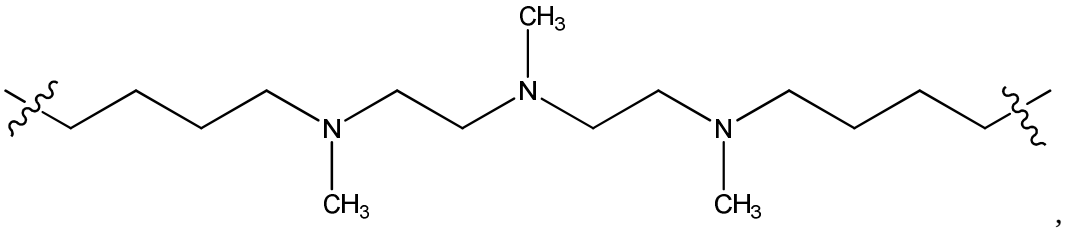


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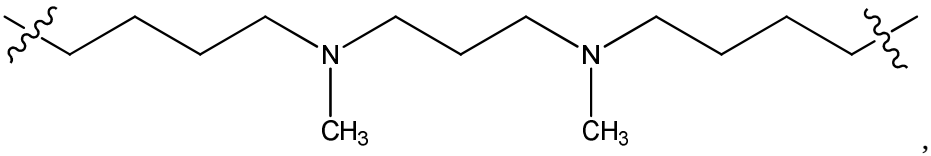
further preferably, X is selected from the group consisting of:



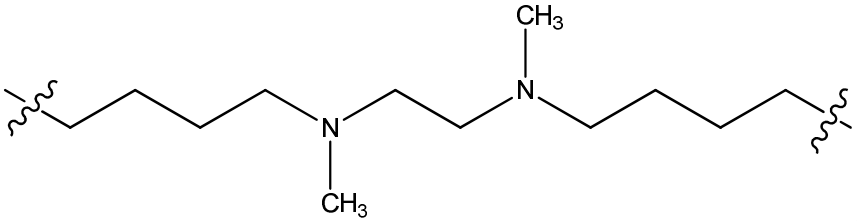
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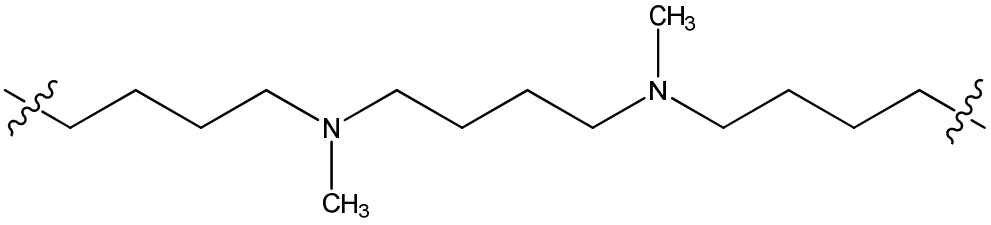
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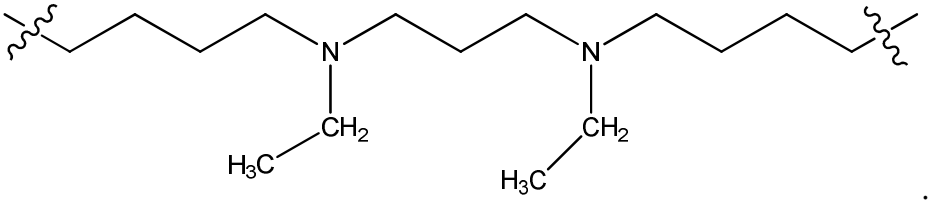
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, and



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4. The compound of claim 1, which is selected from a compound of formula 12-32, 34-38, and 40-43 as described in Example 5, or a salt thereof.

5. A lipid particle comprising the compound of any one of claims 1-4.

6. The lipid particle of claim 5, wherein the lipid particle further comprises a therapeutic agent, wherein the therapeutic agent is a nucleic acid therapeutic agent, an interfering RNA agent, or mRNA.

7. The lipid particle of claim 6, wherein the therapeutic agent is siRNA.

8. A composition comprising a compound of any one of claims 1-4.

9. A pharmaceutical composition comprising a lipid particle of any one of claims 5 to 7, and a pharmaceutically acceptable carrier.

10. The lipid particle of claim 6 or 7 for use in the *in vivo* delivery of a therapeutic agent to a mammalian subject.

11. Use of the lipid particle of claim 6 or 7 in the manufacture of a medicament for the *in vivo* delivery of a therapeutic agent to a mammalian subject.

12. The lipid particle of claim 6 or 7 for use in treating a disease or disorder in a mammalian subject in need thereof.

13. The lipid particle for use of claim 12, wherein the disease or disorder is liver fibrosis or liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

14. Use of the lipid particle of claim 6 or 7 in the manufacture of a medicament for treating a disease or disorder in a mammalian subject in need thereof, wherein the disease or disorder is liver fibrosis or liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

15. A method of delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vitro*, comprising contacting the HSC with the lipid particle of claim 6 or 7.

16. The lipid particle of claim 6 or 7 for use in delivering a therapeutic agent to a hepatic

stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle of claim 7 or 8.

17. Use of the lipid particle of claim 6 or 7 in the manufacture of a medicament for delivering a therapeutic agent to a hepatic stellate cell (HSC), *in vivo*, wherein the HSC is to be contacted with the lipid particle of claim 6 or 7.