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.

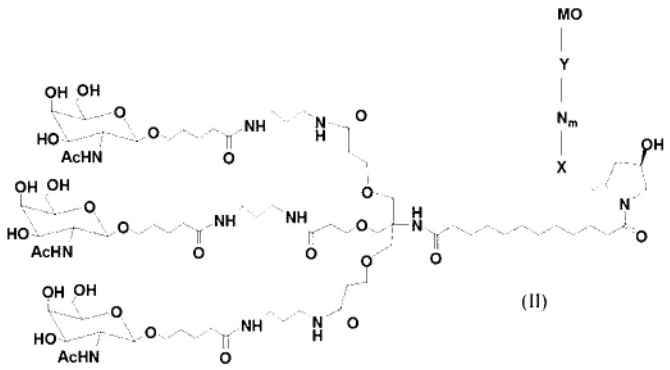
SUMMARY

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 $A_E^{Me}C_EA_E^{Me}C_E^{Me}C_EA_ETTGU_SC_SAC_SAC_STC_SC_S$ (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 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, each bicyclic nucleoside is independently selected from an LNA nucleoside, a cEt nucleoside, and an ENA nucleoside. In certain examples, at least two bicyclic nucleosides are different from one another. In certain examples, all bicyclic nucleosides have the same sugar moiety as one another. In certain examples, each bicyclic nucleoside is a cEt nucleoside. In certain examples, a cEt nucleoside is an S-cEt nucleoside. In certain examples, a cEt nucleoside is an R-cEt nucleoside. In certain examples, each bicyclic nucleoside is an LNA nucleoside.

In certain examples, at least two non-bicyclic nucleosides comprise sugar moieties that are different from one another. In certain examples, each non-bicyclic nucleoside has the same type of sugar moiety. In certain examples, 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, each non-bicyclic nucleoside is independently selected from a β-D-deoxyribonucleoside, and a 2'-O-methoxyethyl nucleoside. In certain examples, each non-bicyclic nucleoside is a β-D-deoxyribonucleoside. In certain examples, each non-bicyclic nucleoside is a 2'-MOE nucleoside. In certain examples, 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, 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, two non-bicyclic nucleosides are 2'-MOE nucleosides and each other non-bicyclic nucleoside is a β-D-deoxyribonucleoside.

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

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

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

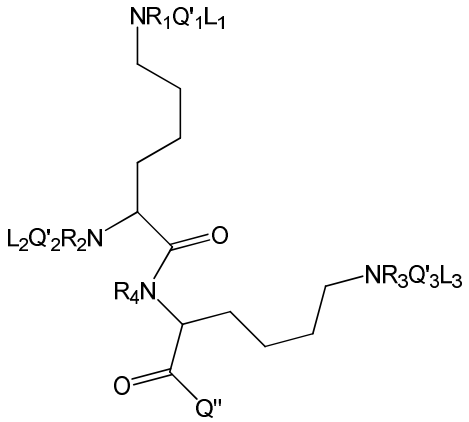
$$\left(\text{L} - \text{Q'} \right)_{\text{n}} \text{S} - \text{Q''} -$$

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

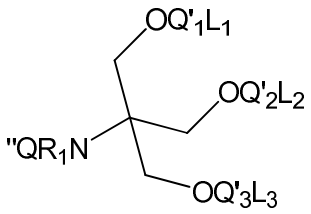
A nonlimiting exemplary Structure E is Structure E(i):



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

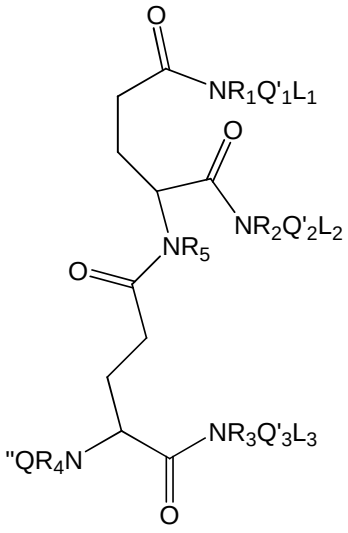
A further nonlimiting exemplary Structure E is Structure E(ii):



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

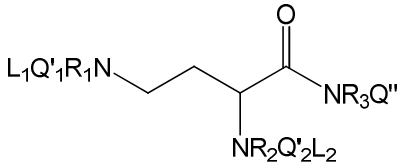
A further nonlimiting exemplary Structure E is Structure E(iii):



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

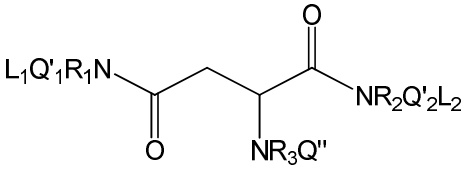
A further nonlimiting exemplary Structure E is Structure E(iv):



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

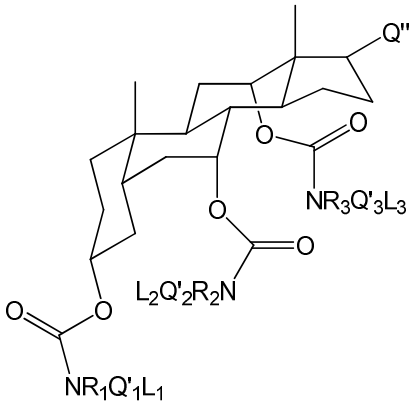
A further nonlimiting exemplary Structure E is Structure E(v):



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

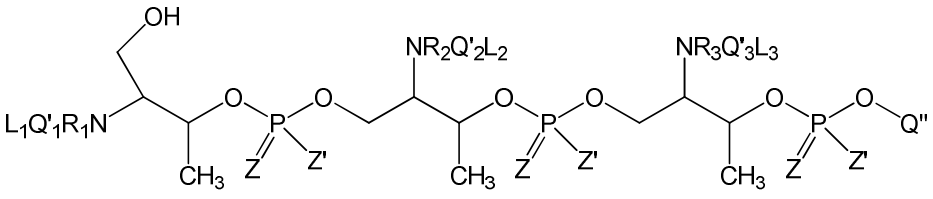
A further nonlimiting exemplary Structure E is Structure E(vi):



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

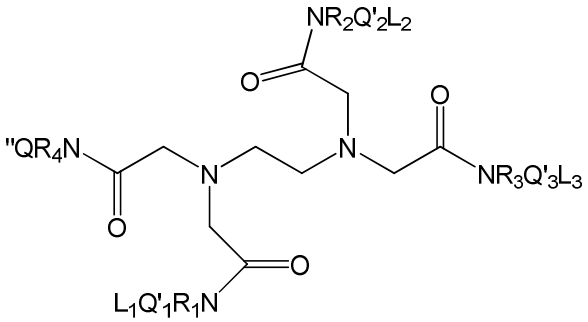
A further nonlimiting exemplary Structure E is Structure E(vii):



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

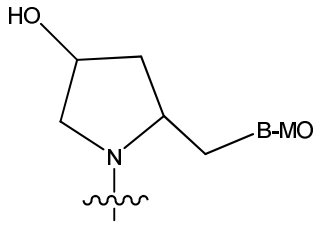
A further nonlimiting exemplary Structure E is Structure E(viii):



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

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

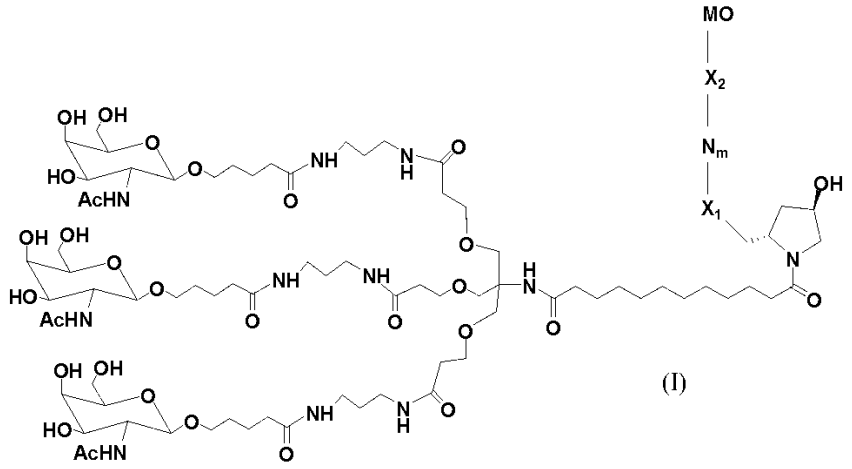
In certain examples, at least one ligand is a carbohydrate.

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

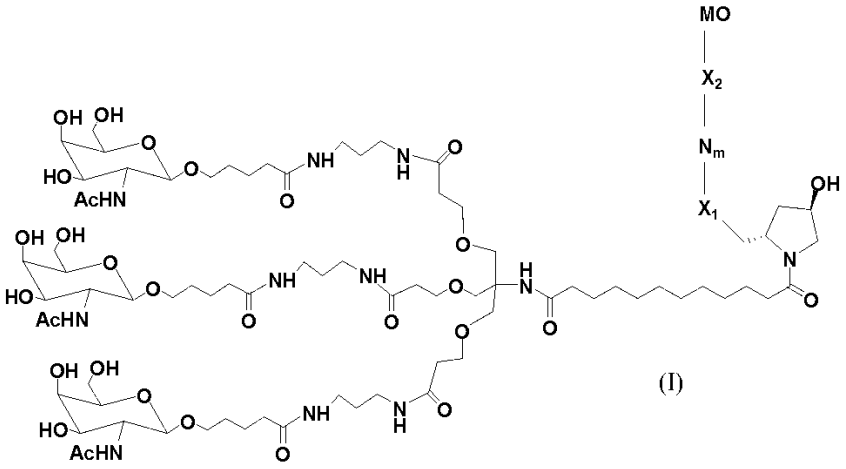
In certain examples, each ligand is N-acetylgalactosamine.

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

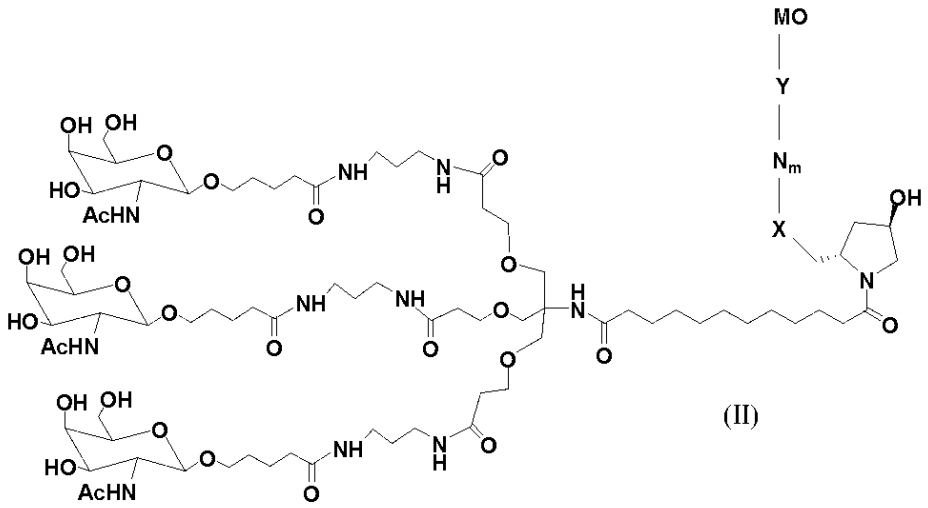
In certain examples, N_m is $N'_pN"$, wherein each N' is, independently, a modifid or unmodified nucleoside and p is from 0 to 4; and N" is a nucleoside comprising an unmodified sugar moiety. In certain examples, p is 0. In certain examples, p is 1, 2, 3, or 4.

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

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

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

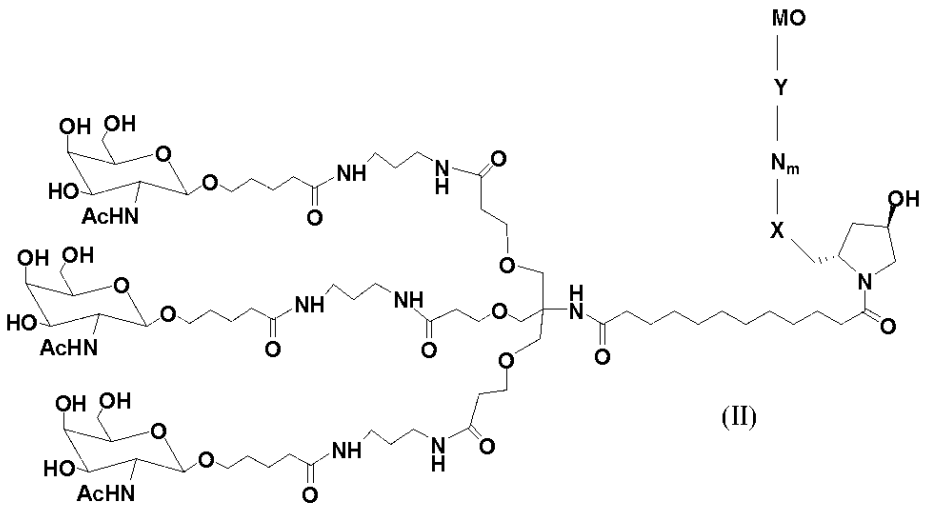


(II)

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.

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:



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, 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, the cell is cell is *in vivo*. In certain examples, cell is *in vitro*.

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

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

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

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

In certain examples, 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

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

In any of the examples 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, 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 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),

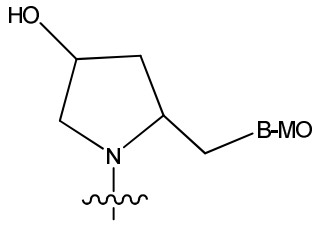
   wherein the superscript "Me" indicates 5-methylcytosine, wherein nucleosides not followed by a subscript are β-D-deoxyribonucleosides, nucleosides followed by a subscript "E" are 2'-MOE nucleosides, nucleosides followed by a subscript "S" are S-cEt nucleosides, and each internucleoside linkage is a phosphorothioate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

2. The compound of claim 1, wherein the compound comprises a conjugate moiety linked to the 5' terminus or the 3' terminus of the modified oligonucleotide.

3. The compound of claim 2, 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 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 the modified oligonucleotide.

4. The compound of claim 3, 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 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;

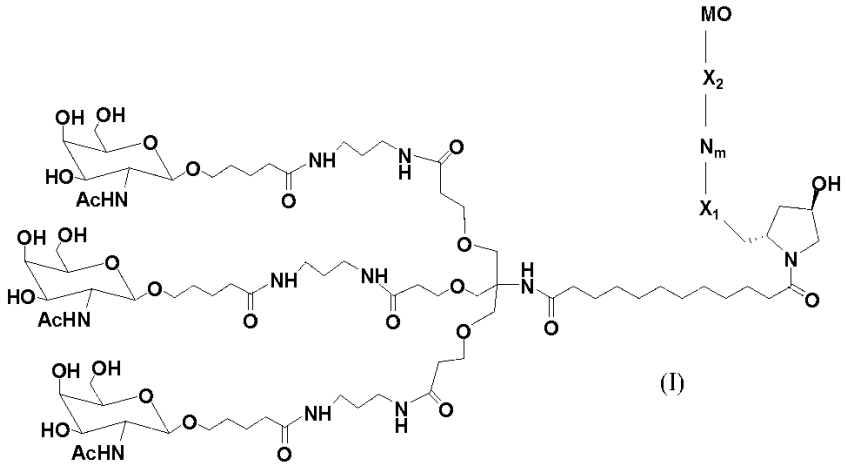
X is selected from a phosphodiester linkage and a phosphorothioate linkage;

Y is a phosphodiester linkage;

each ligand is N-acetylgalactosamine; and

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

5. The compound of claim 3 or claim 4, wherein the compound has the structure:



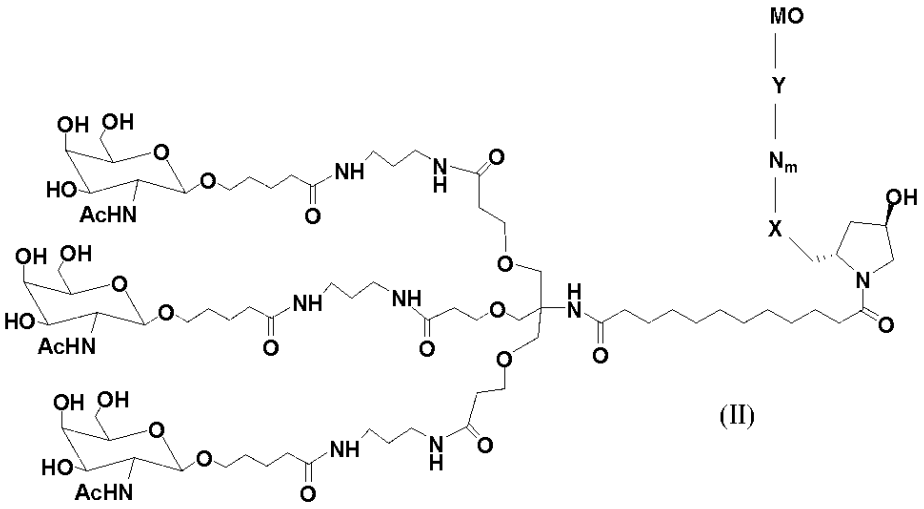
wherein each N of N_m is, independently, a modified or unmodified nucleoside and m is from 1 to 5; X_1 and X_2 are each, independently, a phosphodiester linkage or a phosphorothioate linkage; and MO is the modified oligonucleotide.

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

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

8. The compound of any one of claims 4 to 7, wherein each N comprises an unmodified sugar moiety, wherein each unmodified sugar moiety is, independently, a β-D-ribose or a β-D-deoxyribose.

9. 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.

10. 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 medicament reduces the symptoms of HCV infection, prevents a rebound in serum HCV RNA, and/or delays a rebound in serum HCV RNA.

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

15. The use of any one of claims 12 to 14, wherein the use achieves a sustained virological response.

16. The 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.

17. 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.

18. The use of any one of claims 12 to 17, wherein the medicament is for administration with at least one additional therapeutic agent.

19. 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, an NS5A inhibitor, an NS3/4A inhibitor, a nucleoside NS5B inhibitor, a nucleotide NS5B inhibitor, a non-nucleoside NS5B inhibitor, and an interferon.

20. The use of 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.

21. The use of claim 20, wherein the at least one therapeutic agent is sofosbuvir.

22. The use of claim 20, wherein the at least one therapeutic agent is sofosbuvir and ledipasvir.

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

24. The use of 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.

26. The use of any one of claims 12 to 25, 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.

27. The use of any one of claims 12 to 26, wherein the compound or pharmaceutical composition 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.

28. The 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.