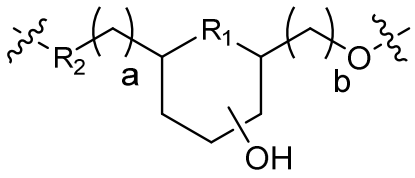
CLAIMS

What is claimed is:

1. A cleavable compound, as shown in formula (Z-1), or pharmaceutically acceptable salt thereof

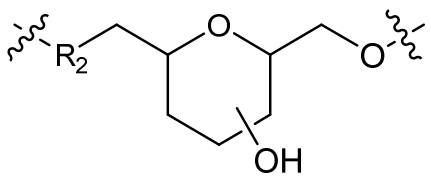


(Z-1) ,

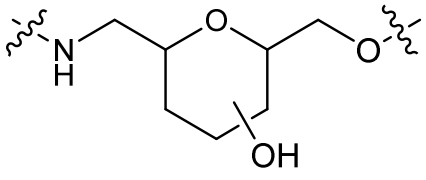
where R_1 is O, S, NR_3, or CR_3R_4, and R_3 and R_4 are independent hydrogen, halogen, substituted or unsubstituted aliphatic group, substituted or unsubstituted aryl group, substituted or unsubstituted heteroaryl group, substituted or unsubstituted heterocyclic group, or substituted or unsubstituted cycloalkyl group;

where R_2 is -O-, -S-, -NH-, $-CH_2-$, -C(O)-, -OC(O)-, -C(O)O-, -NHC(O)-, -C(O)NH-, $-CH_2NH-$, $-CH_2O-$, $-NH-C(O)-CH_2-$, $-C(O)-CH_2-NH-$, or -NH(CO)NH-, wherein the $-CH_2-$ is optionally replaced with a substituent group selected from the group consisting of halogen, alkyl, alkoxy, and alkylamino; a and b are the same or different, and are the integers respectively selected from 0 to 20, preferably from 1 to 10, and further preferably from 1 to 5.

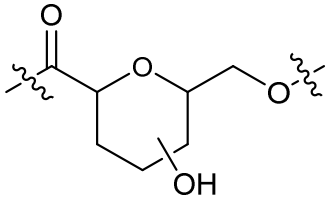
2. The cleavable compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has a structural formula of:



(Z-2) ,

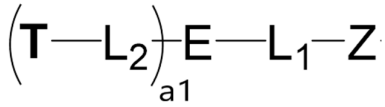


(Z-3) ; or

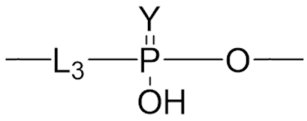


(Z-4) .

3. An oligonucleotide ligand compound or pharmaceutically acceptable salt thereof, comprising the cleavable compound or a pharmaceutically acceptable salt thereof according to claim 1 or 2, and the oligonucleotide ligand compound has a general formula of:



(I) or has a general formula of:

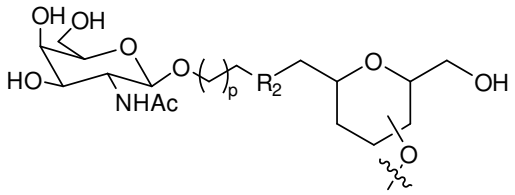


(II),

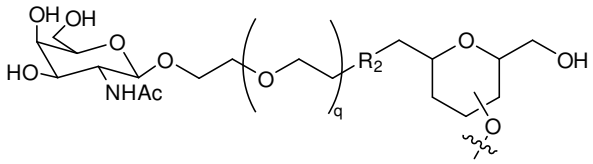
in the general formula (I):

Z is the cleavable compound shown as formula (Z-1) for connection to nucleotide sequence X, L_1 is the second linker, E is the branch point group, the branch point group E is connected to a1 targeting combination(s), and a1 is an integer from 0 to 10, preferably from 1 to 5; the targeting combination comprises a tethered portion L_2 and a targeting portion T in a 1:1 ratio; or

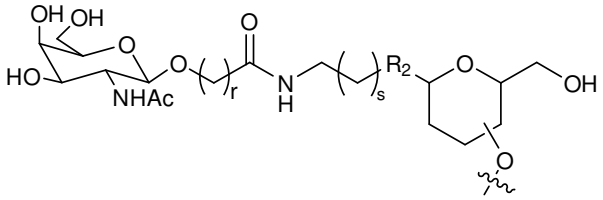
in the general formula (II), Y is O, S, or N, and L_3 has a following structure:



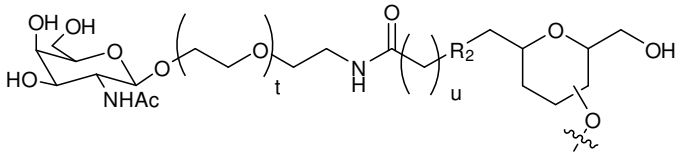
(II-a-I),



(II-a-II),



(II-a-III),



(II-a-III),

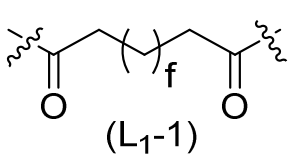
where R_2 is -O-, -S-, -NH-, $-CH_2-$, -C(O)-, -OC(O)-, -C(O)O-, -NHC(O)-, -C(O)NH-, $-CH_2NH-$, -

CH_2O-, -NH-C(O)-CH_2-, -C(O)-CH_2-NH- or -NH(CO)NH-, and -CH_2- is optionally replaced with a substituent group of halogen or alkyl, wherein the alkyl is optionally further replaced with a substituent group selected from the group consisting of hydroxyl, amino, halogen, alkoxy, and alkylamino;

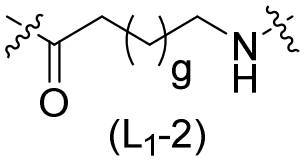
the p, q, r, s, t, and u are integers from 0 to 20, preferably from 1 to 10.

4. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claim 3, wherein the general formula (II) is used for connecting with a nucleotide sequence.

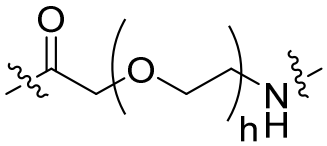
5. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claim 3, wherein the second linker portion L_1 in the general formula (I) has a following structure:



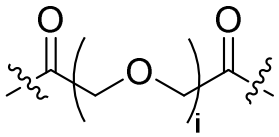
(L_1-1),



(L_1-2),



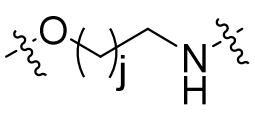
(L_1-3), or



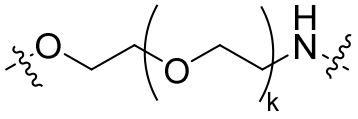
(L_1-4),

and the f, g, h, and i are integers from 1 to 20, preferably from 1 to 10, and further preferably from 1 to 5.

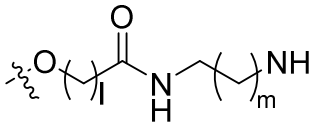
6. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claim 3, wherein the second linker portion L_2 in the general formula (I) has a following structure:



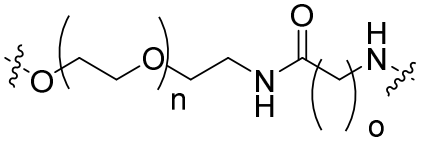
(L_2-1),



(L_2-2),



(L_2-3), or



(L_2-4),

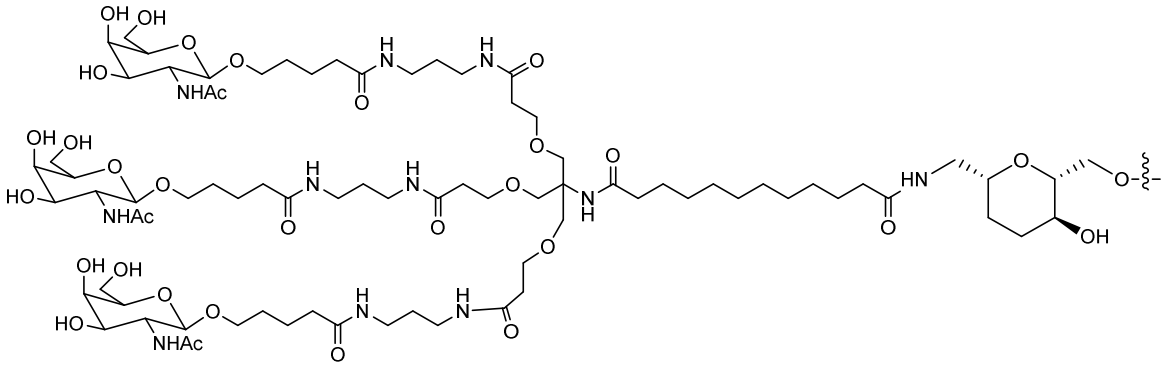
where j, k, l, m, n, and o are integers from 1 to 20, preferably from 1 to 10, and further preferably from 1 to 5.

7. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according

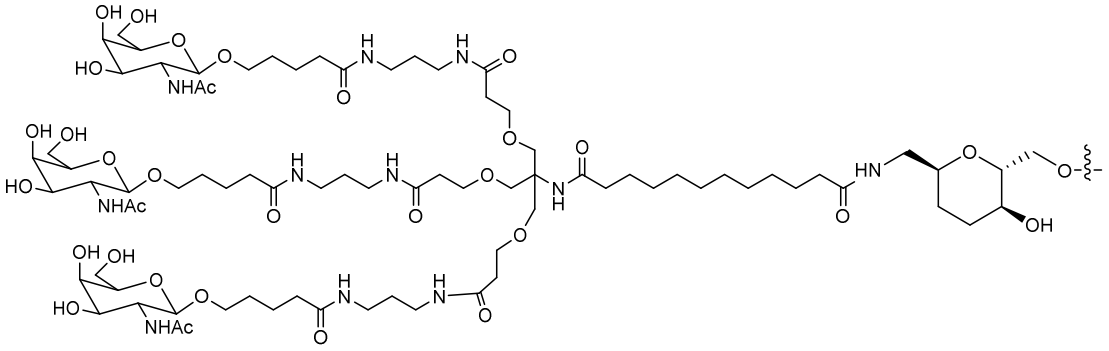
to claim 3, wherein the targeting portion T is selected from a tissue-specific targeting ligand, preferably liver specific targeting ligand; further preferably, the targeting portion T has a structure for enhancing the uptake of oligomers for liver cells.

8. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claim 3, wherein the targeting portion T has the same or different structure as/from L_3.

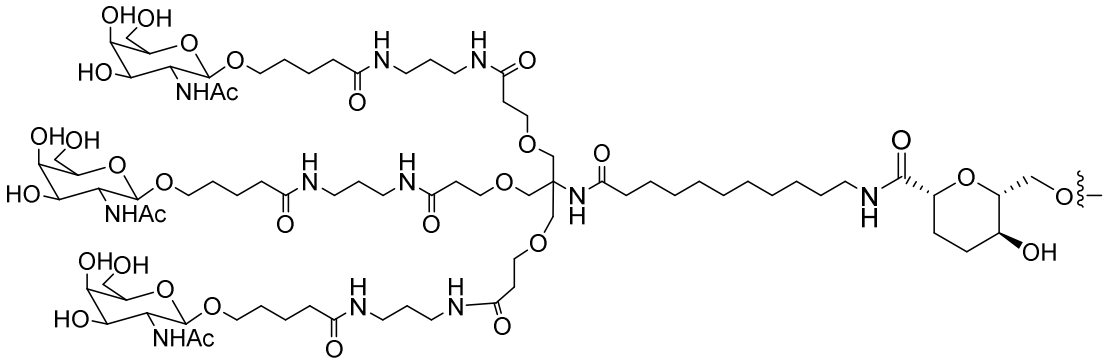
9. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claims 3-8, wherein the ligand compound has a following structure:



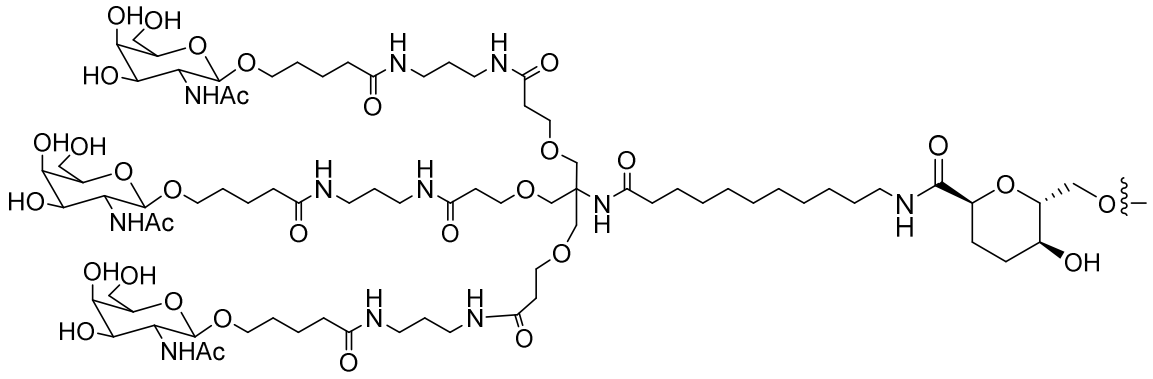
(I-1),



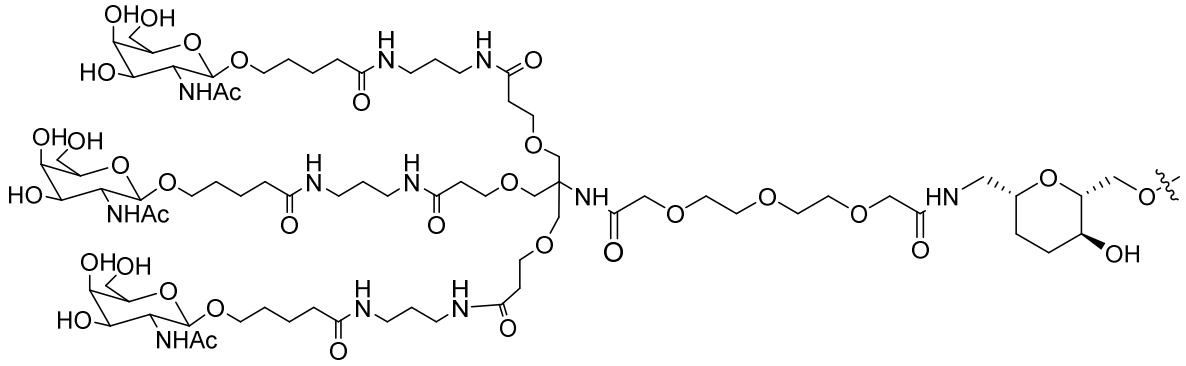
(I-2),



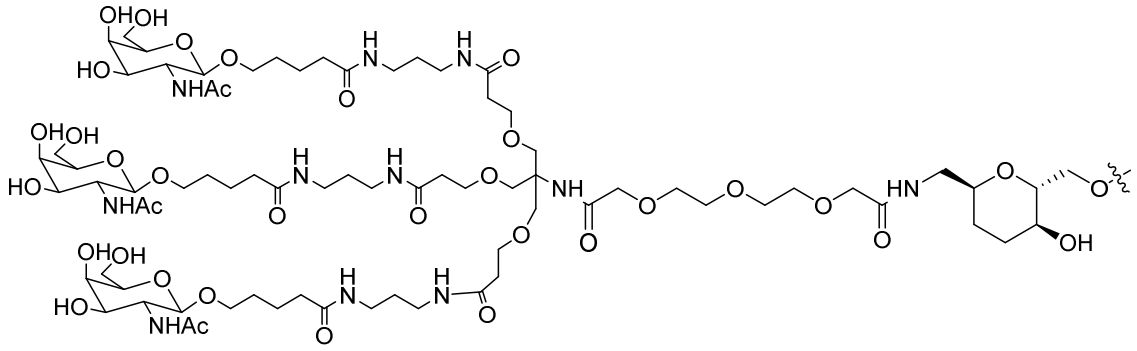
(I-3),



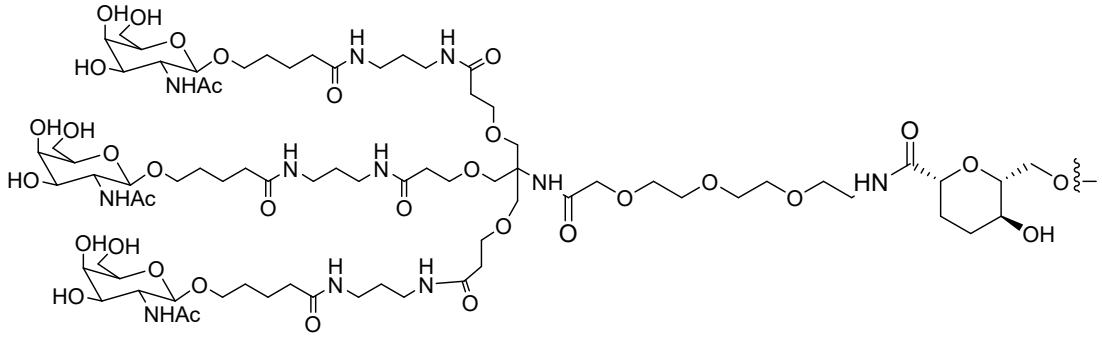
(I-4),



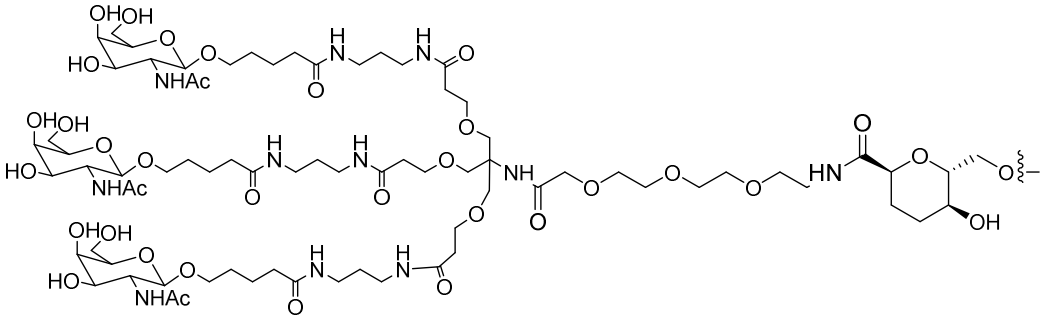
(I-5),



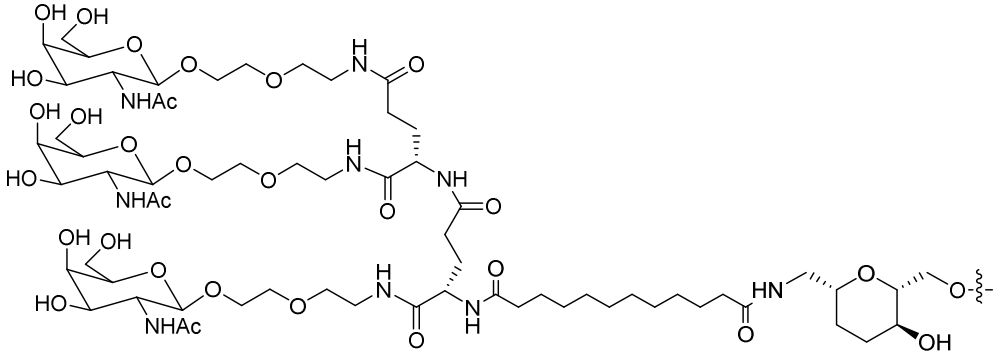
(I-6),



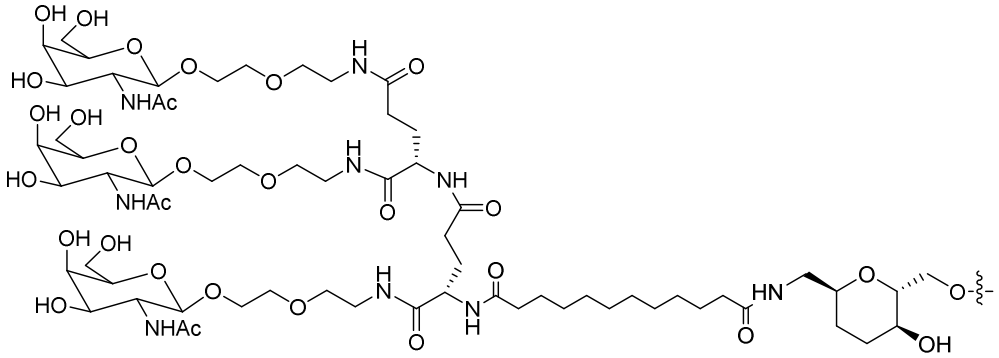
(I-7),



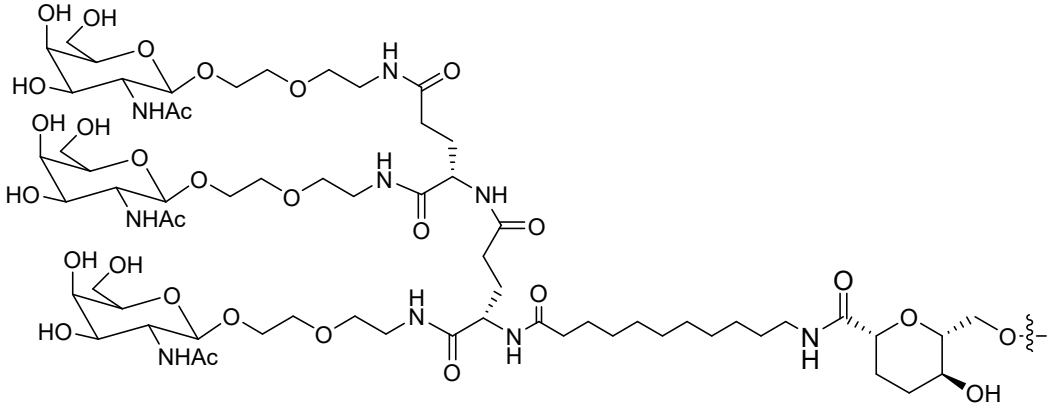
(I-8),



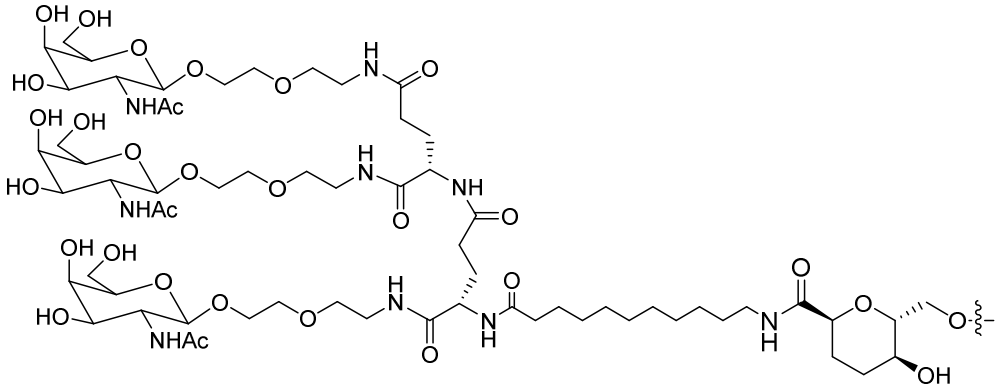
(I-9),



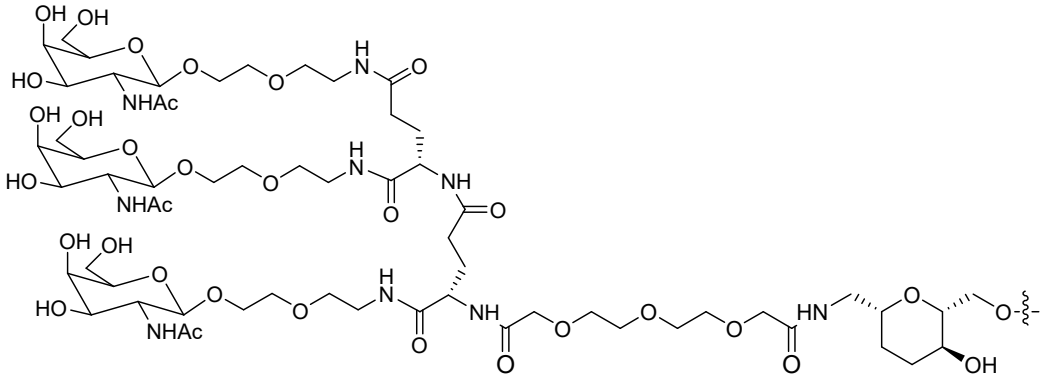
(I-10),



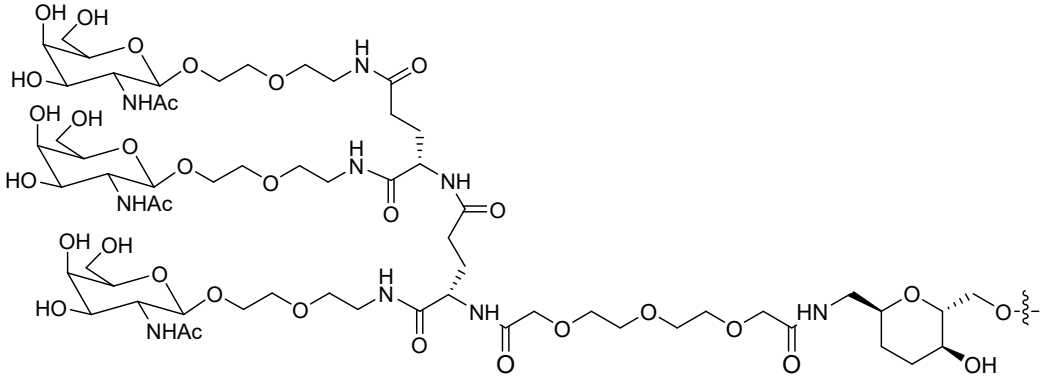
(I-11),



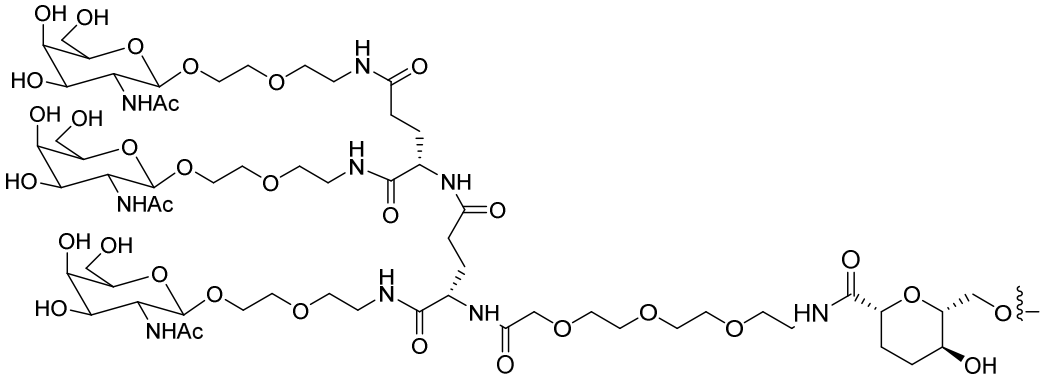
(I-12),



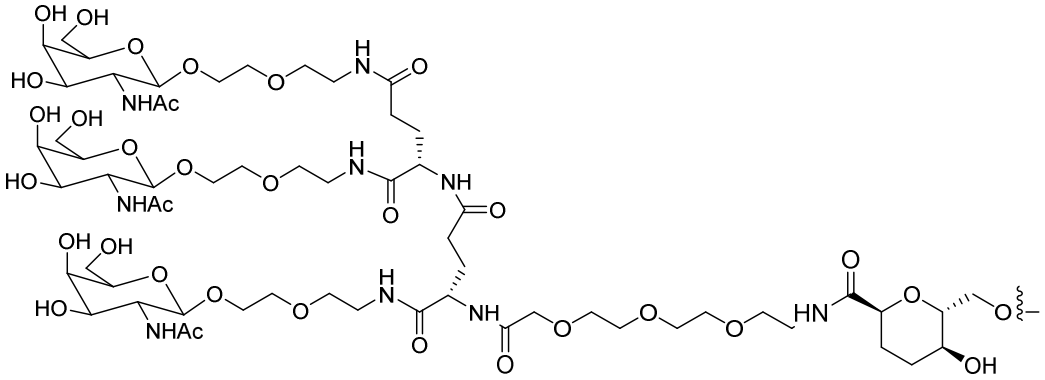
(I-13),



(I-14),

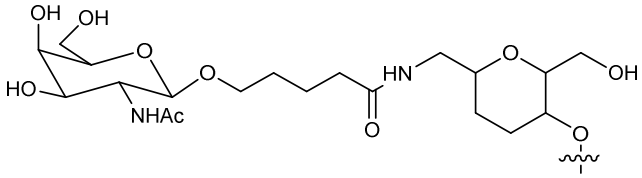


(I-15), or

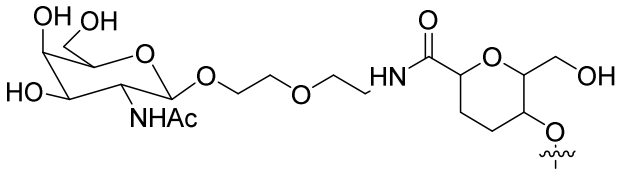


(I-16).

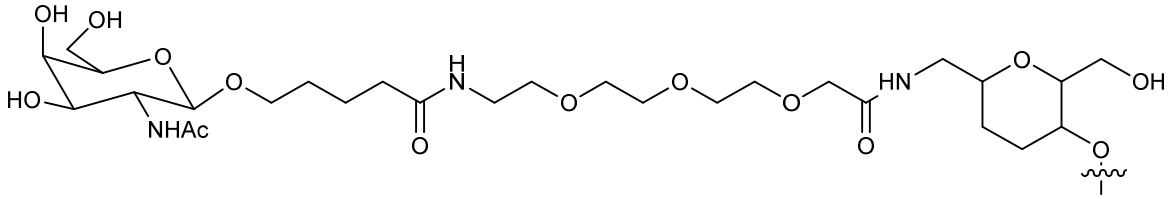
10. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claims 3-8, wherein the ligand compound comprises a following structure:



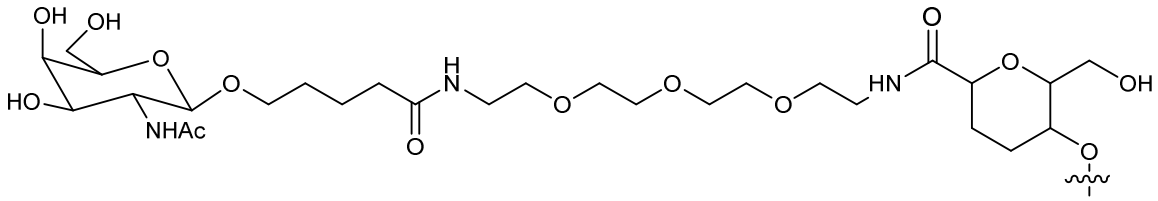
(II-a-1),



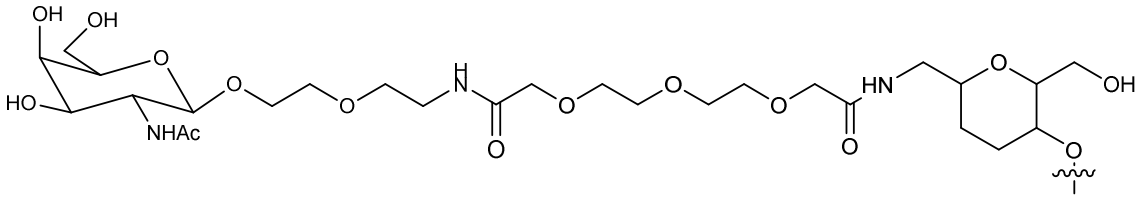
(II-a-2),



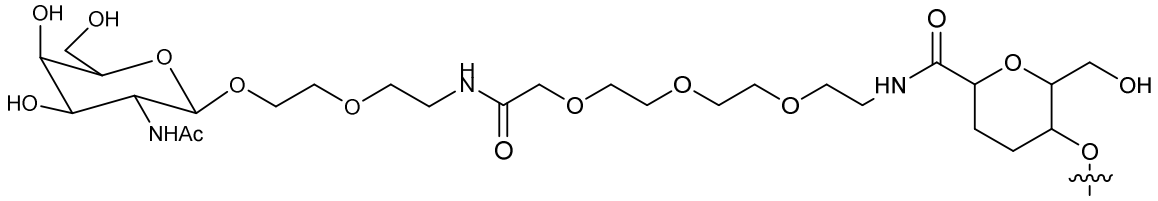
(II-a-3),



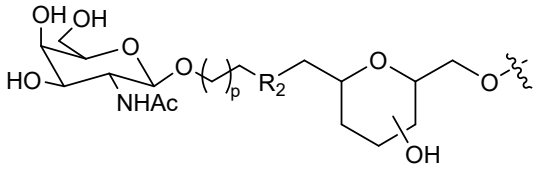
(II-a-4),



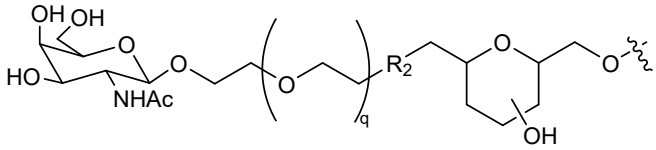
(II-a-5),



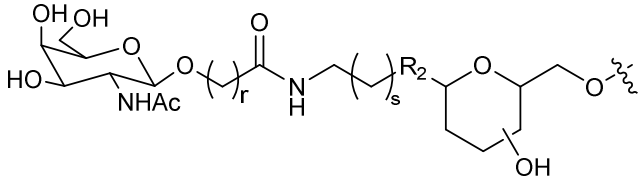
(II-a-6),



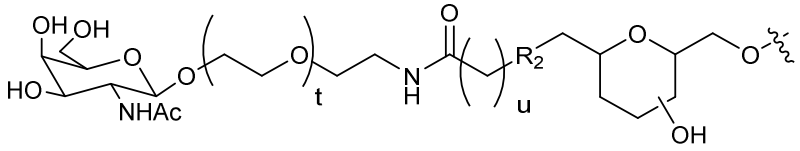
(II-a-IV),



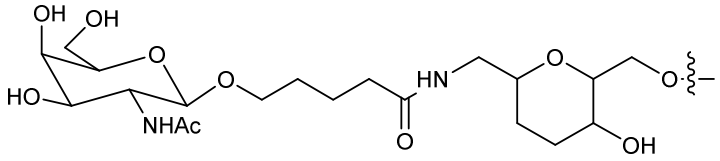
(II-a-V),



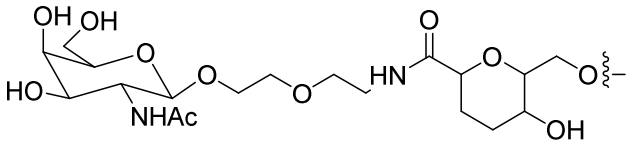
(II-a-VI), or



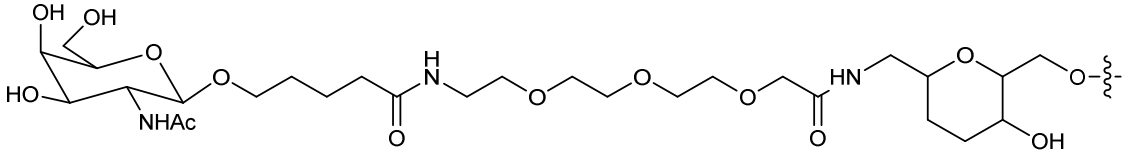
(II-a-VII),



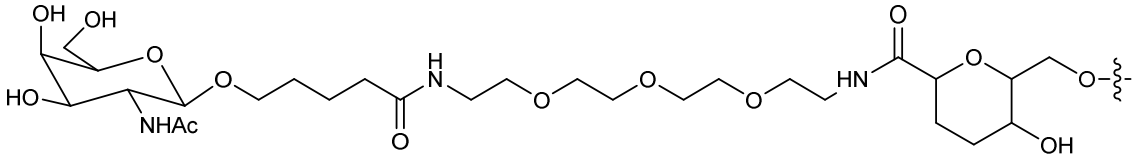
(II-a-7),



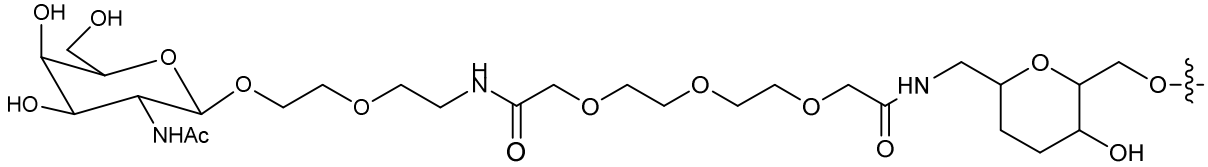
(II-a-8),



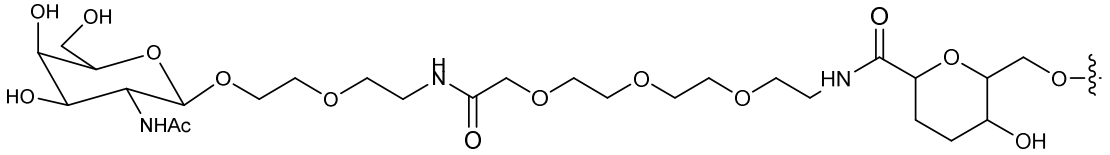
(II-a-9),



(II-a-10),

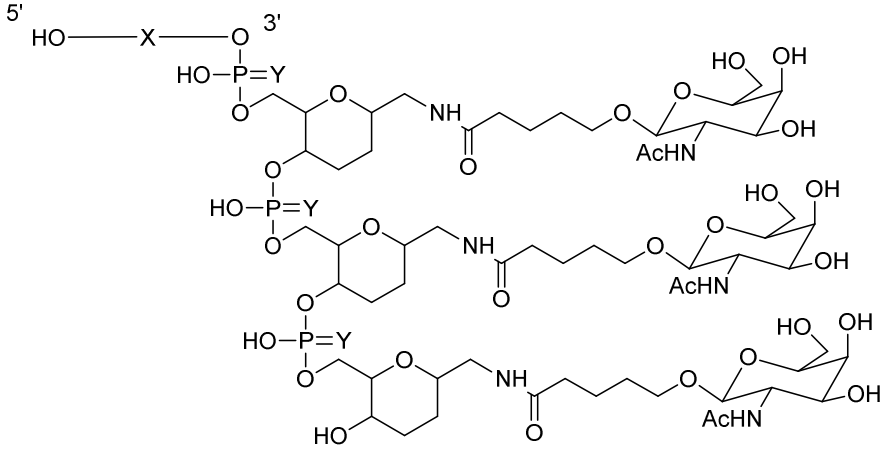


(II-a-11), or

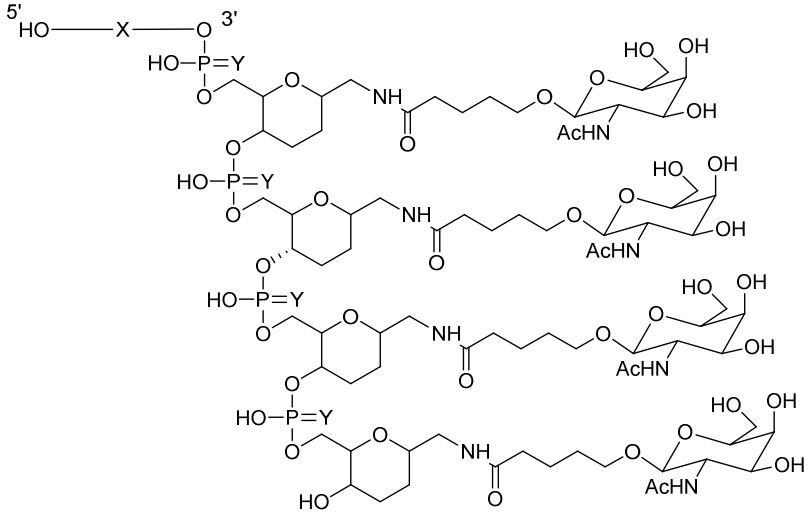


(II-a-12).

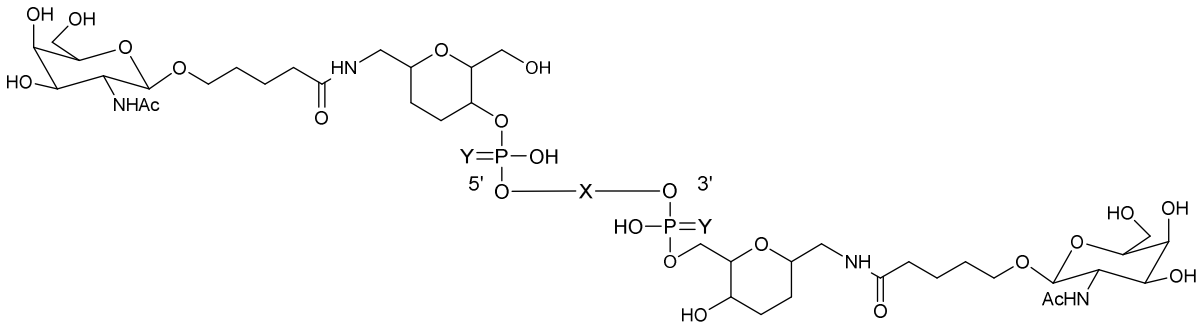
11. The oligonucleotide ligand compound or pharmaceutically acceptable salt thereof according to claims 3-8, wherein the ligand compound has the following structure after binding to nucleotide sequence X:



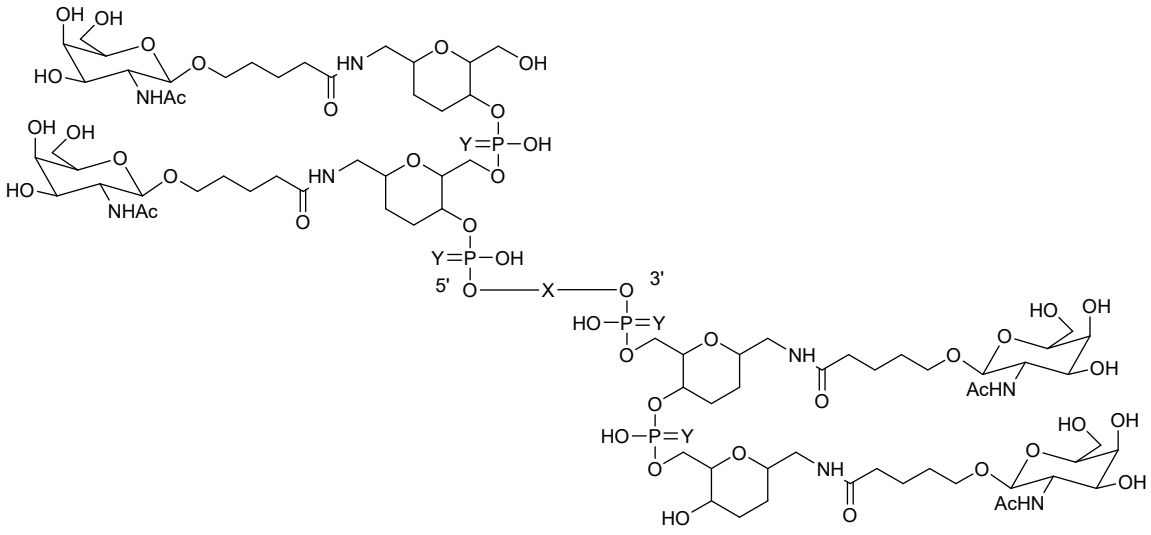
(II-1),



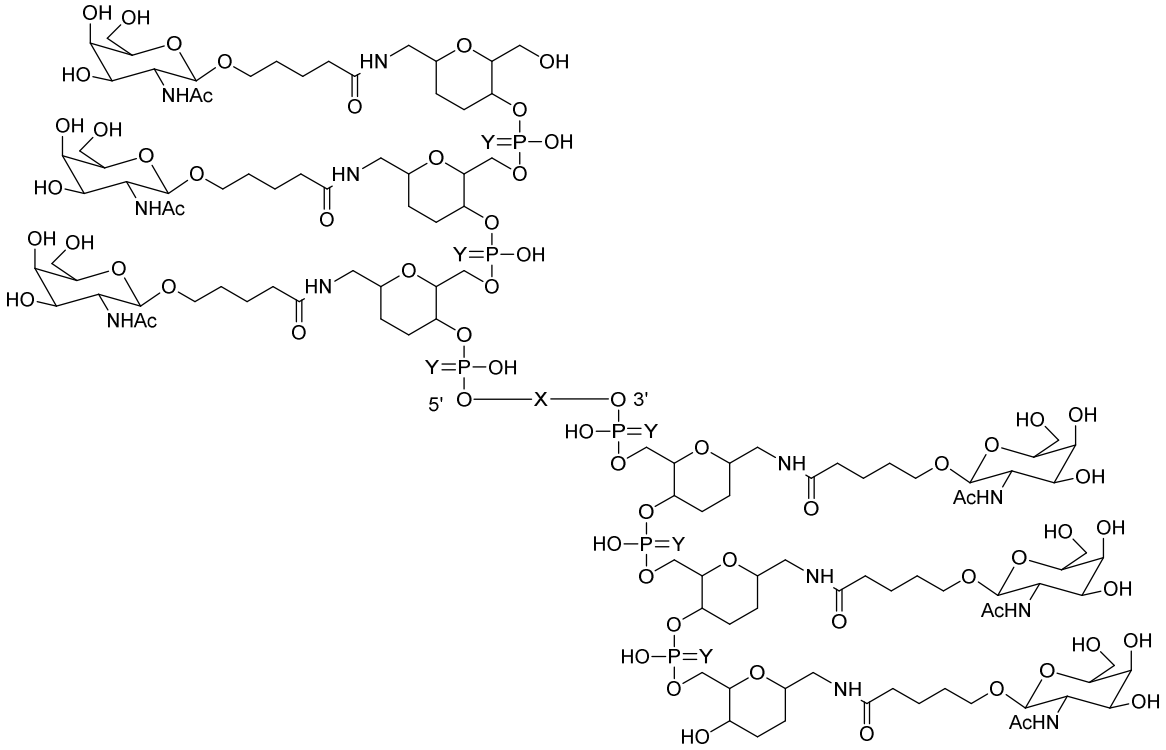
(II-2),



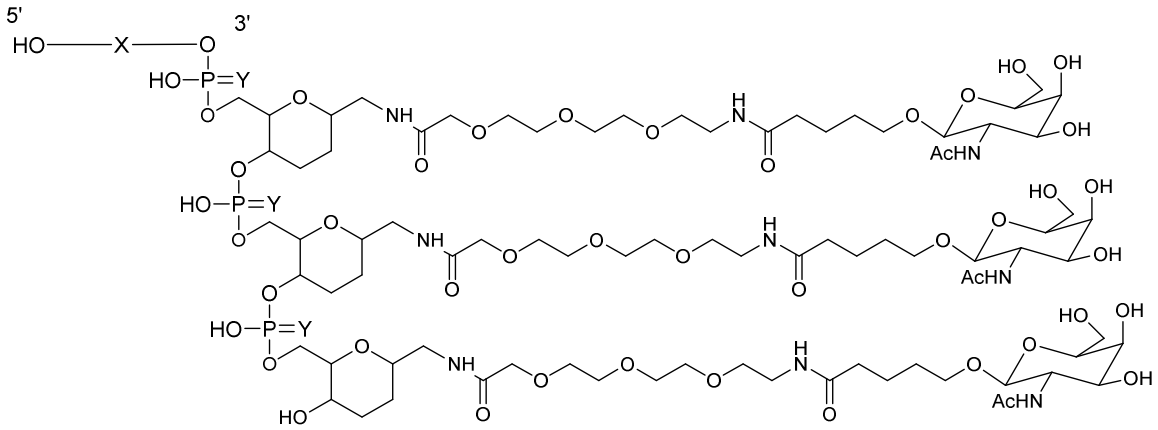
(II-3),



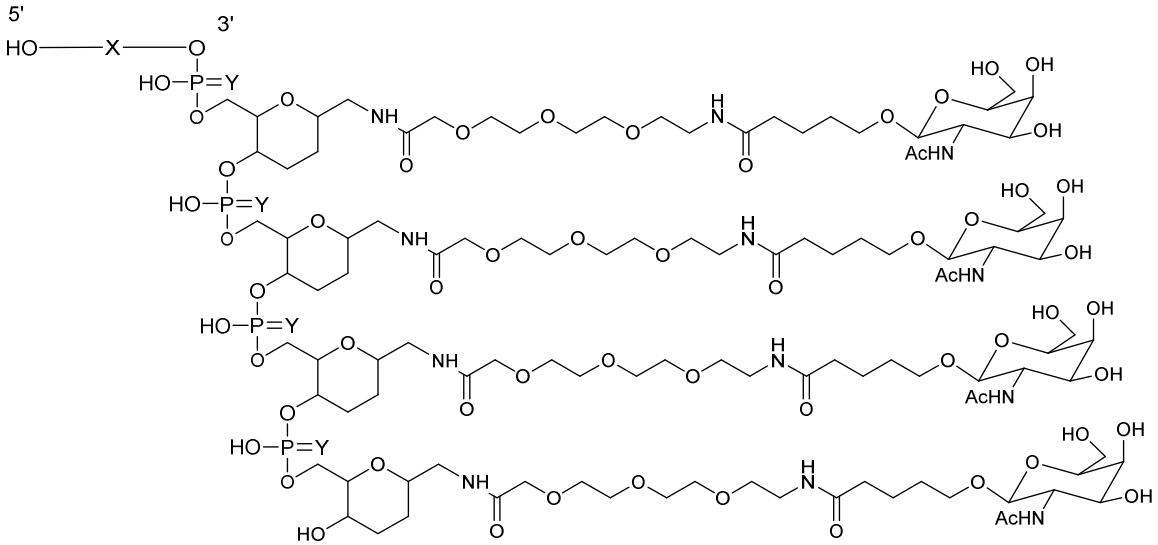
(II-4),



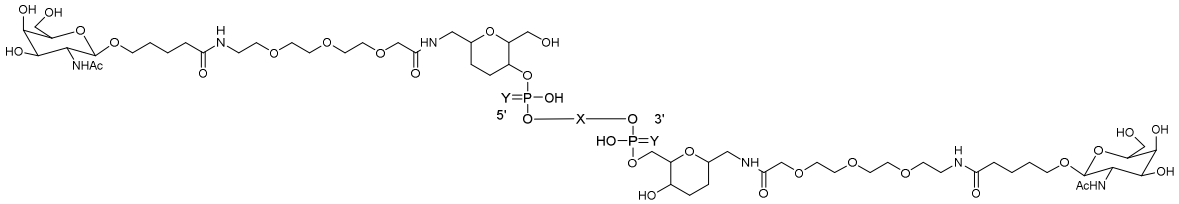
(II-5),



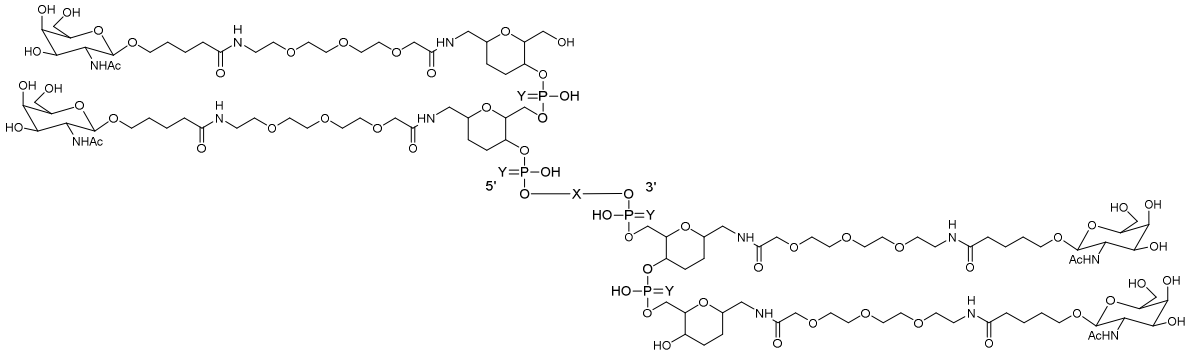
(II-6),



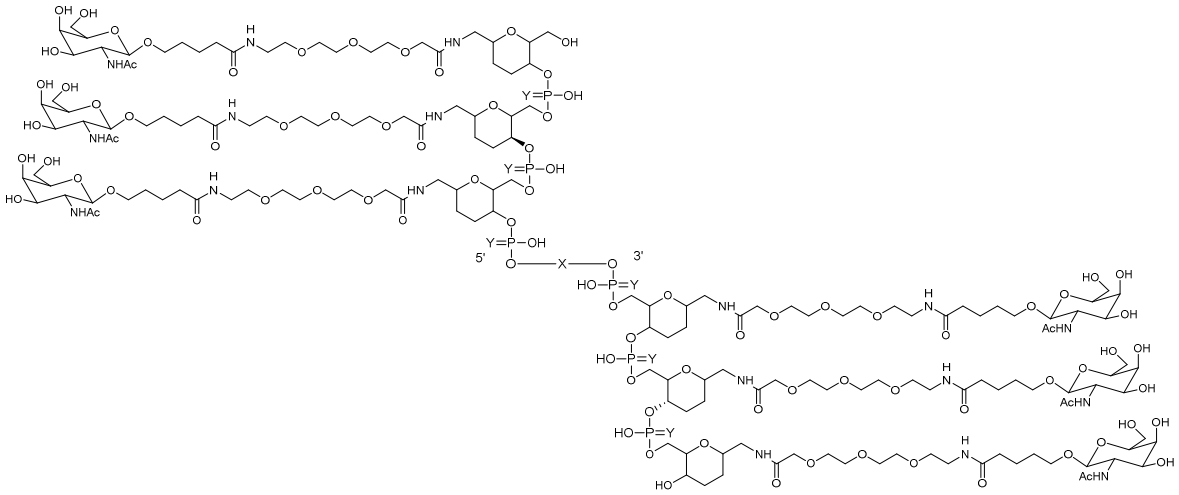
(II-7),



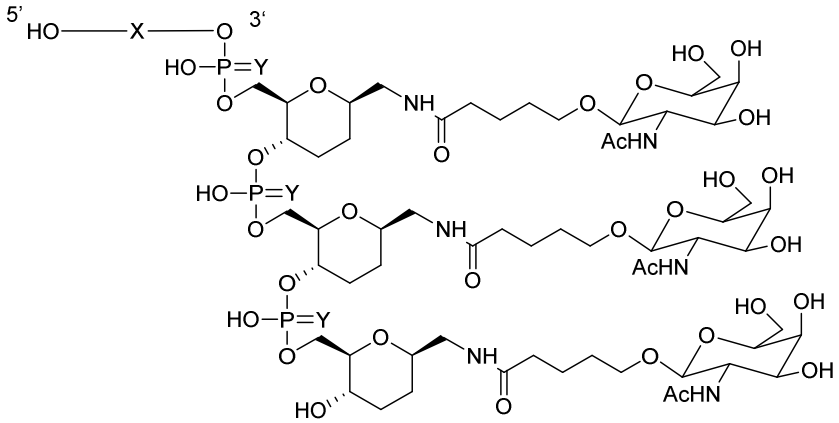
(II-8),



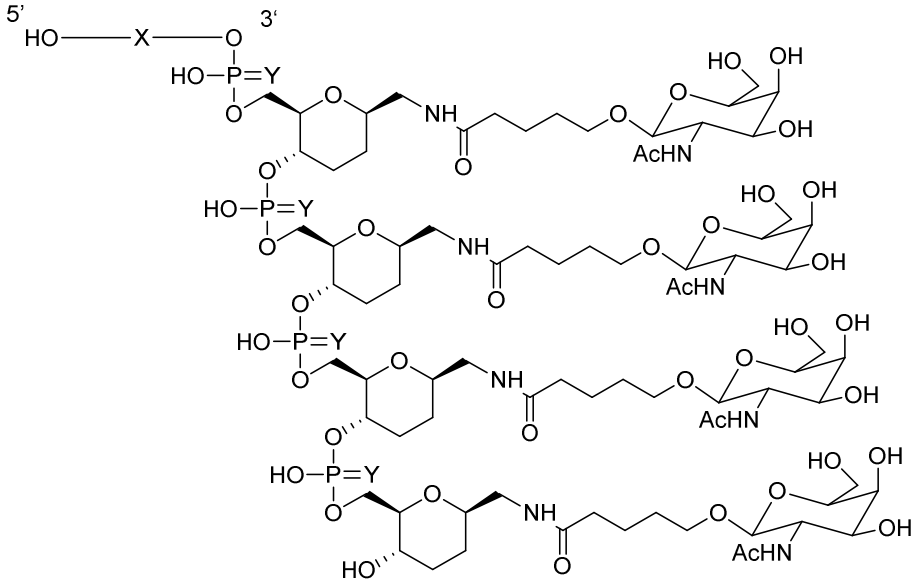
(II-9),



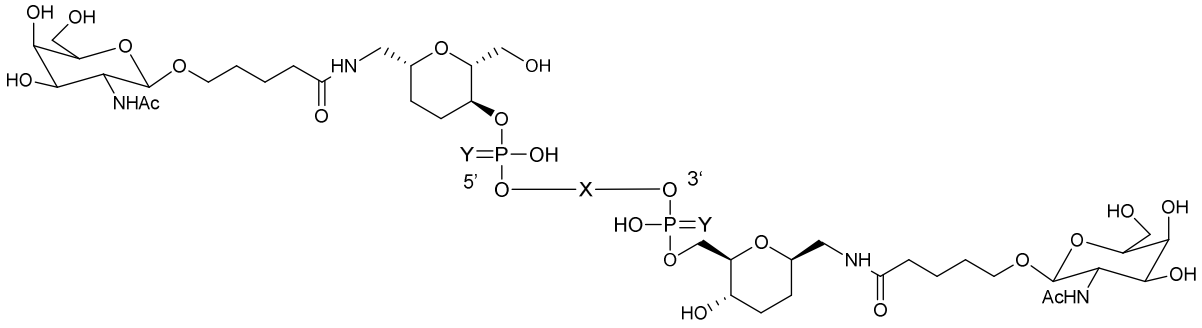
(II-10),



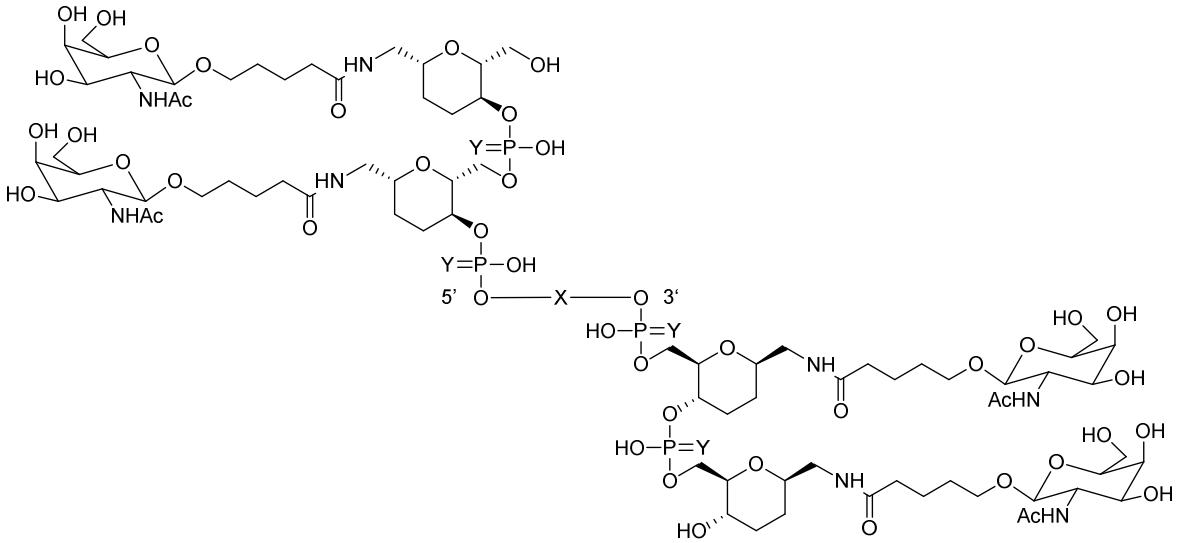
(II-11),



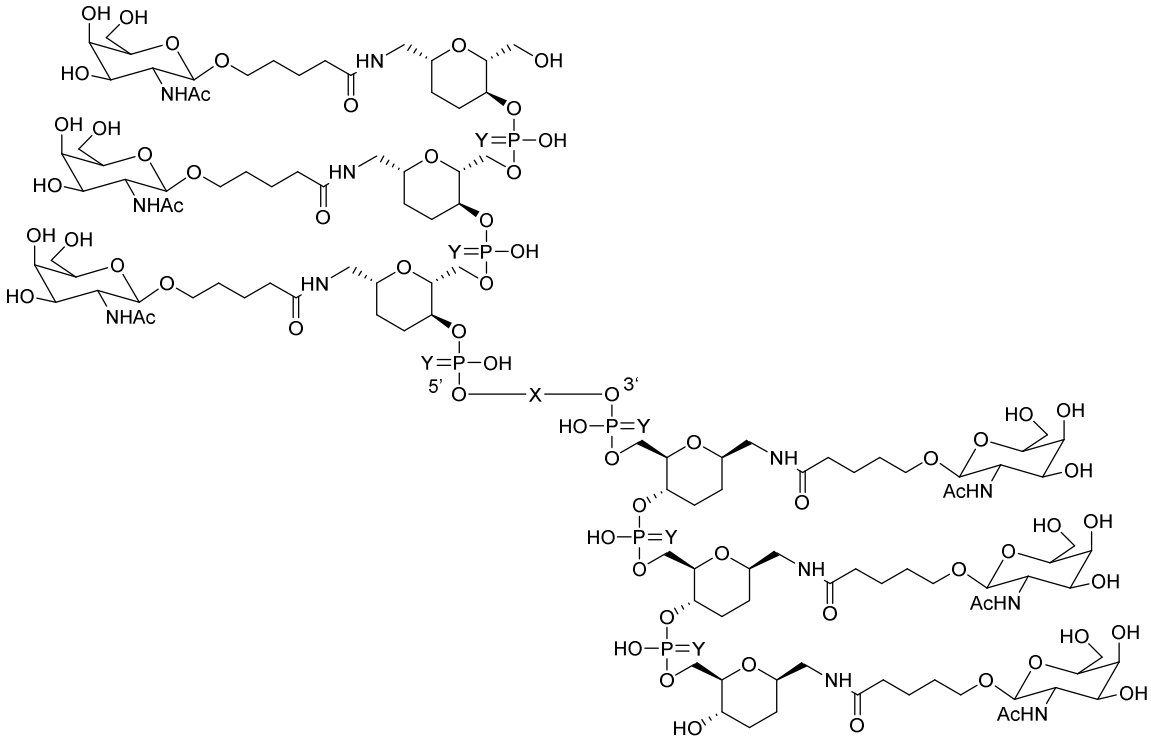
(II-12),



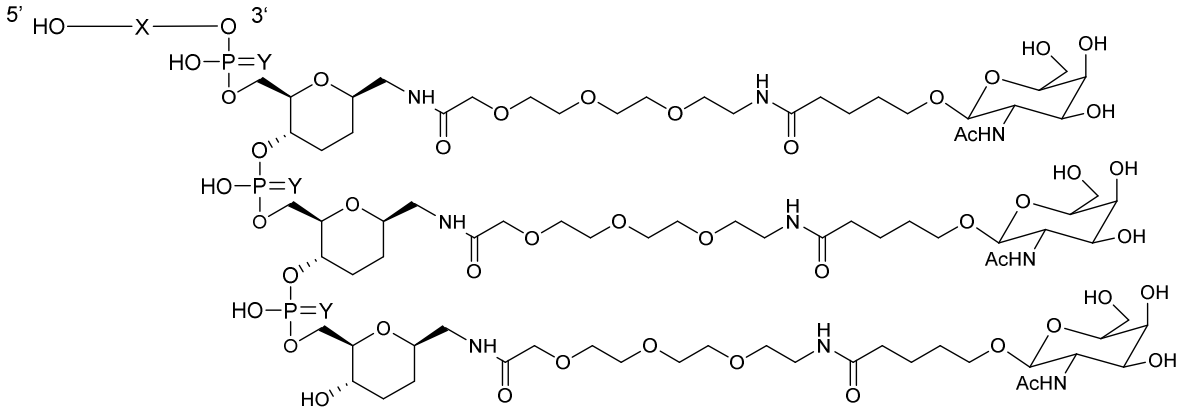
(II-13),



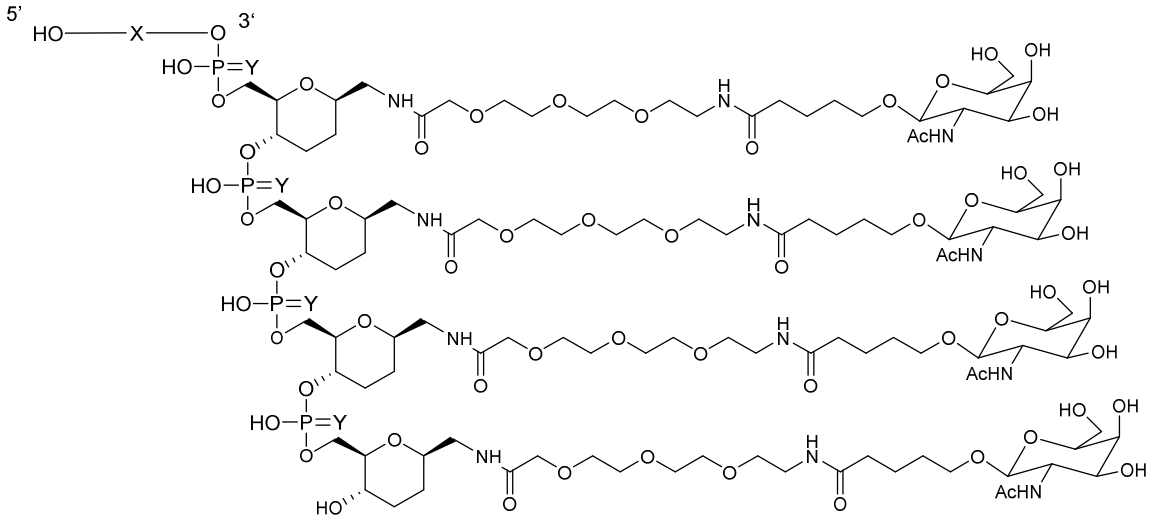
(II-14),



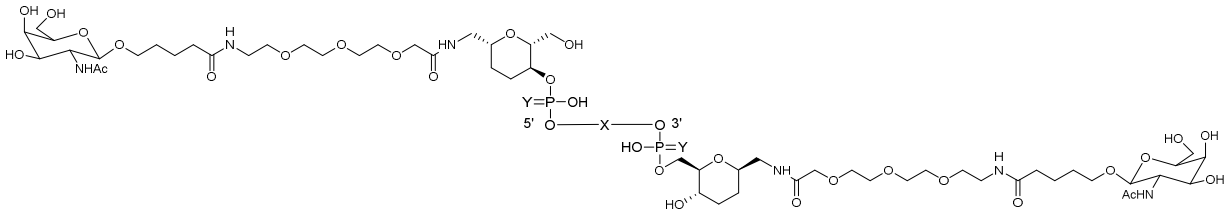
(II-15),



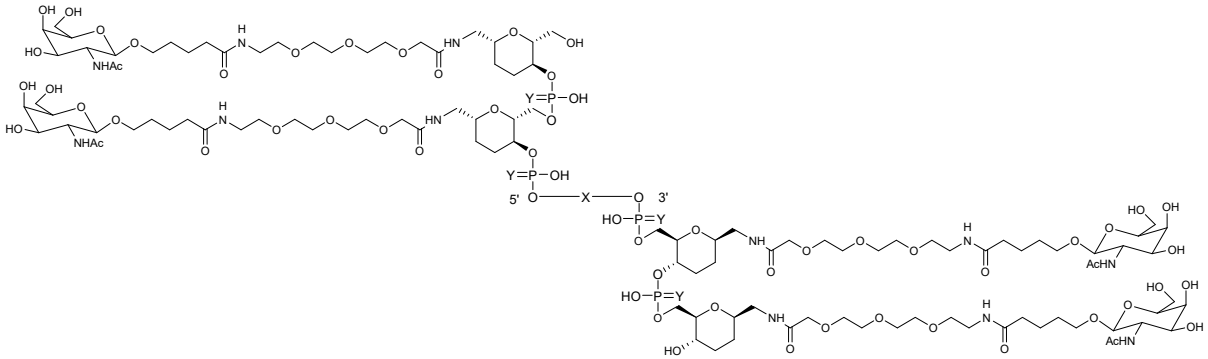
(II-16),



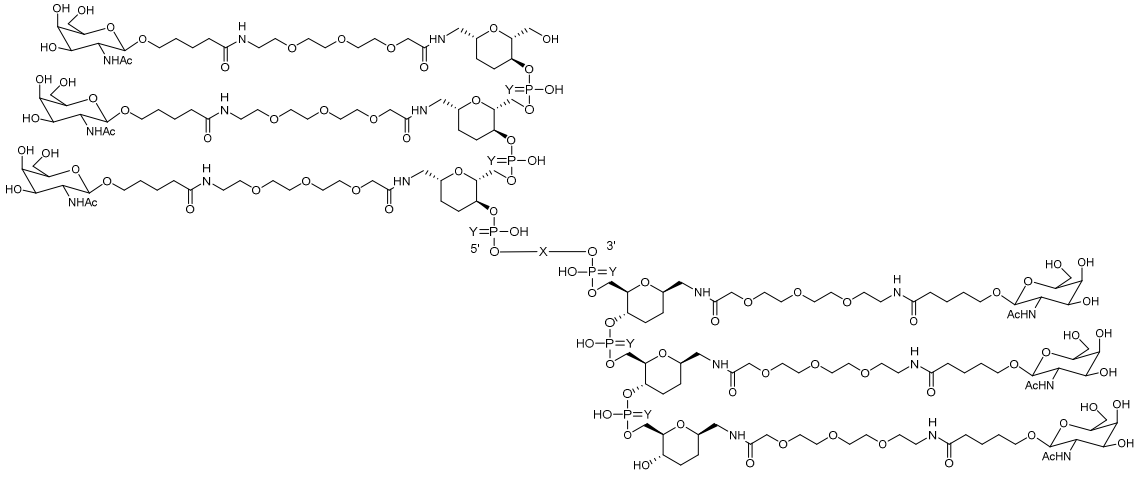
(II-17),



(II-18),



(II-19), or



(II-20),

where Y is either O or S.

12. An RNA interference agent, comprising a sense strand and/or an antisense strand, and an oligonucleotide ligand compound or a pharmaceutically acceptable salt thereof according to any one of claims 3-11.

13. The RNA interference agent according to claim 12, comprising antisense oligonucleotides, siRNA, or miRNA.

14. The RNA interference agent according to claim 12, comprising one or more modified nucleotides.

15. The RNA interference agent according to claim 12, wherein the oligonucleotide ligand compound or pharmaceutically acceptable salt thereof is coupled to a sense and/or antisense strand.