TARGETED NUCLEIC ACID CONJUGATE COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This patent application claims the benefit of priority of U.S. provisional patent application No. 62/321,034, filed 11 April 2016, of U.S. provisional patent application No.62/417,156, filed 03 November 2016, and of U.S. provisional patent application No.62/438,310, filed 22 December 2016, which applications are herein incorporated by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 7, 2017, is named 08155_056WO1_SL.txt and is 7,824 bytes in size.

BACKGROUND

A number of diseases are specific to the liver, for example Hepatitis B and nonalcoholic steatohepatitis (NASH). Accordingly, it would be beneficial to have therapeutic compositions that can be targeted primarily to the liver, kidney, heart, pancreas or other organs in living subjects.

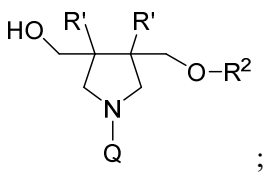
Nucleic acids, including siRNA are useful as therapeutic agents.

Currently there is a need for compositions and methods that can be used to deliver (e.g. target) therapeutic nucleic acids in living subjects.

BRIEF SUMMARY

The invention describes compounds, compositions and methods that can be used therapeutic nucleic acids (e.g. to the liver).

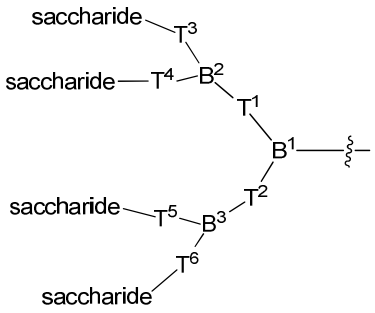
In one aspect, the present disclosure refers to a compound:



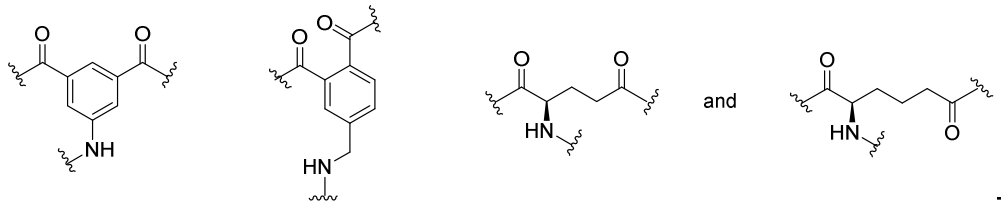
;

or a salt thereof, wherein Q is $-L^1-R^1$; L^1 is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 14 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced with –O-, $-NR^X-$,

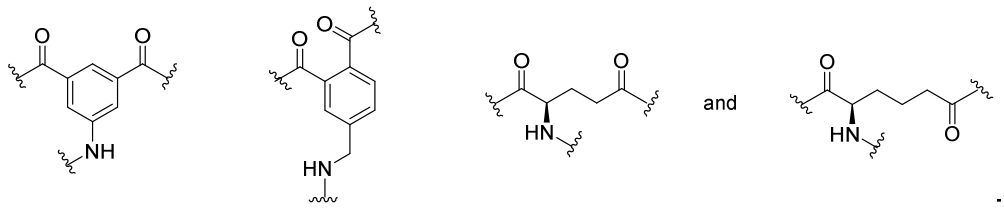
-NR^X-C(=O)-, -C(=O)-NR^X- or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy; R^1 is a targeting ligand that has the following formula:



wherein: B^1 is CH and is covalently bonded to L^1, T^1, and T^2; B^2 is selected from the group consisting of:

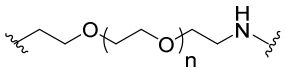


· and is covalently bonded to T^1, T^3, and T^4; B^3 is selected from the group consisting of:

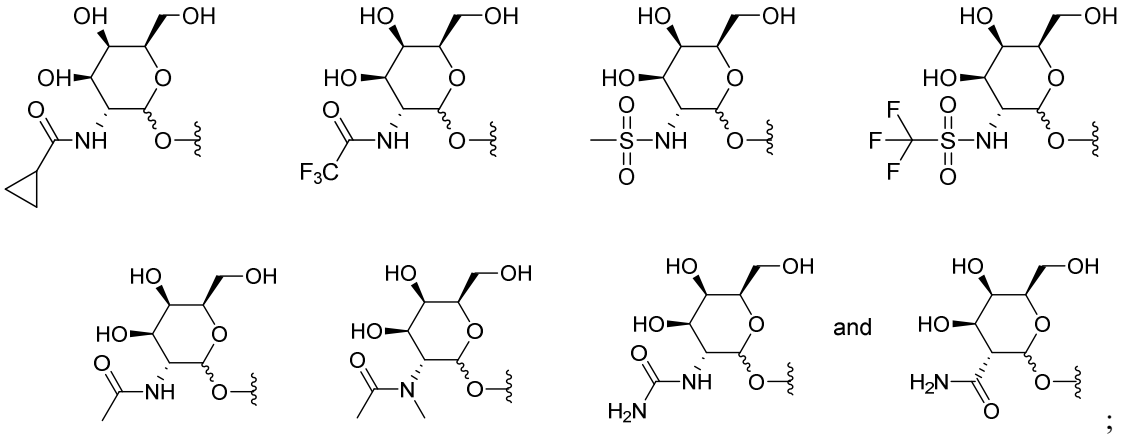


· and is covalently bonded to T^2, T^5, and T^6; T^1 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced by –O-, -NR^X-, -NR^X-C(=O)-, -C(=O)-NR^X- or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy that is covalently bonded to B^1; T^2 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of

the carbon atoms in the hydrocarbon chain is optionally replaced by –O-, -NR^X-, -NR^X-C(=O)-, -C(=O)-NR^X- or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy that is covalently bonded to B^1; each of T^3, T^4, T^5, and T^6 is independently selected from the group consisting of:



n = 1, 2, or 3; each saccharide is independently selected from the group consisting of:

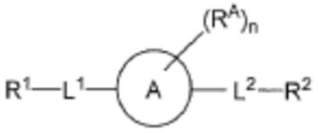


;

R^2 is an siRNA substituent; and R' is C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl; wherein the C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl are optionally substituted with halo or hydroxyl.

In yet another aspect, the present disclosure refers to the use of the compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating liver steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), steatotic liver transplant, hepatitis B, hepatitis D, acute liver damage, fulminant and subfulminant hepatic failure, or hypertriglyceridemia.

Accordingly, in one example, there is described 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 nucleic acid;

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, a protecting group, a covalent bond to a solid support, or a bond to a linking group that is bound to a solid support; and

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

or a salt thereof.

Diseases and conditions which can be treated with the siRNA molecules, including combinations thereof, include liver diseases, e.g., liver diseases associated with or caused by fat accumulation, such as liver steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), steatotic liver transplant, hepatitis (e.g. B or D) and/or acute liver damage, including fulminant and subfulminant hepatic failure, and hypertriglyceridemia.

The disclosure also describes synthetic intermediates and methods disclosed herein that are useful to prepare compounds of formula I.

Other objects, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE FIGURES

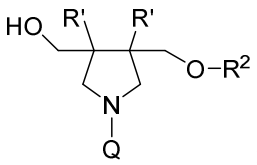
Figure 1: Illustrates an intermediate compound of formula Ie, wherein a targeting ligand/linker is bound to a solid phase support, and wherein Pg^1 is the protecting group DMTr.

Figure 2: Illustrates a representative compound of formula Id wherein a targeting ligand is bound to a solid phase support, with a nucleic acid covalently bound.

Figure 3: Illustrates a representative compound of formula Id, wherein a targeting ligand-nucleic acid conjugate has been cleaved from a solid phase support and deprotected to provide the compound of formula I.

WHAT IS CLAIMED IS:

1. A compound:

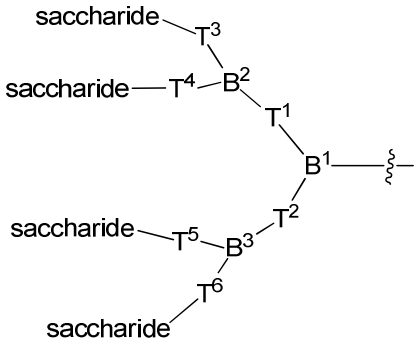


;

or a salt thereof, wherein Q is $-L^1-R^1$;

L^1 is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 14 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced with –O-, $-NR^X-$, $-NR^X-C(=O)-$, $-C(=O)-NR^X-$ or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy;

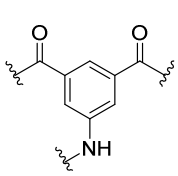
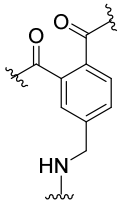
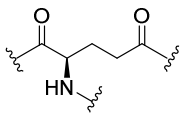
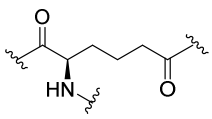
R^1 is a targeting ligand that has the following formula:



wherein:

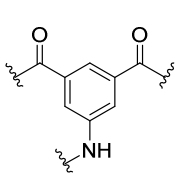
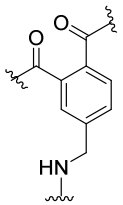
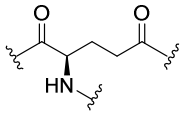
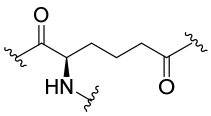
B^1 is CH and is covalently bonded to L^1, T^1, and T^2;

B^2 is selected from the group consisting of:




and

, and

is covalently bonded to T^1, T^3, and T^4;

B^3 is selected from the group consisting of:

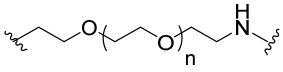



and

· and

is covalently bonded to T^2, T^5, and T^6;

T^1 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced by –O-, -NR^X-, -NR^X-C(=O)-, -C(=O)-NR^X- or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy that is covalently bonded to B^1;

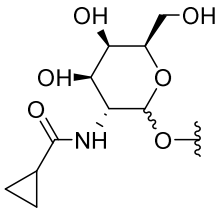
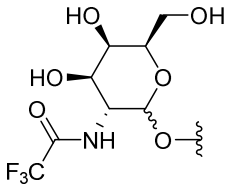
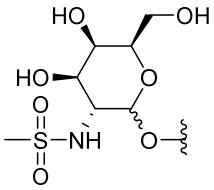
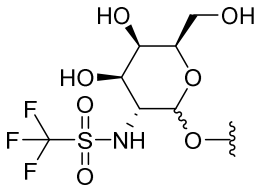
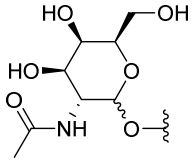
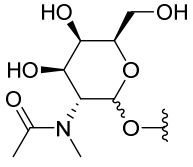
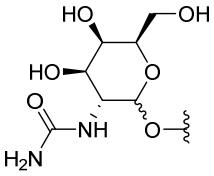
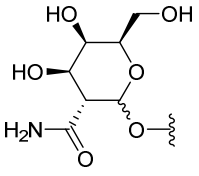
T^2 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced by –O-, -NR^X-, -NR^X-C(=O)-, -C(=O)-NR^X- or –S-, and wherein R^X is hydrogen or (C_1-C_6)alkyl, and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy that is covalently bonded to B^1;

each of T^3, T^4, T^5, and T^6 is independently selected from the group consisting of:



n = 1, 2, or 3;

each saccharide is independently selected from the group consisting of:

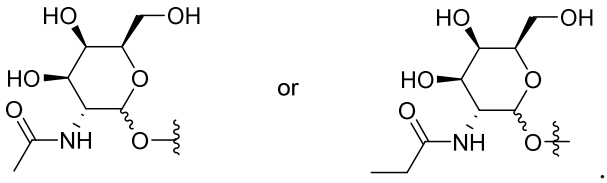







and

;

R^2 is an siRNA substituent; and

R' is C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl; wherein the C_{1-9} alkyl, C_{2-9} alkenyl or C_{2-9} alkynyl are optionally substituted with halo or hydroxyl.

2. The compound or salt of claim 1, wherein L^1 is connected to R^1 through -NH-, -O-, -S-, -(C=O)-, -(C=O)-NH-, -NH-(C=O)-, -(C=O)-O-, -NH-(C=O)-NH-, or –NH-(SO_2)-.

3. The compound or salt of claim 1, wherein each saccharide is independently:



.

4. The compound or salt of claim 1, wherein T^1 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced by –O- and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from halo, hydroxy, and oxo (=O).

5. The compound or salt of claim 1, wherein T^2 is a branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more of the carbon atoms in the hydrocarbon chain is optionally replaced by –O- and wherein the hydrocarbon chain, is optionally substituted with one or more substituents selected from halo, hydroxy, and oxo (=O).

6. Use of the compound as described in any one of claims 1-5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, in the manufacture of a medicament for treating liver steatosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), steatotic liver transplant, hepatitis B, hepatitis D, acute liver damage, fulminant and subfulminant hepatic failure, or hypertriglyceridemia.