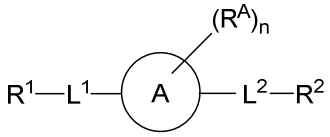
BRIEF SUMMARY

Accordingly, certain ~~embodiment~~examples provide a compound of formula (I):



(I)

wherein:

R^1 a is targeting ligand;

L^1 is absent or a linking group;

L^2 is absent or a linking group;

R^2 is a siRNA molecule selected from a siRNA described herein, *e.g.*, an siRNA selected from any one of siRNA 1 – siRNA 119;

the ring A is absent, a 3-20 membered cycloalkyl, a 5-20 membered aryl, a 5-20 membered heteroaryl, or a 3-20 membered heterocycloalkyl;

each R^A is independently selected from the group consisting of hydrogen, hydroxy, CN, F, Cl, Br, I, -C_{1-2} alkyl-OR^B, C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein the C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally substituted with one or more groups independently selected from halo, hydroxy, and C_{1-3} alkoxy;

R^B is hydrogen or a protecting group; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

or a salt thereof.

In certain ~~embodiment~~examples, R^1 is $–C(H)_{(3-p)}(L^3\text{-saccharide})_p$;

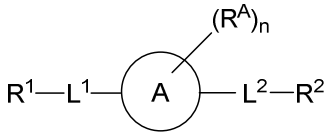
wherein each L^3 is independently a linking group;

p is 1, 2, or 3; and

saccharide is a monosaccharide or disaccharide

or a salt thereof.

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



(I)

wherein:

R^1 a is targeting ligand;

L^1 is absent or a linking group;

L^2 is absent or a linking group;

R^2 is a siRNA molecule selected from any one of siRNA 1 – siRNA 119;

the ring A is absent, a 3-20 membered cycloalkyl, a 5-20 membered aryl, a 5-20 membered heteroaryl, or a 3-20 membered heterocycloalkyl;

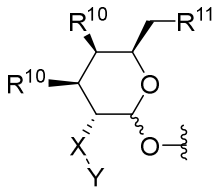
each R^A is independently selected from the group consisting of hydrogen, hydroxy, CN, F, Cl, Br, I, -C_{1-2} alkyl-OR^B, C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein the C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally substituted with one or more groups independently selected from halo, hydroxy, and C_{1-3} alkoxy;

R^B is hydrogen or a protecting group; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

or a salt thereof.

In certain ~~embodiment~~examples, the saccharide is:



wherein:

X is NR^3, and Y is selected from $-(C=O)R^4$, $-SO_2R^5$, and $-(C=O)NR^6R^7$; or X is -(C=O)- and Y is NR^8R^9;

R^3 is hydrogen or $(C_1\text{-}C_4)$alkyl;

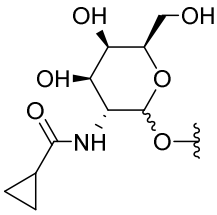
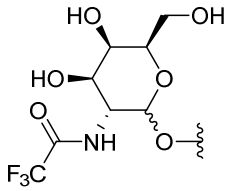
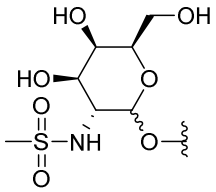
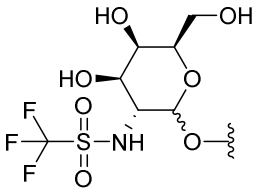
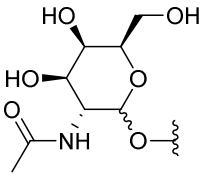
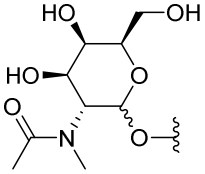
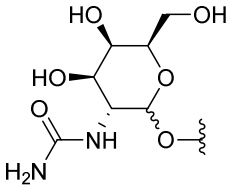
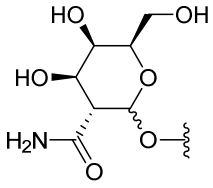
R^4, R^5, R^6, R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, $(C_1\text{-}C_8)$alkoxy and $(C_3\text{-}C_6)$cycloalkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxy and $(C_1\text{-}C_4)$haloalkoxy;

R^{10} is -OH, $-NR^8R^9$ or – F; and

R^{11} is -OH, $-NR^8R^9$, -F or 5 membered heterocycle that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxyl, carboxyl, amino, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxy and $(C_1\text{-}C_4)$haloalkoxy;

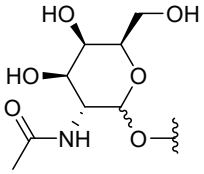
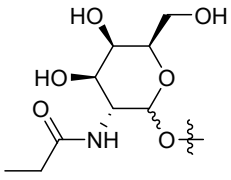
or a salt thereof.

In certain ~~embodiment~~examples, the saccharide is selected from the group consisting of:








and


or a salt thereof.

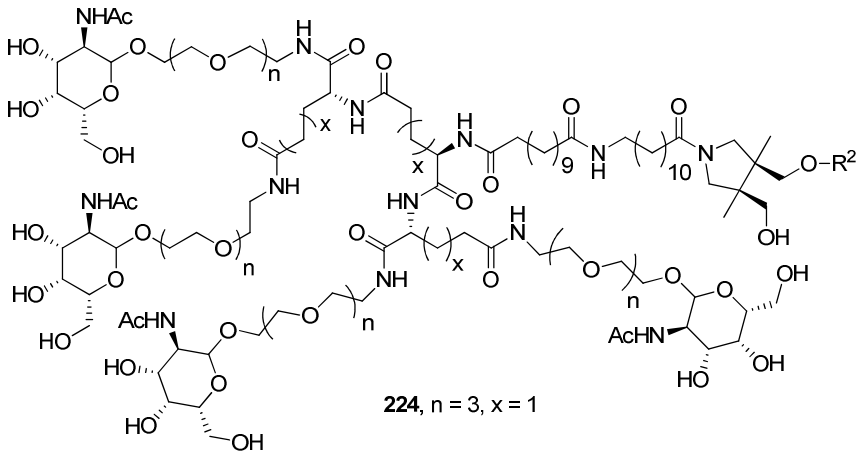
In certain ~~embodiment~~examples, the saccharide is:


or


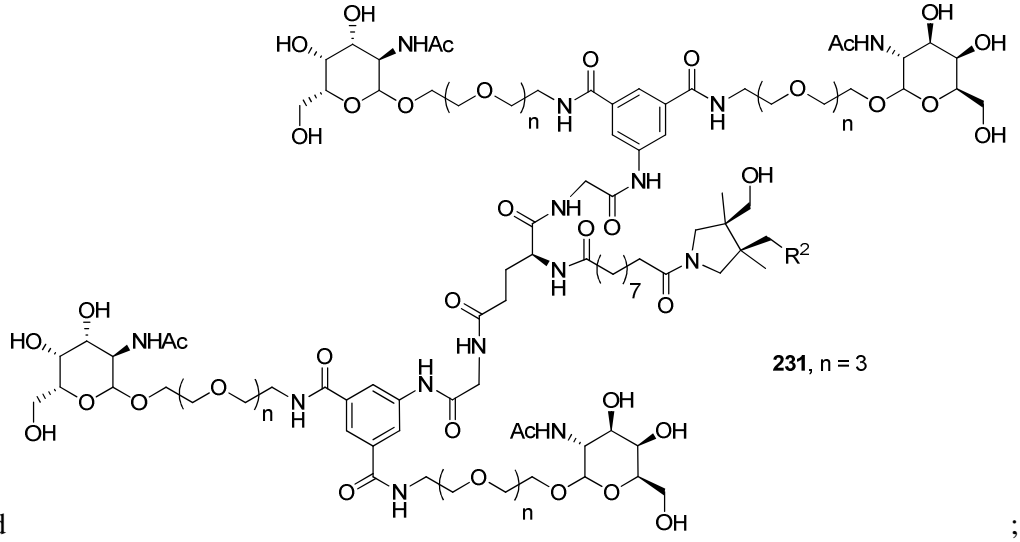
N-Acetylgalactosamine (GalNAc) GalPro

or a salt thereof.

In certain ~~embodiment~~examples, the compound of formula I is selected from the group consisting of:



224, n = 3, x = 1

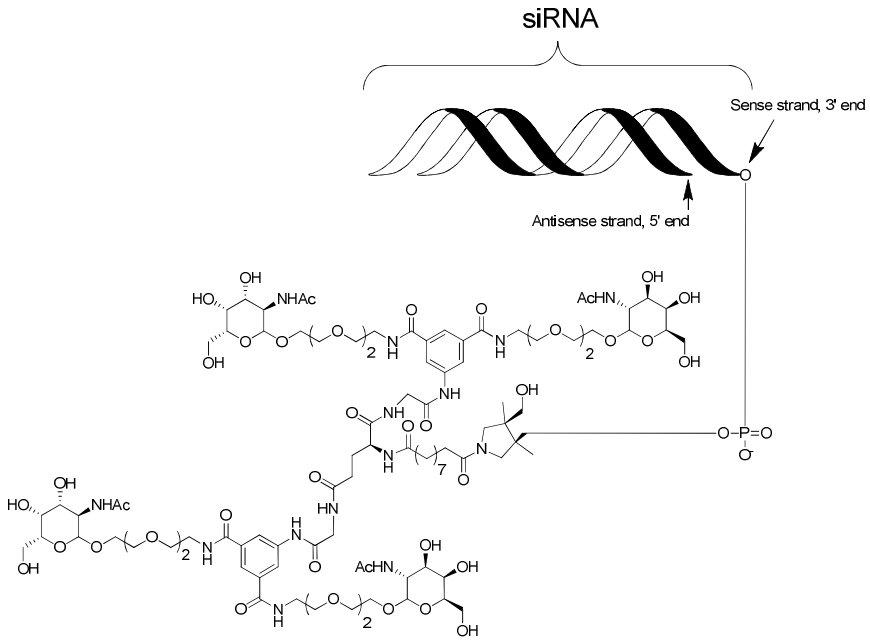


231, n = 3

and ;

and pharmaceutically acceptable salts thereof.

In certain ~~embodiment~~examples, the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof, wherein the siRNA depected is selected from any one of siRNA 1 – siRNA 119.

In certain ~~embodiment~~examples, the siRNA sequence comprises chemically modified nucleotides.

In certain ~~embodiment~~examples, the siRNA comprises at least one 2’ Ome modification or a 2’F modification.

In certain ~~embodiment~~examples, the siRNA comprises at least one 2’ Ome modification and at least one 2’F modification.

In certain ~~embodiment~~examples, the siRNA comprises at least one 2’ Ome modification and at least one 2’F modification.

In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein in the manufacture of a medicament for treating liver fibrosis. Certain ~~embodiment~~examples provide a method of treating liver fibrosis, comprising administering to a patient in need thereof an effective amount of a compound described herein.

In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein for treating non-alcoholic steatohepatitis (NASH). Certain ~~embodiment~~examples provide a method of treating non-alcoholic steatohepatitis (NASH), comprising administering to a patient in need thereof an effective amount of a compound described herein.

In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein in the manufacture of a medicament for treating liver fibrosis associated with non-alcoholic steatohepatitis (NASH). Certain ~~embodiment~~examples provide a method of treating liver fibrosis associated with non-alcoholic steatohepatitis (NASH), comprising administering to a patient in need thereof an effective amount of a compound described herein.

In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein in the manufacture of a medicament for treating alcoholic steatohepatitis (ASH). Certain ~~embodiment~~examples provide a method of treating alcoholic steatohepatitis (ASH), comprising administering to a patient in need thereof an effective amount of a compound described herein.

In one aspect, the present disclosure refers to use of any one of the compounds disclosed herein in the manufacture of a medicament for treating liver fibrosis associated with alcoholic steatohepatitis (ASH). Certain ~~embodiment~~examples provide a method of treating liver fibrosis associated with alcoholic steatohepatitis (ASH), comprising administering to a patient in need thereof an effective amount of a compound described herein.

Certain ~~embodiment~~examples provide the use of an effective amount of a compound described herein to treat liver fibrosis.

Certain ~~embodiment~~examples provide the use of an effective amount of a compound described herein to treat non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

Certain ~~embodiment~~examples provide the use of an effective amount of a compound described herein to treat liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).

In certain ~~embodiment~~examples, the compound of formula (I) is administered subcutaneously.

Certain ~~embodiment~~examples provide a double stranded siRNA molecule selected from the group consisting of siRNA 1 – siRNA 119.

Certain ~~embodiment~~examples provide a composition comprising a double stranded siRNA molecule of claim 21.

Certain ~~embodiment~~examples provide an ~~invention~~disclosure as described herein.

In certain ~~embodiment~~examples, provided herein are nucleic acid molecules (*e.g.*, therapeutic double stranded siRNA molecules), as well as conjugates, compositions and methods that can be used to deliver such nucleic acids. These are useful for treating liver fibrosis, *e.g.*, NASH- or ASH-related liver fibrosis.

Accordingly, one ~~aspect~~ example provides a double stranded siRNA molecule selected from the group consisting of siRNA 1 – siRNA 119, and to individual sense and antisense strands thereof. In one aspect, the present disclosure refers to double stranded siRNA molecule selected from the group consisting of siRNA 1 – siRNA 119. In another aspect, the present disclosure refers to a composition comprising a double stranded siRNA molecule disclosed herein.

Another ~~aspect~~example provides GalNAc conjugates that comprise one of the siRNAs described herein, which conjugates are not limited to conjugates that comprise the ligand-linkers disclosed herein. ~~For example, an aspect~~One example provides a GalNAc conjugate of Formula X:

A-B-C

(**X**)

wherein A is a targeting ligand;

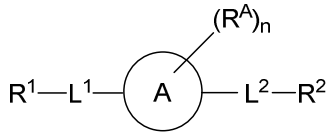
B is an optional linker; and

C is an siRNA molecule described herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

R^1 a is targeting ligand;

L^1 is absent or a linking group;

L^2 is absent or a linking group;

R^2 is a siRNA molecule selected from any one of siRNA 1 – siRNA 119;

the ring A is absent, a 3-20 membered cycloalkyl, a 5-20 membered aryl, a 5-20 membered heteroaryl, or a 3-20 membered heterocycloalkyl;

each R^A is independently selected from the group consisting of hydrogen, hydroxy, CN, F, Cl, Br, I, -C_{1-2} alkyl-OR^B, C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein the C_{1-10} alkyl C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally substituted with one or more groups independently selected from halo, hydroxy, and C_{1-3} alkoxy;

R^B is hydrogen or a protecting group; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

or a salt thereof.

2. The compound of claim 1, wherein R^1 comprises 2-8 saccharides, ~~is $C(H)_{(3-p)}(L^3$-saccharide)$_p$;~~

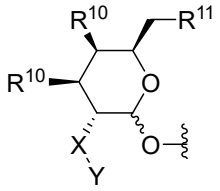
~~wherein each L^3 is independently a linking group;~~

~~p is 1, 2, or 3; and~~

~~saccharide is a monosaccharide or disaccharide~~

or a salt thereof.

3. The compound of claim 2, wherein the saccharide is:



wherein:

X is NR^3, and Y is selected from $-(C=O)R^4$, $-SO_2R^5$, and $-(C=O)NR^6R^7$; or X is -(C=O)- and Y is NR^8R^9;

R^3 is hydrogen or $(C_1\text{-}C_4)$alkyl;

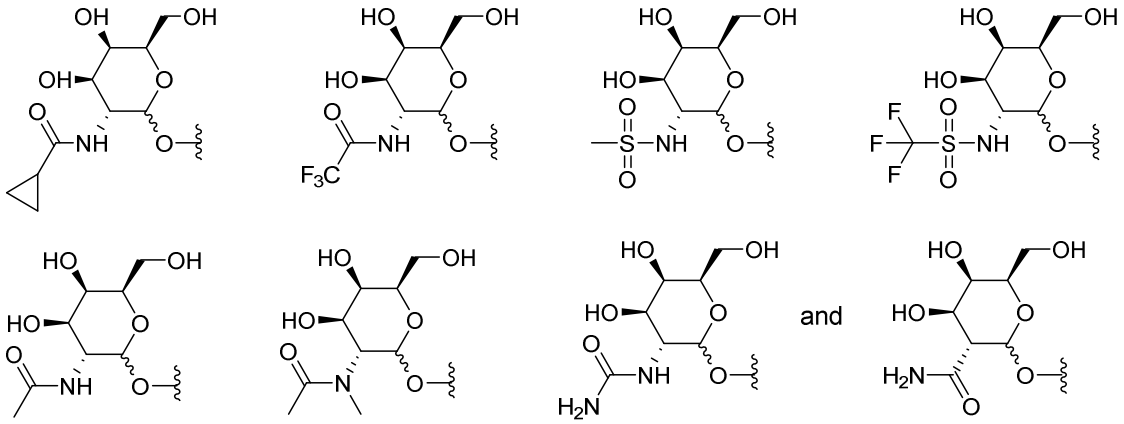
R^4, R^5, R^6, R^7 , R^8 and R^9 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$haloalkyl, $(C_1\text{-}C_8)$alkoxy and $(C_3\text{-}C_6)$cycloalkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxy and $(C_1\text{-}C_4)$haloalkoxy;

R^{10} is -OH, $-NR^8R^9$ or – F; and

R^{11} is -OH, $-NR^8R^9$, -F or 5 membered heterocycle that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxyl, carboxyl, amino, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl, $(C_1\text{-}C_4)$alkoxy and $(C_1\text{-}C_4)$haloalkoxy;

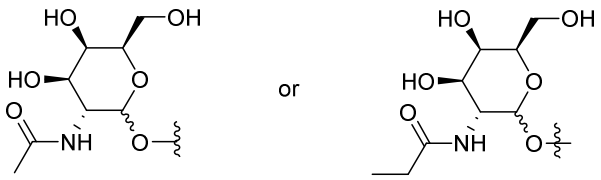
or a salt thereof.

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



or a salt thereof.

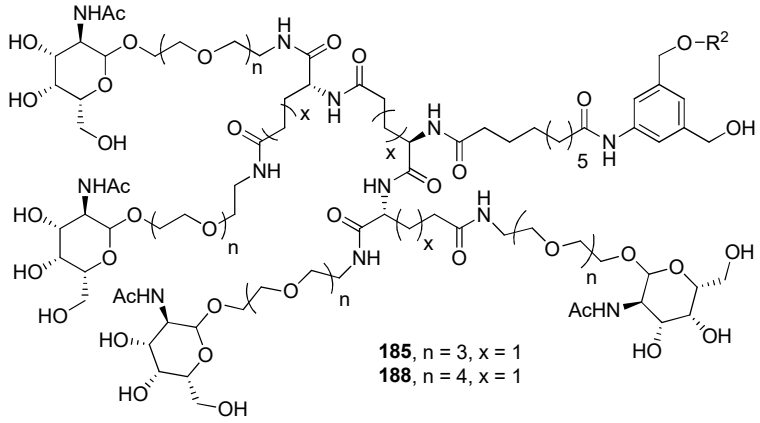
5. The compound of any one of claims 2-4, wherein the saccharide is:

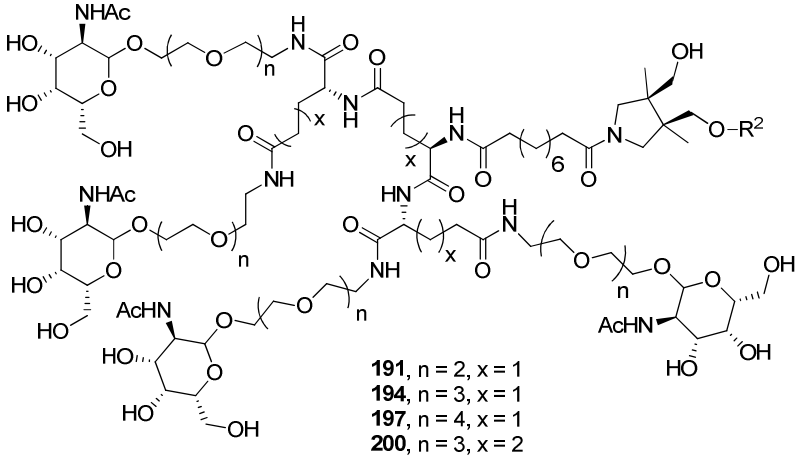


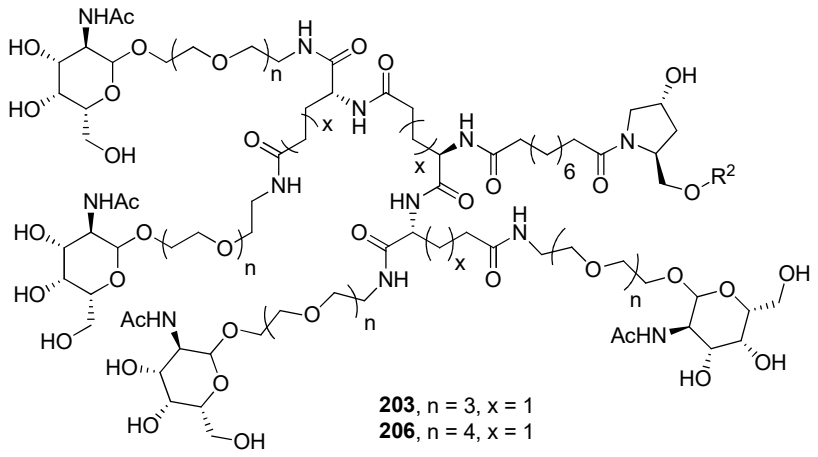
N-Acetylgalactosamine (GalNAc) GalPro

or a salt thereof.

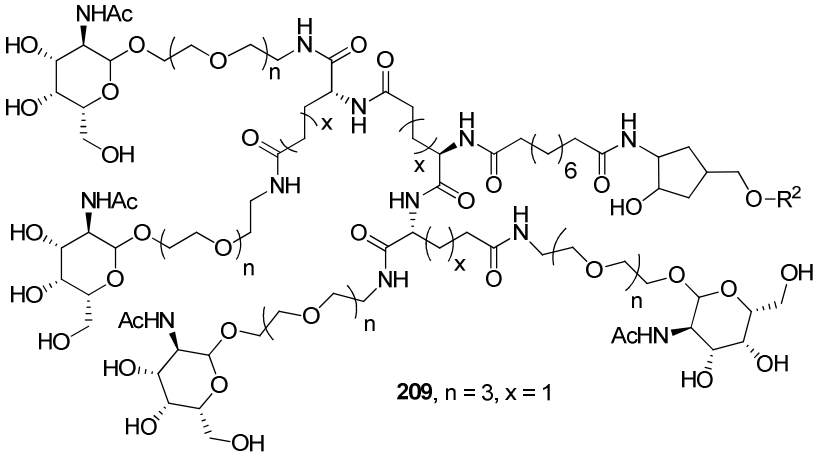
6. The compound of claim 1, wherein the compound of formula I is selected from the group consisting of:



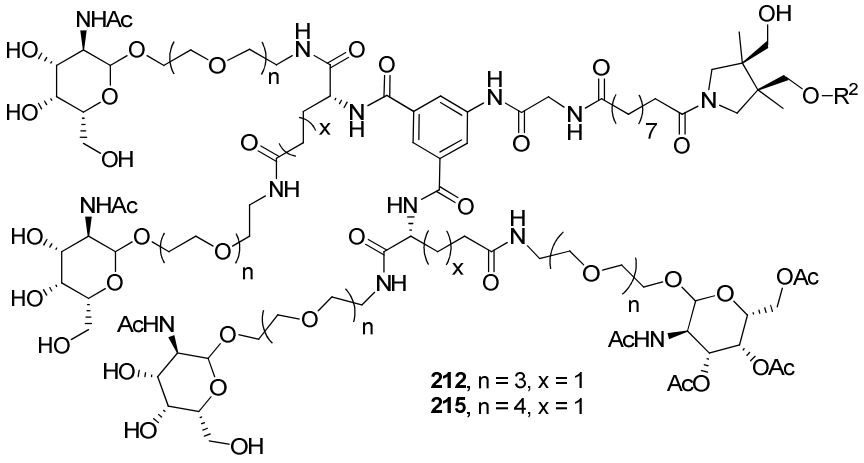




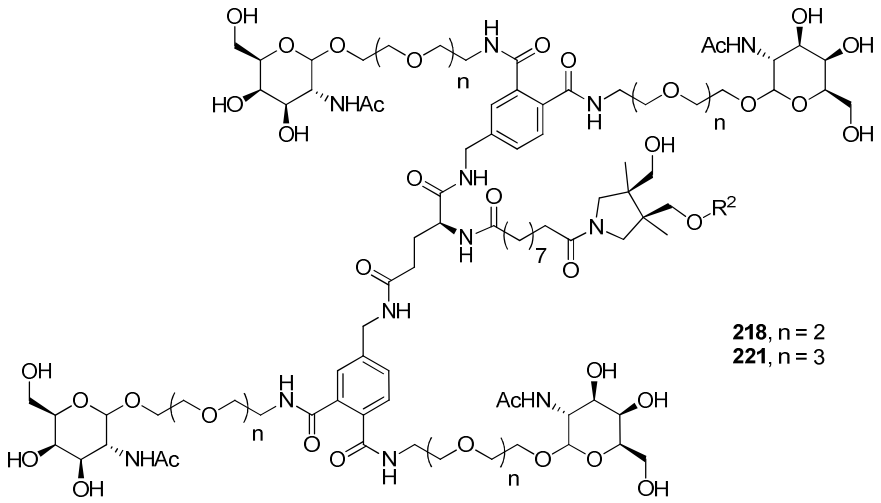
203, n = 3, x = 1
206, n = 4, x = 1



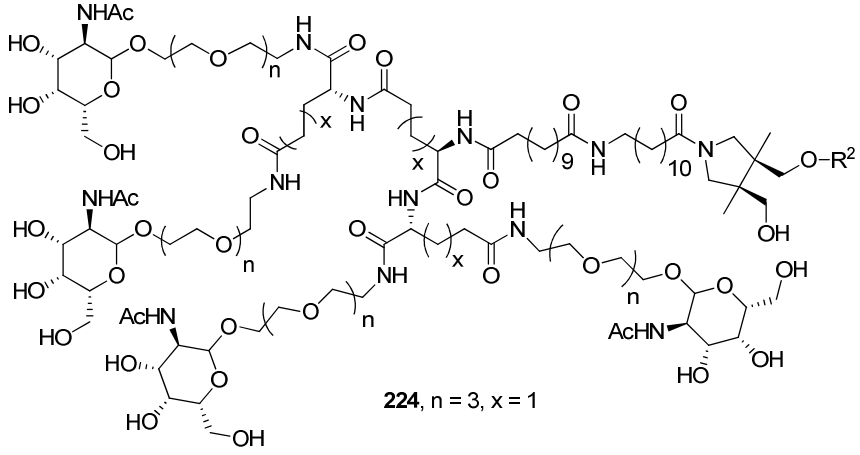
209, n = 3, x = 1



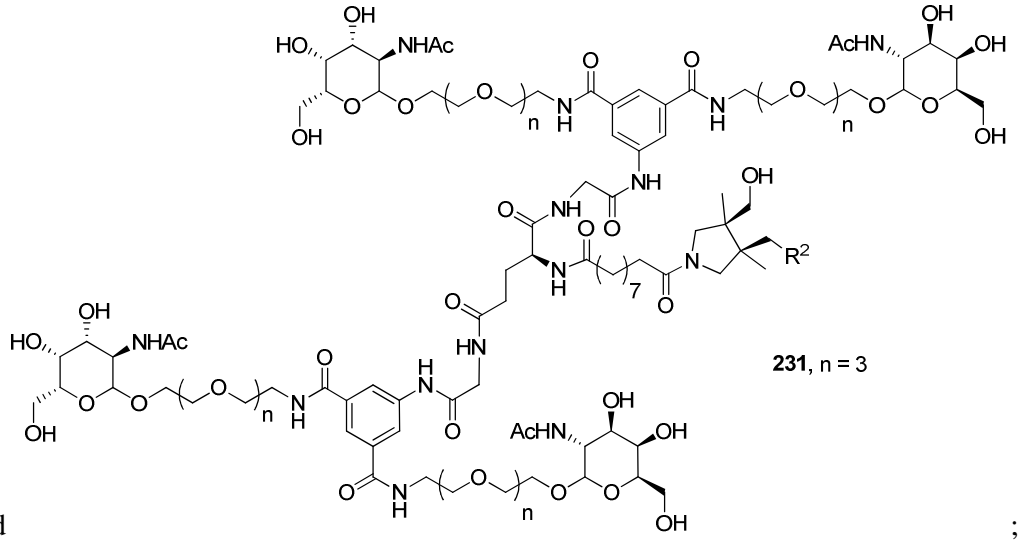
212, n = 3, x = 1
215, n = 4, x = 1



218, n = 2
221, n = 3



224, n = 3, x = 1



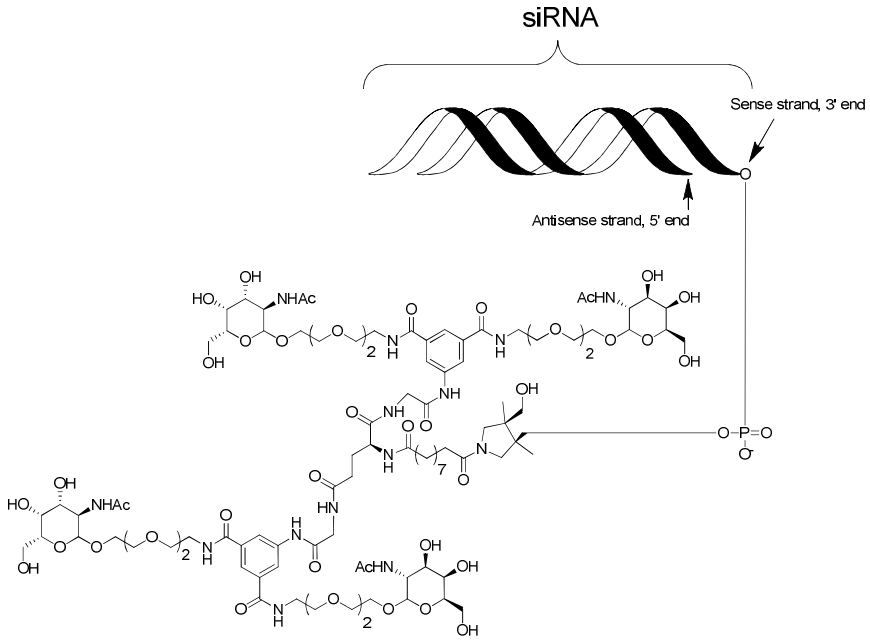
231, n = 3

and ;

and pharmaceutically acceptable salts thereof.

5

7. The compound of claim 1, wherein the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof, wherein the siRNA depected is selected from any one of siRNA 1 – siRNA 119.

8. The compound of any one of claims 1-7, wherein the siRNA sequence comprises chemically modified nucleotides.

9. The compound of claim 8, wherein the siRNA comprises at least one 2' Ome modification or a 2'F modification.

10. The compound of claim 9, wherein the siRNA comprises at least one 2' Ome modification and at least one 2'F modification.

11. The compound of claim 9, wherein the siRNA comprises at least one 2' Ome modification and at least one 2'F modification.

12. ~~A method of treating liver fibrosis, comprising administering to a patient in need thereof an effective amount~~Use of the compound of any one of claims 1-11 in the manufacture of a medicament for treating liver fibrosis.

13. ~~A method of treating non-alcoholic steatohepatitis (NASH), comprising administering to a patient in need thereof an effective amount~~ Use of the compound of any one of claims 1-11 in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH).

14. ~~A method of treating liver fibrosis associated with non-alcoholic steatohepatitis (NASH), comprising administering to a patient in need thereof an effective amount~~ Use of the compound of any one of claims 1-11 in the manufacture of a medicament for treating liver fibrosis associated with non-alcoholic steatohepatitis (NASH).

15. ~~A method of treating alcoholic steatohepatitis (ASH), comprising administering to a patient in need thereof an effective amount~~ Use of the compound of any one of claims 1-11 in the manufacture of a medicament for treating alcoholic steatohepatitis (ASH).

16. ~~A method of treating liver fibrosis associated with alcoholic steatohepatitis (ASH), comprising administering to a patient in need thereof an effective amount~~ Use of the compound of any one of claims 1-11 in the manufacture of a medicament for treating liver fibrosis associated with alcoholic steatohepatitis (ASH).

~~17. The use of an effective amount of the compound of any one of claims 1-11 to treat liver fibrosis.~~

~~18. The use of an effective amount of the compound of any one of claims 1-11 to treat non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).~~

~~19. The use of an effective amount of the compound of any one of claims 1-11 to treat liver fibrosis associated non-alcoholic steatohepatitis (NASH) or alcoholic steatohepatitis (ASH).~~

~~20~~17. The ~~method or~~ use of any one of claims 12-~~19~~16, wherein the compound of formula (I) is to be administered subcutaneously.

~~21~~18. A double stranded siRNA molecule selected from the group consisting of siRNA 1 – siRNA 119.

~~22~~19. A composition comprising a double stranded siRNA molecule of claim ~~21~~18.

~~23. An invention as described herein.~~