emergence of resistance mutations in HCV requires treatment with additional agents. Developing therapies include NS3/4A protease inhibitors, NS5A protein inhibitors, nucleoside/tide NS5B polymerase inhibitors and non-nucleoside NS5B inhibitors. However, there remains a need for additional therapies to treat infected individuals who do not respond to current treatments, who relapse following successful treatment, or who have a low tolerability for one or more currently used drugs. Resistance to antiviral therapy is a major problem associated with a high mutation rate of HCV and is seen even with combinations of drugs working through multiple mechanisms. Accordingly, therapeutics that target conserved, mutation-resistant viral host factors, such as miR-122, represent an opportunity to effect higher and more durable cure rates.

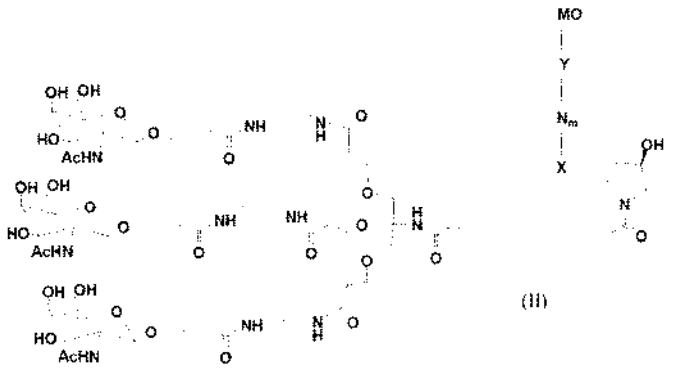
SUMMARY ~~OF INVENTION~~

In one aspect, the present disclosure refers to a compound comprising a modified oligonucleotide consisting of less than 16 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises a nucleobase sequence that is complementary to nucleobases 2 to 9 of miR-122 (SEQ ID NO: 1), and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the following structure:

$A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4),

wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

In another aspect, the present disclosure refers to a compound of the structure:



wherein X is a phosphodiester linkage; m is 1; N of N_m is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is a modified oligonucleotide consisting of less than 16 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises a nucleobase sequence that is

complementary to nucleobases 2 to 9 of miR-122 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 8 contiguous nucleosides of the structure $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage; and wherein Y is linked to the 3' terminus of the modified oligonucleotide.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure refers to use of the compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a hepatitis C virus (HCV)-infected human subject.

Provided herein are compounds comprising a modified oligonucleotide consisting of 16 to 22 linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide is complementary to miR-122 (SEQ ID NO: 1) and wherein the modified oligonucleotide comprises at least 16 contiguous nucleosides of the following nucleoside pattern I in the 5' to 3' orientation:

$(R)_X$-N^Q-N^Q-N^B-N^B-N^Q-N^B-N^Q-N^B-N^Q-N^B-N^B-$(N^Z)_Y$

wherein each R is, independently, a non-bicyclic nucleoside or a bicyclic nucleoside;

X is from 4 to 10;

each N^B is, independently, a bicyclic nucleoside;

each N^Q is, independently, a non-bicyclic nucleoside;

Y is 0 or 1; and

N^Z is a modified nucleoside or an unmodified nucleoside.

In certain ~~embodiments~~examples, a compound provided herein comprises a modified oligonucleotide comprising at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, or 22 contiguous nucleosides of nucleoside pattern I.

In certain example~~embodiment~~s, each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside. In certain example~~embodiment~~s, at least two bicyclic nucleosides are different from one another. In certain example~~embodiment~~s, all bicyclic nucleosides have the same sugar moiety as one another. In certain example~~embodiment~~s, each bicyclic nucleoside is a cEt nucleoside. In certain example~~embodiment~~s, a cEt nucleoside is an S-cEt nucleoside. In certain example~~embodiment~~s, a cEt nucleoside is an R-cEt nucleoside. In certain example~~embodiment~~s, each bicyclic nucleoside is an LNA nucleoside.

In certain example~~embodiment~~s, at least two non-bicyclic nucleosides comprise sugar moieties that are different from one another. In certain example~~embodiment~~s, each non-bicyclic nucleoside has the same type of sugar moiety. In certain example~~embodiment~~s, each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, a β-D-ribonucleoside, 2'-O-methyl nucleoside, a 2'-O-methoxyethyl nucleoside, and a 2'-fluoronucleoside. In certain example~~embodiment~~s, each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, and a 2'-O-methoxyethyl nucleoside. In certain example~~embodiment~~s, each non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain example~~embodiment~~s, each non-bicyclic nucleoside is a 2'-MOE nucleoside. In certain example~~embodiment~~s, no more than two non-bicyclic nucleosides are 2'-MOE nucleosides, wherein each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain example~~embodiment~~s, the 5'-most and the 3'-most non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain example~~embodiment~~s, two non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

In certain example~~embodiment~~s, each R is a 2'-MOE nucleoside. In certain example~~embodiment~~s, X is 4, 5, 6, 7, 8, 9, or 10. In certain example~~embodiment~~s, Y is 0. In certain example~~embodiment~~s, Y is 1.

In certain example~~embodiment~~s, X is 7, each R is a 2'-O-methoxyethyl nucleoside, each N^B is an S-cEt nucleoside, each N^Q is a β-D-deoxyribonucleoside, and Y is 0.

In certain example~~embodiment~~s, X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of N^{R1} and N^{R3} is a S-cEt nucleoside and each of N^{R2} and N^{R4} is a β-D-deoxyribonucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; Y is 1; and N^Z is a β-D-deoxyribonucleoside.

In certain example~~embodiment~~s, X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of N^{R1} and N^{R4} is a S-cEt nucleoside and each of N^{R2} and N^{R3} is a β-D-deoxyribonucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; Y is 1; and N^Z is a 2'-O-methoxyethyl nucleoside.

In certain example~~embodiment~~s, X is 7; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, and N^{R4} and is a 2'-O-methoxyethyl nucleoside, each of N^{R5} and N^{R7} is a β-D-deoxyribonucleoside, and N^{R6} is S-cEt nucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; and Y is 0.

In certain example~~embodiment~~s, X is 7; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, $N^{R4,}$ and N^{R5} is a 2'-O-methoxyethyl nucleoside, N^{R6} is S-cEt nucleoside, and N^{R7} is a β-D-deoxyribonucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; and Y is 0.

In certain example~~embodiment~~s, X is 7; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, and N^{R7} is a β-D-deoxyribonucleoside; each N^B is an S-cEt nucleoside; each N^Q is a β-D-deoxyribonucleoside; and Y is 0.

In certain exampleembodiments, X is 10; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}-N^{R8}-N^{R9}-N^{R10}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, each of N^{R7} and N^{R9} is a an S-cEt nucleoside; each of N^{R8} and N^{R10} is a β-D-deoxyribonucleoside; each N^{B} is an S-cEt nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; and Y is 0.

In certain exampleembodiments, X is 10; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}-N^{R8}-N^{R9}-N^{R10}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, each of N^{R7} and N^{R9} is a an S-cEt nucleoside; and each of N^{R8} and N^{R10} is a β-D-deoxyribonucleoside; each N^{B} is an S-cEt nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; Y is 1 and N_Z is a 2'-O-methoxyethyl nucleoside.

In certain exampleembodiments, X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of $N^{R1}$and N^{R4} is an S-cEt nucleoside, and each of N^{R1} and N^{R3} is a β-D-deoxyribonucleoside; each N^{B} is an S-cEt nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; Y is 1 and N^{Z} is a β-D-deoxyribonucleoside.

In certain exampleembodiments, X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein N^{R1} is a 2'-O-methoxyethyl nucleoside, each of N^{R2} and N^{R4} is an S-cEt nucleoside, and N^{R3} is a β-D-deoxyribonucleoside; each N^{B} is an S-cEt nucleoside; each N^{Q} is a β-D-deoxyribonucleoside; Y is 1 and N^{Z} is a 2'-O-methoxyethyl nucleoside.

In certain exampleembodiments, the nucleobase sequence of the modified oligonucleotide is at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to the nucleobase sequence of miR-122 (SEQ ID NO: 1).

In certain exampleembodiments, wherein at least one internucleoside linkage is a modified internucleoside linkage, or wherein each internucleoside linkage is a modified internucleoside linkage, and, optionally, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

In certain exampleembodiments, the nucleobase sequence of the modified oligonucleotide is selected from SEQ ID NOs: 3 to 6, wherein each T is independently selected from T and U.

In certain exampleembodiments, the modified oligonucleotide has 0, 1, 2, or 3 mismatches with respect to the nucleobase sequence of miR-122.

In certain exampleembodiments a compound has the structure:

$A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4);

$C_SCA_STTGU_SC_SAC_SAC_STC_SC_SA$ (SEQ ID NO: 3);

$^{Me}C_SCAT_STGT_S{}^{Me}C_SA{}^{Me}C_SA{}^{Me}C_ST{}^{Me}C_S{}^{Me}C_SA_E$ (SEQ ID NO: 3);

$A_E{}^{Me}C_EA_E{}^{Me}C_ECA_STTGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4);

$A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_STTGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4);

$A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4);

$^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 5);

$^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_ST_E$ (SEQ ID NO: 6);

$C_SCAU_STGU_SC_SAC_SAC_STC_SC_SA$ (SEQ ID NO: 3); or

$^{Me}C_EC_SAU_STGU_SC_SAC_SAC_STC_SC_SA_E$ (SEQ ID NO: 3);

wherein the superscript "Me" indicates 5-methylcytosine; nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "E" are 2'-MOE nucleosides; nucleosides followed by a subscript "S" are S-cEt nucleosides; and each internucleoside linkage is a phosphorothioate internucleoside linkage.

In some example~~embodiment~~s, a compound has the structure:

$U_STGU_SC_SAC_SAC_STC_SC_SA_S$; or

$C_SA_SC_SA_SC_SU_SC_SC_S$

wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides; nucleosides followed by a subscript "S" are S-cEt nucleosides; and each internucleoside linkage is a phosphorothioate internucleoside linkage. In some such example~~embodiment~~s, the compound is compound 38591, 38633, 38998, or 38634.

Any of the compounds provided herein may comprise a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide. In certain example~~embodiment~~s, the compound comprises a conjugate moiety linked to the 3' terminus of the modified oligonucleotide. In certain example~~embodiment~~s, the compound comprises a conjugate moiety linked to the 5' terminus of the modified oligonucleotide. In certain example~~embodiment~~s, the compound comprises a first conjugate moiety linked to the 3' terminus of the modified oligonucleotide and a second conjugate moiety linked to the 5' terminus of the modified oligonucleotide. In certain example~~embodiment~~s, the conjugate moiety comprises at least one ligand selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid**.**

In certain example~~embodiment~~s, a compound has the structure L_n-linker-MO, wherein each L is, independently, a ligand and n is from 1 to 10; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, a compound has the structure L_n-linker-X-MO, wherein each L is, independently, a ligand and n is from 1 to 10; X is a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, a compound has the structure L_n-linker-X_1-N_m-X_2-MO, wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, a compound has the structure L_n-linker-X-N_m-Y-MO, wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X is a phosphodiester linkage or a phosphorothioate linkage; Y is a phosphodiester linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, a compound has the structure L_n-linker-Y-N_m-Y-MO, wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; each Y is a phosphodiester linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, if n is greater than 1, L_n-linker has the structure:

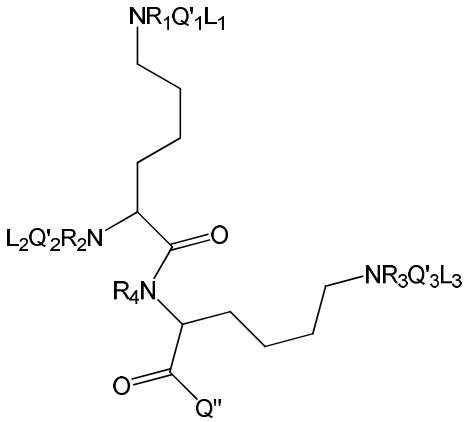
$$\left(\text{L} - \text{Q'}\right)_{\text{n}}\text{S} - \text{Q''} -$$

wherein each L is, independently, a ligand; n is from 1 to 10; S is a scaffold; and Q' and Q" are, independently, linking groups.

In certain example~~embodiment~~s, Q' and Q" are each independently selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid.

In certain example~~embodiment~~s, a scaffold links 2, 3, 4, or 5 ligands to a modified oligonucleotide. In certain example~~embodiment~~s, a scaffold links 3 ligands to a modified oligonucleotide.

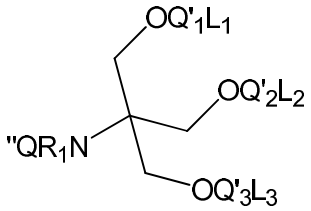
A nonlimiting exemplary Structure E is Structure E(i):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'_1, Q'_2, Q'_3, and Q" are each, independently, a linking group; and R_1, R_2, R_3, and R_4 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'$_1$, Q'$_2$, Q'$_3$, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, R_3, and R_4 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s, R_1, R_2, R_3, and R_4 are each selected from H and methyl.

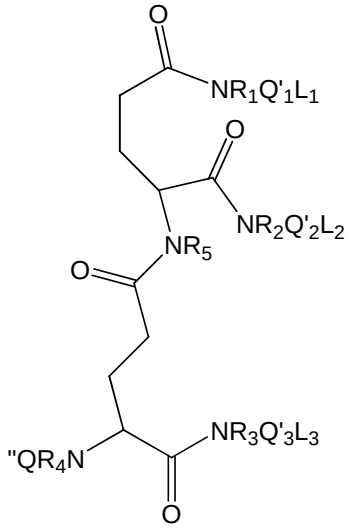
A further nonlimiting exemplary Structure E is Structure E(ii):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'$_1$, Q'$_2$, Q'$_3$, and Q" are each, independently, a linking group; and R_1 is selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'$_1$, Q'$_2$, Q'$_3$, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1 is selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s, R_1 is H or methyl.

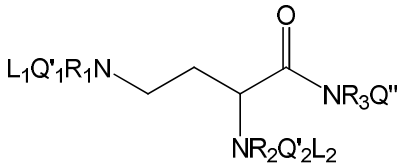
A further nonlimiting exemplary Structure E is Structure E(iii):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'_1, Q'_2, Q'_3, and Q" are each, independently, a linking group; and R_1, R_2, R_3, R_4, and R_5 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'_1, Q'_2, Q'_3, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, R_3, R_4, and R_5 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, R_3, R_4, and R_5 are each selected from H and methyl.

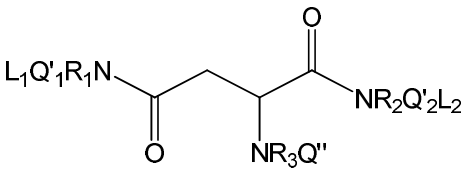
A further nonlimiting exemplary Structure E is Structure E(iv):



wherein L_1 and L_2 are each, independently, a ligand; Q'_1, Q'_2, and Q" are each, independently, a linking group; and R_1, R_2, and R_3 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'_1, Q'_2, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, and R_3 are each selected from H and methyl.

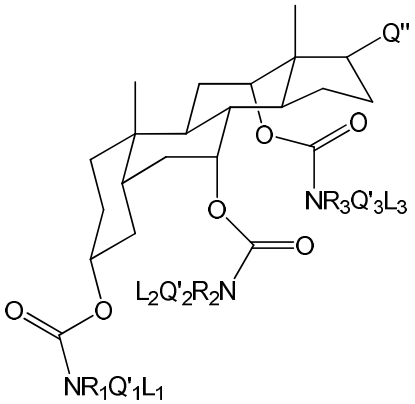
A further nonlimiting exemplary Structure E is Structure E(v):



wherein L_1 and L_2 are each, independently, a ligand; Q'_1, Q'_2, and Q" are each, independently, a linking group; and R_1, R_2, and R_3 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'_1, Q'_2, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, and R_3 are each selected from H and methyl.

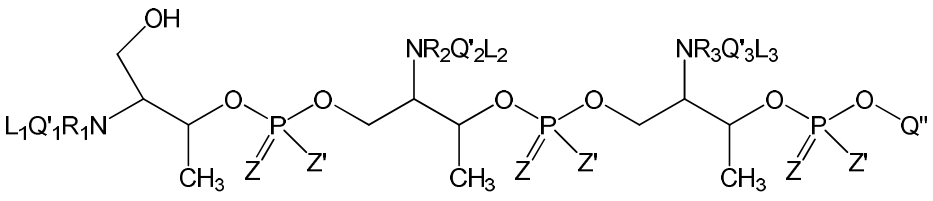
A further nonlimiting exemplary Structure E is Structure E(vi):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'_1, Q'_2, Q'_3, and Q" are each, independently, a linking group; and R_1, R_2, and R_3 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'_1, Q'_2, Q'_3, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, and R_3 are each selected from H and methyl.

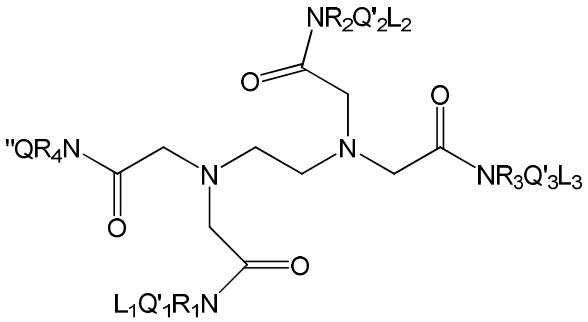
A further nonlimiting exemplary Structure E is Structure E(vii):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'_1, Q'_2, Q'_3, and Q" are each, independently, a linking group; R_1, R_2, and R_3 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl; and Z and Z' are each independently selected from O and S.

In some example~~embodiment~~s, Q'_1, Q'_2, Q'_3, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, and R_3 are each selected from H and methyl. In some example~~embodiment~~s, Z or Z' on at least one P atom is S, and the other Z or Z' is O (i.e., a phosphorothioate linkage). In some example~~embodiment~~s, each –OP(Z)(Z')O- is a phosphorothioate linkage. In some example~~embodiment~~s, Z and Z' are both O on at least one P atom (i.e., a phosphodiester linkage). In some example~~embodiment~~s, each –OP(Z)(Z')O- is a phosphodiester linkage.

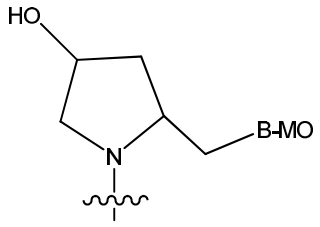
A further nonlimiting exemplary Structure E is Structure E(viii):



wherein L_1, L_2, and L_3 are each, independently, a ligand; Q'_1, Q'_2, Q'_3, and Q" are each, independently, a linking group; and R_1, R_2, R_3, and R_4 are each, independently, selected from H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl.

In some example~~embodiment~~s, Q'_1, Q'_2, Q'_3, and Q" are each, independently, selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid. In some example~~embodiment~~s, R_1, R_2, R_3, and R_4 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some example~~embodiment~~s R_1, R_2, R_3, and R_4 are each selected from H and methyl.

Nonlimiting exemplary scaffolds and/or linkers comprising scaffolds, and synthesis thereof, are described, e.g., PCT Publication No. WO 2013/033230, U.S. Patent No. 8,106,022 B2, U.S. Publication No. 2012/0157509 A1; U.S. Patent No. 5,994,517; U.S. Patent No. 7,491,805 B2; U.S. Patent No. 8,313,772 B2; Manoharan, M., Chapter 16, Antisense Drug Technology, Crooke, S.T., Marcel Dekker, Inc., 2001, 391-469.



In certain example~~embodiment~~s, a compound has the structure:

wherein:

B is selected from –O-, -S-, -N(R^N)-, –Z-P(Z')(Z")O-, –Z-P(Z')(Z")O-N_m-X-, and –Z-P(Z')(Z")O-N_m-Y-;

MO is a modified oligonucleotide;

R^N is selected from H, methyl, ethyl, propyl, isopropyl, butyl, and benzyl;

Z, Z', and Z" are each independently selected from O and S;

each N is, independently, a modified or unmodified nucleoside;

m is from 1 to 5;

X is selected from a phosphodiester linkage and a phosphorothioate linkage;

Y is a phosphodiester linkage; and

the wavy line indicates the connection to the rest of the linker and ligand(s).

In certain example~~embodiment~~s, X is a phosphodiester linkage.

In certain example~~embodiment~~s, n is from 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In certain example~~embodiment~~s, n is 3.

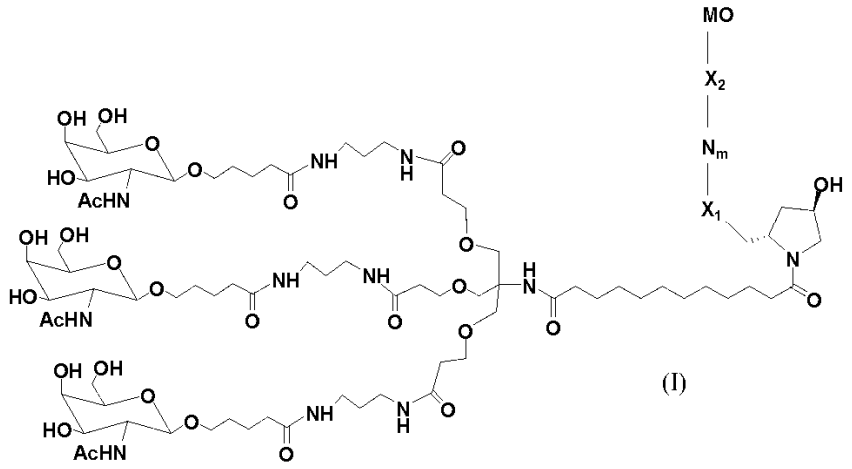
In certain example~~embodiment~~s, at least one ligand is a carbohydrate.

In certain example~~embodiment~~s, at least one ligand is selected from mannose, glucose, galactose, ribose, arabinose, fructose, fucose, xylose, D-mannose, L-mannose, D-galactose, L-galactose, D-glucose, L-glucose, D-ribose, L-ribose, D-arabinose, L-arabinose, D-fructose, L-fructose, D-fucose, L-fucose, D-xylose, L-xylose, alpha-D-mannofuranose, beta-D-mannofuranose, alpha-D-mannopyranose, beta-D-mannopyranose, alpha-D-glucofuranose, Beta-D-glucofuranose, alpha-D-glucopyranose, beta-D-glucopyranose, alpha-D-galactofuranose, beta-D-galactofuranose, alpha-D-galactopyranose, beta-D-galactopyranose, alpha-D-ribofuranose, beta-D-ribofuranose, alpha-D-ribopyranose, beta-D-ribopyranose, alpha-D-fructofuranose, alpha-D-fructopyranose, glucosamine, galactosamine, sialic acid, N-acetylgalactosamine.

In certain example~~embodiment~~s, at least one ligand is selected from N-acetylgalactosamine, galactose, galactosamine, N-formylgalactosamine, N-propionyl-galactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

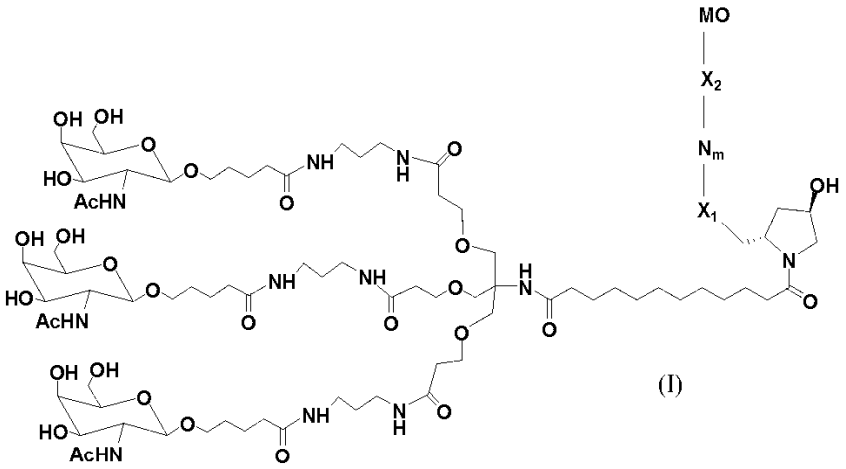
In certain example~~embodiment~~s, each ligand is N-acetylgalactosamine.

In certain example~~embodiment~~s, a compound has the structure:



wherein each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, a compound provided herein comprises a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $C_LCA_LTTG_LT_LCAC_LAC_LTC_LC_L$ (SEQ ID NO: 7), wherein the subscript "L" indicates an LNA and nucleosides not followed by a subscript are β-D-deoxyribonucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage, and wherein the conjugate moiety is linked to the 3' terminus of the modified oligonucleotide and has the structure:



wherein each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.

In certain example~~embodiment~~s, at least one of X_1 and X_2 is a phosphodiester linkage. In certain example~~embodiment~~s, each of X_1 and X_2 is a phosphodiester linkage. In certain example~~embodiment~~s, m is 1. In certain example~~embodiment~~s, m is 2, 3, 4, or 5.

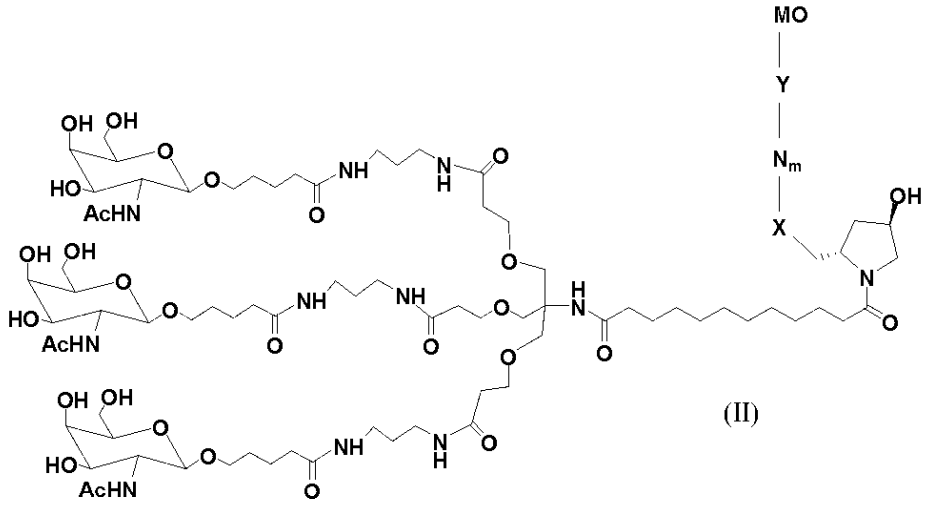
In certain example~~embodiment~~s, N_m is N'_pN'', wherein each N' is, independently, a modifid or unmodified nucleoside and p is from 0 to 4; and N" is a nucleoside comprising an unmodified sugar moiety. In certain example~~embodiment~~s, p is 0. In certain example~~embodiment~~s, p is 1, 2, 3, or 4.

In certain example~~embodiment~~s, each N' comprises an unmodified sugar moiety. In certain example~~embodiment~~s, each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose. In certain example~~embodiment~~s, N" comprises a purine nucleobase. In certain example~~embodiment~~s, N" comprises a pyrimidine nucleobase. In certain example~~embodiment~~s, at least one N' comprises a purine nucleobase. In certain example~~embodiment~~s, each purine nucleobase is independently selected from adenine, guanine, hypoxanthine, xanthine, and 7-methylguanine. In certain example~~embodiment~~s, N" is a β-D-deoxyriboadenosine or a β-D-deoxyriboguanosine. In certain example~~embodiment~~s, at least one N' comprises a pyrimidine nucleobase. In

certain example~~embodiment~~s, each pyrimidine nucleobase is independently selected from cytosine, 5-methylcytosine, thymine, uracil, and 5,6-dihydrouracil.

In any of the example~~embodiment~~s described herein, the sugar moiety of each N is independently selected from a β-D-ribose, a β-D-deoxyribose, a 2'-O-methoxy sugar, a 2'-O-methyl sugar, a 2'-fluoro sugar, and a bicyclic sugar moiety. In certain example~~embodiment~~s, each bicyclic sugar moiety is independently selected from a cEt sugar moiety, an LNA sugar moiety, and an ENA sugar moiety. In certain example~~embodiment~~s, a cEt sugar moiety is an S-cEt sugar moiety. In certain example~~embodiment~~s, a cEt sugar moiety is an R-cEt sugar moiety. In any example~~embodiment~~s described herein, the sugar moiety of each N may be independently selected from β-D-ribose, a β-D-deoxyribose, and a 2'-fluoro sugar.

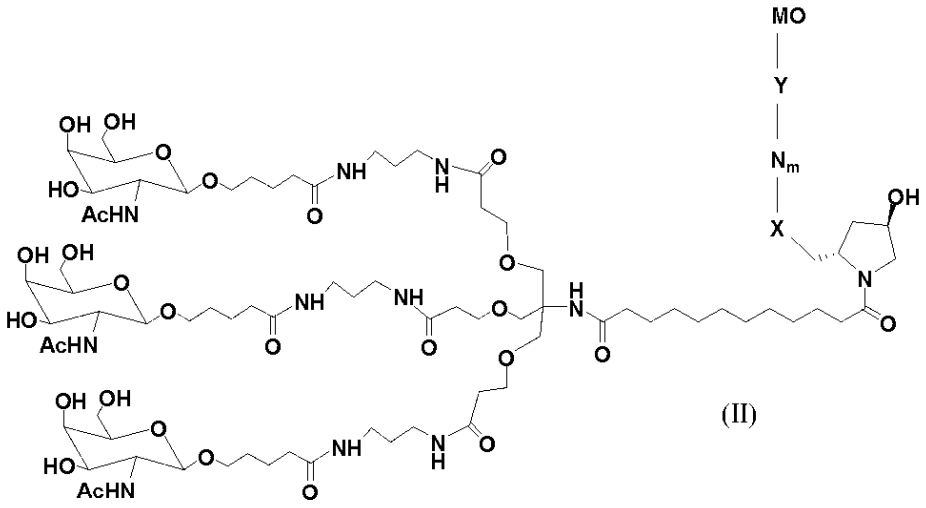
Provided herein are compounds comprising a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage; and wherein the conjugate moiety is linked to the 3' terminus of the modified oligonucleotide and has the structure:



wherein X is a phosphodiester linkage; m is 1; N is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is the modified oligonucleotide.

Provided herein are compounds comprising a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $C_LCA_LTTG_LT_LCAC_LAC_LTC_LC_L$ (SEQ ID NO: 7), wherein the subscript "L" indicates an LNA and nucleosides not followed by a subscript are β-D-

deoxyribonucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage, and wherein the conjugate moiety is linked to the 3' terminus of the modified oligonucleotide and has the structure:



(II)

wherein X is a phosphodiester linkage; m is 1; N is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is the modified oligonucleotide. In some example~~embodiment~~s, all of the C_L nucleosides are $^{Me}C_L$ nucleosides, wherein the superscript "Me" indicates 5-methylcytosine.

Provided herein are methods of inhibiting the activity of miR-122 in a cell comprising contacting a cell with any compound provided herein. In certain example~~embodiment~~s, the cell is cell is *in vivo*. In certain example~~embodiment~~s, cell is *in vitro*.

Provided herein are methods of administering to an HCV-infected subject any of the compouds provided herein. In certain example~~embodiment~~s, the administering reduces the symptoms of HCV infection. In certain example~~embodiment~~s, the administering prevents a rebound in serum HCV RNA. In certain example~~embodiment~~s, the administering delays a rebound in serum HCV RNA. In certain example~~embodiment~~s, a subject having HCV infection is selected for treatment with a compound provided herein. In certain example~~embodiment~~s, an HCV-infected subject is infected with one or more HCV genotypes selected from genotype 1, genotype 2, genotype 3, genotype 4, genotype 5, and genotype 6. In certain example~~embodiment~~s, prior to administration of a compound provided herein, the subject was determined to be infected with one or more HCV genotypes selected from genotype 1, genotype 2, genotype 3, genotype 4, genotype 5, and genotype 6. In certain example~~embodiment~~s, the HCV genotype is selected from genotype 1a, genotype 1b, genotype 2a, genotype 2b, genotype 2c, genotype 2d, genotype 3a, genotype 3b, genotype 3c, genotype 3d, genotype 3e, genotype 3f, genotype 4a, genotype 4b, genotype 4c, genotype 4d, genotype 4e, genotype 4f, genotype 4g,

genotype 4h, genotype 4i, genotype 4j, genotype 5a, and genotype 6a. In certain example~~embodiment~~s, the HCV genotype is selected from genotype 1a, 1b, and 2.

Any of the methods provided here may comprise administering at least one additional therapeutic agent. In certain example~~embodiment~~s, the at least one therapeutic agent is selected from a protease inhibitor, a polymerase inhibitor, a cofactor inhibitor, an RNA polymerase inhibitor, a structural protein inhibitor, a non-structural protein inhibitor, a cyclophilin inhibitor, an entry inhibitor, a TLR7 agonist, and an interferon. In certain example~~embodiment~~s, the at least one therapeutic agent is selected from a protease inhibitor, an NS5A inhibitor, an NS3/4A inhibitor, a nucleoside NS5B inhibitor, a nucleotide NS5B inhibitor, a non-nucleoside NS5B inhibitor, a cyclophilin inhibitor and an interferon. In certain example~~embodiment~~s, the at least one therapeutic agent is selected from interferon alfa-2a, interferon alpha-2b, interferon alfacon-1, peginterferon alpha-2b, peginterferon alpha-2a, interferon-alpha-2b extended release, interferon lambda, sofosbuvir, ribavirin, telapravir, boceprevir, vaniprevir, asunaprevir, ritonavir, setrobuvir, daclastavir, simeprevir, alisporivir, mericitabine, tegobuvir, danoprevir, sovaprevir, and neceprevir. In certain example~~embodiment~~s, the at least one therapeutic agent is selected from an interferon, ribavirin, and telapravir.

In certain example~~embodiment~~s, a subject is infected with an HCV variant that is resistant to at least one therapeutic agent. In certain example~~embodiment~~s, a subject is infected with an HCV variant that is resistant to a direct-acting anti-viral agent. In certain example~~embodiment~~s, a subject is infected with an HCV variant that is resistant to at least one therapeutic agent selected from a protease inhibitor, a polymerase inhibitor, a cofactor inhibitor, an RNA polymerase inhibitor, a structural protein inhibitor, a non-structural protein inhibitor, and a cyclophilin inhibitor. In certain example~~embodiment~~s, a subject is infected with an HCV variant that is resistant to at least one therapeutic agent selected from a protease inhibitor, an NS5A inhibitor, an NS3/4A inhibitor, a nucleoside NS5B inhibitor, a nucleotide NS5B inhibitor, a non-nucleoside NS5B inhibitor, and a cyclophilin inhibitor. In certain example~~embodiment~~s, a subject is infected with an HCV variant that is resistant to at least one therapeutic agent selected from sofosbuvir, ribavirin, telapravir, boceprevir, vaniprevir, asunaprevir, ritonavir, setrobuvir, daclastavir, simeprevir, alisporivir, mericitabine, tegobuvir, danoprevir, sovaprevir, and neceprevir.

In certain example~~embodiment~~s, an HCV-infected subject is a non-responder to at least one therapeutic agent. In certain example~~embodiment~~s, an HCV-infected subject is an interferon non-responder. In certain example~~embodiment~~s, an HCV-infected subject is a direct-acting anti-viral non-responder.

Any of the methods provided herein may comprise selecting a subject having a HCV RNA level greater than 350,000 copies per milliliter of serum. In certain example~~embodiment~~s, a subject has an HCV RNA level between 350,000 and 3,500,000 copies per milliliter of serum. In certain example~~embodiment~~s, a subject has an HCV RNA level greater than 3,500,000 copies per milliliter of serum.

In certain exampleembodiments, an HCV-infected subject has an HCV-associated disease. In certain exampleembodiments, an HCV-associated disease is cirrhosis, liver fibrosis, steatohepatitis, steatosis, or hepatocellular carcinoma.

In certain exampleembodiments, an HCV-infected subject has one or more diseases that are not HCV-associated diseases. In certain exampleembodiments, an HCV-infected subject is infected with one or more viruses other than HCV. In certain exampleembodiments, an HCV-infected subject is infected with human immunodeficiency virus (HIV). In certain exampleembodiments, the methods provided herein comprise administering an additional therapeutic agent is an anti-viral agent used in the treatment of HIV infection. In certain exampleembodiments, an additional therapeutic agent is a non-nucleoside reverse transcriptase inhibitors (NNRTIs). In certain exampleembodiments, an additional therapeutic agent is a nucleoside reverse transcriptase inhibitors (NRTIs). In certain exampleembodiments, an additional therapeutic agent is a protease inhibitor. In certain exampleembodiments, an additional therapeutic agent is an entry inhibitor or fusion inhibitor. In certain exampleembodiments, an additional therapeutic agent is an integrase inhibitor. In certain exampleembodiments, an additional therapeutic agent is selected from efavirenz, etravirine, nevirapine, abacavir, emtricitabine, tenofovir, lamivudine, zidovudine, atazanavir, darunavir, fosamprenavir, ritonavir, enfuvirtide, maraviroc, and raltegravir.

Any of the methods provided herein may comprise administering a dose of the compound sufficient to reduce HCV RNA level. In certain exampleembodiments, the administered dose of the compound reduces HCV RNA level below 40 copies per ml of serum. In certain exampleembodiments, the administered dose of the compound achieves at least a 2-log reduction in HCV RNA level. In certain exampleembodiments, administering a compound provided herein achieves a sustained virological response. In certain exampleembodiments, the administered dose of the compound is sufficient to achieve an HCV RNA level reduction of at least 0.5 fold, at least 1.0 fold, at least 1.5 fold, at least 2.0 fold, or at least 2.5 fold. In certain exampleembodiments, the HCV RNA level reduction is achieved after two weeks, three weeks, four weeks, five weeks, or six weeks of a first administration of the compound. In certain exampleembodiments, a compound provided herein is administered once per week, once per two weeks, once per three weeks, once per four weeks, or once per month. In certain exampleembodiments, a compound provided herein is administered once per two months or once per three months. In some exampleembodiments, a compound provided herein is administered once per four weeks.

In certain exampleembodiments, the dose of the compound administeredis less than or equal to 5 mg/kg per week, less than or equal to 5 mg/kg, less than or equal to 4.5 mg/kg, less than or equal to 4.0 mg/kg, less than or equal to 3.5 mg/kg, less than or equal to 3.0 mg/kg, less than or equal to 2.5 mg/kg, less than or equal to 2.0 mg/kg, less than or equal to 1.5 mg/kg, or less than or equal to 1.0 mg/kg. In certain

exampleembodiments, the compound is administered at a dose within a range of 1 to 5 mg/kg, or 1 to 4 mg/kg, or 2 to 5 mg/kg, or 2 to 4 mg/kg. In certain exampleembodiments, the dose of the compound administered is less than or equal to 10 mg/kg, less than or equal to 7.5 mg/kg, less than or equal to 10 mg/kg per week, or less than or equal to 7.5 mg/kg per week.

In certain exampleembodiments, administration of a compound provided herein normalizes liver enzyme levels, wherein the liver enzyme is optionally alanine aminotransferase.

In any of the exampleembodiments provided herein, the compound is present in a pharmaceutical composition.

Provided herein are compounds for use in treating an HCV-infected subject.

In certain embodimentsexamples, a subject is a human.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1A and 1B. *In vivo* potency of anti-miR-122 modified oligonucleotides. (A) Onset and duration of action of anti-miR-122, following a single administration of compound at the indicated doses. (B) De-repression of ALDOA seven days after a single dose of anti-miR-122 compound at the indicated doses.

Figure 2. Structure of a conjugate moiety comprising three GalNAc ligands.

Figure 3A, 3B, and 3C. Conjugated modified oligonucleotide structures.

Figure 4A, 4B, and 4C. *In vivo* potency of GalNAc-conjugated anti-miR-122 modified oligonucleotides.

Figure 5A and 5B. Antisense inhibition of miR-122 reduces HCV titer.

Figure 6A and 6B. *In vivo* potency of GalNAc-conjugated anti-miR-122 modified oligonucleotides.

Figure 7A and 7B. *In vivo* potency of GalNAc-conjugated anti-miR-122 modified oligonucleotides.

Figure 8A and 8B. *In vivo* potency of GalNAc-conjugated anti-miR-122 modified oligonucleotides.

Figure 9A and 9B. Pharmacokinetics of anti-miR-122 compounds.

DETAILED DESCRIPTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the arts to which the invention belongs. Unless specific definitions are provided, the nomenclature utilized in connection with, and the procedures and techniques

What is claimed:

~~1.~~ A compound comprising a modified oligonucleotide consisting of less than 16~~ to 22~~ linked nucleosides, wherein the nucleobase sequence of the modified oligonucleotide comprises a nucleobase sequence that is complementary to nucleobases 2 to 9 of miR-122 (SEQ ID NO: 1~~)~~), and wherein the modified oligonucleotide comprises at least ~~16~~8 contiguous nucleosides of the following ~~nucleoside pattern I in the 5' to 3' orientation:~~

~~$(R)_X$-N^Q-N^Q-N^B-N^B-N^Q-N^B-N^Q-N^B-N^Q-N^B-N^B-$(N^Z)_Y$~~

~~wherein each R is, independently, a non-bicyclic nucleoside or a bicyclic nucleoside;~~

~~X is from 4 to 10;~~

~~each N^B is, independently, a bicyclic nucleoside;~~

~~each N^Q is, independently, a non-bicyclic nucleoside;~~

~~Y is 0 or 1; and~~

~~N^Z is a modified nucleoside or an unmodified nucleoside.~~

~~2. The compound of claim 1, wherein the modified oligonucleotide comprises at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, or 22 contiguous nucleosides of nucleoside pattern I.~~

~~3. The compound of any one of the preceding claims wherein each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside.~~

~~4. The compound of any one of the preceding claims, wherein at least two bicyclic nucleosides are different from one another.~~

~~5. The compound of any one of claims 1 to 3, wherein all bicyclic nucleosides have the same sugar moiety as one another.~~

~~6. The compound of claim , wherein each bicyclic nucleoside is a cEt nucleoside.~~

~~7. The compound of claim , wherein the cEt nucleoside is an S-cEt nucleoside.~~

~~8. The compound of claim , wherein the cEt nucleoside is an R-cEt nucleoside.~~

~~9. The compound of claim , wherein each bicyclic nucleoside is an LNA nucleoside.~~

~~10. The compound of any one of the preceding claims wherein at least two non-bicyclic nucleosides comprise sugar moieties that are different from one another.~~

11. The compound of any one of claims 1 to wherein each non-bicyclic nucleoside has the same type of sugar moiety.

12. The compound of any one of the preceding claims wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, a β-D-ribonucleoside, 2'-O-methyl nucleoside, a 2'-O-methoxyethyl nucleoside, and a 2'-fluoronucleoside.

13. The compound of any one of the preceding claims wherein each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, and a 2'-O-methoxyethyl nucleoside.

14. The compound of any one of claims 1 to 9 and 11 wherein each non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

15. The compound of any one of claims 1 to 9 and 11 wherein each non-bicyclic nucleoside is a 2'-MOE nucleoside.

16. The compound of any one of claims 1 to 10, 12 and 13 wherein no more than two non-bicyclic nucleosides are 2'-MOE nucleosides, wherein each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

17. The compound of claim 16, wherein the 5'-most and the 3'-most non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

18. The compound of claim 16 wherein two non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

19. The compound of any one of claims 1 to 13 and 15 to , wherein each R is a 2'-MOE nucleoside.

20. The compound of any one of claims 1 to 19, wherein X is 4, 5, 6, 7, 8, 9, or 10.

21. The compound of any one of claims 1 to 20, wherein Y is 0.

22. The compound of any one of claims 1 to 20, wherein Y is 1.

23. The compound of claim 1 wherein:

a) X is 7;

each R is a 2'-O-methoxyethyl nucleoside;

each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and Y is 0;

b) X is 4; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of N^{R1} and N^{R3} is a S-cEt nucleoside and each of N^{R2} and N^{R4} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
Y is 1; and N^Z is a β-D-deoxyribonucleoside

c) X is 4; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of N^{R1} and N^{R4} is a S-cEt nucleoside and each of N^{R2} and N^{R3} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
Y is 1; and N^Z is a 2'-O-methoxyethyl nucleoside

d) X is 7; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, and N^{R4} and is a 2'-O-methoxyethyl nucleoside, each of N^{R5} and N^{R7} is a β-D-deoxyribonucleoside, and N^{R6} is S-cEt nucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside; and Y is 0;

e) X is 7; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, and N^{R5} is a 2'-O-methoxyethyl nucleoside, N^{R6} is S-cEt nucleoside, and N^{R7} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside; and Y is 0;

f) X is 7; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, and N^{R7} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside; and Y is 0;

g) X is 10; $(R)_x$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}-N^{R8}-N^{R9}-N^{R10}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, each of N^{R7} and N^{R9} is a an S-cEt nucleoside; each of N^{R8} and N^{R10} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;

each N^Q is a β-D-deoxyribonucleoside; and Y is 0;

h) X is 10; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}-N^{R5}-N^{R6}-N^{R7}-N^{R8}-N^{R9}-N^{R10}, wherein each of N^{R1}, N^{R2}, N^{R3}, N^{R4}, N^{R5}, and N^{R6} is 2'-O-methoxyethyl nucleoside, each of N^{R7} and N^{R9} is a an S-cEt nucleoside; and each of N^{R8} and N^{R10} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
Y is 1 and N_Z is a 2'-O-methoxyethyl nucleoside;

i) X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein each of N^{R1} and N^{R4} is an S-cEt nucleoside, and each of N^{R1} and N^{R3} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
Y is 1 and N^Z is a β-D-deoxyribonucleoside;

j) X is 4; $(R)_X$ is N^{R1}-N^{R2}-N^{R3}-N^{R4}, wherein N^{R1} is a 2'-O-methoxyethyl nucleoside, each of N^{R2} and N^{R4} is an S-cEt nucleoside, and N^{R3} is a β-D-deoxyribonucleoside;
each N^B is an S-cEt nucleoside;
each N^Q is a β-D-deoxyribonucleoside;
Y is 1 and N^Z is a 2'-O-methoxyethyl nucleoside.

24. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% complementary to the nucleobase sequence of miR-122 (SEQ ID NO: 1).

25. The compound of any one of the preceding claims, wherein at least one internucleoside linkage is a modified internucleoside linkage, or wherein each internucleoside linkage is a modified internucleoside linkage, and, optionally, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

26. The compound of any one of the preceding claims, wherein the nucleobase sequence of the modified oligonucleotide is selected from SEQ ID NOs: 3 to 6, wherein each T is independently selected from T and U.

~~27. The compound of any one of the preceding claims, wherein the modified oligonucleotide has 0, 1, 2, or 3 mismatches with respect to the nucleobase sequence of miR-122.~~

~~28.~~1. ~~The compound of claim 1 having the~~ structure:

$A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$~~;~~ (SEQ ID NO: 4),

~~a) $C_SCA_STTGU_SC_SAC_SAC_STC_SC_SA$;~~

~~b) $^{Me}C_SCAT_STGT_S{}^{Me}C_SA{}^{Me}C_SA{}^{Me}C_ST{}^{Me}C_S{}^{Me}C_SA_E$;~~

~~c) $A_E{}^{Me}C_EA_E{}^{Me}C_ECA_STTGU_SC_SAC_SAC_STC_SC_S$;~~

~~d) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_STTGU_SC_SAC_SAC_STC_SC_S$;~~

~~e) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$;~~

~~f) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_S$~~

~~g) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_ST_E$;~~

~~h) $C_SCAU_STGU_SC_SAC_SAC_STC_SC_SA$; or~~

~~i) $^{Me}C_EC_SAU_STGU_SC_SAC_SAC_STC_SC_SA_E$~~

wherein the superscript "Me" indicates 5-methylcytosine~~;~~, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides~~;~~, nucleosides followed by a subscript "E" are 2'-MOE nucleosides~~;~~, nucleosides followed by a subscript "S" are S-cEt nucleosides~~;~~, and each internucleoside linkage is a phosphorothioate internucleoside linkage.

~~29.~~2. The compound of ~~any one of the preceding claims~~claim 1, wherein the compound comprises a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide.

~~30.~~ The compound of claim ~~, wherein the compound comprises a conjugate moiety linked to the 3' terminus of the modified oligonucleotide.~~

~~31. The compound of claim , wherein the compound comprises a conjugate moiety linked to the 5' terminus of the modified oligonucleotide.~~

~~32. The compound of claim 29, wherein the compound comprises a first conjugate moiety linked to the 3' terminus of the modified oligonucleotide and a second conjugate moiety linked to the 5' terminus of the modified oligonucleotide.~~

~~33. The compound of any one of claims 29 to , wherein the conjugate moiety comprises at least one ligand selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid.~~

~~34.~~3. ~~The compound of any one of claims to 33~~2, wherein the compound has the structure:

~~L_n-linker-MO~~

~~wherein each L is, independently, a ligand and n is from 1 to 10; and MO is a modified oligonucleotide.~~

~~35. The compound of any of one claims 29 to 33, wherein the compound has the structure:~~

~~L_n-linker-X-MO~~

~~wherein each L is, independently, a ligand and n is from 1 to 10; X is a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.~~

~~36. The compound of any one of claims to 33, wherein the compound has the structure:~~

L_n-linker-X_1-N_m-X_2-MO

wherein each L is, independently, a ligand and n is ~~from 1 to 10~~3; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is ~~a~~the modified oligonucleotide.

~~37.~~4. The compound of ~~any one of claims to 33~~claim 3, wherein the compound has the structure:

~~L_n-linker-X-N_m-Y-MO~~

~~wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X is a phosphodiester linkage or a phosphorothioate linkage; Y is a phosphodiester linkage; and MO is a modified oligonucleotide.~~

~~38. The compound of any one of claims to 33, wherein the compound has the structure:~~

~~L_n-linker-Y-N_m-Y-MO~~

~~wherein each L is, independently, a ligand and n is from 1 to 10; each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; each Y is a phosphodiester linkage; and MO is a modified oligonucleotide.~~

~~39. The compound of any of claims 34 to 38, wherein if n is greater than 1, L_n linker has the structure:~~

~~L Q' S Q"~~
~~n~~

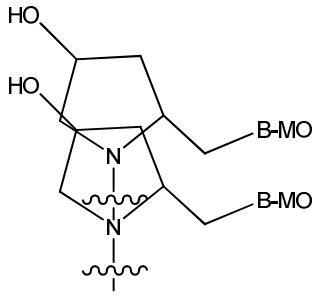
~~wherein each L is, independently, a ligand; n is from 1 to 10; S is a scaffold; and Q' and Q" are, independently, linking groups.~~

~~40. The compound of claim 39, wherein Q' and Q" are each independently selected from a peptide, an ether, polyethylene glycol, an alkyl, a C_1-C_{20} alkyl, a substituted C_1-C_{20} alkyl, a C_2-C_{20} alkenyl, a substituted C_2-C_{20} alkenyl, a C_2-C_{20} alkynyl, a substituted C_2-C_{20} alkynyl, a C_1-C_{20} alkoxy, a substituted C_1-C_{20} alkoxy, amino, amido, a pyrrolidine, 8-amino-3,6-dioxaoctanoic acid (ADO), succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate, and 6-aminohexanoic acid.~~

~~41. The compound of claim 39 or 40, wherein the scaffold links 2, 3, 4, or 5 ligands to a modified oligonucleotide.~~

~~42. The compound of claim 41, wherein the scaffold links 3 ligands to a modified oligonucleotide.~~

~~43. The compound of any one of claims to 42, wherein the compound has the structure:~~



wherein:

B is selected from –O-, -S-, -N(R^N)-, –Z-P(Z')(Z")O-, –Z-P(Z')(Z")O-N_m-X-, and –Z-P(Z')(Z")O-N_m-Y-;

MO is ~~a~~the modified oligonucleotide;

R^N is selected from H, methyl, ethyl, propyl, isopropyl, butyl, and benzyl;

Z, Z', and Z" are each independently selected from O and S;

each N is, independently, a modified or unmodified nucleoside;

m is from 1 to 5;

X is selected from a phosphodiester linkage and a phosphorothioate linkage;

Y is a phosphodiester linkage; ~~and~~

each ligand is N-acetylgalactosamine; and

the wavy line indicates the connection to the rest of the linker and ligand(s).

~~44.~~ The compound of ~~any one of claims 35, 37, 39 and 43, wherein X is a phosphodiester linkage.~~

~~45. The compound of any one of claims to , wherein n is from 1 to 5, 1 to 4, 1 to~~claim 3~~,~~ or ~~1 to 2.~~

~~46. The compound of any of of claims to , wherein n is 3.~~

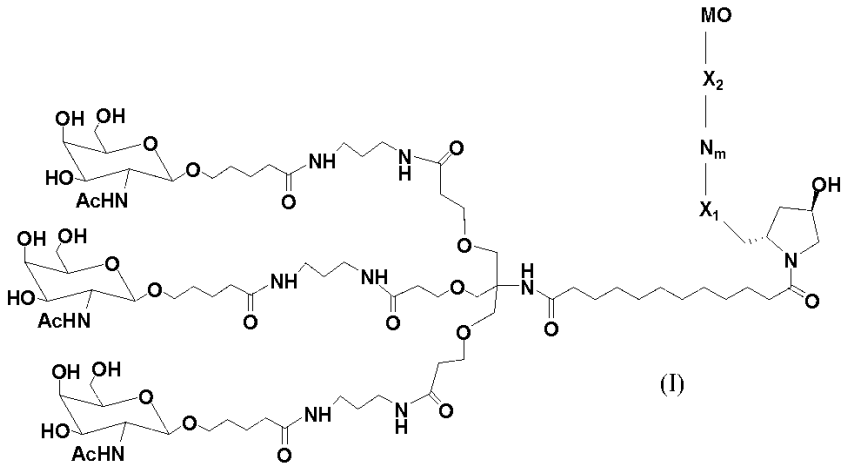
~~47. The compound of any one of claims to , wherein at least one ligand is a carbohydrate.~~

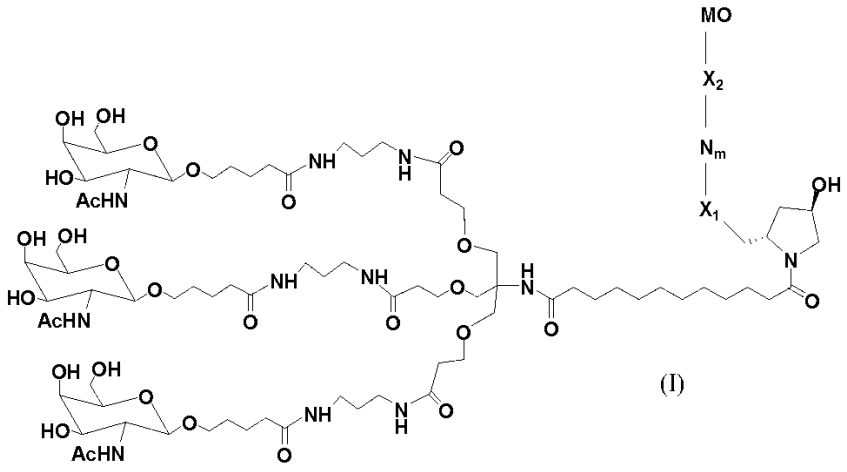
~~48. The compound of any one of claims to , wherein at least one ligand is selected from mannose, glucose, galactose, ribose, arabinose, fructose, fucose, xylose, D-mannose, L-mannose, D-galactose, L-galactose, D-glucose, L-glucose, D-ribose, L-ribose, D-arabinose, L-arabinose, D-fructose, L-fructose, D-fucose, L-fucose, D-xylose, L-xylose, alpha-D-mannofuranose, beta-D-mannofuranose, alpha-D-mannopyranose, beta-D-mannopyranose, alpha-D-glucofuranose, Beta-D-glucofuranose, alpha-D-glucopyranose, beta-D-glucopyranose, alpha-D-galactofuranose, beta-D-galactofuranose, alpha-D-galactopyranose, beta-D-galactopyranose, alpha-D-ribofuranose, beta-D-ribofuranose, alpha-D-ribopyranose, beta-D-ribopyranose, alpha-D-fructofuranose, alpha-D-fructopyranose, glucosamine, galactosamine, sialic acid, N-acetylgalactosamine.~~

~~49. The compound of any one of claims to , wherein at least one ligand is selected from N-acetylgalactosamine, galactose, galactosamine, N-formylgalactosamine, N-propionyl-galactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.~~

~~50. The compound of any one of claims to , wherein each ligand is N-acetylgalactosamine.~~

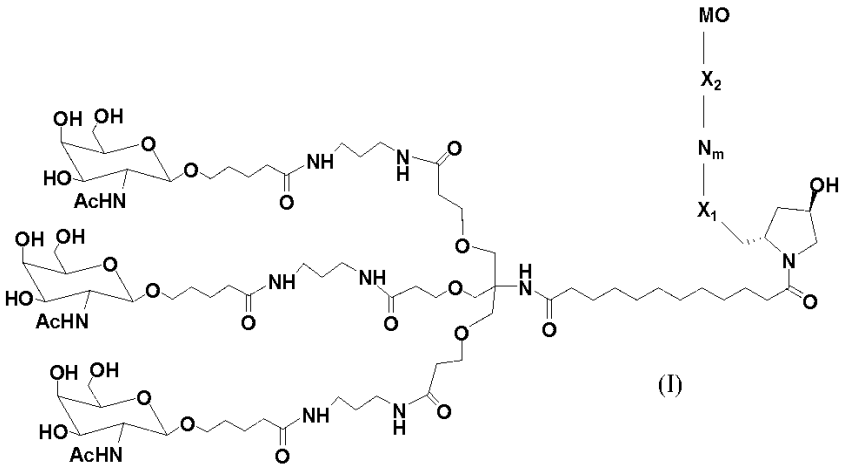
~~51.~~5. ~~The compound of any one of claims to ,~~claim 4, wherein the compound has the structure:





wherein each N <u>of N_m</u> is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is ~~a modified oligonucleotide.~~

~~52. A compound comprising a modified nucleotide and a conjugate moiety, wherein~~ the modified oligonucleotide ~~has the structure $C_LCA_LTTG_LT_LCAC_LAC_LTC_LC_L$, wherein the subscript "L" indicates an LNA and nucleosides not followed by a subscript are β-D-deoxyribonucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage, and wherein the conjugate moiety is linked to the 3' terminus of the modified oligonucleotide and has the structure:~~.



~~wherein each N is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is a modified oligonucleotide.~~

~~53. The compound of claim or claim or , wherein at least one of X_1 and X_2 is a phosphodiester linkage.~~

~~54. The compound of any one of claims to , wherein each of X_1 and X_2 is a phosphodiester linkage.~~

~~55. The compound of any one of claims to , wherein m is 1.~~

~~56. The compound of any one of claims to , wherein m is 2, 3, 4, or 5.~~

~~57. The compound of any one of claims to , wherein N_m is N'$_p$N", wherein each N' is, independently, a modifid or unmodified nucleoside and p is from 0 to 4; and N" is a nucleoside comprising an unmodified sugar moiety.~~

~~58.~~ 6. The compound of claim ~~,~~5, wherein ~~p~~each of X_1 and X_2 is ~~0~~a phosphodiester linkage.

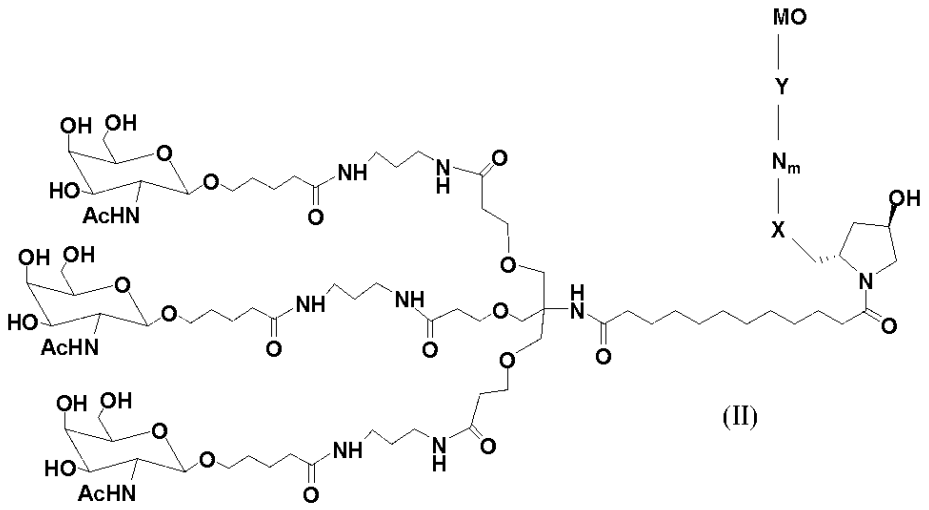
~~59. The compound of claim , wherein p is 1, 2, 3, or 4.~~

7. The compound of any one of claims ~~55~~3 to ~~,~~6, wherein m is 1.

~~60.~~ 8. The compound of any one of claims 4 to 7, wherein each ~~N'~~N comprises an unmodified sugar moiety~~.~~

~~61. The compound of any one of claims to ,~~ wherein each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose.

~~62.~~ 9. ~~The~~A compound of ~~any one of claims to ,~~ the structure:



(II)

wherein ~~N" comprises~~X is a ~~purine nucleobase.~~

~~63. The compound~~phosphodiester linkage; m is 1; N of ~~any one of claims to , wherein N" comprises a pyrimidine nucleobase.~~

~~64. The compound of any one of claims or to , wherein at least one N' comprises a purine nucleobase.~~

~~65. The compound of claim 62 or 64, wherein each purine nucleobase is independently selected from adenine, guanine, hypoxanthine, xanthine, and 7-methylguanine.~~

~~66. The compound of any one of claims to 62, 64, and 65, wherein N"~~N_m is a β-D-deoxyriboadenosine~~ or a β-D-deoxyriboguanosine.~~

~~67. The compound of any one of claims or to 66, wherein at least one N' comprises a pyrimidine nucleobase.~~

~~68. The compound of claim 63 or , wherein each pyrimidine nucleobase is independently selected from cytosine, 5-methylcytosine, thymine, uracil, and 5,6-dihydrouracil.~~

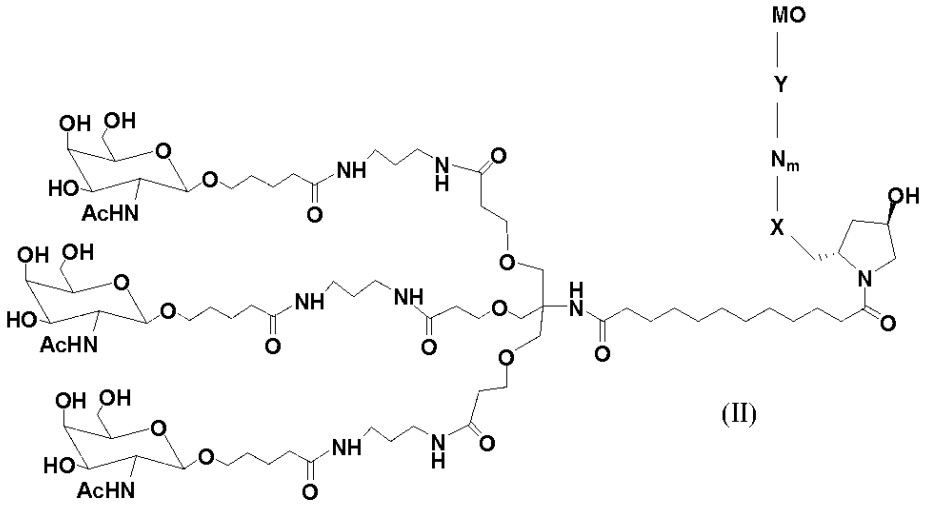
~~69. The compound of any one of claims to , wherein the sugar moiety of each N;~~ Y is ~~independently selected from a β-D-ribose, a β-D-deoxyribose, a 2'-O-methoxy sugar, a 2'-O-methyl sugar, a 2'-fluoro sugar, and a bicyclic sugar moiety.~~

~~70. The compound of claim , wherein each bicyclic sugar moiety is independently selected from a cEt sugar moiety, an LNA sugar moiety, and an ENA sugar moiety.~~

~~71. The compound of claim ,~~a phosphodiester linkage; and MO is a modified oligonucleotide consisting of less than 16 linked nucleosides, wherein the ~~cEt sugar moiety~~nucleobase sequence of the modified oligonucleotide comprises a nucleobase sequence that is ~~an S-cEt sugar moiety.~~

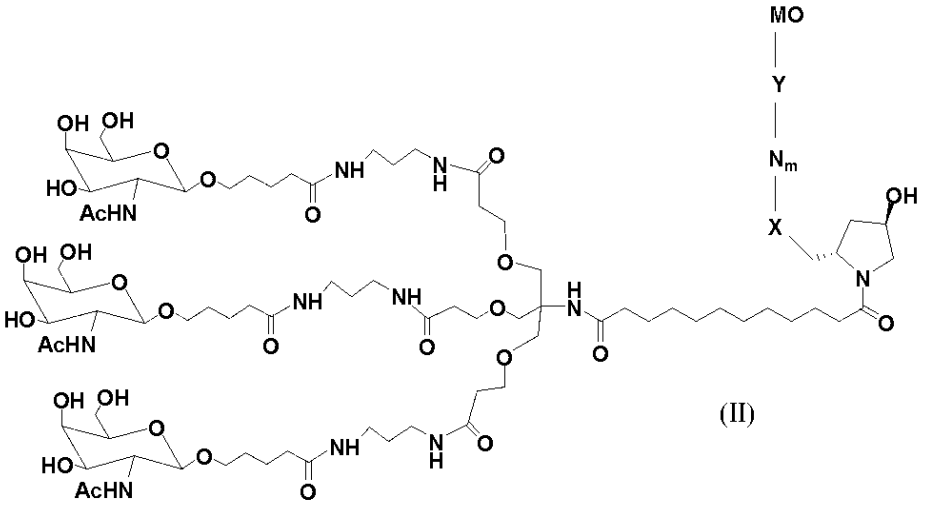
~~72. The compound of claim , wherein the cEt sugar moiety is an R-cEt sugar moiety.~~

~~73. A compound comprising a modified nucleotide and a conjugate moiety,~~ complementary to nucleobases 2 to 9 of miR-122 (SEQ ID NO: 1) and wherein the modified oligonucleotide ~~has~~comprises at least 8 contiguous nucleosides of the structure $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage; and wherein ~~the conjugate moiety~~Y is linked to the 3' terminus of the modified oligonucleotide ~~and has the structure:~~.



~~wherein X is a phosphodiester linkage; m is 1; N is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is the modified oligonucleotide.~~

~~74. A compound comprising a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $C_LCA_LTTG_LT_LCAC_LAC_LTC_LC_L$, wherein the subscript "L" indicates an LNA and nucleosides not followed by a subscript are β-D-deoxyribonucleosides, and each internucleoside linkage is a phosphorothioate internucleoside linkage, and wherein the conjugate moiety is linked to the 3' terminus of the modified oligonucleotide and has the structure:~~



~~wherein X is a phosphodiester linkage; m is 1; N is a β-D-deoxyriboadenosine; Y is a phosphodiester linkage; and MO is the modified oligonucleotide.~~

~~75. A method of inhibiting the activity of miR-122 in a cell comprising contacting a cell with a compound of one any one of claims 1 to .~~

~~76. The method of claim , wherein the cell is *in vivo*.~~

~~77. The method of claim , wherein the cell is *in vitro*.~~

~~78. A method comprising administering to an HCV-infected subject a compound of any one of claims 1 to 74.~~

~~79.~~ 10. ~~The method of~~ A pharmaceutical composition comprising the compound of claim 9 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, which is a sterile aqueous solution.

12. Use of the compound of claim 9, or the pharmaceutical composition of claim 10 or claim 11, in the manufacture of a medicament for treating a hepatitis C virus (HCV)-infected human subject.

13. The use of claim 12 wherein the ~~administering~~medicament reduces the symptoms of HCV infection~~.~~

~~80. The method of claim or claim wherein the administering,~~ prevents a rebound in serum HCV RNA~~.~~

~~81. The method of claim or claim wherein the administering~~, and/or delays a rebound in serum HCV RNA.

14. ~~The method~~ The use of claim 12 or claim 13, wherein the medicament reduces HCV RNA level.

~~82.~~ 15. The use of any one of claims 12 to ~~comprising selecting~~14, wherein the ~~method~~use achieves a ~~subject having HCV infection~~sustained virological response.

~~83.~~ 16. The ~~method~~use of any one of claims 12 to 15, wherein the subject is infected with one or more HCV genotypes selected from genotype 1, genotype 2, genotype 3, genotype 4, genotype 5, and genotype 6.

~~84. The method of any one of claims to wherein prior to administration of the compound, the subject was determined to be infected with one or more HCV genotypes selected from genotype 1, genotype 2, genotype 3, genotype 4, genotype 5, and genotype 6.~~

~~85.~~17. ~~The method of claim or claim ,~~The use of claim 16, wherein the HCV genotype is selected from genotype 1a, genotype 1b, genotype 2a, genotype 2b, genotype 2c, genotype 2d, genotype 3a, genotype 3b, genotype 3c, genotype 3d, genotype 3e, genotype 3f, genotype 4a, genotype 4b, genotype 4c, genotype 4d, genotype 4e, genotype 4f, genotype 4g, genotype 4h, genotype 4i, genotype 4j, genotype 5a, and genotype 6a.

~~86.~~ 18. The ~~method of claim or claim , wherein the HCV genotype is selected from genotype 1a, 1b, and 2.~~

~~87. The method~~use of any one of claims 12 to ~~, comprising administering~~ 17, wherein the medicament is for administration with at least one additional therapeutic agent.

~~88. The method of any one of claims to , wherein the subject is infected with an HCV variant that is resistant to at least one therapeutic agent.~~

~~89.~~19. ~~The method of claim or claim ,~~The use of claim 18, wherein the at least one therapeutic agent is selected from a protease inhibitor, a polymerase inhibitor, a cofactor inhibitor, an RNA polymerase inhibitor, a structural protein inhibitor, a non-structural protein inhibitor, a cyclophilin inhibitor, an entry inhibitor, a TLR7 agonist, ~~and an interferon.~~

~~90. The method of claim or claim , wherein the at least one therapeutic agent is selected from a protease inhibitor,~~ an NS5A inhibitor, an NS3/4A inhibitor, a nucleoside NS5B inhibitor, a nucleotide NS5B inhibitor, a non-nucleoside NS5B inhibitor, ~~a cyclophilin inhibitor~~ and an interferon.

~~91.~~20.The ~~method~~use of claim ~~or claim~~ 18, wherein the at least one therapeutic agent is selected from interferon alfa-2a, interferon alpha-2b, interferon alfacon-1, peginterferon alpha-2b, peginterferon alpha-2a, interferon-alpha-2b extended release, interferon lambda, sofosbuvir,

ledipasvir, ribavirin, telapravir, boceprevir, vaniprevir, asunaprevir, ritonavir, setrobuvir, daclastavir, simeprevir, alisporivir, mericitabine, tegobuvir, danoprevir, sovaprevir, and neceprevir.

~~92.~~21. The ~~method~~use of claim ~~or claim~~ 20, wherein the at least one therapeutic agent is ~~selected from an interferon, ribavirin, and telapravir~~sofosbuvir.

~~93.~~22. The ~~method~~use of ~~any one of claims to~~ claim 20, wherein the ~~subject~~at least one therapeutic agent is ~~a non-responder to~~ sofosbuvir and ledipasvir.

23. The use of claim 20, wherein the at least one therapeutic agent~~.~~ is daclatasvir.

~~94. The method of claim wherein the subject is an interferon non-responder.~~

~~95.~~ 24. The ~~method~~use of claim ~~or claim~~ 20, wherein the at least one therapeutic agent is simeprevir.

25. The use of any one of claims 12 to 24, wherein the subject is a direct-acting anti-viral non-responder.

~~96. The method of any one of claims to comprising selecting a subject having a HCV RNA level greater than 350,000 copies per milliliter of serum.~~

~~97.~~ 26. The ~~method of any one of claims to comprising selecting a subject having a HCV RNA level between 350,000 and 3,500,000 copies per milliliter of serum.~~

~~98. The method~~use of any one of claims ~~to comprising selecting a subject having a HCV RNA level greater than 3,500,000 copies per milliliter of serum.~~

~~99. The method of any one of claims to~~ 12 to 25, wherein the subject has an HCV-associated disease~~.~~

~~100. The method of claim~~ , wherein the HCV-associated disease is optionally selected from cirrhosis, liver fibrosis, steatohepatitis, steatosis, ~~or~~and hepatocellular carcinoma.

~~101.~~ 27. The ~~method~~use of any one of claims 12 to ~~comprising administering a dose of the compound sufficient to reduce HCV RNA level.~~

~~102. The method of claim comprising administering a dose of the compound that reduces HCV RNA level below 40 copies per ml of serum.~~

~~103. The method of claim comprising administering a dose of the compound sufficient to achieve at least a 2-log reduction in HCV RNA level.~~

~~104. The method of any one of claims to~~ 26, wherein the ~~administering achieves a sustained virological response.~~

~~105. The method of any one of claims to comprising administering a dose of the compound sufficient to achieve an HCV RNA level reduction of at least 0.5 fold, at least 1.0 fold, at least 1.5 fold, at least 2.0 fold,~~ compound or ~~at least 2.5 fold.~~

~~106. The method of claim wherein the HCV RNA level reduction~~pharmaceutical composition is ~~achieved after two weeks, three weeks, four weeks, five weeks, or six weeks of a first administration of the compound.~~

~~107. The method of any one of claims to wherein the compound is~~to be administered once per week, once per two weeks, once per three weeks, once per month, once per two months, or once per three months.

~~108.~~ 28. The ~~method~~use of any one of claims 12 to ~~,~~27, wherein the dose of the compound or conjugate is less than or equal to 10 mg/kg, less than or equal to 7.5 mg/kg, less than or equal to 5 mg/kg per week, less than or equal to 4.5 mg/kg, less than or equal to 4.0 mg/kg, less than or equal to 3.5 mg/kg, less than or equal to 3.0 mg/kg, less than or equal to 2.5 mg/kg, less than or equal to 2.0 mg/kg, less than or equal to 1.5 mg/kg, or less than or equal to 1.0 mg/kg.

~~109. The method of any one of claims to wherein the administering normalizes liver enzyme levels, wherein the liver enzyme is optionally alanine aminotransferase.~~

~~110. The method of any one of claims to wherein the subject is a human.~~

~~111. The method of any one of claims to wherein the compound is present in a pharmaceutical composition.~~

~~112. A compound of any one of claims 1 to 74, for use in therapy.~~

~~113. A compound of any one of claims 1 to 74, for use in treating an HCV-infected subject.~~

~~114. A compound for use according to claim 113, wherein the subject is a human.~~