

Claims

What is claimed is:

1. An LPA RNA interference agent, comprising a nucleotide sequence which comprises at least 12 consecutive nucleotides of SEQ ID NO. 10, SEQ ID No. 17, SEQ ID No. 101, or SEQ ID No. 108, or a nucleotide sequence that is complementary thereto, or a sequence that differs not more than 3 nucleotides therefrom.
2. The LPA RNA interference agent of claim 1, wherein the nucleotide sequence comprises a double-stranded structure of an antisense strand and a sense strand.
3. The LPA RNA interference agent of claim 2, wherein the sense strand and/or antisense strand independently comprises one or more 2'- modified nucleotides.
4. The LPA RNA interference agent of claim 3, wherein the nucleotide is at least one selected from the group consisting of 2'-fluoro-modified nucleotide, 2'-O-methyl modified nucleotide, EVP, UNA, and GNA.
5. The LPA RNA interference agent of claim 1, wherein the antisense strand has at least one position, selected from the group consisting of positions 2, 5, 6, 8, 10, 14, and 16 from the 5' end, has a 2' -fluoro-modified nucleotide or O-methyl modified nucleotide, and preferably, 5-7 of these positions have 2' -fluoro-modified nucleotides or O-methyl modified nucleotide.
6. The LPA RNA interference agent of claim 2, wherein the sense strand and/or antisense strand independently comprises one or more phosphorothioate

linkages; preferably, the sense strand comprises two consecutive phosphorothioate linkages between the end nucleotides at the 3' and 5' ends, or the antisense strand comprises two consecutive phosphorothioate linkages between the end nucleotides at the 3' and 5' ends.

7. The LPA RNA interference agent of claim 2, wherein the antisense strand comprises any

AS strand in the following table, or the sense strand comprises any SS strand in the following table:

ID of AS strand	AS strand 5'-3'	Original SEQ ID	ID of SS strand	SS strand 5'-3'	Original SEQ ID
359A S	AmsUfsAmAmCfUm CmUmGm UmCmCm AmUfUm AfCmCm AmUmGms GmsUm	10	370S S	CmsAmsUm GmGmUm AmAmUf GfGfAm CmAmGm AmGmUm UmAmUms	101
384A S	VP(U)sUfsAmAmCf UmCmUmGm UmCmCm AmUfUm AfCmCm AmUmGms GmsUm	10	370S S	CmsAmsUm GmGmUm AmAmUf GfGfAm CmAmGm AmGmUm UmAmUms	101
385A S	AmsUfsAm AmCfUmCmUmGm UmCmCm AmUfUm AfCmCf AmUmGms GmsUm	10	370S S	CmsAmsUm GmGmUm AmAmUf GfGfAm CmAmGm AmGmUm UmAmUms	101
387A S	AmsUfsAm AmCfUfCmUmGm UmCmCm AmUfUm	10	370S S	CmsAmsUm GmGmUm AmAmUf GfGfAm CmAmGm	101

	AfCmCm AmUmGms GmsUm			AmGmUm UmAmUms	
359A S	AmsUfsAm AmCfUmCmUmGm UmCmCm AmUfUm AfCmCm AmUmGms GmsUm	10	397S S	CmsAmsUm GmGmUm AfAmUf GfGfAf CmAmGm AmGmUm UmAmUms	101
LPA- 60AS	AmsAfsGm AmUmUf GmAmCm AmUmGm UmCfCm UfUmCm CmUmGms UmsGm	17	398S S	CmsAmsGm GmAmAm GfGmAf CfAfUm GmUmCm AmAmUm CmUmUms	108
498A S	AmsAfsGm AmUfUm GmAmCm AmUmGm UmCfCm UfUmCm CmUmGms UmsGm	17	511S S	CmsAmsGm GmAmAm GmGmAf CfAfUm GmUmCm AmAmUm CmUmUms	108

,

preferably, the antisense strand comprises: 384AS :

VP(U)sUfsAmAmCfUmCmUmGm UmCmCm AmUfUm AfCmCm
AmUmGms GmsUm,

385AS: AmsUfsAm AmCfUmCmUmGm UmCmCm AmUfUm AfCmCf
AmUmGms GmsUm,

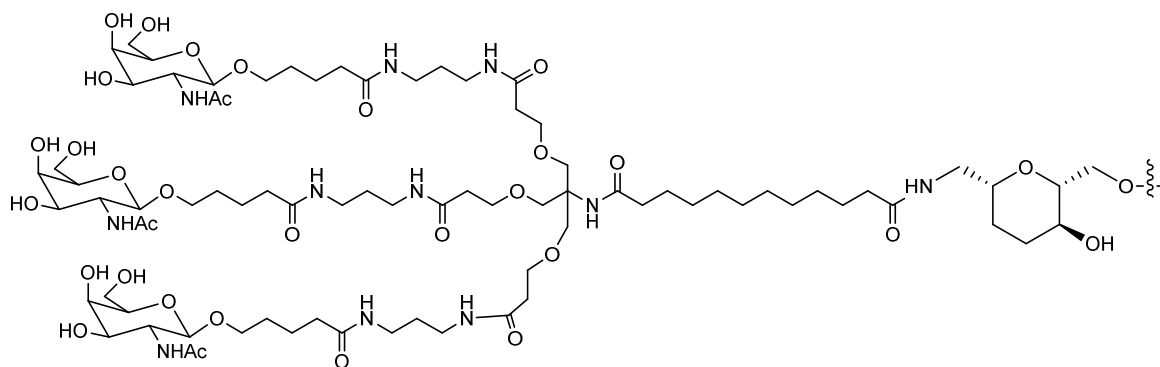
387AS: AmsUfsAm AmCfUfCmUmGm UmCmCm AmUfUm AfCmCm
AmUmGms GmsUm,

359AS: AmsUfsAm AmCfUmCmUmGm UmCmCm AmUfUm AfCmCm
AmUmGms GmsUm,

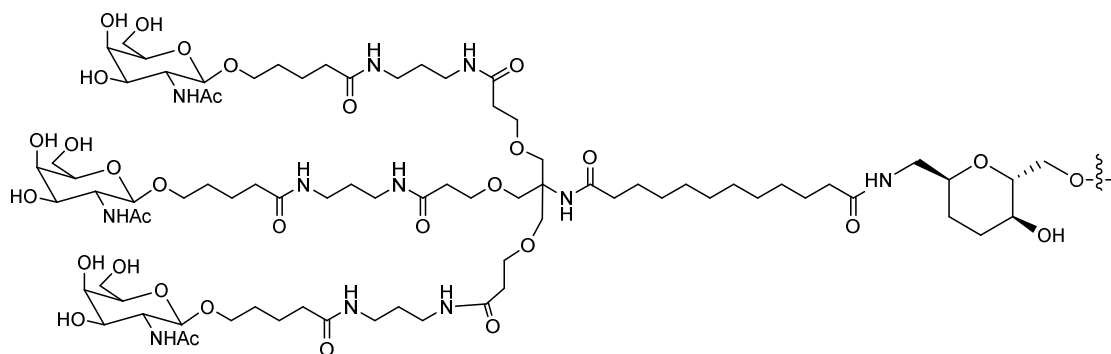
498AS: AmsAfsGm AmUfUm GmAmCm AmUmGm UmCfCm UfUmCm
CmUmGms UmsGm;

more preferably, the antisense strand consists of 359AS or 498AS.

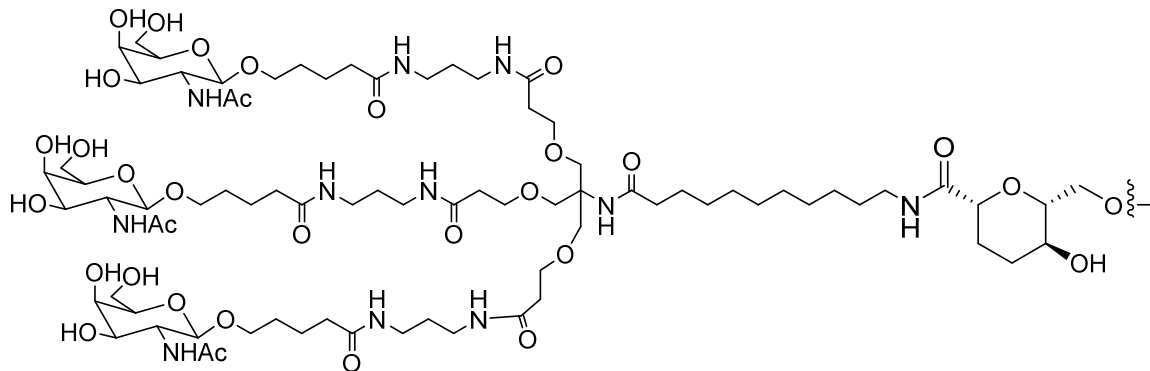
8. The LPA RNA interference agent of any of claims 1 to 7, wherein the RNA interfering agent also comprises a ligand, and the ligand comprises at least one of chemical formulas I-1 to I-16:



(I-1),

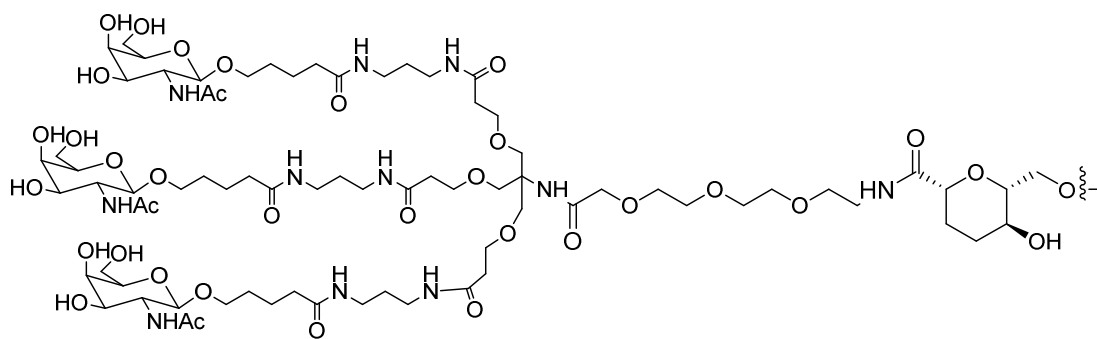


(I-2),

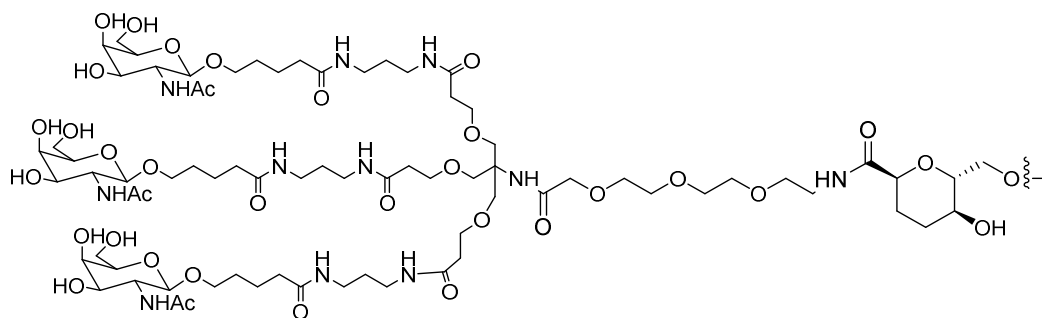


(I-3),

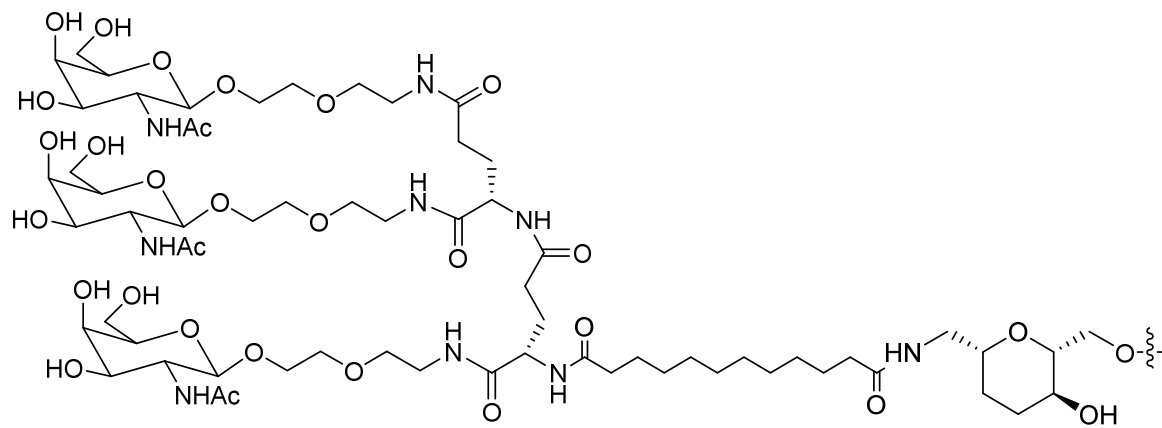




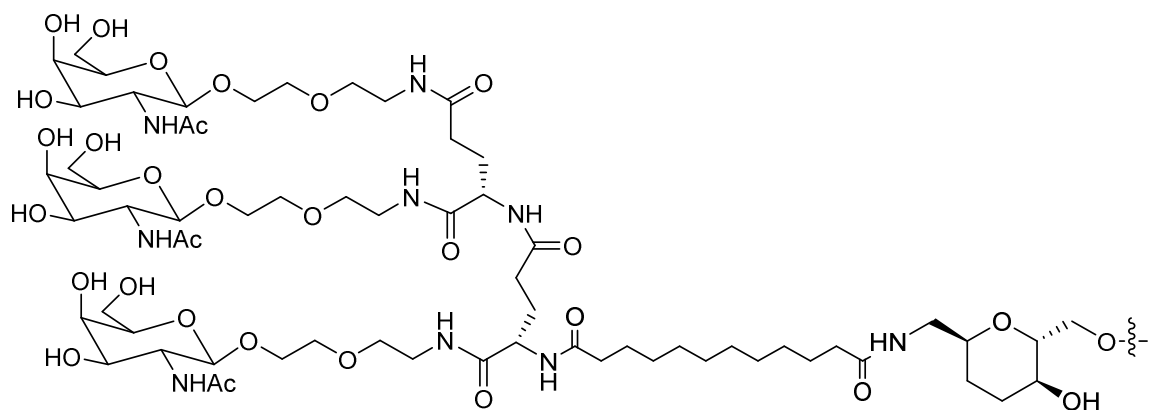
(I-7),



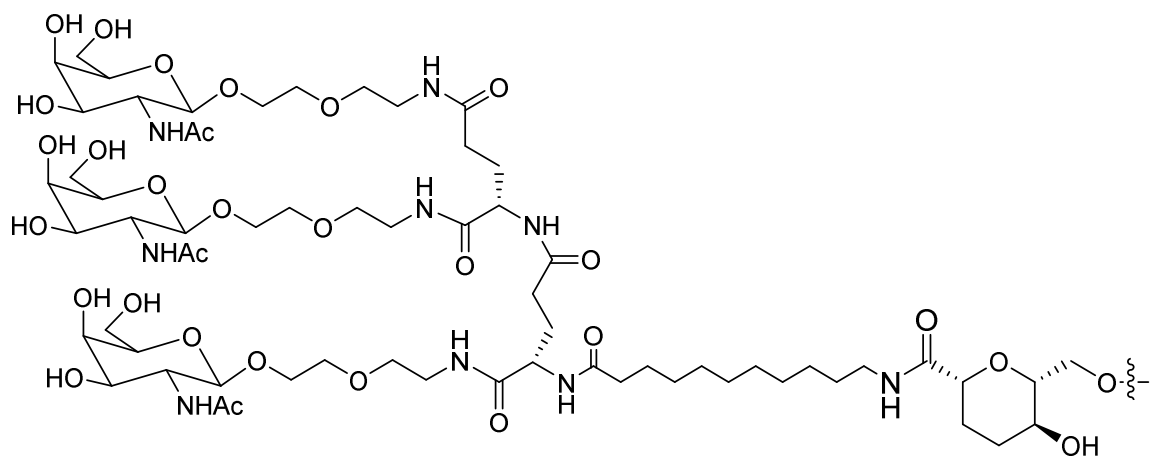
(I-8),



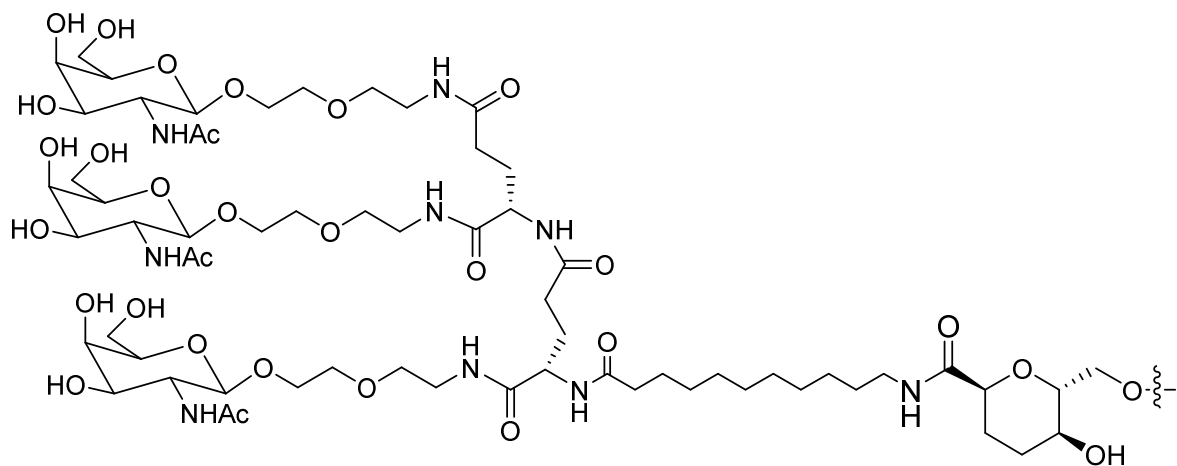
(I-9),



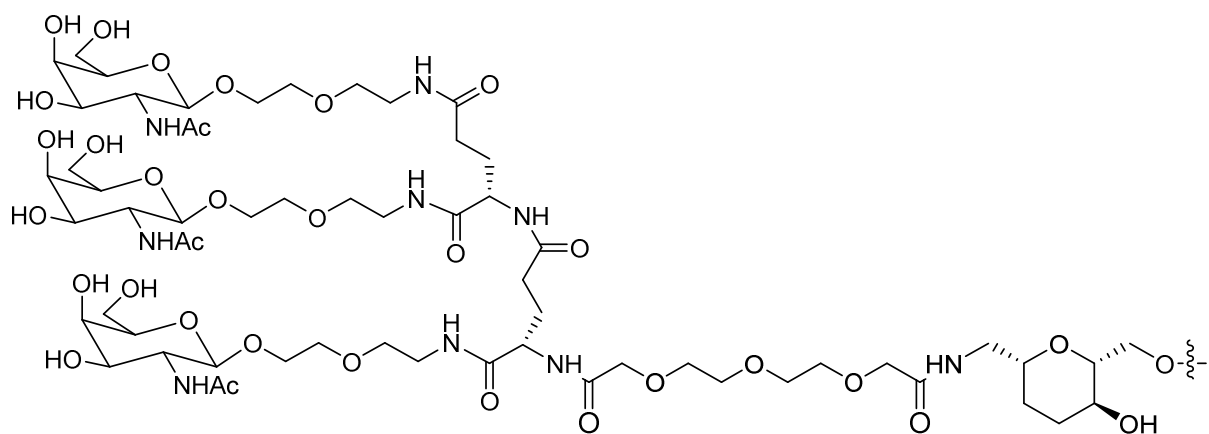
(I-10),



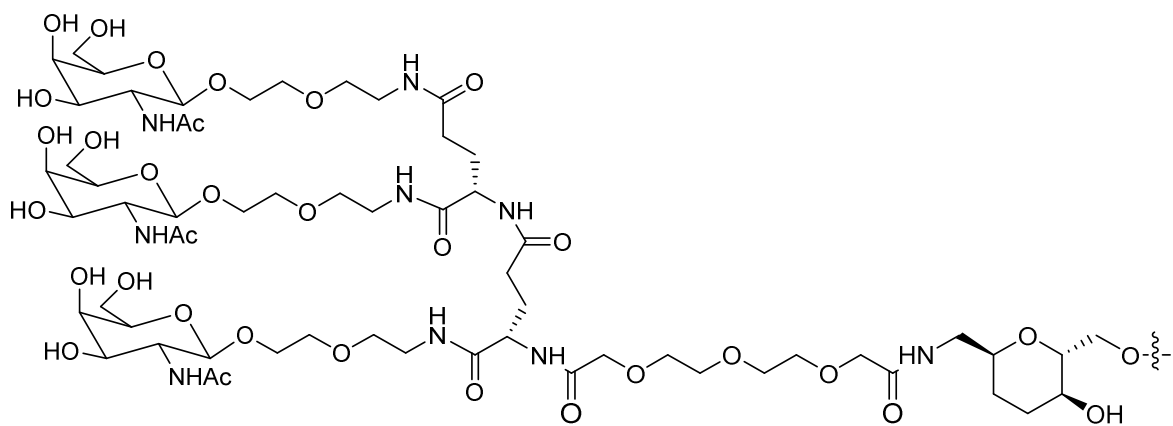
(I-11),



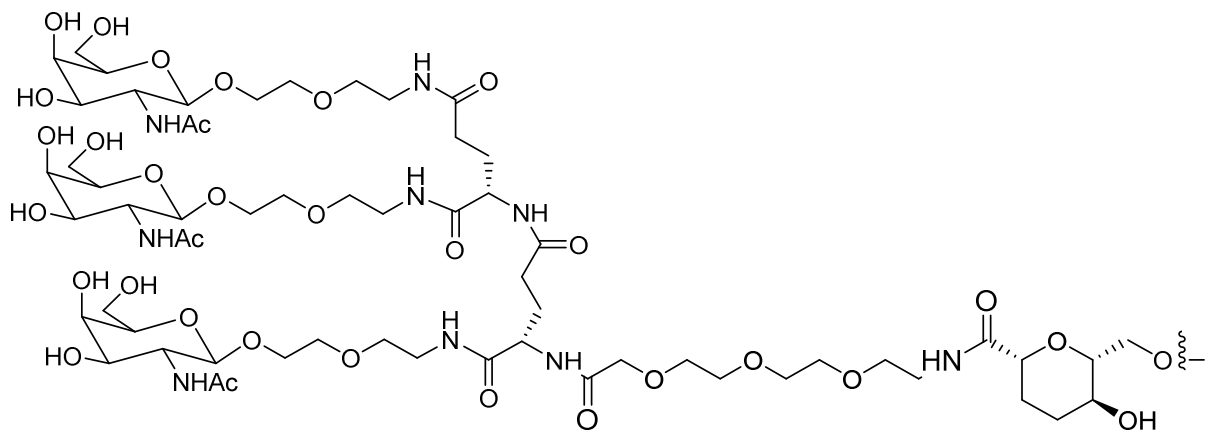
(I-12),



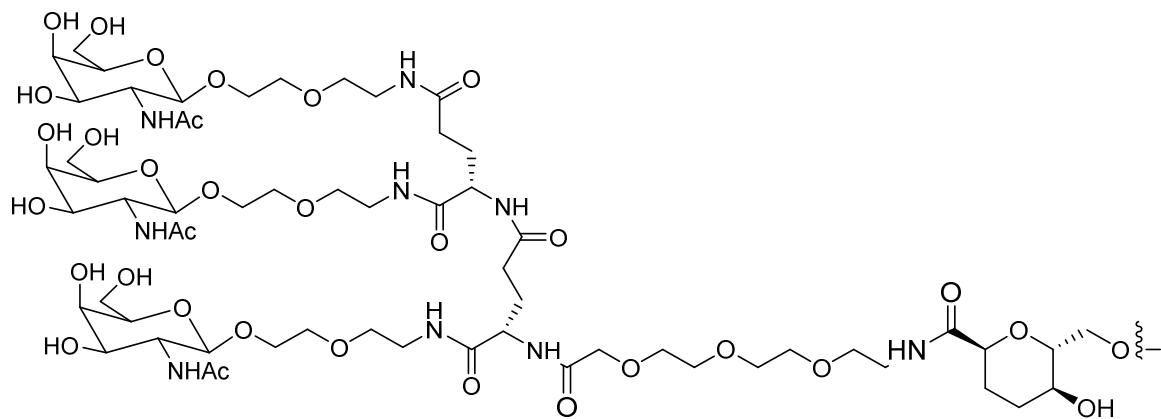
(I-13),



(I-14),

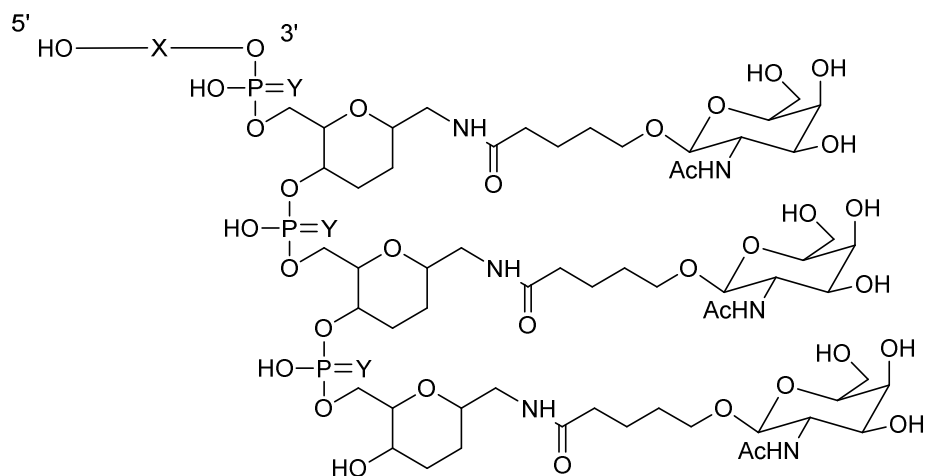


(I-15), or

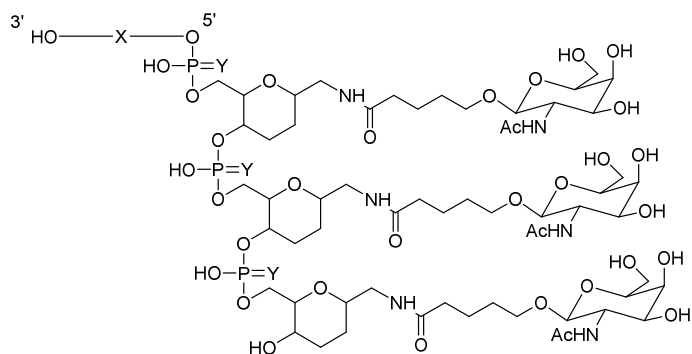


(I-16);

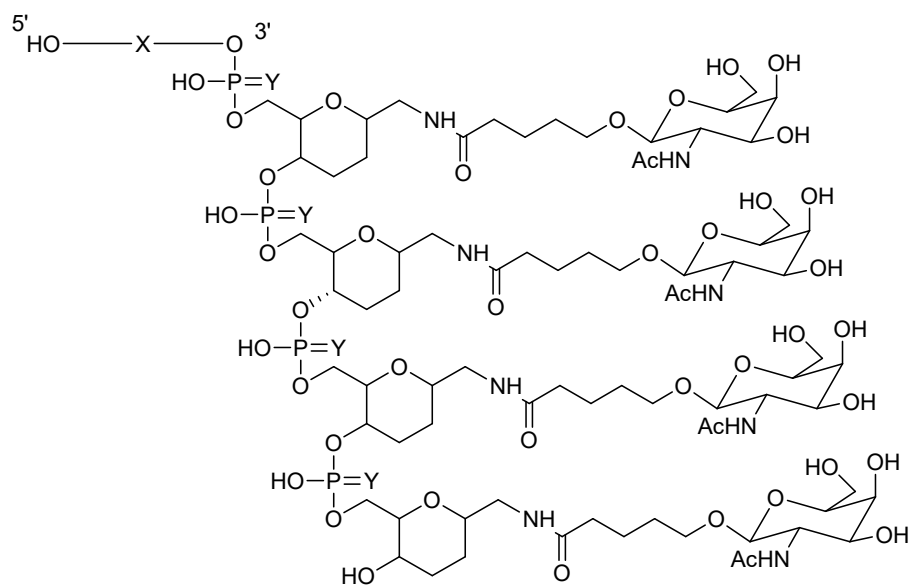
or at least one of chemical formulas II-1 to II-28:



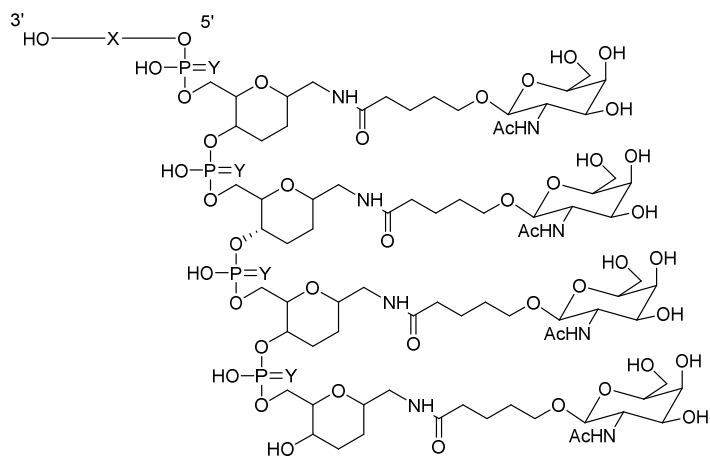
(II-1),



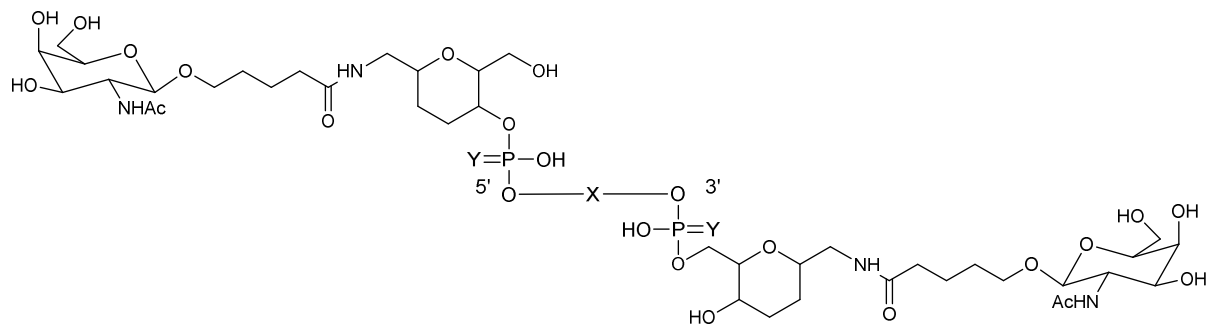
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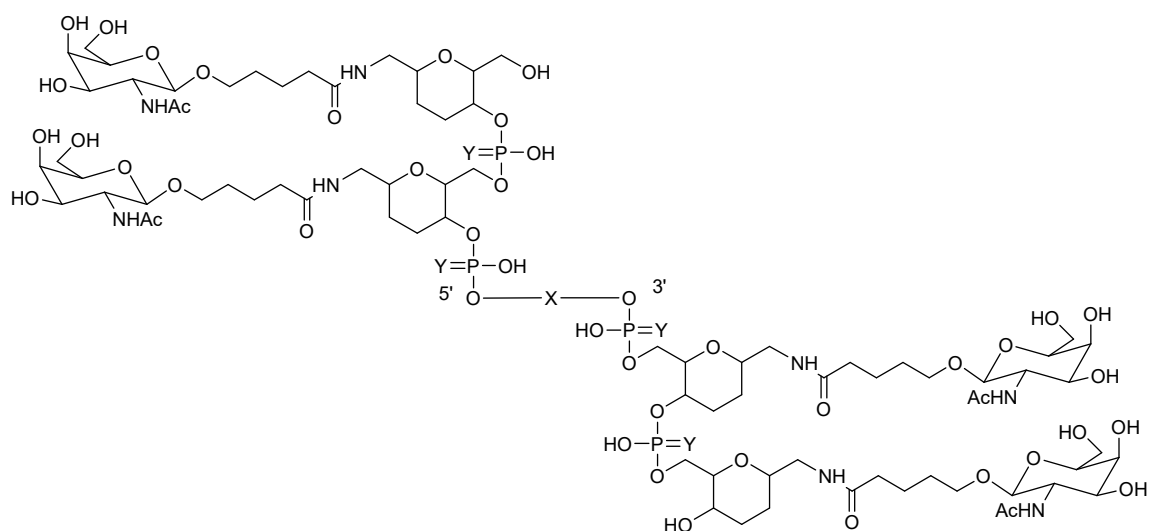
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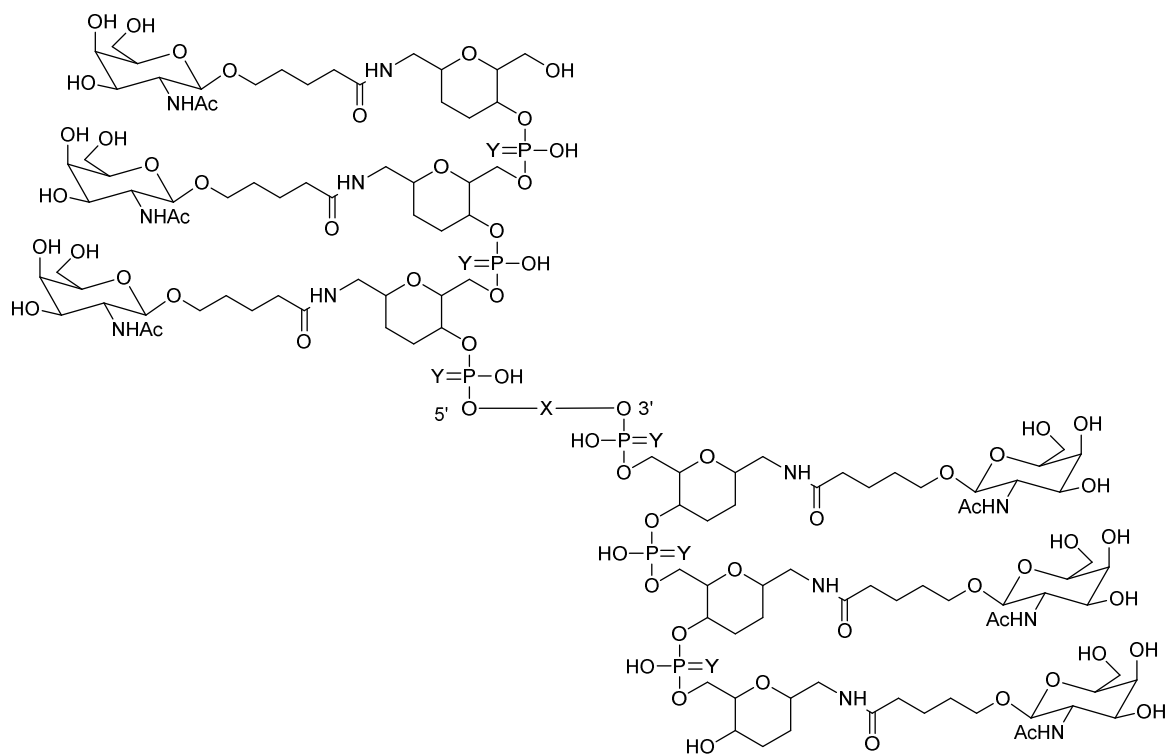
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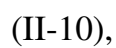
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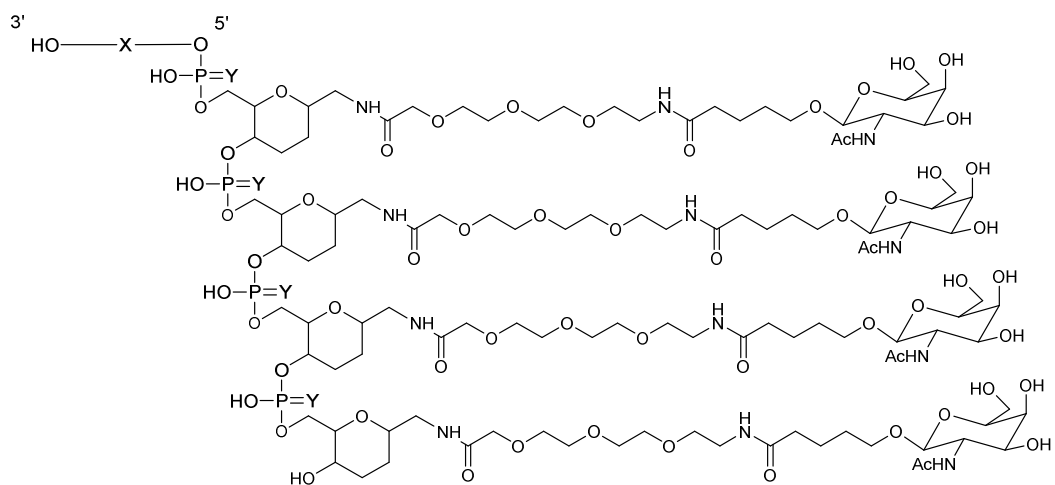


(II-6),

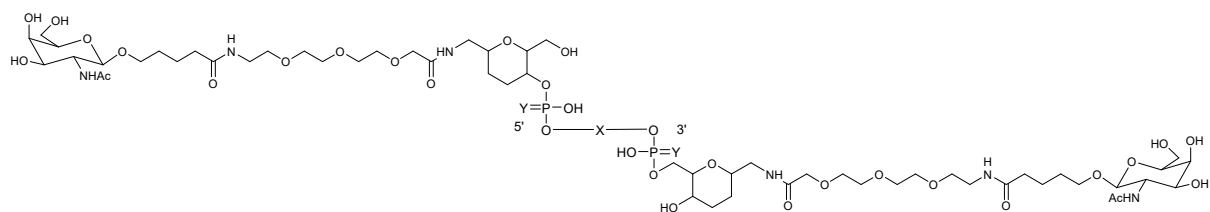


(II-7),

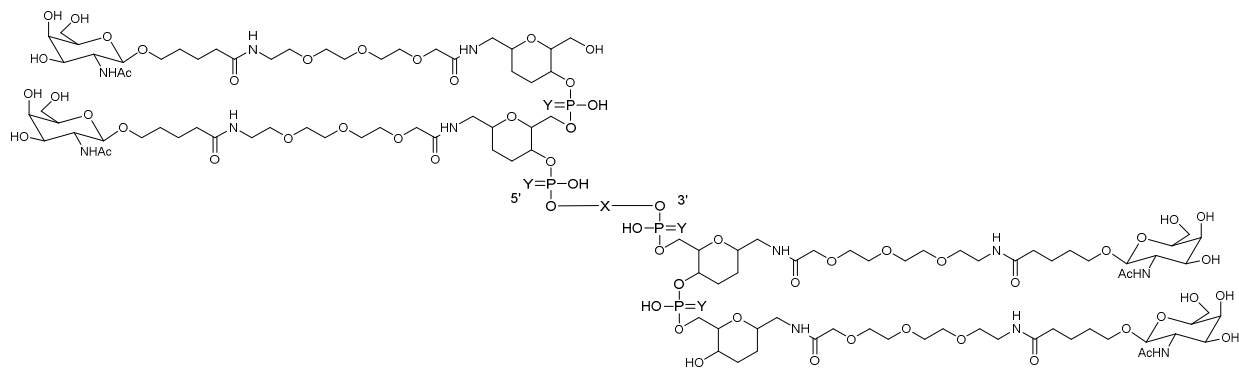




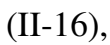
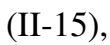
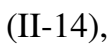
(II-11),

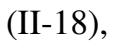
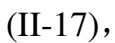


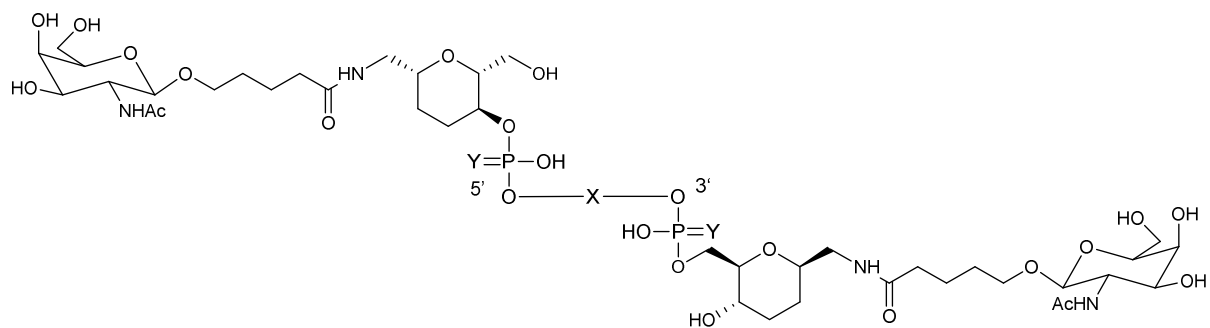
(II-12),



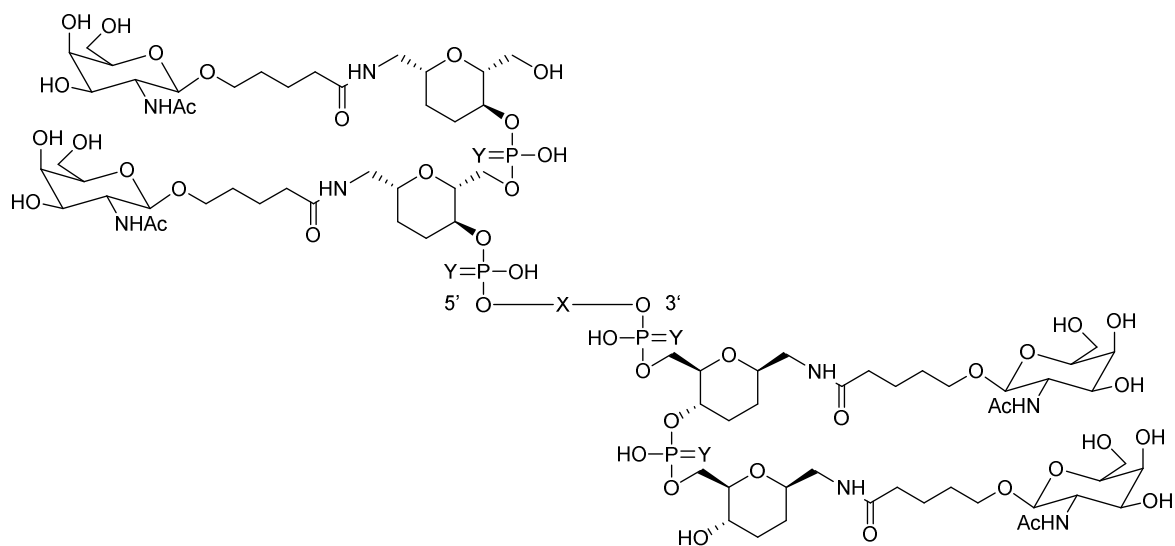
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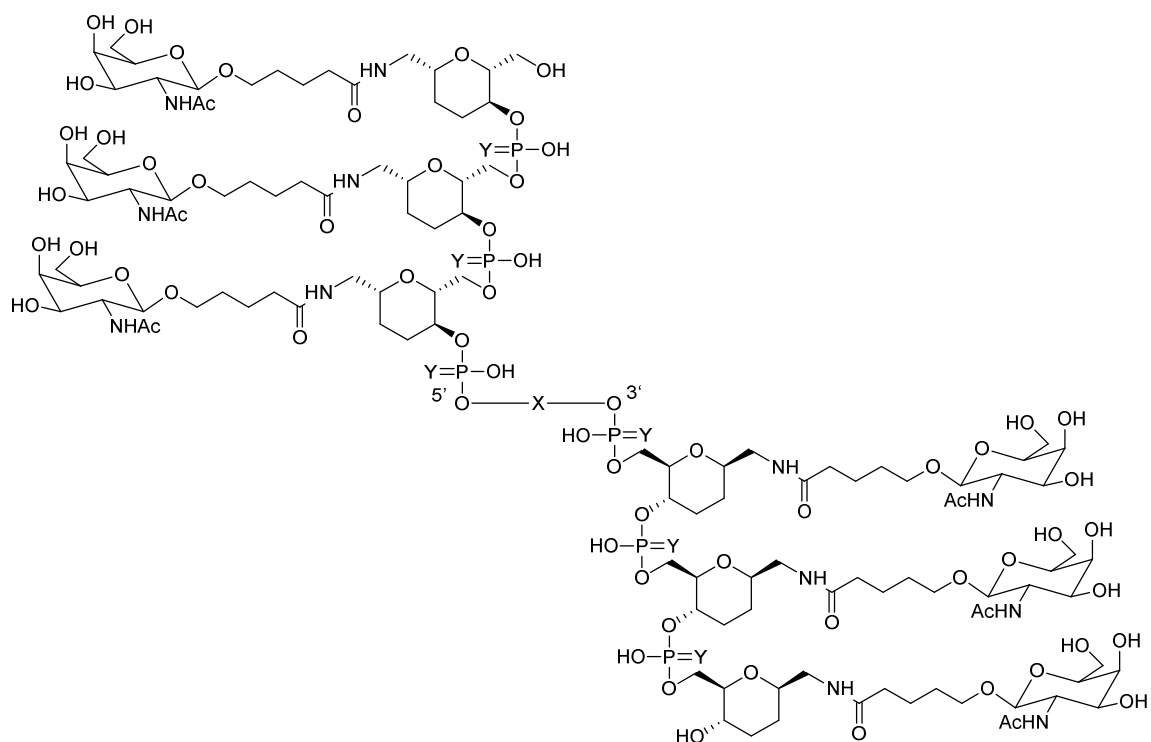




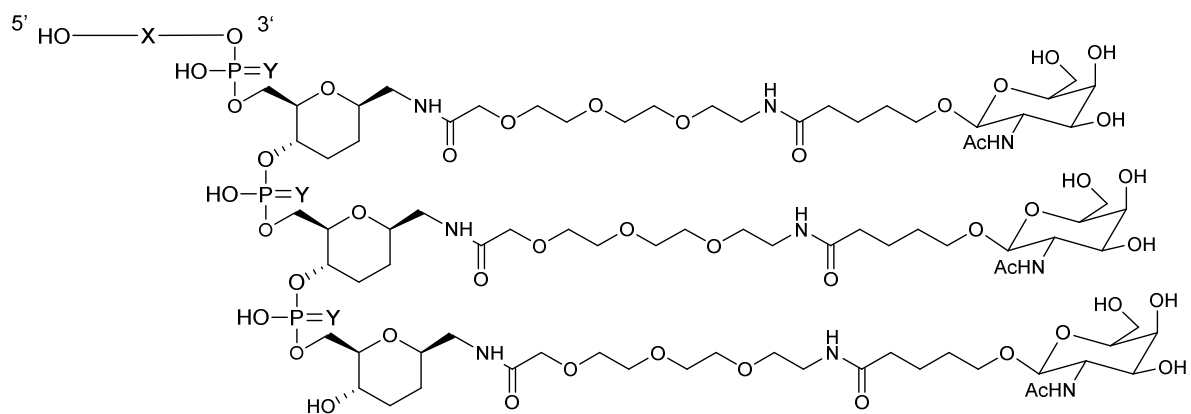
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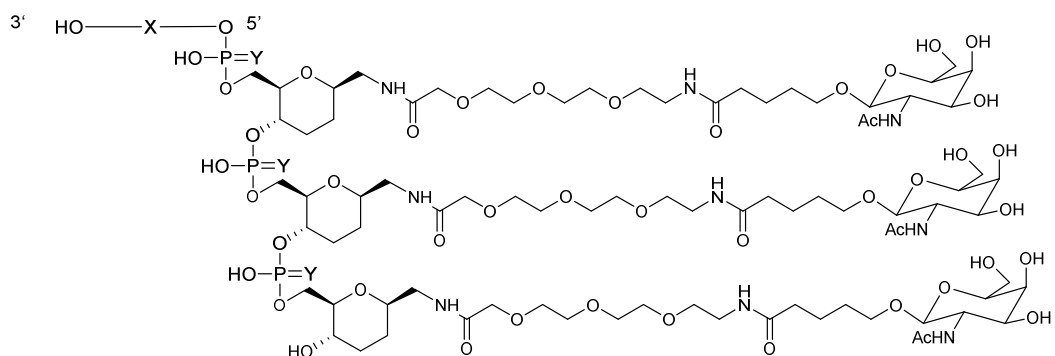
(II-20),



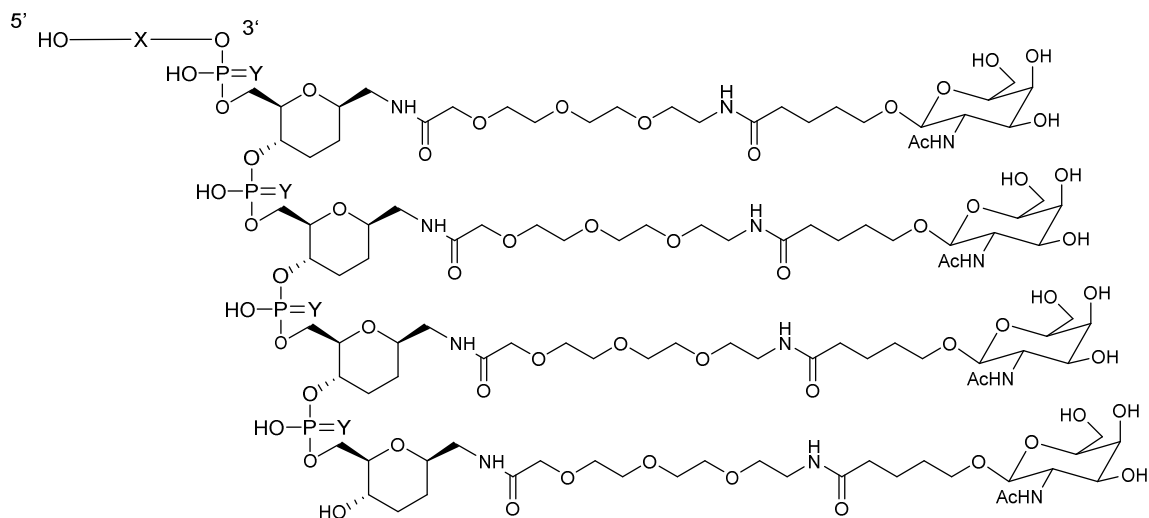
(II-21),



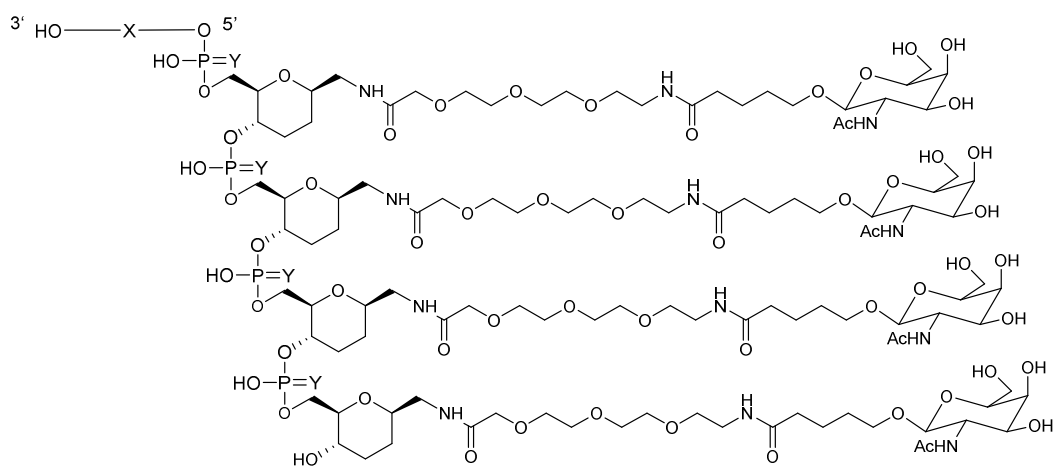
(II-22),



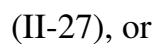
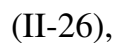
(II-23),



(II-24),



(II-25),



9. The LPA RNA interference agent of claim 8, wherein the ligand is conjugated to the 5' end and/or 3' end of the sense strand.

10. The LPA RNA interference agent of claim 8, wherein a) the antisense strand comprises: 359AS: AmsUfsAmAmCfUmCmUmGm UmCmCm AmUfUm

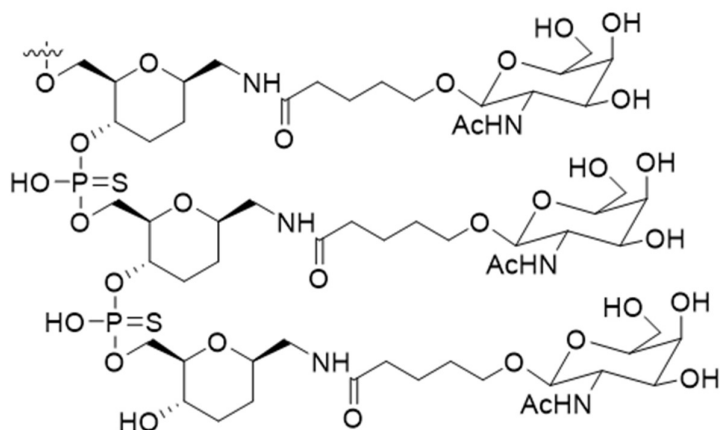
AfCmCm AmUmGms GmsUm, and/or the sense strand comprises: CmsAmsUm
GmGmUm AmAmUf GfGfAm CmAmGm AmGmUm
UmAmUms[Gal-6]s[Gal-6]s[Gal-6]; or

b) the antisense strand comprises: 498AS :

AmsAfsGmAmUfUmGmAmCmAmUmGmUmCfCmUfUmCmCmUmGmsUmsG
m, and the sense strand contains:

CmsAmsGmGmAmAmGmGmAfCfAfUmGmUmCm AmAmUm

CmUmUms[Gal-6]s[Gal-6]s[Gal-6]. The [Gal-6] s [Gal-6] s [Gal-6] structure is
given as follows:



11. A use of the LPA RNA interference agent of any of claims 1 to 10 in the preparation of a drug, wherein the drug is used to reduce LPA mRNA or protein expression in mammals, or to prevent and/or treat diseases or conditions related to LPA expression, or to reduce the risk of diseases or conditions.

12. The use of claim 11, wherein the LP(a) protein has an expression level of 34.100 nmol/L or more.

13. The use of claim 11, wherein the diseases or conditions comprise diseases of liver origin, inflammatory, cardiovascular and cerebrovascular diseases, myocardial infarction, or metabolic diseases, preferably, the cardiovascular and cerebrovascular diseases comprise hyperlipidemia, stroke, atherosclerosis, thrombosis, coronary heart disease, cardiac apoplexy, cerebral apoplexy or aortic stenosis.

14. The use of claim 11, wherein the drug is a composition which further comprises at least one selected from the group consisting of LDL-C, cholesterol, and triglyceride lowering agent.

15. The use of claim 11, wherein the drug is a composition which further comprises a PCSK9 RNAi inhibitor, a PCSK9 antibody inhibitor, and a PCSK9 small molecule inhibitor.