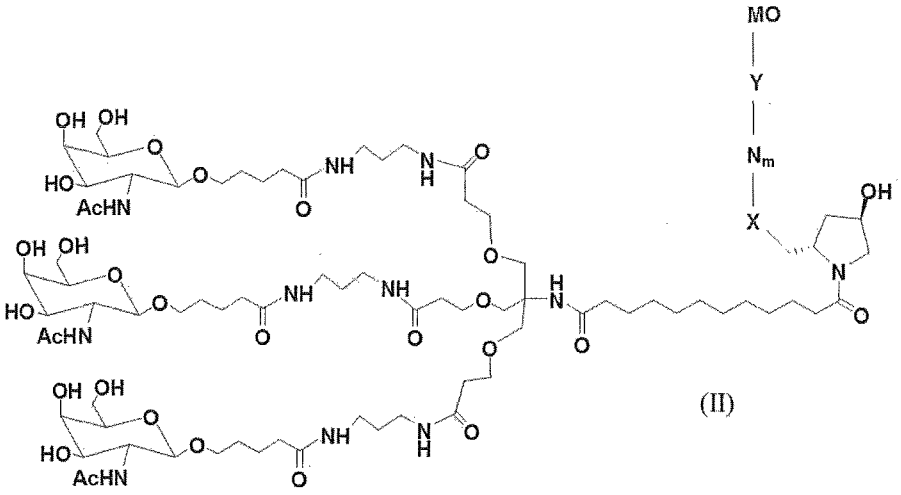
emergence of resistance mutations in HCV requires treatment with additional agents. Developing therapies include NS3/4A protease inhibitors, NS5A protein inhibitors, nucleoside/tide NS5B polymerase inhibitors and non-nucleoside NS5B inhibitors. However, there remains a need for additional therapies to 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 invention refers to a compound 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-NQ-NQ-NB-NB-NQ-NB-NQ-NB-NQ-NB-NB-(NZ)Y, wherein each R is, independently, a non-bicyclic nucleoside or a bicyclic nucleoside; X is from 4 to 10; each NB is, independently, a bicyclic nucleoside; each NQ is, independently, a non-bicyclic nucleoside; Y is 0 or 1; and NZ is a modified nucleoside or an unmodified nucleoside. In another aspect, the present invention refers to a compound of 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 a modified oligonucleotide 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), 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 another aspect, the present invention refers to a pharmaceutical composition comprising the compound as described herein and a pharmaceutically acceptable carrier. In a further aspect, the present invention refers to use of a compound as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating an 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 examples~~embodiments~~, each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside. In certain examples~~embodiments~~, at least two bicyclic nucleosides are different from one another. In certain examples~~embodiments~~, all bicyclic nucleosides have the same sugar moiety as one another. In certain examples~~embodiments~~, each bicyclic nucleoside is a cEt nucleoside. In certain examples~~embodiments~~, a cEt nucleoside is an S-cEt nucleoside. In certain examples~~embodiments~~, a cEt nucleoside is an R-cEt nucleoside. In certain examples~~embodiments~~, each bicyclic nucleoside is an LNA nucleoside.

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

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

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

In certain examples~~embodiments~~ 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, the compound comprises a conjugate moiety linked to the 3' terminus of the modified oligonucleotide. In certain examples~~embodiments~~, the compound comprises a conjugate moiety linked to the 5' terminus of the modified oligonucleotide. In certain examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, if n is greater than 1, L_n-linker has the structure:

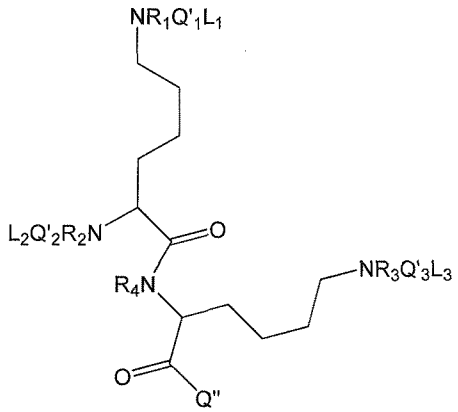
$$\left(L-Q'\right)_n S-Q''-$$

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 examples~~embodiments~~, 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 examples~~embodiments~~, a scaffold links 2, 3, 4, or 5 ligands to a modified oligonucleotide. In certain embodiments, a scaffold links 3 ligands to a modified oligonucleotide.

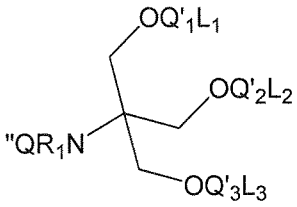
A nonlimiting exemplary Structure E is Structure E(i):



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 examplesembodiments, 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 examplesembodiments, R_1, R_2, R_3, and R_4 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examplesembodiments, R_1, R_2, R_3, and R_4 are each selected from H and methyl.

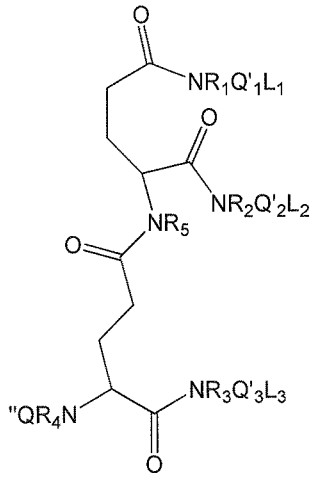
A further nonlimiting exemplary Structure E is Structure E(ii):



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 examplesembodiments, 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 examplesembodiments, R_1 is selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examplesembodiments, R_1 is H or methyl.

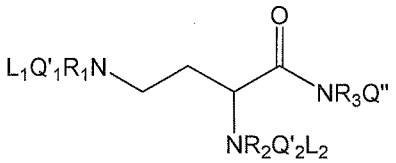
A further nonlimiting exemplary Structure E is Structure E(iii):



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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments R_1, R_2, R_3, R_4, and R_5 are each selected from H and methyl.

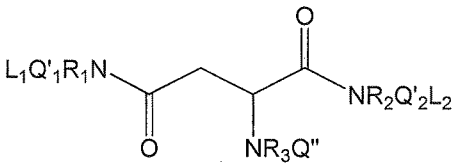
A further nonlimiting exemplary Structure E is Structure E(iv):



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 examplesembodiments, 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 examplesembodiments, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examplesembodiments R_1, R_2, and R_3 are each selected from H and methyl.

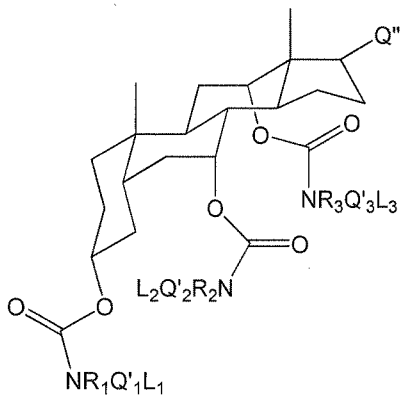
A further nonlimiting exemplary Structure E is Structure E(v):



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 examples~~embodiments~~, 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 examples~~embodiments~~, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examples~~embodiments~~ R_1, R_2, and R_3 are each selected from H and methyl.

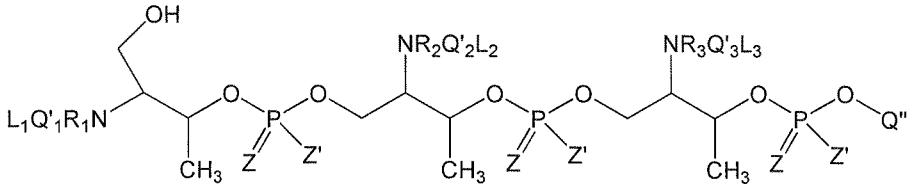
A further nonlimiting exemplary Structure E is Structure E(vi):



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 examples~~embodiments~~, 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 examples~~embodiments~~, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examples~~embodiments~~ R_1, R_2, and R_3 are each selected from H and methyl.

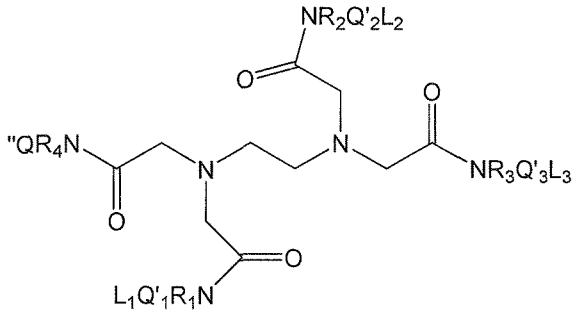
A further nonlimiting exemplary Structure E is Structure E(vii):



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 examples~~embodiments~~, 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 examples~~embodiments~~, R_1, R_2, and R_3 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examples~~embodiments~~ R_1, R_2, and R_3 are each selected from H and methyl. In some examples~~embodiments~~, 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 examples~~embodiments~~, each –OP(Z)(Z')O- is a phosphorothioate linkage. In some examples~~embodiments~~, Z and Z' are both O on at least one P atom (i.e., a phosphodiester linkage). In some examples~~embodiments~~, each –OP(Z)(Z')O- is a phosphodiester linkage.

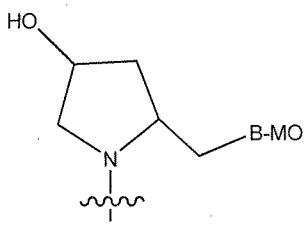
A further nonlimiting exemplary Structure E is Structure E(viii):



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 examples~~embodiments~~, 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 examples~~embodiments~~, R_1, R_2, R_3, and R_4 are each, independently, selected from H, methyl, ethyl, propyl, isopropyl, and butyl. In some examples~~embodiments~~ 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 examples~~embodiments~~, 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 examples~~embodiments~~, X is a phosphodiester linkage.

In certain examples~~embodiments~~, n is from 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In certain examples~~embodiments~~, n is 3.

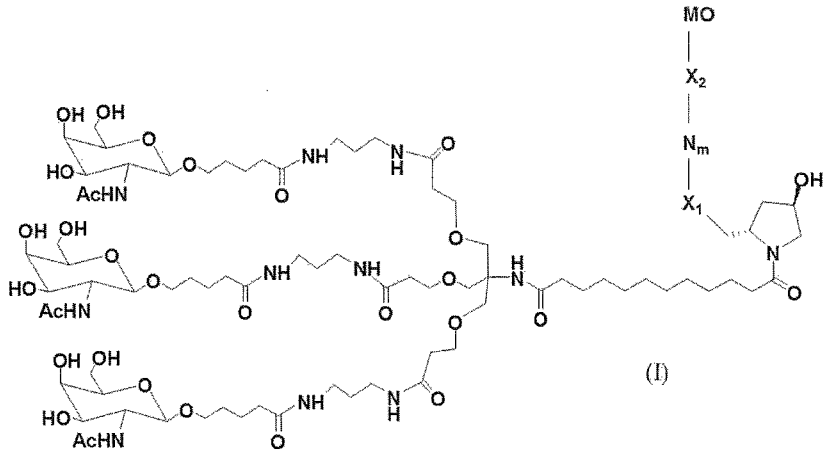
In certain examples~~embodiments~~, at least one ligand is a carbohydrate.

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

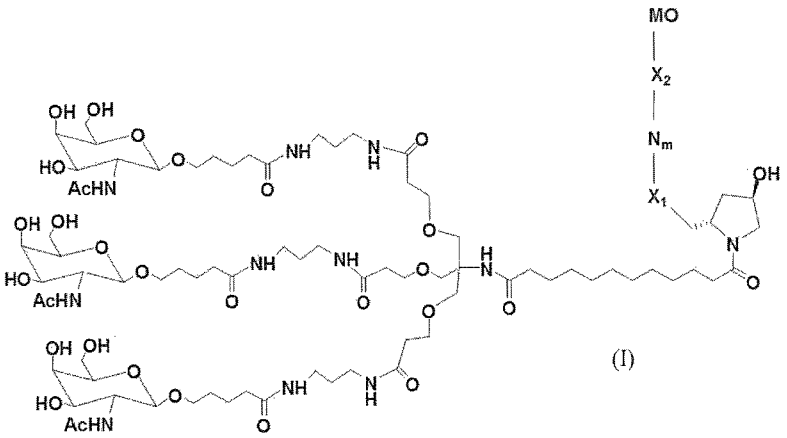
In certain examples~~embodiments~~, each ligand is N-acetylgalactosamine.

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

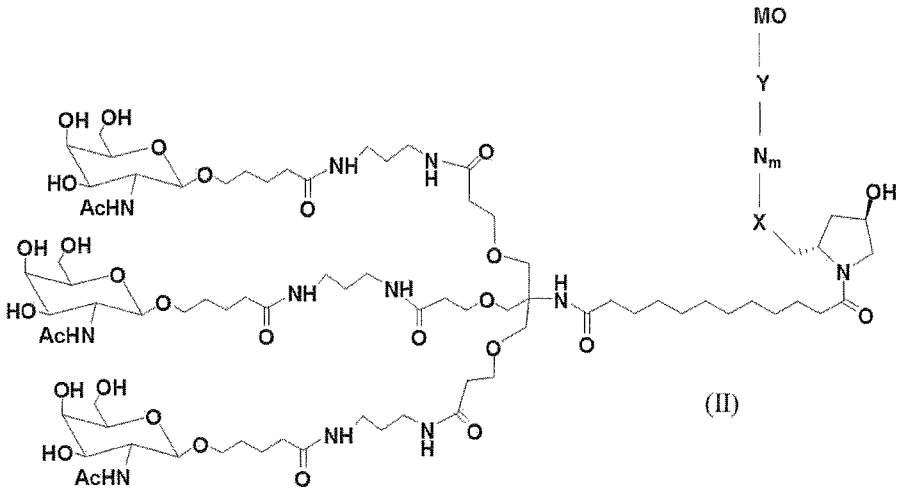
In certain examples~~embodiments~~, N_m is N'_pN'', wherein each N' is, independently, a modifid or unmodified nucleoside and p is from 0 to 4; and N" is a nucleoside comprising an unmodified sugar moiety. In certain examples~~embodiments~~, p is 0. In certain examples~~embodiments~~, p is 1, 2, 3, or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

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

certain examplesembodiments, each pyrimidine nucleobase is independently selected from cytosine, 5-methylcytosine, thymine, uracil, and 5,6-dihydrouracil.

In any of the examplesembodiments 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 examplesembodiments, each bicyclic sugar moiety is independently selected from a cEt sugar moiety, an LNA sugar moiety, and an ENA sugar moiety. In certain examplesembodiments, a cEt sugar moiety is an S-cEt sugar moiety. In certain examplesembodiments, a cEt sugar moiety is an R-cEt sugar moiety. In any examplesembodiments 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.

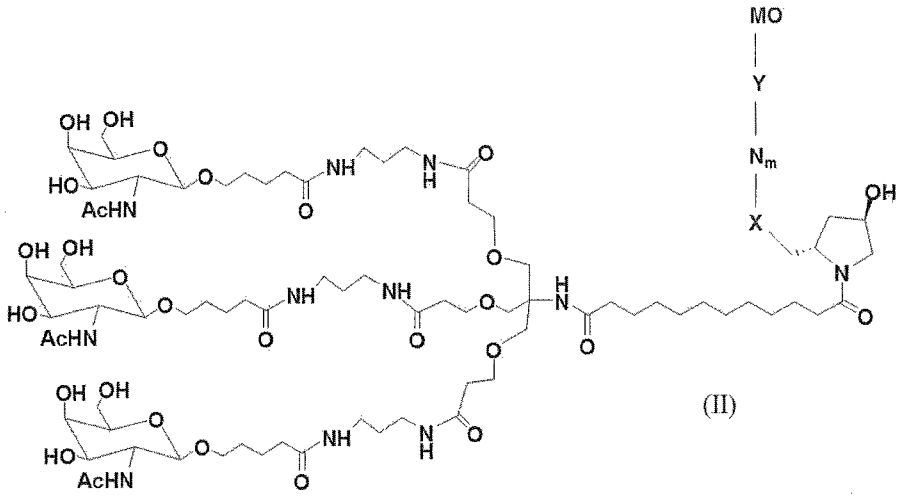
Provided herein are compounds comprising a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$ (SEQ ID NO: 4), wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, 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 examples~~embodiments~~, 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 examples~~embodiments~~, the cell is cell is *in vivo*. In certain examples~~embodiments~~, cell is *in vitro*.

Provided herein are methods of administering to an HCV-infected subject any of the compouds provided herein. In certain examples~~embodiments~~, the administering reduces the symptoms of HCV infection. In certain examples~~embodiments~~, the administering prevents a rebound in serum HCV RNA. In certain examples~~embodiments~~, the administering delays a rebound in serum HCV RNA. In certain examples~~embodiments~~, a subject having HCV infection is selected for treatment with a compound provided herein. In certain examples~~embodiments~~, 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 examples~~embodiments~~, 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 examples~~embodiments~~, 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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, the at least one therapeutic agent is selected from an interferon, ribavirin, and telapravir.

In certain examplesembodiments, a subject is infected with an HCV variant that is resistant to at least one therapeutic agent. In certain examplesembodiments, a subject is infected with an HCV variant that is resistant to a direct-acting anti-viral agent. In certain examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, an HCV-infected subject is a non-responder to at least one therapeutic agent. In certain examplesembodiments, an HCV-infected subject is an interferon non-responder. In certain examplesembodiments, 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 examplesembodiments, a subject has an HCV RNA level between 350,000 and 3,500,000 copies per milliliter of serum. In certain examplesembodiments, a subject has an HCV RNA level greater than 3,500,000 copies per milliliter of serum.

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

In certain examplesembodiments, an HCV-infected subject has one or more diseases that are not HCV-associated diseases. In certain examplesembodiments, an HCV-infected subject is infected with one or more viruses other than HCV. In certain examplesembodiments, an HCV-infected subject is infected with human immunodeficiency virus (HIV). In certain examplesembodiments, the methods provided herein comprise administering an additional therapeutic agent is an anti-viral agent used in the treatment of HIV infection. In certain examplesembodiments, an additional therapeutic agent is a non-nucleoside reverse transcriptase inhibitors (NNRTIs). In certain examplesembodiments, an additional therapeutic agent is a nucleoside reverse transcriptase inhibitors (NRTIs). In certain examplesembodiments, an additional therapeutic agent is a protease inhibitor. In certain examplesembodiments, an additional therapeutic agent is an entry inhibitor or fusion inhibitor. In certain examplesembodiments, an additional therapeutic agent is an integrase inhibitor. In certain examplesembodiments, 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 examplesembodiments, the administered dose of the compound reduces HCV RNA level below 40 copies per ml of serum. In certain examplesembodiments, the administered dose of the compound achieves at least a 2-log reduction in HCV RNA level. In certain examplesembodiments, administering a compound provided herein achieves a sustained virological response. In certain examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, a compound provided herein is administered once per two months or once per three months. In some examplesembodiments, a compound provided herein is administered once per four weeks.

In certain examplesembodiments, 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

~~embodiments~~examples, 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 examples~~embodiments~~, 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 examples~~embodiments~~, administration of a compound provided herein normalizes liver enzyme levels, wherein the liver enzyme is optionally alanine aminotransferase.

In any of the examples~~embodiments~~ provided herein, the compound is present in a pharmaceutical composition.

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

In certain examples~~embodiments~~, 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

CLAIMS

1. A compound 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.

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 claim 3, wherein each bicyclic nucleoside is a cEt nucleoside.

5. The compound of claim 4, wherein the cEt nucleoside is an S-cEt nucleoside.

6. 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.

7. 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.

8. The compound of any one of the preceding claims, wherein each R is a 2'-MOE nucleoside.

9. 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.

10. 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.

11. 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.

12. 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.

13. The compound of claim 1 having the structure:

a) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$;

b) $C_SCA_STTGU_SC_SAC_SAC_STC_SC_SA$;

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

d) $A_E{}^{Me}C_EA_E{}^{Me}C_ECA_STTGU_SC_SAC_SAC_STC_SC_S$;

e) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_STTGU_SC_SAC_SAC_STC_SC_S$;

f) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$;

g) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_S$

h) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_ST_E$;

i) $C_SCAU_STGU_SC_SAC_SAC_STC_SC_SA$; or

j) $^{Me}C_EC_SAU_STGU_SC_SAC_SAC_STC_SC_SA_E$

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.

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

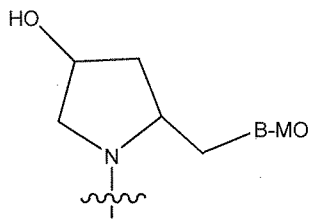
15. The compound of claim 14, wherein the conjugate moiety comprises at least one ligand selected from a carbohydrate, cholesterol, a lipid, a phospholipid, an antibody, a lipoprotein, a hormone, a peptide, a vitamin, a steroid, and a cationic lipid.

16. The compound of claim 14 or claim 15, 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; 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.

17. The compound of claim 16, 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 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

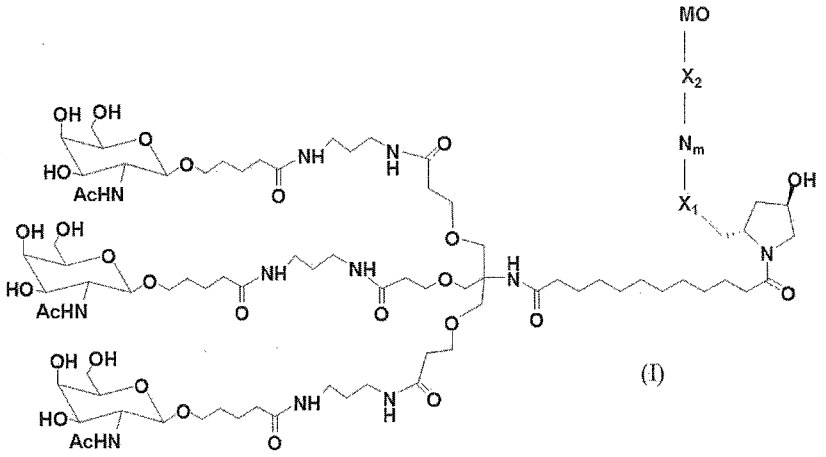
the wavy line indicates the connection to the rest of the linker and ligand(s).

18. The compound of any of claim 16 or claim 17, wherein n is 3.

19. The compound of any one of claims 16 to 18, wherein at least one ligand is a carbohydrate, and wherein the carbohydrate is optionally selected from N-acetylgalactosamine, galactose, galactosamine, N-formylgalactosamine, N-propionyl-galactosamine, N-n-butanoylgalactosamine, and N-iso-butanoyl-galactosamine.

20. The compound of any one of claims 16 to 19, wherein each ligand is N-acetylgalactosamine.

21. The compound of any one of claims 16 to 20, wherein the compound has the structure:



(I)

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.

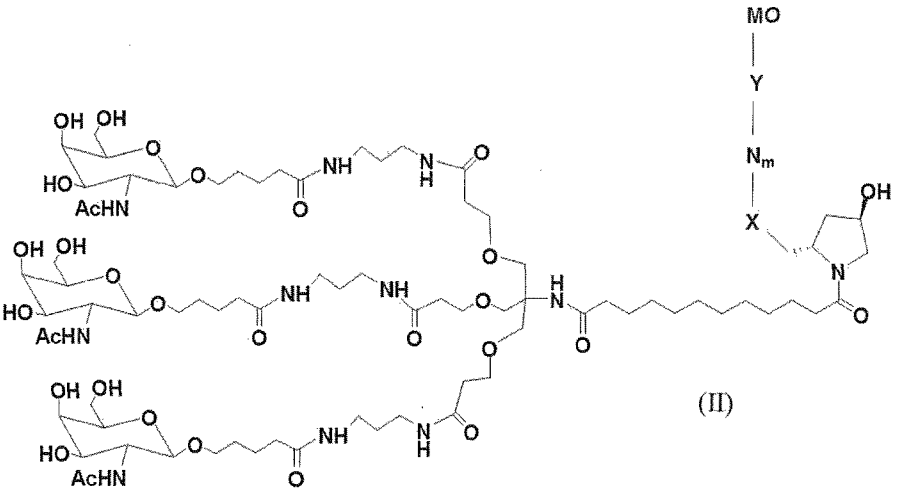
22. The compound of claim 21, wherein each of X_1 and X_2 is a phosphodiester linkage.

23. The compound of any one of claims 16 to 22, wherein m is 1.

24. The compound of any one of claims 21 to 23, wherein each N comprises an unmodified sugar moiety, wherein each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose.

25. The compound of any one of claims 21 to 24, wherein at least one N comprises a purine nucleobase, wherein each purine nucleobase is independently selected from adenine, guanine, hypoxanthine, xanthine, and 7-methylguanine.

26. A compound of 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 a modified oligonucleotide 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), 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.

27. A pharmaceutical composition comprising the compound of any one of claims 1 to 26 and a pharmaceutically acceptable carrier.

28. Use of a compound of any one of claims 1 to 26, or the pharmaceutical composition of claim 27, in the manufacture of a medicament for treating an HCV-infected human subject .

29. The use of claim 28 wherein the medicament reduces the symptoms of HCV infection, prevents a rebound in serum HCV RNA, and/or delays a rebound in serum HCV RNA.

30. The use of claim 28 or claim 29 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.

31. The use of claim 30, 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.

32. The use of any one of claims 28 to 31, comprising administering at least one additional therapeutic agent.

33. The use of claim 32, 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.

34. The use of claim 32, 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.

35. The use of claim 32 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, ribavirin, telapravir,

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

36. The use of any one of claims 28 to 35 wherein the subject is a direct-acting anti-viral non-responder.

37. The use of any one of claims 28 to 36 wherein the subject has an HCV-associated disease, wherein the HCV-associated disease is optionally selected from cirrhosis, liver fibrosis, steatohepatitis, steatosis, and hepatocellular carcinoma.

38. The use of any one of claims 28 to 37 wherein the compound, conjugate, or pharmaceutical composition is administered once per week, once per two weeks, once per three weeks, once per month, once per two months, or once per three months.

39. The use of any one of claims 28 to 38, 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.

What is claimed:

1. A compound 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.

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 5, wherein each bicyclic nucleoside is a cEt nucleoside.

7. The compound of claim 6, wherein the cEt nucleoside is an S-cEt nucleoside.

8. The compound of claim 6, wherein the cEt nucleoside is an R-cEt nucleoside.

9. The compound of claim 5, 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 9 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 18, 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. The compound of claim 1 having the structure:

a) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ET_ETGU_SC_SAC_SAC_STC_SC_S$;

b) $C_SCA_STTGU_SC_SAC_SAC_STC_SC_SA$;

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

d) $A_E{}^{Me}C_EA_E{}^{Me}C_ECA_STTGU_SC_SAC_SAC_STC_SC_S$;

e) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_STTGU_SC_SAC_SAC_STC_SC_S$;

f) $A_E{}^{Me}C_EA_E{}^{Me}C_E{}^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$;

g) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_S$

h) $^{Me}C_EA_EA_EA_E{}^{Me}C_EA_EC_SCA_STTGU_SC_SAC_SAC_STC_SC_ST_E$;

i) $C_SCAU_STGU_SC_SAC_SAC_STC_SC_SA$; or

j) $^{Me}C_EC_SAU_STGU_SC_SAC_SAC_STC_SC_SA_E$

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.

29. The compound of any one of the preceding claims, 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 29, wherein the compound comprises a conjugate moiety linked to the 3' terminus of the modified oligonucleotide.

31. The compound of claim 29, 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 32, 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. The compound of any one of claims 29 to 33, 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 29 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; 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.

37. The compound of any one of claims 29 to 33, 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 29 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:

$$\left[L-Q'\right]_n S-Q''-$$

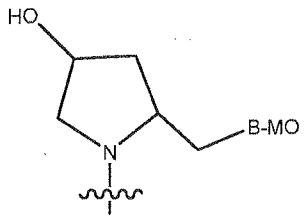
wherein each L is, independently, a ligand; n is from 1 to 10; S is a scaffold; and Q' and Q" are, independently, linking groups.

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 34 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 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).

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 34 to 43, wherein n is from 1 to 5, 1 to 4, 1 to 3, or 1 to 2.

46. The compound of any of of claims 34 to 43, wherein n is 3.

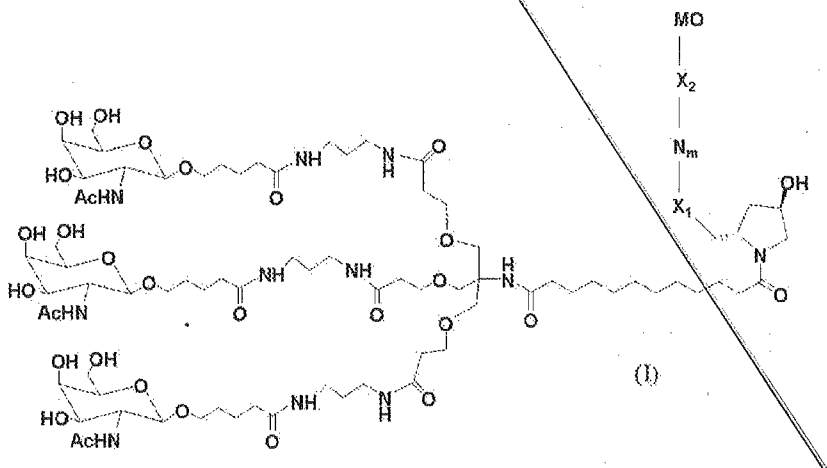
47. The compound of any one of claims 34 to 46, wherein at least one ligand is a carbohydrate.

48. The compound of any one of claims 34 to 47, 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 34 to 47, 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.

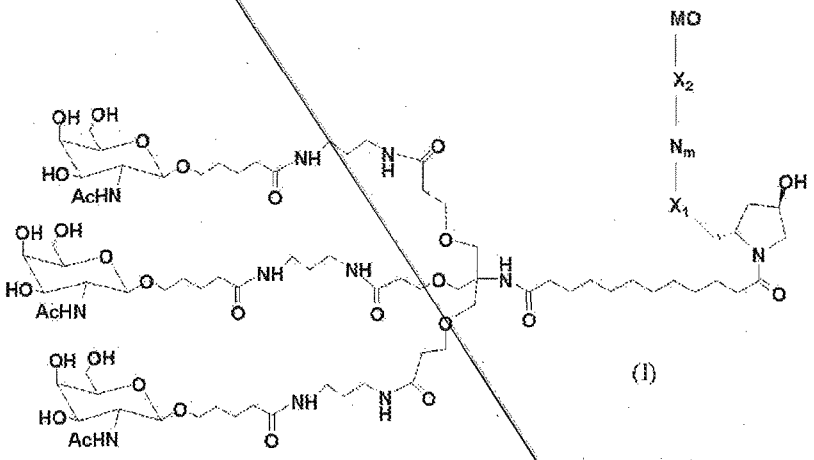
50. The compound of any one of claims 34 to 47, wherein each ligand is N-acetylgalactosamine.

51. The compound of any one of claims 34 to 50, wherein the 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.

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 51 or claim or 52, wherein at least one of X_1 and X_2 is a phosphodiester linkage.

54. The compound of any one of claims 51 to 53, wherein each of X_1 and X_2 is a phosphodiester linkage.

55. The compound of any one of claims 35 to 54, wherein m is 1.

56. The compound of any one of claims 35 to 54, wherein m is 2, 3, 4, or 5.

57. The compound of any one of claims 35 to 56, wherein 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.

58. The compound of claim 57, wherein p is 0.

59. The compound of claim 57, wherein p is 1, 2, 3, or 4.

60. The compound of any one of claims 55 to 59, wherein each N' comprises an unmodified sugar moiety.

61. The compound of any one of claims 57 to 60, wherein each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose.

62. The compound of any one of claims 57 to 61, wherein N" comprises a purine nucleobase.

63. The compound of any one of claims 57 to 61, wherein N" comprises a pyrimidine nucleobase.

64. The compound of any one of claims 57 or 59 to 62, 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 57 to 62, 64, and 65, wherein N" is a β-D-deoxyriboadenosine or a β-D-deoxyriboguanosine.

67. The compound of any one of claims 57 or 59 to 66, wherein at least one N' comprises a pyrimidine nucleobase.

68. The compound of claim 63 or 67, wherein each pyrimidine nucleobase is independently selected from cytosine, 5-methylcytosine, thymine, uracil, and 5,6-dihydrouracil.

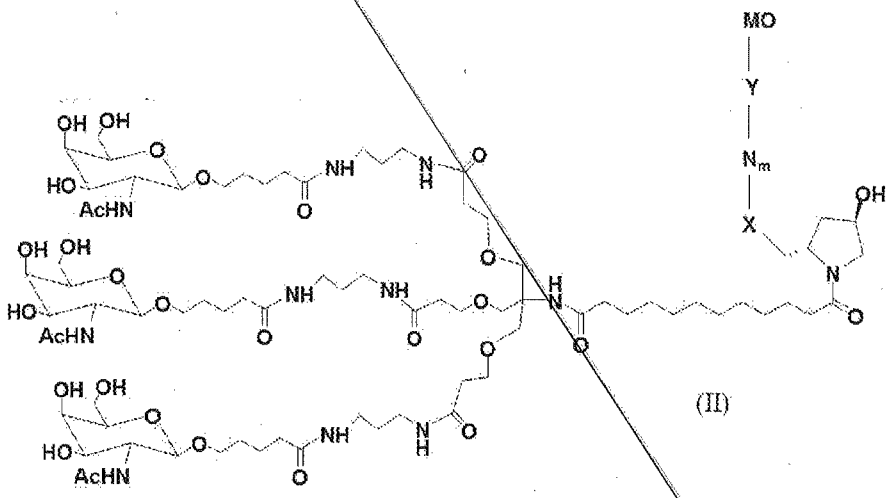
69. The compound of any one of claims 35 to 68, wherein the sugar moiety of each N is independently selected from a β-D-ribose, a β-D-deoxyribose, a 2'-O-methoxy sugar, a 2'-O-methyl sugar, a 2'-fluoro sugar, and a bicyclic sugar moiety.

70. The compound of claim 69, 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 70, wherein the cEt sugar moiety is an S-cEt sugar moiety.

72. The compound of claim 70, wherein the cEt sugar moiety is an R-cEt sugar moiety.

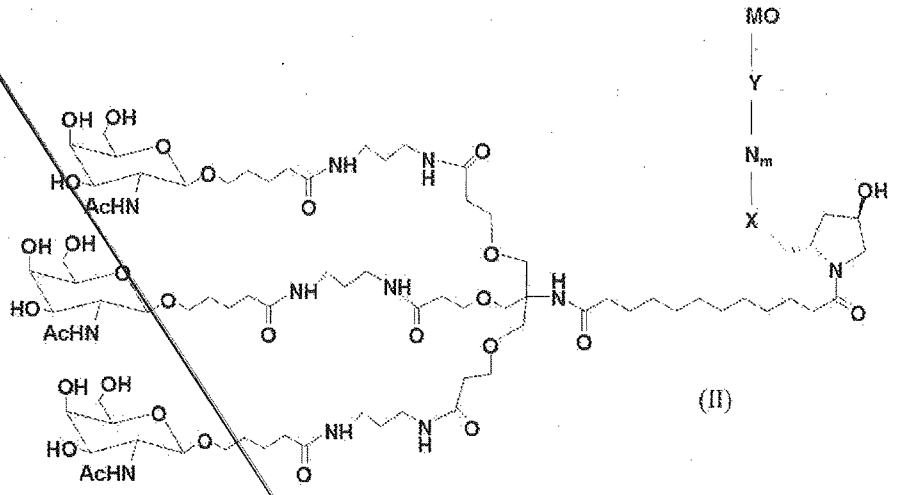
73. A compound comprising a modified nucleotide and a conjugate moiety, wherein the modified oligonucleotide has the structure $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "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:



(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.

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:



(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.

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 74 above.

76. The method of claim 75 above, wherein the cell is *in vivo*.

77. The method of claim 75 above, 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. The method of claim 78 wherein the administering reduces the symptoms of HCV infection.

80. The method of claim 78 or claim 79 wherein the administering prevents a rebound in serum HCV RNA.

81. The method of claim 78 or claim 79 wherein the administering delays a rebound in serum HCV RNA.

82. The method of any one of claims 78 to 81 comprising selecting a subject having HCV infection.

83. The method of any one of claims 78 to 82 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 78 to 83 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. The method of claim 83 or claim 84, 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. The method of claim 83 or claim 84, wherein the HCV genotype is selected from genotype 1a, 1b, and 2.

87. The method of any one of claims 78 to 86, comprising administering at least one additional therapeutic agent.

88. The method of any one of claims 78 to 87, wherein the subject is infected with an HCV variant that is resistant to at least one therapeutic agent.

89. The method of claim 87 or claim 88, 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 87 or claim 88, 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. The method of claim 87 or claim 88 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, ribavirin,

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

92. The method of claim 87 or claim 88 wherein the at least one therapeutic agent is selected from an interferon, ribavirin, and telapravir.

93. The method of any one of claims 78 to 92 wherein the subject is a non-responder to at least one therapeutic agent.

94. The method of claim 93 wherein the subject is an interferon non-responder.

95. The method of claim 93 or claim 94 wherein the subject is a direct-acting anti-viral non-responder.

96. The method of any one of claims 78 to 95 comprising selecting a subject having a HCV RNA level greater than 350,000 copies per milliliter of serum.

97. The method of any one of claims 78 to 95 comprising selecting a subject having a HCV RNA level between 350,000 and 3,500,000 copies per milliliter of serum.

98. The method of any one of claims 78 to 95 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 78 to 98 wherein the subject has an HCV-associated disease.

100. The method of claim 99 wherein the HCV-associated disease is cirrhosis, liver fibrosis, steatohepatitis, steatosis, or hepatocellular carcinoma.

101. The method of any one of claims 78 to 100 comprising administering a dose of the compound sufficient to reduce HCV RNA level.

102. The method of claim 101 comprising administering a dose of the compound that reduces HCV RNA level below 40 copies per ml of serum.

103. The method of claim 101 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 78 to 103 wherein the administering achieves a sustained virological response.

105. The method of any one of claims 78 to 104 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, or at least 2.5 fold.

106. The method of claim 105 wherein 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.

107. The method of any one of claims 78 to 106 wherein the compound is 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. The method of any one of claims 78 to 107, wherein the dose of the compound 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 78 to 108 wherein the administering normalizes liver enzyme levels, wherein the liver enzyme is optionally alanine aminotransferase.

110. The method of any one of claims 78 to 109 wherein the subject is a human.

111. The method of any one of claims 78 to 110 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.