

RNA INHIBITOR FOR INHIBITING APOC3 GENE EXPRESSION AND USE THEREOF

Cross-reference of the relevant application

The present invention claims the priority of the Chinese patent applications 202210936491.5, 202310260531.3 and 202310655563.3 with the names of “An RNA inhibitor for inhibiting APOC3 gene expression and application thereof”, “APOC3 inhibitors and application thereof” and “An RNA inhibitor for inhibiting APOC3 gene expression and application thereof” filed on August 5, 2022, March 17, 2023 and June 5, 2023, the entire content of which are incorporated in the present invention by reference.

Technical field

The present invention relates to the biomedical field, specifically involving an RNA inhibitor that suppresses APOC3 gene expression and its application.

Background Art

RNA inhibitor

RNA inhibitor (RNA interference) was discovered by Andrew Z. Fire et al. during antisense RNA inhibition experiments in *Caenorhabditis elegans* in 1998, and this process was called RNA inhibitor. This discovery was rated as one of the top ten scientific advances in 2001 by Science magazine, and ranked first among the top ten scientific advances in 2002. Since then, siRNA with RNAi as its mechanism of action has received widespread attention as a potential gene therapy drug. In 2006, Andrew Z. Fire and Craig C. Mello won the Nobel Prize in physiology or medicine for their contributions in the study of RNAi mechanism. RNAi is triggered by double stranded RNA (dsRNA) in many organisms, including animals, plants and fungi. In the process of RNAi, an endonuclease called "Dicer" cleaves or "dices" long strand of dsRNA into small segments of 21-25 nucleotides long. These small segments are known as small interfering RNAs (siRNAs), whose antisense strands are loaded onto Argonaute protein (AGO2). AGO2 loading occurs in the RISC-loading complex, a ternary complex consisting of Argonaute protein, Dicer, and dsRNA binding protein (TRBP for short). During loading, the sense strand is cleaved by AGO2 and discharged. Then, AGO2 uses the antisense strand to bind to mRNA containing fully complementary sequences, and then catalyzes the cleavage of these mRNA, resulting in mRNA cleavage to loss the role as a translation template, thereby preventing the synthesis

of related proteins. After cleavage, the cleaved mRNA is released, and the RISC-loading complex loaded with the antisense strand is recycled for another round of cleavage.

According to statistics, among the disease-related proteins in human body, about more than 80% of them cannot be targeted by current conventional small molecule drugs and biological macromolecule preparations, and are considered as undruggable proteins. Gene therapy, which aims to treat diseases through gene expression, silencing and other functions, is considered by the industry to be the third generation of therapeutic drugs after chemical small molecule drugs and biological macromolecular drugs. This therapy treats diseases at the genetic level and is not restricted by undruggable proteins. As the most mainstream type of gene therapy, RNAi technology treats diseases at the mRNA level and has higher efficiency as compared with chemical small molecule drugs and biological macromolecular drugs at the protein level. RNAi technology can be used to design the sense strand and antisense strand sequences of siRNAs with high specificity and good inhibitory effect according to the specific gene sequence. These single strand sequences are synthesized through solid-phase synthesis, and then the sense strand and antisense strand are paired into siRNA in a specific annealing buffer according to the principle of base pairing. Finally, it is delivered to the corresponding target site in the body through the vehicle system, degrading the target mRNA, and destroying the function of the target mRNA as a translation template, thus preventing the synthesis of related proteins.

Delivery system of siRNA

siRNA is unstable in blood and tissues and easily degraded by nucleases. In order to improve the stability of siRNA, the sense strand and/or antisense strand of siRNA can be modified, but these chemical modifications only provide limited protection from nuclease degradation and may ultimately affect the activity of siRNA. Therefore, a corresponding delivery system is needed to ensure that siRNA can safely and efficiently pass through cell membrane. Due to its large molecular weight, large amount of negative charge, and high water solubility, siRNA itself cannot smoothly pass through cell membrane to enter the cell.

Liposome is basically composed of a hydrophilic core and a phospholipid bilayer. It has a phospholipid bilayer similar to a biological membrane and has high biocompatibility, therefore liposome once became the most popular and widely used siRNA vehicle. Liposome-mediated siRNA delivery mainly encapsulates siRNA into liposomes to protect siRNA from degradation by nucleases, improves the efficiency of siRNA passing through cell membrane barriers, and thereby promotes cellular

absorption. Examples of liposomes include, for example, anionic liposomes, pH sensitive liposomes, immunoliposomes, fusogenic liposomes, and cationic lipids etc. Despite some progress, liposomes themselves are prone to triggering inflammatory reactions, a variety of antihistamines and hormones such as cetirizine and dexamethasone must be used before administration to reduce possible acute inflammatory reactions. Therefore, they are not suitable for all treatment fields in actual clinical application, especially some chronic disease treatment fields. Possible accumulated toxicity resulting from long-term use is a potential safety hazard. Therefore, a safer and more effective vehicle system is needed to deliver siRNA.

Asialoglycoprotein receptor (ASGPR) in the liver is a receptor specifically expressed on hepatocytes and is a highly efficient endocytic receptor. Due to the fact that under physiological conditions in the body, after enzymatic or acid hydrolysis of sialic acids, the exposed secondary ends of various glycoproteins are galactose residues, the sugar specifically bound to ASGPR is galactosyl, so ASGPR is also called galactose-specific receptor. Monosaccharide and polysaccharide molecules such as galactose, galactosamine, and N-acetylgalactosamine all have high affinity for ASGPR. ASGPR mainly has the physiological function of mediating the clearance of asialoglycoprotein, lipoprotein and other substances in the blood, and it is closely related to the occurrence and development of liver diseases such as viral hepatitis, liver cirrhosis, liver cancer and so on. The discovery of this characteristic of ASGPR plays an important role in the diagnosis and treatment of hepatogenic diseases (Ashwell G and Harford J, Carbohydrate specific Receptors of the Liver, Ann Rev Biochem 1982 51:531-554). The therapeutic drug for hepatogenic diseases containing galactose or galactosamine and their derivatives in the structure can have specific affinity with ASGPR, so it actively targets liver and does not need other vehicle systems to deliver.

APOC3 and cardiovascular and cerebrovascular diseases

APOC3 (apolipoprotein C-III) is the gene encoding apolipoprotein C3, with a full length of about 3.1 kb. It is an 8.8 kD glycoprotein composed of 79 amino acid residues and mainly synthesized in the liver. APOC3 has the function of inhibiting the activities of lipoprotein lipase and hepatic lipase, it interferes with the ApoE-mediated binding of triglyceride (TG)-rich lipoproteins to hepatic lipase, affects the balance of lipid metabolism, and easily leads to hypertriglyceridemia. A large number of related studies have shown that the polymorphism at the Sst I restriction site of the APOC3 gene is

associated with hypertriglyceridemia, and therefore may also be associated with other cardiovascular diseases caused by hypertriglyceridemia.

APOC3 plays a key role in the metabolism of triglyceride-rich lipoproteins. It is mainly combined with high-density lipoprotein cholesterol (HDL-c) (about 70%) in normal fasting plasma, while the plasma APOC3 levels in patients with hypertriglyceridemia is significantly increased, which are primarily (about 86%) bound to very low-density lipoprotein (VLDL).

Domestic and foreign studies have shown that elevated plasma APOC3 level can cause hypertriglyceridemia, and plasma APOC3 level is positively correlated with plasma triglyceride and triglyceride level in very low-density lipoprotein. Currently, a large number of literature have reported that APOC3 gene functions are related to cardiovascular and cerebrovascular diseases such as coronary atherosclerosis, type 2 diabetes, and cerebral infarction.

Familial hyperchylomicronemia (FCS), also known as lipoprotein lipase deficiency, is a rare autosomal recessive disorder, also known as primary hyperlipoproteinemia type I, which requires long-term restriction of the fat amount in the diet. Before November 2012, there was no specific drug to treat FCS. In addition to elevated triglycerides, the clinical features of FCS also include recurrent pancreatitis. In November 2012, the European Commission (EC) approved Glybera, the first gene therapy drug in the Western world, but Glybera is very expensive. The cost per patient is expected to be up to 1.25 million Euros (approximately \$1.6 million). There is an urgent need for a specific drug to treat FCS. APOC3 is an important regulator of lipid metabolism. Loss-of-function mutations in APOC3 will inhibit hepatocytes from clearing triglyceride-rich lipoprotein particles, leading to increased TG and VLDL levels and decreased HDL-c level in the blood. By silencing the expression of APOC3, harmful lipoprotein indicators (i.e. TG and VLDL levels) are reduced and the level of "good" cholesterol HDL-c is increased. APOC3 small interfering inhibitors are being developed for the treatment of hypertriglyceridemia (HTG), severe hypertriglyceridemia (sHTG), and familial chylomicronemia syndrome (FCS). This gives new hope for the treatment of chylomicronemia.

Existing technology can already use RNA interference technology to inhibit APOC3 gene expression, but the inhibition efficiency and persistence still need to be improved. The market needs an RNA inhibitor with higher inhibition efficiency and longer lasting effect.

Invention content

In order to solve the above problems, the present invention provides an RNA inhibitor for inhibiting

the expression of APOC3 gene or a pharmaceutically acceptable salt thereof, which specifically interferes with the mRNA of APOC3 gene, destroys its function as a translation template, and prevents the expression of APOC3 protein, thereby preventing and/or treating APOC3 gene-mediated related diseases. The RNA inhibitor of the present invention has excellent APOC3 protein expression inhibition effect, long-lasting action time, and therefore has high medical application value.

In one aspect, the present invention provides an RNA inhibitor for inhibiting the expression of APOC3 gene or a pharmaceutically acceptable salt thereof, wherein the RNA inhibitor is formed by base pairing of a sense strand and an antisense strand with chain length of 15-30 nucleotides each independently, the chain length is preferably 19-23 nucleotides each independently, and at least 80% of the bases between the sense strand and the antisense strand are complementary.

In some embodiments, the antisense strand is preferably selected from a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b): 5'uugguggcgugcucauguaatt 3' (SEQ ID NO. 212), 5'uaaccugcaugaagcugagatt 3' (SEQ ID NO. 216), 5'uuaacggugcuccaguagucutt 3' (SEQ ID NO. 224), 5'cagagaacuuguccuuaacggtt 3' (SEQ ID NO. 225), 5' uauugaggucucaggcagccatt 3' (SEQ ID NO. 241), 5'ugaaguuggucugaccucaggtt 3' (SEQ ID NO. 255), 5' gcacugagaauacuguccuuuu 3' (SEQ ID NO. 256), 5'gcacugagaauacuguccuu3' (SEQ ID NO. 459), 5' acacugagaauacuguccua 3' (SEQ ID NO. 461), 5' ugaauacuguccuuuuuagc 3' (SEQ ID NO. 465), 5' cugagaauacuguccuuuuu 3' (SEQ ID NO. 471), 5' acugagaauacuguccuuua 3' (SEQ ID NO. 472), 5' uaaucuguccuuuuuagcaa 3' (SEQ ID NO. 438), 5'ugaggucucaggcagccagg3' (SEQ ID NO. 600), 5'uggauaggcagguggacuugg3' (SEQ ID NO. 620), 5'caggauggauaggcaggugga3' (SEQ ID NO. 624), 5'gagcacugagaauacugucc3' (SEQ ID NO. 668), 5'acacugagaauacugucguc3' (SEQ ID NO. 687), 5'acacugagaauacugucguu3' (SEQ ID NO. 700), 5' ucacugagaauacuguccuu 3' (SEQ ID NO. 519);

where, g= guanylate, a= adenylate, u= uridylate, c= cytidylate, t= thymidylate

It should be noted that, at least 15 consecutive nucleotides each independently represent: 15, 16, 17, 18, 19, 20, 21 ... etc. consecutive nucleotides, and the difference of no more than 3 nucleotides each independently indicates: 1, 2 or 3 different nucleotides. The sense strands and antisense strands exemplified below are not limited to the combinations shown in the examples of the present invention to form RNA inhibitors. As long as they can be complementary paired to form double strands, the sense strand and the antisense strand can be combined at will and are not limited by the examples.

In some embodiments, more preferably, the sense strand and the antisense strand are selected from:
a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b). The sequence combination of the sense strand and the antisense strand is as follows:

SEQ ID NO.	single strand code	sense strand 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
161	S58	uuacaugaagcacgccaccaatt	212	AS58	uugguggcgugcuucauguaatt
165	S62	ucucagcuucaugcaggguuat t	216	AS62	uaaccugcaugaagcugagatt
173	S70	agacuacuggagcacccguaat t	224	AS70	uuaacggugcuccaguagucutt
174	S71	ccguuaaggacaaguucucugt t	225	AS71	cagagaacuuguccuuaacggtt
190	S87	uggcugccugagaccucaauat t	241	AS87	uauugaggucucaggcagccatt
204	S101	ccugaggucagaccaacuucat t	255	AS10 1	ugaaguuggucugaccucaggtt
205	S102	aagggacaguauucucagugct t	256	AS10 2	gcacugagaauacuguccuuuu
440	S268	gggacaguauucucagugcua	459	AS27 0	gcacugagaauacuguccuu
442	S270	uagggacaguauuctcagugu	461	AS27 2	acacugagaauacuguccua
446	S274	gcuuaaaagggacaguauuca	465	AS27 6	ugaauacuguccuuuaagc
452	S280	aaagggacaguauucucagug	471	AS28 2	cugagaauacuguccuuua
453	S281	aagggacaguauucucagugc	472	AS28 3	acugagaauacuguccuuua
702	S194	gcuuaaaagggacaguauuca	438	AS19 4	uaauacuguccuuuaagcaa
864	S356	guggcugccugagaccucaau	600	AS35 6	ugaggucucaggcagccacgg
884	S376	aaguccaccugccuauccauc	620	AS37 6	uggauaggcagguggacuugg
888	S380	caccugccuauccauccugaa	624	AS38 0	caggauggauaggcaggugga

931	S423	gggacagauuucucagugcuu	667	AS42 3	gcacugagaauacuguccuu
932	S424	gacagauuucucagugcucu	668	AS42 4	gagcacugagaauacugucc
951	S443	gagcgacagauuucucagugu	687	AS44 3	acacugagaauacugucgcuc
964	S456	aagcgacagauuucucagugu	700	AS45 6	acacugagaauacugucgcuu
781	S273	aaggacagauuucucaguga	519	AS27 5	ucacugagaauacuguccuu

where, g=guanylate, a=adenylate, u=uridylate, c=cytidylate, t=thymidylate。

In the RNA inhibitor of the present invention, one or more nucleotides on the sense strand and/or the antisense strand can be modified to form modified nucleotides.

Preferably, in the RNA inhibitor of the present invention, the sense strand and/or the antisense strand contains at least one 2'-modified nucleotide, and the 2'-modified nucleotide includes: 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoronucleotide, 2'-deoxynucleotide, 2'-methoxyethyl nucleotide, 2'-amino nucleotide or 2'-alkyl nucleotide.

More preferably, in the RNA inhibitor of the present invention, the sense strand and/or the antisense strand contains at least one 2'-O-methyl nucleotide or 2'-deoxy-2'-fluoronucleotide.

Preferably, in the RNA inhibitor of the present invention, the phosphate bonds among three adjacent nucleotides at at least one of the ends of the sense strand and/or antisense strand can be thiolated.

In the above technical solutions, preferably, the sense strand and the antisense strand are selected from: a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

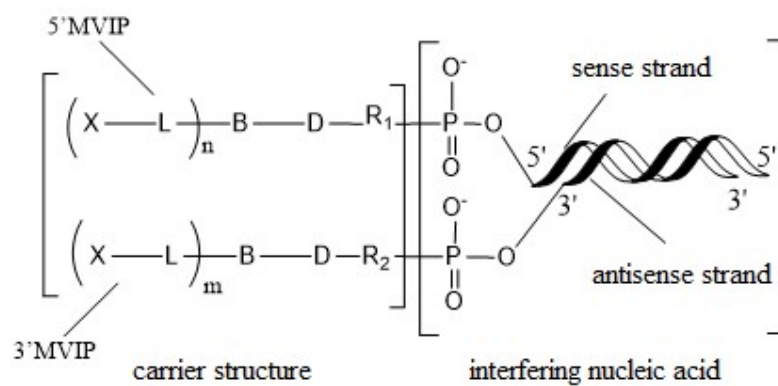
SE	singl		SE		
Q	e		Q	single	
ID	stran	sense strand 5'→3'	ID	strand	antisense strand 5'→3'
NO.	d		NO.	code	
	code				
411	S16	UsUsACAUGAfAfGfCACGCC	381	AS16	UsfUsGfGUfGGfCGUGCUfUCfA
	7	ACCsAsA		7	UGUsAsA

SE Q ID NO.	singl e stran d code	sense strand 5'→3'	SE Q ID NO.	single strand code	antisense strand 5'→3'
412	S16 8	UcCsUCAGCUfUfCfAUGCAG GGUsUsA	382	AS16 8	UsfAsAfCCfCUfGCAUGAfAGfC UGAsGsA
417	S17 3	AsGsACUACUfGfGfAGCACC GUUsAsA	387	AS17 3	UsfUsAfACfGGfUGCUCcfAGfU AGUsCsU
418	S17 4	CsCsGUUAAGfGfAfCAAGU UCUCsUsG	388	AS17 4	CsfAsGfAGfAAfCUUGUCfCUfU AACsGsG
428	S18 4	UsGsGCUGCCfUfGfAGACCU CAAsUsA	398	AS18 4	UsfAsUfUGfAGfGUCUCAfGGfC AGCsCsA
435	S19 1	CsCsUGAGGUfCfAfGACCAA CUUsCsA	405	AS19 1	UsfGsAfAGfUfUGGUCUGfACfC UCAsGsG
436	S19 2	AsAsGGGACAfGfUfAUUCU CAGUsGsC	406	AS19 2	GsfCsAfCUfGAfGAAUACfUGfU CCCUUsUsU
478	S28 7	GsGsGAfCAfGfUfAUUCUCA GUGCsUsA	507	AS28 9	GsCsACUGfAGAAUfACfUGUCC CsUsU
481	S29 0	UsAsGGfGAfCfAfGUAAUUCT CAGUsGsU	510	AS29 2	AsCsACUGfAGAAUfACfUGUCC CsUsA
486	S29 5	GsCsUUAAAAfGfGfGACAG UAUUsCsA	515	AS29 7	UsfGsAfAUfACfUGfUCfCCfUUF UUFAsGsC
497	S30 6	AsAsAGfGGfAfCfAGUAUUC UCAGsUsG	526	AS30 8	CsfUsGfAGfAAfUACUGUfCCfC UUUsUsA
499	S30 8	AsAsGGfGAfCfAfGUAAUUCU CAGUsGsC	527	AS30 9	AsCsUGAGfAAUACfUGfUCCCCU UsUsA
486	S29 5	GsCsUUAAAAfGfGfGACAG UAUUsCsA	532	AS31 4	UsAsfAUfACfUGfUCfCCfUUFU fAAGCsAsA

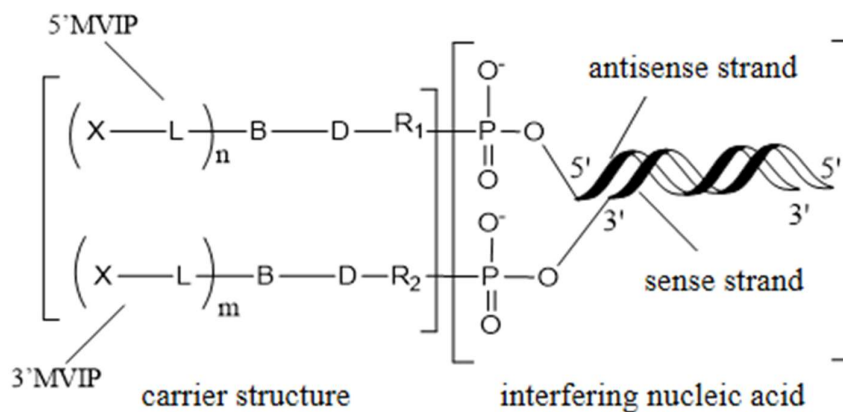
SE	singl		SE	single	
Q	e		Q	strand	
ID	stran	sense strand 5'→3'	ID	strand	antisense strand 5'→3'
NO.	d		NO.	code	
102	S45	GsUsGGCUGCfCfUfGAGACC	965	AS45	UsfGsAfGGfUCfUCAGGCfAGfC
8	7	UCAsAsU	7	7	CfACsfGsG
102	S45	AsAsGUCCACfCfUfGCCUAU	966	AS45	UsfGsGfAUfAGfGCAGGUfGGfA
9	8	CCAsUsC	8	8	CfUUsfGsG
103	S45	CsAsCCUGCCfUfAfUCCAUC	967	AS45	CsfAsGfGAfUGfGAUAGGfCAfG
0	9	CUGsAsA	9	9	GfUGsfGsA
103	S46	GsGsGACAGUfAfUfUCUCA	968	AS46	GsfCsAfCUfGAfGAAUACfUGfU
1	0	GUGCsUsU	0	0	CfCCsfUsU
103	S46	GsAsCAGUAUfUfCfUCAGU	969	AS46	GsfAsGfCAfCUfGAGAAUfACfU
2	1	GCUCsUsU	1	1	GfUCsfCsC
103	S46	GsAsGCGACAfGfUfAUUCU	970	AS46	AsfCsAfCUfGAfGAAUACfUGfU
3	2	CAGUsGsU	2	2	CfGCsfUsC
103	S46	GsAsGCGACAfGfUfAUUCU	976	AS46	AsfCsAfCUfGAfGafAUACfUGfU
9	8	CAGUsGsU	8	8	CfGCsUsC
111	S53	AsAsGCGACAfGfUfAUUCU	102	AS51	AsfCsAfCUfGAfGAAUACfUGfU
0	9	CAGUsGsU	4	6	CfGCsfUsU
112	S55	AsAsGGfGAfCfAfGUAUUCU	115	AS52	UsCsACUGfAGAAUfACfUGUCC
1	0	CAGUsGsA	1	9	CsUsU

where, G=2'-O-methylguanylate, A=2'-O-methyladenylate, U=2'-O-methyluridylate, C=2'-O-methylcytidylate; fG=2'-fluoroguanlylate, fA=2'-fluoroadenylate, fU=2'-fluorouridylate, fC=2'-fluorocytidylate, Gs=2'-O-methyl-3'-thioguanlylate, As=2'-O-methyl-3'-thioadenylate, Us=2'-O-methyl-3'-thiouridylate, Cs=2'-O-methyl-3'-thiocytidylate, fGs=2'-fluoro-3'-thioguanlylate, fAs=2'-fluoro-3'-thioadenylate, fUs=2'-fluoro-3'-thiouridylate, fCs=2'-fluoro-3'-thiocytidylate, T=thymidylate.

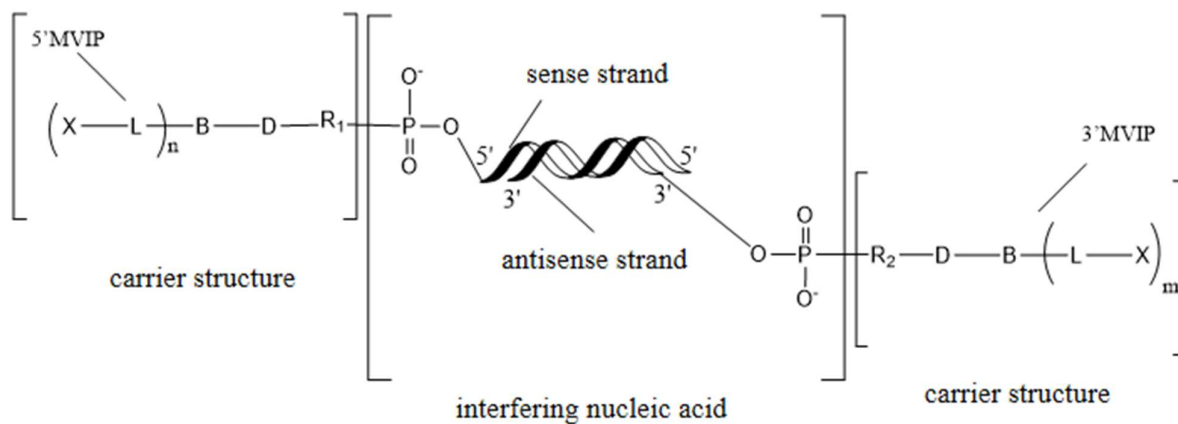
In some technical solutions, preferably, the RNA inhibitor or pharmaceutically acceptable salt thereof further contains a carrier structure, and the RNA inhibitor is as shown in Formule Ia, Ib or Ic:



Ia



Ib



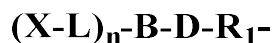
Ic

wherein,

the carrier structure includes a 5'MVIP and a 3'MVIP;

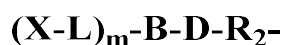
The 5'MVIP is composed of a transition point R_1 , a linking chain D, a linker B, a branched chain L and a liver targeting specific ligand X and is connected with the 5' end of sense strand or the 5' end of

antisense strand through the transition point R₁. The structure is shown in the formula I:



I

The 3'MVIP is composed of a transition point R₂, a linking chain D, a linker B, a branched chain L and a liver targeting specific ligand X and is connected with the 3' end of sense strand or the 3' end of antisense strand through the transition point R₂. The structure is shown in the formula II:

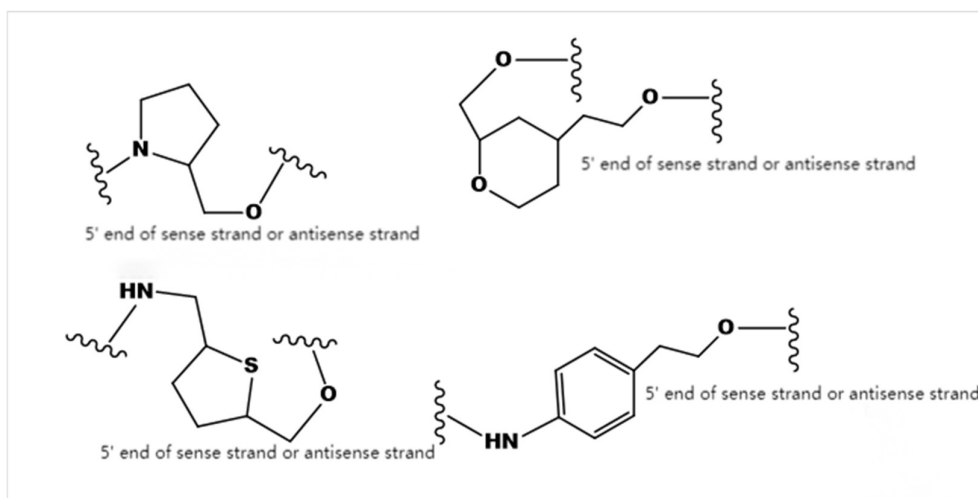


II

wherein,

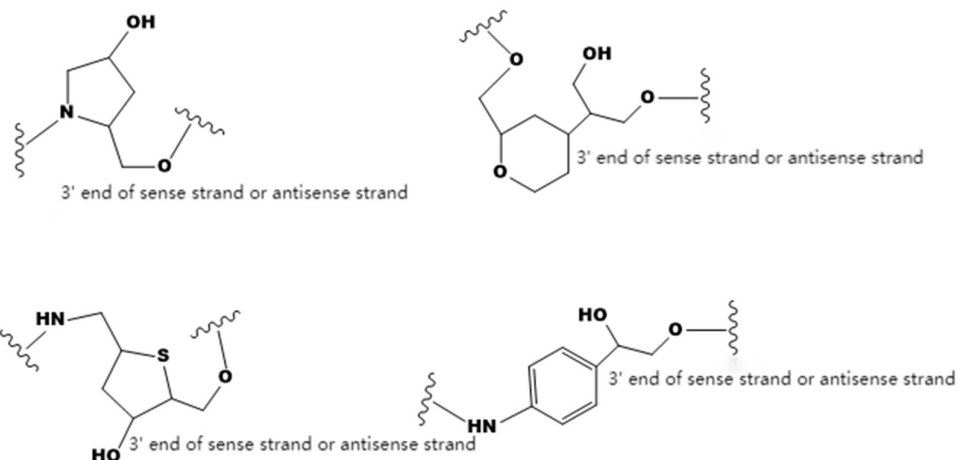
n and m are each independently any integer of 0-4, each independently preferably an integer of 1-3, and n+m = an integer of 2-6, preferably n+m=2, 3 or 4, more preferably 4.

As an example, the transition point R₁ is a heterocyclic or carbocyclic structure containing N, S or O as shown below,



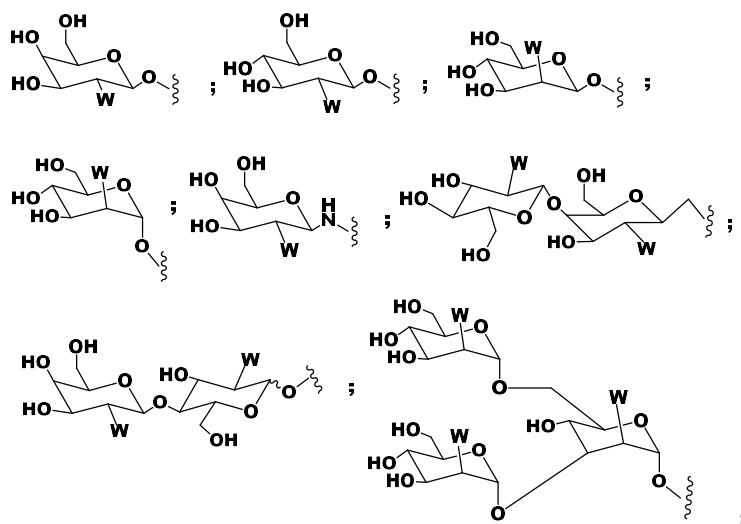
Alternatively, R₁ is -NH(CH₂)_xCH₂O-, wherein x is any integer of 3-12, preferably any integer of 4-6;

As an example, the transition point R₂ is a heterocyclic or carbocyclic structure containing N, S or O as shown below,



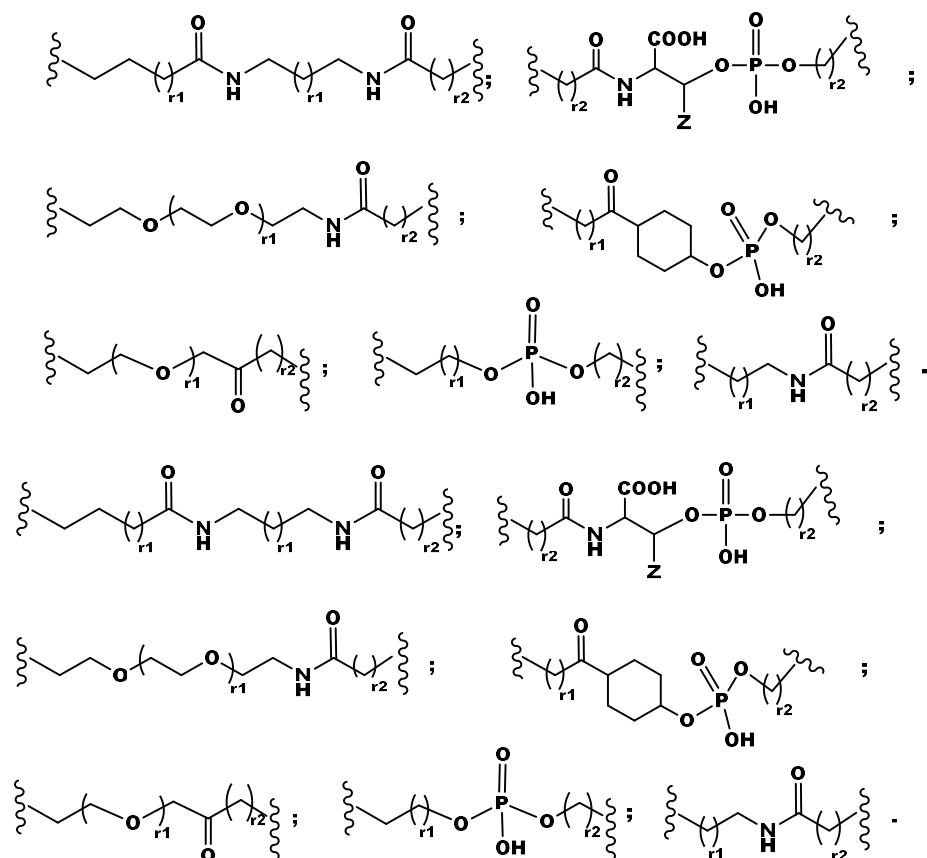
Alternatively, the transition point R_2 is $-\text{NH}(\text{CH}_2)_{x1}\text{CH}(\text{OH})(\text{CH}_2)_{x2}\text{CH}_2\text{O}-$, wherein $x1$ is any integer of 1-4, and $x2$ is any integer of 0-4;

The liver targeting specific ligand X may be the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, and is selected from monosaccharides and their derivatives, preferably selected from N-acetylgalactosamine and their derivatives, and more preferably selected from the following structures:



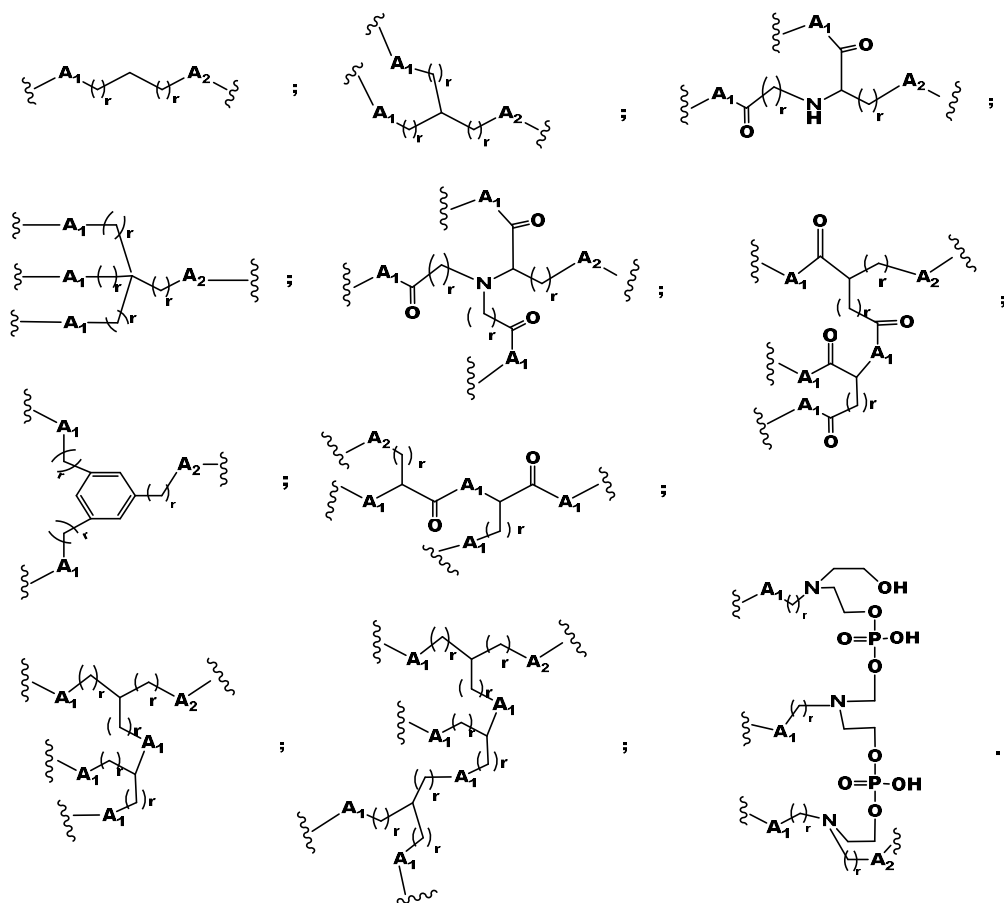
Wherein, as an example, W is selected from one or two of $-\text{OH}$, $-\text{NHCOOH}$ and $-\text{NHCO}(\text{CH}_2)_q\text{CH}_3$, wherein q is an integer of 0-4.;

As an example, the branch chain L is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from one or more of the following structures:



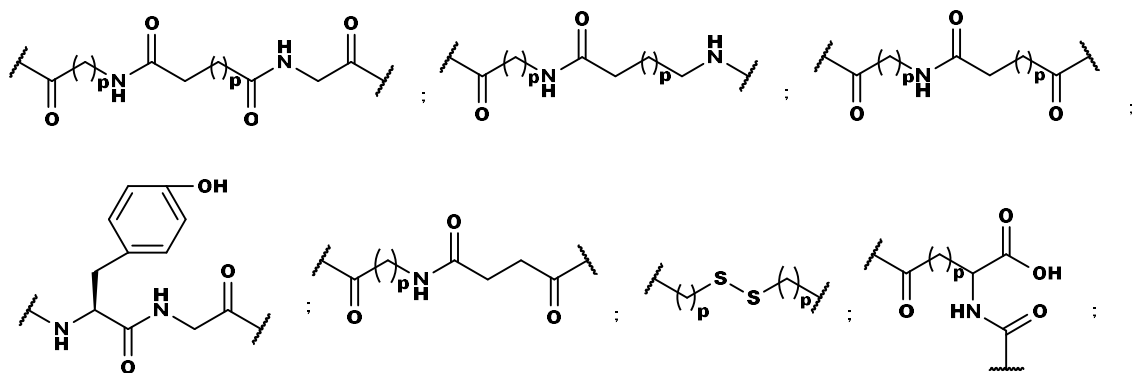
wherein, r_1 is any integer of 1-12, r_2 is any integer of 0-20, and Z is H, alkyl or amido. Alkyl is, for example, C_1 - C_5 alkyl;

As an example, the linker B is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from the following structures:

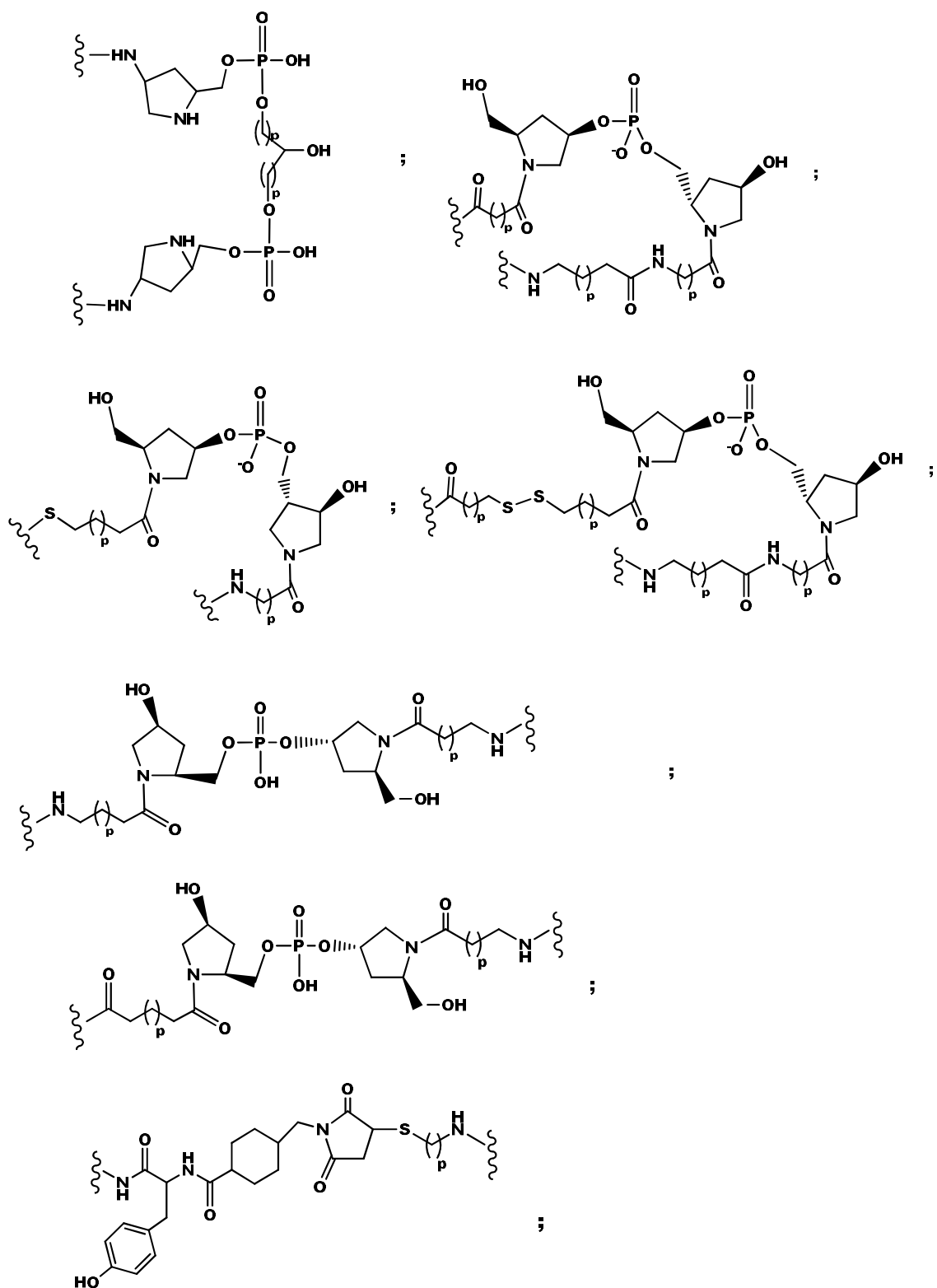


wherein, A₁ and A₂ are each independently C, O, S, -NH-, carbonyl, amido, phosphoryl or thiophosphoryl, and r is any integer of 0-4;

As an example, the linking chain D is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from the following structures:







wherein, each p is independently any integer of 1-20; s is any integer of 2-13; Z_1 and Z_2 are the same or different substituent groups.

It should be noted that, the above structures are not exhaustive. As long as it is a carrier connected to the sequence of the present invention, regardless of the disclosed or undisclosed delivery method,

targeting any receptor or any structure is within the scope of the present invention.

The published delivery methods include: conjugated carrier delivery method and lipid encapsulation delivery method. The conjugated carrier delivery method includes: cholesterol conjugate, antibody conjugate, folic acid conjugate and GalNac conjugate, etc.; the lipid encapsulation delivery method includes: lipid nanoparticles (LNP), polymer nanoparticles and extracellular vesicles, etc.

More preferably, in the RNA inhibitor or a pharmaceutically acceptable salt thereof of the present invention, the carrier structure at the 5' end of the sense strand is 5'MVIP17, the carrier structure at the 3' end of the sense strand is 3'MVIP17, the combination of sense strand 5'MVIP and antisense strand 3'MVIP is 5'MVIP01/3'MVIP01, 5'MVIP01/3'MVIP17, 5'MVIP17/3'MVIP01 or 5'MVIP09/3'MVIP09, or the combination of sense strand 5'MVIP and sense strand 3'MVIP is 5'MVIP01/3'MVIP09, 5'MVIP09/3'MVIP01 or 5'MVIP01/3'MVIP01。

Further preferably, in the RNA inhibitor or a pharmaceutically acceptable salt thereof of the present invention, the RNA inhibitor is selected from: Ky-12-DS23001, Ky-12-DS25001, Ky-12-DS25401, Ky-12-DS29701, Ky-12-DS29801, Ky-12-DS31701, Ky-12-DS31702, Ky-12-DS31703, Ky-12-DS31704, Ky-12-DS31705, Ky-12-DS31706, Ky-12-DS31707, Ky-12-DS31708, Ky-12-DS31709, Ky-12-DS31711, Ky-12-DS31712, Ky-12-DS31713, Ky-12-DS33001, Ky-12-DS33006, Kylo-12-DS1071, Kylo-12-DS1081, Kylo-12-DS1131, Kylo-12-DS1141, Kylo-12-DS1241, Kylo-12-DS1311, Kylo-12-DS1321, Kylo-12-DS5911, Kylo-12-DS2911, Kylo-12-DS2611, Kylo-12-DS2311, Kylo-12-DS3111 and Kylo-12-DS5411。

In another aspect, the present invention also provides the use of the above-mentioned RNA inhibitor or a pharmaceutically acceptable salt thereof in the preparation of a drug for treating and/or preventing a disease associated with an elevated APOC3 level, wherein the disease associated with an elevated APOC3 level includes hepatic diseases, which comprise inflammatory, cardiovascular and cerebrovascular and metabolic diseases, wherein the cardiovascular and cerebrovascular diseases include hyperlipidemia, stroke, atherosclerosis, thrombosis, coronary heart disease, aortic valve stenosis, hypertriglyceridemia (HTG), severe hypertriglyceridemia (sHTG) or familial chylomicronemia syndrome (FCS)。

In yet another aspect, the present invention provides a pharmaceutical composition, which comprises the above-mentioned RNA inhibitor or a pharmaceutically acceptable salt thereof for

inhibiting APOC3 gene expression and optional pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipients may be pharmaceutically acceptable excipients, vehicles and/or diluents, and the dosage form of the pharmaceutical composition is an oral preparation, an intravenous injection, or a subcutaneous or intramuscular injection, preferably a subcutaneous injection.

In yet another aspect, the present invention also provides a method for treating and/or preventing a disease, condition or syndrome associated with an elevated level of APOC3, the method comprising administering to a subject in need thereof a therapeutically effective amount of an RNA inhibitor or a pharmaceutically acceptable salt thereof that inhibits APOC3 gene expression, or a pharmaceutical composition comprising the RNA inhibitor or pharmaceutically acceptable salt thereof and optional pharmaceutically acceptable excipients. The mode of administration to the subject (administration method) includes oral administration, intravenous injection, subcutaneous or intramuscular injection, rectal or intraperitoneal application, and aerosol inhalation. Those skilled in the art will readily appreciate other aspects and advantages of the present invention from the detailed description below. The detailed description below only shows and describes exemplary embodiments of the present invention. As those skilled in the art will realize, the content of the present invention enables those skilled in the art to modify the specific embodiments disclosed without departing from the spirit and scope of the invention involved in the present invention. Accordingly, the drawings and descriptions in the specification of the present invention are merely exemplary and not restrictive.

Description of drawings

The specific features of the invention involved in the present invention are shown in the appended claims. The features and advantages of the inventions of the present invention can be better understood by referring to the exemplary embodiments and drawings described in detail below. A brief description of the drawings is as follows:

Figure 1 is a schematic diagram of the average hAPOC3 level in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 9 of the present invention;

Figure 2 is a schematic diagram of the inhibitory effect on APOC3 mRNA level after intervention with RNA inhibitor in Example 10 of the present invention;

Figure 3 is a schematic diagram of the inhibitory effect on APOC3 mRNA level in HepG 2 cells after intervention with RNA inhibitor in Example 11 of the present invention;

Figure 4 is a schematic diagram of the inhibitory effect on APOC3 mRNA level in PHH cells after intervention with RNA inhibitor in Example 12 of the present invention;

Figure 5 is a schematic diagram of the average hAPOC3 level in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 13 of the present invention;

Figure 6 is a schematic diagram of the average TG level in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 13 of the present invention;

Figure 7 is a schematic diagram of the inhibitory effect on hAPOC3 in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 14 of the present invention;

Figure 8 is a schematic diagram of the reduction effect of TC in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 14 of the present invention;

Figure 9 is a schematic diagram of the reduction effect of TG in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 14 of the present invention;

Figure 10 is a schematic diagram of the reduction effect of LDL-c in the serum of hAPOC3 Tg mice after intervention with RNA inhibitor in Example 14 of the present invention;

Figure 11 is a schematic diagram of the inhibition effect on APOC3 in the serum of hyperlipidemia cynomolgus monkey after intervention with RNA inhibitor in Example 15 of the present invention;

Figure 12 is a schematic diagram of the reduction effect of TG in the serum of hyperlipidemia cynomolgus monkey after intervention with RNA inhibitor in Example 15 of the present invention;

Figure 13 is a schematic diagram of the change in HDL-c level in the serum of hyperlipidemia cynomolgus monkey after intervention with RNA inhibitor in Example 15 of the present invention;

Figure 14 is a schematic diagram of the reduction effect of LDL-c in the serum of hyperlipidemia cynomolgus monkey after intervention with RNA inhibitor in Example 15 of the present invention;

Figure 15 is a schematic diagram of the reduction effect of TC in the serum of hyperlipidemia cynomolgus monkey after intervention with RNA inhibitor in Example 15 of the present invention.

Mode of carrying out the invention

The implementation of the present invention will be described below with specific examples. Those familiar with this technology can easily understand other advantages and effects of the present invention from the contents disclosed in the specification.

Definition of terms

In the present invention, examples of APOC3 mRNA sequences are easily obtained using public databases such as GenBank, UniProt and OMIM. The term "APOC3" includes human APOC3, cynomolgus monkey APOC3, macaque APOC3, mouse APOC3, rat (*Rattus norvegicus*) APOC3, rabbit (*Oryctolagus*) APOC3, etc. As long as the organisms actually exist and have the APOC3 gene, they are within the scope of the present invention. The mRNA sequence of human APOC3 can be found, for example, in GenBank NM_000040.3. The amino acid sequence and complete coding sequence of cynomolgus monkey APOC3 can be found, for example, in GenBank accession number GI:544489959(XM_05579730 .1). The amino acid sequence and complete coding sequence of macaque APOC3 can be found, for example, in GenBank accession number GI:297269260(XM_001090312 .2); the amino acid sequence and complete coding sequence of mouse APOC3 can be found, for example, in GenBank accession number GI:577019555(NM_023114 .4); the amino acid sequence and complete coding sequence of rat (*Rattus norvegicus*) APOC3 can be found, for example, in GenBank accession number GI:402534545 (NM_012501.2); and rabbit (*Oryctolagus*) APOC3, GenBank accession number GI:655601498(XM_002708371 .2).

In the present invention, the terms "iRNA", "RNA inhibitor", "iRNA agent" and "RNA interfering agent" can be used interchangeably, and generally refer to agents containing RNA as defined by the terms herein, which can mediate the targeted cleavage of RNA transcripts through the RNA-induced silencing complex (RISC) pathway. iRNA guides the sequence specific degradation of mRNA via a process called RNA interference (RNA inhibitor). iRNA regulates (e.g., inhibits) the expression of APOC3 gene in cells (e.g., cells in a subject such as a mammalian subject).

In some embodiments, RNA inhibitor may be single stranded siRNAs (ssRNA inhibitors) introduced into a cell or organism to inhibit target mRNA. Single stranded RNA inhibitors bind the RISC endonuclease Argonaute 2, which then cleaves the target mRNA. Single stranded siRNAs are generally 15 to 30 nucleotides and chemically modified.

In some embodiments, the "iRNA" used in the present invention is a double stranded RNA, and is referred to herein as "double stranded RNA inhibitor", "double stranded RNA (dsRNA) molecule", "dsRNA agent" or "dsRNA". The term "dsRNA" refers to a complex of ribonucleic acid molecules with a duplex structure containing two antiparallel and essentially complementary nucleic acid strands, known as having a "sense" and "antisense" orientation relative to the target RNA (i.e., APOC3 gene). In

some embodiments of the present invention, double stranded RNA (dsRNA) triggers the degradation of target RNA (e.g., mRNA) through a post transcriptional gene silencing mechanism (herein referred to as RNA interference or RNA inhibitor).

The duplex structure can be any length that allows the required target RNA to be specifically degraded through the RISC pathway, and can have a length in range of about 19 to 36 base pairs, for example, the length of about 19-30 base pairs, for example, the length of about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 or 36 base pairs. The ranges and lengths within the above ranges and lengths are also included as part of the present invention. In some embodiments, the iRNA agent of the present invention is a dsRNA containing 15-23 nucleotides in each strand, which interacts with the target RNA sequence (e.g., APOC3 gene) to guide the cleavage of the target RNA. In some embodiments, the iRNA of the present invention is a dsRNA containing 24-30 nucleotide, which interacts with the target RNA sequence (e.g., APOC3 target mRNA sequence) to guide the cleavage of the target RNA.

Generally, most nucleotides of each chain of dsRNA molecule are ribonucleotides, but as detailed herein, each chain or both chains can also include one or more non-ribonucleotides, such as deoxyribonucleotides or modified nucleotides. In addition, the "iRNA" used herein may include ribonucleotides with chemical modifications; iRNA can include substantial modifications at multiple nucleotides. The term "modified nucleotide" used herein refers to a nucleotide that independently has a modified sugar moiety, a modified internucleotide linkage or a modified nucleobase, or any combination thereof. Therefore, the term "modified nucleotide" covers the substitution, addition, or removal of, for example, functional groups or atoms of internucleotide linkages, sugar moieties, or nucleobases. The modifications applicable to the agent of the present invention include all types of modifications disclosed herein or known in the art.

In the present invention, the terms "nucleic acid" and "polynucleotide" can be used interchangeably and refer to the polymeric form of nucleotides (deoxyribonucleotides or ribonucleotides or analogues thereof) of any length. Polynucleotides can have any three-dimensional structure and can perform any function. The following are non-limiting examples of polynucleotides: genes or gene segments (such as probes, primers, EST or SAGE tags), exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, siRNA, miRNA, shRNA, RNA inhibitor reagents and primers. Polynucleotides may be modified or substituted at one or

more bases, sugars, and/or phosphates with any of the various modifications or substitutions described in the present invention or known in the art. Polynucleotides can contain modified nucleotides, such as methylated nucleotides and nucleotide analogues. If present, the nucleotide structure can be modified before or after polymer assembly. Nucleotide sequences can be blocked by non-nucleotide components. Polynucleotides can be modified after polymerization, for example by conjugating with labeled components. The term can be double stranded and single stranded molecules. Unless otherwise stated or required, any embodiment as a polynucleotide of the present invention includes a double stranded form and each of the two complementary single stranded forms known or predicted to constitute the double stranded form.

In the present invention, the term "target nucleic acid" or "target sequence" generally refers to the consecutive part of the nucleotide sequence of the mRNA molecule formed during the transcription of the APOC3 gene, including mRNA as the main transcription product of RNA processing. The target part of the sequence should be at least long enough to serve as a substrate for iRNA-guided cleavage at or near that portion of the nucleotide sequence of mRNA molecule formed during APOC3 gene transcription. In one embodiment, the target sequence is within the protein coding region of APOC3. The target sequence can be about 19-36 nucleotides in length, for example, it is preferred to be about 19-30 nucleotides in length. The ranges and lengths within the above ranges and lengths are also included as part of the present invention.

In the present invention, the term "nucleotide sequence" usually refers to a series or a certain sequence of nucleobases, nucleotides and/or nucleosides, whether modified or unmodified, described by a series of letters using standard nucleotide nomenclature and a list of symbols for modified nucleotides described in the present invention.

In the present invention, the term "oligonucleotide" generally refers to a polymer composed of multiple nucleotide residues (deoxyribonucleotide or ribonucleotide, or related structural variant or synthetic analog thereof) connected by phosphodiester bond (or related structural variant or synthetic analog thereof). Therefore, although the term "oligonucleotide" generally refers to the nucleotide polymer in which the nucleotide residues and the linkage between them are naturally occurred, it should be understood that the scope of the term also includes various analogues, including but not limited to: peptide nucleic acid (PNA), aminophosphate, thiophosphate, methyl phosphonate, 2-O-methyl ribonucleic acid, etc. The exact size of the molecule may depend on the specific application.

Oligonucleotides are generally short in length, usually about 10-30 nucleotide residues, but the term can also refer to molecules of any length, although the term "polynucleotide" or "nucleic acid" is generally used for larger oligonucleotides.

In some embodiments, the oligonucleotides comprise one or more unmodified ribonucleosides (RNA) and/or unmodified deoxyribonucleosides (DNA) and/or one or more modified nucleosides. The term "modified oligonucleotide" generally refers to an oligonucleotide containing at least one modified nucleoside and/or at least one modified internucleoside linkage.

In the present invention, the term "modified nucleoside" generally means a nucleoside containing at least one chemical modification compared with a naturally occurring RNA or DNA nucleoside. Modified nucleosides contain modified sugar moieties and/or modified nucleobases.

In the present invention, the term "nucleobase" generally refers to a heterocyclic pyrimidine or purine compound, which is a component of all nucleic acids and includes adenine, guanine, cytosine, thymine and uracil. Nucleotides may include modified nucleotides or nucleotide mimics, abasic sites (Ab or X), or the part substituted by the substituent. As used herein, "nucleobase sequence" generally means a sequence of consecutive nucleobases that does not depend on any sugar, linkage or nucleobase modification. The term "unmodified nucleobase" or "naturally occurring nucleobase" generally means naturally occurring heterocyclic nucleobases of RNA or DNA: purine bases adenine and guanine; and the pyrimidine bases thymine, cytosine and uracil. "Modified nucleobase" usually means any nucleobase that is not a naturally occurring nucleobase.

The "g", "c", "a", "t" and "u" each generally represent nucleotides containing guanine, cytosine, adenine, thymine and uracil as bases, respectively. However, it should be understood that, the term "ribonucleotide" or "nucleotide" may also refer to modified nucleotides, as shown in Tables 1 and 2. It is well known to those skilled in the art that guanine, cytosine, adenine, thymidine and uracil can be replaced by other moieties without significantly changing the base pairing properties of the oligonucleotide containing the nucleotides bearing such substituted moieties. For example, but not limited to, i (inosinic acid), also called hypoxanthine, can be base paired with a, c, and u. In some cases, the i can also be paired with the g. This phenomenon is called the wobble phenomenon. Thus, a nucleotide comprising the a, c or u can be replaced by a nucleotide comprising, for example, the i in the nucleotide sequence of a dsRNA characterized in the present invention. In another example, the a and c anywhere in the oligonucleotide can be replaced by the g and u respectively, to form a g-u wobble base

pairing with the target mRNA. Sequences containing such replacement moieties are suitable for use in the compositions and methods of the present invention.

In the present invention, the term "sugar moiety" generally refers to the naturally occurring sugar moiety or modified sugar moiety of a nucleoside. The term "naturally occurring sugar moiety" generally refers to a ribofuranosyl as found in naturally occurring RNA or a deoxyribofuranosyl as found in naturally occurring DNA. "Modified sugar moiety" means a substituted sugar moiety or sugar substitute.

In the present invention, the term "internucleoside linkage" generally refers to the covalent linkage between adjacent nucleosides in oligonucleotides. "Naturally occurring internucleoside linkage" means 3' to 5' phosphodiester linkage. "Modified internucleoside linkage" means any internucleoside linkage other than the naturally occurring internucleoside linkage.

In the present invention, the term "antisense oligonucleotide" refers to a single stranded oligonucleotide molecule with a nucleobase sequence complementary to the corresponding segment of the target nucleic acid (e.g., the target genome sequence, mRNA precursor, or mRNA molecule). In some embodiments, the antisense oligonucleotide is 12 to 30 nucleobases in length. In some embodiments, the antisense oligonucleotide is an unmodified or modified nucleic acid with a nucleotide sequence complementary to the sequence of target nucleic acid (such as APOC3 polynucleotide).

In the present invention, the term "antisense strand" generally refers to the strand of RNA inhibitor (such as dsRNA) that includes a region that are substantially complementary to the target sequence. When used herein, the term "complementary region" generally refers to a region on the antisense strand that is substantially complementary to the sequence defined in the present invention (e.g., target sequence). When the complementary region is not fully complementary to the target sequence, the mismatch can be in the inner or terminal region of the molecule. In general, the most tolerated mismatches are in the terminal region, for example, within 5, 4, 3, or 2 nucleotides at the 5' and/or 3' ends.

In the present invention, the term "sense strand" (S) generally refers to such a strand of RNA inhibitor, which includes a region that is substantially complementary to a region of the antisense strand as the term defined herein. The "sense" strand is sometimes referred to as the "passenger" strand or "anti-guide" strand. With their sequences, the antisense strand targets the desired mRNA, while the sense strand targets different targets. Therefore, if the antisense strand is incorporated into RISC, the correct target is targeted. The incorporation of sense strand can lead to off-target effects. These off-target effects

can be limited by the use of modifications or 5' end caps on the sense strand.

In the present invention, the term "complementary" when used to describe the first nucleotide sequence (such as RNA inhibitor sense strand or APOC3 mRNA) in terms of the second nucleotide sequence (such as RNA inhibitor antisense strand) refers to the ability of oligonucleotides or polynucleotides containing the first nucleotide sequence to hybridize (form base pair hydrogen bonds) with oligonucleotides or polynucleotides containing the second nucleotide sequence and form duplex or double helix structures under certain conditions. Complementary sequences include Watson-Crick base pairs or non-Watson-Crick base pairs, and include natural or modified nucleotides or nucleotide mimics, as long as the above requirements for their hybridization ability are realized. "Complementary" does not require nucleobase complementarity on each nucleoside. On the contrary, some mismatches can be tolerated.

In the present invention, the term "fully complementary" generally means that all (100%) bases in the consecutive sequence of the first polynucleotide will hybridize with the same number of bases in the consecutive sequence of the second polynucleotide. The consecutive sequence may comprise all or part of the first or second nucleotide sequence. As used herein, "partially complementary" generally means that in the hybridized nucleobase sequence pairs, at least about 70% of the bases in the consecutive sequence of the first polynucleotide will hybridize with the same number of bases in the consecutive sequence of the second polynucleotide. As used herein, "substantially complementary" generally means that in the hybridized nucleobase sequence pairs, at least about 80% of the bases in the consecutive sequence of the first polynucleotide will hybridize with the same number of bases in the consecutive sequence of the second polynucleotide. The terms "complementary", "fully complementary" and "substantially complementary" as used herein can be used in terms of base matching between the sense strand and antisense strand of RNA inhibitor or between the antisense strand of RNA inhibitor and the sequence of APOC3 mRNA. Sequence identity or complementarity does not depend on modification. For the purpose of determining identity or complementarity, for example, A and fA are complementary to U (or T) and identical to a.

In the present invention, the term "homologous" or "homology" generally refers to the number of nucleotides of the subject nucleic acid sequence that have matched the same nucleotide of the reference nucleic acid sequence, which is usually determined by sequence analysis programs (for example, Karlin and Altschul, 1990, PNAS 87:2264-2268; Karlin and Altschul, 1993, PNAS 90:5873-5877), or by visual

inspection. As used herein, the term "complete homology" or "fully homologous" generally refers to complete (100%) homology or "identity" between the reference sequence and the subject nucleic acid sequence. As used herein, the term "substantially homologous" or "substantial homology" generally refers to the fact that nucleotides at the same nucleotide positions in the subject sequence and the reference sequence are at least 50% (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99%) homologous.

In the present invention, the term "ligand" generally refers to any compound or molecule that can be covalently or otherwise chemically bound to bioactive substances (such as oligonucleotides). In some embodiments, the ligand is able to interact directly or indirectly with another compound such as a receptor, the receptor interacting with the ligand may exist on the cell surface, or alternatively may be an intracellular and/or intercellular receptor, the interaction of the ligand with the receptor may lead to a biochemical reaction, or may simply be a physical interaction or binding.

In the present invention, the terms "induce", "inhibit", "strengthen", "elevate", "increase", "decrease", "reduce" and the like usually indicate quantitative differences between two states. For example, "the amount that effectively inhibits the activity or expression of APOC3" means that the level of APOC3 activity or expression in the treated samples will be lower than that in the untreated samples. The terms described apply, for example, to expression levels and activity levels. The terms "decrease" and "reduce" are used interchangeably and usually indicate any changes less than the original. "Decrease" and "reduce" are relative terms that need to be compared before and after measurement. "Decrease" and "reduce" include complete depletion.

In some embodiments, the term "reduce" may refer to an overall reduction of about 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100% in the expression level/amount of a gene/gene product such as protein or biomarker in a first sample compared to the expression level/amount of the corresponding gene/gene product such as protein or biomarker in a second sample, as detected by standard methods known in the art, such as those described in the present invention. In some embodiments, the term "reduce" refers to a reduction in the expression level / amount of a gene or biomarker in the first sample, wherein the reduction is at least about 0.9 times, 0.8 times, 0.7 times, 0.6 times, 0.5 times, 0.4 times, 0.3 times, 0.2 times, 0.1 times, 0.05 times, or 0.01 times the expression level / amount of the corresponding gene or biomarker in the second sample. In some embodiments, the first sample is a sample obtained from a subject, while the second sample is a reference sample.

In the present invention, the term "expression" generally refers to the process by which a gene eventually produces a protein. The expression includes, but is not limited to, transcription, post transcriptional modifications (e.g., splicing, polyadenylation, addition of 5' - caps), and translation.

In the present invention, the term "pharmaceutically acceptable" generally refers to one or more non-toxic substances that do not interfere with the effectiveness of the biological activity of the active ingredient. Such preparations may generally contain salts, excipients, buffers, preservatives, compatible vehicles, and optionally other therapeutic agents. Such pharmaceutically acceptable preparations may also generally contain compatible solid or liquid fillers, diluents, or encapsulation materials suitable for administration to humans. When used in medicine, salts should be pharmaceutically acceptable salts, but non-pharmaceutically acceptable salts can be conveniently used to prepare pharmaceutically acceptable salts, which cannot be excluded from the scope of the present invention. Such pharmacologically and pharmaceutically acceptable salts include but are not limited to those prepared from the following acids: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, maleic acid, acetic acid, salicylic acid, citric acid, boric acid, formic acid, malonic acid, succinic acid, etc. The pharmaceutically acceptable salts can also be prepared into alkali metal salts or alkaline earth metal salts, such as sodium salt, potassium salt or calcium salt.

In the present invention, the term "lipid nanoparticles" or "LNP" generally refers to nanoparticles containing encapsulated pharmacologically active molecules, such as nucleic acid molecules, for example, iRNA or plasmid from which iRNA is transcribed. The iRNA may contain no ligand or may contain a ligand, such as a GalNAc derivative. LNP is described in, for example, Chinese patent No. CN103189057B, the complete contents of which are incorporated herein by reference.

In the present invention, the term "prevent and/or treat" not only includes the prevention and/or treatment of disease, but also generally includes the prevention of the onset of disease, slowing or reversing the progression of disease, preventing or slowing the onset of one or more symptoms related to disease, reducing and/or alleviating one or more symptoms related to disease, reducing the severity and/or duration of the disease and/or any symptom associated with it and/or preventing further increases in the severity of the disease and/or any symptom associated with it, preventing, reducing or reversing any physiological damage caused by the disease, and any pharmacological effects that are generally beneficial to the patient being treated. The RNA inhibitor or pharmaceutical composition of the present invention does not need to achieve complete cure or eradication of any symptoms or manifestations of

the disease to form a feasible therapeutic agent. As recognized in relevant fields, drugs used as therapeutic agents can reduce the severity of a given disease state, but do not need to eliminate every manifestation of the disease to be considered as useful therapeutic agents. Similarly, treatments administered prophylactically to constitute viable prophylactic agents do not need to be completely effective in preventing the onset of the condition. Simply reducing the impact of disease in subjects (for example, by reducing the numbers or severity of their symptoms, or by improving the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood of disease occurrence or exacerbation is sufficient.

In the present invention, the term "disease" or "condition" can be used interchangeably, and generally refers to any deviation from the normal state of the subject, such as any change in the state of the body or some organs, which hinders or disturbs the performance of the function, and/or causes symptoms such as discomfort, dysfunction, pain or even death in the person who is ill or in contact with him. Disease or condition can also be called distemper, ailing, ailment, malady, disorder, sicknesses, illnesses and complaints.

In the present invention, the term "administration" generally refers to the introduction of the pharmaceutical preparation of the present invention into the subject's body through any route of introduction or delivery. Any method known to those skilled in the art for contacting a cell, organ or tissue with the drug can be adopted. The administration may include, but is not limited to, intravenous, intra-arterial, intranasal, intra-abdominal, intramuscular, subcutaneous transdermal or oral administration. The daily dose can be divided into one, two or more suitable forms of dose to be administered at one, two or more times during a certain time period.

In the present invention, the term "contact" generally refers to the contact of two or more different types of substances in any order, in any way and for any duration. Contact can occur in vivo, ex vivo, or in vitro. In some embodiments, it may mean that the RNA inhibitor or composition of the present invention directly contacts cell or tissue. In other embodiments, the term refers to making the RNA inhibitor or composition of the present invention contact cell or tissue indirectly. For example, the method of the present invention includes a method in which the subject is exposed to the RNA inhibitor or composition of the present invention, and then the RNA inhibitor or composition contacts the cell or tissue through diffusion or any other active or passive transport process known in the art through which the compound circulates in the body.

In the present invention, the term "effective amount" or "effective dose" generally refers to an amount sufficient to achieve or at least partially achieve the desired effect. The "therapeutically effective amount" or "therapeutically effective dose" of a drug or therapeutic agent is generally any amount of drug that, when used alone or in combination with another therapeutic agent, promotes disease regression (as evidenced by a decrease in the severity of disease symptoms, an increase in the frequency and duration of asymptomatic periods of disease, or prevention of impairment or disability due to the disease). The "preventive effective amount" or "preventive effective dose" of a drug usually refers to the amount of drug that inhibits the development or recurrence of disease when administered alone or in combination with another therapeutic agent to subjects at risk of disease development or disease recurrence. A variety of methods known to those skilled in the art can be used to evaluate the ability of therapeutic or preventive agents to promote disease regression or inhibit disease development or recurrence, such as predicting efficacy in humans in human subjects during clinical trials and in animal model systems, or determining the activity of the agent in in vitro assays. In some embodiments, "effective amount" refers to the amount of RNA inhibitor that produces the expected pharmacological, therapeutic or preventive results.

In the present invention, the term "subject" generally refers to humans or non-human animals (including mammals) that need diagnosis, prognosis, improvement, prevention and/or treatment of diseases, such as humans, non-human primates (apes, gibbons, gorillas, chimpanzees, orangutans, macaques), domestic animals (dogs and cats), farm animals (poultry such as chickens and ducks, horses, cattle, goats, sheep, pigs) and experimental animals (mice, rats, rabbits, guinea pigs). Human subjects include fetal, newborn, infant, adolescent and adult subjects. Subjects include animal disease models.

In the present invention, the terms "include", "comprise", "have", "may/can", "contain" and their variants are generally intended to be open-ended transitional phrases, terms or words, which do not exclude the possibility of additional actions or structures. The term "consisting of/composed of" usually means that no other component (or similarly, feature, integer, step, etc.) can exist.

In the present invention, the term "about" usually means approximately, in the region of, roughly, or around. When the term "about" is used to refer to the range of values, the cut-off value or specific value is used to indicate that the stated value may differ by up to 10% from the enumerated value. Therefore, the term "about" can be used to cover variation from a specific value of $\pm 10\%$ or less, $\pm 5\%$ or less, $\pm 1\%$ or less, $\pm 0.5\%$ or less, or $\pm 0.1\%$ or less.

It should be understood that, the term "at least" before a number or series of numbers includes the number adjacent to the term "at least", and all subsequent numbers or integers logically included, that is, "greater than or equal to". For example, the number of nucleotides in a nucleic acid molecule must be an integer. For example, "at least 15 nucleotides " means 15,16,17,18,19,20, 21 or more nucleotides, "at least 16 nucleotides" means 16, 17, 18, 19, 20, 21 or more nucleotides; "at least 17 nucleotides" means 17, 18, 19, 20, 21 or more nucleotides; and so on. When "at least" appears before a series of numbers or ranges, it should be understood that "at least" can modify each number in the series or ranges.

It should be understood that "no more than" used herein refers to a value or integer that is adjacent to the value and logically lower than that value, that is, "less than or equal to", such as from the context logic, to zero. For example, having "no more than 3 nucleotides" means having 3, 2 or 1 nucleotide(s). When "no more than" appears before a series of numbers or ranges, it should be understood that "no more than" can modify each number in the series or ranges. The range used herein includes both upper and lower limits.

Detail of invention

In one aspect, the present invention provides an RNA inhibitor or a pharmaceutically acceptable salt thereof for inhibiting the expression of APOC3 gene.

In some embodiments, the RNA inhibitor comprises a single-stranded oligonucleotide or double-stranded ribonucleic acid (dsRNA) molecule for inhibiting the expression of APOC3 gene in cells, such as cells of a subject (e.g., a mammal, such as a person susceptible to APOC3-related disorders such as hyperlipidemia), wherein the dsRNA comprises an antisense strand having a complementary region complementary to at least a portion of mRNA formed in the expression of APOC3 gene. The complementary region is about 15-30 nucleotides in length (e.g., about 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16 or 15 nucleotides in length).

The dsRNA includes two RNA strands, which can be complementary and hybridize to form a duplex structure (complementary region) under the conditions in which the dsRNA uses them. One strand (antisense strand) of the dsRNA includes a complementary region that is substantially, and often completely, complementary to the target sequence. The target sequence can be derived from the sequence of mRNA formed during the expression of APOC3 gene. The other strand (sense strand) includes a region complementary to the antisense strand, so that when combined under appropriate conditions, the two strands can hybridize and form a duplex structure. Typically, duplex structures are 15 to 30 base

pairs in length. Similarly, the length of the region complementary to the target sequence is 15 to 30 nucleotides.

In some embodiments, the dsRNA is about 19 to about 23 nucleotides in length, or about 24 to about 30 nucleotides in length. In general, the dsRNA is long enough to be used as a substrate for Dicer. For example, it is known in the art that the dsRNA with a length greater than about 21-23 nucleotides can be used as a substrate for Dicer. Those skilled in the art also understand that the region of RNA targeted for cleavage is usually part of larger RNA molecules (usually mRNA molecules). A "part" of the target is consecutive nucleotides of the mRNA target, which is long enough to allow it to be a substrate for RNA inhibitor-guided cleavage (i.e., cleavage via RISC pathway).

Those skilled in the art should also understand that the duplex region is the main functional part of dsRNA, for example, the duplex region of about 19 to about 30 base pairs, such as, about 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20 base pairs. Therefore, in one embodiment, in order to achieve the extent of becoming a functional duplex (for example, 15-30 base pairs) that targets the required RNA for cleavage, RNA molecules or complexes of RNA molecules with duplex regions of more than 30 base pairs are dsRNA.

In one aspect of the present invention, the RNA inhibitor or pharmaceutically acceptable salt thereof of the present invention comprises an antisense strand, wherein the antisense strand comprises at least 15 consecutive nucleotides that are substantially complementary to the nucleotides at the corresponding positions of APOC3 mRNA NM_000040.3 (SEQ ID NO. 1 :
ctgctcagttcatccctagaggcagctgctccaggaaacagaggtgcatgcagccccgggtactcctgtgttgccctcctggcgctcctggcctct
gccccgagcttcagaggccgaggatgcctcccttctcagcttcagtcagggttacatgaagcacgccaccaagaccgccaaggatgcactgagcag
cgtgcaggagtgccaggtggcccagcaggccaggggctgggtgaccgatggcttcagttccctgaaagactactggagcaccgtaaggacaag
ttctctgagttctgggatttgaccctgaggtcagaccaacttcagccgtggctgcctgagacctcaataccccaagtccacctgcctatccatcctgc
gagctccttgggtcctgcaatctccagggtgcccctgtaggttgcttaaaaggacagtattctcagtgctctcctacccacctcatgcctggcccc
cctccaggcatgctggcctcccaataaagctggacaagaagctgctatga) or a sequence that differs from it by no more than 3 nucleotides.

In some embodiments, the antisense strand and the sense strand form a duplex structure (complementary region), and the complementary region includes at least 15, 16, 17, 18, 19, 20, 21, 22, or 23 consecutive nucleotides.

In some embodiments, the sense strand of the RNA inhibitor is substantially homologous to the

target sequences in Table 1.

Table 1 target sequence of the RNA inhibitor

SEQ ID NO.	target sequence 5'→3'
2	gcttaaaaggacagtattct
3	ggagcaccgtaaggacaagt
4	gagcaccgtaaggacaagtt
5	gcaccgtaaggacaagttct
6	gcatgctggcctccaataaa
7	gttctctgagttctgggattt
8	ttacatgaagcacgccaccaa
9	gctgcctgagacctcaatacc
10	gtccacctgcctatccatct
11	gatggcttcagttccctgaaa
12	tctcagcttcagcagggtta
13	tcagcttcagcagggttaca
14	gcttcagcagggttacatga
15	ctctgagttctgggatttgga
16	gcttcagttccctgaaagact
17	cagttccctgaaagactactg
18	ttccctgaaagactactggag
19	aaagactactggagcaccgtt
20	agactactggagcaccgttaa
21	ccgttaaggacaagttctctg
22	ggacaagttctctgagttctg
23	tctgagttctgggatttgac
24	tgaggtcagaccaactcagc
25	tgagacctcaatacccaagt
26	tatccatcctgcgagctcctt
27	ctgcccctgtaggttgcttaa
28	tgcccctgtaggttgcttaa
29	cccctgtaggttgcttaaaag
30	agaccgccaaggatgcactga
31	taggttgcttaaaaggacag
32	cagtattctcagtgtctctct
33	tattctcagtgtctctctacc

SEQ ID NO.	target sequence 5'→3'
34	tgctctcctacccacctcat
35	gtccttgggtcctgcaatct
36	tcagaccaacttcagccgtgg
37	tggctgcctgagacctcaata
38	ttctgggatttgaccctgag
39	tgggatttgaccctgaggctc
40	atttgaccctgaggtcagac
41	agaccaacttcagccgtggct
42	ttgggtcctgcaatctccagg
43	acctgcctatccatcctgcga
44	tgcctatccatcctgcgagct
45	gagctccttgggtcctgcaat
46	acagtattctcagtgtctcc
47	acagtattctcagtgtctcc
48	tccttgggtcctgcaatctcc
49	tggaccctgaggtcagaccaa
50	accctgaggtcagaccaactt
51	cctgaggtcagaccaacttca
52	aaggacagttattctcagtgc

where, g=guanylate, a=adenylate, c=cytidylate, t=thymidylate.

In some embodiments, the sense strand of the RNA inhibitor is substantially homologous to target sequences in Table 1, and is selected from a) sequences in Table 2, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

Table 2 sense strand sequences of the RNA inhibitor

SEQ ID NO.	single strand code	sense strand 5'→3'
53	S1	gcuuaaaaggacaguauucu
54	S2	ggagcaccguuaaggacaagu
55	S3	gagcaccguuaaggacaaguu

SEQ ID NO.	single strand code	sense strand 5'→3'
56	S4	gcaccguuaaggacaaguucu
57	S5	gcaugcuggccucccauauaa
58	S6	guucucugaguucugggauuu
59	S7	uuacaugaagcacgccaccaa
60	S8	gcugccugagaccucaauacc
61	S9	guccaccugccuauccaucuu
62	S10	gauggcuucaguucccugaaa
63	S11	ucucagcuucaugcaggguuu
64	S12	ucagcuucaugcaggguuaca
65	S13	gcuucaugcaggguuacauga
66	S14	cucugaguucugggauuugga
67	S15	gcuucaguucccugaaagacu
68	S16	caguucccugaaagacuacug
69	S17	uucccugaaagacuacuggag
70	S18	aaagacuacuggagcaccguu
71	S19	agacuacuggagcaccguuua
72	S20	ccguuaaggacaaguucucug
73	S21	ggacaaguucucugaguucug
74	S22	ucugaguucugggauuuggac
75	S23	ugaggucagaccaacuucagc
76	S24	ugagaccucaauacccaagu
77	S25	uauccauccugcgagcuccuu
78	S26	cugccccuguagguugcuuaa
79	S27	ugccccuguagguugcuuaaa
80	S28	ccccuguagguugcuuaaaag
81	S29	agaccgccaaggaugcacuga

SEQ ID NO.	single strand code	sense strand 5'→3'
82	S30	uagguugcuuaaaaggacag
83	S31	caguauucucagugcucuccu
84	S32	uauucucagugcucuccuacc
85	S33	ugcucuccuaccccaccucau
86	S34	gcuccuuggguccugcaauuc
87	S35	ucagaccaacuucagccgugg
88	S36	uggcugccugagaccucaaua
89	S37	uucugggauuuggaccugag
90	S38	ugggauuuggaccugagguc
91	S39	auuuggaccugaggucagac
92	S40	agaccaacuucagccguggcu
93	S41	uuggguccugcaaucuccagg
94	S42	accugccuauccauccugcga
95	S43	ugccuauccauccugcgagcu
96	S44	gagcuccuuggguccugcaau
97	S45	acaguauucucagugcucucc
98	S46	ucucagugcucuccuaccca
99	S47	uccuuggguccugcaaucucc
100	S48	uggaccugaggucagaccaa
101	S49	accugaggucagaccaacuu
102	S50	ccugaggucagaccaacuca
103	S51	aaggacaguauucucagugc
701	S193	aggacaguauucucagugcu
702	S194	gcuaaaaggacaguaauca
703	S195	cugcccagcuucagaggcuu
704	S196	cccagcuucagaggccgauu

SEQ ID NO.	single strand code	sense strand 5'→3'
705	S197	ccgagcuucagaggccgagga
706	S198	cgagcuucagaggccgaggau
707	S199	gagcuucagaggccgaggaua
708	S200	agcuucagaggccgaggauaa
709	S201	gcuucagaggccgaggauaa
710	S202	cuucagaggccgaggauccu
711	S203	ucagaggccgaggauccucu
712	S204	aggccgaggauccuccuuc
713	S205	gccgaggauccuccuucuc
714	S206	cgaggauccuccuucucag
715	S207	gaggauccuccuucucaga
716	S208	aggauccuccuucucagcu
717	S209	gaugccuccuucucagcuua
718	S210	augccuccuucucagcuuca
719	S211	gccuccuucucagcuucaug
720	S212	ccuccuucucagcuucauaa
721	S213	cuccuucucagcuucaugca
722	S214	uccuucucagcuucaugcag
723	S215	ccuucucagcuucaugcauu
724	S216	ccuucucagcuucaugcagaa
725	S217	cuucucagcuucaugcaggggu
726	S218	uucucagcuucaugcagggguu
727	S219	ucucagcuucaugcagggguuc
728	S220	cucagcuucaugcagggguuac
729	S221	cagcuucaugcagggguuacag
730	S222	agcuucaugcagggguucaug

SEQ ID NO.	single strand code	sense strand 5'→3'
731	S223	cuucaugcaggguuacaugaa
732	S224	uucaugcaggguuacaugaag
733	S225	ucaugcaggguuacaugaaga
734	S226	caugcaggguuacaugaagca
735	S227	augcaggguuacaugaagcac
736	S228	ugcaggguuacaugaagcauu
737	S229	gcaggguuacaugaagcacuu
738	S230	caggguuacaugaagcacgaa
739	S231	aggguuacaugaagcacgcaa
740	S232	ggguuacaugaagcacgccac
741	S233	gguuacaugaagcacgccaca
742	S234	guuacaugaagcacgccacca
743	S235	uacaugaagcacgccaccaag
744	S236	caugaagcacgccaccaagac
745	S237	augaagcacgccaccaagaca
746	S238	ugaagcacgccaccaagacca
747	S239	gaagcacgccaccaagaccuu
748	S240	cagccaccaagaccgccaau
749	S241	acgccaccaagaccgccaauu
750	S242	cgccaccaagaccgccaagga
751	S243	gccaccaagaccgccaaggau
752	S244	ccaccaagaccgccaaggau
753	S245	caccaagaccgccaaggauaa
754	S246	accaagaccgccaaggau
755	S247	ccaagaccgccaaggau
756	S248	caagaccgccaaggau

SEQ ID NO.	single strand code	sense strand 5'→3'
757	S249	aagaccgccaagggaugcacua
758	S250	gaccgccaagggaugcacugag
759	S251	accgccaagggaugcacugagu
760	S252	ccgccaagggaugcacugagca
761	S253	cgccaagggaugcacugagcag
762	S254	gccaagggaugcacugagcauu
763	S255	ccaagggaugcacugagcagcg
764	S256	caagggaugcacugagcagcgu
765	S257	aagggaugcacugagcagcgug
766	S258	agggaugcacugagcagcguuu
767	S259	gggaugcacugagcagcgugca
768	S260	gaugcacugagcagcgugcag
769	S261	augcacugagcagcgugcauu
770	S262	ugcacugagcagcgugcagga
771	S263	gcacugagcagcgugcaggau
772	S264	cacugagcagcgugcaggagu
773	S265	acugagcagcgugcaggaguc
774	S266	cugagcagcgugcaggaguaa
775	S267	ugagcagcgugcaggagucaa
776	S268	gagcagcgugcaggaguccaa
777	S269	gcagcgugcaggagucccagu
778	S270	cagcgugcaggagucccaggu
779	S271	gcgugcaggagucccagguga
780	S272	cgugcaggagucccaggugaa
781	S273	aagggacaguauucucaguga
782	S274	gcaggagucccagguggccua

SEQ ID NO.	single strand code	sense strand 5'→3'
783	S275	aggaguccagguggcccauu
784	S276	aguccagguggccagcauu
785	S277	agcaggccaggggcuggguaa
786	S278	caggccaggggcugggugaca
787	S279	ccaggggcugggugaccgauc
788	S280	caggggcugggugaccgaucu
789	S281	gggcugggugaccgauggcuu
790	S282	gcugggugaccgauggcuuca
791	S283	ugggugaccgauggcuucagu
792	S284	ggugaccgauggcuucagugu
793	S285	gugaccgauggcuucaguuaa
794	S286	ugaccgauggcuucaguucau
795	S287	gaccgauggcuucaguuccau
796	S288	ccgauggcuucaguucccuga
797	S289	cgauggcuucaguucccugaa
798	S290	gauggcuucaguucccugaaa
799	S291	auggcuucaguucccugaaag
800	S292	uggcuucaguucccugaaaau
801	S293	ggcuucaguucccugaaagac
802	S294	cuucaguucccugaaagacua
803	S295	uucaguucccugaaagacuau
804	S296	ucaguucccugaaagacuacu
805	S297	aguucccugaaagacuacuga
806	S298	guucccugaaagacuacugga
807	S299	ucccugaaagacuacuggauu
808	S300	cccugaaagacuacuggagca

SEQ ID NO.	single strand code	sense strand 5'→3'
809	S301	ccugaaagacuacuggagcac
810	S302	cugaaagacuacuggagcauu
811	S303	ugaaagacuacuggagcacua
812	S304	gaaagacuacuggagcaccgu
813	S305	aagacuacuggagcaccguua
814	S306	gacuacuggagcaccguuaau
815	S307	acuacuggagcaccguuaagu
816	S308	cuacuggagcaccguuaagga
817	S309	uacuggagcaccguuaaggau
818	S310	acuggagcaccguuaaggaaa
819	S311	cuggagcaccguuaaggacau
820	S312	uggagcaccguuaaggacaag
821	S313	agcaccguuaaggacaaguua
822	S314	gcaccguuaaggacaaguucu
823	S315	caccguuaaggacaaguucuu
824	S316	accguuaaggacaaguucucu
825	S317	cguuaaggacaaguucucuga
826	S318	guuaaggacaaguucucugau
827	S319	uuaaggacaaguucucugagu
828	S320	uaaggacaaguucucugaguu
829	S321	aaggacaaguucucugaguuc
830	S322	ggacaaguucucugaguucua
831	S323	gacaaguucucugaguucuga
832	S324	acaaguucucugaguucugaa
833	S325	caaguucucugaguucuggga
834	S326	aaguucucugaguucugggau

SEQ ID NO.	single strand code	sense strand 5'→3'
835	S327	aguucucugaguucugggauu
836	S328	uucucugaguucugggauuuc
837	S329	ucucugaguucugggauuuuaa
838	S330	ugaguucugggauuuggacaa
839	S331	gaguucugggauuuggaccau
840	S332	aguucugggauuuggaccua
841	S333	guucugggauuuggaccuaa
842	S334	ucugggauuuggaccugaa
843	S335	cugggauuuggaccugagau
844	S336	gggauuuggaccugagguca
845	S337	ggauuuggaccugaggucaa
846	S338	gauuuggaccugaggucaga
847	S339	uuuggaccugaggucagaaa
848	S340	uuggaccugaggucagacua
849	S341	gaccugaggucagaccaacu
850	S342	ccugaggucagaccaacuuc
851	S343	cugaggucagaccaacuucag
852	S344	gaggucagaccaacuucagaa
853	S345	aggucagaccaacuucagcaa
854	S346	ggucagaccaacuucagccuu
855	S347	gucagaccaacuucagccguu
856	S348	ucagaccaacuucagccguaa
857	S349	cagaccaacuucagccgugaa
858	S350	gaccaacuucagccguggcua
859	S351	accaacuucagccguggcuuu
860	S352	ccaacuucagccguggcugaa

SEQ ID NO.	single strand code	sense strand 5'→3'
861	S353	caacuucagccguggcugcua
862	S354	acuucagccguggcugccuga
863	S355	uucagccguggcugccugaga
864	S356	guggcugccugagaccucaau
865	S357	ggcugccugagaccucaauac
866	S358	cugccugagaccucaauacuu
867	S359	ugccugagaccucaauaccaa
868	S360	gccugagaccucaauaccaa
869	S361	ccugagaccucaauaccccau
870	S362	cugagaccucaauaccccau
871	S363	gagaccucaauacccaaguc
872	S364	agaccucaauacccaaguuu
873	S365	gaccucaauacccaagucca
874	S366	accucaauacccaaguccac
875	S367	ccucaauacccaaguccauu
876	S368	cucaauacccaaguccaccu
877	S369	ucaauacccaaguccaccua
878	S370	aaauacccaaguccaccugaa
879	S371	uacccaaguccaccugccua
880	S372	acccaaguccaccugccuau
881	S373	ccaaguccaccugccuauaa
882	S374	ccaaguccaccugccuaucca
883	S375	caaguccaccugccuauccau
884	S376	aaguccaccugccuauccauc
885	S377	aguccaccugccuauccauaa
886	S378	uccaccugccuauccaucuu

SEQ ID NO.	single strand code	sense strand 5'→3'
887	S379	ccaccugccuauccauccugu
888	S380	caccugccuauccauccugaa
889	S381	ccugccuauccauccugcgag
890	S382	cugccuauccauccugcgauu
891	S383	ugccuauccauccugcgagcu
892	S384	ccuauccauccugcgagcucu
893	S385	cuauccauccugcgagcuccu
894	S386	auccauccugcgagcuccuua
895	S387	uccauccugcgagcuccuuga
896	S388	ccauccugcgagcuccuuguu
897	S389	cauccugcgagcuccuuggau
898	S390	auccugcgagcuccuuggguc
899	S391	uccugcgagcuccuuggguaa
900	S392	ccugcgagcuccuuggguccu
901	S393	cugcgagcuccuuggguccua
902	S394	ugcgagcuccuuggguccuaa
903	S395	agcuccuuggguccugcaauu
904	S396	gcuccuuggguccugcaauaa
905	S397	cuccuuggguccugcaaucua
906	S398	ccuuggguccugcaaucucuu
907	S399	cuuggguccugcaaucuccau
908	S400	uggguccugcaaucuccagaa
909	S401	ggguccugcaaucuccaggaa
910	S402	gguccugcaaucuccaggguu
911	S403	guccugcaaucuccagggcua
912	S404	uccugcaaucuccagggcuaa

SEQ ID NO.	single strand code	sense strand 5'→3'
913	S405	ccugcaaucuccagggcugaa
914	S406	cugcaaucuccagggcugcau
915	S407	ugcaaucuccagggcugccaa
916	S408	aaucuccagggcugcccuua
917	S409	agggcugccccuguagguuga
918	S410	gcugccccuguagguugcuua
919	S411	ugccccuguagguugcuuaaa
920	S412	cuguagguugcuuaaaaggga
921	S413	uguagguugcuuaaaaggga
922	S414	agguugcuuaaaagggacauu
923	S415	guugcuuaaaagggacaguau
924	S416	uugcuuaaaagggacaguauc
925	S417	ugcuuaaaagggacaguaucu
926	S418	cuuaaaagggacaguauucua
927	S419	uaaaagggacaguauucucua
928	S420	aaaagggacaguauucucauu
929	S421	aaagggacaguauucucagaa
930	S422	agggacaguauucucaguuu
931	S423	gggacaguauucucagucuu
932	S424	gacaguauucucagucucuu
933	S425	aguauucucagucucuccaa
934	S426	guauucucagucucuccuaa
935	S427	auucucagucucuccuacuu
936	S428	cucagucucuccuaccccaa
937	S429	ucagucucuccuaccccauu
938	S430	agugcucuccuaccccaccua

SEQ ID NO.	single strand code	sense strand 5'→3'
939	S431	gugcucuccuaccccaccuaa
940	S432	gcucuccuaccccaccucauu
941	S433	cucuccuaccccaccucauau
942	S434	cuccuaccccaccucaugcau
943	S435	ccuaccccaccucaugccuaa
944	S436	uaccccaccucaugccugguc
945	S437	ccuccaggcaugcuggccuaa
946	S438	uccaggcaugcuggccuccua
947	S439	aaggacagauuuctcagugu
948	S440	gaggacagauuucucagugu
949	S441	caggacagauuucucagugu
950	S442	gggacagauuucucagugcua
951	S443	gagcgacagauuucucagugu
952	S444	uaggacagauuucucagugu
953	S445	auggacagauuucucagugu
954	S446	aggacagauuucucagugua
955	S447	aaggacagauuucucagu
956	S448	gcuuaaaaggacagauuua
957	S449	gcuuaaaaggacagauuucu
958	S450	cuuuaaaaggacagauuucuc
959	S451	uuuuaaaaggacagauuucua
960	S452	uuuaggacagauuucucag
961	S453	aaaaggacagauuucucagc
962	S454	aaaggacagauuucucagug
963	S455	uaaaggacagauuucucagu
964	S456	aagcgacagauuucucagugu

where, g=guanylate, a=adenylate, u=uridylate, c=cytidylate.

In some embodiments, the antisense strand of the RNA inhibitor is selected from a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

Table3 antisense strand sequences of the RNA inhibitor

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
104	AS1	agaauacugucccuuuuaagc
105	AS2	acuuguccuuaacggugcucc
106	AS3	aacuuguccuuaacggugcuc
107	AS4	agaacuuguccuuaacggugc
108	AS5	uuuauugggaggccagcaugc
109	AS6	aaauccagaacucagagaac
110	AS7	uugguggcgugcucauguaa
111	AS8	gguaauaggucucaggcagc
112	AS9	aggauaggauaggcagguggac
113	AS10	uuucaggaacugaagccauc
114	AS11	uaaccugcaugaagcugaga
115	AS12	uguaaccugcaugaagcuga
116	AS13	ucauguaaccugcaugaagc
117	AS14	uccaaauccagaacucagag
118	AS15	agucuucagggaaacugaagc
119	AS16	caguagucuucagggaaacug
120	AS17	cuccaguagucuucagggaa
121	AS18	aacggugcuccaguagucuuu
122	AS19	uuaacggugcuccaguagucu
123	AS20	cagagaacuuguccuuaacgg
124	AS21	cagaacucagagaacuugucc
125	AS22	guccaaauccagaacucaga

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
126	AS23	gcugaaguuggucugaccuca
127	AS24	acuuggggguauugaggucuca
128	AS25	aaggagcucgcaggauaggaua
129	AS26	uuaagcaaccuacaggggcag
130	AS27	uuuaagcaaccuacaggggca
131	AS28	cuuuuaagcaaccuacagggg
132	AS29	ucagugcauccuuggcggu
133	AS30	cuguccuuuuagcaaccua
134	AS31	aggagagcacugagaauacug
135	AS32	gguaaggagagcacugagaaua
136	AS33	augagguggguaggagagca
137	AS34	agauugcaggaccaaggagc
138	AS35	ccacggcugaaguuggucuga
139	AS36	uauugaggucucaggcagcca
140	AS37	cucaggguccaaaucccagaa
141	AS38	gaccucaggguccaaauccca
142	AS39	gucugaccucaggguccaaau
143	AS40	agccacggcugaaguuggucu
144	AS41	ccuggagauugcaggacccaa
145	AS42	ucgcaggauaggauaggcaggu
146	AS43	agcucgcaggauaggauaggca
147	AS44	auugcaggaccaaggagcuc
148	AS45	ggagagcacugagaauacugu
149	AS46	ugggguaaggagagcacugaga
150	AS47	ggagauugcaggaccaagga
151	AS48	uuggucugaccucagggucca
152	AS49	aaguuggucugaccucagggu

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
153	AS50	ugaaguuggucugaccucagg
154	AS51	gcacugagaauacugucccuuuu
437	AS193	cacugagaauacugucccuua
438	AS194	uaauacugucccuuuuaagcaa
439	AS195	gccucugaagcucgggcagag
440	AS196	ucggccucugaagcucgggca
441	AS197	cucggccucugaagcucgggc
442	AS198	ccucggccucugaagcucggg
443	AS199	uccucggccucugaagcucgg
444	AS200	auccucggccucugaagcucg
445	AS201	cauccucggccucugaagcuc
446	AS202	gcauccucggccucugaagcu
447	AS203	aggcauccucggccucugaag
448	AS204	agggaggcauccucggccucu
449	AS205	gaaggagggauccucggccu
450	AS206	gagaaggagggauccucggc
451	AS207	ugagaaggagggauccucgg
452	AS208	cugagaaggagggauccucg
453	AS209	agcugagaaggagggauccu
454	AS210	aagcugagaaggagggaucc
455	AS211	ugaagcugagaaggagggauc
456	AS212	augaagcugagaaggaggga
457	AS213	caugaagcugagaaggaggc
458	AS214	gcaugaagcugagaaggagg
459	AS215	ugcaugaagcugagaaggagg
460	AS216	cugcaugaagcugagaaggga
461	AS217	ccugcaugaagcugagaaggg

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
462	AS218	cccugcaugaagcugagaagg
463	AS219	accugcaugaagcugagaag
464	AS220	aaccugcaugaagcugagaa
465	AS221	guaaccugcaugaagcugag
466	AS222	uguaaccugcaugaagcuga
467	AS223	cauguaaccugcaugaagcu
468	AS224	ucauguaaccugcaugaagc
469	AS225	uucauguaaccugcaugaag
470	AS226	cuucauguaaccugcaugaa
471	AS227	gcuucauguaaccugcauga
472	AS228	ugcuucauguaaccugcaug
473	AS229	gugcuucauguaaccugcau
474	AS230	cgugcuucauguaaccugca
475	AS231	gcgugcuucauguaaccugc
476	AS232	ggcgugcuucauguaaccug
477	AS233	uggcgugcuucauguaaccu
478	AS234	guggcgugcuucauguaacc
479	AS235	ugguggcgugcuucaugaac
480	AS236	cuugguggcgugcuucaugua
481	AS237	ucuugguggcgugcuucaugu
482	AS238	gucuugguggcgugcuucaug
483	AS239	ggucuugguggcgugcuucau
484	AS240	uggcgggucuugguggcgugcu
485	AS241	uuggcgggucuugguggcgugc
486	AS242	cuuggcgggucuugguggcgug
487	AS243	ccuuggcgggucuugguggcggu
488	AS244	uccuuggcgggucuugguggcg

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
489	AS245	auccuuggcggucuugguggc
490	AS246	cauccuuggcggucuuggugg
491	AS247	gcauccuuggcggucuuggug
492	AS248	ugcauccuuggcggucuuggu
493	AS249	gugcauccuuggcggucuugg
494	AS250	cagugcauccuuggcggucuu
495	AS251	ucagugcauccuuggcggucu
496	AS252	cucagugcauccuuggcgguc
497	AS253	gcucagugcauccuuggcggg
498	AS254	ugcucagugcauccuuggcgg
499	AS255	cugcucagugcauccuuggcg
500	AS256	gcugcucagugcauccuuggc
501	AS257	cgcugcucagugcauccuugg
502	AS258	acgcugcucagugcauccuug
503	AS259	cacgcugcucagugcauccuu
504	AS260	gcacgcugcucagugcauccu
505	AS261	ugcacgcugcucagugcaucc
506	AS262	cugcacgcugcucagugcauc
507	AS263	ccugcacgcugcucagugcau
508	AS264	uccugcacgcugcucagugca
509	AS265	cuccugcacgcugcucagugc
510	AS266	acuccugcacgcugcucagug
511	AS267	gacuccugcacgcugcucagu
512	AS268	ggacuccugcacgcugcucag
513	AS269	ugggacuccugcacgcugcuc
514	AS270	cugggacuccugcacgcugcu
515	AS271	accugggacuccugcacgcug

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
516	AS272	caccugggacuccugcacgcu
517	AS273	ccaccugggacuccugcacgc
518	AS274	ggccaccugggacuccugcac
519	AS275	ugggccaccugggacuccugc
520	AS276	ugcuggggccaccuggggacucc
521	AS277	accagccccuggccugcugg
522	AS278	ucaccagccccuggccugcu
523	AS279	ucggucaccagccccuggcc
524	AS280	aucggucaccagccccuggc
525	AS281	gccaucggucaccagccccu
526	AS282	aagccaucggucaccagccc
527	AS283	ugaagccaucggucaccagc
528	AS284	acugaagccaucggucacca
529	AS285	aacugaagccaucggucaccc
530	AS286	gaacugaagccaucggucacc
531	AS287	ggaacugaagccaucggucac
532	AS288	agggaacugaagccaucgguc
533	AS289	cagggaacugaagccaucggu
534	AS290	ucagggaacugaagccaucgg
535	AS291	uucagggaacugaagccaucg
536	AS292	uuucagggaacugaagccauc
537	AS293	cuuucagggaacugaagccau
538	AS294	gucuucagggaacugaagcc
539	AS295	agucuucagggaacugaagc
540	AS296	uagucuucagggaacugaag
541	AS297	aguagucuucagggaacuga
542	AS298	caguagucuucagggaacug

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
543	AS299	uccaguagucuuucagggaac
544	AS300	cuccaguagucuuucagggaa
545	AS301	gcuccaguagucuuucagggga
546	AS302	ugcuccaguagucuuucagggg
547	AS303	gugcuccaguagucuuucagg
548	AS304	ggugcuccaguagucuuucag
549	AS305	acggugcuccaguagucuuuc
550	AS306	uaacggugcuccaguagucuu
551	AS307	uuaacggugcuccaguagucu
552	AS308	cuuaacggugcuccaguaguc
553	AS309	ccuuaacggugcuccaguagu
554	AS310	uccuuaacggugcuccaguag
555	AS311	guccuuaacggugcuccagua
556	AS312	uguccuuaacggugcuccagu
557	AS313	acuuguccuuaacggugcucc
558	AS314	aacuuguccuuaacggugcuc
559	AS315	gaacuuguccuuaacggugcu
560	AS316	agaacuuguccuuaacggugc
561	AS317	agagaacuuguccuuaacgggu
562	AS318	cagagaacuuguccuuaacgg
563	AS319	ucagagaacuuguccuuaacg
564	AS320	cucagagaacuuguccuuaac
565	AS321	acucagagaacuuguccuuaa
566	AS322	gaacucagagaacuuguccuu
567	AS323	agaacucagagaacuuguccu
568	AS324	cagaacucagagaacuugucc
569	AS325	ccagaacucagagaacuuguc

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
570	AS326	cccagaacucagagaacuugu
571	AS327	ucccagaacucagagaacuug
572	AS328	aaucccagaacucagagaacu
573	AS329	aaaucccagaacucagagaac
574	AS330	guccaaaucccagaacucaga
575	AS331	gguccaaaucccagaacucag
576	AS332	ggguccaaaucccagaacuca
577	AS333	aggguccaaaucccagaacuc
578	AS334	ucaggguccaaaucccagaac
579	AS335	cucaggguccaaaucccagaa
580	AS336	accucaggguccaaaucccag
581	AS337	gaccucaggguccaaauccca
582	AS338	ugaccucaggguccaaauccc
583	AS339	ucugaccucaggguccaaauc
584	AS340	gucugaccucaggguccaaaau
585	AS341	uuggucugaccucagggucca
586	AS342	aguuggucugaccucaggguc
587	AS343	gaaguuggucugaccucaggg
588	AS344	cugaaguuggucugaccucag
589	AS345	gcugaaguuggucugaccuca
590	AS346	ggcugaaguuggucugaccuc
591	AS347	cggcugaaguuggucugaccu
592	AS348	acggcugaaguuggucugacc
593	AS349	cacggcugaaguuggucugac
594	AS350	gccacggcugaaguuggucug
595	AS351	agccacggcugaaguuggucu
596	AS352	cagccacggcugaaguugguc

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
597	AS353	gcagccacggcugaaguuggu
598	AS354	aggcagccacggcugaaguug
599	AS355	ucaggcagccacggcugaagu
600	AS356	ugaggucucaggcagccacgg
601	AS357	auugaggucucaggcagccac
602	AS358	guauugaggucucaggcagcc
603	AS359	gguaauugaggucucaggcagc
604	AS360	ggguaauugaggucucaggcag
605	AS361	gggguaauugaggucucaggca
606	AS362	ugggguaauugaggucucaggc
607	AS363	cuugggguaauugaggucucag
608	AS364	acuugggguaauugaggucuca
609	AS365	gacuugggguaauugaggucuc
610	AS366	ggacuugggguaauugaggucu
611	AS367	uggacuugggguaauugagguc
612	AS368	guggacuugggguaauugaggu
613	AS369	gguggacuugggguaauuaggg
614	AS370	cagguggacuugggguaauuga
615	AS371	ggcagguggacuugggguaau
616	AS372	aggcagguggacuugggguaau
617	AS373	auaggcagguggacuugggggu
618	AS374	gauaggcagguggacuuggggg
619	AS375	ggauaggcagguggacuugggg
620	AS376	uggauaggcagguggacuuggg
621	AS377	auggauaggcagguggacuug
622	AS378	ggauggauaggcagguggacu
623	AS379	aggauaggauaggcagguggac

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
624	AS380	caggauggauaggcaggugga
625	AS381	cgcaggauggauaggcaggug
626	AS382	ucgcaggauggauaggcaggu
627	AS383	cucgcaggauggauaggcagg
628	AS384	agcucgcaggauggauaggca
629	AS385	gagcucgcaggauggauaggc
630	AS386	aggagcucgcaggauggauag
631	AS387	aaggagcucgcaggauggaua
632	AS388	caaggagcucgcaggauggau
633	AS389	ccaaggagcucgcaggaugga
634	AS390	ccaaggagcucgcaggaugg
635	AS391	accaaggagcucgcaggaug
636	AS392	gaccaaggagcucgcaggau
637	AS393	ggaccaaggagcucgcagga
638	AS394	aggaccaaggagcucgcagg
639	AS395	uugcaggaccaaggagcucg
640	AS396	auugcaggaccaaggagcuc
641	AS397	gauugcaggaccaaggagcu
642	AS398	gagauugcaggaccaaggag
643	AS399	ggagauugcaggaccaagga
644	AS400	cuggagauugcaggaccaag
645	AS401	ccuggagauugcaggaccaa
646	AS402	cccuggagauugcaggacca
647	AS403	gcccuggagauugcaggacc
648	AS404	agcccuggagauugcaggacc
649	AS405	cagcccuggagauugcaggac
650	AS406	gcagcccuggagauugcagga

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
651	AS407	ggcagcccuggagauugcagg
652	AS408	aggggcagcccuggagauugc
653	AS409	aaccuacaggggcagcccugg
654	AS410	agcaaccuacaggggcagccc
655	AS411	uaagcaaccuacaggggcagc
656	AS412	ccuuuuagcaaccuacaggg
657	AS413	ccuuuuagcaaccuacagg
658	AS414	uguccuuuuagcaaccuac
659	AS415	acuguccuuuuagcaaccu
660	AS416	uacuguccuuuuagcaacc
661	AS417	auacuguccuuuuagcaac
662	AS418	gaauacuguccuuuuagca
663	AS419	gagaauacuguccuuuuag
664	AS420	ugagaauacuguccuuuuaa
665	AS421	cugagaauacuguccuuuuu
666	AS422	cacugagaauacuguccuuu
667	AS423	gcacugagaauacuguccuu
668	AS424	gagcacugagaauacugucc
669	AS425	ggagagcacugagaauacugu
670	AS426	aggagagcacugagaauacug
671	AS427	guaggagagcacugagaauac
672	AS428	gggguaggagagcacugagaa
673	AS429	ugggguaggagagcacugaga
674	AS430	ggugggguaggagagcacuga
675	AS431	aggugggguaggagagcacug
676	AS432	ugaggugggguaggagagcac
677	AS433	augaggugggguaggagagca

SEQ ID NO.	single strand code	antisense strand sequence 5'→3'
678	AS434	gcaugagguggggguaggagag
679	AS435	aggcaugagguggggguaggag
680	AS436	ccaggcaugagguggggguagg
681	AS437	aggccagcaugccuggagggg
682	AS438	ggaggccagcaugccuggagg
683	AS439	acacugagaauacuguccuu
684	AS440	acacugagaauacuguccuc
685	AS441	acacugagaauacuguccug
686	AS442	gcacugagaauacuguccuu
687	AS443	acacugagaauacugucgcuc
688	AS444	acacugagaauacuguccua
689	AS445	acacugagaauacuguccau
690	AS446	ucacugagaauacuguccuu
691	AS447	ucacugagaauacuguccuu
692	AS448	ugaauacuguccuuuuagc
693	AS449	aaucuguccuuuuagcaa
694	AS450	gaauacuguccuuuuagca
695	AS451	agaauacuguccuuuuagc
696	AS452	gagaauacuguccuuuuag
697	AS453	ugagaauacuguccuuuuaa
698	AS454	cugagaauacuguccuuuuu
699	AS455	acugagaauacuguccuuuu
700	AS456	acacugagaauacugucgcuu

where, g=guanylate, a=adenylate, u=uridylylate, c=cytidylate.

In some screened embodiments, the RNA inhibitor is selected from a) a combination of a sense strand in Table 2 and an antisense strand in Table 3, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

In some embodiments, the RNA inhibitor is selected from a) sequences in Table 5, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

Table 5 RNA inhibitors

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS67	S193	701	AS193	437
Ky-12-DS68	S194	702	AS194	438
Ky-12-DS69	S195	703	AS195	439
Ky-12-DS70	S196	704	AS196	440
Ky-12-DS71	S197	705	AS197	441
Ky-12-DS72	S198	706	AS198	442
Ky-12-DS73	S199	707	AS199	443
Ky-12-DS74	S200	708	AS200	444
Ky-12-DS75	S201	709	AS201	445
Ky-12-DS76	S202	710	AS202	446
Ky-12-DS77	S203	711	AS203	447
Ky-12-DS78	S204	712	AS204	448
Ky-12-DS79	S205	713	AS205	449
Ky-12-DS80	S206	714	AS206	450
Ky-12-DS81	S207	715	AS207	451
Ky-12-DS82	S208	716	AS208	452
Ky-12-DS83	S209	717	AS209	453
Ky-12-DS84	S210	718	AS210	454
Ky-12-DS85	S211	719	AS211	455
Ky-12-DS86	S212	720	AS212	456
Ky-12-DS87	S213	721	AS213	457
Ky-12-DS88	S214	722	AS214	458

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS89	S215	723	AS215	459
Ky-12-DS90	S216	724	AS216	460
Ky-12-DS91	S217	725	AS217	461
Ky-12-DS92	S218	726	AS218	462
Ky-12-DS93	S219	727	AS219	463
Ky-12-DS94	S220	728	AS220	464
Ky-12-DS95	S221	729	AS221	465
Ky-12-DS96	S222	730	AS222	466
Ky-12-DS97	S223	731	AS223	467
Ky-12-DS98	S224	732	AS224	468
Ky-12-DS99	S225	733	AS225	469
Ky-12-DS100	S226	734	AS226	470
Ky-12-DS101	S227	735	AS227	471
Ky-12-DS102	S228	736	AS228	472
Ky-12-DS103	S229	737	AS229	473
Ky-12-DS104	S230	738	AS230	474
Ky-12-DS105	S231	739	AS231	475
Ky-12-DS106	S232	740	AS232	476
Ky-12-DS107	S233	741	AS233	477
Ky-12-DS108	S234	742	AS234	478
Ky-12-DS109	S235	743	AS235	479
Ky-12-DS110	S236	744	AS236	480
Ky-12-DS111	S237	745	AS237	481
Ky-12-DS112	S238	746	AS238	482
Ky-12-DS113	S239	747	AS239	483
Ky-12-DS114	S240	748	AS240	484

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS115	S241	749	AS241	485
Ky-12-DS116	S242	750	AS242	486
Ky-12-DS117	S243	751	AS243	487
Ky-12-DS118	S244	752	AS244	488
Ky-12-DS119	S245	753	AS245	489
Ky-12-DS120	S246	754	AS246	490
Ky-12-DS121	S247	755	AS247	491
Ky-12-DS122	S248	756	AS248	492
Ky-12-DS123	S249	757	AS249	493
Ky-12-DS124	S250	758	AS250	494
Ky-12-DS125	S251	759	AS251	495
Ky-12-DS126	S252	760	AS252	496
Ky-12-DS127	S253	761	AS253	497
Ky-12-DS128	S254	762	AS254	498
Ky-12-DS129	S255	763	AS255	499
Ky-12-DS130	S256	764	AS256	500
Ky-12-DS131	S257	765	AS257	501
Ky-12-DS132	S258	766	AS258	502
Ky-12-DS133	S259	767	AS259	503
Ky-12-DS134	S260	768	AS260	504
Ky-12-DS135	S261	769	AS261	505
Ky-12-DS136	S262	770	AS262	506
Ky-12-DS137	S263	771	AS263	507
Ky-12-DS138	S264	772	AS264	508
Ky-12-DS139	S265	773	AS265	509
Ky-12-DS140	S266	774	AS266	510

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS141	S267	775	AS267	511
Ky-12-DS142	S268	776	AS268	512
Ky-12-DS143	S269	777	AS269	513
Ky-12-DS144	S270	778	AS270	514
Ky-12-DS145	S271	779	AS271	515
Ky-12-DS146	S272	780	AS272	516
Ky-12-DS147	S273	781	AS273	517
Ky-12-DS148	S274	782	AS274	518
Ky-12-DS149	S275	783	AS275	519
Ky-12-DS150	S276	784	AS276	520
Ky-12-DS151	S277	785	AS277	521
Ky-12-DS152	S278	786	AS278	522
Ky-12-DS153	S279	787	AS279	523
Ky-12-DS154	S280	788	AS280	524
Ky-12-DS155	S281	789	AS281	525
Ky-12-DS156	S282	790	AS282	526
Ky-12-DS157	S283	791	AS283	527
Ky-12-DS158	S284	792	AS284	528
Ky-12-DS159	S285	793	AS285	529
Ky-12-DS160	S286	794	AS286	530
Ky-12-DS161	S287	795	AS287	531
Ky-12-DS162	S288	796	AS288	532
Ky-12-DS163	S289	797	AS289	533
Ky-12-DS164	S290	798	AS290	534
Ky-12-DS165	S291	799	AS291	535
Ky-12-DS166	S292	800	AS292	536

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS167	S293	801	AS293	537
Ky-12-DS168	S294	802	AS294	538
Ky-12-DS169	S295	803	AS295	539
Ky-12-DS170	S296	804	AS296	540
Ky-12-DS171	S297	805	AS297	541
Ky-12-DS172	S298	806	AS298	542
Ky-12-DS173	S299	807	AS299	543
Ky-12-DS174	S300	808	AS300	544
Ky-12-DS175	S301	809	AS301	545
Ky-12-DS176	S302	810	AS302	546
Ky-12-DS177	S303	811	AS303	547
Ky-12-DS178	S304	812	AS304	548
Ky-12-DS179	S305	813	AS305	549
Ky-12-DS180	S306	814	AS306	550
Ky-12-DS181	S307	815	AS307	551
Ky-12-DS182	S308	816	AS308	552
Ky-12-DS183	S309	817	AS309	553
Ky-12-DS184	S310	818	AS310	554
Ky-12-DS185	S311	819	AS311	555
Ky-12-DS186	S312	820	AS312	556
Ky-12-DS187	S313	821	AS313	557
Ky-12-DS188	S314	822	AS314	558
Ky-12-DS189	S315	823	AS315	559
Ky-12-DS190	S316	824	AS316	560
Ky-12-DS191	S317	825	AS317	561
Ky-12-DS192	S318	826	AS318	562

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS193	S319	827	AS319	563
Ky-12-DS194	S320	828	AS320	564
Ky-12-DS195	S321	829	AS321	565
Ky-12-DS196	S322	830	AS322	566
Ky-12-DS197	S323	831	AS323	567
Ky-12-DS198	S324	832	AS324	568
Ky-12-DS199	S325	833	AS325	569
Ky-12-DS200	S326	834	AS326	570
Ky-12-DS201	S327	835	AS327	571
Ky-12-DS202	S328	836	AS328	572
Ky-12-DS203	S329	837	AS329	573
Ky-12-DS204	S330	838	AS330	574
Ky-12-DS205	S331	839	AS331	575
Ky-12-DS206	S332	840	AS332	576
Ky-12-DS207	S333	841	AS333	577
Ky-12-DS208	S334	842	AS334	578
Ky-12-DS209	S335	843	AS335	579
Ky-12-DS210	S336	844	AS336	580
Ky-12-DS211	S337	845	AS337	581
Ky-12-DS212	S338	846	AS338	582
Ky-12-DS213	S339	847	AS339	583
Ky-12-DS214	S340	848	AS340	584
Ky-12-DS215	S341	849	AS341	585
Ky-12-DS216	S342	850	AS342	586
Ky-12-DS217	S343	851	AS343	587
Ky-12-DS218	S344	852	AS344	588

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS219	S345	853	AS345	589
Ky-12-DS220	S346	854	AS346	590
Ky-12-DS221	S347	855	AS347	591
Ky-12-DS222	S348	856	AS348	592
Ky-12-DS223	S349	857	AS349	593
Ky-12-DS224	S350	858	AS350	594
Ky-12-DS225	S351	859	AS351	595
Ky-12-DS226	S352	860	AS352	596
Ky-12-DS227	S353	861	AS353	597
Ky-12-DS228	S354	862	AS354	598
Ky-12-DS229	S355	863	AS355	599
Ky-12-DS230	S356	864	AS356	600
Ky-12-DS231	S357	865	AS357	601
Ky-12-DS232	S358	866	AS358	602
Ky-12-DS233	S359	867	AS359	603
Ky-12-DS234	S360	868	AS360	604
Ky-12-DS235	S361	869	AS361	605
Ky-12-DS236	S362	870	AS362	606
Ky-12-DS237	S363	871	AS363	607
Ky-12-DS238	S364	872	AS364	608
Ky-12-DS239	S365	873	AS365	609
Ky-12-DS240	S366	874	AS366	610
Ky-12-DS241	S367	875	AS367	611
Ky-12-DS242	S368	876	AS368	612
Ky-12-DS243	S369	877	AS369	613
Ky-12-DS244	S370	878	AS370	614

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS245	S371	879	AS371	615
Ky-12-DS246	S372	880	AS372	616
Ky-12-DS247	S373	881	AS373	617
Ky-12-DS248	S374	882	AS374	618
Ky-12-DS249	S375	883	AS375	619
Ky-12-DS250	S376	884	AS376	620
Ky-12-DS251	S377	885	AS377	621
Ky-12-DS252	S378	886	AS378	622
Ky-12-DS253	S379	887	AS379	623
Ky-12-DS254	S380	888	AS380	624
Ky-12-DS255	S381	889	AS381	625
Ky-12-DS256	S382	890	AS382	626
Ky-12-DS257	S383	891	AS383	627
Ky-12-DS258	S384	892	AS384	628
Ky-12-DS259	S385	893	AS385	629
Ky-12-DS260	S386	894	AS386	630
Ky-12-DS261	S387	895	AS387	631
Ky-12-DS262	S388	896	AS388	632
Ky-12-DS263	S389	897	AS389	633
Ky-12-DS264	S390	898	AS390	634
Ky-12-DS265	S391	899	AS391	635
Ky-12-DS266	S392	900	AS392	636
Ky-12-DS267	S393	901	AS393	637
Ky-12-DS268	S394	902	AS394	638
Ky-12-DS269	S395	903	AS395	639
Ky-12-DS270	S396	904	AS396	640

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS271	S397	905	AS397	641
Ky-12-DS272	S398	906	AS398	642
Ky-12-DS273	S399	907	AS399	643
Ky-12-DS274	S400	908	AS400	644
Ky-12-DS275	S401	909	AS401	645
Ky-12-DS276	S402	910	AS402	646
Ky-12-DS277	S403	911	AS403	647
Ky-12-DS278	S404	912	AS404	648
Ky-12-DS279	S405	913	AS405	649
Ky-12-DS280	S406	914	AS406	650
Ky-12-DS281	S407	915	AS407	651
Ky-12-DS282	S408	916	AS408	652
Ky-12-DS283	S409	917	AS409	653
Ky-12-DS284	S410	918	AS410	654
Ky-12-DS285	S411	919	AS411	655
Ky-12-DS286	S412	920	AS412	656
Ky-12-DS287	S413	921	AS413	657
Ky-12-DS288	S414	922	AS414	658
Ky-12-DS289	S415	923	AS415	659
Ky-12-DS290	S416	924	AS416	660
Ky-12-DS291	S417	925	AS417	661
Ky-12-DS292	S418	926	AS418	662
Ky-12-DS293	S419	927	AS419	663
Ky-12-DS294	S420	928	AS420	664
Ky-12-DS295	S421	929	AS421	665
Ky-12-DS296	S422	930	AS422	666

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS297	S423	931	AS423	667
Ky-12-DS298	S424	932	AS424	668
Ky-12-DS299	S425	933	AS425	669
Ky-12-DS300	S426	934	AS426	670
Ky-12-DS301	S427	935	AS427	671
Ky-12-DS302	S428	936	AS428	672
Ky-12-DS303	S429	937	AS429	673
Ky-12-DS304	S430	938	AS430	674
Ky-12-DS305	S431	939	AS431	675
Ky-12-DS306	S432	940	AS432	676
Ky-12-DS307	S433	941	AS433	677
Ky-12-DS308	S434	942	AS434	678
Ky-12-DS309	S435	943	AS435	679
Ky-12-DS310	S436	944	AS436	680
Ky-12-DS311	S437	945	AS437	681
Ky-12-DS312	S438	946	AS438	682
Ky-12-DS313	S439	947	AS439	683
Ky-12-DS314	S440	948	AS440	684
Ky-12-DS315	S441	949	AS441	685
Ky-12-DS316	S442	950	AS442	686
Ky-12-DS317	S443	951	AS443	687
Ky-12-DS318	S444	952	AS444	688
Ky-12-DS319	S445	953	AS445	689
Ky-12-DS320	S446	954	AS446	690
Ky-12-DS321	S447	955	AS447	691
Ky-12-DS322	S448	956	AS448	692

RNA inhibitor	sense strand code	sense strand SEQ ID NO.	antisense strand code	antisense strand SEQ ID NO.
Ky-12-DS323	S449	957	AS449	693
Ky-12-DS324	S450	958	AS450	694
Ky-12-DS325	S451	959	AS451	695
Ky-12-DS326	S452	960	AS452	696
Ky-12-DS327	S453	961	AS453	697
Ky-12-DS328	S454	962	AS454	698
Ky-12-DS329	S455	963	AS455	699
Ky-12-DS330	S456	964	AS456	700

In some embodiments, the RNA inhibitor can be added into the cell line through cell transfection methods or liposome-nucleic acid nanoparticle methods well known in the art for sequence screening. Patents US9233971B2, US9080186B2, CN102985548B and CN103189057B related to methods for preparing lipid compounds and liposome-nucleic acid nanoparticles are incorporated into this specification in their entirety.

In some embodiments, the amphoteric lipids in the lipid compounds described therein are preferably macrocyclic lipids D1C1, T1C1, T1C6, T4C4, B2C1, B2C6, B2C7 and M10C1.

The person skilled in the art knows that dsRNA with a duplex structure of about 19 to 23 base pairs, for example, 21 base pairs, has been considered to be particularly effective in inducing RNA interference (Elbashir et al., EMBO 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures are also effective (Chu and Rana (2007) RNA14:1714-1719; Kim et al (2005) Nat Biotech 23:222-226). It is reasonable to expect that new sequences designed by those skilled in the art by subtracting or adding a few nucleotides at one or both ends of a sequence in Tables 1-3 and 5 can be similarly effective compared with the sequences of the present invention. Therefore, sequences containing at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to sequences in Tables 1-3 and 5 should all be within the scope of protection of the present invention. At least 15 consecutive nucleic acids refer to: sequences having 15, 16, 17, 18, 19, 20, 21, 22, 23 or more consecutive nucleotides and having an inhibitory effect that differs from the sequence of the present invention by no more than about 5, 10, 15, 20, 25 or 30% in terms of the ability to inhibit APOC3 gene expression are included in

the scope of protection of the present invention.

The dsRNA described in the present invention may further include one or more single stranded nucleotide protruding end, for example, 1, 2, 3 or 4 nucleotides. The nucleotide protruding end may comprise nucleotide/nucleoside analogues or their combination, including deoxynucleotides/nucleosides. The protruding end may be on the sense strand, the antisense strand, or any combination thereof. In addition, the nucleotides on protruding end can exist at the 5'- end, 3'- end or both ends of the antisense or sense strand of dsRNA. The protruding end can be caused by one strand being longer than the other, or by two strands of the same length crosslinking. The protruding end may form a mismatch with the target mRNA or it may be complementary to the targeted gene sequence or may be another sequence.

The dsRNA can also contain only a single protruding end, which can enhance the interference activity of RNA inhibitors without affecting their overall stability. For example, the single-stranded protruding end can be located at the 3'- end of the sense strand, or alternatively, at the 3'- end of the antisense strand. The RNA inhibitors can also have blunt end, located at the 5'- end of the antisense strand (or the 3'- end of the sense strand), and vice versa. Generally, the antisense strand of RNA inhibitors has a nucleotide protruding end at the 3'- end and a blunt end at the 5'- end.

In some embodiments, the protruding end exists at the 3'-end of the sense strand, the antisense strand, or both strands. In some embodiments, such 3'-protruding end is present in the antisense strand. In some embodiments, such 3'-protruding end exists in the sense strand.

In some embodiments, the dsRNA has a length of 21 nucleotide and is blunt ended on both ends.

In some embodiments, the dsRNA has a length of 21 nucleotides, and both the sense strand and antisense strand have protruding ends of 2 nucleotide at their 3' ends.

In some embodiments, the sense strand of the dsRNA has a length of 19 nucleotides, the antisense strand has a length of 21 nucleotides, and the antisense strand has a protruding end of 2 nucleotides at its 3' end.

In some embodiments, the sense strand of the dsRNA has a length of 21 nucleotides, the antisense strand has a length of 23 nucleotides, and the antisense strand has a protruding end of 2 nucleotides at its 3' end.

In order to enhance the stability of the RNA inhibitor described in the present invention in vivo, the sense strand and antisense strand of the RNA inhibitor can be modified without affecting its activity or

even enhancing its activity, and the nucleotide therein can have a modification group to modify the whole strand or part of it. In some embodiments, one or more nucleotides on the sense strand and/or antisense strand are modified to form modified nucleotides.

In some embodiments, the RNA of the RNA inhibitor (e.g., dsRNA) of the present invention is unmodified and does not include, for example, chemical modification or conjugations known in the art and described herein. In other embodiments, the RNA of the RNA inhibitor (e.g., dsRNA) of the present invention is chemically modified to enhance stability or other favorable properties. In other embodiments of the application, all nucleotides or basically all nucleotides of the RNA inhibitor of the application are modified, that is, no more than 5, 4, 3, 2 or 1 unmodified nucleotide exists in the strand of the RNA inhibitor.

Nucleic acids described in the present invention can be synthesized and/or modified by methods well known in the art, such as those described in "Current protocols in nucleic acid chemistry", Beaucage, S.L. et al. (eds.), John Wiley & Sons, Inc, New York, NY, USA, which is incorporated herein by reference. Modification includes, for example, end modification, such as, 5'-end modification (phosphorylation, conjugation, reverse ligation) or 3'-end modification (conjugation, DNA nucleotide, reverse ligation, etc.); base modification, such as replacing with stabilized bases, destabilized bases or bases paired with an expanded repertoire of partners, removing bases (abasic nucleotides) or conjugating bases; sugar modification (e.g., 2'- or 4' -position) or sugar substitution; or backbone modification, including modification or substitution of phosphodiester linkages. In the RNA inhibitor provided by the present invention, both the sense strand and antisense strand of the RNA inhibitor do not need uniform modification, and one or more modifications can be incorporated into a single nucleotide therein.

In some embodiments, the modified nucleotides comprise deoxyribonucleotides, nucleotide mimics, abasic nucleotides, 2'- modified nucleotides, 3'- to 3'-linkage (inverted) nucleotides, nucleotides containing unnatural bases, bridged nucleotides, peptide nucleic acids (PNA), unlocked nucleobase analogues, locked nucleotides, 3'-O-methoxy (2' inter-nucleoside linkage) nucleotides, 2'-F-arabinose nucleotides, 5'-Me/2'-Fluoro-nucleotides, morpholino nucleotides, vinyl phosphonate deoxyribonucleotides, nucleotides containing vinyl phosphonate and nucleotides containing cyclopropyl phosphonate.

In some embodiments, the 2'-modified nucleotides include: 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoronucleotide, 2'-deoxynucleotide, 2'-methoxyethyl nucleotide, 2'-amino nucleotide and/or 2'-alkyl

nucleotide.

In some embodiments, some or all of the 2' positions of the nucleotide glycosyls at odd-numbered positions from the 5' end of the sense strand are fluorine.

In some embodiments, the 2' positions of the glycosyls of at least 3 or 4 nucleotides on the sense strand are fluorine.

In some embodiments, some or all of the 2' positions of the nucleotide glycosyls at even-numbered positions from the 5' end of the antisense strand are fluorine.

In some embodiments, the 2' positions of the glycosyls of at least 2 or 4 nucleotides on the antisense strand are fluorine.

In some embodiments, at least one 2' positions of the nucleotides glycosyls at positions 2, 4, 6, 8, 14 and 16 from the 5' end of the antisense strand is fluorine, for example, 2' positions of the nucleotides glycosyls at positions 2, 4, 6, 8, 14 and 16 from the 5' end of the antisense strand are all fluorine.

In some embodiments, except for the nucleotides at positions 2, 4, 6, 8, 14 and 16 starting from the 5' end of the antisense strand, at least one 2' positions of the remaining nucleotide glycosyls is methoxy.

In some embodiments, at least one 2' positions of the nucleotides glycosyls at positions 9,10 and 11 from the 5' end of the sense strand is fluorine, for example, 2' positions of the nucleotides glycosyls at positions 9,10 and 11 from the 5' end of the sense strand are all fluorine.

In some embodiments, except for the nucleotides at positions 9,10 and 11 starting from the 5' end of the sense strand, at least one 2' positions of the remaining nucleotide glycosyls is methoxy.

In some embodiments, except for the nucleotides at positions 7, 9,10 and 11 starting from the 5' end of the sense strand, at least one 2' positions of the remaining nucleotide glycosyls is methoxy.

For example, the -OH at 2' positions of some or all of the nucleotide glycosyls of the sense strand and/or antisense strand could be substituted, the substituent group is fluorine or methoxy, preferably 2' positions of the nucleotides glycosyls at positions 9,10 and 11 from the 5' end of the sense strand are fluorine, 2' positions of the nucleotides glycosyls at positions 2, 4, 6, 8, 14, 16,18 and 20 from the 5' end of the antisense strand are fluorine, and 2' positions of the remaining nucleotide glycosyls are methoxy, or preferably 2' positions of the nucleotides glycosyls at positions 5, 7, 8 and 9 from the 5' end of the sense strand are fluorine, 2' positions of the nucleotides glycosyls at positions 7,12 and 14 from the 5' end of the antisense strand are fluorine, and 2' positions of the remaining nucleotide glycosyls are methoxy.

In some embodiments, there are at least two consecutive phosphorothioate linkages among the nucleotides of the sense strand and/or antisense strand.

In some embodiments, there are at least two consecutive phosphorothioate linkages among three consecutive nucleotides at the end of the sense strand and/or the end of the antisense strand.

For example, there are at least two consecutive phosphorothioate linkages among three consecutive nucleotides at the 5' and 3' ends of the sense and antisense strands.

For another example, the 2' positions of nucleotide glycosyls at positions 9, 10 and 11 starting from the 5' end of the sense strand are fluorine, and the 2' positions of nucleotide glycosyls at positions 2, 4, 6, 8, 14, 16, 18 and 20 starting from the 5' end of the antisense strand are fluorine, and the 2' positions of the remaining nucleotide glycosyls are methoxy, and there are at least two consecutive phosphorothioate linkages among the 3 consecutive nucleotides at the 5' end and the 3' end of the sense strand and the antisense strand.

In some embodiments, the 2' positions of some nucleotides in the sense strand are fluorine or methoxy, and the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated. The 2' positions of nucleotides at positions 5, 7, 8 and 9 or positions 3, 5, 7, 9, 11, 13, and 15 starting from the 5' end of the sense strand are fluorine, the 2' positions of the remaining nucleotides are methoxy, the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated.

In some embodiments, the 2' positions of some nucleotides in the sense strand are fluorine or methoxy, and the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated. The 2' positions of nucleotides at positions 9, 10 and 11 or positions 3, 5, 7, 9, 11, 13, 15 and/or 17 starting from the 5' end of the sense strand are fluorine, the 2' positions of the remaining nucleotides are methoxy, the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated.

In some screened embodiments, the 3' ends of the sense strand and the antisense strand can each have two thhangings. The sense strand and the antisense strand of the RNA inhibitor are selected from a) sequences in Table 6, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

Table 6 RNA inhibitors

RNA inhibitor	sense strand			antisense strand		
	SEQ ID NO.	single strand code	Sequence 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
DS52	155	S52	gcuuaaaaggacaguauucutt	206	AS52	agaauacuguccuuuaagctt
DS53	156	S53	ggagcaccguuaaggacaagutt	207	AS53	acuuguccuuaacggugcuctt
DS54	157	S54	gagcaccguuaaggacaagutt	208	AS54	aacuuguccuuaacggugcuctt
DS55	158	S55	gcaccguuaaggacaaguucutt	209	AS55	agaacuuguccuuaacggugctt
DS56	159	S56	gcaugcuggccucccauaaat t	210	AS56	uuuauugggaggccagcaugc tt
DS57	160	S57	guucucugaguucugggauu utt	211	AS57	aaauccagaacucagagaactt
DS58	161	S58	uuacaugaagcacgccaccaat t	212	AS58	uugguggcgugcuucauguaa tt
DS59	162	S59	gcugccugagaccucaauacct t	213	AS59	gguauugaggucucaggcagc tt
DS60	163	S60	guccaccugccuauccaucutt t	214	AS60	aggauaggauaggcagguggac tt
DS61	164	S61	gauggcuucaguucccugaaa tt	215	AS61	uuucagggaacugaagccauct t
DS62	165	S62	ucucagcuucaugcaggguaa tt	216	AS62	uaaccugcaugaagcugagat t

RNA inhibitor	sense strand			antisense strand		
	SEQ ID NO.	single strand code	Sequence 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
DS63	166	S63	ucagcucaugcaggguuaca tt	217	AS63	uguaaccugcaugaagcugat t
DS64	167	S64	gcuucaugcaggguuacauga tt	218	AS64	ucauguaaccugcaugaagct t
DS65	168	S65	cucugaguucugggauuugg att	219	AS65	uccaaaucccagaacucagagtt
DS66	169	S66	gcuucaguucccugaaagacu tt	220	AS66	agucuucagggaacugaagct t
DS67	170	S67	caguucccugaaagacuacug tt	221	AS67	caguagucuucagggaacug tt
DS68	171	S68	uucccugaaagacuacuggag tt	222	AS68	cuccaguagucuucagggaat t
DS69	172	S69	aaagacuacuggagcaccguu tt	223	AS69	aacggugcuccaguagucuuu tt
DS70	173	S70	agacuacuggagcaccguuaa tt	224	AS70	uuaacggugcuccaguagucu tt
DS71	174	S71	ccguuaaggacaaguucucug tt	225	AS71	cagagaacuuguccuuaacggt t
DS72	175	S72	ggacaaguucucugaguucug tt	226	AS72	cagaacucagagaacuugucct t
DS73	176	S73	ucugaguucugggauuugga ctt	227	AS73	guccaaaucccagaacucagatt

RNA inhibitor	sense strand			antisense strand		
	SEQ ID NO.	single strand code	Sequence 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
DS74	177	S74	ugaggucagaccaacuucagc tt	228	AS74	gcugaaguuggucugaccuca tt
DS75	178	S75	ugagaccucaauacccaagut t	229	AS75	acuugggguaauugaggucuca tt
DS76	179	S76	uauccaucugcgagcuccuu tt	230	AS76	aaggagcucgcaggauggauat t
DS77	180	S77	cugccccuguagguugcuuaa tt	231	AS77	uuaagcaaccuacaggggcagt t
DS78	181	S78	ugccccuguagguugcuuaaa tt	232	AS78	uuuaagcaaccuacaggggcagt t
DS79	182	S79	ccccuguagguugcuuaaaag tt	233	AS79	cuuuuaagcaaccuacaggggt t
DS80	183	S80	agaccgccaagggaugcacugat t	234	AS80	ucagugcauccuuggcgggucu tt
DS81	184	S81	uagguugcuuaaaaggacag tt	235	AS81	cuguccuuuuuagcaaccuat t
DS82	185	S82	caguaucucagugcucuccu tt	236	AS82	aggagagcacugagaauacugt t
DS83	186	S83	uauucucagugcucuccuacc tt	237	AS83	gguaaggagagcacugagaauat t
DS84	187	S84	ugcucuccuaccccaccucaut t	238	AS84	augaggugggguaaggagagca tt

RNA inhibitor	sense strand			antisense strand		
	SEQ ID NO.	single strand code	Sequence 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
DS85	188	S85	gcuccuugggucugcaau tt	239	AS85	agauugcaggaccaaggagct t
DS86	189	S86	ucagaccaacuucagccgugg tt	240	AS86	ccacggcugaaguuggucuga tt
DS87	190	S87	uggcugccugagaccucaau tt	241	AS87	uauugaggucucaggcagccat t
DS88	191	S88	uucugggauuuggaccuga gtt	242	AS88	cucaggguccaaaucccagaatt
DS89	192	S89	ugggauuuggaccucaggu ctt	243	AS89	gaccucaggguccaaaucccatt
DS90	193	S90	auuuggaccucagaggucagac tt	244	AS90	gucugaccucaggguccaaaut t
DS91	194	S91	agaccaacuucagccguggcu tt	245	AS91	agccacggcugaaguuggucu tt
DS92	195	S92	uugggucugcaaucuccagg tt	246	AS92	ccuggagauugcaggaccaat t
DS93	196	S93	accugccuauccauccugcgat t	247	AS93	ucgcaggauggauaggcaggu tt
DS94	197	S94	ugccuauccauccugcgagcu tt	248	AS94	agcucgcaggauggauaggcat t
DS95	198	S95	gagcuccuugggucugcaau tt	249	AS95	auugcaggaccaaggagcuct t

RNA inhibitor	sense strand			antisense strand		
	SEQ ID NO.	single strand code	Sequence 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
DS96	199	S96	acaguauucucagugcucucc tt	250	AS96	ggagagcacugagaauacugut t
DS97	200	S97	ucucagugcucuccuaccccat t	251	AS97	uggggguaggagagcacugaga tt
DS98	201	S98	uccuugggucugcaaucucc tt	252	AS98	ggagauugcaggaccaaggat t
DS99	202	S99	uggaccugaggucagaccaa tt	253	AS99	uuggucugaccucagggucca tt
DS100	203	S100	accugaggucagaccaacuut t	254	AS100	aaguuggucugaccucagggu tt
DS101	204	S101	ccugaggucagaccaacuucac t	255	AS101	ugaaguuggucugaccucagg tt
DS102	205	S102	aaggacagauuucucagugc tt	256	AS102	gcacugagaauacuguccuu uu

where g=guanylate, a=adenylate, u=uridylate, c=cytidylate, t=thymidylate.

In some embodiments, the 2' positions of some nucleotides in the sense strand are fluorine, and the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated.

In some embodiments, the sense strand in the RNA inhibitor is preferably selected from the sense strand sequences in Tables 6-1 and 6-2 below.

Table 6-1 modified sequence of the sense strand

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'
257	S103	GsGsAGfCAfCfCfGUUAAGGACAAsgsU
258	S104	GsAsGCfACfCfGfUUAAGGACAAGsUsU
259	S105	GsCsACfCGfUfUfAAGGACAAGUUsCsU
260	S106	GsCsAUfGCfUfGfGCCUCCCAAUAsAsA
261	S107	UsUsACfAUfGfAfAGCACGCCACCsAsA
262	S108	UsCsUCfAGfCfUfUCAUGCAGGGUsUsA
263	S109	GsCsUUfCAfGfUfUCCCUGAAAGAsCsU
264	S110	CsAsGUfUCfCfCfUGAAAGACUACsUsG
265	S111	UsUsCCfCUfGfAfAAGACUACUGGsAsG
266	S112	AsAsAGfACfUfAfCUGGAGCACCGsUsU
267	S113	AsGsACfUAfCfUfGGAGCACCGUUsAsA
268	S114	CsCsGUfUAfAfGfGACAAGUUCUCsUsG
269	S115	GsGsACfAAfGfUfUUCUCUGAGUUCsUsG
270	S116	UsCsUGfAGfUfUfCUGGGAUUUGGsAsC
271	S117	UsGsAGfACfCfUfCAAUACCCCAAsGsU
272	S118	CsUsGCfCCfCfUfGUAGGUUGCUUsAsA
273	S119	UsGsCCfCCfUfGfUAGGUUGCUUAsAsA
274	S120	CsCsCCfUGfUfAfGGUUGCUUAAAsAsG
275	S121	UsAsGGfUfUfGfCfUUAAGGGACsAsG
276	S122	CsAsGUfAUfUfCfUcAGUGCUCUCsCsU
277	S123	UsAsUUfCUfCfAfGUGCUCUCCUAsCsC
278	S124	UsGsGCfUGfCfCfUGAGACCUCAAsUsA
279	S125	UsUsGGfGUfCfCfUGCAAUCUCCAsGsG
280	S126	UsGsCCfUAfUfCfCAUCCUGCGAGsCsU
281	S127	GsAsGCfUCfCfUfUGGGUCCUGCAAsUsU
282	S128	AsCsAGfUAfUfUfCUCAGUGCUCUsCsC

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'
309	S155	UsUsfGGfGUfCfCfUGfCAfAUfCUCCAsGsG
310	S156	UsGs fCCfUAfUfCfCAfUCfCUfGCGAGsCsU
311	S157	GsAsfGCfUCfCfUfUGfGGfUCfCUGCAsAsU
312	S158	AsCs fAGfUAfUfUfCUfCAfGUfGCUCUsCsC
313	S159	UsCs fUCfAGfUfGfCUfCUfCCfUACCCsCsA
314	S160	AsCs fCCfUGfAfGfGUfCAfGAfCCAACsUsU
315	S161	CsCs fUGfAGfGfUfCAfGAfCCfAACUUsCsA
316	S162	AsAs fGGfGAfCfAfGUfAUfUCfUCAGUsGsC
407	S163	GsGsAGCACCCfGfUfUAAGGACAAsGsU
408	S164	GsAsGCACCGfUfUfAAGGACAAGsUsU
409	S165	GsCsACCGUUFaAfAGGACAAGUUsCsU
410	S166	GsCsAUGCUGfGfCfCUCCCAAUAsAsA
411	S167	UsUsACAUGAfAfGfCACGCCACCsAsA
412	S168	UsCsUCAGCUfUfCfAUGCAGGGUsUsA
413	S169	GsCsUUCAGUfUfCfCCUGAAAGAsCsU
414	S170	CsAsGUUCCCFUfGfAAAGACUACsUsG
415	S171	UsUsCCCUGAfAfAfGACUACUGGsAsG
416	S172	AsAsAGACUAFcUfGGAGCACCGsUsU
417	S173	AsGsACUACUfGfGfAGCACCGUUsAsA
418	S174	CsCsGUUAAGfGfAfCAAGUUCUCsUsG
419	S175	GsGsACAAGUfUfCfUCUGAGUUCsUsG
420	S176	UsCsUGAGUUFcUfGGGAUUUGGsAsC
421	S177	UsGsAGACCUfCfAfAUACCCCAAsGsU
422	S178	CsUsGCCCCUfGfUfAGGUUGCUUsAsA
423	S179	UsGsCCCCUGfUfAfGGUUGCUUAsAsA
424	S180	CsCsCCUGUAFgGfGUUGCUUAAAAsAsG

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'
425	S181	UsAsGGUUGCfUfUfAAAAGGGACsAsG
426	S182	CsAsGUAUUCfUfCfAGUGCUCUCsCsU
427	S183	UsAsUUCUCAfGfUfGCUCUCCUAsCsC
428	S184	UsGsGCUGCCfUfGfAGACCUCAsUsA
429	S185	UsUsGGGUCCfUfGfCAAUCUCCAsGsG
430	S186	UsGsCCUAUCfCfAfUCCUGCGAGsCsU
431	S187	GsAsGCUCCUfUfGfGGUCCUGCAsAsU
432	S188	AsCsAGUAUUfCfUfCAGUGCUCUsCsC
433	S189	UsCsUCAGUGfCfUfCUCCUACCCsCsA
434	S190	AsCsCCUGAGfGfUfCAGACCAACsUsU
435	S191	CsCsUGAGGUfCfAfGACCAACUUsCsA
436	S192	AsAsGGGACAfGfUfAUUCUCAGUsGsC

Table 6-2 modified sequence of sense strand

SEQ ID NO.	sense strand code	sense strand 5'→3'
1028	S457	GsUsGGCUGCfCfUfGAGACCUCAsAsU
1029	S458	AsAsGUCCACfCfUfGCCUAUCCAsUsC
1030	S459	CsAsCCUGCCfUfAfUCCAUCCUGsAsA
1031	S460	GsGsGACAGUfAfUfUCUCAGUGCsUsU
1032	S461	GsAsCAGUAUfUfCfUCAGUGCUCsUsU
1033	S462	GsAsGCGACAfGfUfAUUCUCAGUsGsU
1034	S463	GsUsGGCUfGCfCfUfGAGACCUCAsAsU
1035	S464	AsAsGUCCfACfCfUfGCCUAUCCAsUsC
1036	S465	CsAsCCUGfCCfUfAfUCCAUCCUGsAsA
1037	S466	GsGsGACAfGUfAfUfUCUCAGUGCsUsU

SEQ ID NO.	sense strand code	sense strand 5'→3'
1038	S467	GsAsCAGUfAUfUfCfUCAGUGCUCsUsU
1039	S468	GsAsGCGAfCAfGfUfAUUCUCAGUsGsU
1040	S469	GUGGCUGCfCfUfGAGACCUCAsAsU
1041	S470	AAGUCCACfCfUfGCCUAUCCAsUsC
1042	S471	CACCUGCCfUfAfUCCAUCCUGsAsA
1043	S472	GGGACAGUfAfUfUCUCAGUGCsUsU
1044	S473	GACAGUAUfUfCfUCAGUGCUCsUsU
1045	S474	GUGGCUfGCfCfUfGAGACCUCAsAsU
1046	S475	AAGUCCfACfCfUfGCCUAUCCAsUsC
1047	S476	CACCUGfCCfUfAfUCCAUCCUGsAsA
1048	S477	GGGACAfGUfAfUfUCUCAGUGCsUsU
1049	S478	GACAGUfAUfUfCfUCAGUGCUCsUsU
1050	S479	GAGCGACAfGfUfAUUCUCAGUsGsU
1051	S480	GAGCGAfCAfGfUfAUUCUCAGUsGsU
1052	S481	GAGCGACAfGfUfAUUCUCAsGsU
1053	S482	GsUsGGCUGCfCfUfGAGACCUCAsAsA
1054	S483	AsAsGUCCACfCfUfGCCUAUCCAsUsA
1055	S484	CsGsCCUGCCfUfAfUCCAUCCUGsAsA
1056	S485	GsGsGACAGUfAfUfUCUCAGUGCsUsA
1057	S486	GsAsCAGUAUfUfCfUCAGUGCUCsUsA
1058	S487	GsUsGGCUfGCfCfUfGAGACCUCAsAsA
1059	S488	AsAsGUCCfACfCfUfGCCUAUCCAsUsA
1060	S489	CsGsCCUGfCCfUfAfUCCAUCCUGsAsA
1061	S490	GsGsGACAfGUfAfUfUCUCAGUGCsUsA
1062	S491	GsAsCAGUfAUfUfCfUCAGUGCUCsUsA
1063	S492	AsAsGCGACAfGfUfAUUCUCAGUsGsA
1064	S493	AsAsGCGAfCAfGfUfAUUCUCAGUsGsA

SEQ ID NO.	sense strand code	sense strand 5'→3'
1065	S494	AsAsGCGACAfGfUfAUUCUCAsGsA
1066	S495	GUGGCUGCfCfUfGAGACCUCAsAsA
1067	S496	AAGUCCACfCfUfGCCUAUCCAsUsA
1068	S497	CGCCUGCCfUfAfUCCAUCCUGsAsA
1069	S498	GGGACAGUfAfUfUCUCAGUGCsUsA
1070	S499	GACAGUAUfUfCfUCAGUGCUCsUsA
1071	S500	GUGGCUfGCfCfUfGAGACCUCAsAsA
1072	S501	AAGUCCfACfCfUfGCCUAUCCAsUsA
1073	S502	CGCCUGfCCfUfAfUCCAUCCUGsAsA
1074	S503	GGGACAfGUfAfUfUCUCAGUGCsUsA
1075	S504	GACAGUfAUfUfCfUCAGUGCUCsUsA
1076	S505	AAGCGACAfGfUfAUUCUCAGUsGsA
1077	S506	AAGCGAfCAfGfUfAUUCUCAGUsGsA
1078	S507	AAGCGACAfGfUfAUUCUCAsGsA
1079	S508	GsUsGGCUGCfCfUfGAGACCUUsCsA
1080	S509	GsAsGUCCACfCfUfGCCUAUCsCsA
1081	S510	CsAsCCUGCCfUfAfUCCAUCCsUsA
1082	S511	GsGsGACAGUfAfUfUCUCAGUsGsA
1083	S512	GsAsCAGUAUfUfCfUCAGUGCsUsA
1084	S513	GsTsGGCUfGCfCfUfGAGACCUUsCsA
1085	S514	AsAsGUCCfACfCfUfGCCUAUCsCsA
1086	S515	CsAsCCUGfCCfUfAfUCCAUCCsUsA
1087	S516	GsGsGACAfGUfAfUfUCUCAGUsGsA
1088	S517	GsAsCAGUfAUfUfCfUCAGUGCsUsA
1089	S518	GsAsGCGACAfGfUfAUUCUCAsGsU
1090	S519	GsCsGCGAfCAfGfUfAUUCUCAsGsU
1091	S520	GsCsGCGACAfGfUfAUUCTCAsGsA

SEQ ID NO.	sense strand code	sense strand 5'→3'
1092	S521	GsUsGGCUfGcFcUfGAGACCUscsA
1093	S522	AsAsGUCCACfCfUfGCCUAUCscsA
1094	S523	CsAsCCUGCCfUfAfUCCAUCCUGscsG
1095	S524	CsAsCCUGfCCfUfAfUCCAUCCUGscsG
1096	S525	CsAsCCUGCCfUfAfUCCAUCCscUsG
1097	S526	CsAsCCUGfCCfUfAfUCCAUCCscUsG
1098	S527	GsGsGACAGUfAfUfUCUCAGUGCsUsC
1099	S528	GsGsGACAfGUfAfUfUCUCAGUGCsUsC
1100	S529	GsGsGACAGUfAfUfUCUCAGUsGsC
1101	S530	GsGsGACAfGUfAfUfUCUCAGUsGsC
1102	S531	GsAsCAGUAUfUfCfUCAGUGCUCsUsC
1103	S532	GsAsCAGUfAUfUfCfUCAGUGCUCsUsC
1104	S533	GsAsCAGUAUfUfCfUCAGUGCsUsC
1105	S534	GsAsCAGUfAUfUfCfUCAGUGCsUsC
1106	S535	AsAsGGGACAfGfUfAUUCUCAGUsGsC
1107	S536	AsAsGGGAfCAfGfUfAUUCUCAGUsGsC
1108	S537	AsAsGGGACAfGfUfAUUCUCAsGsU
1109	S538	AsAsGGGAfCAfGfUfAUUCUCAsGsU
1110	S539	AsAsGCGACAfGfUfAUUCUCAGUsGsU
1111	S540	AsAsGCGfACAfGfUfAUUCUCAGUsGsU
1112	S541	AsAsGGfGAfCfAfGUAUUCTCAGUsGsU
1113	S542	GsAsGGfGAfCAfGUAUUCUCAGUsGsU
1114	S543	CsAsGGfGAfCfAfGUAUUCUCAGUsGsU
1115	S544	GsGsGAfCAfGfUfAUUCUCAGUGCsUsA
1116	S545	GsAsGGfGAfCfAfGUAUUCUCAGUsGsU
1117	S546	GsAsGCfGAfCfAfGUAUUCTCAGUsGsU
1118	S547	UsAsGGfGAfCfAfGUAUUCTCAGUsGsU

SEQ ID NO.	sense strand code	sense strand 5'→3'
1119	S548	AsUsGGfGfCfAfGUAUUCTCAGUsGsU
1120	S549	AsGsGGfACfAfGfUAUUCUCAGUGsUsA
1121	S550	AsAsGGfGfCfAfGUAUUCUCAGUsGsA
1122	S551	GsCsUUfAAfAfAfGGGACAGUAUUsCsA
1123	S552	GsCsUUAAAAfGfGfGACAGUAUUsCsA
1124	S553	GsCsUUfAAfAfAfGGGACAGUAUUsCsU
1125	S554	GsCsUfUfAAfAfAfGGfGfCfAfGUAUUsCsU
1126	S555	CsUsUAfAAfAfGfGGACAGUAUUCsUsC
1127	S556	CsUsfUAfAAfAfGfGGfACfAGfUAUUCsUsC
1128	S557	UsUsAAfAAfGfGfGACAGUAUUCUsCsA
1129	S558	UsUsfAAfAAfGfGfGfGfCfAfGUfAUUCUsCsA
1130	S559	UsAsAAfAGfGfGfACAGUAUUCUCsAsG
1131	S560	UsAsfAAfAGfGfGfACfAGfUAfUUCUCsAsG
1132	S561	AsAsAAfGGfGfAfCAGUAUUCUCAsGsC
1133	S562	AsAsfAAfGGfGfAfCfGfGfUAfUUCUCAsGsC
1134	S563	AsAsAGfGGfAfCfAGUAUUCUCAGsUsG
1135	S564	AsAsAfGGfGfCfAfGfGfUAfUUCfUCAGsUsG
1136	S565	AsAsGGfGfCfAfGUAUUCUCAGUsGsC
1137	S566	AsAsfGGfGfCfAfGfGfUAfUUCfUCAGUsGsC
1138	S567	AsGsGGfACfAfGfUAUUCUCAGUGsCsU
1139	S568	AsGsGGfACfAfGfUAfUUCfUCAGUGsCsU
1140	S569	GsCsUUfAAfAfAfGGGACAGUAUUsCsA
1141	S570	GsCsUUAAAAfGfGfGACAGUAUUsCsA

where, G=2'-O-methylguanylate, A=2'-O-methyladenylate, U=2'-O-methyluridylate, C=2'-O-methylcytidylate; fG=2'-fluoroguanlylate, fA=2'-fluoroadenylate, fU=2'-fluorouridylate, fC=2'-fluorocytidylate, Gs=2'-O-methyl-3'-thioguanlylate, As=2'-O-methyl-3'-thioadenylate, Us=2'-O-methyl-3'-thiouridylate, Cs=2'-O-methyl-3'-thiocytidylate, fGs=2'-fluoro-3'-thioguanlylate, fAs=2'-

fluoro-3'-thioadenylate, fUs=2'-fluoro-3'-thiouridylate, fCs=2'-fluoro-3'-thiocytidylate, T=thymidylate, Ts=3'-thiothymidylate.

In some embodiments, the sense strand of the RNA inhibitor of the present invention is selected from a) sequences in Tables 6-1 and 6-2, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

In some embodiments, the 2' positions of some nucleotides in the antisense strand are fluorine, and the phosphate bonds among at least three adjacent nucleotides at the end of the antisense strand can be thiolated. The antisense strand of the RNA inhibitor is preferably selected from a) sequences in Tables 7-1 and 7-2, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

Table 7-1 modified sequences of antisense strand

SEQ ID NO.	antisense strand code	antisense strand 5'→3'
317	AS103	AsCsUUGUfCCUUAfACfGGUGCUscsC
318	AS104	AsAsCUUGfUCCUUAfAAfCGGUGCscsC
319	AS105	AsGsAACUfUGUCCfUUAACGGUsgsC
320	AS106	UsUsUAUUAfGGGAGfGCfCAGCAUsgsC
321	AS107	UsUsGGUGfGCGUGfCUfUCAUGUscsA
322	AS108	UsAsACCCfUGCAUfGAfAGCUGAsGsA
323	AS109	AsGsUCUUAfUCAGGfGAfACUGAAsgsC
324	AS110	CsAsGUAGfUCUUUAfCAfGGGAACscsG
325	AS111	CsUsCCAGfUAGUCfUUAfUCAGGGsAsA
326	AS112	AsAsCGGUfGCUCCfAGfUAGUCUscsU
327	AS113	UsUsAACGfGUGCUfCCfAGUAGUscsU
328	AS114	CsAsGAGAfACUUGfUCfCUUAACsgsG
329	AS115	CsAsGAACfUCAGAfGAfACUUGUscsC
330	AS116	GsUsCCAAfAUCCCFAGfAACUCAsGsA
331	AS117	AsCsUUGGfGGUAUfUGfAGGUCUscsA
332	AS118	UsUsAAGCfAACCfUfACfAGGGGcsAsG
333	AS119	UsUsUAAGfCAACCfUfCAGGGGcsCsA
334	AS120	CsUsUUUAfAGCAAfCCfUACAGGsgsG

SEQ ID NO.	antisense strand code	antisense strand 5'→3'
335	AS121	CsUsGUCCfCUUUUfAAfGCAACCsUsA
336	AS122	AsGsGAGAfGCACUfGAfGAAUACsUsG
337	AS123	GsGsUAGGfAGAGCfACfUGAGAAUsUsA
338	AS124	UsAsUUGAfGGUCUfCAfGGCAGCsCsA
339	AS125	CsCsUGGAfGAUUGfCAfGGACCCsAsA
340	AS126	AsGsCUCGfCAGGAfUGfGAUAGGsCsA
341	AS127	AsUsUGCAfGGACCFCAfAGGAGCsUsC
342	AS128	GsGsAGAGfCACUGfAGfAAUACUsGsU
343	AS129	UsGsGGGUfAGGAGfAGfCACUGAsGsA
344	AS130	AsAsGUUGfGUCUGfACfCUCAGGsGsU
345	AS131	UsGsAAGUfUGGUCfUGfACCUCAsGsG
346	AS132	GsCsACUGfAGAAUfACfUGUCCCUUsUsU
347	AS133	AsfCsUUGfUCfCfUfUAACfGfGfUGCUsCsC
348	AS134	AsfAsCUUfGUfCfCfUUAfCfGfGUGCsUsC
349	AS135	AsfGsAACfUUfGfUfCCUUFaAfCGGUUsGsC
350	AS136	UsfUsUAUfUGfGfGfAGGCfCfAfGCAUsGsC
351	AS137	UsfUsGGUfGGfCfGfUGCUfUfCfAUGUsAsA
352	AS138	UsfAsACCFCUfGfCfAUGAfAfGfCUGAsGsA
353	AS139	AsfGsUCUfUUfCfAfGGGAfAfCfUGAAsGsC
354	AS140	CsfAsGUAfGUfCfUfUUCAfGfGfGAACsUsG
355	AS141	CsfUsCCAfGUfAfGfUCUUFUfCfAGGGsAsA
356	AS142	AsfAsCGGfUGfCfUfCCAGfUfAfGUCUsUsU
357	AS143	UsfUsAACfGGfUfGfCUCCfAfGfUAGUsCsU
358	AS144	CsfAsGAGfAAfCfUfUGUCfCfUfUAACsGsG
359	AS145	CsfAsGAAfCUfCfAfGAGAfAfCfUUGUsCsC
360	AS146	GsfUsCCAfAAfUfCfCCAGfAfAfCUCAsGsA
361	AS147	AsfCsUUGfGGfGfUfAUUGfAfGfGUCUsCsA
362	AS148	UsfUsAAGfCAfAfCfCUACfAfGfGGGCsAsG
363	AS149	UsfUsUAAfGCfAfAfCCUAFcAfGGGGsCsA
364	AS150	CsfUsUUUfAAfGfCfAACCfUfAfCAGGsGsG
365	AS151	CsfUsGUCfCCfUfUfUUAfGfCfAACCsUsA
366	AS152	AsfGsGAGfAGfCfAfCUGAfGfAfAUACsUsG

SEQ ID NO.	antisense strand code	antisense strand 5'→3'
367	AS153	GsfGsUAGfGAfGfAfGCACfUfGfAGAAUsA
368	AS154	UsfAsUUGfAGfGfUfCUCAfGfGfCAGCsCsA
369	AS155	CsfCsUGGfAGfAfUfUGCAfGfGfACCCsAsA
370	AS156	AsfGsCUCfGCfAfGfGAUGfGfAfUAGGsCsA
371	AS157	AsfUsUGCfAGfGfAfCCCAfAfGfGAGCsUsC
372	AS158	GsfGsAGAfGCfAfCfUGAGfAfAfUACUsGsU
373	AS159	UsfGsGGGfUafGfGfAGAGfCfAfCUGAsGsA
374	AS160	AsfAsGUUfGGfUfCfUGACfCfUfCAGGsGsU
375	AS161	UsfGsAAGfUUfGfGfUCUGfAfCfCUCAsGsG
376	AS162	GsfCsACUfGAfGfAfAUACfUfGfUCCCUUsUsU
377	AS163	AsfCsUfUGfUCfCUUAACfGGfUGCUUsCsC
378	AS164	AsfAsCfUUfGUfCCUUAafCGfGUGCsUsC
379	AS165	AsfGsAfACfUufGUCCUufAAfCGGUsGsC
380	AS166	UsfUsUfAUfUGfGGAGGCfCAfGCAUsGsC
381	AS167	UsfUsGfGUfGGfCGUGCUfUCfAUGUsAsA
382	AS168	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
383	AS169	AsfGsUfCUfUUfCAGGGAfACfUGAAUsGsC
384	AS170	CsfAsGfUAfGUfCUUUCAfGGfGAACsUsG
385	AS171	CsfUsCfCAfGUfAGUCUufUCfAGGGsAsA
386	AS172	AsfAsCfGGfUGfCUCCAGfUAfGUCUsUsU
387	AS173	UsfUsAfACfGGfUGCUCCfAGfUAGUsCsU
388	AS174	CsfAsGfAGfAAfCUUGUCfCUfUAACsGsG
389	AS175	CsfAsGfAAfCUfCAGAGAfACfUUGUsCsC
390	AS176	GsfUsCfCAfAAfUCCCAGfAAfCUCAsGsA
391	AS177	AsfCsUfUGfGGfGUAUUGfAGfGUCUsCsA
392	AS178	UsfUsAfAGfCAfACCUACfAGfGGGCsAsG
393	AS179	UsfUsUfAAfGCfAACCUAfCAfGGGGsCsA
394	AS180	CsfUsUfUUfAAfGCAACCFUAfCAGGsGsG
395	AS181	CsfUsGfUCfCCfUUUUAafGCfAACCsUsA
396	AS182	AsfGsGfAGfAGfCACUGAfGAfAUACsUsG
397	AS183	GsfGsUfAGfGAfGAGCACfUGfAGAAUsA
398	AS184	UsfAsUfUGfAGfGUCUCAfGGfCAGCsCsA

SEQ ID NO.	antisense strand code	antisense strand 5'→3'
399	AS185	CsfCsUfGGfAGfAUUGCAfGGfACCCsAsA
400	AS186	AsfGsCfUCfGCfAGGAUGfGAfUAGGsCsA
401	AS187	AsfUsUfGCfAGfGACCCAfAGfGAGCsUsC
402	AS188	GsfGsAfGAfGCfACUGAGfAAfUACUsGsU
403	AS189	UsfGsGfGGfUAfGGAGAGfCAfCUGAsGsA
404	AS190	AsfAsGfUUfGGfUCUGACfCUfCAGGsGsU
405	AS191	UsfGsAfAGfUUfGGUCUGfACfCUCAsGsG
406	AS192	GsfCsAfCUfGAfGAAUACfUGfUCCCUUsUsU

Table 7-2 modified sequences of antisense strand

SEQ ID NO.	antisense strand code	antisense strand 5'-3'
965	AS457	UsfGsAfGGfUCfUCAGGCfAGfCCfACsfGsG
966	AS458	UsfGsGfAUfAGfGCAGGUfGGfACfUUsfGsG
967	AS459	CsfAsGfGAfUGfGAUAGGfCAfGGfUGsfGsA
968	AS460	GsfCsAfCUfGAfGAAUACfUGfUCfCCsfUsU
969	AS461	GsfAsGfCAfCUfGAGAAUfACfUGfUCsfCsC
970	AS462	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
971	AS463	UsfGsAfGGfUCfUCfAGGCfAGfCCfACsGsG
972	AS464	UsfGsGfAUfAGfGCfAGGUfGGfACfUUsGsG
973	AS465	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGsGsA
974	AS466	GsfCsAfCUfGAfGAfAUACfUGfUCfCCsUsU
975	AS467	GsfAsGfCAfCUfGAfGAAUfACfUGfUCsCsC
976	AS468	AsfCsAfCUfGAfGAfAUACfUGfUCfGCsUsC
977	AS469	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCsUsU
978	AS470	UsfGsAfGGfUCfUCAGGCfAGfCCfACfGG
979	AS471	UsfGsGfAUfAGfGCAGGUfGGfACfUUfGG
980	AS472	CsfAsGfGAfUGfGAUAGGfCAfGGfUGfGA
981	AS473	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUU
982	AS474	GsfAsGfCAfCUfGAGAAUfACfUGfUCfCC

SEQ ID NO.	antisense strand code	antisense strand 5'-3'
983	AS475	UsfGsAfGGfUCfUCfAGGCfAGfCCfACGG
984	AS476	UsfGsGfAUfAGfGCfAGGUfGGfACfUUGG
985	AS477	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGGA
986	AS478	GsfCsAfCUfGAfGAfAUACfUGfUCfCCUU
987	AS479	GsfAsGfCAfCUfGAfGAAUfACfUGfUCCC
988	AS480	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUC
989	AS481	AsfCsAfCUfGAfGAfAUACfUGfUCfGCUC
990	AS482	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCUU
991	AS483	UsfGsAfGGfUCfUCAGGCfAGfCCfACfGsG
992	AS484	UsfGsGfAUfAGfGCAGGUfGGfACfUfGsG
993	AS485	CsfAsGfGAfUGfGAUAGGfCAfGGfUGfGsA
994	AS486	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUsU
995	AS487	GsfAsGfCAfCUfGAGAAUfACfUGfUCfCsC
996	AS488	UsfGsAfGGfUCfUCfAGGCfAGfCCfACGsG
997	AS489	UsfGsGfAUfAGfGCfAGGUfGGfACfUUGsG
998	AS490	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGGsA
999	AS491	GsfCsAfCUfGAfGAfAUACfUGfUCfCCUsU
1000	AS492	GsfAsGfCAfCUfGAfGAAUfACfUGfUCCsC
1001	AS493	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUsC
1002	AS494	AsfCsAfCUfGAfGAfAUACfUGfUCfGCUUsC
1003	AS495	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCUsU
1004	AS496	AsfUsUfGAfGGfUCUCAGfGCfAGfCCsfAsC
1005	AS497	AsfUsUfGAfGGfUCfUCAGfGCfAGfCCsAsC
1006	AS498	AsfUsUfGAfGGfUCUCAGfGCfAGfCCfACsGsG
1007	AS499	AsfUsUfGAfGGfUCfUCAGfGCfAGfCCACsGsG
1008	AS500	GsfAsUfGGfAUfAGGCAGfGUfGGfACsfUsU
1009	AS501	GsfAsUfGGfAUfAGfGCAGfGUfGGfACsUsU

SEQ ID NO.	antisense strand code	antisense strand 5'-3'
1010	AS502	GsfAsUfGGfAUfAGGCAGfGUfGGfACfUUUsGsG
1011	AS503	GsfAsUfGGfAUfAGfGCAGfGUfGGfACUUUsGsG
1012	AS504	CsfGsCfAGfGAfUGGAUafGGfCAfGGsfUsG
1013	AS505	CsfGsCfAGfGAfUGfGAUafGGfCAfGGsUsG
1014	AS506	CsfGsCfAGfGAfUGGAUafGGfCAfGGfUGsGsA
1015	AS507	CsfGsCfAGfGAfUGfGAUafGGfCAfGGUGsGsA
1016	AS508	GsfAsGfCAfCUfGAGAAUfACfUGfUCfCCsUsU
1017	AS509	GsfAsGfCAfCUfGAfGAAUfACfUGfUCCCsUsU
1018	AS510	GsfAsGfAGfCAfCUGAGAfAUfACfUGsfUsC
1019	AS511	GsfAsGfAGfCAfCUfGAGAfAUfACfUGsUsC
1020	AS512	GsfAsGfAGfCAfCUGAGAfAUfACfUGfUCsCsC
1021	AS513	GsfAsGfAGfCAfCUfGAGAfAUfACfUGUCsCsC
1022	AS514	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUUUsUsU
1023	AS515	GsfCsAfCUfGAfGAfAUACfUGfUCfCCUUUsUsU
1024	AS516	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsU
1025	AS517	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUUUsUsU
1026	AS518	AsfCsAfCUfGAfGAfAUACfUGfUCfGCsUsU
1027	AS519	AsfCsAfCUfGAfGAfAUACfUGfUCfGCUUsUsU
1142	AS520	AsCsACUGfAGAAUfACfUGUCCCsUsU
1143	AS521	AsCsACUGfAGAAUfACfUGUCCCsUsC
1144	AS522	AsCsACUGfAGAAUfACfUGUCCCsUsG
1145	AS523	GsCsACUGfAGAAUfACfUGUCCCsUsU
1146	AS524	AsCsACUGfAGAAUfACfUGUCCCsUsC
1147	AS525	AsCsACUGfAGAAUfACfUGUCGCsUsC
1148	AS526	AsCsACUGfAGAAUfACfUGUCCCsUsA
1149	AS527	AsCsACUGfAGAAUfACfUGUCCCsAsU
1150	AS528	UsCsACUGfAGAAUfACfUGUCCCsUsU

SEQ ID NO.	antisense strand code	antisense strand 5'-3'
1151	AS529	UsCsACUGfAGAAUfACfUGUCCCsUsU
1152	AS530	UsGsAAUAfCUGUCfCCfUUUUAAsgsC
1153	AS531	UsfGsAfAUfACfUGfUCfCCfUUfUUfAAsgsC
1154	AS532	AsAsUACUfGUCCcfUUfUUAAGCsAsA
1155	AS533	AsfAsUfACfUGfUCCCUUfUUfAAGCsAsA
1156	AS534	GsAsAUACfUGUCCfCUfUUUAAGsCsA
1157	AS535	GsfAsAfUAfCUfGUCCCUfUUfUAAGsCsA
1158	AS536	AsGsAAUAfCUGUCfCCfUUUUAAsgsC
1159	AS537	AsfGsAfAUfACfUGUCCcfUUfUUAAsGsC
1160	AS538	GsAsGAAUfACUGUfCCfCUUUUAsAsG
1161	AS539	GsfAsGfAAfUAfCUGUCCfCUfUUUAsAsG
1162	AS540	UsGsAGAAfUACUGfUCfCCUUUUUsAsA
1163	AS541	UsfGsAfGAfAUfACUGUCfCCfUUUUUsAsA
1164	AS542	CsfUsGfAGfAAfUACUGUfCCfCUUUUsUsA
1165	AS543	CsfUsGfAGfAAfUACUGUfCCfCUUUUsUsA
1166	AS544	AsCsUGAGfAAUACfUGfUCCCUUsUsA
1167	AS545	AsfCsUfGAfGAfAUACUGfUCfCCUUsUsA
1168	AS546	CsAsCUGAfGAAUAfCUfGUCCCUUsUsA
1169	AS547	CsfAsCfUGfAGfAAUACUfGUfCCCUUsUsA
1170	AS548	UsAsAUAFcUGUCfCCfUUUUAAAGCsAsA
1171	AS549	UsAsfAUfACfUGfUCfCCfUUfUUfAAGCsAsA

where, G=2'-O-methylguanylate, A=2'-O-methyladenylate, U=2'-O-methyluridylate, C=2'-O-methylcytidylate, fG=2'-fluoroguanlylate, fA=2'-fluoroadenylate, fU=2'-fluorouridylate, fC=2'-fluorocytidylate, Gs=2'-O-methyl-3'-thioguanlylate, As=2'-O-methyl-3'-thioadenylate, Us=2'-O-methyl-3'-thiouridylate, Cs=2'-O-methyl-3'-thiocytidylate, fGs=2'-fluoro-3'-thioguanlylate, fAs=2'-fluoro-3'-thioadenylate, fUs=2'-fluoro-3'-thiouridylate, fCs=2'-fluoro-3'-thiocytidylate, T=thymidylate.

In some embodiments, the antisense strand of the RNA inhibitor of the present invention is selected from a) sequences in Tables 7-1 and 7-2, b) sequences having at least 15 consecutive nucleotides

identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b).

In some embodiments, the sense strand and antisense strand of the RNA inhibitor is selected from the following Table 8.

Table 8 RNA inhibitors with modified sequences

RNA inhibitor	sense strand SEQ ID NO.	sense strand code	antisense strand SEQ ID NO.	antisense strand code
DS103	407	S163	377	AS163
DS104	408	S164	378	AS164
DS105	409	S165	379	AS165
DS106	410	S166	380	AS166
DS107	411	S167	381	AS167
DS108	412	S168	382	AS168
DS109	413	S169	383	AS169
DS110	414	S170	384	AS170
DS111	415	S171	385	AS171
DS112	416	S172	386	AS172
DS113	417	S173	387	AS173
DS114	418	S174	388	AS174
DS115	419	S175	389	AS175
DS116	420	S176	390	AS176
DS117	421	S177	391	AS177
DS118	422	S178	392	AS178
DS119	423	S179	393	AS179
DS120	424	S180	394	AS180
DS121	425	S181	395	AS181
DS122	426	S182	396	AS182

RNA inhibitor	sense strand SEQ ID NO.	sense strand code	antisense strand SEQ ID NO.	antisense strand code
DS123	427	S183	397	AS183
DS124	428	S184	398	AS184
DS125	429	S185	399	AS185
DS126	430	S186	400	AS186
DS127	431	S187	401	AS187
DS128	432	S188	402	AS188
DS129	433	S189	403	AS189
DS130	434	S190	404	AS190
DS131	435	S191	405	AS191
DS132	436	S192	406	AS192

In some embodiments, the distribution, targeting or stability of the RNA inhibitor can be altered by introducing ligands of target tissue receptors into the vector. For example, a specific ligand can provide an enhanced affinity for a selected target (e.g., molecule, cell, or cell type, compartment (e.g., cell or organ compartment, body tissue, organ, or region) compared to species where no ligand is present.

Ligands can include naturally occurring substances, such as proteins (such as human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrates (such as glucan, pullulan, chitin, chitosan, inulin, cyclodextrin, N-acetylglucosamine, N-acetylgalactosamine, or hyaluronic acid); or lipids. Ligands can also be recombinant or synthetic molecules, such as synthetic polymers, such as synthetic polyamino acids.

Ligands may also include targeting groups, such as cell- or tissue-targeting agents that bind to a specific cell type such as kidney cells, for example, lectins, glycoproteins, lipids or proteins, such as antibodies. The targeting groups can be thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyamino acids, multivalent galactose, transferrin, bisphosphonate, polyglutamic acid, polyaspartic acid, lipid, cholesterol, steroid,

cholic acid, folic acid, vitamin B12, vitamin A, biotin, or RGD peptide or RGD peptide mimetics. In some embodiments, the ligand is a multivalent galactose, for example, N-acetyl-galactosamine.

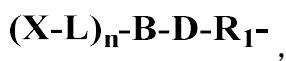
The sense strand and antisense strand contained in the RNA inhibitors of the present invention can be conveniently and routinely prepared by the well-known technique of solid-phase synthesis. Additionally or alternatively, any other method known in the art for such synthesis, such as liquid-phase synthesis or fermentation, may be used. It is also known to use similar techniques to prepare other oligonucleotides, such as phosphorothioates and alkylated derivatives.

In some embodiments, in addition to standard nucleoside phosphoramidite monomers and non-standard nucleoside phosphoramidite monomers that are commercially available and routinely used in oligonucleotide synthesis, the oligonucleotides or linked nucleotides of the present invention can be synthesized by an automated synthesizer using phosphoramidite method derived from the carrier-nucleoside phosphoramidite monomer.

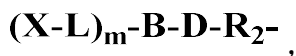
In some embodiments, the ligand of the present invention is conjugated by conjugating to the 5' end and/or 3' end of the antisense strand, and/or the 5' end and/or 3' end of the sense strand through a carrier structure.

For example, the carrier structure can be conjugated to the 5' end and/or 3' end of the sense strand; or the carrier structure can be conjugated to the 5' end of the antisense strand, and the carrier structure is conjugated to the 3' end of the sense strand; or the carrier structure can be conjugated to the 3' end of the antisense strand, and the carrier structure is conjugated to the 5' end of the sense strand.

In some embodiments, the carrier structure includes 5'MVIP and 3'MVIP, wherein the 5'MVIP is conjugated at the 5' end of the sense strand and/or antisense strand, the 3'MVIP is conjugated at the 3' end of the antisense strand and/or sense strand, the structure of the 5'MVIP is shown in formula I, the structure of the 3'MVIP is shown in formula II,



I



II

wherein,

X is a liver targeting specific ligand;

L is a branched chain;

B is a linker;

D is a linking chain;

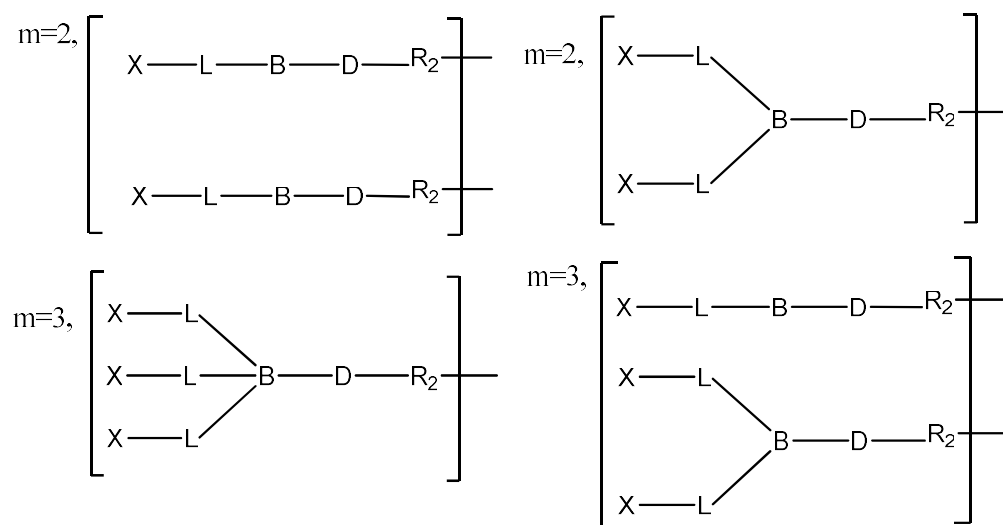
R₁ and R₂ are transition points;

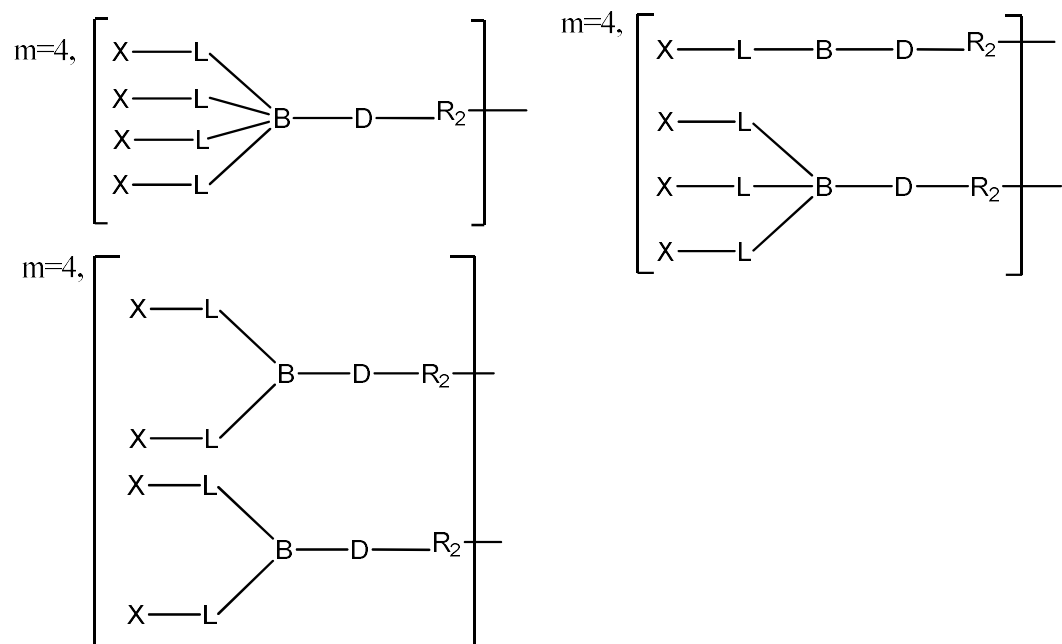
The 5'MVIP is connected with the 5' end of the sense strand or the 5' end of the antisense strand through the transition point R₁, and the 3'MVIP is connected with the 3' end of the sense strand or the 3' end of the antisense strand through the transition point R₂. n and m are each independently any integer of 0-4, and n+m=an integer of 2-6, preferably n+m=2, 3 or 4, more preferably 4.

In some embodiments, the R₁ or R₂ is connected to the sense or antisense strand through a phosphate or modified phosphate, preferably through a phosphate or phosphorothioate.

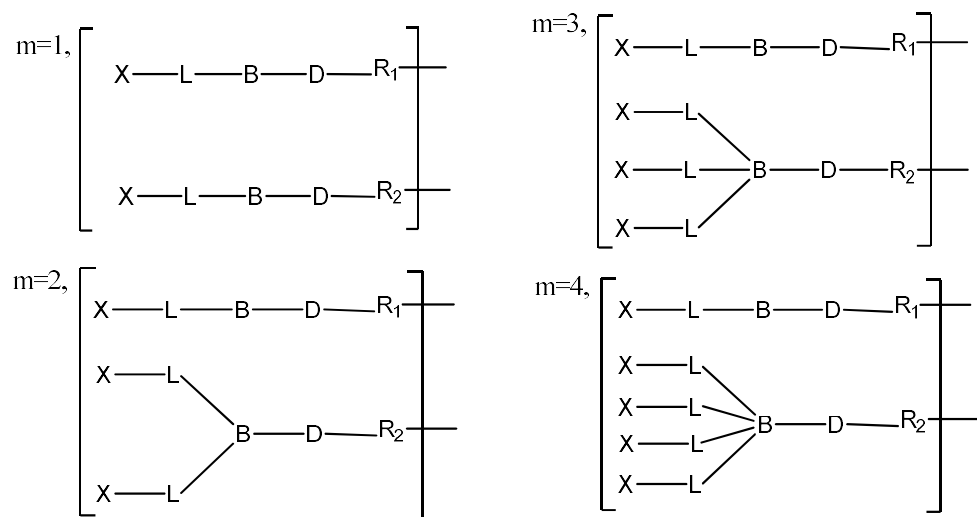
In some embodiments, m or n can be 0, that is, there is no 3'MVIP or 5'MVIP.

In some embodiments, when n=0 (that is, there is no 5'MVIP), the structure of the 3'MVIP can be

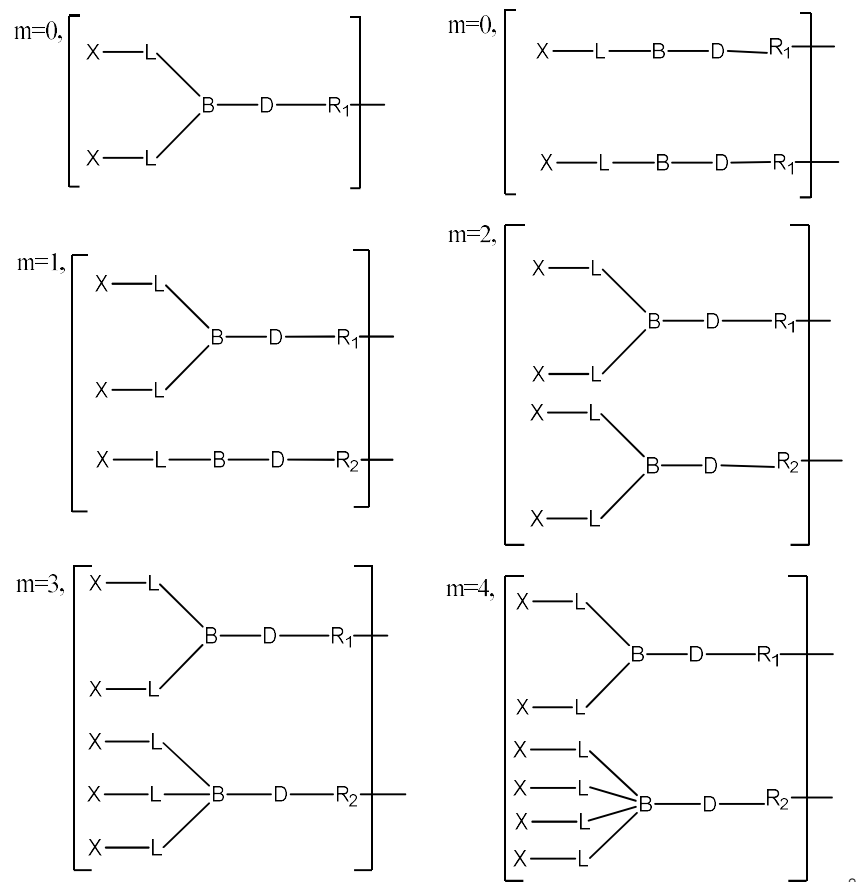




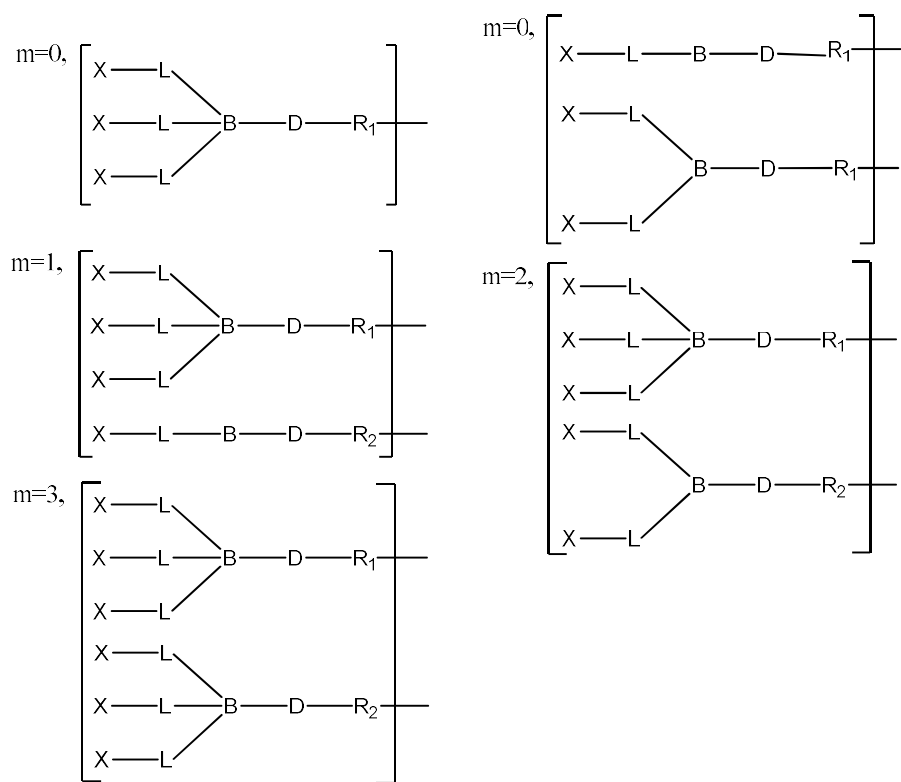
In some embodiments, when $n=1$, the structure of the 3'MVIP can be



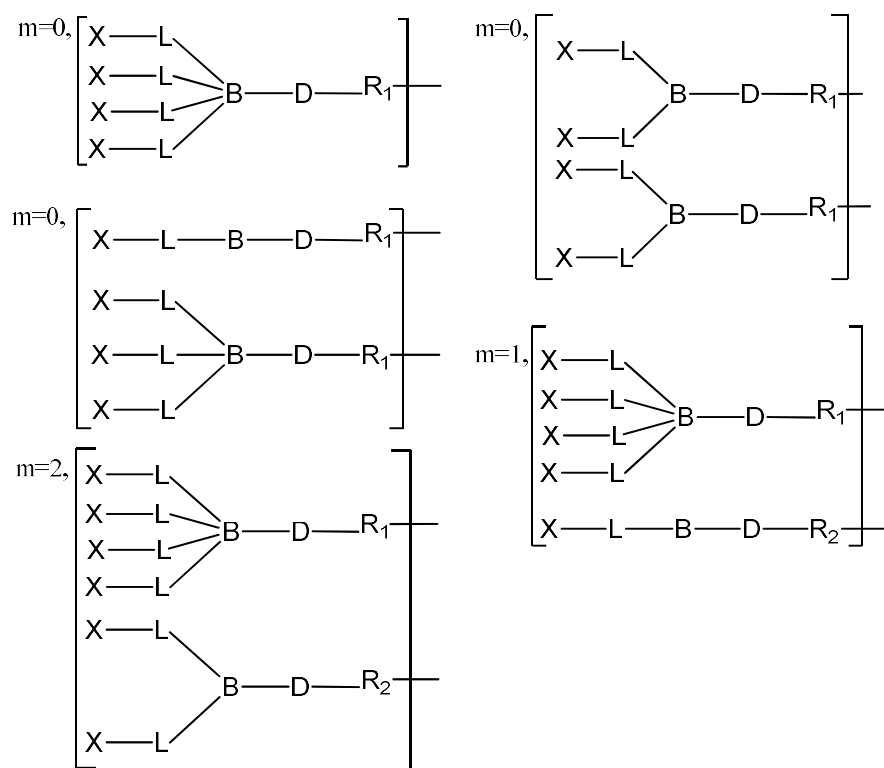
In some embodiments, when $n=2$, the structure of the 3'MVIP can be



In some embodiments, when $n=3$, the structure of the 3'MVIP can be:



In some embodiments, when $n=4$, the structure of the 3'MVIP can be:



In some embodiments, the n refers to the sum of n in the 5'MVIP at 5' ends of the sense strand and antisense strand of the RNA inhibitor respectively, and the m refers to the sum of m in the 3'MVIP at 3' ends of the sense strand and antisense strand of the RNA inhibitor respectively.

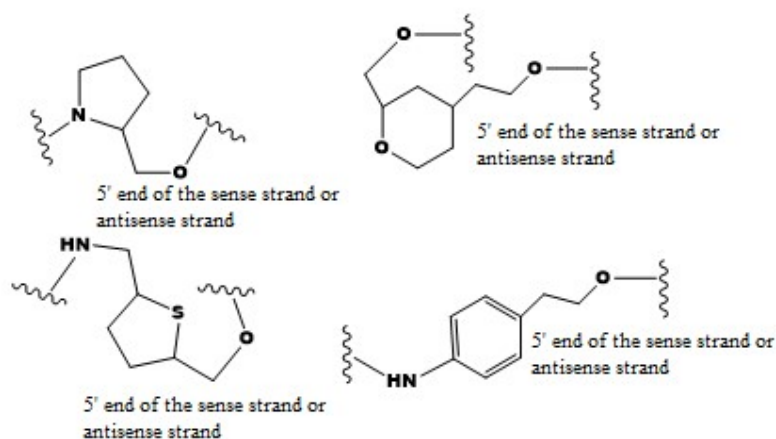
In some embodiments, the transition points R₁ and R₂ contain -NH-, -S-, and/or -O- in their structures, R₁ and R₂ are respectively connected with the linking chain D and the 5' and 3' ends of the sense strand and/or antisense strand through -NH-, -S-, or -O- in the structure., and R₁ and R₂ are the same or different.

In some embodiments, the R₁ and R₂ are optionally straight chain, or straight chain or cyclic structure with amido, carboxyl, or alkyl branched chain, and the cyclic structure includes saturated or unsaturated aliphatic carbocyclyl, or five or six membered heterocyclyl or aromatic hydrocarbyl containing sulfur, oxygen, or nitrogen atom.

In some embodiments, the R₁ and/or R₂ are -E₁(CH₂)_xCH₂E₂-, wherein x is any integer of 3-12, and the groups E₁ and E₂ can be -NH-, -S-, or -O-, respectively.

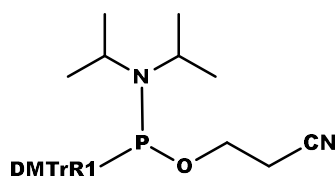
In some embodiments, the R₁ and/or R₂ are -E₁(CH₂)_{x1}CH(OH)(CH₂)_{x2}E₂-, wherein x1 or x2 are each independently any integer of 3-10, and E₁ and E₂ can be -NH-, -S-, or -O-, respectively.

In some embodiments, the R₁ is a heterocyclic or carbocyclic structure containing N, S or O as shown below.

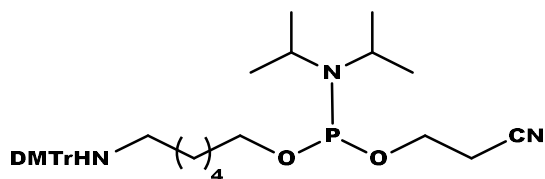


In some embodiments, the transition point R_1 is $-\text{NH}(\text{CH}_2)_x\text{CH}_2\text{O}-$, wherein x is any integer of 3-12, preferably any integer of 4-6, which can be introduced by the following two phosphoramidite monomers:

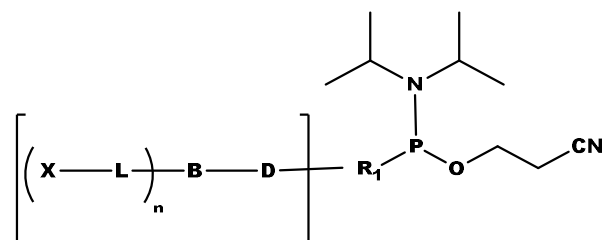
i. One of -O- or -S- in structure of R_1 is used for the synthesis of R_1 phosphoramidite monomer, and is connected to the 5' end of the sense strand or antisense strand of RNA inhibitor by solid-phase synthesis. In the structure, -NH-, -S-, or -O- is used to connect with the linking chain D in the 5'MVIP, thereby introducing the liver targeting specific ligand X at the 5' end of the sense strand or antisense strand of the RNA inhibitor. An exemplary structure of a monomer introduced to the 5' end of the sense or antisense strand of the RNA inhibitor is as follows.



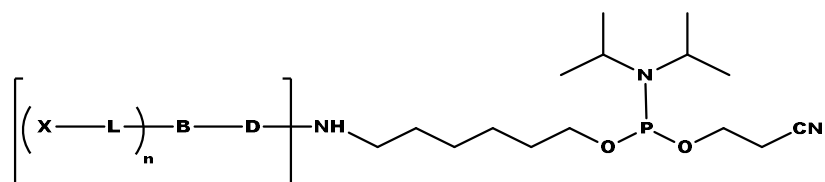
In some embodiments, the following structure is preferred:



ii. One of -NH-, -S-, or -O- in structure of R_1 is first connected with the linking chain D, and another -NH-, -S-, or -O- is used to form ester with phosphoramidite in the synthesis of 5'MVIP phosphoramidite monomer. The exemplary structure of 5'MVIP phosphoramidite monomer of sense strand or antisense strand is as follows:



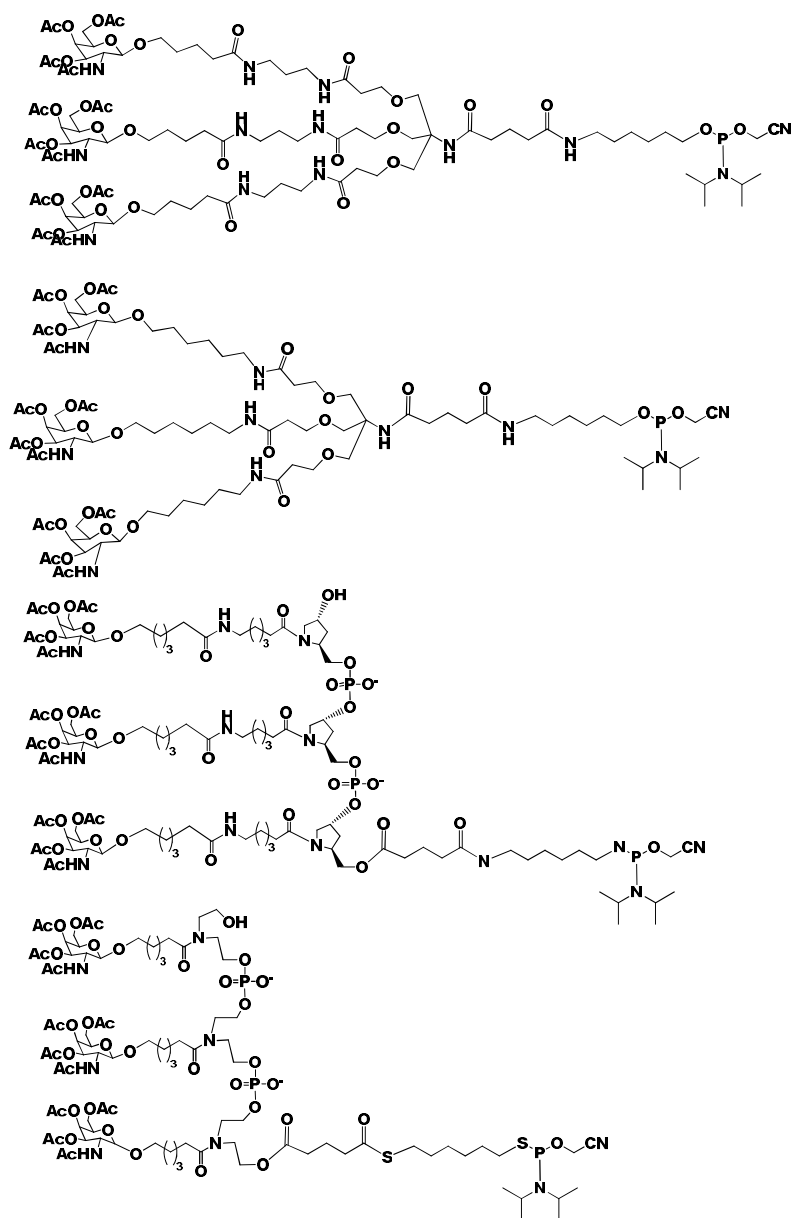
In some embodiments, the 5'MVIP phosphoramidite monomer of the sense strand or antisense strand preferably has the following structure:

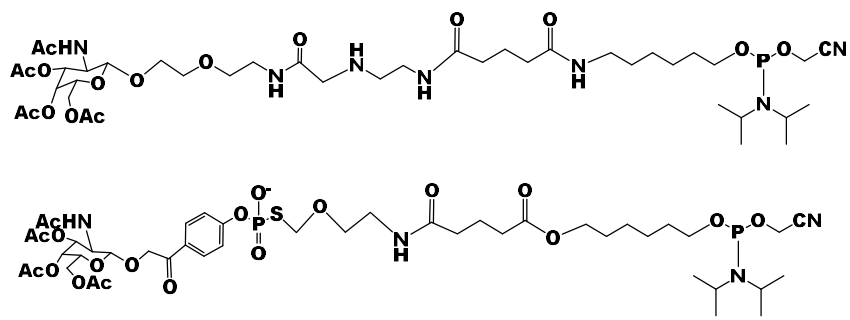


When n in the general formula is 1-4, the linker B part of the above monomer is branched for 1 to 4 times respectively to obtain the corresponding monomer compounds. With the help of the above monomer compounds, the liver targeting specific ligand X is introduced to the 5' end of the sense or antisense strand through solid-phase synthesis.

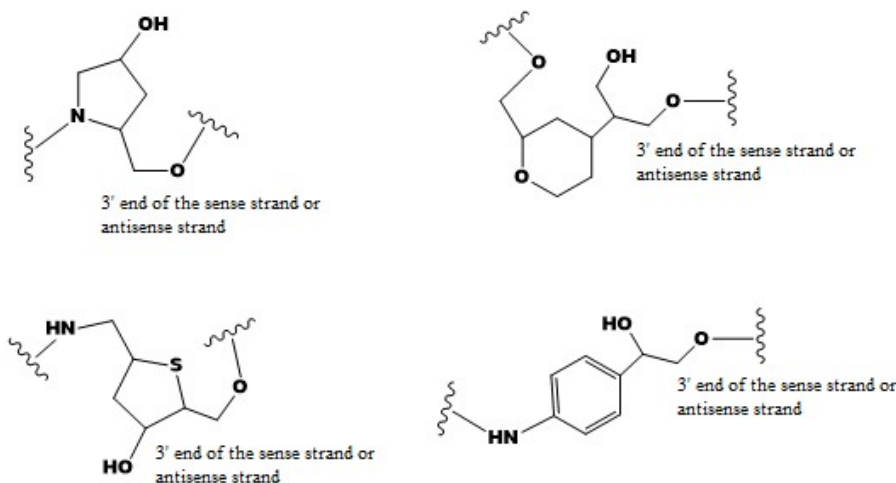
In some embodiments, the transition point R₁ is -NH(CH₂)_xCH₂O-, wherein x can be an integer of 3-12, preferably an integer of 4-6.

In some embodiments, the 5'MVIP phosphoramidite monomer has the structure selected from the following structures:





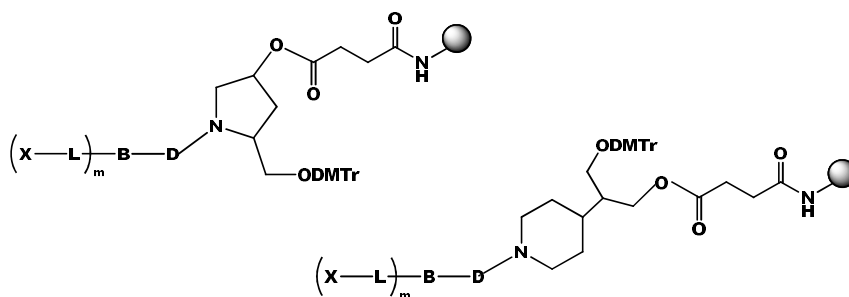
In some embodiments, the transition point R_2 is a heterocyclic or carbocyclic structure containing N, S or O as shown below:



In some embodiments, the transition point R_2 is $-\text{NH}(\text{CH}_2)_{x1}\text{CH}(\text{OH})(\text{CH}_2)_{x2}\text{CH}_2\text{O}-$, wherein x_1 is any integer of 1-4, x_2 is any integer of 0-4.

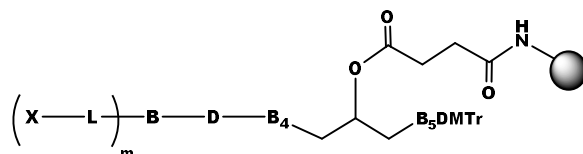
The transition point R_2 described in the present invention forms ester or amide with $-\text{NH}-$, $-\text{S}-$, or $-\text{O}-$ in the structure of R_2 through succinic anhydride, and at the same time conjugates with $-\text{NH}-$ in blank solid support to form 3'MVIP solid support, and then 3'MVIP is introduced to the 3' end of the sense strand or antisense strand by phosphoramidite solid-phase synthesis.

In some embodiments, the heterocycle in the structure of transition point R_2 is a pyrrole ring or a piperidine ring, which is connected with the linking chain D of 3'MVIP through the nitrogen heteroatom in the ring. The exemplary structures of the introduced 3'MVIP solid support are as follows:



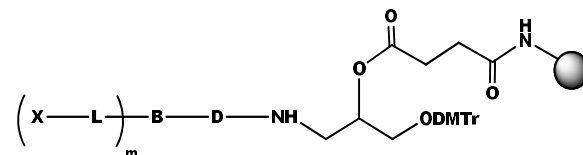
When m in the general formula is 1-4, the linker B part in the monomer above is branched for 1 to 4 times respectively to obtain the corresponding Solid Supports.

In some embodiments, the transition point R₂ is -B₄(CH₂)_{x1}CH(OH)(CH₂)_{x2}CH₂B₅-, wherein x₁ is any integer of 1-4, x₂ is any integer of 0-4, and B₄ and B₅ are -NH-, -S-, or -O- respectively, the exemplary formula of the introduced 3' MVIP solid support is as follows:



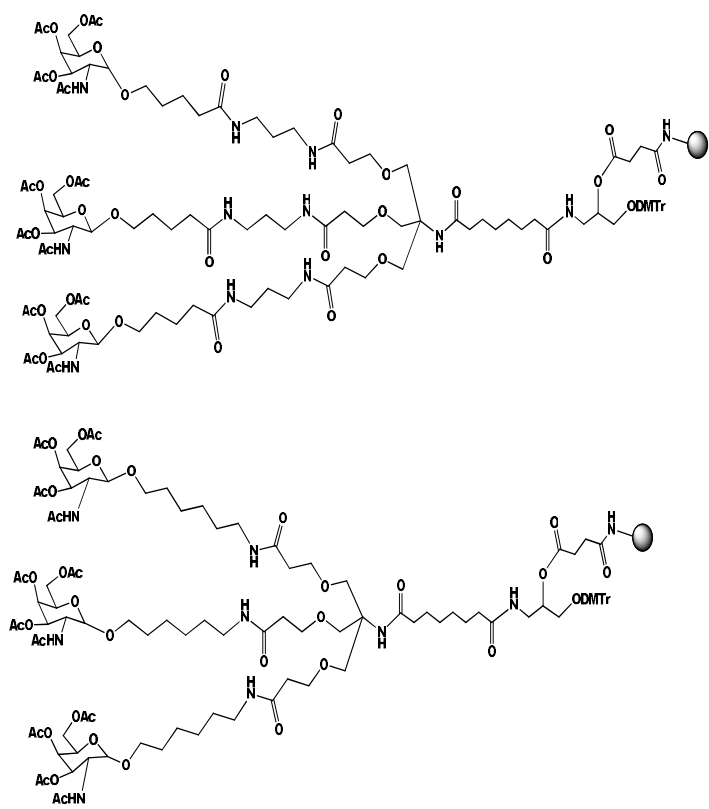
When m in the general formula is 1-4, the linker B part in the monomer above is branched for 1 to 4 times respectively to obtain the corresponding Solid Supports.

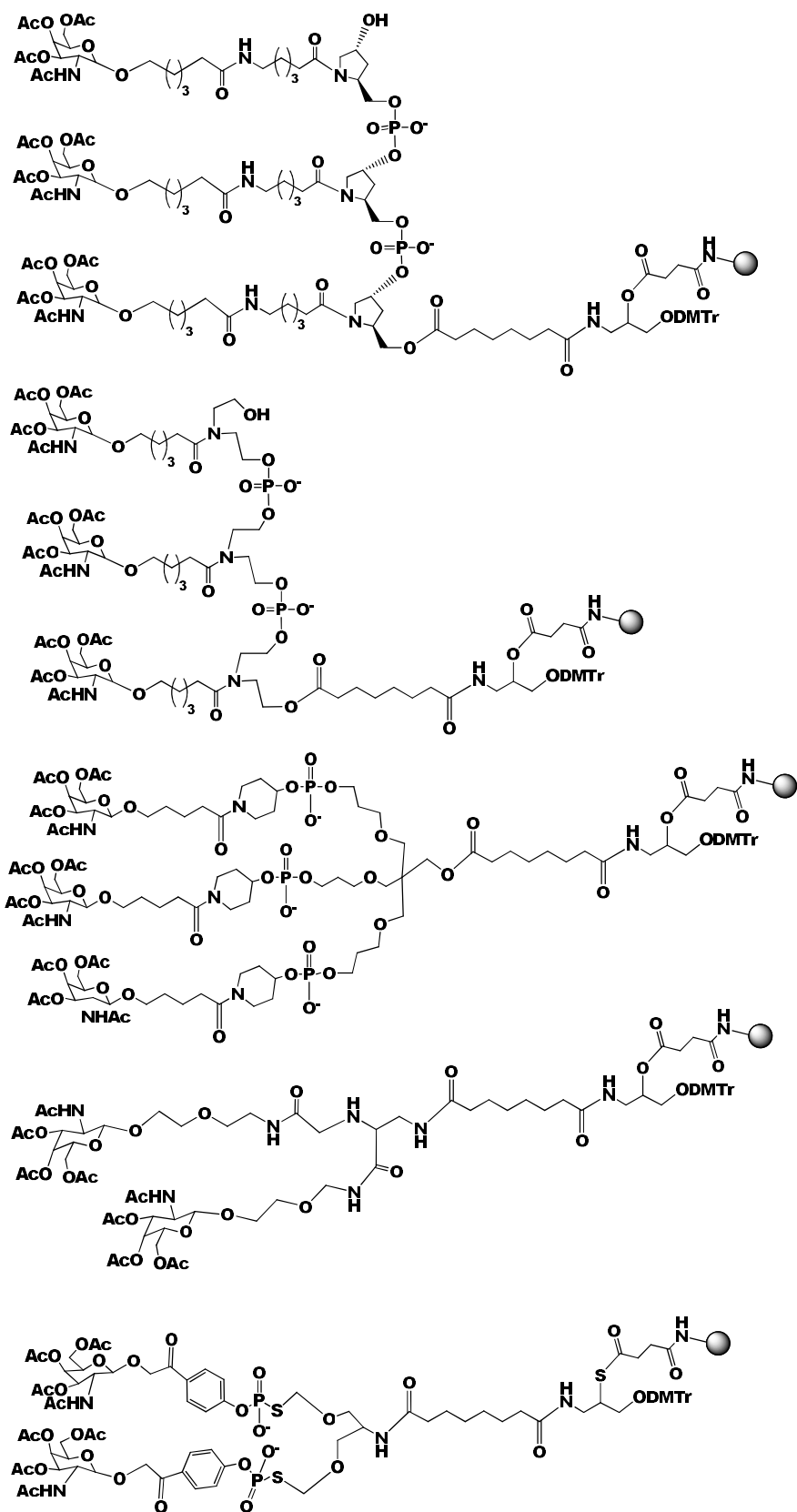
In some embodiments, R₂ is -NHCH₂CH(OH)CH₂O-, the exemplary formula of the introduced 3' MVIP solid support is as follows:

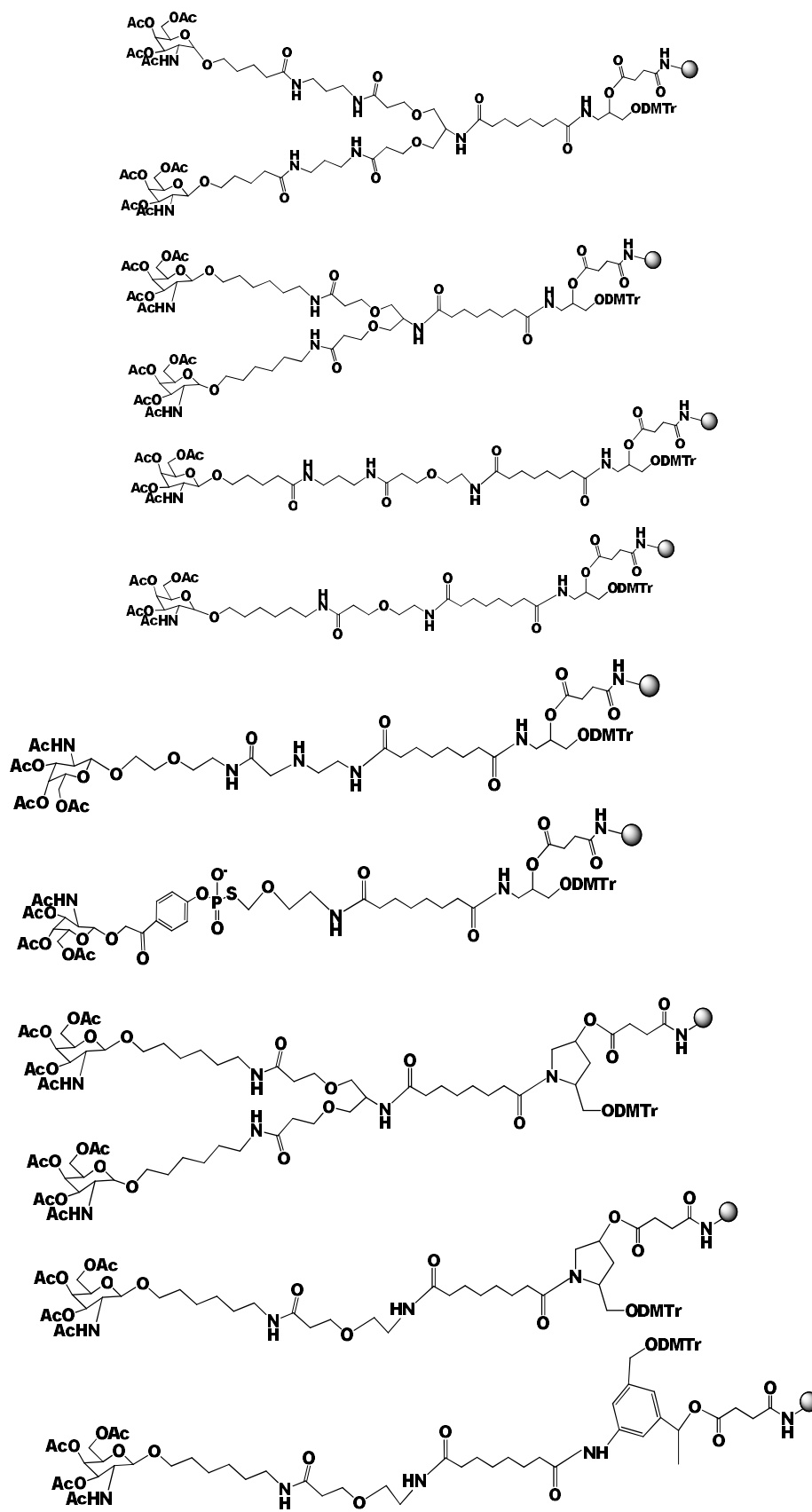


When m in the general formula is 1-4, the linker B part in the monomer above is branched for 1 to 4 times respectively to obtain the corresponding Solid Supports.

In some embodiments, the structure of 3' MVIP solid support is as follows:





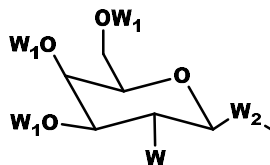


In some embodiments, the liver targeting specific ligand X is selected from structures used to enhance the uptake of RNA inhibitor by hepatocytes, which can be lipids, steroids, vitamins, sugars,

proteins, peptides, polyamines and peptide mimetic structures. In the RNA inhibitor provided by the present invention, the liver targeting specific ligand X introduced to the end of the sense strand or antisense strand of the RNA inhibitor can be the same or different. For example, in terms of characteristics, some can enhance liver targeting, some can be the structure that regulates the pharmacokinetics of the RNA inhibitor in vivo, and some can be the structure with dissolution activity in vivo. In some embodiments, the liver targeting specific ligand X is selected from one or more monosaccharides and derivatives thereof in the following structures.

In some embodiments, the monosaccharide is selected from one or more of the following structures: mannose, galactose, D-arabinose, glucose, fructose, xylose, glucosamine, ribose. The monosaccharide derivatives is selected from mannose derivatives, galactose derivatives, glucose derivatives, ribose derivatives, and other derivatives.

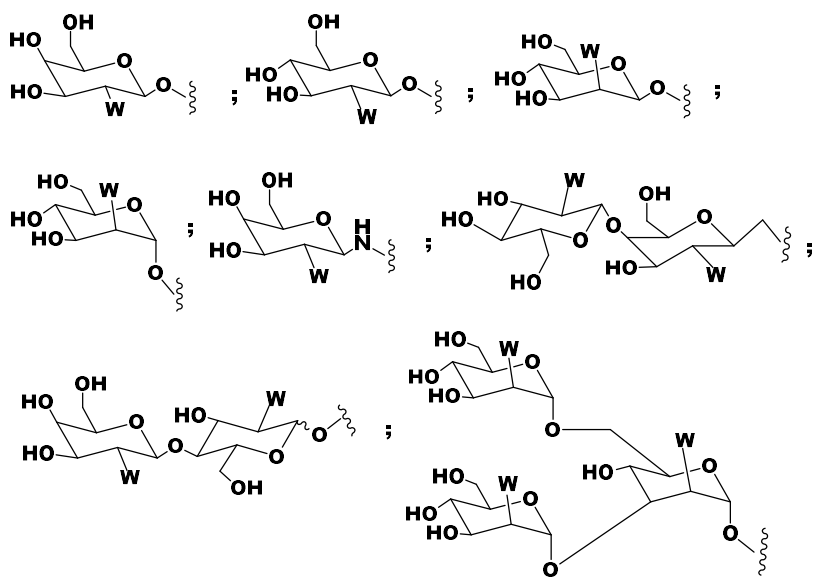
In some embodiments, the liver targeting specific ligand X is selected from galactose, galactosamine, N-acetylgalactosamine and their derivatives, and its general structural formula is as follows:



wherein, W_1 is a hydrogen or hydroxyl protecting group, which can be the same or different; W is $-OH$, $-NHCOOH$ or $-NHCO(CH_2)_qCH_3$, wherein q is an integer of 0-4; W_2 is $-NH-$, O , S or C .

In some embodiments, the liver targeting specific ligand X is N-acetylgalactosamine and its derivatives.

In some embodiments, the liver targeting specific ligand X is selected from the following structures:



wherein W is selected from one or two of -OH, -NHCOOH or -NHCO(CH₂)_qCH₃, wherein q is an integer of 0-4.

In some embodiments, the liver targeting specific ligand X may be the same or different in the same 5'MVIP or 3'MVIP structure.

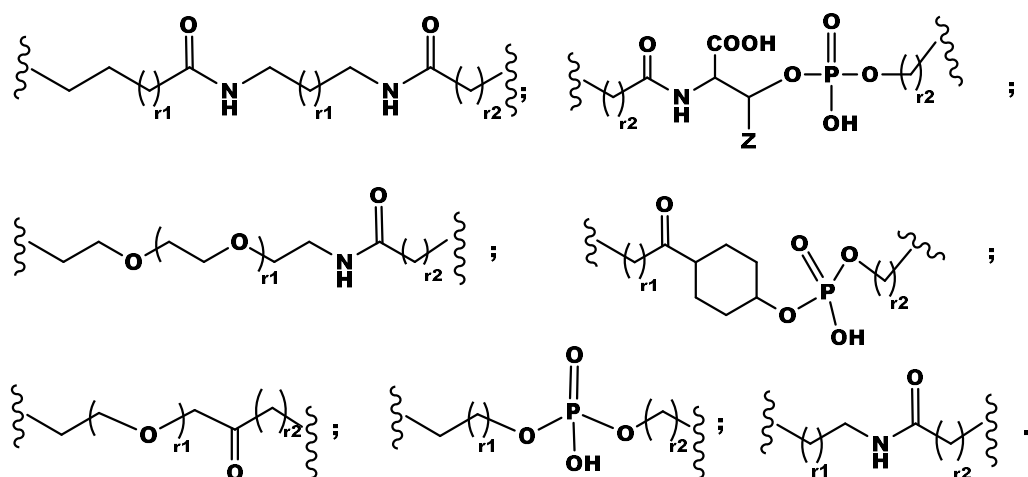
In some embodiments, the X between 5'MVIP and 3'MVIP can be the same or different.

In some embodiments, the branched chain L is a C₄-C₁₈ carbon chain containing -NH-, -C(=O)-, -O-, -S-, amido, phosphoryl, thiophosphoryl, C₄-C₁₀ aliphatic carbocyclyl, phenyl, or a combination of these groups.

In some embodiments, the branched chain L also has a side chain of hydroxyethyl or carboxylic acids group.

In some embodiments, the branched chain L is a C₇-C₁₈ carbon chain containing amido group or six-membered aliphatic carbocyclyl group.

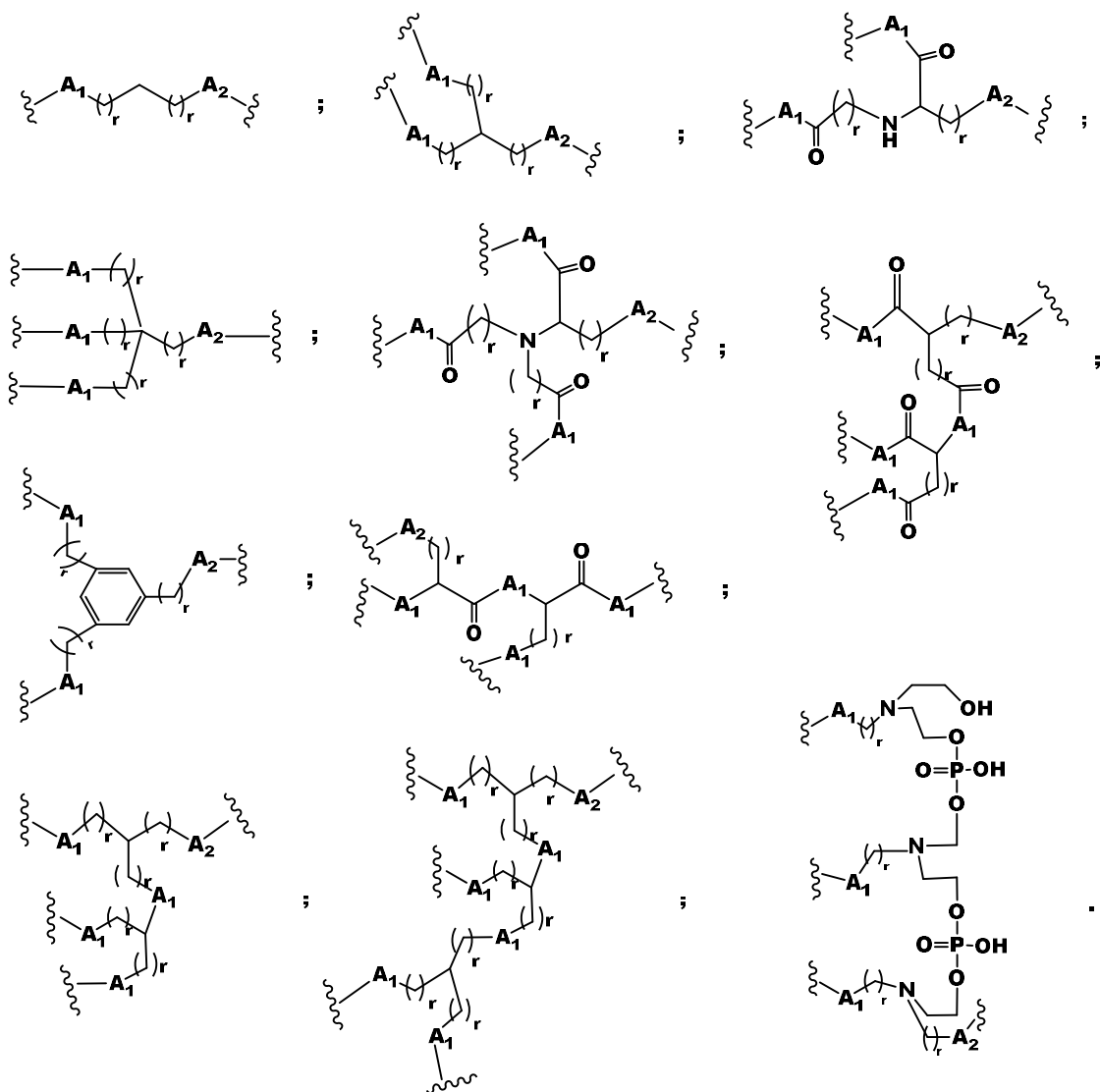
In some embodiments, the branched chain L is selected from one or more of the following structures:



wherein, r_1 is any integer of 1-12, r_2 is any integer of 0-20, and Z is H, alkyl or amido group, the alkyl is such as C_1 - C_5 alkyl.

In some embodiments, the structure of the linker B is related to the number of X that can be introduced. The linker B contains -NH-, C, O, S, amido, phosphoryl, thiophosphoryl. When n or m is 1, it is a straight chain, and when n or m is 2, 3, or 4, the number of branches is 2, 3, or 4 respectively.

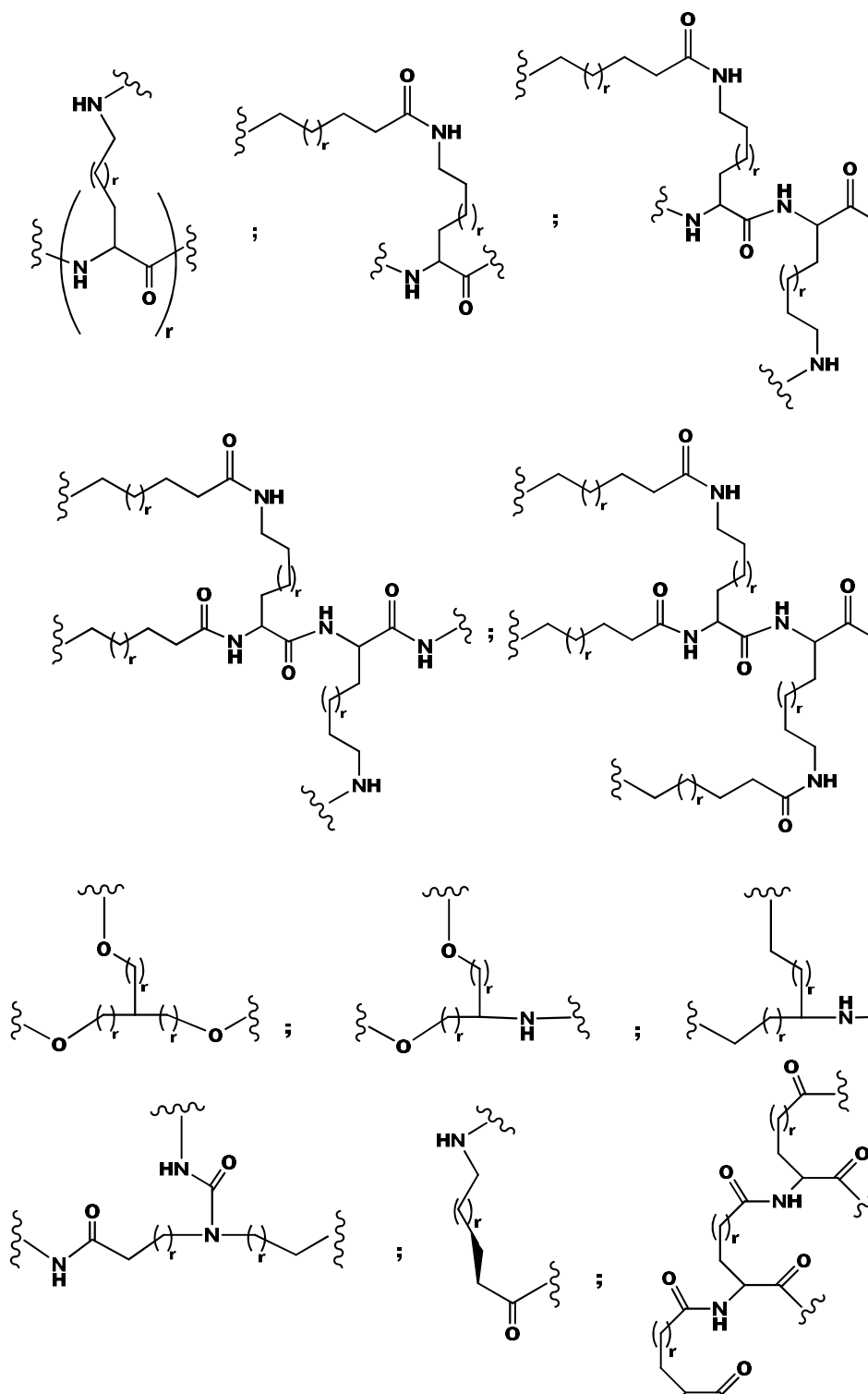
In some embodiments, the linker B is selected from the following structures:



wherein, A₁ and A₂ are each independently C, O, S, -NH-, carbonyl, amido, phosphoryl or thiophosphoryl, and r is an integer of 0-4.

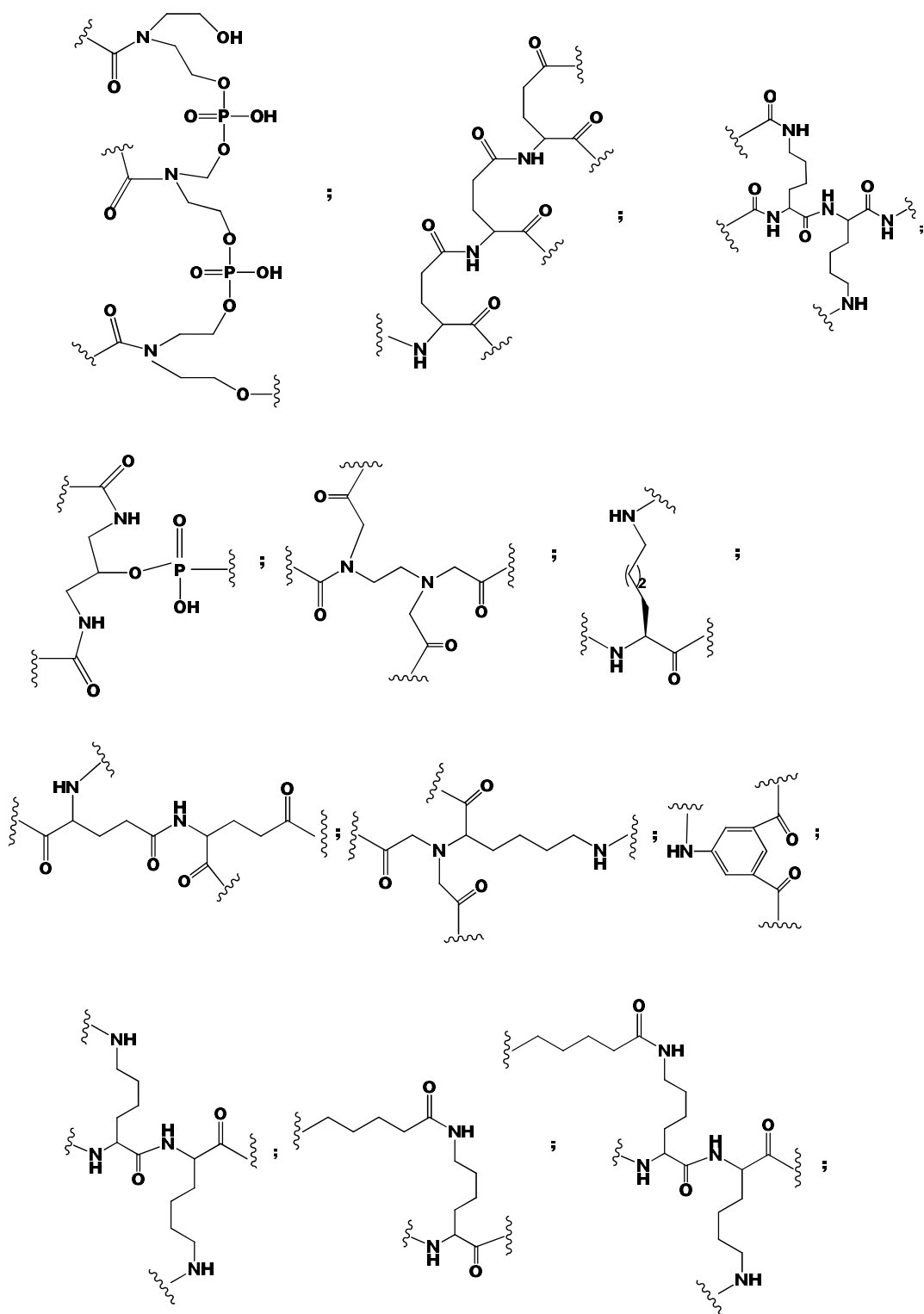
In some embodiments, the linker B is selected from the following structures:

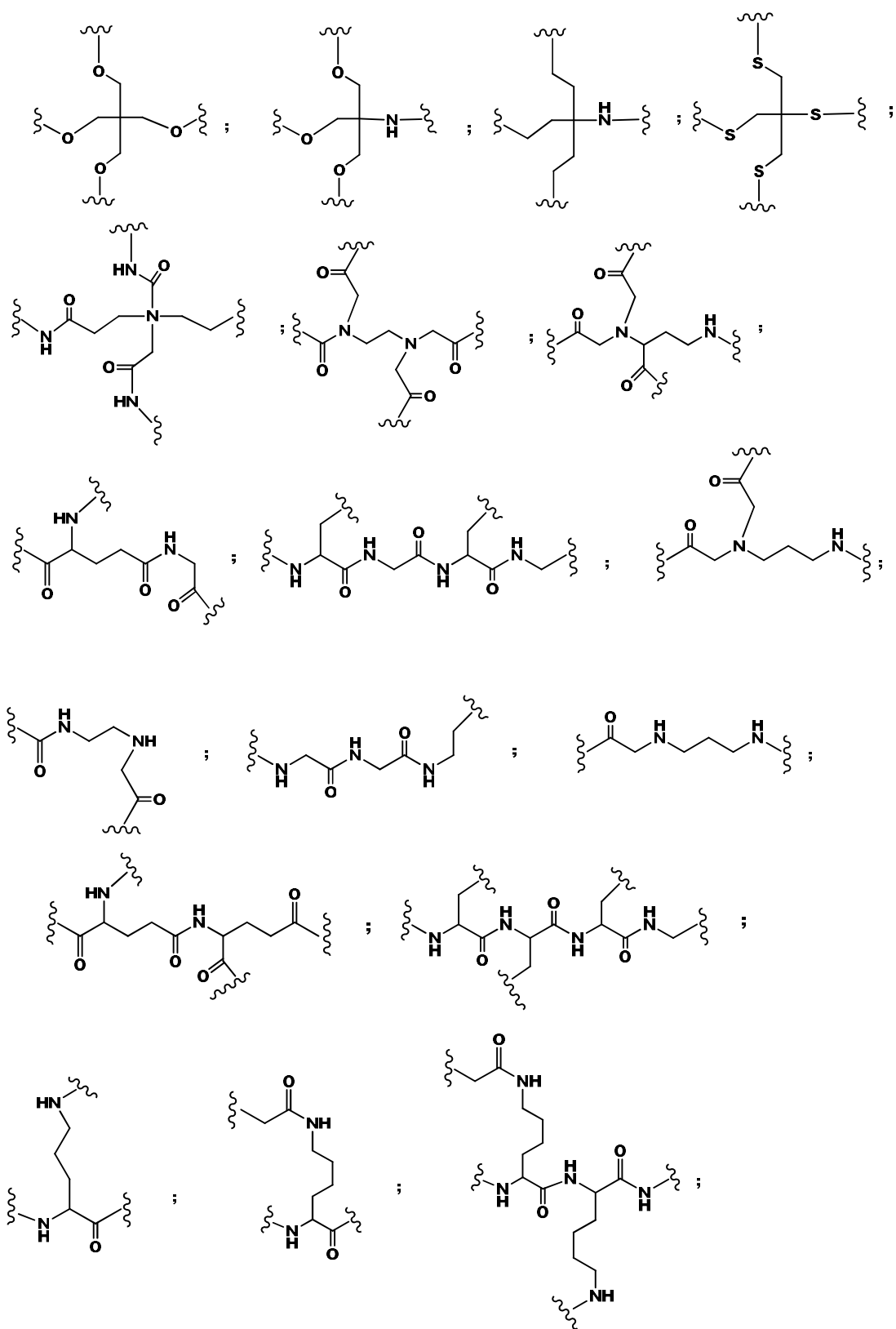


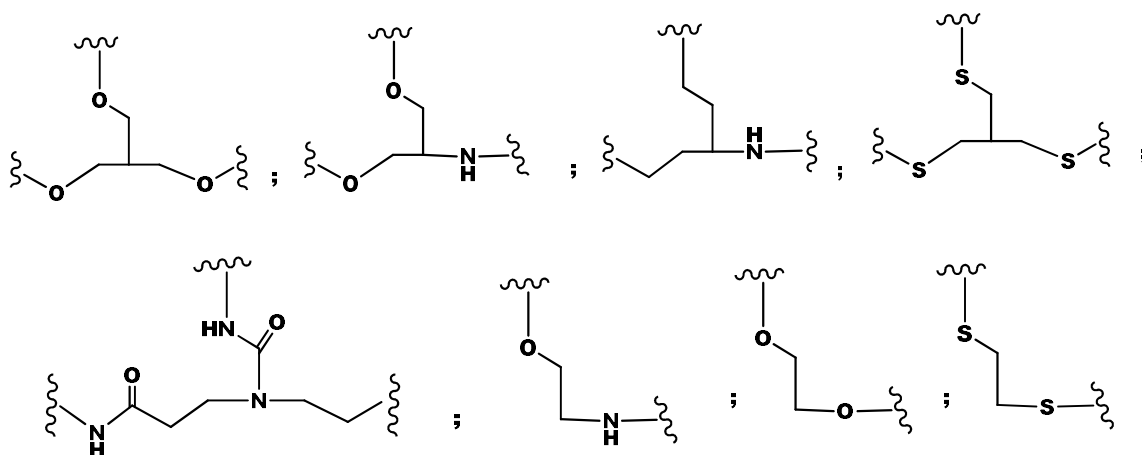


wherein, r is any integer of 0-4.

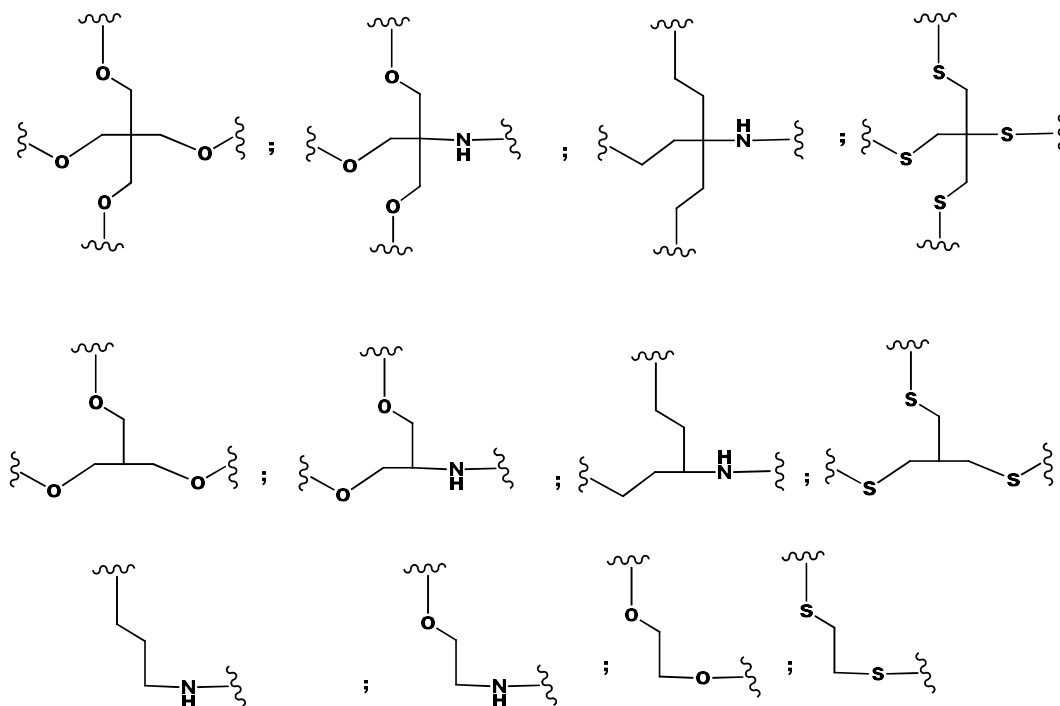
In some embodiments, the linker B is selected from the following structures:







In some embodiments, the linker B is selected from the following structures:



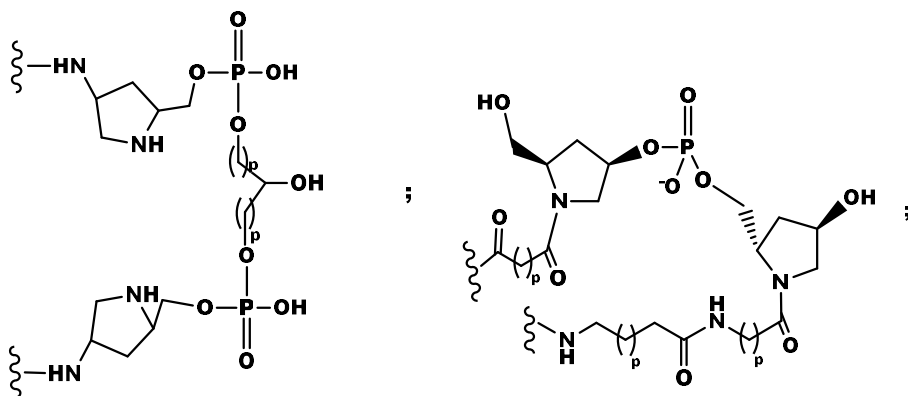
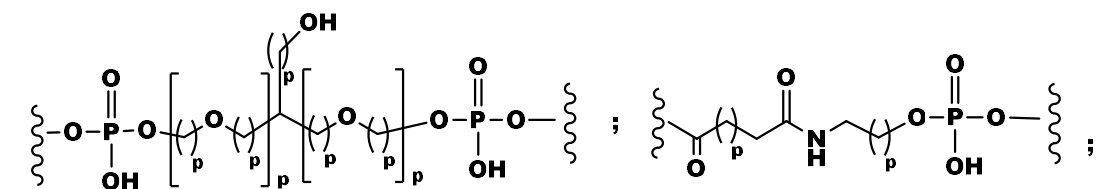
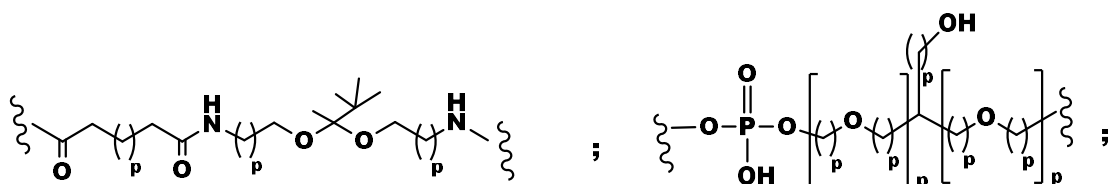
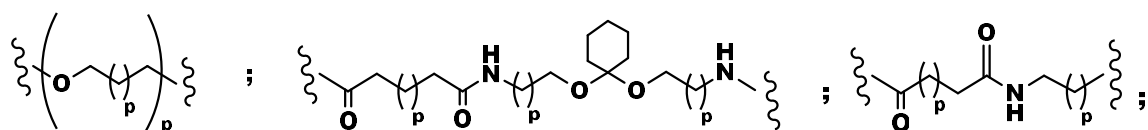
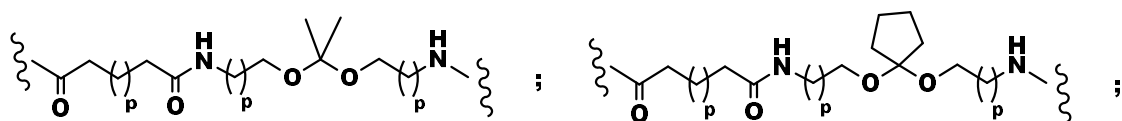
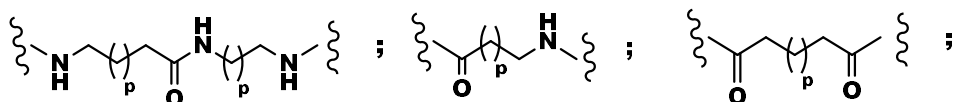
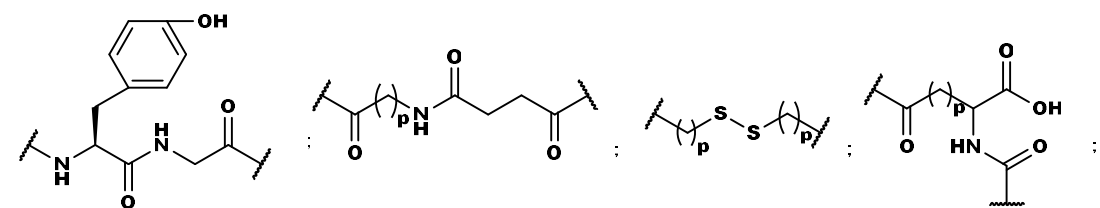
In some embodiments, the linking chain D is a C₃-C₁₈ carbon chain containing -NH-, C=O, O, S, amido, phosphoryl, thiophosphoryl, aromatic hydrocarbonyl, C₄-C₁₀ aliphatic carbocyclyl, five- or six-membered heterocyclyl containing 1-3 nitrogen, or a combination of these groups.

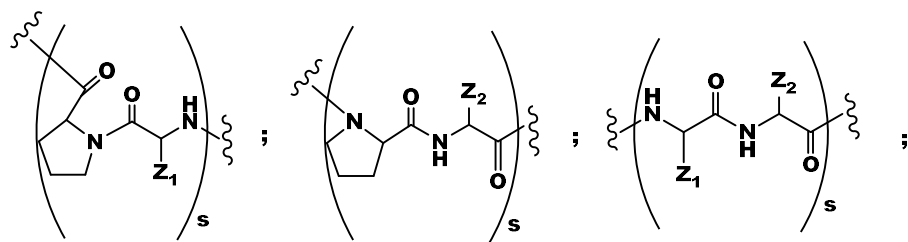
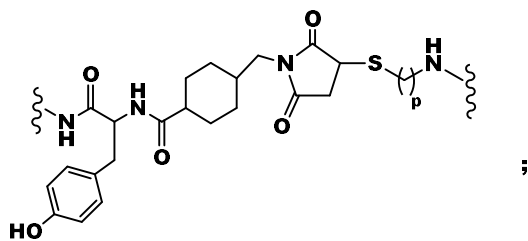
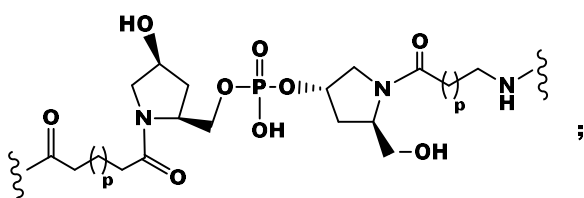
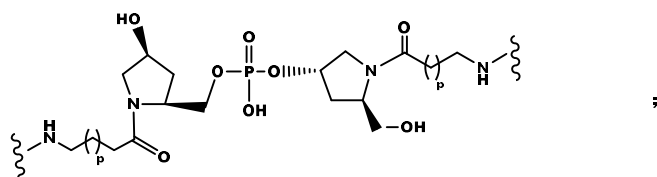
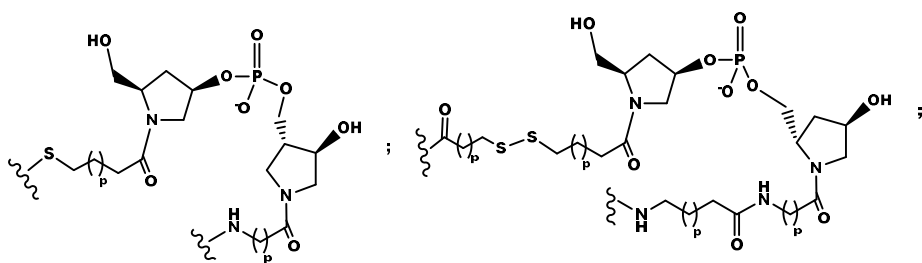
In some embodiments, the linking chain D also has side chains of hydroxymethyl, methyl tert-butyl, methylphenyl, and C₅-C₆ aliphatic cyclic groups.

In some embodiments, the linking chain D is a C₃-C₁₀ carbon chain containing two C=O, six-membered aliphatic carbocyclyl or phenyl groups.

In some embodiments, the linking chain D is a C₃-C₁₀ carbon chain containing two C=O.

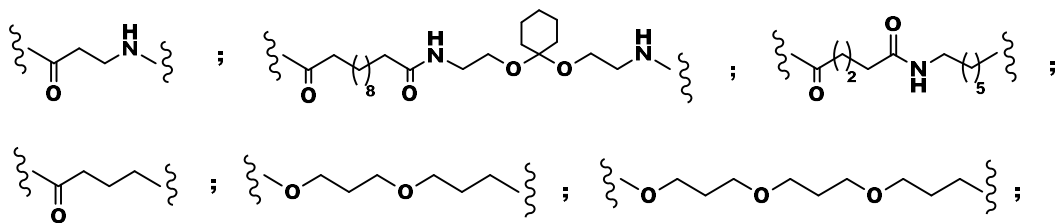
In some embodiments, the linking chain D is selected from the following structures:



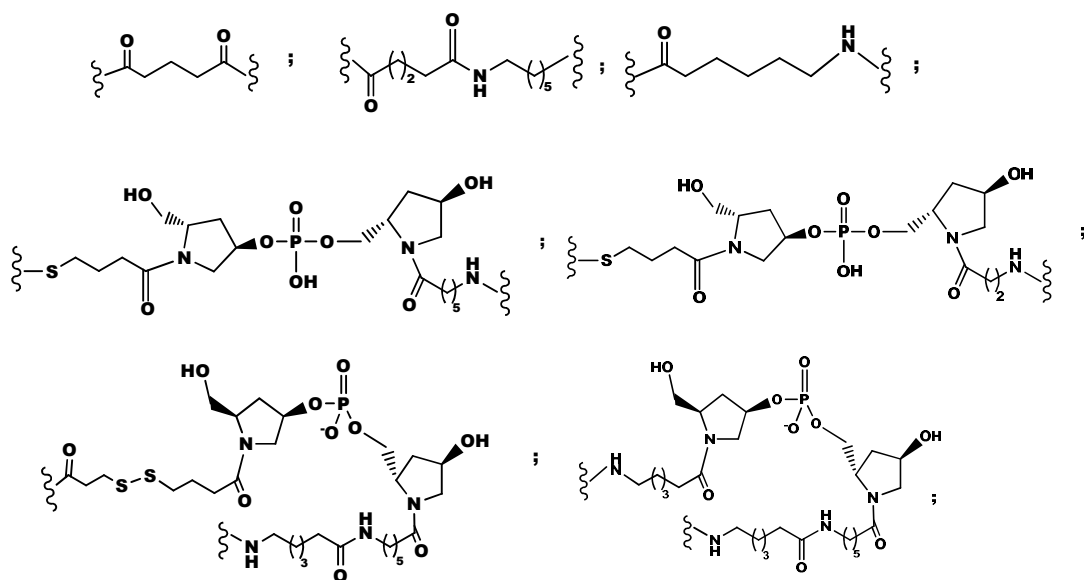


wherein, each p is independently any integer of 1-20; s is an integer of 2-13; Z_1 and Z_2 are the same or different substituents, such as C_3 - C_{10} alkyl.

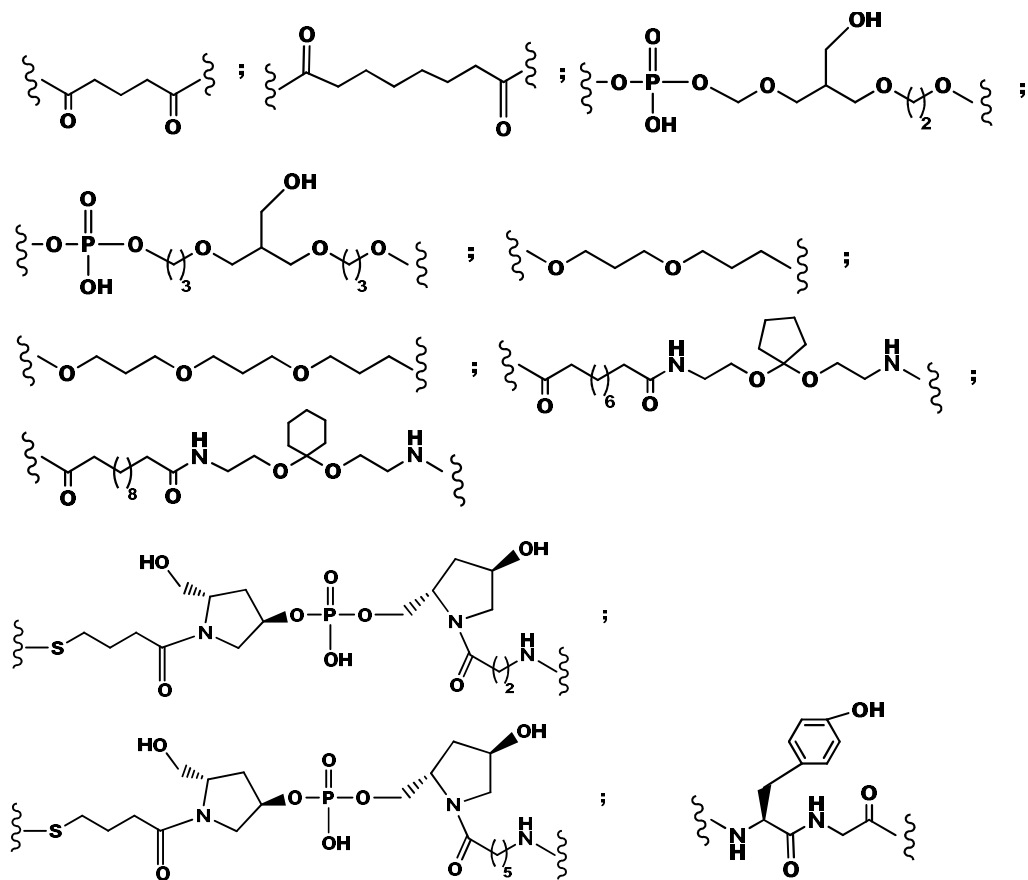
In some embodiments, the linking chain D is selected from the following structures:



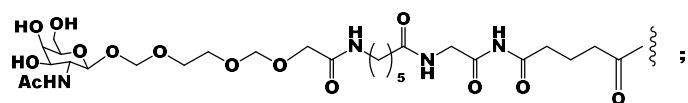
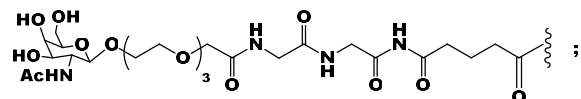
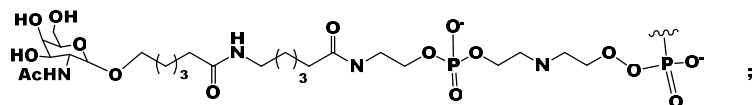
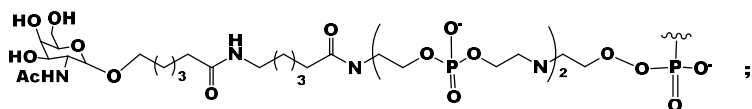
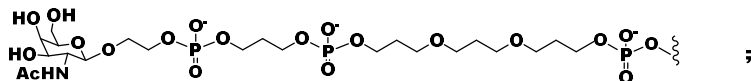
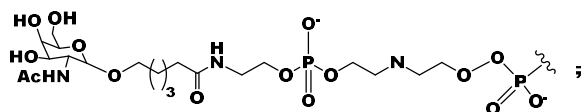
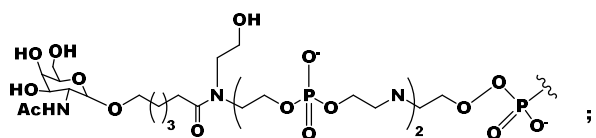
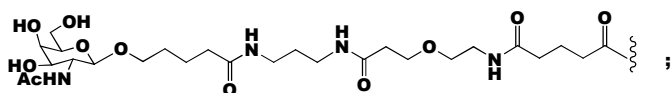
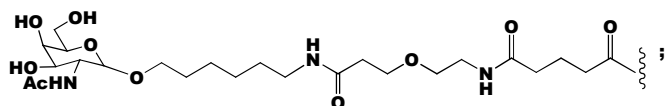
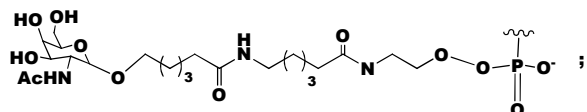
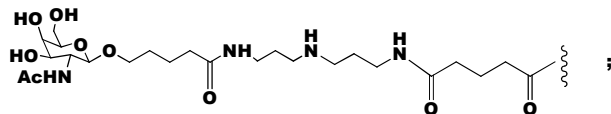
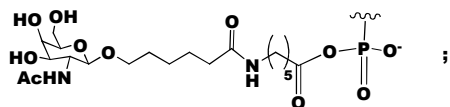
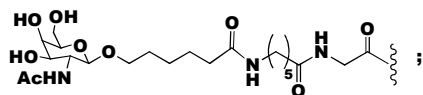
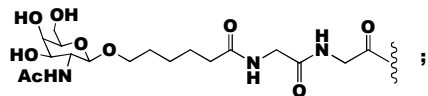
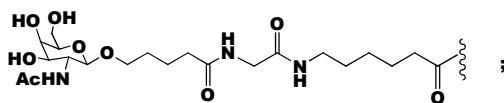


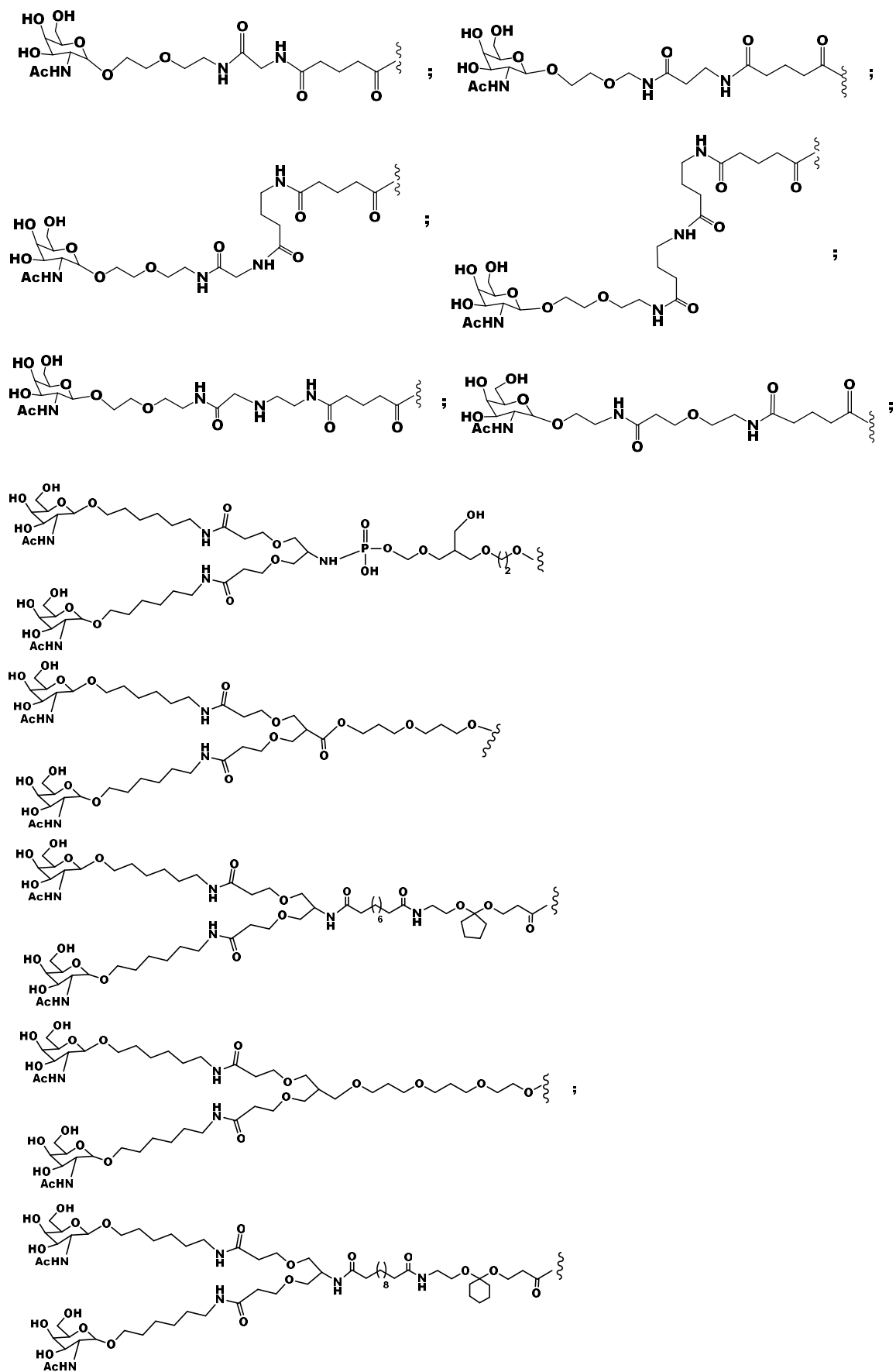


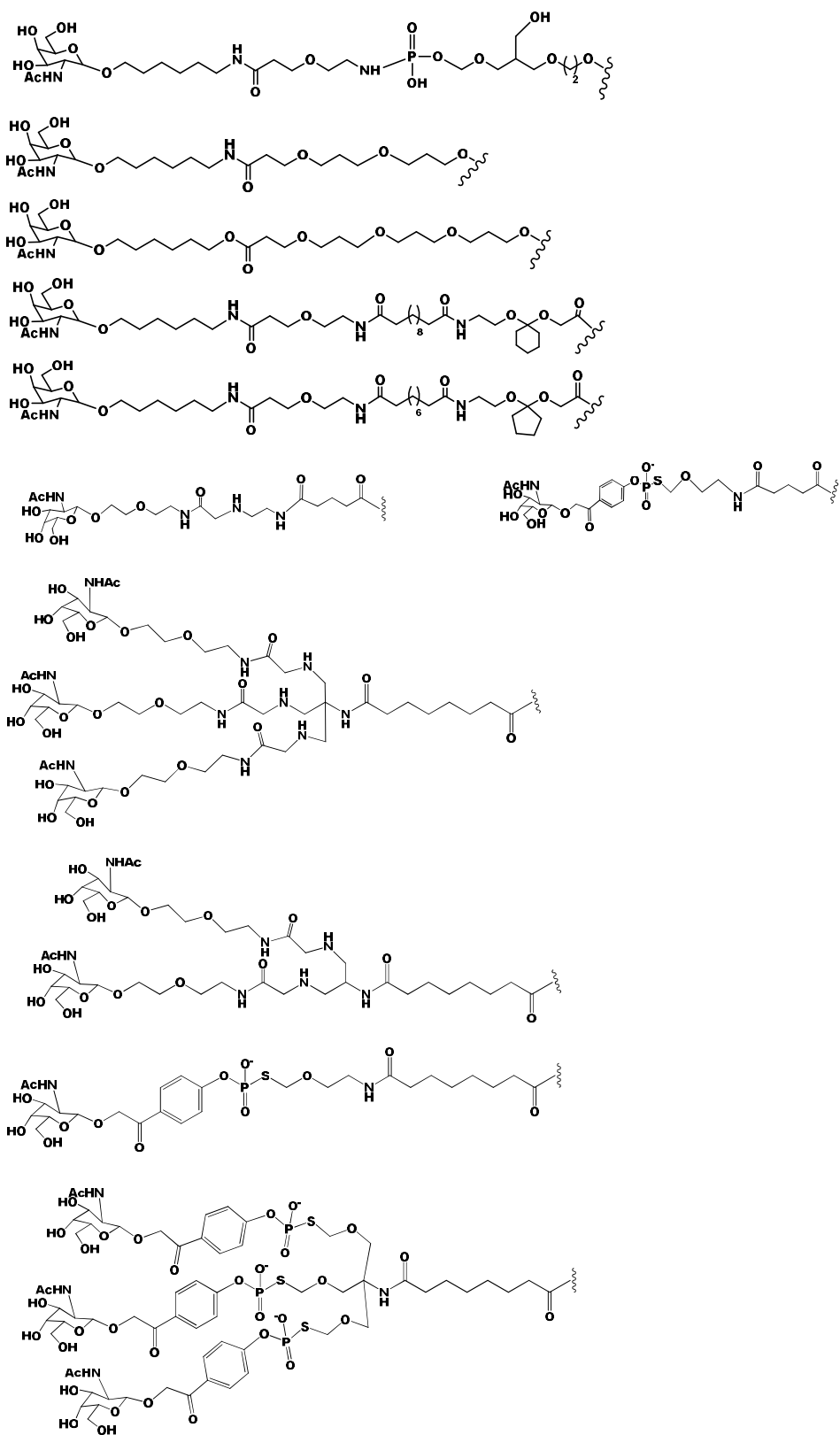
In some embodiments, the linking chain D is selected from the following structures:

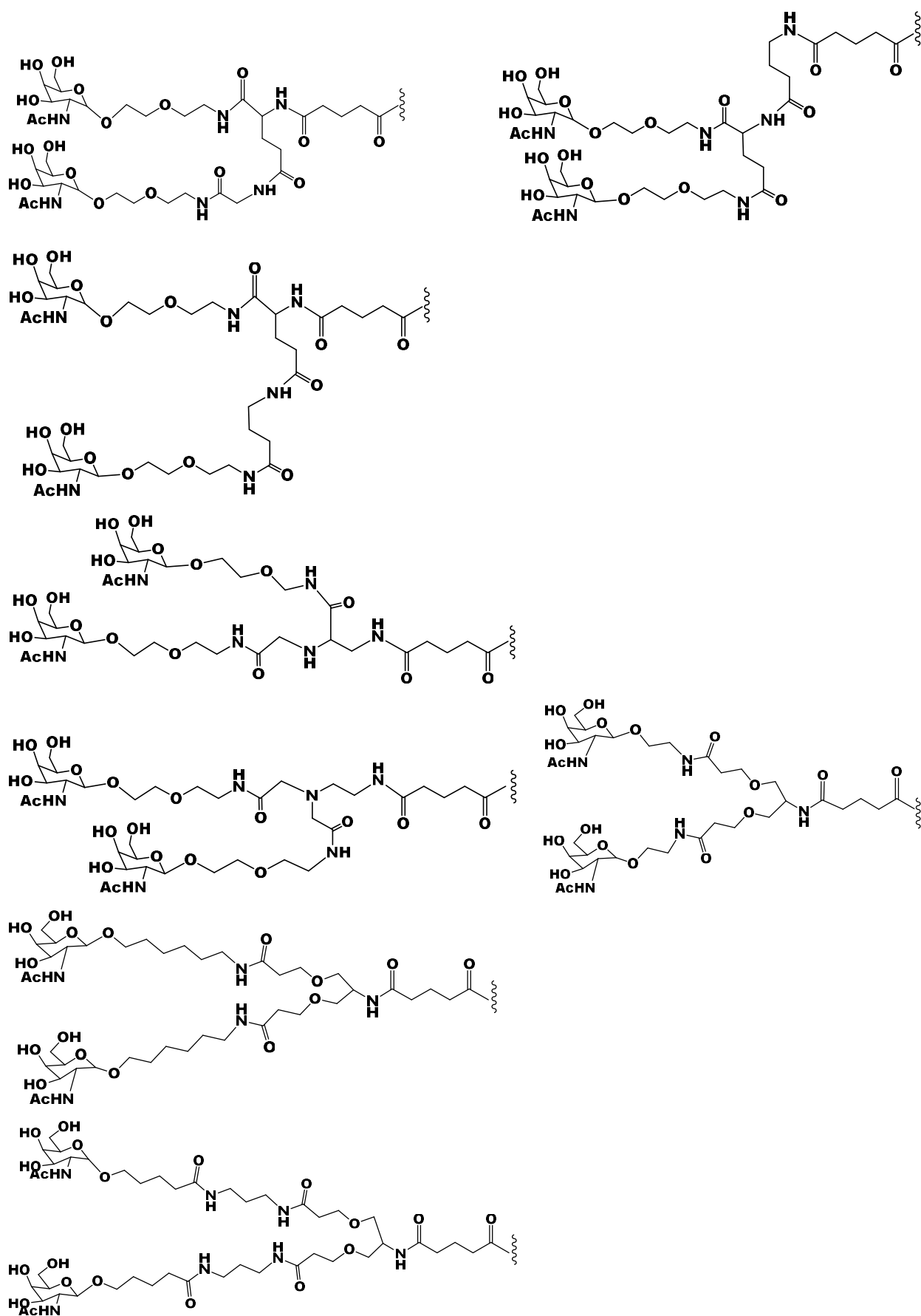


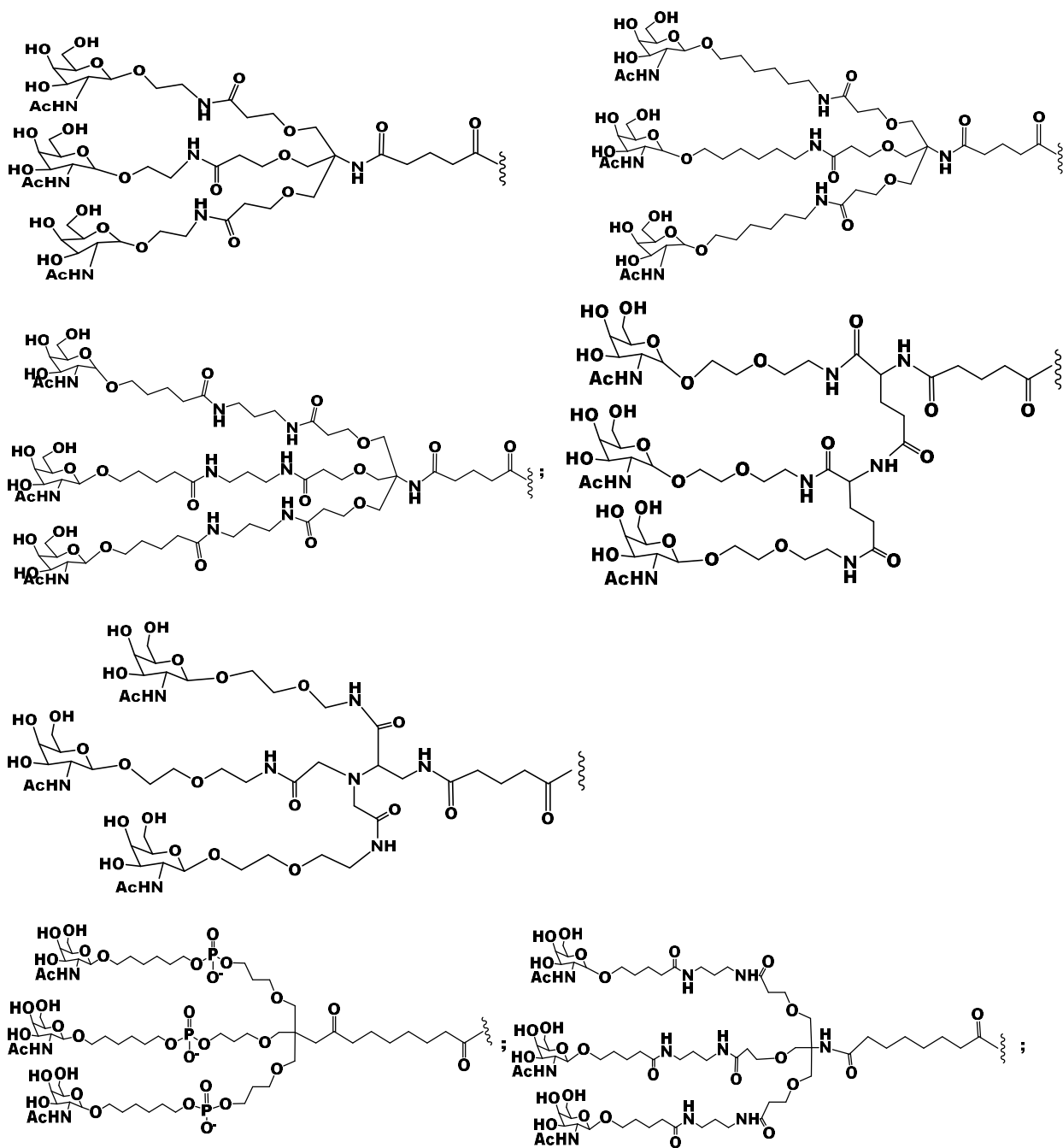
In some embodiments, (X-L)_n-B-D- in the structure of 5'MVIP and (X-L)_m-B-D- in the structure of 3'MVIP are selected from one or more of the following structures:

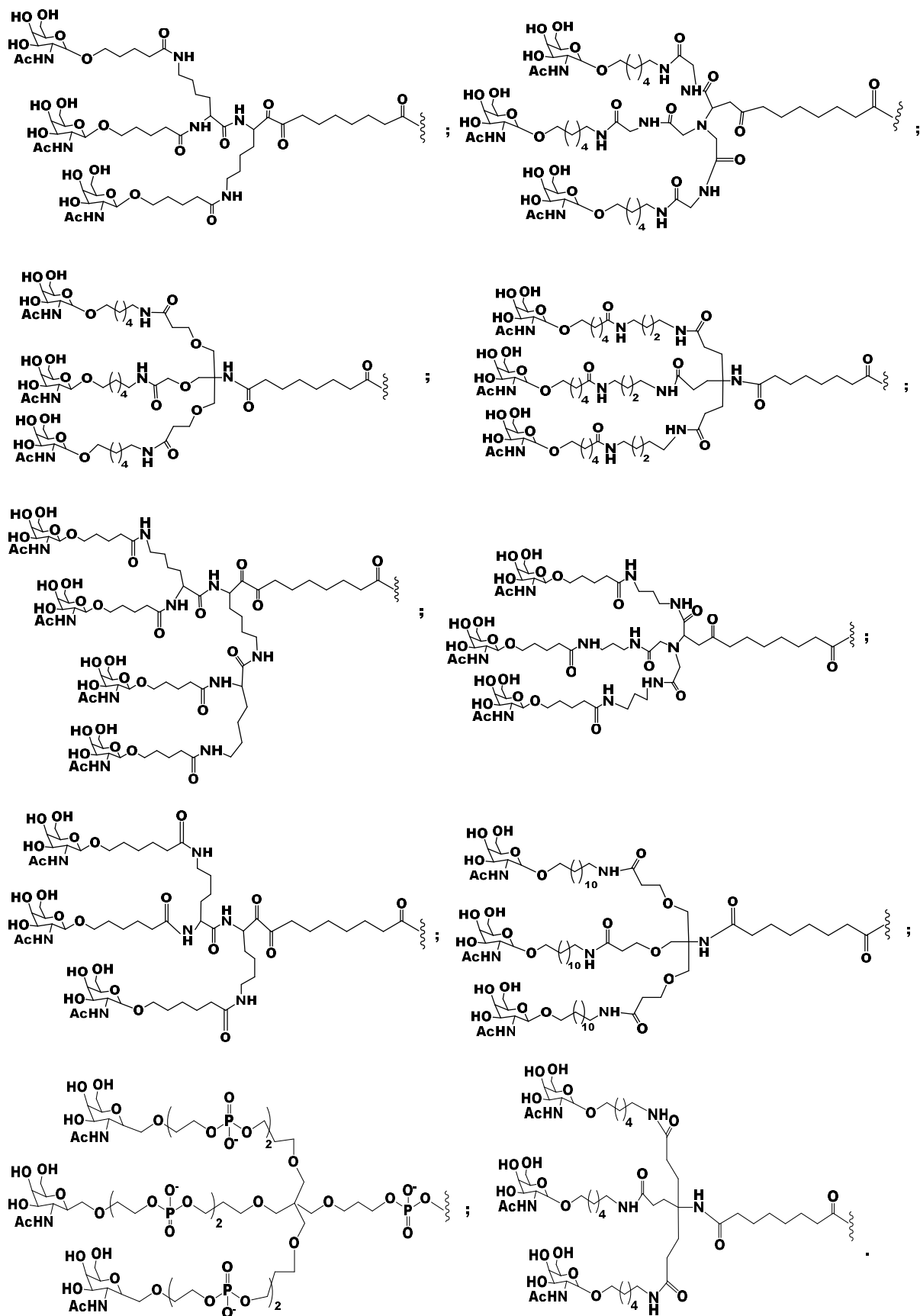


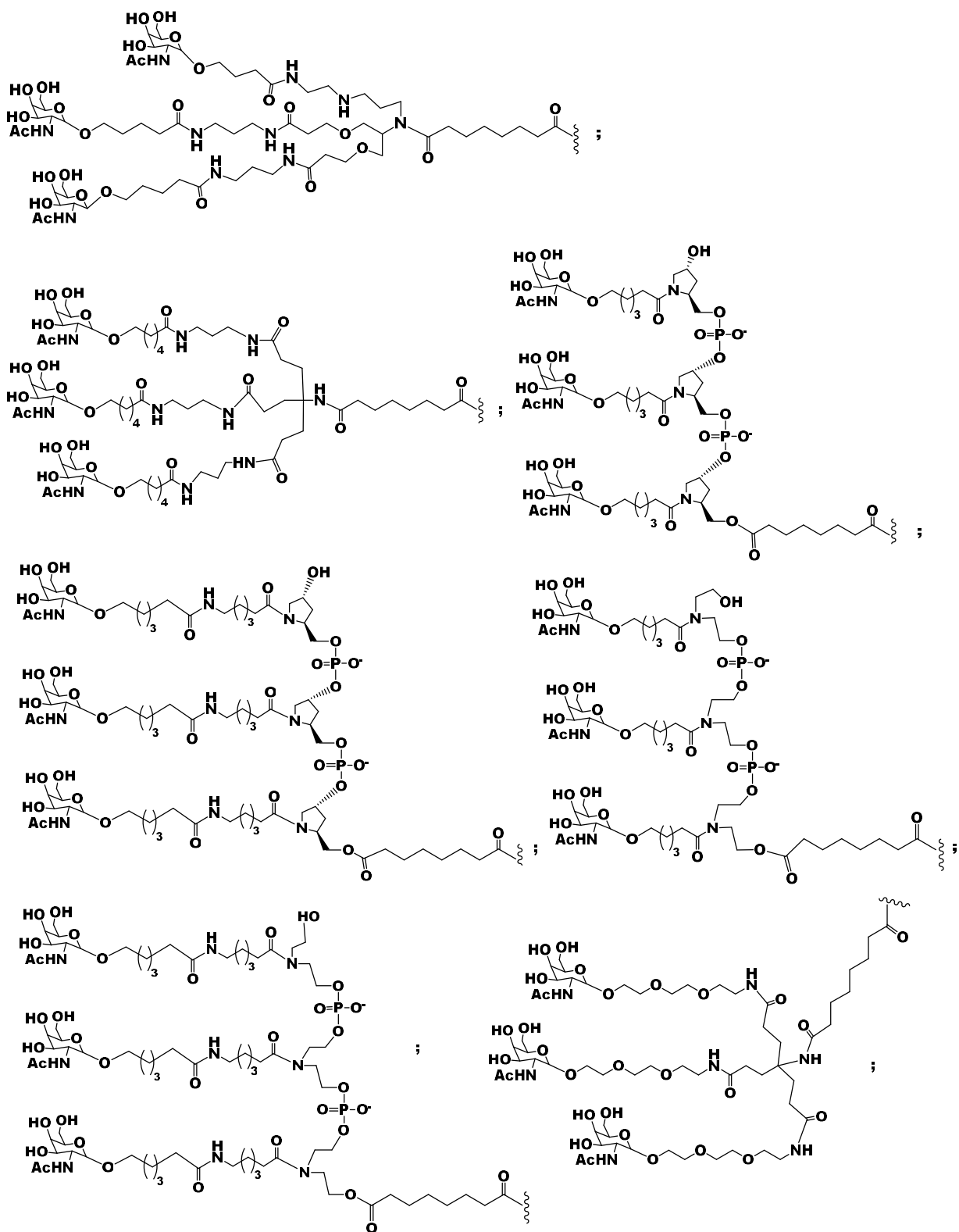


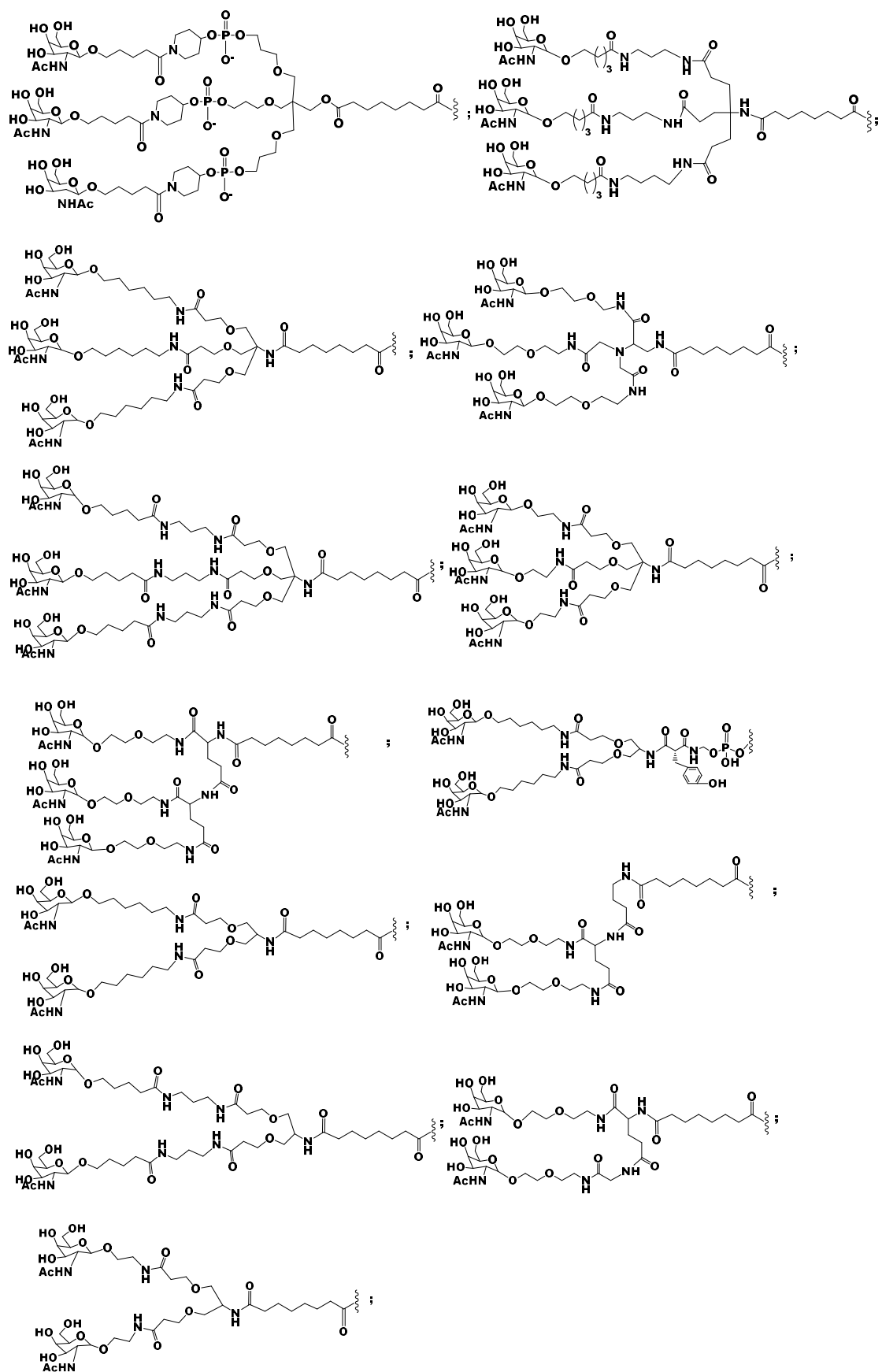


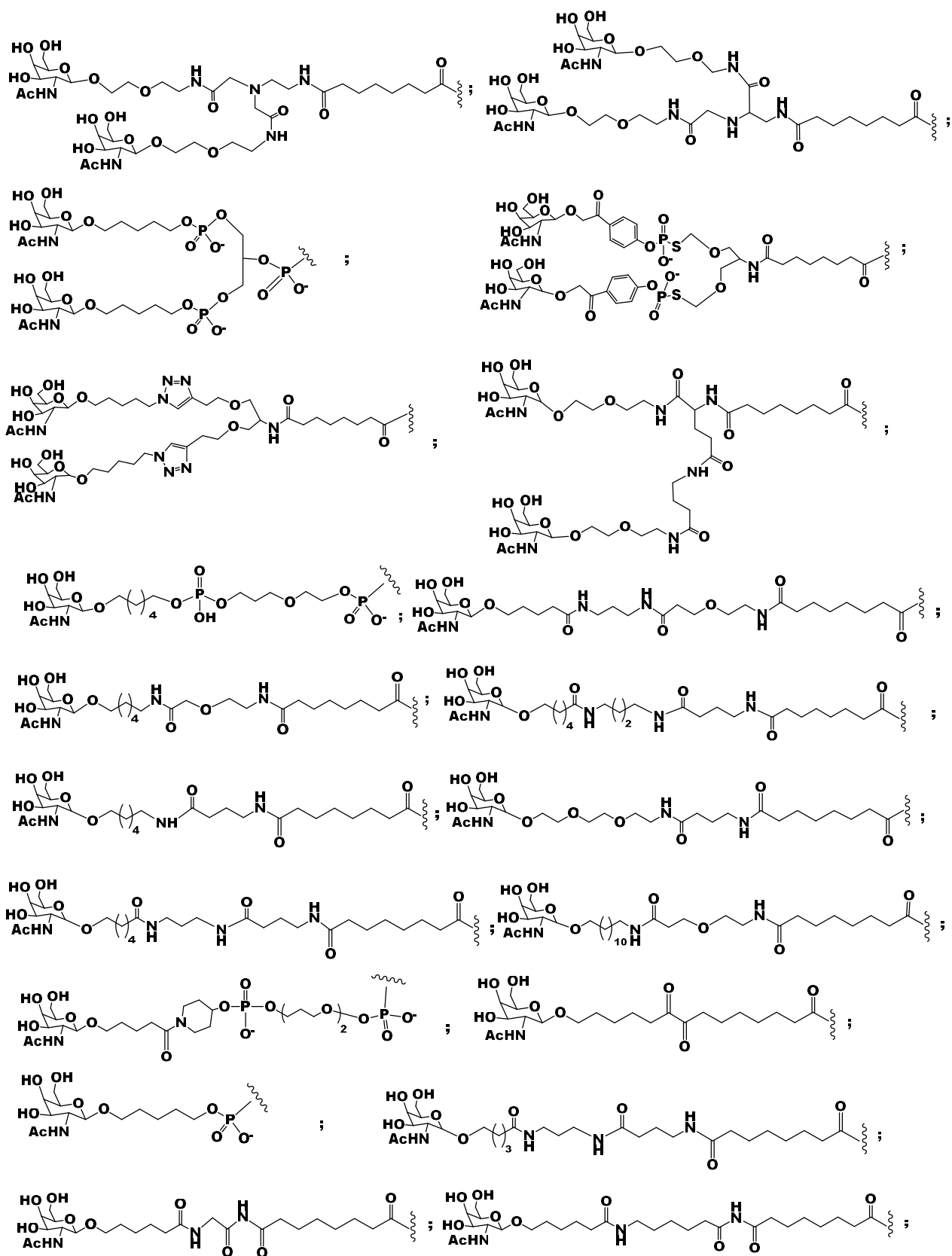


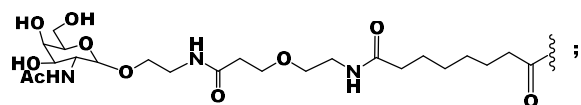
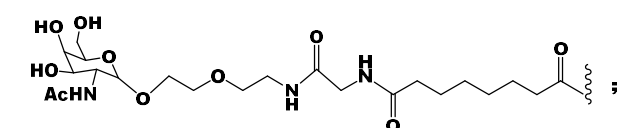
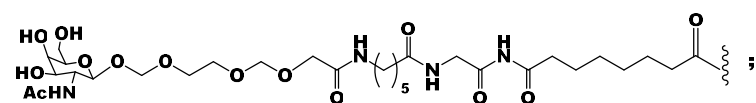
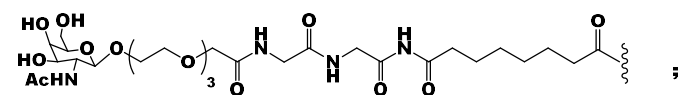
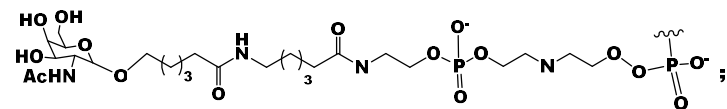
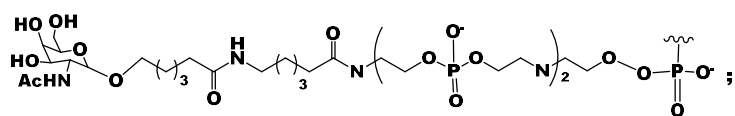










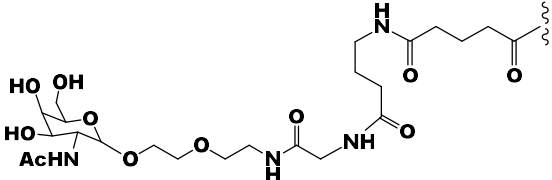
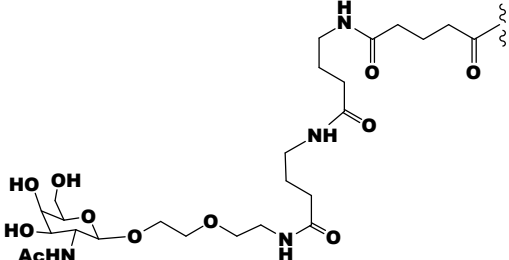
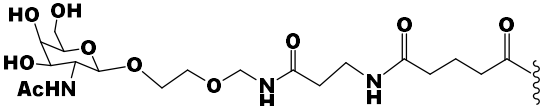
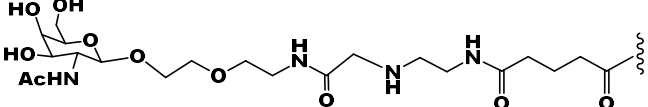
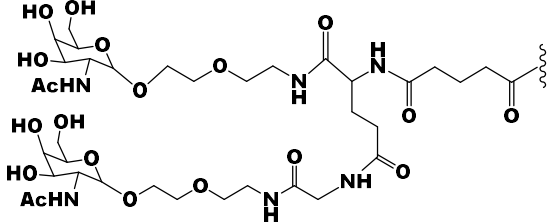
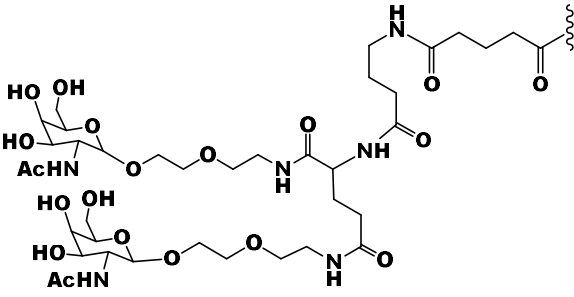
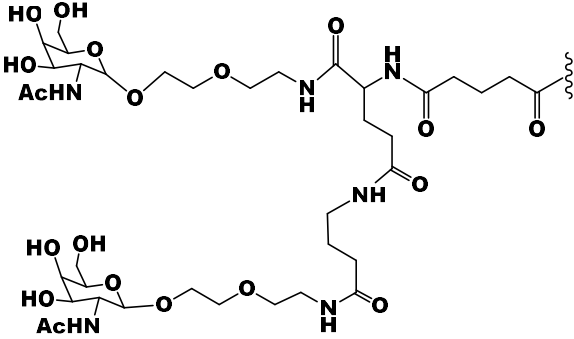


In some embodiments, the X, L, B and D are the same or different within the respective 5' MVIP and 3' MVIP or between the 5' MVIP and 3' MVIP.

In some embodiments, $(X-L)_n-B-D-$ in the structure of 5' MVIP is selected from the structures shown in Table 9:

Table 9 $(X-L)_n-B-D-$ in structures of 5' MVIP

No.	code	Structural formula
1	5'YICdd-01	
2	5'YICd-01	
3	5'YICc-01	
4	5'YICa-01	

No.	code	Structural formula
5	5'YICa-02	
6	5'YICa-03	
7	5'YICa-04	
8	5'YICa-05	
9	5'ERCa-01	
10	5'ERCa-02	
11	5'ERCa-03	

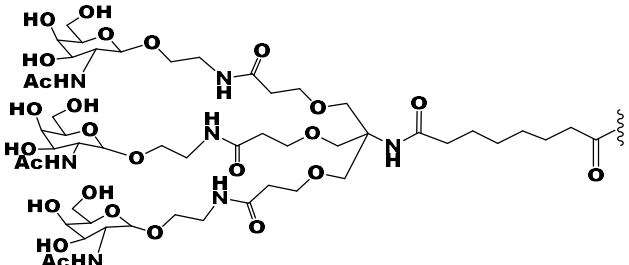
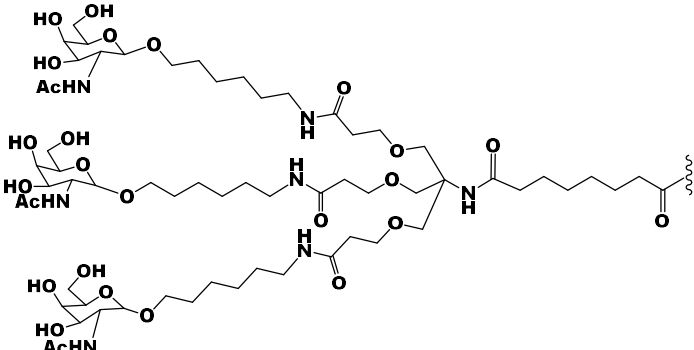
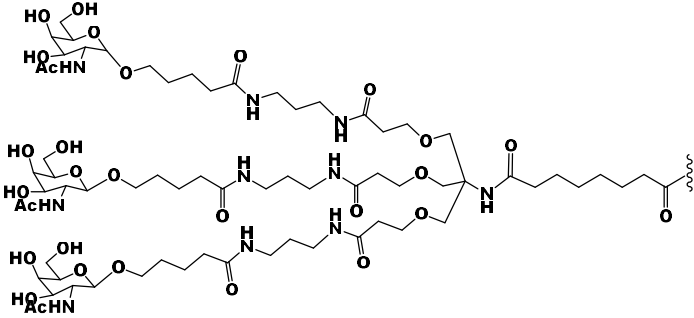
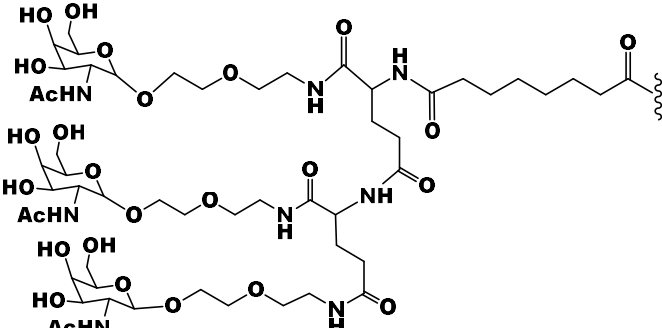
No.	code	Structural formula
12	5'ERCa-04	
13	5'ERCa-05	
14	5'ERCdd-01	
15	5'ERCd-01	
16	5'ERCc-01	
17	5'SANCdd-01	

No.	code	Structural formula
18	5'SANCd-01	
19	5'SANCc-01	
20	5'SANCa-01	
21	5'SANCa-02	
22	5'SANCa-03	

In some embodiments, 5'MVIP may not exist, in which case m may be any integer of 2-4.

In some embodiments, $(X-L)_m-B-D-$ in the structure of 3'MVIP is selected from the structures shown in Table 10:

Table 10 (X-L)_m-B-D- in structure of 3'MVIP

No.	code	structure
1	3'SANCdd-01	
2	3'SANCd-01	
3	3'SANCC-01	
4	3'SANCa-01	

No.	code	structure
5	3'SANCa-02	
6	3'SANCa-03	
7	3'ERCdd-01	
8	3'ERCd-01	
9	3'ERCc-01	
10	3'ERCa-01	

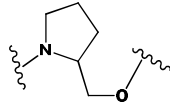
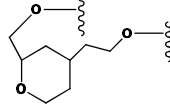
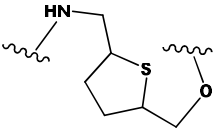
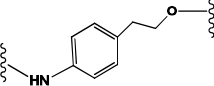
No.	code	structure
11	3'ERCa-02	
12	3'ERCa-03	
13	3'ERCa-04	
14	3'ERCa-05	
15	3'YICa-01	
16	3'YICa-02	

No.	code	structure
17	3'YICa-03	
18	3'YICa-04	
19	3'YICa-05	
20	3'YICdd-01	
21	3'YICd-01	
22	3'YICc-01	

In some embodiments, the combinations of $(X-L)_n$ -B-D- and R_1 in the carrier structure of 5'MVIP are shown in Table 11.

Table 11 combinations of $(X-L)_n$ -B-D- and R_1 in 5'MVIP

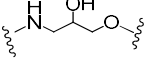
No.	$(X-L)_n$ -B-D- code	R_1	5'MVIP code
1	5'YICd-01	-NH(CH ₂) ₆ O-	5'MVIP01
2	5'YICc-01	-NH(CH ₂) ₆ O-	5'MVIP02
3	5'YICa-01	-O(CH ₂) ₆ O-	5'MVIP03
4	5'YICa-02	-O(CH ₂) ₆ O-	5'MVIP04
5	5'YICa-03	-S(CH ₂) ₆ O-	5'MVIP05
6	5'YICa-04	-NH(CH ₂) ₆ S-	5'MVIP06
7	5'YICa-05	-NH(CH ₂) ₈ O-	5'MVIP07

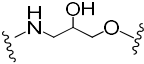
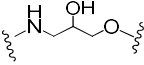
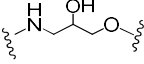
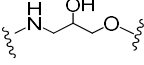
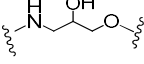
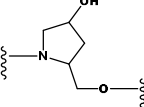
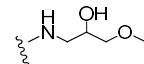
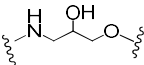
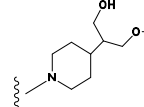
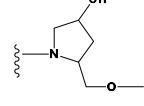
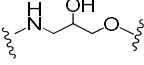
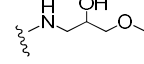
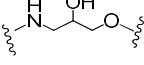
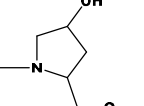
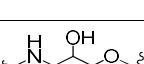
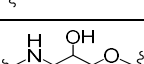
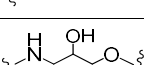
No.	(X-L) _n -B-D- code	R ₁	5'MVIP code
8	5'YICr-06	-NH(CH ₂) ₈ O-	5'MVIP08
9	5'ERCd-01	-NH(CH ₂) ₆ O-	5'MVIP09
10	5'ERCc-01	-NH(CH ₂) ₆ O-	5'MVIP10
11	5'ERCa-01	-NH(CH ₂) ₅ CH(CH ₂ CH ₃)O-	5'MVIP11
12	5'ERCa-02	-O(CH ₂) ₆ O-	5'MVIP12
13	5'ERCa-03	-S(CH ₂) ₆ O-	5'MVIP13
14	5'ERCa-04	-O(CH ₂) ₆ O-	5'MVIP14
15	5'ERCa-05	-O(CH ₂) ₆ O-	5'MVIP15
16	5'ERCr-06	-S(CH ₂) ₄ CH(CH ₃)O-	5'MVIP16
17	5'SANCD-01	-NH(CH ₂) ₆ O-	5'MVIP17
18	5'SANCC-01	-NH(CH ₂) ₆ O-	5'MVIP18
19	5'ERCd-01		5'MVIP19
20	5'ERCd-01		5'MVIP20
21	5'YICd-01		5'MVIP21
22	5'SANCD-01		5'MVIP22

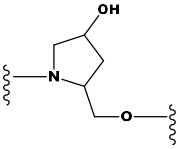
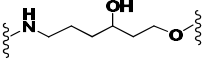
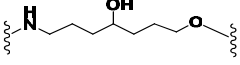
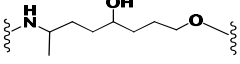
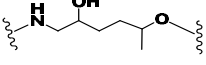
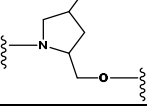
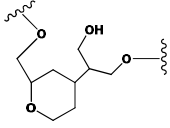
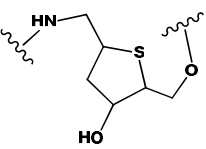
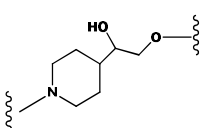
In some embodiments, 3'MVIP may not exist, in which case n may be any integer of 2-4.

In some embodiments, the combinations of (X-L)_m-B-D- and R₂ in the carrier structure of 3'MVIP are shown in Table 12.

Table 12 combinations of (X-L)_m-B-D- and R₂ in 3'MVIP

No.	(X-L) _m -B-D- code	R ₂	3'MVIP code
1	3'YICd-01		3'MVIP01

No.	(X-L) _m -B-D- code	R ₂	3'MVIP code
2	3'YICc-01		3'MVIP02
3	3'YICa-01		3'MVIP03
4	3'YICa-02		3'MVIP04
5	3'YICa-03		3'MVIP05
6	3'YICa-04		3'MVIP06
7	3'YICa-05		3'MVIP07
8	3'YICr-06		3'MVIP08
9	3'ERCd-01		3'MVIP09
10	3'ERCc-01		3'MVIP10
11	3'ERCa-01		3'MVIP11
12	3'ERCa-02		3'MVIP12
13	3'ERCa-03		3'MVIP13
14	3'ERCa-04		3'MVIP14
15	3'ERCa-05		3'MVIP15
16	3'ERCr-06		3'MVIP16
17	3'SANCd-01		3'MVIP17
18	3'SANCc-01		3'MVIP18

No.	(X-L) _m -B-D- code	R ₂	3'MVIP code
19	3'SANCa-01		3'MVIP19
20	3'ERCd-01		3'MVIP20
21	3'ERCd-01		3'MVIP21
22	3'ERCd-01		3'MVIP22
23	3'ERCd-01		3'MVIP23
24	3'ERCd-01		3'MVIP24
25	3'ERCd-01		3'MVIP25
26	3'ERCd-01		3'MVIP26
27	3'ERCd-01		3'MVIP27

In some embodiments, the 5'MVIP is selected from any one or more of 5'MVIP01 to 5'MVIP22 in Table 11.

In some embodiments, the 3'MVIP is selected from any one or more of 3'MVIP01 to 3'MVIP27 in Table 12.

In some embodiments, there is a possibility of combining any of the 5'MVIP in Table 11 with any of the 3'MVIP in Table 12, where n+m=2, 3, 4, 5 or 6.

In some embodiments, the sense strand in the RNA inhibitor can be selected from the sequences in Table 13 below.

Table 13 sense strand conjugated to 5'MVIP09

sense strand code	sense strand sequence 5'→3'
S19301	5'MVIP09-GsAsGCfACfCfGfUUAAGGACAAGsUsU
S19401	5'MVIP09-GsCsACfCGfUfUfAAGGACAAGUUsCsU
S19501	5'MVIP09-UsUsACAUGAfAfGfCACGCCACCsAsA
S19601	5'MVIP09-UsCsUCAGCUfUfCfAUGCAGGGUUsUsA
S19701	5'MVIP09-GsCsUUfCAfGfUfUCCCUGAAAGAsCsU
S19801	5'MVIP09-UsUsCCfCUfGfAfAAGACUACUGGsAsG
S19901	5'MVIP09-AsGsACUACUfGfGfAGCACCGUUsAsA
S20001	5'MVIP09-CsCsGUUAAGfGfAfCAAGUUCUCsUsG
S20101	5'MVIP09-CsUsGCfCCfCfUfGUAGGUUGCUUsAsA
S20201	5'MVIP09-CsAsGUfAUfUfCfUCAGUGCUCUCsCsU
S20301	5'MVIP09-UsGsGCUGCCfUfGfAGACCUCAAsUsA
S20401	5'MVIP09-GsAsGCfUCfCfUfUGGGUCCUGCAsAsU
S20501	5'MVIP09-CsCsUGAGGUfCfAfGACCAACUUsCsA
S20601	5'MVIP09-AsAsGGGACAfGfUfAUUCUCAGUsGsC

In some embodiments, the sense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 13 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 13.

In some embodiments, the antisense strand in the RNA inhibitor can be selected from the sequences in Table 14 below.

Table 14 antisense strand conjugated to 3'MVIP09

antisense strand code	antisense strand sequence 5'→3'
AS19301	AsAsCUUGfUCCUufAAfCGGUGCsUsC-3'MVIP09
AS19401	AsGsAACUfUGUCCfUUfAACGGUsGsC-3'MVIP09
AS19501	UsfUsGfGUfGGfCGUGCUfUCfAUGUsAsA-3'MVIP09
AS19601	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3'MVIP09
AS19701	AsGsUCUufUCAGGfGAfACUGAAsGsC-3'MVIP09
AS19801	CsUsCCAGfUAGUCfUUfUCAGGGsAsA-3'MVIP09
AS19901	UsfUsAfACfGGfUGCUCfAGfUAGUsCsU-3'MVIP09
AS20001	CsfAsGfAGfAAfCUUGUCfCUfUAACsGsG-3'MVIP09
AS20101	UsUsAAGCfAACCfACfAGGGGCsAsG-3'MVIP09
AS20201	AsGsGAGAfGCACUfGAfGAAUACsUsG-3'MVIP09
AS20301	UsfAsUfUGfAGfGUCUCAfGGfCAGCsCsA-3'MVIP09
AS20401	AsUsUGCAfGGACcfCAfAGGAGCsUsC-3'MVIP09
AS20501	UsfGsAfAGfUUfGGUCUGfACfCUCAsGsG-3'MVIP09
AS20601	GsfCsAfCUfGAfGAAUACfUGfUCCCUUsUsU-3'MVIP09

In some embodiments, the antisense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 14 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 14.

In some in vivo experimental embodiments, the RNA inhibitor described in the present invention is selected from the sequences in Table 15.

Table 15 RNA inhibitors containing 5'MVIP09/3'MVIP09 combination

RNA inhibitor	sense strand code	antisense strand code
Kylo-12-DS1041	S19301	AS19301
Kylo-12-DS1051	S19401	AS19401
Kylo-12-DS1071	S19501	AS19501
Kylo-12-DS1081	S19601	AS19601
Kylo-12-DS1091	S19701	AS19701

RNA inhibitor	sense strand code	antisense strand code
Kylo-12-DS1111	S19801	AS19801
Kylo-12-DS1131	S19901	AS19901
Kylo-12-DS1141	S20001	AS20001
Kylo-12-DS1181	S20101	AS20101
Kylo-12-DS1221	S20201	AS20201
Kylo-12-DS1241	S20301	AS20301
Kylo-12-DS1261	S20401	AS20401
Kylo-12-DS1311	S20501	AS20501
Kylo-12-DS1321	S20601	AS20601

In some embodiments, the sense strand and antisense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 15 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 15.

It should be noted that, the combinations in Tables 13, 14, and 15 are not exhaustive. The sequences of the present invention can be connected to MVIPs of any structure, and the connection sites and number of connections are not limited. The “connection site is not limited” means that the site can be at 5' end, 3' end, or not at the end. The “number of connections is not limited” means that the number can be one or more and there is no limit.

In some embodiments, the 5' end and/or 3' end of the antisense strand of the RNA inhibitor UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA (SEQ ID NO: 382) is connected to 5'MVIP and/or 3'MVIP of different structures, and the antisense strand and its carrier structure are selected from the following Table 16:

Table 16 antisense strand conjugated to 5'MVIP and/or 3'MVIP

antisense strand code	antisense strand sequence 5'→3'
AS19601	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3'MVIP09
AS20701	5' MVIP17-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS20801	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP01
AS20901	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP17

antisense strand code	antisense strand sequence 5'→3'
AS21001	5' MVIP01-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP01
AS21101	5' MVIP09-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP09
AS21201	5' MVIP17-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP17
AS21301	5' MVIP01-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP17
AS21401	5' MVIP17-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP01
AS21501	5' MVIP01-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP09
AS21601	5' MVIP09-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP01
AS21701	5' MVIP09-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP17
AS21801	5' MVIP17-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP09
AS21901	5' MVIP12-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS22001	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP19
AS22101	5'MVIP16- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA - 3'MVIP16
AS22201	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP17
AS22301	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP18
AS22401	5' MVIP03-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS22501	5' MVIP08-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS22601	5'MVIP16-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA

antisense strand code	antisense strand sequence 5'→3'
AS22701	5'MVIP13-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA- 3'MVIP06
AS22801	5'MVIP04-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA- 3'MVIP06
AS22901	5' MVIP11-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23001	5' MVIP11-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP14
AS23101	5' MVIP15-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23201	5' MVIP02-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23301	5' MVIP05-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23401	5' MVIP06-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23501	5' MVIP07-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23601	5' MVIP10- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23701	5' MVIP14- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23801	5' MVIP18- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS23901	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP02
AS24001	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP03
AS24101	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP04
AS24201	5' MVIP04-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP04
AS24301	5' MVIP03-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP19
AS24401	5' MVIP18- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP18
AS24501	5' MVIP08- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP18
AS24601	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP05

antisense strand code	antisense strand sequence 5'→3'
AS24701	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP07
AS24801	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP10
AS24901	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP11
AS25001	5' MVIP11- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP11
AS25101	5' MVIP15- UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA-3' MVIP15
AS25201	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP06
AS25301	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP08
AS25401	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP12
AS25501	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP13
AS25601	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP14
AS25701	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP15
AS25801	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP16
AS25901	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP24
AS26001	UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA -3' MVIP27
AS26101	5' MVIP19-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS26201	5' MVIP20-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS26301	5' MVIP21-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS26401	5' MVIP22-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS26501	5' MVIP01-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA
AS26601	5' MVIP09-UsfAsAfCCfCUfGCAUGAfAGfCUGAsGsA

In some embodiments, the antisense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 16 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 16.

In some embodiments, the antisense strand conjugated to 5'MVIP and/or 3'MVIP in Table 16 can be obtained by conjugating the sequence in Tables 7-1 and 7-2 with 5'MVIP and/or 3'MVIP.

In some embodiments, the 5' end and/or 3' end of the sense strand of the RNA inhibitor U_sC_sUCAGCUfUfCfAUGCAGGGU_sU_sA (SEQ ID NO: 412) is connected to 5'MVIP and/or 3'MVIP of different structures, and the sense strand and its carrier structure are selected from the following Table 17.

Table 17 sense strand conjugated to 5'MVIP and/or 3'MVIP

sense strand code	sense strand sequence 5'→3'
S19601	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S20701	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A - 3'MVIP17
S20801	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP09
S20901	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A-3'MVIP01
S21001	5'MVIP17- U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S21101	5'MVIP01- U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S21201	5'MVIP01-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP01
S21301	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP09
S21401	5'MVIP17-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP17
S21501	5'MVIP01-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP17
S21601	5'MVIP17-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP01
S21701	5'MVIP01-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP09
S21801	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP01
S21901	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP17
S22001	5'MVIP17-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP09
S22101	5'MVIP12-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S22201	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP19
S22301	5'MVIP16-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP16
S22401	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP17
S22501	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP18
S22601	5' MVIP03-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S22701	5' MVIP08-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A

sense strand code	sense strand sequence 5'→3'
S19601	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S22801	5' MVIP16-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S22901	5'MVIP13-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP06
S23001	5'MVIP04-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP06
S23101	5'MVIP11-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23201	5'MVIP11-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3'MVIP14
S23301	5'MVIP15-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23401	5'MVIP02-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23501	5'MVIP05-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23601	5'MVIP06-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23701	5'MVIP07-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23801	5'MVIP10-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S23901	5'MVIP14-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S24001	5'MVIP18-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S24101	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP02
S24201	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP03
S24301	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP04
S24401	5' MVIP04-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP04
S24501	5' MVIP03-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP19
S24601	5' MVIP18-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP18
S24701	5' MVIP08-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP18
S24801	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP05
S24901	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP07
S25001	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP10
S25101	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP11
S25201	5' MVIP11-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP11
S25301	5' MVIP15-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVIP15

sense strand code	sense strand sequence 5'→3'
S19601	5'MVIP09-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S25401	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP06
S25501	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP08
S25601	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP12
S25701	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP13
S25801	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP14
S25901	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP15
S26001	U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A -3' MVP16
S26101	5' MVP19-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S26201	5' MVP20-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S26301	5' MVP21-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A
S26401	5' MVP22-U _s C _s UCAGCUfUfCfAUGCAGGGU _s U _s A

In some embodiments, the sense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 17 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 17.

In some embodiments, the 5' end and/or 3' end of the antisense strand of the RNA inhibitor AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC (SEQ ID NO: 970) is connected to 5'MVIP and/or 3'MVIP of different structures, and the antisense strand and its carrier structure are selected from the following Table 18.

Table 18 antisense strand conjugated to 5'MVIP and/or 3'MVIP

antisense strand code	antisense strand sequence 5'→3'
Ky-12AS01	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP09
Ky-12AS02	5'MVIP17-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS03	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP01
Ky-12AS04	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS05	5'MVIP01-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP01
Ky-12AS06	5'MVIP09-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP09

antisense strand code	antisense strand sequence 5'→3'
Ky-12AS07	5'MVIP17-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS08	5'MVIP01-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS09	5'MVIP17-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP01
Ky-12AS10	5'MVIP01-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP09
Ky-12AS11	5'MVIP09-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP01
Ky-12AS12	5'MVIP09-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS13	5'MVIP17-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP09
Ky-12AS14	5'MVIP12-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS15	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP19
Ky-12AS16	5'MVIP16-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP16
Ky-12AS17	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS18	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP18
Ky-12AS19	5'MVIP03-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS20	5'MVIP08-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS21	5'MVIP16-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS22	5'MVIP13-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP06
Ky-12AS23	5'MVIP04-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP06
Ky-12AS24	5'MVIP11-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS25	5'MVIP11-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP14
Ky-12AS26	5'MVIP15-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS27	5'MVIP02-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS28	5'MVIP05-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS29	5'MVIP06-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS30	5'MVIP07-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS31	5'MVIP10-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS32	5'MVIP14-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS33	5'MVIP18-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC

antisense strand code	antisense strand sequence 5'→3'
Ky-12AS34	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP02
Ky-12AS35	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP03
Ky-12AS36	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP04
Ky-12AS37	5'MVIP04-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP04
Ky-12AS38	5'MVIP03-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP19
Ky-12AS39	5'MVIP18-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP18
Ky-12AS40	5'MVIP08-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP18
Ky-12AS41	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP05
Ky-12AS42	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP07
Ky-12AS43	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP10
Ky-12AS44	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP11
Ky-12AS45	5'MVIP11-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP11
Ky-12AS46	5'MVIP15-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP15
Ky-12AS47	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP06
Ky-12AS48	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP08
Ky-12AS49	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP12
Ky-12AS50	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP13
Ky-12AS51	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP14
Ky-12AS52	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP15
Ky-12AS53	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP16
Ky-12AS54	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP24
Ky-12AS55	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP27
Ky-12AS56	5'MVIP19-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS57	5'MVIP20-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS58	5'MVIP21-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS59	5'MVIP22-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC
Ky-12AS60	5'MVIP01-AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC

antisense strand code	antisense strand sequence 5'→3'
Ky-12AS61	5'MVIP09-AsfCsAfcUfGAfGAAUACfUGfUCfGCsfUsC

In some embodiments, the antisense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 18 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 18.

It should be noted that, the combinations in Table 18 are not exhaustive. The sequences of the present invention can be connected to MVIPs of any structure, and the connection sites and number of connections are not limited. The “connection site is not limited” means that the site can be at 5' end, 3' end, or not at the end. The “number of connections is not limited” means that the number can be one or more and there is no limit.

In some embodiments, the 5' end and/or 3' end of the sense strand of the RNA inhibitor GsAsGCGACAfGfUfAUUCUCAGUsGsU (SEQ ID NO: 1033) is connected to 5'MVIP and/or 3'MVIP of different structures, and the sense strand and its carrier structure are selected from the following Table 19:

Table 19 sense strand conjugated to 5'MVIP and/or 3'MVIP

sense strand code	sense strand sequence 5'→3'
Ky-12S01	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S02	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S03	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP09
Ky-12S04	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP01
Ky-12S05	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S06	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S07	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP01
Ky-12S08	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP09
Ky-12S09	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S10	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S11	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP01
Ky-12S12	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP09
Ky-12S13	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP01

sense strand code	sense strandsequence 5'→3'
Ky-12S14	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S15	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP09
Ky-12S16	5'MVIP12-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S17	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP19
Ky-12S18	5'MVIP16-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP16
Ky-12S19	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S20	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP18
Ky-12S21	5'MVIP03-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S22	5'MVIP08-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S23	5'MVIP16-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S24	5'MVIP13-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP06
Ky-12S25	5'MVIP04-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP06
Ky-12S26	5'MVIP11-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S27	5'MVIP11-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP14
Ky-12S28	5'MVIP15-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S29	5'MVIP02-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S30	5'MVIP05-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S31	5'MVIP06-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S32	5'MVIP07-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S33	5'MVIP10-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S34	5'MVIP14-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S35	5'MVIP18-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S36	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP02
Ky-12S37	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP03
Ky-12S38	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP04
Ky-12S39	5'MVIP04-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP04
Ky-12S40	5'MVIP03-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP19
Ky-12S41	5'MVIP18-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP18

sense strand code	sense strand sequence 5'→3'
Ky-12S42	5'MVIP08-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP18
Ky-12S43	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP05
Ky-12S44	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP07
Ky-12S45	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP10
Ky-12S46	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP11
Ky-12S47	5'MVIP11-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP11
Ky-12S48	5'MVIP15-GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP15
Ky-12S49	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP06
Ky-12S50	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP08
Ky-12S51	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP12
Ky-12S52	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP13
Ky-12S53	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP14
Ky-12S54	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP15
Ky-12S55	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP16
Ky-12S56	5'MVIP19-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S57	5'MVIP20-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S58	5'MVIP21-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S59	5'MVIP22-GsAsGCGACAfGfUfAUUCUCAGUsGsU

In some embodiments, the sense strand of the RNA inhibitor described in the present invention differs from each sequence in Table 19 by 1, 2, or 3 nucleotides, or has at least 15, 16, 17, 18, 19, 20, 21 consecutive nucleotides identical to the sequences in Table 19.

It should be noted that, the combinations in Table 19 are not exhaustive. The sequences of the present invention can be connected to MVIPs of any structure, and the connection sites and number of connections are not limited. The “connection site is not limited” means that the site can be at 5' end, 3' end, or not at the end. The “number of connections is not limited” means that the number can be one or more and there is no limit.

In some embodiments, the antisense strand of the RNA inhibitor can be obtained by conjugating the antisense strand sequence exemplified above with any 5'MVIP and/or 3'MVIP.

In some embodiments, the sense strand of the RNA inhibitor can be obtained by conjugating the sense strand sequence exemplified above with any 5'MVIP and/or 3'MVIP.

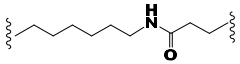
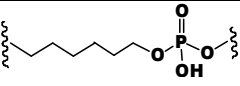
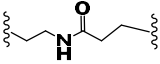
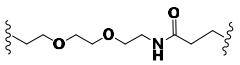
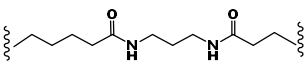
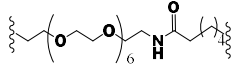
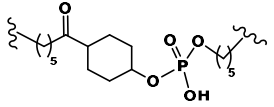
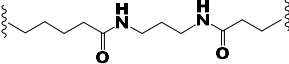
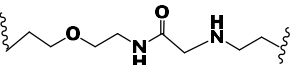
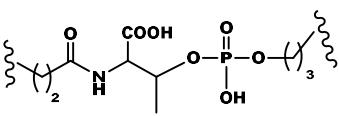
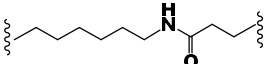
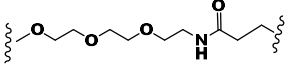
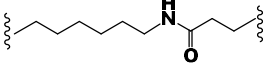
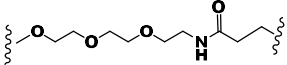
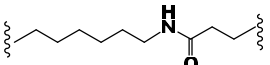
In some embodiments, the sequences within the protection scope of the present invention can be connected to any number of 5' MVIP or 3' MVIP in any structure at any position to form RNA inhibitors. These RNA inhibitors are all within the protection scope of the present invention and are inspired by the present invention.

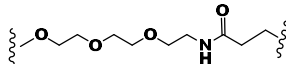
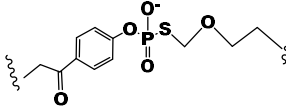
Chinese patent CN113171371B provides a detailed examination of the effects of different X, L, B, D, R₁, and R₂ in the structures of 5'MVIP and/or 3'MVIP on the activity of RNA inhibitors. The full text of this patent is incorporated herein by reference. When one of X, L, B, D, R₁, and R₂ is different, the other parts of the corresponding 5'MVIP and/or 3'MVIP are the same as those of 5'MVIP 09/3'MVIP 09.

When X is galactose, galactosamine, N-acetylgalactosamine and their derivatives respectively, the RNA inhibitor provided by the present invention preferably uses N-acetylgalactosamine and its derivatives as liver targeting specific ligands.

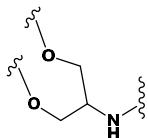
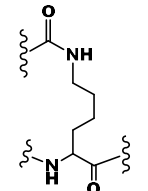
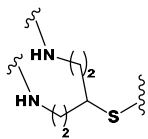
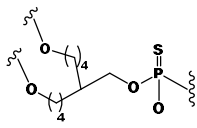
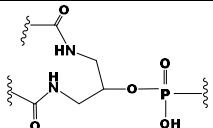
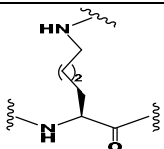
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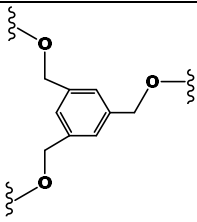
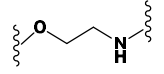
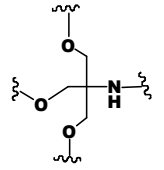
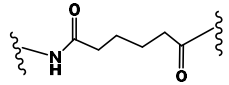
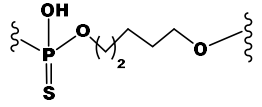
The length of L has a great impact on the effect of RNA inhibitors. The L chain should not be too short or too long. When L contains -NH-, C=O, O, S, amido, phosphoryl, thiophosphoryl, aliphatic carbocyclyl such as cyclohexane, or a combination of these groups, or has different structures in the same 5'MVIP, 3'MVIP structures or between 5'MVIP and 3'MVIP, the activities of the resulting RNA inhibitors do not differ significantly in the range of carbon chain length of C7-C18.

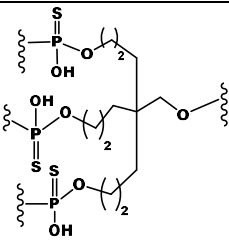
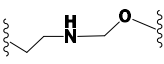
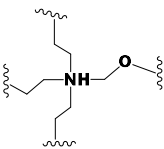
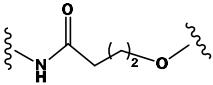
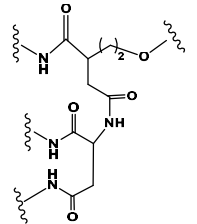
L code	L structure
L1	
L2	
L3	
L4	
L5	
L6	
L7	
L8	
L9	
L10	
L11	L in 5' MVIP for S:  L in 3' MVIP for AS: 
L12	L in 5' MVIP for S:  L in 3' MVIP for AS: 
L13	L in 5' MVIP for S: 

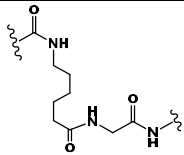
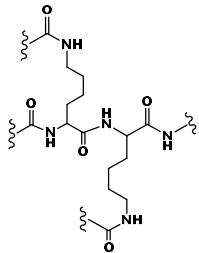
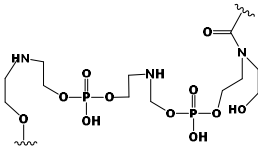
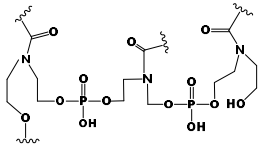
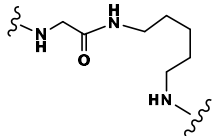
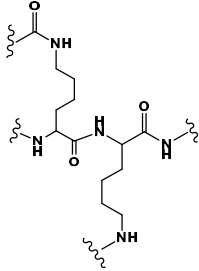
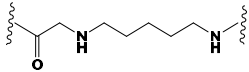
L code	L structure
	L in 3'MVIP for AS: 
L14	

Except for the change in the structure of the linker B, when X, L, D and R₁/R₂ are consistent with those in the combination 5'MVIP09/3'MVIP09, A₁ and A₂ in the general formula of linker B are each independently C, O, S, -NH-, carbonyl, amido, phosphoryl or thiophosphoryl, and r is any integer of 0-4, and when the linker B is the same or different between 5'MVIP and 3'MVIP, the inhibitory activity of resulting RNA inhibitor does not differ significantly.

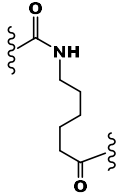
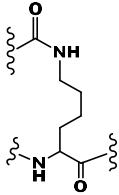
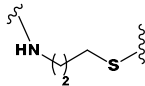
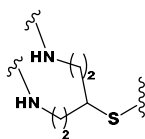
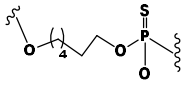
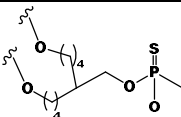
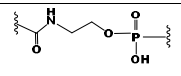
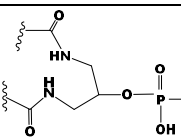
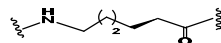
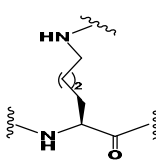
B code	B structure
B1	
B2	
B3	
B4	
B5	
B6	

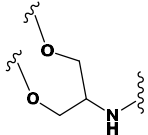
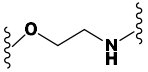
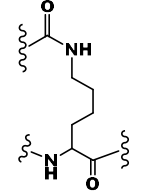
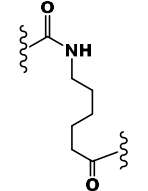
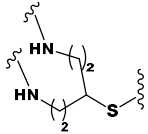
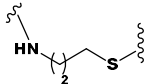
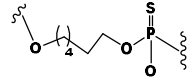
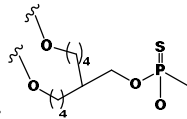
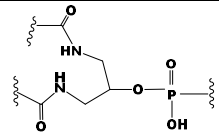
B code	B structure
B7	
B8	B in 5'MVIP for S:
	
B9	B in 3'MVIP for AS:
	
B10	B in 5'MVIP for S:
	
B11	B in 3'MVIP for AS:
	

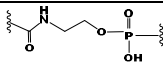
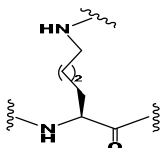
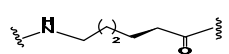
B code	B structure
	
B12	B in 5'MVIP for S:
	
B13	B in 3'MVIP for AS:
	
B14	B in 5'MVIP for S:
	
B15	B in 3'MVIP for AS:
	
B16	B in 5'MVIP for S:

B code	B structure
	
	B in 3'MVIP for AS: 
B16	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B17	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B18	B in 5'MVIP for S: 

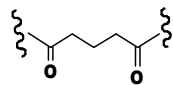
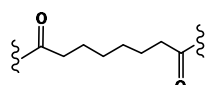
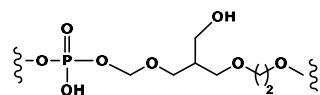
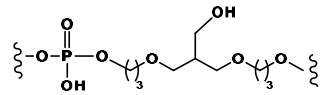
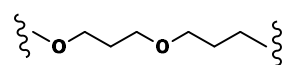
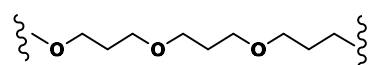
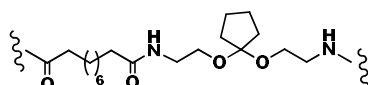
B code	B structure
	B in 3'MVIP for AS:
B19	B in 5'MVIP for S:
	B in 3'MVIP for AS:
B20	
B21	
B22	
B23	
B24	
B25	
B26	
B27	B in 5'MVIP for S:
	B in 3'MVIP for AS:

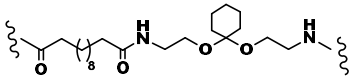
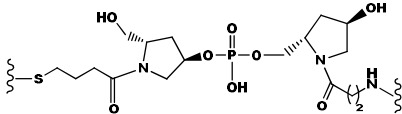
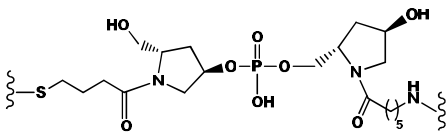
B code	B structure
B28	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B29	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B30	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B31	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B32	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 

B code	B structure
B33	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B34	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B35	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B36	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 
B37	B in 5'MVIP for S: 

B code	B structure
	B in 3'MVIP for AS: 
B38	B in 5'MVIP for S: 
	B in 3'MVIP for AS: 

When the MVIP structure and RNA inhibitor are the same, different linking chain D will have an impact on the activity of the RNA inhibitor. Among them, the effects of D1, D2, and D4 are similar and better than D3.

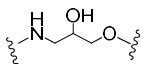
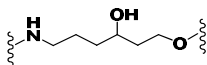
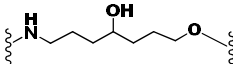
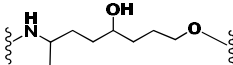
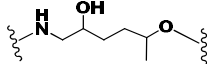
D code	D structure
D1	D in 5'MVIP for S: 
	D in 3'MVIP for AS: 
D2	D in 5'MVIP for S: 
	D in 3'MVIP for AS: 
D3	D in 5'MVIP for S: 
	D in 3'MVIP for AS: 
D4	D in 5'MVIP for S: 

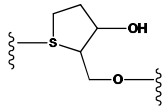
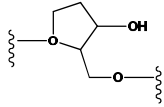
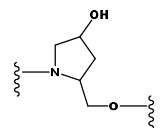
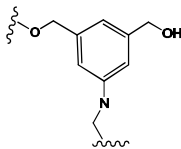
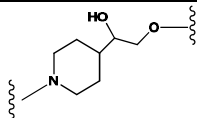
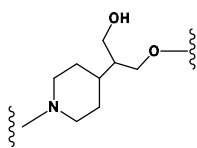
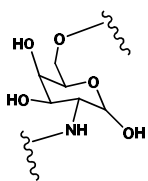
D code	D structure
	D in 3'MVIP for AS: 
D5	D in 5'MVIP for S: 
	D in 3'MVIP for AS: 

Different transition point R_1 will affect the activity of RNA inhibitor, among which the RNA inhibitor obtained by using R1-1 as the transition point has the best activity.

R_1 code	R_1 structure
R1-1	$-\text{NH}(\text{CH}_2)_6\text{O}-$
R1-2	$-\text{O}(\text{CH}_2)_6\text{O}-$
R1-3	$-\text{S}(\text{CH}_2)_6\text{O}-$
R1-4	$-\text{NH}(\text{CH}_2)_8\text{O}-$
R1-5	$-\text{NH}(\text{CH}_2)_5\text{CH}(\text{CH}_2\text{CH}_3)\text{O}-$
R1-6	$-\text{S}(\text{CH}_2)_4\text{CH}(\text{CH}_3)\text{O}-$

Different transition point R_2 will affect the activity of RNA inhibitor, among which the RNA inhibitor obtained by using R2-1 as the transition point has the best activity.

R_2 code	R_2 structure
R2-1	
R2-2	
R2-3	
R2-4	
R2-5	

R ₂ code	R ₂ structure
R2-6	
R2-7	
R2-8	
R2-9	
R2-10	
R2-11	
R2-12	

In some embodiments, the $n+m$ of the RNA inhibitor described in the present invention is 2, 3, 4, 5 and 6, respectively. The positions for 5'MVIP and/or 3'MVIP conjugating include 5' end and/or 3' end of the antisense strand, 5' end and/or 3' end of the sense strand, 5' end of the antisense strand and 3' end of the sense strand, and 5' end of the sense strand and 3' end of the antisense strand. The antisense strand and the sense strand are base-paired to anneal, where $n + m = 2, 3, 4, 5$ and 6, as shown in Table 20.

Table 20 Positions of 5'MVIP and 3'MVIP conjugated to sense strand and/or antisense strand

Carrier structure		Carrier structure		n+m	Position of carrier structure conjugated to sense strand and/or antisense strand (S:AS)
5'MVIP09	n=2	3'MVIP09	m=2	4	n:m
5'MVIP01	n=1	3' MVIP01	m=1	2	n:m
5'MVIP21	n=1	3' MVIP01	m=1	2	n:m
5'MVIP01	n=1	3' MVIP07	m=1	2	n:m
5'MVIP01/3'MVIP01	n=1/m=1	/	/	2	nm:/
3'MVIP01	m=1	5'MVIP01	n=1	2	m:n
3' MVIP07	m=1	5'MVIP21	n=1	2	m:n
5'MVIP01	n=1	3'MVIP09	m=2	3	n:m
5' MVIP08	n=1	3'MVIP15	m=2	3	n:m
5'MVIP09	n=2	3'MVIP01	m=1	3	n:m
5' MVIP19	n=2	3' MVIP07	m=1	3	n:m
5'MVIP01/3'MVIP09	n=1/m=2	/	/	3	nm:/
5'MVIP09/3'MVIP01	n=2/m=1	/	/	3	nm:/
3'MVIP09	m=2	5'MVIP01	n=1	3	m:n
3'MVIP11	m=2	5'MVIP06	n=1	3	m:n
3'MVIP01	m=1	5' MVIP20	n=2	3	m:n
3' MVIP07	m=1	5' MVIP19	n=2	3	m:n
5'MVIP01	n=1	3' MVIP17	m=3	4	n:m
5' MVIP21	n=1	3' MVIP17	m=3	4	n:m
5'MVIP17	n=3	3' MVIP01	m=1	4	n:m
5' MVIP22	n=3	3' MVIP07	m=1	4	n:m
5' MVIP20	n=2	3' MVIP10	m=2	4	n:m
5' MVIP19	n=2	3'MVIP15	m=2	4	n:m
5' MVIP10	n=2	3'MVIP12	m=2	4	n:m
5'MVIP09/3'MVIP09	n=2/m=2	/	/	4	nm:/

Carrier structure		Carrier structure		n+m	Position of carrier structure conjugated to sense strand and/or antisense strand (S:AS)
3'MVIP09	m=2	5' MVIP09	n=2	4	m:n
3'MVIP10	m=2	5' MVIP20	n=2	4	m:n
3'MVIP01	m=1	5' MVIP17	n=3	4	m:n
3'MVIP02	m=1	5' MVIP18	n=3	4	m:n
3'MVIP17	m=3	5' MVIP01	n=1	4	m:n
3'MVIP18	m=3	5' MVIP21	n=1	4	m:n
5'MVIP09	n=2	3' MVIP17	m=3	5	n:m
5'MVIP20	n=2	3' MVIP19	m=3	5	n:m
5'MVIP17	n=3	3'MVIP09	m=2	5	n:m
5'MVIP22	n=3	3'MVIP11	m=2	5	n:m
5'MVIP09/3'MVIP1 7	n=2/m=3	/	/	5	nm:/
5'MVIP17/3'MVIP0 9	n=3/m=2	/	/	5	nm:/
3'MVIP17	m=3	5' MVIP20	n=2	5	m:n
3'MVIP19	m=3	5' MVIP16	n=2	5	m:n
3'MVIP09	m=2	5' MVIP17	n=3	5	m:n
3' MVIP15	m=2	5' MVIP17	n=3	5	m:n
5'MVIP17	n=3	3' MVIP17	m=3	6	n:m
5' MVIP22	n=3	3' MVIP19	m=3	6	n:m
5'MVIP17/3'MVIP1 7	n=3/m=3	/		6	nm:/
3'MVIP17	m=3	5' MVIP17	n=3	6	m:n
3'MVIP18	m=3	5' MVIP22	n=3	6	m:n

In some embodiments, n and m are each independently any integer of 0-4, each independently preferably an integer of 1-3, and n+m= an integer of 2-6, preferably n+m=2, 3 or 4, more preferably 4.

In some embodiments, the sense strand and antisense strand conjugated to 5'MVIP and/or 3'MVIP are selected from the following Table 21.

Table 21 Sense strand and antisense strand conjugated to 5'MVIP and/or 3'MVIP

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12AS62	UsfGsAfGGfUCfUCAGGCfAGfCCfACsfGsG-3'MVIP09
Ky-12AS63	UsfGsAfGGfUCfUCAGGCfAGfCCfACsfGsG-3'MVIP01
Ky-12AS64	UsfGsAfGGfUCfUCAGGCfAGfCCfACsfGsG-3'MVIP17
Ky-12AS65	UsfGsGfAUfAGfGCAGGUfGGfACfUUsfGsG-3'MVIP09
Ky-12AS66	UsfGsGfAUfAGfGCAGGUfGGfACfUUsfGsG-3'MVIP01
Ky-12AS67	UsfGsGfAUfAGfGCAGGUfGGfACfUUsfGsG-3'MVIP17
Ky-12AS68	CsfAsGfGAfUGfGAUAGGfCAfGGfUGsfGsA-3'MVIP09
Ky-12AS69	CsfAsGfGAfUGfGAUAGGfCAfGGfUGsfGsA-3'MVIP01
Ky-12AS70	CsfAsGfGAfUGfGAUAGGfCAfGGfUGsfGsA-3'MVIP17
Ky-12AS71	GsfCsAfCUfGAfGAAUACfUGfUCfCCsfUsU-3'MVIP09
Ky-12AS72	GsfCsAfCUfGAfGAAUACfUGfUCfCCsfUsU-3'MVIP01
Ky-12AS73	GsfCsAfCUfGAfGAAUACfUGfUCfCCsfUsU-3'MVIP17
Ky-12AS74	GsfAsGfCAfCUfGAGAAUfACfUGfUCsfCsC-3'MVIP09
Ky-12AS75	GsfAsGfCAfCUfGAGAAUfACfUGfUCsfCsC-3'MVIP01
Ky-12AS76	GsfAsGfCAfCUfGAGAAUfACfUGfUCsfCsC-3'MVIP17
Ky-12AS77	UsfGsAfGGfUCfUCfAGGCfAGfCCfACsGsG-3'MVIP09
Ky-12AS78	UsfGsAfGGfUCfUCfAGGCfAGfCCfACsGsG-3'MVIP01
Ky-12AS79	UsfGsAfGGfUCfUCfAGGCfAGfCCfACsGsG-3'MVIP17
Ky-12AS80	UsfGsGfAUfAGfGCfAGGUfGGfACfUUsGsG-3'MVIP09
Ky-12AS81	UsfGsGfAUfAGfGCfAGGUfGGfACfUUsGsG-3'MVIP01
Ky-12AS82	UsfGsGfAUfAGfGCfAGGUfGGfACfUUsGsG-3'MVIP17
Ky-12AS83	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGsGsA-3'MVIP09
Ky-12AS84	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGsGsA-3'MVIP01
Ky-12AS85	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGsGsA-3'MVIP17
Ky-12AS86	GsfCsAfCUfGAfGAfAUACfUGfUCfCCsUsU-3'MVIP09

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12AS87	GsfCsAfCUfGAfGAfAUACfUGfUCfCCsUsU-3'MVIP01
Ky-12AS88	GsfCsAfCUfGAfGAfAUACfUGfUCfCCsUsU-3'MVIP17
Ky-12AS89	GsfAsGfCAfCUfGAfGAAUfACfUGfUCsCsC-3'MVIP09
Ky-12AS90	GsfAsGfCAfCUfGAfGAAUfACfUGfUCsCsC-3'MVIP01
Ky-12AS91	GsfAsGfCAfCUfGAfGAAUfACfUGfUCsCsC-3'MVIP17
Ky-12AS01	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP09
Ky-12AS03	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP01
Ky-12AS04	AsfCsAfCUfGAfGAAUACfUGfUCfGCsfUsC-3'MVIP17
Ky-12AS92	AsfCsAfCUfGAfGAfAUACfUGfUCfGCsUsC-3'MVIP09
Ky-12AS93	AsfCsAfCUfGAfGAfAUACfUGfUCfGCsUsC-3'MVIP01
Ky-12AS94	AsfCsAfCUfGAfGAfAUACfUGfUCfGCsUsC-3'MVIP17
Ky-12AS95	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCsUsU- 3'MVIP09
Ky-12AS96	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCsUsU- 3'MVIP01
Ky-12AS97	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCsUsU- 3'MVIP17
Ky-12AS98	UsfGsAfGGfUCfUCAGGCfAGfCCfACfGG-3'MVIP09
Ky-12AS99	UsfGsGfAUfAGfGCAGGUfGGfACfUUfGG-3'MVIP09
Ky-12AS100	CsfAsGfGAfUGfGAUAGGfCAfGGfUGfGA-3'MVIP09
Ky-12AS101	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUU-3'MVIP09
Ky-12AS102	GsfAsGfCAfCUfGAGAAUfACfUGfUCfCC-3'MVIP09
Ky-12AS103	UsfGsAfGGfUCfUCfAGGCfAGfCCfACGG-3'MVIP09
Ky-12AS104	UsfGsGfAUfAGfGCfAGGUfGGfACfUUGG-3'MVIP09
Ky-12AS105	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGGA-3'MVIP09
Ky-12AS106	GsfCsAfCUfGAfGAfAUACfUGfUCfCCUU-3'MVIP09

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12AS107	GsfAsGfCAfCUfGAfGAAUfACfUGfUCCC-3'MVIP09
Ky-12AS108	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUC-3'MVIP09
Ky-12AS109	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUC-3'MVIP17
Ky-12AS110	AsfCsAfCUfGAfGAfAUACfUGfUCfGCUC-3'MVIP09
Ky-12AS111	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCUU- 3'MVIP09
Ky-12AS112	UsfGsAfGGfUCfUCAGGCfAGfCCfACfGsG-3'MVIP09
Ky-12AS113	UsfGsGfAUfAGfGCAGGUfGGfACfUfGsG-3'MVIP09
Ky-12AS114	CsfAsGfGAfUGfGAUAGGfCAfGGfUGfGsA-3'MVIP09
Ky-12AS115	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUsU-3'MVIP09
Ky-12AS116	GsfAsGfCAfCUfGAGAAUfACfUGfUCfCsC-3'MVIP09
Ky-12AS117	UsfGsAfGGfUCfUCfAGGCfAGfCCfACGsG-3'MVIP09
Ky-12AS118	UsfGsGfAUfAGfGCfAGGUfGGfACfUUGsG-3'MVIP09
Ky-12AS119	CsfAsGfGAfUGfGAfUAGGfCAfGGfUGGsA-3'MVIP09
Ky-12AS120	GsfCsAfCUfGAfGAfAUACfUGfUCfCCUsU-3'MVIP09
Ky-12AS121	GsfAsGfCAfCUfGAfGAAUfACfUGfUCCsC-3'MVIP09
Ky-12AS122	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUsC-3'MVIP09
Ky-12AS123	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUsC-3'MVIP17
Ky-12AS124	AsfCsAfCUfGAfGAfAUACfUGfUCfGCUsc-3'MVIP09
Ky-12AS125	AsfCsAfCUfGAfGAAUACfUGfUCfGCfUCUsU- 3'MVIP09
Ky-12AS128	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUUsUsU- 3'MVIP09
Ky-12AS129	GsfCsAfCUfGAfGAAUACfUGfUCfCCfUUsUsU- 3'MVIP17
Ky-12S60	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUCAsAsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S61	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUCAsAsU
Ky-12S62	5'MVIP17-GsUsGGCUGCfCfUfGAGACCUCAsAsU
Ky-12S63	GsUsGGCUGCfCfUfGAGACCUCAsAsU-3'MVIP17
Ky-12S64	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUCAsAsU- 3'MVIP09
Ky-12S65	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUCAsAsU- 3'MVIP01
Ky-12S66	5'MVIP09-AsAsGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S67	5'MVIP01-AsAsGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S68	5'MVIP17-AsAsGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S69	AsAsGUCCACfCfUfGCCUAUCCAsUsC-3'MVIP17
Ky-12S70	5'MVIP01-AsAsGUCCACfCfUfGCCUAUCCAsUsC- 3'MVIP09
Ky-12S71	5'MVIP09-AsAsGUCCACfCfUfGCCUAUCCAsUsC- 3'MVIP01
Ky-12S72	5'MVIP09-CsAsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S73	5'MVIP01-CsAsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S74	5'MVIP17-CsAsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S75	CsAsCCUGCCfUfAfUCCAUCCUGsAsA-3'MVIP17
Ky-12S76	5'MVIP01-CsAsCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S77	5'MVIP09-CsAsCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S78	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUGCsUsU
Ky-12S79	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUGCsUsU
Ky-12S80	5'MVIP17-GsGsGACAGUfAfUfUCUCAGUGCsUsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S81	GsGsGACAGUfAfUfUCUCAGUGCsUsU-3'MVIP17
Ky-12S82	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUGCsUsU- 3'MVIP09
Ky-12S83	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUGCsUsU- 3'MVIP01
Ky-12S84	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S85	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S86	5'MVIP17-GsAsCAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S87	GsAsCAGUAUfUfCfUCAGUGCUCsUsU-3'MVIP17
Ky-12S88	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCUCsUsU- 3'MVIP09
Ky-12S89	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCUCsUsU- 3'MVIP01
Ky-12S90	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCUCsUsU- 3'MVIP01
Ky-12S91	5'MVIP09-GsUsGGCUfGCfCfUfGAGACCUCAsAsU
Ky-12S92	5'MVIP01-GsUsGGCUfGCfCfUfGAGACCUCAsAsU
Ky-12S93	5'MVIP17-GsUsGGCUfGCfCfUfGAGACCUCAsAsU
Ky-12S94	GsUsGGCUfGCfCfUfGAGACCUCAsAsU-3'MVIP17
Ky-12S95	5'MVIP01-GsUsGGCUfGCfCfUfGAGACCUCAsAsU- 3'MVIP09
Ky-12S96	5'MVIP09-GsUsGGCUfGCfCfUfGAGACCUCAsAsU- 3'MVIP01
Ky-12S97	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCCAsUsC
Ky-12S98	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCCAsUsC
Ky-12S99	5'MVIP17-AsAsGUCCfACfCfUfGCCUAUCCAsUsC

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S100	AsAsGUCCfACfCfUfGCCUAUCCAsUsC-3'MVIP17
Ky-12S101	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCCAsUsC- 3'MVIP09
Ky-12S102	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCCAsUsC- 3'MVIP01
Ky-12S103	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCCAsUsC- 3'MVIP01
Ky-12S104	5'MVIP09-CsAsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S105	5'MVIP01-CsAsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S106	5'MVIP17-CsAsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S107	CsAsCCUGfCCfUfAfUCCAUCCUGsAsA-3'MVIP17
Ky-12S108	5'MVIP01-CsAsCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S109	5'MVIP09-CsAsCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S110	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUGCsUsU
Ky-12S111	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUGCsUsU
Ky-12S112	5'MVIP17-GsGsGACAfGUfAfUfUCUCAGUGCsUsU
Ky-12S113	GsGsGACAfGUfAfUfUCUCAGUGCsUsU-3'MVIP17
Ky-12S114	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUGCsUsU- 3'MVIP09
Ky-12S115	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUGCsUsU- 3'MVIP01
Ky-12S116	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCUCsUsU
Ky-12S117	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCUCsUsU
Ky-12S118	5'MVIP17-GsAsCAGUfAUfUfCfUCAGUGCUCsUsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S119	GsAsCAGUfAUfUfCfUCAGUGCUCsUsU-3'MVIP17
Ky-12S120	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCUCsUsU- 3'MVIP09
Ky-12S121	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCUCsUsU- 3'MVIP01
Ky-12S01	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S06	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S05	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S01	GsAsGCGACAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S12	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP09
Ky-12S13	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S07	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S122	5'MVIP09-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU
Ky-12S123	5'MVIP01-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU
Ky-12S124	5'MVIP17-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU
Ky-12S125	GsAsGCGAfCAfGfUfAUUCUCAGUsGsU-3'MVIP17
Ky-12S126	5'MVIP01-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU- 3'MVIP09
Ky-12S127	5'MVIP09-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S128	5'MVIP01-GsAsGCGAfCAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S129	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAsGsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S130	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAsGsU
Ky-12S131	5'MVIP17-GsAsGCGACAfGfUfAUUCUCAsGsU
Ky-12S132	GsAsGCGACAfGfUfAUUCUCAsGsU-3'MVIP17
Ky-12S133	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAsGsU- 3'MVIP09
Ky-12S134	5'MVIP09-GsAsGCGACAfGfUfAUUCUCAsGsU- 3'MVIP01
Ky-12S135	5'MVIP01-GsAsGCGACAfGfUfAUUCUCAsGsU- 3'MVIP01
Ky-12S136	5'MVIP09-GsUGGCUGCfCfUfGAGACCUCAsAsU
Ky-12S137	5'MVIP01-GsUGGCUGCfCfUfGAGACCUCAsAsU
Ky-12S138	5'MVIP17-GsUGGCUGCfCfUfGAGACCUCAsAsU
Ky-12S139	GsUsGGCUGCfCfUfGAGACCUCAsAsU-3'MVIP17
Ky-12S140	5'MVIP01-GsUGGCUGCfCfUfGAGACCUCAsAsU- 3'MVIP09
Ky-12S141	5'MVIP09-GsUGGCUGCfCfUfGAGACCUCAsAsU- 3'MVIP01
Ky-12S142	5'MVIP09-AsAGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S143	5'MVIP01-AsAGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S144	5'MVIP17-AsAGUCCACfCfUfGCCUAUCCAsUsC
Ky-12S145	AsAsGUCCACfCfUfGCCUAUCCAsUsC-3'MVIP17
Ky-12S146	5'MVIP01-AsAGUCCACfCfUfGCCUAUCCAsUsC- 3'MVIP09
Ky-12S147	5'MVIP09-AsAGUCCACfCfUfGCCUAUCCAsUsC- 3'MVIP01
Ky-12S148	5'MVIP09-CsACCUGCCfUfAfUCCAUCCUGsAsA

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S149	5'MVIP01-CsACCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S150	5'MVIP17-CsACCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S151	CsAsCCUGCCfUfAfUCCAUCCUGAsA-3'MVIP17
Ky-12S152	5'MVIP01-CsACCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S153	5'MVIP09-CsACCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S154	5'MVIP09-GsGGACAGUfAfUfUCUCAGUGCsUsU
Ky-12S155	5'MVIP01-GsGGACAGUfAfUfUCUCAGUGCsUsU
Ky-12S156	5'MVIP17-GsGGACAGUfAfUfUCUCAGUGCsUsU
Ky-12S157	GsGsGACAGUfAfUfUCUCAGUGCsUsU-3'MVIP17
Ky-12S158	5'MVIP01-GsGGACAGUfAfUfUCUCAGUGCsUsU- 3'MVIP09
Ky-12S159	5'MVIP09-GsGGACAGUfAfUfUCUCAGUGCsUsU- 3'MVIP01
Ky-12S160	5'MVIP09-GsACAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S161	5'MVIP01-GsACAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S162	5'MVIP17-GsACAGUAUfUfCfUCAGUGCUCsUsU
Ky-12S163	GsAsCAGUAUfUfCfUCAGUGCUCUsU-3'MVIP17
Ky-12S164	5'MVIP01-GsACAGUAUfUfCfUCAGUGCUCsUsU- 3'MVIP09
Ky-12S165	5'MVIP09-GsACAGUAUfUfCfUCAGUGCUCsUsU- 3'MVIP01
Ky-12S166	5'MVIP09-GsUGGCUfGCfCfUfGAGACCUCAsAsU
Ky-12S167	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAsUsC
Ky-12S168	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAsUsC

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S169	5'MVIP17-AsAGUCCfACfCfUfGCCUAUCCAsUsC
Ky-12S170	AsAsGUCCfACfCfUfGCCUAUCCAUsc-3'MVIP17
Ky-12S171	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAsUsC- 3'MVIP09
Ky-12S172	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAsUsC- 3'MVIP01
Ky-12S173	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAUscsU- 3'MVIP01
Ky-12S174	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAUscsU
Ky-12S175	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAUscsU
Ky-12S176	5'MVIP17-AsAGUCCfACfCfUfGCCUAUCCAUscsU
Ky-12S177	AsAsGUCCfACfCfUfGCCUAUCCAUcsU-3'MVIP17
Ky-12S178	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAUscsU- 3'MVIP09
Ky-12S179	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAUscsU- 3'MVIP01
Ky-12S180	5'MVIP09-CsACCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S181	5'MVIP01-CsACCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S182	5'MVIP17-CsACCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S183	CsAsCCUGfCCfUfAfUCCAUCCUGAsA-3'MVIP17
Ky-12S184	5'MVIP01-CsACCUGfCCfUfAfUCCAUCCUGAsA- 3'MVIP09
Ky-12S185	5'MVIP09-CsACCUGfCCfUfAfUCCAUCCUGAsA- 3'MVIP01
Ky-12S186	5'MVIP09-GsGGACAfGUfAfUfUCUCAGUGCsUsU
Ky-12S187	5'MVIP01-GsGGACAfGUfAfUfUCUCAGUGCsUsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S188	5'MVIP17-GsGGACAfGUfAfUfUCUCAGUGCsUsU
Ky-12S189	GGGACAfGUfAfUfUCUCAGUGCsUsU-3'MVIP17
Ky-12S190	5'MVIP01-GsGGACAfGUfAfUfUCUCAGUGCsUsU- 3'MVIP09
Ky-12S191	5'MVIP09-GsGGACAfGUfAfUfUCUCAGUGCsUsU- 3'MVIP01
Ky-12S192	5'MVIP09-GsACAGUfAUfUfCfUCAGUGCUCsUsU
Ky-12S193	5'MVIP01-GsACAGUfAUfUfCfUCAGUGCUCsUsU
Ky-12S194	5'MVIP17-GsACAGUfAUfUfCfUCAGUGCUCsUsU
Ky-12S195	GsAsCAGUfAUfUfCfUCAGUGCUCsUsU-3'MVIP17
Ky-12S196	5'MVIP01-GsACAGUfAUfUfCfUCAGUGCUCsUsU- 3'MVIP09
Ky-12S197	5'MVIP09-GsACAGUfAUfUfCfUCAGUGCUCsUsU- 3'MVIP01
Ky-12S198	5'MVIP09-GsAGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S199	5'MVIP01-GsAGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S200	5'MVIP17-GsAGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S201	GsAsGCGACAfGfUfAUUCUCAGUGsU-3'MVIP17
Ky-12S202	5'MVIP01-GsAGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP09
Ky-12S203	5'MVIP09-GsAGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S204	5'MVIP01-GsAGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S205	5'MVIP09-GsAGCGAfCAfGfUfAUUCUCAGUsGsU
Ky-12S206	5'MVIP01-GsAGCGAfCAfGfUfAUUCUCAGUsGsU

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S207	5'MVIP17-GsAGCGAfCAfGfUfAUUCUCAGUsGsU
Ky-12S208	GsAsGCGAfCAfGfUfAUUCUCAGUGsU-3'MVIP17
Ky-12S209	5'MVIP01-GsAGCGAfCAfGfUfAUUCUCAGUsGsU- 3'MVIP09
Ky-12S210	5'MVIP09-GsAGCGAfCAfGfUfAUUCUCAGUsGsU- 3'MVIP01
Ky-12S211	5'MVIP09-GsAGCGACAfGfUfAUUCUCAsGsU
Ky-12S212	5'MVIP01-GsAGCGACAfGfUfAUUCUCAsGsU
Ky-12S213	5'MVIP17-GsAGCGACAfGfUfAUUCUCAsGsU
Ky-12S214	GsAsGCGACAfGfUfAUUCUCAGsU-3'MVIP17
Ky-12S215	5'MVIP01-GsAGCGACAfGfUfAUUCUCAsGsU- 3'MVIP09
Ky-12S216	5'MVIP09-GsAGCGACAfGfUfAUUCUCAsGsU- 3'MVIP01
Ky-12S217	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S218	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S219	5'MVIP17-GsUsGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S220	GsUsGGCUGCfCfUfGAGACCUCAsAsA-3'MVIP17
Ky-12S221	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUCAsAsA- 3'MVIP09
Ky-12S222	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUCAsAsA- 3'MVIP01
Ky-12S223	5'MVIP09-AsAsGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S224	5'MVIP01-AsAsGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S225	5'MVIP17-AsAsGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S226	AsAsGUCCACfCfUfGCCUAUCCAsUsA-3'MVIP17

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S227	5'MVIP01-AsAsGUCCACfCfUfGCCUAUCCAsUsA- 3'MVIP09
Ky-12S228	5'MVIP09-AsAsGUCCACfCfUfGCCUAUCCAsUsA- 3'MVIP01
Ky-12S229	5'MVIP09-CsGsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S230	5'MVIP01-CsGsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S231	5'MVIP17-CsGsCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S232	CsGsCCUGCCfUfAfUCCAUCCUGsAsA-3'MVIP17
Ky-12S233	5'MVIP01-CsGsCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S234	5'MVIP09-CsGsCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S235	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S236	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S237	5'MVIP17-GsGsGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S238	GsGsGACAGUfAfUfUCUCAGUGCsUsA-3'MVIP17
Ky-12S239	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUGCsUsA- 3'MVIP09
Ky-12S240	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUGCsUsA- 3'MVIP01
Ky-12S241	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S242	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S243	5'MVIP17-GsAsCAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S244	GsAsCAGUAUfUfCfUCAGUGCUCsUsA-3'MVIP17
Ky-12S245	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCUCsUsA- 3'MVIP09

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S246	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCUCsUsA- 3'MVIP01
Ky-12S247	5'MVIP09-GsUsGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S248	5'MVIP01-GsUsGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S249	5'MVIP17-GsUsGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S250	GsUsGGCUfGCfCfUfGAGACCUCAsAsA-3'MVIP17
Ky-12S251	5'MVIP01-GsUsGGCUfGCfCfUfGAGACCUCAsAsA- 3'MVIP09
Ky-12S252	5'MVIP09-GsUsGGCUfGCfCfUfGAGACCUCAsAsA- 3'MVIP01
Ky-12S253	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S254	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S255	5'MVIP17-AsAsGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S256	AsAsGUCCfACfCfUfGCCUAUCCAsUsA-3'MVIP17
Ky-12S257	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCCAsUsA- 3'MVIP09
Ky-12S258	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCCAsUsA- 3'MVIP01
Ky-12S259	5'MVIP09-CsGsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S260	5'MVIP01-CsGsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S261	5'MVIP17-CsGsCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S262	CsGsCCUGfCCfUfAfUCCAUCCUGsAsA-3'MVIP17
Ky-12S263	5'MVIP01-CsGsCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S264	5'MVIP09-CsGsCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP01

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S265	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S266	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S267	5'MVIP17-GsGsGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S268	GsGsGACAfGUfAfUfUCUCAGUGCsUsA-3'MVIP17
Ky-12S269	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUGCsUsA- 3'MVIP09
Ky-12S270	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUGCsUsA- 3'MVIP01
Ky-12S271	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S272	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S273	5'MVIP17-GsAsCAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S274	GsAsCAGUfAUfUfCfUCAGUGCUCsUsA-3'MVIP17
Ky-12S275	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCUCsUsA- 3'MVIP09
Ky-12S276	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCUCsUsA- 3'MVIP01
Ky-12S277	5'MVIP09-AsAsGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S278	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S279	5'MVIP17-AsAsGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S280	AsAsGCGACAfGfUfAUUCUCAGUsGsA-3'MVIP17
Ky-12S281	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAGUsGsA- 3'MVIP09
Ky-12S282	5'MVIP09-AsAsGCGACAfGfUfAUUCUCAGUsGsA- 3'MVIP01
Ky-12S283	5'MVIP09-AsAsGCGAfCAfGfUfAUUCUCAGUsGsA
Ky-12S284	5'MVIP01-AsAsGCGAfCAfGfUfAUUCUCAGUsGsA

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S285	5'MVIP17-AsAsGCGAfCAfGfUfAUUCUCAGUsGsA
Ky-12S286	AsAsGCGAfCAfGfUfAUUCUCAGUsGsA-3'MVIP17
Ky-12S287	5'MVIP01-AsAsGCGAfCAfGfUfAUUCUCAGUsGsA- 3'MVIP09
Ky-12S288	5'MVIP09-AsAsGCGAfCAfGfUfAUUCUCAGUsGsA- 3'MVIP01
Ky-12S289	5'MVIP09-AsAsGCGACAfGfUfAUUCUCAsGsA
Ky-12S290	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAsGsA
Ky-12S291	5'MVIP17-AsAsGCGACAfGfUfAUUCUCAsGsA
Ky-12S292	AsAsGCGACAfGfUfAUUCUCAsGsA-3'MVIP17
Ky-12S293	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAsGsA- 3'MVIP09
Ky-12S294	5'MVIP09-AsAsGCGACAfGfUfAUUCUCAsGsA- 3'MVIP01
Ky-12S295	5'MVIP09-GsUGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S296	5'MVIP01-GsUGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S297	5'MVIP17-GsUGGCUGCfCfUfGAGACCUCAsAsA
Ky-12S298	GsUsGGCUGCfCfUfGAGACCUCAsAsA-3'MVIP17
Ky-12S299	5'MVIP01-GsUGGCUGCfCfUfGAGACCUCAsAsA- 3'MVIP09
Ky-12S300	5'MVIP09-GsUGGCUGCfCfUfGAGACCUCAsAsA- 3'MVIP01
Ky-12S301	5'MVIP09-AsAGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S302	5'MVIP01-AsAGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S303	5'MVIP17-AsAGUCCACfCfUfGCCUAUCCAsUsA
Ky-12S304	AsAsGUCCACfCfUfGCCUAUCCAsUsA-3'MVIP17

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S305	5'MVIP01-AsAGUCCACfCfUfGCCUAUCCAsUsA- 3'MVIP09
Ky-12S306	5'MVIP09-AsAGUCCACfCfUfGCCUAUCCAsUsA- 3'MVIP01
Ky-12S307	5'MVIP09-CsGCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S308	5'MVIP01-CsGCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S309	5'MVIP17-CGCCUGCCfUfAfUCCAUCCUGsAsA
Ky-12S310	CsGsCCUGCCfUfAfUCCAUCCUGAsA-3'MVIP17
Ky-12S311	5'MVIP01-CsGCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP09
Ky-12S312	5'MVIP09-CsGCCUGCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S313	5'MVIP09-GsGGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S314	5'MVIP01-GsGGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S315	5'MVIP17-GsGGACAGUfAfUfUCUCAGUGCsUsA
Ky-12S316	GsGsGACAGUfAfUfUCUCAGUGCUsA-3'MVIP17
Ky-12S317	5'MVIP01-GsGGACAGUfAfUfUCUCAGUGCsUsA- 3'MVIP09
Ky-12S318	5'MVIP09-GsGGACAGUfAfUfUCUCAGUGCsUsA- 3'MVIP01
Ky-12S319	5'MVIP01-GsGGACAGUfAfUfUCUCAGUGCsUsA- 3'MVIP01
Ky-12S320	5'MVIP09-GsACAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S321	5'MVIP01-GsACAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S322	5'MVIP17-GsACAGUAUfUfCfUCAGUGCUCsUsA
Ky-12S323	GsAsCAGUAUfUfCfUCAGUGCUCUsA-3'MVIP17

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S324	5'MVIP01-GsACAGUAUfUfCfUCAGUGCUCsUsA- 3'MVIP09
Ky-12S325	5'MVIP09-GsACAGUAUfUfCfUCAGUGCUCsUsA- 3'MVIP01
Ky-12S326	5'MVIP09-GsUGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S327	5'MVIP01-GsUGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S328	5'MVIP17-GsUGGCUfGCfCfUfGAGACCUCAsAsA
Ky-12S329	GsUsGGCUfGCfCfUfGAGACCUCAsAsA-3'MVIP17
Ky-12S330	5'MVIP01-GsUGGCUfGCfCfUfGAGACCUCAsAsA- 3'MVIP09
Ky-12S331	5'MVIP09-GsUGGCUfGCfCfUfGAGACCUCAsAsA- 3'MVIP01
Ky-12S332	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S333	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S334	5'MVIP17-AsAGUCCfACfCfUfGCCUAUCCAsUsA
Ky-12S335	AsAsGUCCfACfCfUfGCCUAUCCAsUsA-3'MVIP17
Ky-12S336	5'MVIP01-AsAGUCCfACfCfUfGCCUAUCCAsUsA- 3'MVIP09
Ky-12S337	5'MVIP09-AsAGUCCfACfCfUfGCCUAUCCAsUsA- 3'MVIP01
Ky-12S338	5'MVIP09-CsGCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S339	5'MVIP01-CsGCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S340	5'MVIP17-CsGCCUGfCCfUfAfUCCAUCCUGsAsA
Ky-12S341	CsGsCCUGfCCfUfAfUCCAUCCUGAsA-3'MVIP17
Ky-12S342	5'MVIP01-CsGCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP09

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S343	5'MVIP09-CsGCCUGfCCfUfAfUCCAUCCUGsAsA- 3'MVIP01
Ky-12S344	5'MVIP09-GsGGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S345	5'MVIP01-GsGGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S346	5'MVIP17-GsGGACAfGUfAfUfUCUCAGUGCsUsA
Ky-12S347	GsGsGACAfGUfAfUfUCUCAGUGCUsA-3'MVIP17
Ky-12S348	5'MVIP01-GsGGACAfGUfAfUfUCUCAGUGCsUsA- 3'MVIP09
Ky-12S349	5'MVIP09-GsGGACAfGUfAfUfUCUCAGUGCsUsA- 3'MVIP01
Ky-12S350	5'MVIP09-GsACAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S351	5'MVIP01-GsACAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S352	5'MVIP17-GsACAGUfAUfUfCfUCAGUGCUCsUsA
Ky-12S353	GsAsCAGUfAUfUfCfUCAGUGCUCUsA-3'MVIP17
Ky-12S354	5'MVIP01-GsACAGUfAUfUfCfUCAGUGCUCsUsA- 3'MVIP09
Ky-12S355	5'MVIP09-GsACAGUfAUfUfCfUCAGUGCUCsUsA- 3'MVIP01
Ky-12S356	5'MVIP09-AsAGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S357	5'MVIP01-AsAGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S358	5'MVIP17-AsAGCGACAfGfUfAUUCUCAGUsGsA
Ky-12S359	AsAsGCGACAfGfUfAUUCUCAGUGsA-3'MVIP17
Ky-12S360	5'MVIP01-AsAGCGACAfGfUfAUUCUCAGUsGsA- 3'MVIP09
Ky-12S361	5'MVIP09-AsAGCGACAfGfUfAUUCUCAGUsGsA- 3'MVIP01

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S362	5'MVIP09-AsAGCGAfCAfGfUfAUUCUCAGUsGsA
Ky-12S363	5'MVIP01-AsAGCGAfCAfGfUfAUUCUCAGUsGsA
Ky-12S364	5'MVIP17-AsAGCGAfCAfGfUfAUUCUCAGUsGsA
Ky-12S365	AsAsGCGAfCAfGfUfAUUCUCAGUGsA-3'MVIP17
Ky-12S366	5'MVIP01-AsAGCGAfCAfGfUfAUUCUCAGUsGsA- 3'MVIP09
Ky-12S367	5'MVIP09-AsAGCGAfCAfGfUfAUUCUCAGUsGsA- 3'MVIP01
Ky-12S368	5'MVIP09-AsAGCGACAfGfUfAUUCUCAsGsA
Ky-12S369	5'MVIP01-AsAGCGACAfGfUfAUUCUCAsGsA
Ky-12S370	5'MVIP17-AsAGCGACAfGfUfAUUCUCAsGsA
Ky-12S371	AsAsGCGACAfGfUfAUUCUCAGsA-3'MVIP17
Ky-12S372	5'MVIP01-AsAGCGACAfGfUfAUUCUCAsGsA- 3'MVIP09
Ky-12S373	5'MVIP09-AsAGCGACAfGfUfAUUCUCAsGsA- 3'MVIP01
Ky-12S374	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUsCsA
Ky-12S375	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUsCsA
Ky-12S376	5'MVIP17-GsUsGGCUGCfCfUfGAGACCUsCsA
Ky-12S377	GsUsGGCUGCfCfUfGAGACCUsCsA-3'MVIP17
Ky-12S378	5'MVIP01-GsUsGGCUGCfCfUfGAGACCUsCsA- 3'MVIP09
Ky-12S379	5'MVIP09-GsUsGGCUGCfCfUfGAGACCUsCsA- 3'MVIP01
Ky-12S380	5'MVIP09-GsAsGUCCACfCfUfGCCUAUCsCsA
Ky-12S381	5'MVIP01-GsAsGUCCACfCfUfGCCUAUCsCsA

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S382	5'MVIP17-GsAsGUCCACfCfUfGCCUAUCsCsA
Ky-12S383	GsAsGUCCACfCfUfGCCUAUCsCsA-3'MVIP17
Ky-12S384	5'MVIP01-GsAsGUCCACfCfUfGCCUAUCsCsA- 3'MVIP09
Ky-12S385	5'MVIP09-GsAsGUCCACfCfUfGCCUAUCsCsA- 3'MVIP01
Ky-12S386	5'MVIP09-CsAsCCUGCCfUfAfUCCAUCCsUsA
Ky-12S387	5'MVIP01-CsAsCCUGCCfUfAfUCCAUCCsUsA
Ky-12S388	5'MVIP17-CsAsCCUGCCfUfAfUCCAUCCsUsA
Ky-12S389	CsAsCCUGCCfUfAfUCCAUCCsUsA-3'MVIP17
Ky-12S390	5'MVIP01-CsAsCCUGCCfUfAfUCCAUCCsUsA- 3'MVIP09
Ky-12S391	5'MVIP09-CsAsCCUGCCfUfAfUCCAUCCsUsA- 3'MVIP01
Ky-12S392	5'MVIP01-CsAsCCUGCCfUfAfUCCAUCCsUsA- 3'MVIP01
Ky-12S393	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUsGsA
Ky-12S394	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUsGsA
Ky-12S395	5'MVIP17-GsGsGACAGUfAfUfUCUCAGUsGsA
Ky-12S396	GsGsGACAGUfAfUfUCUCAGUsGsA-3'MVIP17
Ky-12S397	5'MVIP01-GsGsGACAGUfAfUfUCUCAGUsGsA- 3'MVIP09
Ky-12S398	5'MVIP09-GsGsGACAGUfAfUfUCUCAGUsGsA- 3'MVIP01
Ky-12S399	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCsUsA
Ky-12S400	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCsUsA

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S401	5'MVIP17-GsAsCAGUAUfUfCfUCAGUGCsUsA
Ky-12S402	GsAsCAGUAUfUfCfUCAGUGCsUsA-3'MVIP17
Ky-12S403	5'MVIP01-GsAsCAGUAUfUfCfUCAGUGCsUsA- 3'MVIP09
Ky-12S404	5'MVIP09-GsAsCAGUAUfUfCfUCAGUGCsUsA- 3'MVIP01
Ky-12S405	5'MVIP09-GsTsGGCUfGCfCfUfGAGACCUcCsA
Ky-12S406	5'MVIP01-GsTsGGCUfGCfCfUfGAGACCUcCsA
Ky-12S407	5'MVIP17-GsTsGGCUfGCfCfUfGAGACCUcCsA
Ky-12S408	GsTsGGCUfGCfCfUfGAGACCUcCsA-3'MVIP17
Ky-12S409	5'MVIP01-GsTsGGCUfGCfCfUfGAGACCUcCsA- 3'MVIP09
Ky-12S410	5'MVIP09-GsTsGGCUfGCfCfUfGAGACCUcCsA- 3'MVIP01
Ky-12S411	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCsCsA
Ky-12S412	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCsCsA
Ky-12S413	5'MVIP17-AsAsGUCCfACfCfUfGCCUAUCsCsA
Ky-12S414	AsAsGUCCfACfCfUfGCCUAUCsCsA-3'MVIP17
Ky-12S415	5'MVIP01-AsAsGUCCfACfCfUfGCCUAUCsCsA- 3'MVIP09
Ky-12S416	5'MVIP09-AsAsGUCCfACfCfUfGCCUAUCsCsA- 3'MVIP01
Ky-12S417	5'MVIP09-CsAsCCUGfCCfUfAfUCCAUCCsUsA
Ky-12S418	5'MVIP01-CsAsCCUGfCCfUfAfUCCAUCCsUsA
Ky-12S419	5'MVIP17-CsAsCCUGfCCfUfAfUCCAUCCsUsA
Ky-12S420	CsAsCCUGfCCfUfAfUCCAUCCsUsA-3'MVIP17

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S421	5'MVIP01-CsAsCCUGfCCfUfAfUCCAUCCsUsA- 3'MVIP09
Ky-12S422	5'MVIP09-CsAsCCUGfCCfUfAfUCCAUCCsUsA- 3'MVIP01
Ky-12S423	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUsGsA
Ky-12S424	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUsGsA
Ky-12S425	5'MVIP17-GsGsGACAfGUfAfUfUCUCAGUsGsA
Ky-12S426	GsGsGACAfGUfAfUfUCUCAGUsGsA-3'MVIP17
Ky-12S427	5'MVIP01-GsGsGACAfGUfAfUfUCUCAGUsGsA- 3'MVIP09
Ky-12S428	5'MVIP09-GsGsGACAfGUfAfUfUCUCAGUsGsA- 3'MVIP01
Ky-12S429	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCsUsA
Ky-12S430	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCsUsA
Ky-12S431	5'MVIP17-GsAsCAGUfAUfUfCfUCAGUGCsUsA
Ky-12S432	GsAsCAGUfAUfUfCfUCAGUGCsUsA-3'MVIP17
Ky-12S433	5'MVIP01-GsAsCAGUfAUfUfCfUCAGUGCsUsA- 3'MVIP09
Ky-12S434	5'MVIP09-GsAsCAGUfAUfUfCfUCAGUGCsUsA- 3'MVIP01
Ky-12S435	5'MVIP09-GsAsGCGACAfGfUfAUUCTCAsGsU
Ky-12S436	5'MVIP01-GsAsGCGACAfGfUfAUUCTCAsGsU
Ky-12S437	5'MVIP17-GsAsGCGACAfGfUfAUUCTCAsGsU
Ky-12S438	GsAsGCGACAfGfUfAUUCTCAsGsU-3'MVIP09
Ky-12S439	GsAsGCGACAfGfUfAUUCTCAsGsU-3'MVIP17

sense strand/antisense strand code	sense strand/antisense strand sequence 5'→3'
Ky-12S440	5'MVIP01-GsAsGCGACAfGfUfAUUCTCAsGsU- 3'MVIP09
Ky-12S441	5'MVIP09-GsAsGCGACAfGfUfAUUCTCAsGsU- 3'MVIP01
Ky-12S442	5'MVIP09-GsCsGCGAfCAfGfUfAUUCTCAsGsU
Ky-12S443	5'MVIP01-GsCsGCGAfCAfGfUfAUUCTCAsGsU
Ky-12S444	5'MVIP17-GsCsGCGAfCAfGfUfAUUCTCAsGsU
Ky-12S445	GsCsGCGAfCAfGfUfAUUCTCAsGsU-3'MVIP09
Ky-12S446	GsCsGCGAfCAfGfUfAUUCTCAsGsU-3'MVIP17
Ky-12S447	5'MVIP01-GsCsGCGAfCAfGfUfAUUCTCAsGsU- 3'MVIP09
Ky-12S448	5'MVIP09-GsCsGCGAfCAfGfUfAUUCTCAsGsU- 3'MVIP01
Ky-12S449	5'MVIP09-GsCsGCGACAfGfUfAUUCTCAsGsA
Ky-12S450	5'MVIP01-GsCsGCGACAfGfUfAUUCTCAsGsA
Ky-12S451	5'MVIP17-GsCsGCGACAfGfUfAUUCTCAsGsA
Ky-12S452	GsCsGCGACAfGfUfAUUCTCAsGsA-3'MVIP09
Ky-12S453	GsCsGCGACAfGfUfAUUCTCAsGsA-3'MVIP17
Ky-12S454	5'MVIP01-GsCsGCGACAfGfUfAUUCTCAsGsA- 3'MVIP09
Ky-12S455	5'MVIP09-GsCsGCGACAfGfUfAUUCTCAsGsA- 3'MVIP01
Ky-12S456	5'MVIP09-AsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S457	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAGUsGsU
Ky-12S458	5'MVIP01-AsAsGCGACAfGfUfAUUCUCAGUsGsU- 3'MVIP09

In some embodiments, the RNA inhibitor is selected from Tables 22-1 and 22-2, wherein the sense strand and/or antisense strand differ from each sequence in Tables 22-1 and 22-2 by 1, 2 or 3 nucleotides, or have sequences of at least 15 consecutive nucleotides identical to those in Tables 22-1 and 22-2.

Table 22-1 RNA inhibitor

RNA inhibitor	sense strand 5'→3'	antisense strand 5'→3'
Ky-12-DS23001	5'MVIP09- GsUsGGCUGCfCfUfGAGACCUCAsAs U	UsfGsAfGGfUCfUCAGGCfAGfCCfA CsfGsG-3'MVIP09
Ky-12-DS25001	5'MVIP09- AsAsGUCCACfCfUfGCCUAUCCAsUs C	UsfGsGfAUfAGfGCAGGUfGGfACfU UsfGsG-3'MVIP09
Ky-12-DS25401	5'MVIP09- CsAsCCUGCCfUfAfUCCAUCCUGsAs A	CsfAsGfGAfUGfGAUAGGfCAfGGfU GsfGsA-3'MVIP09
Ky-12-DS29701	5'MVIP09- GsGsGACAGUfAfUfUCUCAGUGCsUs U	GsfCsAfCUfGAfGAAUACfUGfUCfC CsfUsU-3'MVIP09
Ky-12-DS29801	5'MVIP09- GsAsCAGUAUfUfCfUCAGUGCUCsUs U	GsfAsGfCAfCUfGAGAAUfACfUGfU CsfCsC-3'MVIP09
Ky-12-DS31701	5'MVIP09- GsAsGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP09
Ky-12-DS31702	5'MVIP09- GsAsGCGAfCAfGfUfAUUCUCAGUsG sU	AsfCsAfCUfGAfGAfAUACfUGfUCfG CsUsC-3'MVIP09

RNA inhibitor	sense strand 5'→3'	antisense strand 5'→3'
Ky-12-DS31703	5'MVIP09- GsAsGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUCsUsU-3'MVIP09
Ky-12-DS31704	5'MVIP09- GsAsGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP09
Ky-12-DS31705	5'MVIP01- GsAsGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP17
Ky-12-DS31706	5'MVIP01- GsAsGCGACAfGfUfAUUCUCAGUsGs U-3'MVIP01	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC
Ky-12-DS31707	5'MVIP01- GsAsGCGACAfGfUfAUUCUCAGUsGs U-3'MVIP09	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC
Ky-12-DS31708	5'MVIP09- GsAsGCGACAfGfUfAUUCUCAGUsGs U-3'MVIP01	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC
Ky-12-DS31709	5'MVIP01- GsAsGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP01
Ky-12-DS31710	GsAsGCGACAfGfUfAUUCUCAsGsU- 3'MVIP09	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP09
Ky-12-DS31711	5'MVIP17- GsAsGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC
Ky-12-DS31712	GsAsGCGACAfGfUfAUUCUCAsGsU- 3'MVIP17	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC
Ky-12-DS31713	5'MVIP17- GsAsGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsC-3'MVIP01

RNA inhibitor	sense strand 5'→3'	antisense strand 5'→3'
Ky-12-DS33001	5'MVIP09- AsAsGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CsfUsU-3'MVIP09
Ky-12-DS33002	5'MVIP09- AsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsU-3'MVIP09
Ky-12-DS33003	5'MVIP09- AsAGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsU-3'MVIP09
Ky-12-DS33004	5'MVIP01- AsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsU-3'MVIP17
Ky-12-DS33005	5'MVIP09- AsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsU-3'MVIP09
Ky-12-DS23002	5'MVIP09- GsUGGCUGCfCfUfGAGACCUCAsAs U	UsfGsAfGGfUCfUCAGGCfAGfCCfA CfGsG-3'MVIP09
Ky-12-DS25002	5'MVIP09- AsAGUCCACfCfUfGCCUAUCCAsUsC	UsfGsGfAUfAGfGCAGGUfGGfACfU UfGsG-3'MVIP09
Ky-12-DS25402	5'MVIP09- CsACCUGCCfUfAfUCCAUCCUGsAsA	CsfAsGfGAfUGfGAUAGGfCAfGGfU GfGsA-3'MVIP09
Ky-12-DS29702	5'MVIP09- GsGGACAGUfAfUfUCUCAGUGCsUs U	GsfCsAfCUfGAfGAAUACfUGfUCfC CfUsU-3'MVIP09
Ky-12-DS29802	5'MVIP09- GsACAGUAUfUfCfUCAGUGCUCsUs U	GsfAsGfCAfCUfGAGAAUfACfUGfU CfCsC-3'MVIP09

RNA inhibitor	sense strand 5'→3'	antisense strand 5'→3'
Ky-12-DS31714	5'MVIP09- GsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsC-3'MVIP09
Ky-12-DS31715	5'MVIP09- GsAGCGAfCAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAfAUACfUGfUCfG CUsc-3'MVIP09
Ky-12-DS31716	5'MVIP09- GsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUCUsU-3'MVIP09
Ky-12-DS31717	5'MVIP09- GsAGCGACAfGfUfAUUCUCAsGsU	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUsC-3'MVIP09
Ky-12-DS33006	5'MVIP09- AsAGCGACAfGfUfAUUCUCAGUsGs U	AsfCsAfCUfGAfGAAUACfUGfUCfG CfUCUsU-3'MVIP09

Table 22-2 RNA inhibitor

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S196	5'MVIP09	n=2	AS196	3'MVIP09	m=2	Kylo-12-DS1081	4	n:m
S211	5'MVIP01	n=1	AS208	3'MVIP01	m=1	Kylo-12-DS131	2	n:m
S263	5'MVIP21	n=1	AS208	3'MVIP01	m=1	Kylo-12-DS132	2	n:m

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S211	5'MVIP01	n=1	AS247	3' MVIP07	m=1	Kylo-12-DS133	2	n:m
S212	5'MVIP01/3' MVIP01	n=1/ m=1	AS108	/	/	Kylo-12-DS134	2	nm:/
S209	3'MVIP01	m=1	AS265	5'MVIP01	n=1	Kylo-12-DS135	2	m:n
S249	3' MVIP07	m=1	AS263	5'MVIP21	n=1	Kylo-12-DS136	2	m:n
S211	5'MVIP01	n=1	AS196	3'MVIP09	m=2	Kylo-12-DS137	3	n:m
S227	5' MVIP08	n=1	AS257	3'MVIP15	m=2	Kylo-12-DS138	3	n:m
S196	5'MVIP09	n=2	AS208	3'MVIP01	m=1	Kylo-12-DS139	3	n:m
S261	5' MVIP19	n=2	AS247	3' MVIP07	m=1	Kylo-12-DS140	3	n:m
S217	5'MVIP01/3' MVIP09	n=1/ m=2	AS108	/	/	Kylo-12-DS141	3	nm:/
S218	5'MVIP09/3' MVIP01	n=2/ m=1	AS108	/	/	Kylo-12-DS142	3	nm:/
S208	3'MVIP09	m=2	AS265	5'MVIP01	n=1	Kylo-12-DS143	3	m:n
S251	3'MVIP11	m=2	AS234	5'MVIP06	n=1	Kylo-12-DS144	3	m:n

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S209	3'MVIP01	m=1	AS262	5' MVIP20	n=2	Kylo-12-DS145	3	m:n
S249	3' MVIP07	m=1	AS261	5' MVIP19	n=2	Kylo-12-DS146	3	m:n
S231	5'MVIP01	n=1	AS209	3' MVIP17	m=3	Kylo-12-DS147	4	n:m
S263	5' MVIP21	n=1	AS209	3' MVIP17	m=3	Kylo-12-DS148	4	n:m
S210	5'MVIP17	n=3	AS208	3' MVIP01	m=1	Kylo-12-DS149	4	n:m
S264	5' MVIP22	n=3	AS247	3' MVIP07	m=1	Kylo-12-DS150	4	n:m
S262	5' MVIP20	n=2	AS248	3' MVIP10	m=2	Kylo-12-DS151	4	n:m
S261	5' MVIP19	n=2	AS257	3'MVIP15	m=2	Kylo-12-DS152	4	n:m
S238	5' MVIP10	n=2	AS254	3'MVIP12	m=2	Kylo-12-DS153	4	n:m
S213	5'MVIP09/3' MVIP09	n=2/ m=2	AS108	/	/	Kylo-12-DS154	4	nm:/

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S208	3'MVIP09	m=2	AS266	5' MVIP09	n=2	Kylo-12-DS155	4	m:n
S250	3'MVIP10	m=2	AS262	5' MVIP20	n=2	Kylo-12-DS156	4	m:n
S209	3'MVIP01	m=1	AS207	5' MVIP17	n=3	Kylo-12-DS157	4	m:n
S241	3'MVIP02	m=1	AS238	5' MVIP18	n=3	Kylo-12-DS158	4	m:n
S207	3'MVIP17	m=3	AS265	5' MVIP01	n=1	Kylo-12-DS159	4	m:n
S225	3'MVIP18	m=3	AS263	5' MVIP21	n=1	Kylo-12-DS160	4	m:n
S196	5'MVIP09	n=2	AS209	3' MVIP17	m=3	Kylo-12-DS161	5	n:m
S262	5'MVIP20	n=2	AS220	3' MVIP19	m=3	Kylo-12-DS162	5	n:m
S210	5'MVIP17	n=3	AS196	3'MVIP09	m=2	Kylo-12-DS163	5	n:m
S264	5'MVIP22	n=3	AS249	3'MVIP11	m=2	Kylo-12-DS164	5	n:m

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S219	5'MVIP09/3' MVIP17	n=2/ m=3	AS108	/	/	Kylo-12-DS165	5	nm:/
S220	5'MVIP17/3' MVIP09	n=3/ m=2	AS108	/	/	Kylo-12-DS166	5	nm:/
S207	3'MVIP17	m=3	AS262	5' MVIP20	n=2	Kylo-12-DS167	5	m:n
S222	3'MVIP19	m=3	AS226	5' MVIP16	n=2	Kylo-12-DS168	5	m:n
S208	3'MVIP09	m=2	AS207	5' MVIP17	n=3	Kylo-12-DS169	5	m:n
S259	3' MVIP15	m=2	AS207	5' MVIP17	n=3	Kylo-12-DS170	5	m:n
S210	5'MVIP17	n=3	AS209	3' MVIP17	m=3	Kylo-12-DS171	6	n:m
S264	5' MVIP22	n=3	AS220	3' MVIP19	m=3	Kylo-12-DS172	6	n:m
S214	5'MVIP17/3' MVIP17	n=3/ m=3	AS108	/	/	Kylo-12-DS173	6	nm:/
S207	3'MVIP17	m=3	AS207	5' MVIP17	n=3	Kylo-12-DS174	6	m:n

single strand code	carrier structure		single strand code	carrier structure		Double Strand code	n + m	Position of carrier structure conjugated to siRNA (S:AS)
S225	3'MVIP18	m=3	AS264	5' MVP2 2	n=3	Kylo-12-DS175	6	m:n

In some embodiments, the RNA inhibitor or its pharmaceutically acceptable salt described in the present invention is preferably prepared or synthesized in the form of sodium salt, triethylamine salt or other pharmaceutically acceptable salt.

In some embodiments, the RNA inhibitor or its pharmaceutically acceptable salt is more preferably sodium salt or triethylamine salt.

The present invention also provides a pharmaceutical composition comprising the above-mentioned RNA inhibitor or pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides a pharmaceutical composition comprising the above-mentioned RNA inhibitor or pharmaceutically acceptable salt thereof and pharmaceutically acceptable pharmaceutical adjuvants. The pharmaceutical composition containing the RNA inhibitor can be used to prevent and/or treat diseases associated with elevated levels of APOC3, such as hepatic diseases, inflammatory, cardiovascular and cerebrovascular, and metabolic diseases, wherein the cardiovascular and cerebrovascular diseases include hyperlipidemia, stroke, atherosclerosis, thrombosis, coronary heart disease, aortic valve stenosis, hypertriglyceridemia (HTG), severe hypertriglyceridemia (sHTG) or familial chylomicronemia syndrome (FCS). Such pharmaceutical compositions are formulated according to the mode of delivery. An embodiment is to formulate as a composition for systemic administration by parenteral delivery, such as, subcutaneous (SC), intramuscular (IM), or intravenous (IV) delivery. The pharmaceutical composition of the present invention can be administered at a dose sufficient to inhibit APOC3 gene expression.

The pharmaceutically acceptable "adjuvants" or "excipients" are pharmaceutically acceptable solvents, suspensions or any other pharmaceutically inert vehicles used to deliver one or more nucleic

acids to animals. The excipients may be liquid or solid and are selected taking account of the intended mode of administration to provide the required volume, consistency, etc. when combined with nucleic acids and other components in a given pharmaceutical composition. The RNA inhibitor can be delivered in a manner that targets specific tissues (e.g., hepatocytes).

In some embodiments, the pharmaceutical composition further comprises a delivery vehicle (such as nanoparticles, dendrimers, polymers, liposomes, or cation delivery systems).

In some embodiments, the delivery vehicle comprises liposomes.

In some embodiments, the delivery vehicle comprises nanolipids that is capable of forming a liposome-nucleic acid nanoparticle with nucleic acid molecule.

In some embodiments, the delivery vehicle comprises amphoteric lipid compounds M10C1.

The pharmaceutical composition provided in the present invention includes (but is not limited to) solutions, emulsions, and preparations containing liposomes. These compositions can be produced from a variety of components, including (but not limited to) pre-formed liquids, self-emulsifying solids, and self-emulsifying semisolids. Preparations include those targeting the liver. The pharmaceutical preparations of the present invention, which can conveniently exist in a unit dosage form, can be prepared according to the conventional technology known to the pharmaceutical industry. Such technologies include steps of combining active ingredients with pharmaceutical adjuvants or excipients.

Purpose

In yet another aspect, the present invention further provides a method for reducing APOC3 mRNA or protein expression in cell or tissue, which includes contacting the cell or tissue with an effective amount of the aforementioned RNA inhibitor or pharmaceutically acceptable salt thereof that inhibits APOC3 gene expression, and/or the aforementioned pharmaceutical composition.

The cell suitable for treatment using the method of the present invention can be any cell expressing APOC3 gene, such as liver cell, brain cell, gallbladder cell, heart cell or kidney cell, but preferably liver cell. The cell suitable for the method of the present invention can be mammalian cell. When in contact with cell expressing APOC3 gene, RNA inhibitor inhibits the expression of APOC3 gene (for example, human, primate, non-primate or rat APOC3 gene) by at least about 50%. For example, it can be determined by PCR or methods based on branched DNA (bDNA), or methods based on protein, such as immunofluorescence, Western blotting or flow cytometry.

In some embodiments, the tissue is liver tissue.

The term "inhibit" used herein may be used interchangeably with "reduce", "decrease", "silence", "downregulate", "repress" and other similar terms, and includes any level of inhibition. The expression of APOC3 gene can be evaluated according to the level or level change of any variable related to APOC3 gene expression, for example, APOC3 mRNA level or APOC3 protein level. Such level can be analyzed in single cell or population of cells (including, for example, a sample from a subject). Inhibition can be evaluated by the decrease in absolute or relative levels of one or more variables associated with APOC3 expression compared with control levels. The control level can be any type of control level adopted in the art, for example, the baseline level before dosing or the level measured from similar subjects, cells or samples that have never been treated or received control treatment (e.g., only buffer control or inactive agent control).

The inhibition of APOC3 gene expression can be represented by a decrease in the amount of mRNA expressed by a first cell or cells population that inhibit APOC3 gene expression (such cells may be, for example, present in a sample from a subject) in which the APOC3 gene is transcribed and treated (for example, by contacting one or more cells with the RNA inhibitor of the present invention, or by administering the RNA inhibitor of the present invention to a subject in which the cell is present) compared to a second cell or cells population (control cells not treated with RNA inhibitor or RNA inhibitor targeting the gene of interest) that is essentially the same as that first cell or cells population but not so treated. In a preferred embodiment, the inhibition is evaluated in a cell line that highly expresses APOC3 by the method provided in Example 2 using an appropriate concentration of siRNA, and the mRNA level in the interfered cells is expressed as a percentage of the mRNA levels in the uninterfered control cells.

In other embodiments, the inhibition of APOC3 gene expression can be evaluated by the reduction of parameters functionally related to APOC3 gene expression, such as APOC3 protein levels in the blood or serum of subjects. APOC3 gene silencing can be determined in any APOC3 expressing cell (endogenous or exogenous from the expression constructs) and by any assay known in the art.

The inhibition of APOC3 protein expression can be manifested by the reduction of APOC3 protein levels expressed by cell or cells population or subject samples (e.g., protein levels in blood samples derived from subjects). As mentioned above, for the evaluation of mRNA inhibition, the inhibition of protein expression levels of treated cell or cells population can be similarly shown as a percentage of protein levels of control cell or cells population, or changes in protein levels in subject samples (e.g.,

blood or serum derived from it).

The cell, cells population or subject samples in control group that can be used to evaluate APOC3 gene inhibition include cell, cells population or subject samples that have not been exposed to the RNA inhibitor of the present invention. For example, control cell, cells population, or subject samples may be derived from a single subject (e.g., human or animal subjects) or an appropriately matched group controls before treatment with RNA inhibitor.

APOC3 mRNA levels expressed by cell or cells population can be determined using any method known in the art for evaluating mRNA expression. For example, qRT-PCR evaluates the reduction of gene expression. The reduction in protein production can be evaluated by any method known in the art, for example, ELISA. In some embodiments, the liver biopsy sample is used as tissue material to monitor the reduction of APOC3 gene or protein expression. In other embodiments, blood samples are used as subject samples for monitoring the reduction of APOC3 protein expression.

In yet another aspect, the present invention further provides use of the aforementioned RNA inhibitor or pharmaceutically acceptable salt thereof for inhibiting APOC3 gene expression, or the aforementioned pharmaceutical composition in the preparation of drugs for preventing and/or treating diseases or conditions or reducing the risk of diseases or conditions.

In some embodiments, the disease or condition includes APOC3 related disease or condition.

In some embodiments, the disease or condition is selected from: atherosclerosis, vascular disease, myocardial infarction, angina, stroke, kidney disease, renal failure, obesity, glucose intolerance, type 2 diabetes (non-insulin-dependent diabetes mellitus), and metabolic syndrome.

In yet another aspect, the present invention provides a method for preventing and/or treating diseases or conditions, which includes administering to a subject in need an effective amount of the aforementioned RNA inhibitor or pharmaceutically acceptable salt thereof that inhibits APOC3 gene expression, and/or the aforementioned pharmaceutical composition.

The in vivo method of the present invention may comprise administering to a subject a composition comprising an RNA inhibitor, wherein the RNA inhibitor comprises a nucleotide sequence complementary to at least a portion of the RNA transcript of the APOC3 gene of a mammal receiving the administration of the RNA inhibitor. The composition may be administered in any manner known in the art, including (but not limited to): oral, intraperitoneal or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, subcutaneous,

transdermal, airway (aerosol), nasal, rectal, and local (including buccal and sublingual) administration. In some embodiments, the composition is administered by intravenous infusion or injection. In some embodiments, the composition is administered by subcutaneous injection. In some embodiments, the composition is administered by intramuscular injection.

The RNA inhibitor of the present invention can also be administered as a "free RNA inhibitor". The free RNA inhibitors are administered in the absence of a pharmaceutical composition. Naked RNA inhibitors can be in a suitable buffer. The buffer may contain acetate, citrate, prolamin, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer is phosphate buffered saline (PBS). The pH and osmotic pressure of the buffer containing RNA inhibitor can be adjusted to be suitable for administration to subjects.

Alternatively, the RNA inhibitor of the present invention may be administered as a pharmaceutical composition, such as a liposome preparation.

The pharmaceutical composition of the present invention can be administered at a dosage sufficient to inhibit APOC3 gene expression. In some examples, the appropriate dosage of the RNA inhibitor of the present invention is in the range of about 0.001 to about 1000.0 mg per kilogram of recipient body weight per day. In some examples, the appropriate dosage of the RNA inhibitor of the present invention is in the range of about 1 to 50 mg per kilogram body weight per day. In some examples, the appropriate dosage of the RNA inhibitor of the present invention is in the range of about 0.1 mg/kg to about 10.0.0 mg/kg, for example, in the range of about 0.3mg/kg to about 3.0mg/kg.

In one embodiment, the method includes administering the pharmaceutical composition of the present invention such that the target APOC3 gene expression is reduced for, such as approximately 1, 2, 3, 4, 5, 6, 1-6, 1-3, or 3-6 months per dose. In some embodiments, the composition is administered every 3-6 months.

In some embodiments, after the initial treatment regimen, treatment is administered at less frequency. The repeated dosage regimen may include regular administration of therapeutic amounts of the RNA inhibitor, such as once a month to once a year. In some embodiments, the RNA inhibitor is administered approximately once a month to approximately once every three months, or approximately once every three months to approximately once every six months.

After the initial treatment regimen, treatment can be administered at a lower frequency. The duration of treatment can be determined according to the severity of the disease.

In other embodiments, a single dose of the pharmaceutical composition may be long-acting, such that the dose is administered at intervals of no more than 1, 2, 3, or 4 months. In some embodiments of the present invention, a single dose of the pharmaceutical composition is administered approximately once a month. In other embodiments of the present invention, a single dose of the pharmaceutical composition is administered quarterly (i.e. about every 3 months). In other embodiments of the present invention, a single dose of the pharmaceutical composition is administered twice a year (i.e., about once every 6 months).

The person skilled in the art should understand that certain factors can affect the dosage and duration of administration required to effectively treat a subject, including (but not limited to): the mutation existing in the subject, previous treatment, the general health/age and presence of other diseases of the subject. In addition, treating a subject with a prophylactically and/or therapeutically effective amount of the composition as needed may include a single treatment or a series of treatments.

In some embodiments, the method further includes determining APOC3 levels in samples from the subject.

For example, the method further includes determining the APOC3 level in blood sample, serum sample or urine sample from the subject.

In some embodiments, the method further includes administering to the subject an additional therapeutic agent for the treatment of hyperlipidemia.

For example, the additional therapeutic agent can be selected from statins, such as atorvastatin, rosuvastatin, etc.; cholesterol absorption inhibitors such as ezetimibe; PCSK9 inhibitors.

In yet another aspect, the present invention further provides a cell, which contains the aforementioned RNA inhibitor or pharmaceutically acceptable salt thereof for inhibiting APOC3 gene expression.

In yet another aspect, the present invention further provides a kit, which contains the aforementioned RNA inhibitor or pharmaceutically acceptable salt thereof for inhibiting APOC3 gene expression, or the aforementioned pharmaceutical composition.

Without intending to be bound by any theory, the following examples are only for the purpose of explaining the RNA inhibitor, preparation method and use of the present invention, and are not used to limit the scope of the invention.

Examples

Explanation:

The name of DMSO is dimethyl sulfoxide;

The name of DMF is N, N-dimethylformamide;

The name of HOBt is 1-hydroxybenzotriazole;

The name of HBTU is O-benzotriazole-tetramethylurea hexafluorophosphate;

The name of DIPEA (DIEA) is N, N-diisopropylethylamine;

The name of DCM is dichloromethane;

The name of DMAP is 4-dimethylaminopyridine;

The name of DMT-CL is 4,4'- dimethoxytriphenylchloromethane;

The name of MEOW is methanol;

The name of TBTU is O-benzotriazole-N, N, N', N'- tetramethylurea tetrafluoroboric acid;

The name of  is solid support, such as macroporous aminomethyl resin (Resin).

Example 1 Synthesis of RNA inhibitor

The sense strand and antisense strand of the unconjugated carrier structure were synthesized using a solid phase synthesizer according to the standard solid-phase phosphoramidite method. The sense strand and the corresponding antisense strand were annealed to obtain RNA inhibitor.

The basic steps of the solid-phase phosphoramidite method include:

- 1) Deprotection: removing hydroxyl protecting group (DMTr) of starting monomer Solid Support;
- 2) Conjugating: adding a first phosphoramidite monomer, the conjugating occurs through the 3' to 5' direction;
- 3) Oxidation: oxidizing the resulting nucleoside phosphite to a more stable nucleoside phosphate (that is, trivalent phosphorus is oxidized to pentavalent phosphorus);
- 4) Blocking: adding a cap to the 5'-OH of the failed nucleotide sequence in the previous step to prevent from further participating in subsequent reaction; repeating the above steps until the last phosphoramidite monomer is introduced; then cleaving the ester bond between Solid Support and the starting monomer with methylamine aqueous solution and ammonia water, and removing the protecting groups on each base and phosphate on the resulting nucleotide sequence; after separation and purification by HPLC, filter sterilizing and lyophilizing to obtain the corresponding sense strand or antisense strand.

Description of the synthesis process of RNA inhibitors:

Redissolved the sense strand and antisense strand freeze-dried powders separately, mixed them in an equal molar ratio, added into an appropriate amount of water for injection, and added into an appropriate amount of TRIS buffer solution. Shaked gently for about 1 to 2 min to mix the solution evenly. Heated a water bath to 92°C~95 °C and placed the above reaction solution in the water bath to heat for 3~ 5min, shaked gently to heat the solution evenly. Let it to cool naturally to room temperature to obtain colorless or yellowish transparent liquid. Took samples for testing to measure concentrations.

Example 2-1 Experiment 1 of RNA inhibitor to inhibit APOC3 gene expression in vitro

The RNA inhibitors in this Example (DS52~DS102) were prepared by the method described in Example 1. The aqueous solution of RNA inhibitor agent and organic solution of DOTMA were mixed to form water-insoluble precipitate, which was separated, dried, dissolved in chloroform, and further mixed with a solution of other lipid chloroform, including M10C1 and PEG600-cholesterol. The mixture was evaporated and dried overnight by vacuum centrifugation to obtain nanolipid-encapsulated RNA inhibitor, in which the weight ratios of DOTMA, M10C1 and PEG600-cholesterol to RNA inhibitor were 1~1.6, 1.5~2.5 and 2.5~3.5.

DMEM containing 10% fetal bovine serum was used to prepare the nanolipid-encapsulated RNA inhibitor sample solution with corresponding concentration. HepG 2 cells were inoculated at a density of 10^5 cells. After incubation for 24h in DMEM medium supplemented with 10% fetal bovine serum, 37°C, 5%CO₂, a sample of 10nM was added for interference. After incubation for 72h, collected the cell samples, added 1 ml Ezol lysate to the collected cell samples and mixed well by a vortex shaker. Added 0.2 ml trichloromethane, shook vigorously for 10 s, and left at room temperature for 1 min. Centrifuged at 12000 x g for 15 min at 4 °C. Transferred the upper clear water phase to another new RNase free centrifuge tube, and added an equal volume of 100% ethanol. Pipetted all of the sample and added it to a mini-spin centrifuge column with a 2 ml collection tube. Centrifuged at 8000 x g, room temperature for 15 seconds, and discarded the flow-through liquid. Transferred the remaining sample to a centrifuge column and repeated the previous step. Added 700 µl WB to the centrifuge column, gently closed the cover, centrifuged at 8000 × g, room temperature for 15 seconds, discarded the flow-through liquid. Repeated the previous step, and used 500 µ L WB to wash the centrifuge column twice. APOC3 mRNA levels were determined by qRT-PCR. Compared with the supernatant of

HepG 2 cells without intervention, the relative expression levels of APOC3 mRNA in the intervention group were calibrated.

Data analysis $\Delta\Delta C_t$ method (Ct difference comparative method):

The housekeeping gene GAPDH is expressed in all cells, and its product is necessary for maintaining cell survival. The expression level or genome copy number in the cell is constant and is less affected by the environment. Therefore, GAPDH is used as the internal reference gene. After qRT-PCR, the CT value of the internal reference will be recorded at the same time, which is called Ct (GAPDH), and the CT value of the sample is called Ct (sample).

$$\Delta C_t (\text{sample}) = C_t (\text{sample}) - C_t (\text{GAPDH})$$

$$\Delta C_t (\text{control}) = C_t (\text{control}) - C_t (\text{GAPDH})$$

$$\Delta \Delta C_t = \Delta C_t (\text{sample}) - \Delta C_t (\text{control})$$

$$\text{Relative expression level of gene} = 2^{-\Delta \Delta C_t}$$

The experimental results are shown in Table 23 below.

Table 23 APOC3 mRNA levels in HepG2 cell after RNA inhibitor intervention

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta \Delta C_t}$	Mean value
DS52	25.06	36.73	11.67	0.040949794	0.059042056
	25.01	36.81	11.8	0.03742121	
	25.04	35.44	10.4	0.098755164	
DS53	21.47	32.2	10.73	0.07856334	0.06000476
	21.4	32.61	11.21	0.05632815	
	21.3	32.83	11.53	0.04512279	
DS54	23.13	33.31	10.18	0.11502346	0.0984873
	23.25	33.67	10.42	0.09739557	
	22.73	33.38	10.65	0.08304286	
DS55	20.53	33.19	12.66	0.02061731	0.01934869
	20.82	33.26	12.44	0.02401367	
	20.85	34.13	13.28	0.01341508	
DS56	19.97	31.99	12.02	0.03212856	0.03902712
	19.9	31.43	11.53	0.04512279	
	19.84	31.55	11.71	0.03983002	
DS57	24.35	34.31	9.96	0.13397168	0.20733798

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta\Delta Ct}$	Mean value
	24.44	33.55	9.11	0.24148408	
	24.31	33.39	9.08	0.24655818	
DS58	20.28	31.4	11.12	0.05995401	0.06233004
	20.33	31.22	10.89	0.07031616	
	20.22	31.42	11.2	0.05671995	
DS59	22.01	30.22	8.21	0.45062523	0.54905108
	22.11	30.08	7.97	0.53218509	
	22.56	30.21	7.65	0.66434291	
DS60	22.22	32.2	9.98	0.13212726	0.12281597
	22.07	32.32	10.25	0.10942972	
	21.97	32.01	10.04	0.12674493	
DS61	23.66	29.66	6	2.08493152	2.10135682
	23.66	29.72	6.06	2	
	23.6	29.51	5.91	2.21913894	
DS62	21.19	32.95	11.76	0.03847326	0.03523392
	21.26	33.24	11.98	0.03303181	
	21.22	33.15	11.93	0.03419668	
DS63	20.83	31.03	10.2	0.11343989	0.11783809
	21.03	31.42	10.39	0.09944206	
	21.32	31.21	9.89	0.14063231	
DS64	22.04	31.39	9.35	0.20447551	0.21274677
	22.09	31.24	9.15	0.23488069	
	21.96	31.35	9.39	0.19888412	
DS65	26.65	34.7	8.05	0.50347778	0.4294787
	26.65	34.74	8.09	0.48971015	
	26.63	35.45	8.82	0.29524817	
DS66	20.5	31.66	11.16	0.0241807	0.02752831
	20.56	31.53	10.97	0.02758447	
	20.52	31.33	10.81	0.03081977	
DS67	20.19	31.06	10.87	0.0295643	0.02970701
	20.24	30.98	10.74	0.03235203	
	20.24	31.23	10.99	0.02720471	

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta\Delta Ct}$	Mean value
DS68	19.35	31.59	12.24	0.01143817	0.01242943
	19.36	31.36	12	0.01350839	
	19.29	31.37	12.08	0.01277972	
DS69	22.1	33.31	11.21	0.02335702	0.02969232
	22.15	32.69	10.54	0.03716272	
	22.25	33.17	10.92	0.02855723	
DS70	19.32	32.88	13.56	0.00458139	0.00418037
	19.33	32.77	13.44	0.00497875	
	19.3	33.48	14.18	0.00298098	
DS71	21.66	32.75	11.09	0.02538289	0.02743428
	21.59	32.5	10.91	0.02875586	
	21.64	32.58	10.94	0.02816408	
DS72	20.83	32.4	11.57	0.01819896	0.0167851
	20.88	32.57	11.69	0.01674646	
	20.95	32.76	11.81	0.01540989	
DS73	20.09	31	10.91	0.02875586	0.0321474
	20.38	31.06	10.68	0.03372588	
	20.56	31.23	10.67	0.03396046	
DS74	22.53	31.38	8.85	0.11990801	0.14334036
	22.51	31.04	8.53	0.14968484	
	22.47	30.9	8.43	0.16042824	
DS75	21.4	31.59	10.19	0.04736614	0.04188562
	21.47	32.06	10.59	0.03589682	
	21.38	31.73	10.35	0.04239389	
DS76	24.82	30.54	5.72	1.04971668	1.0337533
	24.76	30.75	5.99	0.87055056	
	24.82	30.37	5.55	1.18099266	
DS77	24.95	34.52	9.57	0.07279585	0.09858007
	25.11	34.52	9.41	0.08133387	
	25.09	33.7	8.61	0.14161049	
DS78	27.42	36.86	9.44	0.07966004	0.08846432
	27.47	36.4	8.93	0.11343989	

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta\Delta Ct}$	Mean value
	27.42	37		0.07229301	
DS79	23.29	34.53	11.24	0.02287634	0.04030962
	23.19	33.71	10.52	0.03768149	
	23.14	32.98	9.84	0.06037102	
DS80	26.25	36.44	10.19	0.13869618	0.17461278
	26.18	35.8	9.62	0.20589775	
	26.07	35.89	9.82	0.17924441	
DS81	23.34	33.68	10.34	0.125	0.1427191
	23.46	33.73	10.27	0.13121459	
	23.35	33.23	9.88	0.17194273	
DS82	26.77	38.02	11.25	0.06652314	0.05729203
	26.77	38.12	11.35	0.06206828	
	26.65	38.52	11.87	0.04328467	
DS83	25.69	37.66	11.97	0.04038603	0.04889128
	25.73	37.36	11.63	0.05111888	
	25.81	37.33	11.52	0.05516894	
DS84	25.01	33.7	8.69	0.39229205	0.36010911
	24.87	33.79	8.92	0.33448189	
	24.81	33.65	8.84	0.35355339	
DS85	24.79	34.31	9.52	0.22067429	0.20805055
	24.79	34.4	9.61	0.20732989	
	24.71	34.4	9.69	0.19614602	
DS86	26.21	36.31	10.1	0.14762408	0.1700243
	26.25	35.93	9.68	0.19751033	
	26.21	36.15	9.94	0.16493849	
DS87	23.5	34.78	11.28	0.06515411	0.06397548
	23.54	34.83	11.29	0.06470406	
	23.78	35.13	11.35	0.06206828	
DS88	27.83	33.68	5.85	2.80888975	2.69058589
	27.33	33.41	6.08	2.39495741	
	27.72	33.54	5.82	2.8679105	
DS89	28.04	37.2	9.16	0.28322097	0.42813277

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta\Delta Ct}$	Mean value
	28.01	36.42		0.476319	
	28.04	36.31	8.27	0.52485834	
	24.08	33.39	9.31	0.25525303	
DS90	24.09	33.53	9.44	0.23325825	0.23639568
	24.13	33.65	9.52	0.22067429	
	26.34	36.75	10.41	0.11907975	0.16009295
DS91	26.49	36.25	9.76	0.18685616	
	26.51	36.37	9.86	0.17434296	
DS92	23.55	34.18	10.63	0.10223776	0.09572549
	23.45	34.52	11.07	0.07536299	
	23.35	33.88	10.53	0.10942972	
DS93	28.25	38.07	9.82	0.17924441	0.18518687
	28.36	39.4	11.04	0.07694653	
	28.26	37.34	9.08	0.29936968	
DS94	24.52	35.54	11.02	0.0476956	0.06091932
	24.57	35.16	10.59	0.06425711	
	24.41	34.86	10.45	0.07080524	
DS95	21.05	33.27	12.22	0.02076072	0.01817949
	21.01	33.45	12.44	0.01782443	
	21.04	33.64	12.6	0.01595331	
DS96	26.81	38.08	11.27	0.04010706	0.06210346
	26.9	37.36	10.46	0.07031616	
	26.82	37.17	10.35	0.07588718	
DS97	25.26	35.26	10	0.09672281	0.10383615
	25.33	35.51	10.18	0.08537752	
	25.6	35.18	9.58	0.12940812	
DS98	27.65	37.03	9.38	0.14865089	0.16856626
	27.66	36.89	9.23	0.16493849	
	27.57	36.58	9.01	0.1921094	
DS99	30.82	38.29	7.47	0.55864357	1.5028866
	30.65	37.37	6.72	0.93952275	
	30.81	35.85	5.04	3.01049349	

RNA inhibitor	CT value		APOC3-GAPDH	Relative expression level	
	GAPDH	APOC3		$2^{-\Delta\Delta Ct}$	Mean value
DS100	24.46	34.53	10.07	0.09214183	0.09505216
	24.43	34.58	10.15	0.08717148	
	24.58	34.45	9.87	0.10584316	
DS101	24.97	34.69	9.72	0.11744034	0.10968828
	25.01	35	9.99	0.09739557	
	25.15	34.91	9.76	0.11422893	
DS102	26.75	37.24	10.49	0.06886907	0.08281502
	26.52	36.08	9.56	0.13121459	
	26.42	37.42	11	0.04836141	

The test results showed that the RNA inhibitors in Table 6 showed varying degrees of inhibitory effects on APOC3 mRNA expression levels in HepG2 cells at different concentrations, among which DS52-58, DS60, DS62-64, DS66-75, DS77-87, DS90-98 and DS100-102 significantly inhibited APOC3 mRNA expression levels in HepG2 cells.

Example 2-2 Experiment 2 of RNA inhibitor to inhibit APOC3 gene expression in vitro

The sequence of the RNA inhibitor in this example is selected from Table 5 and prepared by the method described in Example 1. The RNA inhibitor HepG2 cells were seeded in a 96-well plate to spread. At the same time, the siRNA compound was transfected into the cells with a transfection reagent and the siRNA was tested at concentrations of 1 nM and 0.1nM. The cells were cultured overnight in a 37°C, 5% CO2 incubator, and 3 replicates were measured in parallel. A control group was also set up.

qPCR detection of target gene mRNA expression level:

After 48 hours of transfection, RNA was extracted, and the target cDNA was detected by qPCR. GAPDH cDNA was also detected as an internal control for parallel detection. 8 μ L of the prepared qPCR reaction solution and 2 μ L of sample cDNA were added to 384 wells. The qPCR reaction program was: heating at 95°C for 10 min, then going into cycle mode, heating at 95°C for 15 sec, then 60°C for 1 min, for a total of 40 cycles. Compared with the supernatant of HepG 2 cells without intervention, the relative expression level of APOC3 mRNA in the sample intervention group was calibrated. Tested three times and took the average of the relative expression levels of APOC3. The test results obtained at concentrations of 1 nM and 0.1 nM are shown in Tables 24 and 25 below.

Table 24 Effect of RNA inhibitors on APOC3 gene inhibition in vitro (1nM)

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS69	0.44	0.01
Ky-12-DS70	0.58	0.01
Ky-12-DS71	0.75	0.01
Ky-12-DS72	0.67	0.01
Ky-12-DS73	0.78	0.04
Ky-12-DS74	0.50	0.04
Ky-12-DS75	0.64	0.02
Ky-12-DS76	0.76	0.02
Ky-12-DS77	0.88	0.01
Ky-12-DS78	0.79	0.02
Ky-12-DS79	0.67	0.01
Ky-12-DS80	0.45	0.07
Ky-12-DS81	0.39	0.04
Ky-12-DS82	0.59	0.01
Ky-12-DS83	0.68	0.03
Ky-12-DS84	0.70	0.01
Ky-12-DS85	0.90	0.09
Ky-12-DS86	0.51	0.07
Ky-12-DS87	0.53	0.05
Ky-12-DS88	0.77	0.09
Ky-12-DS89	0.51	0.05
Ky-12-DS90	0.83	0.03
Ky-12-DS91	0.84	0.08
Ky-12-DS92	0.86	0.07
Ky-12-DS93	0.87	0.06
Ky-12-DS94	0.89	0.06
Ky-12-DS95	0.75	0.08

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS96	0.65	0.03
Ky-12-DS97	0.84	0.05
Ky-12-DS98	0.88	0.08
Ky-12-DS99	0.78	0.10
Ky-12-DS100	0.77	0.02
Ky-12-DS101	0.75	0.02
Ky-12-DS102	0.82	0.09
Ky-12-DS103	0.90	0.09
Ky-12-DS104	0.59	0.04
Ky-12-DS105	0.56	0.04
Ky-12-DS106	0.64	0.09
Ky-12-DS107	0.58	0.10
Ky-12-DS108	0.49	0.02
Ky-12-DS109	0.94	0.07
Ky-12-DS110	0.59	0.09
Ky-12-DS111	0.37	0.05
Ky-12-DS112	0.89	0.01
Ky-12-DS113	0.69	0.01
Ky-12-DS114	0.67	0.10
Ky-12-DS115	0.65	0.02
Ky-12-DS116	0.90	0.06
Ky-12-DS117	0.94	0.04
Ky-12-DS118	0.55	0.05
Ky-12-DS119	0.59	0.04
Ky-12-DS120	0.62	0.02
Ky-12-DS121	0.96	0.01
Ky-12-DS122	0.94	0.07

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS123	0.77	0.06
Ky-12-DS124	0.71	0.06
Ky-12-DS125	0.80	0.03
Ky-12-DS126	0.52	0.06
Ky-12-DS127	0.94	0.03
Ky-12-DS128	0.67	0.04
Ky-12-DS129	0.52	0.08
Ky-12-DS130	0.74	0.06
Ky-12-DS131	0.92	0.02
Ky-12-DS132	0.51	0.02
Ky-12-DS133	0.23	0.09
Ky-12-DS134	0.50	0.01
Ky-12-DS135	0.78	0.09
Ky-12-DS136	0.73	0.10
Ky-12-DS137	0.62	0.09
Ky-12-DS138	0.53	0.01
Ky-12-DS139	0.85	0.04
Ky-12-DS140	0.80	0.09
Ky-12-DS141	0.34	0.02
Ky-12-DS142	0.80	0.03
Ky-12-DS143	0.66	0.03
Ky-12-DS144	0.98	0.09
Ky-12-DS145	1.00	0.04
Ky-12-DS146	0.86	0.08
Ky-12-DS147	0.95	0.07
Ky-12-DS148	0.70	0.07
Ky-12-DS149	0.53	0.02

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS150	0.70	0.06
Ky-12-DS151	0.97	0.03
Ky-12-DS152	0.85	0.09
Ky-12-DS153	0.65	0.05
Ky-12-DS154	0.94	0.01
Ky-12-DS155	0.97	0.08
Ky-12-DS156	0.47	0.03
Ky-12-DS157	0.56	0.02
Ky-12-DS158	0.61	0.02
Ky-12-DS159	0.56	0.02
Ky-12-DS160	0.83	0.10
Ky-12-DS161	0.93	0.06
Ky-12-DS162	0.78	0.04
Ky-12-DS163	0.30	0.01
Ky-12-DS164	0.23	0.05
Ky-12-DS165	0.55	0.11
Ky-12-DS166	0.48	0.02
Ky-12-DS167	0.54	0.07
Ky-12-DS168	0.79	0.07
Ky-12-DS169	0.78	0.03
Ky-12-DS170	0.41	0.08
Ky-12-DS171	0.46	0.05
Ky-12-DS172	0.76	0.02
Ky-12-DS173	0.60	0.08
Ky-12-DS174	0.49	0.03
Ky-12-DS175	0.97	0.06
Ky-12-DS176	0.29	0.05

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS177	0.83	0.07
Ky-12-DS178	0.60	0.02
Ky-12-DS179	0.40	0.02
Ky-12-DS180	0.34	0.06
Ky-12-DS181	0.54	0.06
Ky-12-DS182	0.62	0.07
Ky-12-DS183	0.60	0.02
Ky-12-DS184	0.45	0.04
Ky-12-DS185	0.69	0.02
Ky-12-DS186	0.46	0.03
Ky-12-DS187	0.51	0.01
Ky-12-DS188	0.51	0.04
Ky-12-DS189	0.42	0.09
Ky-12-DS190	0.57	0.12
Ky-12-DS191	0.41	0.08
Ky-12-DS192	0.61	0.06
Ky-12-DS193	0.53	0.02
Ky-12-DS194	0.67	0.09
Ky-12-DS195	0.46	0.04
Ky-12-DS196	0.47	0.05
Ky-12-DS197	0.41	0.05
Ky-12-DS198	0.52	0.03
Ky-12-DS199	0.45	0.07
Ky-12-DS200	0.95	0.08
Ky-12-DS201	0.56	0.02
Ky-12-DS202	0.50	0.08
Ky-12-DS203	0.61	0.07

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS204	0.94	0.07
Ky-12-DS205	1.00	0.08
Ky-12-DS206	0.96	0.03
Ky-12-DS207	0.96	0.10
Ky-12-DS208	0.51	0.03
Ky-12-DS209	0.72	0.09
Ky-12-DS210	0.84	0.02
Ky-12-DS211	0.76	0.02
Ky-12-DS212	0.97	0.02
Ky-12-DS213	0.89	0.01
Ky-12-DS214	0.52	0.09
Ky-12-DS215	0.60	0.10
Ky-12-DS216	0.50	0.03
Ky-12-DS217	0.94	0.05
Ky-12-DS218	0.57	0.05
Ky-12-DS219	0.54	0.04
Ky-12-DS220	0.68	0.05
Ky-12-DS221	0.68	0.01
Ky-12-DS222	0.70	0.09
Ky-12-DS223	0.58	0.03
Ky-12-DS224	0.68	0.09
Ky-12-DS225	0.80	0.09
Ky-12-DS226	0.83	0.06
Ky-12-DS227	0.57	0.11
Ky-12-DS228	0.75	0.11
Ky-12-DS229	1.00	0.07
Ky-12-DS230	0.16	0.04

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS231	0.46	0.06
Ky-12-DS232	0.70	0.07
Ky-12-DS233	0.94	0.06
Ky-12-DS234	0.63	0.02
Ky-12-DS235	0.94	0.07
Ky-12-DS236	0.66	0.03
Ky-12-DS237	0.86	0.08
Ky-12-DS238	0.52	0.01
Ky-12-DS239	0.66	0.02
Ky-12-DS240	0.80	0.01
Ky-12-DS241	0.23	0.01
Ky-12-DS242	0.47	0.02
Ky-12-DS243	0.95	0.05
Ky-12-DS244	0.98	0.04
Ky-12-DS245	0.95	0.11
Ky-12-DS246	0.32	0.03
Ky-12-DS247	0.29	0.07
Ky-12-DS248	0.36	0.08
Ky-12-DS249	0.59	0.05
Ky-12-DS250	0.14	0.11
Ky-12-DS251	0.35	0.03
Ky-12-DS252	0.77	0.05
Ky-12-DS253	0.39	0.06
Ky-12-DS254	0.12	0.02
Ky-12-DS255	0.49	0.11
Ky-12-DS256	0.20	0.07
Ky-12-DS257	0.67	0.02

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS258	0.53	0.04
Ky-12-DS259	0.42	0.03
Ky-12-DS260	0.51	0.10
Ky-12-DS261	0.43	0.02
Ky-12-DS262	0.52	0.07
Ky-12-DS263	0.53	0.09
Ky-12-DS264	0.94	0.09
Ky-12-DS265	0.85	0.07
Ky-12-DS266	0.73	0.03
Ky-12-DS267	0.47	0.06
Ky-12-DS268	0.63	0.03
Ky-12-DS269	0.34	0.05
Ky-12-DS270	0.52	0.10
Ky-12-DS271	0.69	0.06
Ky-12-DS272	0.63	0.07
Ky-12-DS273	0.91	0.03
Ky-12-DS274	0.89	0.03
Ky-12-DS275	0.79	0.05
Ky-12-DS276	0.66	0.10
Ky-12-DS277	0.88	0.09
Ky-12-DS278	0.64	0.04
Ky-12-DS279	0.78	0.04
Ky-12-DS280	0.67	0.08
Ky-12-DS281	0.47	0.07
Ky-12-DS282	0.79	0.03
Ky-12-DS283	0.57	0.03
Ky-12-DS284	0.76	0.09

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS285	0.45	0.04
Ky-12-DS286	0.78	0.02
Ky-12-DS287	0.76	0.04
Ky-12-DS288	0.48	0.06
Ky-12-DS289	0.78	0.03
Ky-12-DS290	0.58	0.05
Ky-12-DS291	0.63	0.02
Ky-12-DS292	0.98	0.04
Ky-12-DS293	0.82	0.09
Ky-12-DS294	0.90	0.05
Ky-12-DS295	0.82	0.05
Ky-12-DS296	0.46	0.11
Ky-12-DS297	0.19	0.05
Ky-12-DS298	0.14	0.07
Ky-12-DS299	0.58	0.05
Ky-12-DS300	0.50	0.08
Ky-12-DS301	0.98	0.05
Ky-12-DS302	0.25	0.05
Ky-12-DS303	0.94	0.08
Ky-12-DS304	0.59	0.08
Ky-12-DS305	0.58	0.01
Ky-12-DS306	0.62	0.05
Ky-12-DS307	0.95	0.02
Ky-12-DS308	0.89	0.02
Ky-12-DS309	0.79	0.04
Ky-12-DS310	0.48	0.08
Ky-12-DS311	0.90	0.02

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS312	0.55	0.10
Ky-12-DS313	0.36	0.05
Ky-12-DS314	0.40	0.04
Ky-12-DS315	0.37	0.04
Ky-12-DS316	0.45	0.02
Ky-12-DS317	0.10	0.05
Ky-12-DS318	0.44	0.01
Ky-12-DS319	0.53	0.10
Ky-12-DS320	0.56	0.04
Ky-12-DS321	0.53	0.02
Ky-12-DS322	0.70	0.02
Ky-12-DS323	0.66	0.03
Ky-12-DS324	0.66	0.06
Ky-12-DS325	0.73	0.02
Ky-12-DS326	0.78	0.09
Ky-12-DS327	0.54	0.05
Ky-12-DS328	0.50	0.01
Ky-12-DS329	0.41	0.06
Ky-12-DS330	0.12	0.02

Table 25 Effect of RNA inhibitors on APOC3 gene inhibition in vitro (0.1nM)

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS74	0.91	0.05
Ky-12-DS80	0.76	0.01
Ky-12-DS81	0.70	0.05
Ky-12-DS86	0.93	0.07

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS89	0.89	0.06
Ky-12-DS107	0.85	0.01
Ky-12-DS108	0.81	0.03
Ky-12-DS111	0.81	0.02
Ky-12-DS118	0.80	0.07
Ky-12-DS119	0.97	0.02
Ky-12-DS126	0.79	0.08
Ky-12-DS132	0.96	0.07
Ky-12-DS133	0.70	0.01
Ky-12-DS134	0.90	0.05
Ky-12-DS141	0.65	0.09
Ky-12-DS156	0.97	0.06
Ky-12-DS157	0.96	0.07
Ky-12-DS163	0.75	0.11
Ky-12-DS164	0.97	0.01
Ky-12-DS166	0.95	0.01
Ky-12-DS167	0.87	0.10
Ky-12-DS170	0.80	0.06
Ky-12-DS171	0.79	0.10
Ky-12-DS174	0.91	0.09
Ky-12-DS176	0.96	0.09
Ky-12-DS179	0.89	0.03
Ky-12-DS180	0.89	0.04
Ky-12-DS184	0.76	0.08
Ky-12-DS185	0.95	0.07
Ky-12-DS186	0.95	0.06
Ky-12-DS187	0.53	0.08

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS188	0.61	0.06
Ky-12-DS189	0.73	0.05
Ky-12-DS190	0.96	0.05
Ky-12-DS192	0.83	0.04
Ky-12-DS195	1.16	0.08
Ky-12-DS196	0.74	0.03
Ky-12-DS197	0.51	0.04
Ky-12-DS199	0.96	0.09
Ky-12-DS201	0.73	0.07
Ky-12-DS202	0.68	0.02
Ky-12-DS216	0.60	0.07
Ky-12-DS223	0.97	0.03
Ky-12-DS230	0.33	0.05
Ky-12-DS231	0.90	0.06
Ky-12-DS241	0.44	0.02
Ky-12-DS242	0.53	0.08
Ky-12-DS246	0.52	0.03
Ky-12-DS247	0.32	0.10
Ky-12-DS248	0.55	0.04
Ky-12-DS250	0.31	0.06
Ky-12-DS251	0.66	0.05
Ky-12-DS253	0.36	0.01
Ky-12-DS254	0.25	0.02
Ky-12-DS255	0.55	0.09
Ky-12-DS256	0.53	0.04
Ky-12-DS259	0.56	0.05
Ky-12-DS261	0.87	0.08

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS267	0.64	0.09
Ky-12-DS269	0.78	0.04
Ky-12-DS284	0.76	0.02
Ky-12-DS285	0.88	0.02
Ky-12-DS286	1.23	0.07
Ky-12-DS287	0.88	0.08
Ky-12-DS288	0.92	0.03
Ky-12-DS289	0.89	0.07
Ky-12-DS290	0.69	0.03
Ky-12-DS291	0.72	0.01
Ky-12-DS292	0.86	0.07
Ky-12-DS293	0.83	0.07
Ky-12-DS294	0.59	0.03
Ky-12-DS295	0.91	0.10
Ky-12-DS296	0.76	0.04
Ky-12-DS297	0.29	0.07
Ky-12-DS298	0.28	0.05
Ky-12-DS299	0.69	0.09
Ky-12-DS300	0.96	0.02
Ky-12-DS301	0.86	0.09
Ky-12-DS302	0.95	0.03
Ky-12-DS303	0.87	0.01
Ky-12-DS304	0.85	0.09
Ky-12-DS305	0.97	0.00
Ky-12-DS306	0.60	0.03
Ky-12-DS307	0.83	0.05
Ky-12-DS308	0.57	0.02

RNA inhibitor	relative expression level ($2^{-\Delta\Delta Ct}$ mean)	SD
Ky-12-DS309	0.80	0.05
Ky-12-DS310	0.76	0.07
Ky-12-DS313	0.49	0.05
Ky-12-DS314	0.50	0.05
Ky-12-DS315	0.50	0.04
Ky-12-DS316	0.55	0.04
Ky-12-DS317	0.26	0.04
Ky-12-DS318	0.56	0.03
Ky-12-DS319	0.59	0.09
Ky-12-DS320	0.62	0.06
Ky-12-DS321	0.62	0.05
Ky-12-DS322	0.62	0.06
Ky-12-DS323	0.66	0.03
Ky-12-DS324	0.69	0.17
Ky-12-DS325	0.74	0.06
Ky-12-DS326	0.78	0.02
Ky-12-DS327	0.79	0.03
Ky-12-DS328	0.83	0.07
Ky-12-DS329	0.84	0.03
Ky-12-DS330	0.31	0.02

RNA inhibitors Ky-12-DS230, Ky-12-DS250, Ky-12-DS254, Ky-12-DS297, Ky-12-DS298, Ky-12-DS317, and Ky-12-DS330 were perfectly selected for EC_{50} value study. The experimental results are shown in Table 26.

Table 26 EC₅₀ value

RNA inhibitor	HepG 2 cells	Huh-7 cells
	EC ₅₀ (nM)	EC ₅₀ (nM)
Ky-12-DS230	0.052	0.005
Ky-12-DS250	0.020	0.003
Ky-12-DS254	0.034	0.020
Ky-12-DS297	0.020	0.002
Ky-12-DS298	0.027	0.003
Ky-12-DS317	0.022	0.001
Ky-12-DS330	0.093	0.005

Example 3 Experiment 2 of RNA inhibitor to inhibit APOC3 gene expression in vitro

The sequences of this example were selected from Table 8. The 2' positions of the glycosyls in sequences of the sense strand and antisense strand were methoxylated or fluorinated. The modified sequences of the sense strand and antisense strand were shown in Table 6-1 and Table 7-1, respectively. Selected the corresponding sequences in Table 6-1 and Table 7-1 to anneal and synthesize RNA inhibitors.

Took the RNA inhibitor prepared by the method described in Example 1. The RNA inhibitor was transfected into HepG 2 cells to study the intervention effect of the RNA inhibitor on cells at a concentration of 1.0 nM. The APOC3 mRNA level was measure by qRT-PCR. Compare with the supernatant of HepG 2 cells without intervention, the relative expression level of APOC3 mRNA in the sample intervention group was calibrated. The obtained test results were shown in Table 27.

Table 27 APOC3 mRNA levels in HepG2 cells after RNA inhibitor intervention

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
DS103	21.22	31.59	10.37	2.143547	1.818354
	21.18	31.57	10.39	2.114036	
	21.04	32.25	11.21	1.197479	
DS104	19.18	31.87	12.69	0.429283	0.43886
	19.32	31.61	12.29	0.566442	
	19.06	32.17	13.11	0.320856	
DS105	18.9	31.66	12.76	0.408951	0.366182
	18.79	32.01	13.22	0.297302	
	18.97	31.79	12.82	0.392292	

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
DS106	19.41	31.54	12.13	0.632878	0.590938
	19.56	32.16	12.6	0.456916	
	19.52	31.54	12.02	0.68302	
DS107	18.45	30.72	12.27	0.574349	0.442755
	18.38	31.08	12.7	0.426317	
	18.21	31.29	13.08	0.327598	
DS108	18.52	31.21	12.69	0.429283	0.426716
	18.78	31.23	12.45	0.50698	
	19.04	32.05	13.01	0.343885	
DS109	18.75	31.11	12.36	0.539614	0.416712
	18.26	31.15	12.89	0.373712	
	18.41	31.45	13.04	0.336808	
DS110	17.62	30.25	12.63	0.447513	0.549706
	17.25	30.04	12.79	0.400535	
	18.26	30.05	11.79	0.80107	
DS111	17.27	29.9	12.63	0.447513	0.407824
	17.18	29.8	12.62	0.450625	
	17.05	30.14	13.09	0.325335	
DS112	18.87	31.26	12.39	0.528509	0.768558
	19.26	30.79	11.53	0.959264	
	19.32	31.08	11.76	0.817902	
	18.17	29.64	11.47	1	
	18.23	29.97	11.74	0.82932	
DS113	18.66	31.06	12.4	0.479632	0.468569
	18.51	30.72	12.21	0.547147	
	18.49	31.23	12.74	0.378929	
DS114	18.51	31.38	12.87	0.346277	0.302763
	18.67	31.45	12.78	0.368567	
	18.23	31.94	13.71	0.193446	
DS115	18.66	30.83	12.17	0.562529	0.576077
	18.61	30.92	12.31	0.510506	
	18.58	30.53	11.95	0.655197	
DS116	18.65	29.42	10.77	1.484524	

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
	18.43	29.68	11.25	1.06437	1.295607
	18.4	29.32	10.92	1.337928	
DS117	18.53	29.42	10.89	1.36604	1.028067
	18.37	29.98	11.61	0.82932	
	18.39	29.9	11.51	0.888843	
DS118	17.97	30.68	12.71	0.386891	0.4461
	18.05	30.67	12.62	0.411796	
	18.56	30.79	12.23	0.539614	
DS119	19.55	31.09	11.54	0.870551	0.587075
	18.72	30.97	12.25	0.532185	
	18.8	31.62	12.82	0.358489	
DS120	18.44	30.79	12.35	0.496546	0.592164
	18.31	30.8	12.49	0.450625	
	18.75	30.36	11.61	0.82932	
DS122	18.38	31.36	12.98	0.320856	0.229129
	18.15	31.5	13.35	0.248273	
	17.78	32.2	14.42	0.118257	
DS123	20.19	31.08	10.89	1.36604	1.335014
	20.3	31.08	10.78	1.474269	
	20.44	31.56	11.12	1.164734	
DS124	18.65	30.81	12.16	0.429283	0.436352
	18.71	30.55	11.84	0.535887	
	18.58	31.06	12.48	0.343885	
DS125	19.39	30.01	10.62	1.248331	1.396799
	19.57	29.78	10.21	1.658639	
	19.32	29.9	10.58	1.283426	
DS126	20.26	31.57	11.31	0.773782	0.712237
	20.21	31.5	11.29	0.784584	
	20.33	32.06	11.73	0.578344	
DS127	18.05	31.16	13.11	0.222211	0.262199
	18.32	30.74	12.42	0.358489	
	18.02	31.24	13.22	0.205898	
DS128	19.98	31.35	11.37	0.742262	

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
	19.77	31.16	11.39	0.732043	0.708325
	19.74	31.3	11.56	0.650671	
DS129	19.37	31.2	11.83	0.539614	0.600899
	19.58	31.11	11.53	0.664343	
	19.84	31.52	11.68	0.598739	
DS130	19.92	31.12	11.2	0.835088	0.582446
	19.18	31.17	11.99	0.482968	
	19.35	31.51	12.16	0.429283	
DS131	18.78	31.86	13.08	0.22688	0.346228
	18.72	31.25	12.53	0.332171	
	19.15	31.15	12	0.479632	
DS132	18.93	32.21	13.28	0.19751	0.188774
	18.65	32.26	13.61	0.157127	
	18.65	31.83	13.18	0.211686	

The RNA inhibitors DS104-105, DS107-109, DS111, DS113-114, DS118, DS122, DS124, DS127, DS131 and DS132 were selected for further activity studies.

Example 4 Experiment 3 of RNA inhibitor to inhibit APOC3 gene expression in vitro

The sequences of this example were selected from Table 8. The 2' positions of the glycosyls in sequences of the sense strand and antisense strand were methoxylated or fluorinated. The modified sequences of the sense strand and antisense strand were shown in Table 6-1 and Table 7-1, respectively. The corresponding sequences in Table 6-1 and Table 7-1 were annealed to synthesize RNA inhibitors. Investigation of the effect of RNA inhibitors on APOC3 in cells at a low concentration of 0.1 nM. Took the RNA inhibitor prepared by the method described in Example 1. The RNA inhibitor was transfected into HepG 2 cells and the APOC3 mRNA level was measure by qRT-PCR. Compare with the supernatant of HepG 2 cells without intervention, the relative expression level of APOC3 mRNA in the sample intervention group was calibrated. The obtained test results were shown in Table 28.

Table 28

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
DS104	15.88	30.31	14.43	0.939522749	1.043193741
	16.27	30.21	13.94	1.319507911	
	15.77	30.31	14.54	0.870550563	

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
DS105	15.64	30.4	14.76	0.747424624	0.675779913
	15.49	30.53	15.04	0.615572207	
	15.47	30.4	14.93	0.664342907	
DS107	15.2	30.42	15.22	0.543367431	0.607211557
	15.66	30.54	14.88	0.687770909	
	15.52	30.62	15.1	0.590496331	
DS108	15.3	31.36	16.06	0.303548721	0.269799651
	15.84	32.03	16.19	0.277392368	
	16.01	32.48	16.47	0.228457863	
DS109	15.81	30.86	15.05	0.611320139	0.617098626
	15.55	30.61	15.06	0.607097442	
	15.35	30.35	15	0.632878297	
DS111	14.62	29.75	15.13	0.578344092	0.656424156
	14.66	29.58	14.92	0.668963777	
	14.92	29.73	14.81	0.721964598	
DS113	15.3	30.77	15.47	0.456915725	0.521149998
	15.35	30.49	15.14	0.574349177	
	15.34	30.59	15.25	0.532185091	
DS114	14.99	31.04	16.05	0.305660069	0.304330291
	15.23	31.25	16.02	0.312082637	
	15.29	31.39	16.1	0.295248165	
DS118	16.17	31.04	14.87	0.692554734	0.823958851
	15.84	31.07	15.23	0.539614118	
	15.85	29.88	14.03	1.2397077	
DS122	15.23	29.8	14.57	0.852634892	0.770469348
	15.35	30.6	15.25	0.532185091	
	15.98	30.43	14.45	0.926588062	
DS124	14.84	31.13	16.29	0.258816231	0.280412995
	14.95	31.05	16.1	0.295248165	
	15.17	31.31	16.14	0.287174589	
DS127	15.22	30.14	14.92	0.668963777	0.71356103
	15.81	30.51	14.7	0.77916458	
	15.72	30.59	14.87	0.692554734	

RNA inhibitor	GAPDH	APOC3	APOC3-GAPDH	$2^{-\Delta\Delta Ct}$	Mean value
DS131	15.5	31.36	15.86	0.348685917	0.35881844
	15.37	30.94	15.57	0.426317446	
	15.34	31.41	16.07	0.301451957	
DS132	15.5	32.05	16.55	0.216134308	0.242261641
	15.48	31.92	16.44	0.233258248	
	15.44	31.63	16.19	0.277392368	

Results: DS107, DS108, DS113, DS114, DS124, DS131 and DS132 were further selected for the next EC₅₀ test.

Example 5 Experiment of RNA inhibitor to inhibit APOC3 gene expression in vitro

This example detects the EC₅₀ values of DS107, DS108, DS113, DS114, DS124, DS131 and DS132.

The RNA inhibitor was transfected into HepG 2 cells to study the intervention effect of the RNA inhibitor on cells at a concentration of 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, 0.05 nM and 0.01 nM. The APOC3 mRNA level was measure by qRT-PCR. EC₅₀ was calculated and the test results were shown in Table 29.

Table 29 EC₅₀ value of RNA inhibitor

RNA inhibitor	Absolute EC ₅₀ (nM)
DS107	0.035
DS108	<0.01
DS113	<0.01
DS114	0.029
DS124	0.042
DS131	0.018
DS132	0.019

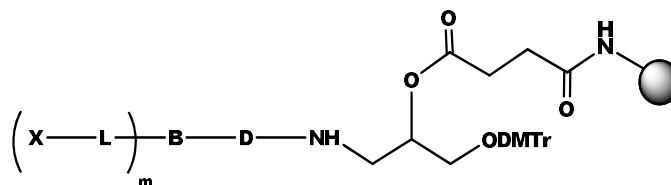
DS107, DS108, DS113, DS114, DS124, DS131 and DS132 were selected for the next step of conjugating with 5'MVIP/3'MVIP.

Example 6 Synthesis of 5'MVIP and 3'MVIP compounds

When the 3' end of the sense strand or antisense strand of the RNA inhibitor of the present invention is conjugated with a carrier structure 3'MVIP, the Solid Support of 3'MVIP is used as the starting monomer for solid-phase synthesis. When the 5' end of the sense strand or antisense strand of

the RNA inhibitor of the present invention is conjugated with a carrier structure 5'MVIP, the 5'MVIP phosphoramidite monomer is used as the last monomer for solid-phase synthesis.

When the 3' end of the sense strand or antisense strand of the RNA inhibitor of the present invention is conjugated with 3'MVIP, the solid support of 3'MVIP is used as the starting monomer for solid-phase synthesis. The general formula of solid support of 3'MVIP is as follows:



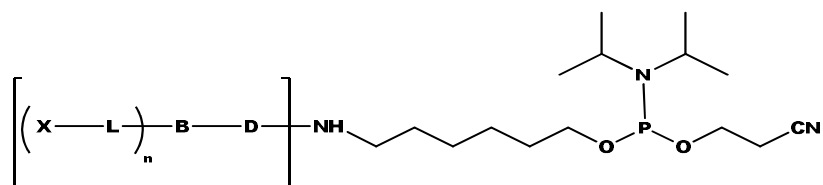
When m is 1-4, the linker B part in the general formula is branched for 1 to 4 times respectively to obtain the corresponding Solid Support of 3'MVIP.

For example, when m is 1, the obtained Solid Support serves as the starting monomer for solid-phase synthesis of the sense strand of the RNA inhibitors Kylo-12-DS134~ Kylo-12-DS136, Kylo-12-DS142, Kylo-12-DS145, Kylo-12-DS146, Kylo-12-DS157 and Kylo-12-DS158 and the antisense strand of Kylo-12-DS131~ Kylo-12-DS133, Kylo-12-DS139, Kylo-12-DS140, Kylo-12-DS149, Kylo-12-DS150 and other RNA inhibitors described in the present invention;

when m is 2, the obtained Solid Support serves as the starting monomer for solid-phase synthesis of the sense strand of the RNA inhibitors Kylo-12-DS141, Kylo-12-DS143, Kylo-12-DS144, Kylo-12-DS154~Kylo-12-DS156, Kylo-12-DS166, Kylo-12-DS169 and Kylo-12-DS170 and the antisense strand of Kylo-12-DS1081, Kylo-12-DS137, Kylo-12-DS138, Kylo-12-DS151~ Kylo-12-DS153, Kylo-12-DS163, Kylo-12-DS164 and other RNA inhibitors described in the present invention;

when m is 3, the obtained Solid Support serves as the starting monomer for solid-phase synthesis of the sense strand of the RNA inhibitors Kylo-12-DS159, Kylo-12-DS160, Kylo-12-DS165, Kylo-12-DS167, Kylo-12-DS168, Kylo-12-DS174 and Kylo-12-DS175 and the antisense strand of Kylo-12-DS147, Kylo-12-DS148, Kylo-12-DS161, Kylo-12-DS162, Kylo-12-DS171, Kylo-12-DS172 and other RNA inhibitors described in the present invention.

When the 5' end of the sense strand or antisense strand of the RNA inhibitor of the present invention has 5'MVIP, the 5'MVIP phosphoramidite monomer is the last phosphoramidite monomer for solid-phase synthesis of the sense strand or antisense strand. The general formula of 5'MVIP phosphoramidite monomer is as follows:



When n is 1-4, the linker B part in the general formula is branched for 1 to 4 times respectively to obtain the corresponding 5'MVIP phosphoramidite monomer.

For example, when n is 1, the resulting 5'MVIP phosphoramidite monomer is used as the last monomer for solid-phase synthesis of the sense strand of RNA inhibitors Kylo-12-DS131~ Kylo-12-DS134, Kylo-12-DS137, Kylo-12-DS138, Kylo-12-DS141, Kylo-12-DS147, Kylo-12-DS148 and other RNA inhibitors described in the present invention and the antisense strand of Kylo-12-DS135, Kylo-12-DS136, Kylo-12-DS143, Kylo-12-DS144, Kylo-12-DS159, Kylo-12-DS160 and other RNA inhibitors described in the present invention.

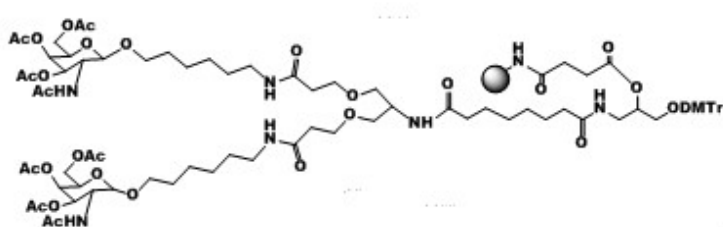
When n is 2, the resulting 5'MVIP phosphoramidite monomer is used as the last monomer for solid-phase synthesis of the sense strand of Kylo-12-DS1081, Kylo-12-DS139, Kylo-12-DS140, Kylo-12-DS142, Kylo-12-DS151~Kylo-12-DS154, Kylo-12-DS161, Kylo-12-DS162, Kylo-12-DS165 and other RNA inhibitors described in the present invention and the antisense strand of Kylo-12-DS145, Kylo-12-DS146, Kylo-12-DS155, Kylo-12-DS156, Kylo-12-DS167, Kylo-12-DS168 and other RNA inhibitors described in the present invention.

When n is 3, the resulting 5'MVIP phosphoramidite monomer with three liver targeting specific ligands X is used as the last monomer for solid-phase synthesis of the sense strand of Kylo-12-DS149, Kylo-12-DS150, Kylo-12-DS163, Kylo-12-DS164, Kylo-12-DS166, Kylo-12-DS171~Kylo-12-DS173 and other RNA inhibitors described in the present invention and the antisense strand of Kylo-12-DS157, Kylo-12-DS158, Kylo-12-DS169, Kylo-12-DS170, Kylo-12-DS174, Kylo-12-DS175 and other RNA inhibitors described in the present invention.

The above is only an exemplary list of some RNA inhibitors. This rule is also applicable to the RNA inhibitors described in the present invention but not listed, that is, when the 3' end of the sense strand or antisense strand of the RNA inhibitor of the present invention is conjugated with the carrier structure 3'MVIP, the solid support of 3'MVIP is used as the starting monomer for solid phase synthesis. When the 5' end of the sense strand or antisense strand of the RNA inhibitor of the present invention is conjugated with the carrier structure 5'MVIP, the 5'MVIP phosphoramidite monomer is used as the last monomer of solid phase synthesis.

This example only provides an exemplary chemical synthesis process of several 3'MVIP Solid Supports and 5'MVIP phosphoramidite monomers of the RNA inhibitor of the present invention. Those skilled in the art can easily synthesize other 3'MVIP Solid Support and 5'MVIP phosphoramidite monomers not listed herein. The synthesis process is described as follows:

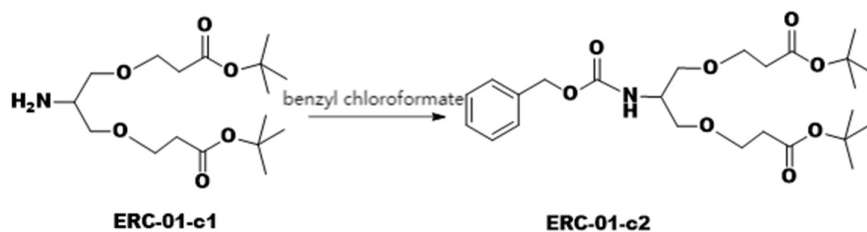
4.1.1 Synthesis of Solid Support of 3'MVIP09



Description of synthesis process:

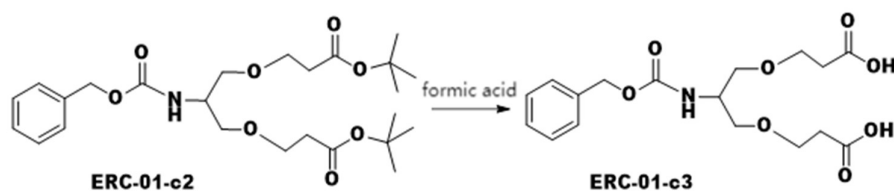
tert-butyl acrylate + 2-amino-1,3-propanediol $\longrightarrow$ ERC-01-c1

4.1.1.2 Synthesis of ERC-01-c2



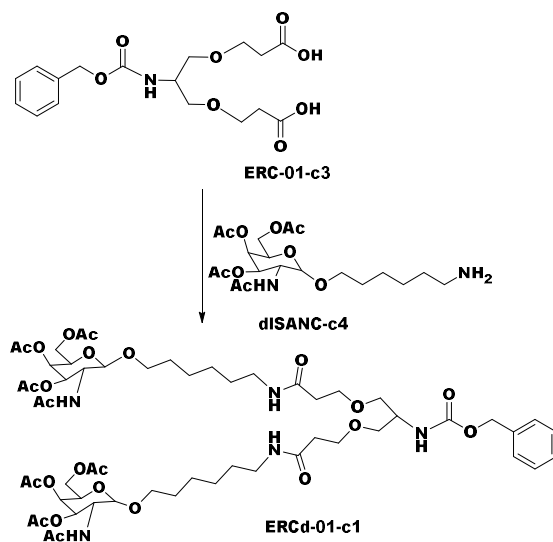
Weighed ERC-01-c1 (6.2g, 17.9mmol), added 50ml of dichloromethane, 23ml of sodium carbonate solution (25%), added benzyl chloroformate (8.2ml, 57.4mmol) dropwise at room temperature for 2 hours, let it react overnight at room temperature, washed with saturated salt water for three times, dried with anhydrous sodium sulfate, evaporated the solvent, passed it through a chromatography column (ethyl acetate: petroleum ether =5%-30%), and obtained 4.0g of oil.

4.1.1.3 Synthesis of ERC-01-c3



Weighed ERC-01-c2 (4.0g, 8.3mmol), added 12ml of formic acid, let it react overnight at room temperature, evaporated the solvent under reduced pressure to obtain 2.8g of product.

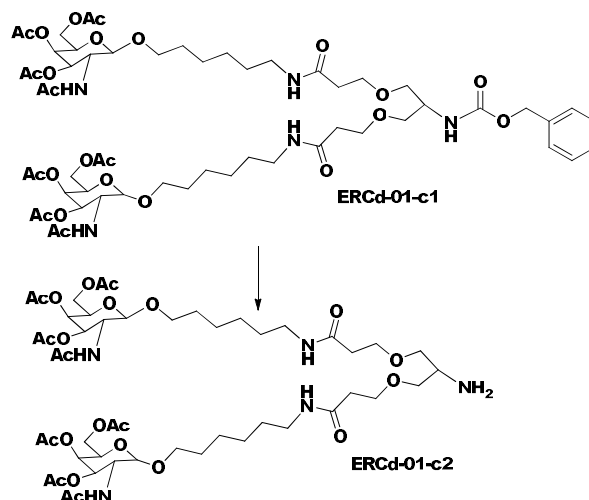
4.1.1.4 Synthesis of ERCd-01-c1



Added compounds ERC-01-c3 (1.11g, 3.0mmol) and dISANC-c4 (3.6g, 8.04mmol) to DMF (60 ml), then added HOBt (2.24g) and HBTU (3.36g), and then slowly added DIEA (4.16ml). Stirred the reaction solution for 3 hours at room temperature. Then added water and extracted the aqueous layer

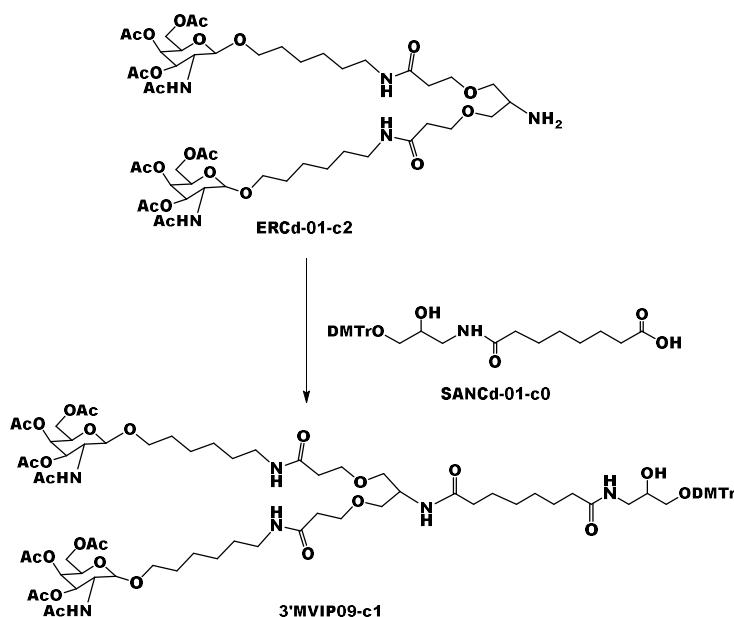
with dichloromethane (2x10ml). Combined the organic layers, and then washed with saturated sodium bicarbonate (80 ml), water (2x60 ml), and saturated salt water (60ml) successively. Dried with anhydrous sodium sulfate, evaporated to dryness under reduced pressure, and purified by silica gel column chromatography (eluent: 3-15% MeOH in DCM). Obtained light yellow solid 3.24g.

4.1.1.5 Synthesis of ERCd-01-c2



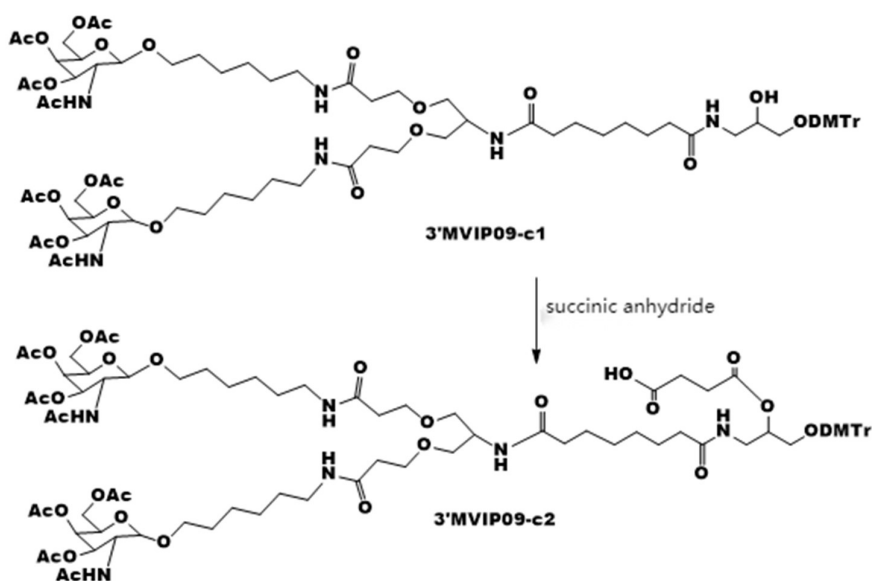
Dissolved ERCd-01-c1 (3.24g, 2.6mmol) in methanol (60ml), and added 10% palladium carbon (0.3g) and acetic acid (2.0ml). Then introduced hydrogen at atmospheric pressure to react overnight. The reaction solution was filtered with diatomite, and the filtrate was evaporated to dryness under reduced pressure to obtain 2.9g of oil ERCd-01-c2.

4.1.1.6 Synthesis of 3'MVIP09-c1



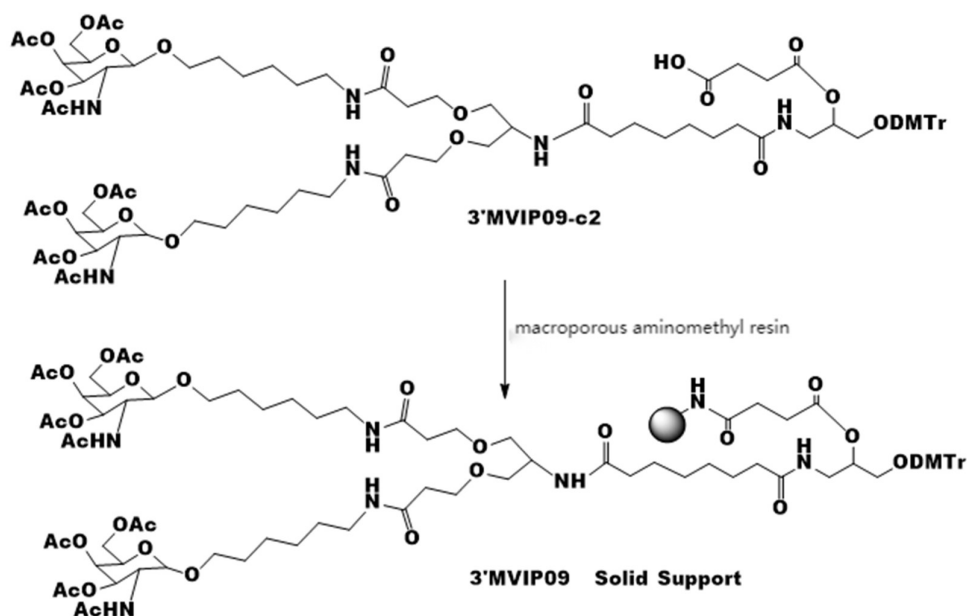
Successively added SANCd-01-c0 (0.824g, 1.5mmol) and ERCd-01-c2 (1.09g, 1.0mmol) into a vial, then added 10ml of DCM, stirred until dissolved, then successively added TBTU (0.963g) and DIPEA (0.517g), let is react overnight, added water, extracted with DCM, washed the organic phase with saturated salt water, dried, filtered and concentrated, and finally purified by a silica gel column to obtain 1.3g of product.

4.1.1.7 Synthesis of 3'MVIP09-c2



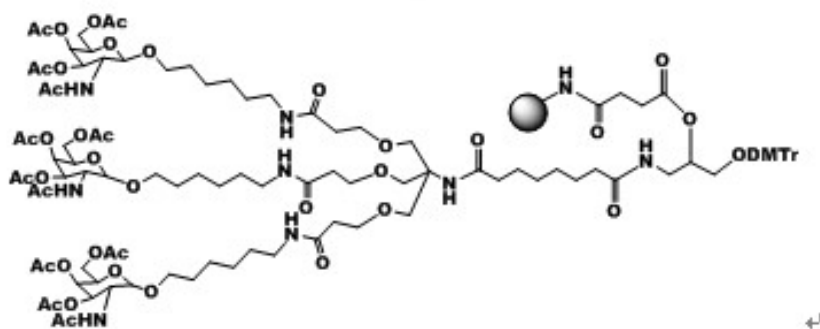
Added 3'MVIP09-c1 (1.62g, 1 μmol) and 10ml of DCM into a vial in turn, stirred at room temperature until dissolved, then added DMAP (0.366g) and succinic anhydride (0.2g, 3 μmol) in turn, stirred at room temperature to react. Concentrated DCM after the reaction is validated by TLC analysis, added water, extracted with DCM, washed the organic phase with saturated salt water, dried the organic phase by anhydrous sodium sulfate, filtered and concentrated, and finally purified by a silica gel column to obtain 1.55g product.

4.1.1.8 Synthesis of Solid Support of 3'MVIP09



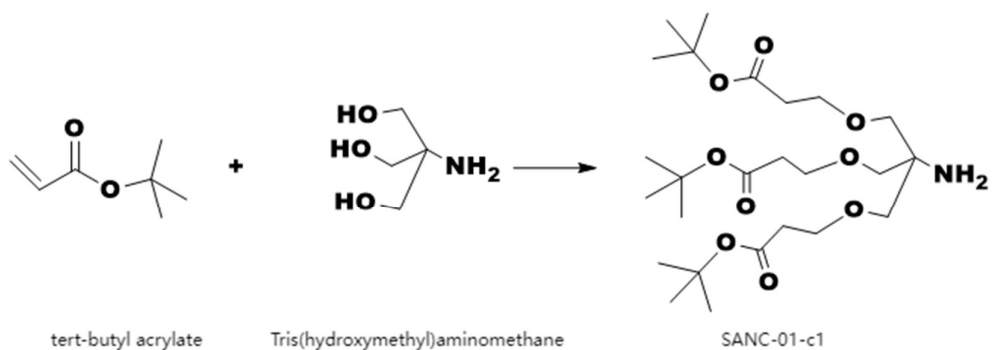
Added 3'MVIP09-c2 (0.86g, 0.5 μmol) and 10ml DMF into a vial in turn, after dissolution, added HBTU (0.19g), DIPEA (0.194g) and macroporous aminomethyl resin (2.0g) in turn, placed on the shaker for 24h, filtered, washed the resin with 10% methanol/DCM, and then used 25% acetic acid/pyridine for end capping, with a degree of substitution of 150 $\mu\text{mol/g}$.

4.1.2 Synthesis of Solid Support of 3'MVIP17



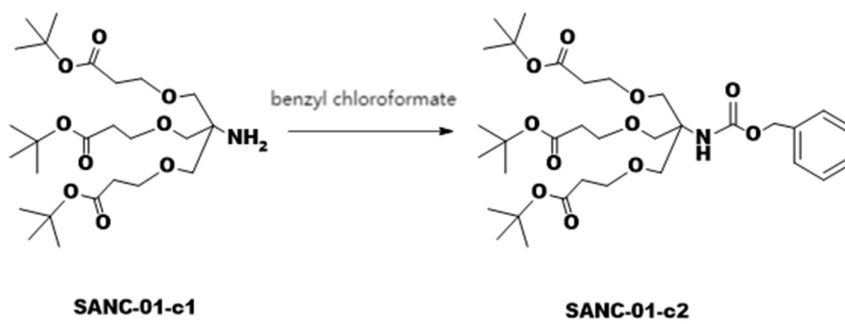
3'MVIP17 Solid Support

4.1.2.1 Synthesis of SANC-01-c1



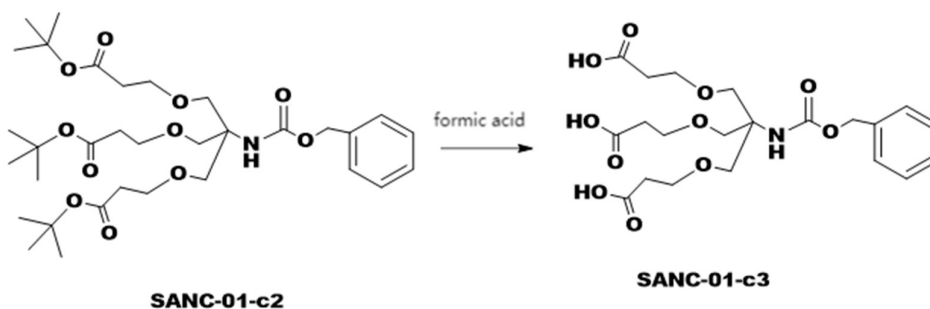
The synthesis steps are referred to 4.1.1.1 synthesis of ERC-01-c1.

4.1.2.2 Synthesis of SANC-01-c2



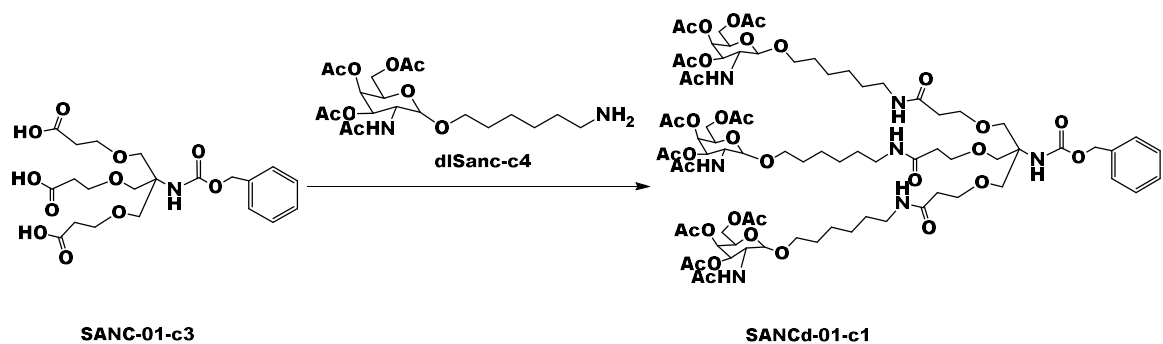
The synthesis steps are referred to 4.1.1.2. synthesis of ERC-01-c2.

4.1.2.3 Synthesis of SANC-01-c3



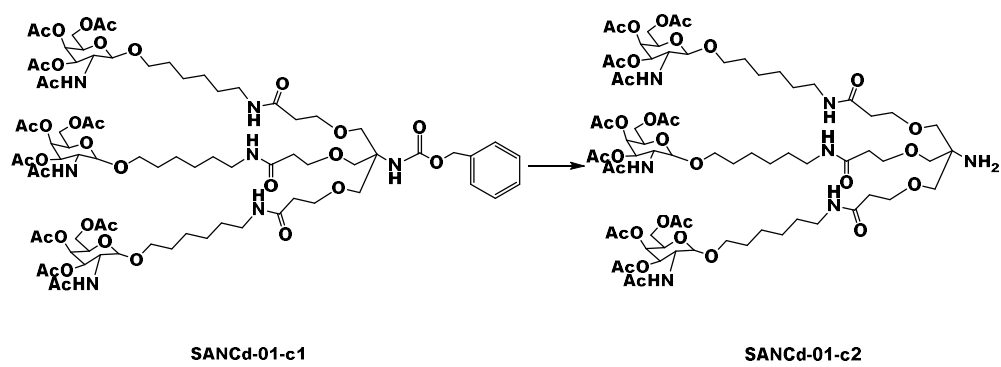
The synthesis steps are referred to 4.1.1.3. Synthesis of ERC-01-c3.

4.1.2.4 Synthesis of SANCd-01-c1



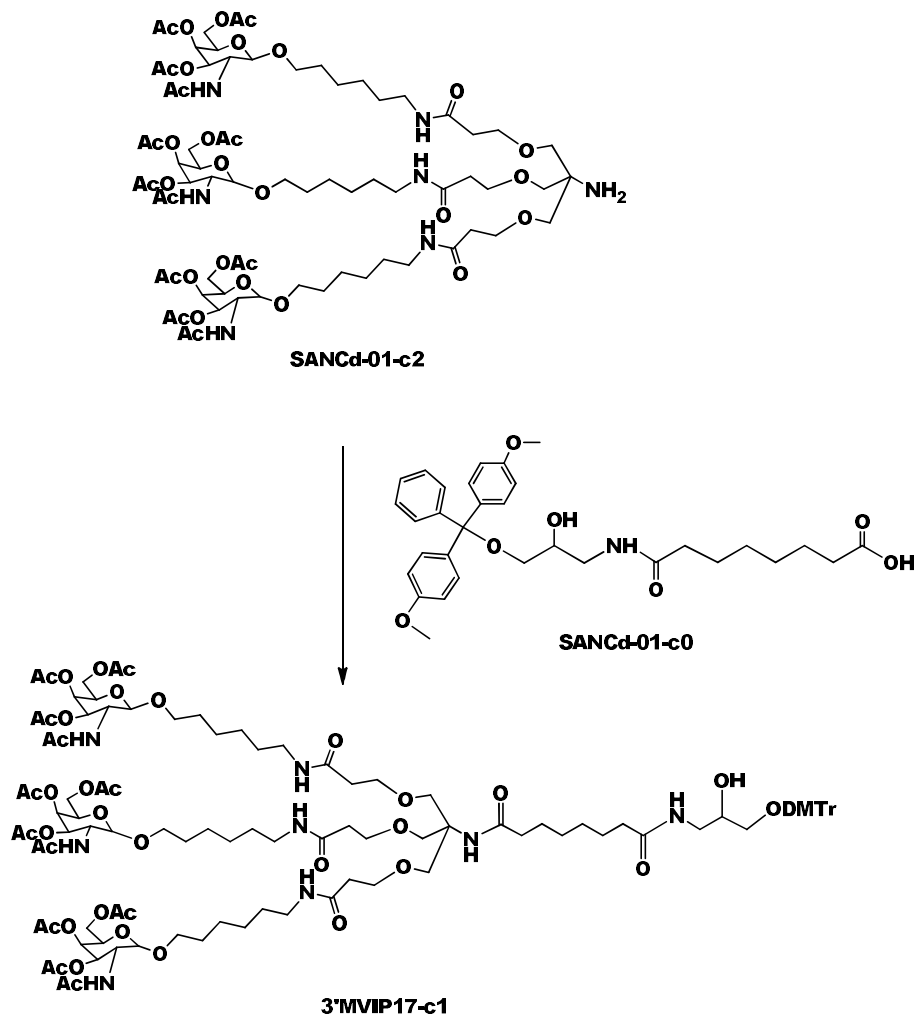
The synthesis steps are referred to 4.1.1.4. Synthesis of ERCd-01-c1.

4.1.2.5 Synthesis of SANCd-01-c2



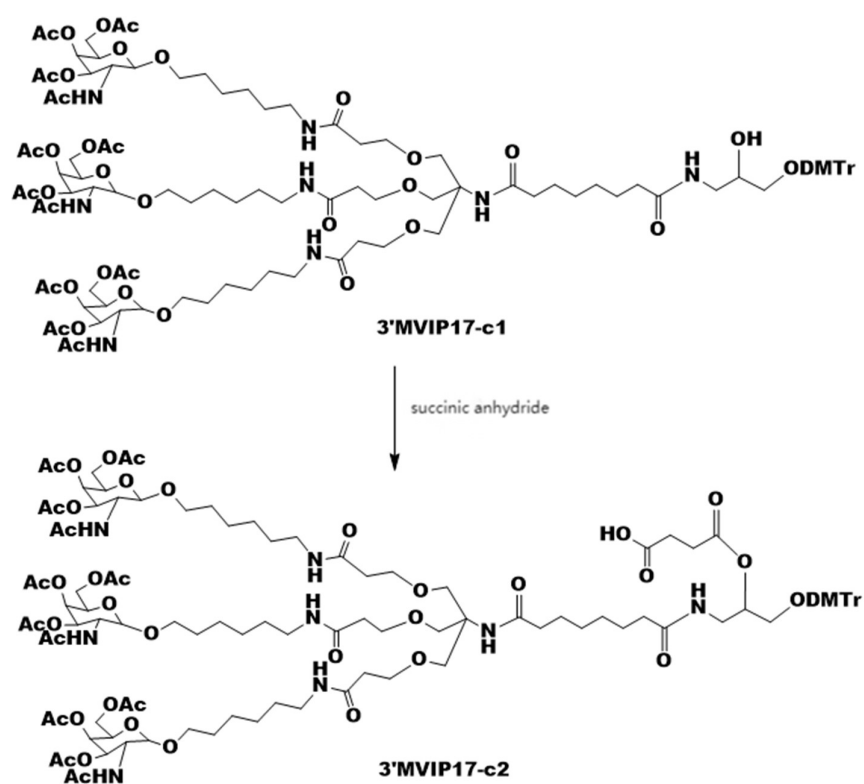
The synthesis steps are referred to 4.1.1.5. Synthesis of ERCd-01-c2.

4.1.2.6 Synthesis of 3'MVIP17-c1



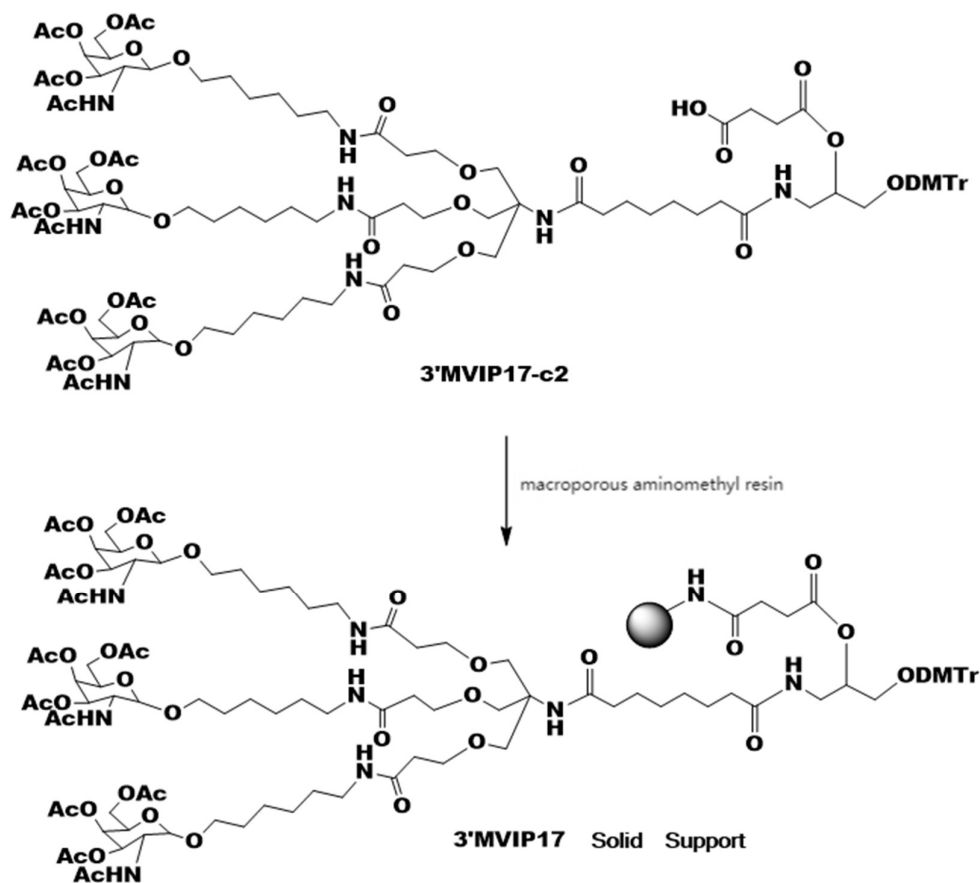
The synthesis steps are referred to 4.1.1.6. Synthesis of 3'MVIP09-c1, 3'MVIP17-c1 was synthesized.

4.1.2.7 Synthesis of 3'MVIP17-c2



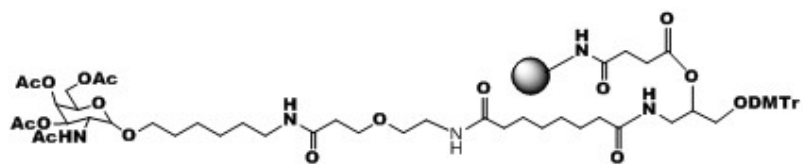
The synthesis steps are referred to 4.1.1.7. Synthesis of 3'MVIP09-c2.

4.1.2.8 Synthesis of Solid Support of 3'MVIP17



The synthesis steps are referred to 4.1.1.8 Synthesis of Solid Support of 3'MVIP09.

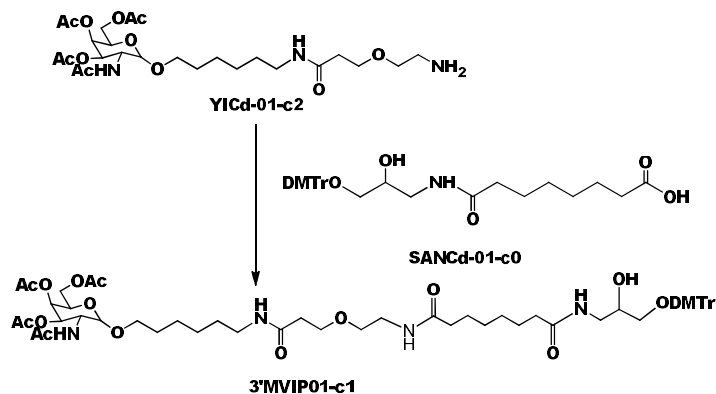
4.1.3 Synthesis of Solid Support of 3'MVIP01:



3'MVIP01 Solid Support

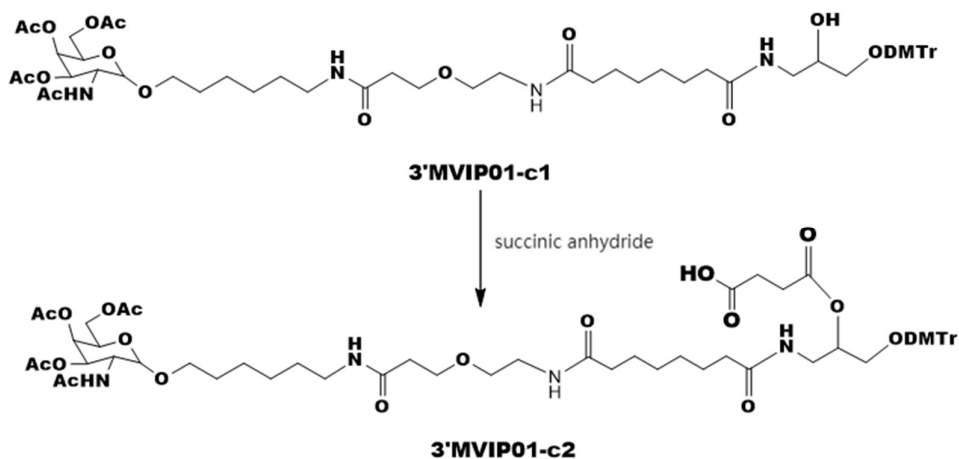
Description of synthesis process:

4.1.3.1 Synthesis of 3'MVIP01-c1



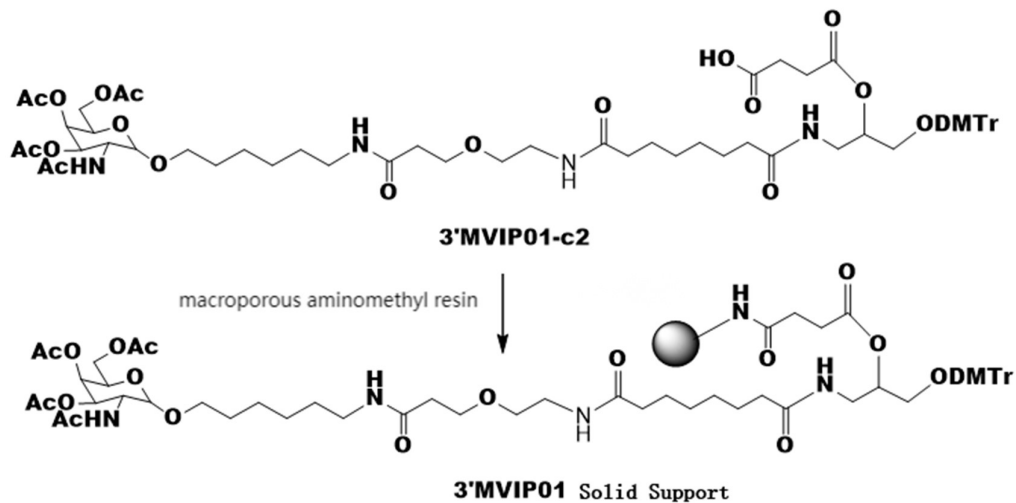
The synthesis steps are referred to 4.1.1.6. synthesis of 3'MVIP09-c1.

4.1.3.2 Synthesis of 3'MVIP01-c2



The synthesis steps are referred to 5.1.1.7. synthesis of 3'MVIP09-c2.

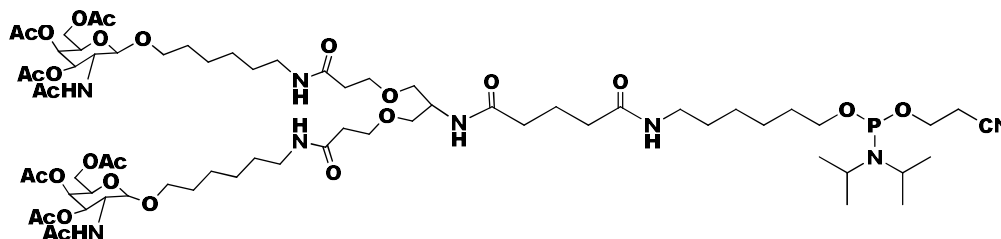
4.1.3.3 Synthesis of Solid Support of 3'MVIP01



The synthesis steps are referred to 4.1.1.8. synthesis of Solid Support of 3'MVIP09.

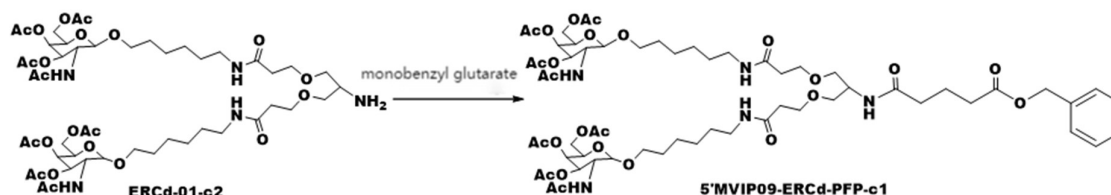
4.2. Synthesis of 5'MVIP phosphoramidite monomer

4.2.1 Synthesis of 5'MVIP09 phosphoramidite monomer:



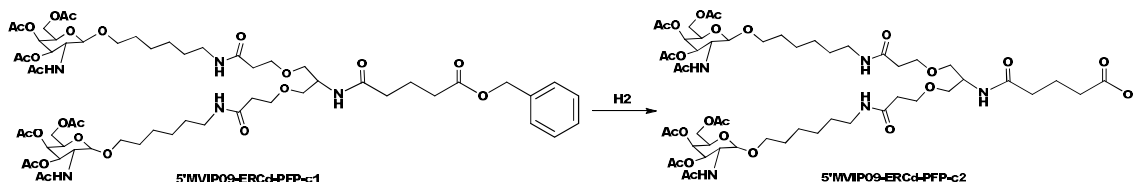
5'MVIP09 phosphoramidite monomer

4.2.1.1 Synthesis of 5'MVIP09-ERCd-PFP-c1



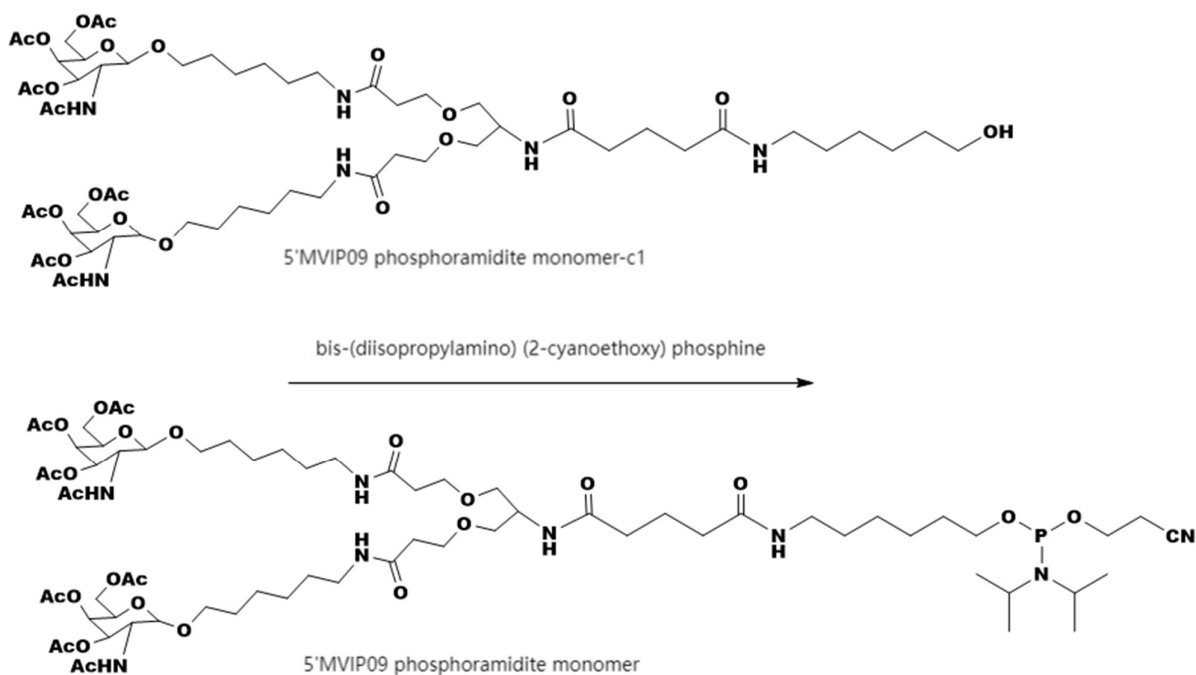
Weighed ERCd-01-c2 (2.18g, 2.0mmol) to dissolve in DMF (50ml), added monobenzyl glutarate (0.53g, 2.4mmol), DIPEA (0.78g) and TBTU (0.84g), stirred at room temperature overnight, added water to quench (50ml), extracted with DCM (30ml*3), washed with 10% citric acid (50ml*3), 50ml saturated sodium bicarbonate and 100ml pyridine, dried with anhydrous sodium sulfate, filtered, conducted rotary evaporation, and purified by a column to obtain the product 5'MVIP09-ERCd-PFP-c1 (2.15g).

4.2.1.2 Synthesis of 5'MVIP09-ERCd-PFP-c2



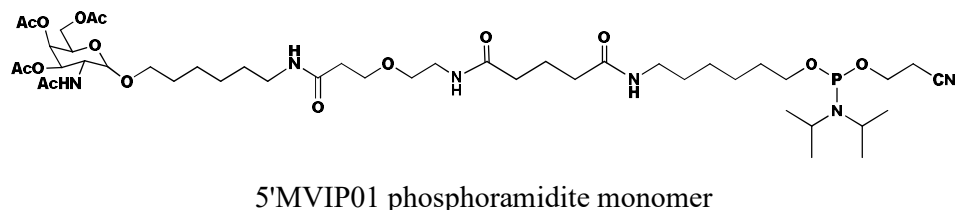
Weighed 5'MVIP09-ERCd-PFP-c1 (2.15g, 1.66mmol) and 10% palladium carbon (0.21g), added methanol (50ml), and hydrogenated overnight with stirring at room temperature, filtered palladium carbon with diatomite after the reaction, conducted rotary evaporation to obtain 5'MVIP09-ERCd-PFP-c2 crude product (1.9g).

4.2.1.3 Synthesis of 5'MVIP09-ERCd-PFP



Weighed 5'MVIP09 phosphoramidite monomer-c1 (1.3g, 1.0mmol) to dissolve in acetonitrile (30ml), added diisopropylamine triazole (0.22g), added bis-(diisopropylamino) (2-cyanoethoxy) phosphine (0.36g, 1.2mmol) dropwise in an ice bath, let it react for 4h at room temperature, after the reaction is validated by HPLC in-process control, concentrated and purified by a column to obtain the product 5'MVIP09 monomer (1.2g).

4.2.2 Synthesis of 5'MVIP01 phosphoramidite monomer:



Except for weighing YICd-01-c2 (1.12g, 2.0mmol) as the phosphoramidite monomer of 5'MVIP01, refer to 4.2.1.1~4.2.1.5 for the remaining operations.

Example 7 Synthesis of RNA inhibitor with different siRNA conjugated to 5'MVIP09/ 3'MVIP09

Description of synthesis of the antisense strand and its carrier structure: purged a reagent bottle with argon for at least 2 min. Added phosphoramidite monomer and acetonitrile into the reagent bottle in turn, tightened the bottle cap and shook until the solid is completely dissolved by visual inspection.

Then added 3A molecular sieve and let it stand for more than 8 h for later use. Purged a reagent bottle with argon for at least 2 min. Added xanthane hydride and dried pyridine into the reagent bottle in turn, tightened the bottle cap, shook until the solid is completely dissolved by visual inspection, and stored temporarily for later use. Ensure to carry out the following operations at room temperature of 20~30 °C: weighed 3'MVIP carrier, added it to a reagent bottle, then added acetonitrile, shook until mix evenly. Transferred the carrier to a synthesis column, and eluted the residual carrier in the reagent bottle with acetonitrile and transferred to the synthesis column. After elution, added acetonitrile to fill the synthetic column, and recorded the amount of acetonitrile used. Installed and fixed the synthetic column according to the instrument instructions.

Connected the monomer solution prepared above, CAP A, CAP B, oxidant, thioreagent, activator, decapping agent and acetonitrile to the pipeline corresponding to AKTA PILOT100, and ensured that the pipeline is inserted into the bottom of the reagent bottle.

After the synthesis method is set, the instrument is ready for all work, clicked Run to start the synthesis. Observed and recorded each detritylation peak area online. During the synthesis process, added additional amount according to the actual amount of deprotection reagent used.

After the synthesis, purged the synthetic column with argon for at least 2 h, and unloaded the synthetic column according to the operating procedures. Transferred the solid phase support in the synthesis column to a reaction bottle, added methylamine aqueous solution and ammonia water, and put the reaction bottle into a shaker at 35 °C for 2-3 hours. Filtered the solution into a round bottom flask, washed the residual solid phase with 50% ethanol aqueous solution, filtered again and mixed with the previous filtrate, connected the round bottom flask with a rotary evaporator, set the water temperature at 50°C and evaporated until there is no distillate, added ethanol into the round bottom flask, mixed well and evaporated again until there is no distillate. Repeated the operation until white powder appeared at the bottom of the flask. Prepared the obtained white powder into a solution, purified by a reverse chromatography column, and sampled to detect OD260 and purity. Divided the purified antisense strand solution into vials and lyophilized for future use, and stored the product sealed in a -20°C refrigerator.

The synthesis process of sense strand and its carrier structure is the same as that of antisense strand and its carrier structure, in which the carrier loaded in the column is Universal carrier. Added DIPEA to the obtained intermediate to prepare a solution, added 5'MVIP phosphoramidite monomer, mixed well, and put the reaction bottle into a shaker at 35 °C for 2-3 hours.

Description of synthetic annealing process of RNA inhibitor:

Took a sense strand and its carrier structure, took an antisense strand and its carrier structure, mixed

them in a reaction bottle in an equimolar ratio of 1:1. Turned off the power of the water bath after 5 minutes of 95°C water bath, let it naturally cool down to below 40 °C. Added 3M sodium acetate aqueous solution to the solution containing double strands, mixed well, then added an appropriate volume of absolute ethanol, mixed well, and put the reaction solution into a -20 °C refrigerator for 45min. Set the high-speed freezing centrifuge to pre-cooling at 4 °C, put in the solution containing double strands after the temperature is reached, and started the centrifuge. Took out the centrifuged solution containing double strands, removed the supernatant, added ultrapure water to completely dissolve the solid, and took samples to detect OD260 and purity, obtained the RNA inhibitors in Table 14. Divided the purified finished solution into vials and lyophilized for future use, and stored the product sealed in a -20 °C refrigerator.

Example 8-1 Study on the use of PHH to evaluate the activity of RNA inhibitors containing 5'MVIP09/3'MVIP09 structure

Primary human hepatocytes (PHH) were used to evaluate the in vitro activity of the RNA inhibitors in Table 15. Thawed frozen PHH and adjusted the cell density to 6×10^5 cells per ml. Took from the dilution plate the prepared RNA inhibitors and added it to a 96-well cell culture plate (10 µL/well), and added 90 µL/well of cells to the 96-well plate, with a final volume of 100 µL per well. The RNA inhibitors were diluted 10-fold starting from 200 nM, with a total of 3 concentration points and triplicate wells. After addition, the cells were placed in a 5% CO₂, 37°C incubator for 48 hours. Extracted RNA from cells and then reverse transcribed it into cDNA. Detected target gene cDNA using qPCR. GAPDH was used as an internal reference gene and qPCR was performed in a 384-well plate. The qPCR reaction program was: 95°C for 10 minutes; then 95°C for 15 seconds and 60°C for 1 minute for 40 cycles. Detected the relative expression level of APOC3 mRNA. The test results were shown in Table 31.

Table 31 Relative expression level of APOC3 mRNA after RNA inhibitor intervention

RNA inhibitor	APOC3 mRNA Relative expression level ($2^{-\Delta\Delta Ct}$)			SD		
	200 nM	20 nM	2 nM	200 nM	20 nM	2 nM
Kylo-12-DS1071	0.35	0.49	0.77	0.00	0.07	0.04
Kylo-12-DS1081	0.46	0.58	0.84	0.21	0.09	0.07
Kylo-12-DS1131	0.31	0.55	0.81	0.03	0.13	0.02
Kylo-12-DS1141	0.39	0.47	0.74	0.04	0.15	0.05
Kylo-12-DS1241	0.41	0.57	0.80	0.02	0.12	0.06
Kylo-12-DS1311	0.37	0.56	0.75	0.03	0.11	0.04
Kylo-12-DS1321	0.34	0.45	0.65	0.00	0.07	0.03

This example demonstrated that the 5'MVIP09/3'MVIP09 carrier combination can achieve self-delivery of siRNA.

Example 8-2 Evaluation of the activity of RNA inhibitors with 5'MVIP/3'MVIP using PHH

This example used primary human hepatocytes to evaluate the in vitro activity of the modified RNA inhibitors in Table 22-1. Thawed frozen PHH and adjusted the cell density to 6×10^5 cells per ml. Took from the dilution plate the prepared RNA inhibitors and added it to a 96-well cell culture plate (10 μ L/well), and added 90 μ L/well of cells to a 96-well plate, with a final volume of 100 μ L per well. The RNA inhibitors were at 2 concentrations: 200 nM and 20nM, in triplicate wells. After addition, the cells were placed in a 5% CO₂, 37°C incubator for 48 hours. Extracted RNA from cells and then reverse transcribed it into cDNA. Detected target gene cDNA using qPCR. GAPDH was used as an

internal reference gene and qPCR was performed in a 384-well plate. The qPCR reaction program was: 95°C for 10 minutes; then 95°C for 15 seconds and 60°C for 1 minute for 40 cycles. Detected the relative expression level of APOC3 mRNA. The test results were shown in Table 32.

Table 32 Relative expression level of APOC3 mRNA

RNA inhibitor	APOC3 mRNA relative expression level ($2^{-\Delta\Delta Ct}$)		SD	
	200nM	20nM	200nM	20nM
Ky-12-DS23001	0.2915	0.3771	0.0511	0.0302
Ky-12-DS25001	0.2386	0.3765	0.0616	0.0131
Ky-12-DS25401	0.3168	0.39	0.0971	0.1088
Ky-12-DS29701	0.2174	0.3763	0.0257	0.0749
Ky-12-DS29801	0.2075	0.3136	0.0517	0.0802
Ky-12-DS31701	0.1899	0.211	0.0496	0.0702
Ky-12-DS31702	0.2568	0.378	0.0237	0.0359
Ky-12-DS31703	0.2378	0.3218	0.0329	0.0219
Ky-12-DS31704	0.2977	0.4077	0.0642	0.0528
Ky-12-DS31705	0.2193	0.397	0.0384	0.0512

RNA inhibitor	APOC3 mRNA relative expression level ($2^{-\Delta\Delta Ct}$)		SD	
	200nM	20nM	200nM	20nM
Ky-12-DS31706	0.242	0.3585	0.0725	0.0233
Ky-12-DS31707	0.2364	0.3901	0.0459	0.0126
Ky-12-DS31708	0.2936	0.3789	0.0669	0.0402
Ky-12-DS31709	0.2872	0.3422	0.019	0.0712
Ky-12-DS31711	0.23	0.3988	0.071	0.0321
Ky-12-DS31712	0.2482	0.3679	0.0209	0.0715
Ky-12-DS31713	0.2641	0.4012	0.0362	0.0556
Ky-12-DS33001	0.2066	0.3198	0.0433	0.0521
Ky-12-DS33006	0.2577	0.3834	0.0236	0.0424

The test results showed that RNA inhibitors, which were formed by the carrier structure 5'MVIP17 at 5' end of the modified sense strand, the carrier structure 3'MVIP17 at 3' end of the modified sense strand, the combination 5' MVIP01/3'MVIP01, 5'MVIP01/3'MVIP17, 5'MVIP17/3'MVIP01 or 5'MVIP09/3'MVIP09 of the modified sense strand and antisense strand conjugating carrier 5'MVIP/3'MVIP, or the combination 5'MVIP01/3'MVIP09, 5'MVIP09/3'MVIP01 or 5'MVIP01/3'MVIP01 of the sense strand 5'MVIP and the sense strand 3'MVIP, can be freely taken up into PHH cells and exhibit significant inhibitory effects on APOC3 mRNA in PHH cells.

Example 9 Study on the effect of different structures of 5'MVIP and 3'MVIP conjugated to the same siRNA on the activity of RNA inhibitors

Selected the antisense strand and the sense strand respectively, paired and annealed to synthesize RNA inhibitors according to the method described in Example 7 (see Table 22-2). Examined the effect on the activity of RNA inhibitors when X, L, B, D, R₁ or R₂ are different in the structures of 5'MVIP and/or 3'MVIP. Selected APOC3 Tg mouse model of appropriate age for experimental evaluation. Administered 3mg/kg by subcutaneous injection on Day0. Collected blood on Day14 after administration, isolated serum and determined the levels of APOC3 in serum by ELISA method. The test results were shown in Table 33 and Figure 1.

Table 33 Average level of APOC3 in serum of APOC3 Tg mice (normalized)

RNA inhibitor	average APOC3 level after RNA inhibitor intervention
Saline group	1.000
Kylo-12-DS131	0.331
Kylo-12-DS141	0.312
Kylo-12-DS142	0.291
Kylo-12-DS147	0.138
Kylo-12-DS148	0.136
Kylo-12-DS149	0.101
Kylo-12-DS150	0.127
Kylo-12-DS1081	0.179
Kylo-12-DS151	0.193
Kylo-12-DS152	0.184
Kylo-12-DS153	0.100
Kylo-12-DS154	0.134
Kylo-12-DS155	0.199
Kylo-12-DS156	0.142
Kylo-12-DS157	0.178
Kylo-12-DS158	0.211

RNA inhibitor	average APOC3 level after RNA inhibitor intervention
Kylo-12-DS159	0.243
Kylo-12-DS160	0.191

Note: Normalization is to divide the TG level of an animal at a time point by the TG level of the animal on Day 0 to obtain a ratio A1, and to divide the average TG level of the control group at a time point by the average TG level of the control group on Day 0 to obtain a ratio A2. A1 divided by A2 is the normalized average TG level in the blood. The test results showed that the overall activity of the RNA inhibitors with n+m=4 in the 5'MVIP/3'MVIP combination is slightly higher than that of the combination with n+m=3.

Example 10 Investigation of the effect of different 5' or 3' end nucleotides on RNA inhibitor activity

Transfected RNA inhibitor into HepG2 cells, and measured APOC3 mRNA level by qRT-PCR. Compared with the supernatant of HepG 2 cells without intervention, the relative percentage of APOC3 mRNA in the intervention group was calibrated. The test results are shown in Table 34 and Figure 2.

Table 34 Inhibition rate of APOC3 mRNA after RNA inhibitor intervention

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strands code	Average Inhibition	
							1nM	0.1nM
947	S439	aaggacagauuc tcagugu	683	AS439	acacugagaauacug ucccuu	DS321	0.951	0.819
948	S266	gaggacagauuc ucagugu	684	AS268	acacugagaauacug ucccuc	DS331	0.941	0.782
949	S267	caggacagauuc ucagugu	685	AS269	acacugagaauacug ucccug	DS341	0.941	0.664
950	S268	gggacagauuc agugcua	686	AS270	gcacugagaauacu guccuu	DS351	0.924	0.768

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strands code	Average Inhibition	
							1nM	0.1nM
951	S269	gagcgacaguauuc tcagugu	687	AS271	acacugagaauacug ucgcuc	DS361	0.961	0.54
952	S270	uagggacaguauuc tcagugu	688	AS272	acacugagaauacug ucccua	DS371	0.922	0.643
953	S271	augggacaguauuc tcagugu	689	AS273	acacugagaauacug ucccau	DS381	0.573	0.411
954	S272	agggacaguauucu cagugua	690	AS274	ucacugagaauacu gucccuu	DS391	0.954	0.352
955	S273	aagggacaguauuc ucagu	691	AS275	ucacugagaauacu gucccuu	DS401	0.906	0.513
956	S274	gcuuaaaagggaca guauuca	692	AS276	ugaauacugucccu uuuaagc	DS411	0.951	0.819
957	S275	gcuuaaaagggaca guauucu	693	AS277	aaucuguccuuu uaagcaa	DS601	0.903	0.956
958	S276	cuuaaaagggacag uauucuc	694	AS278	gaauacugucccu uuaagca	DS611	0.825	0.892
959	S277	uuaaaagggacagu auucuca	695	AS279	agaauacugucccu uuuaagc	DS621	0.882	0.877
960	S278	uaaaagggacagua uucucag	696	AS280	gagaauacuguccc uuuaag	DS631	0.452	0.383
961	S279	aaaagggacaguau ucucagc	697	AS281	ugagaauacugucc cuuuuaa	DS641	0.419	0.973
962	S280	aaagggacaguauu cucagug	698	AS282	cugagaauacuguc ccuuuaa	DS651	0.913	0.897

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strands code	Average Inhibition	
							1nM	0.1nM
963	S281	aaggacagauuuc ucagugc	699	AS283	acugagaauacugu cccuua	DS661	0.88	0.908
964	S282	aggacagauuucu cagugcu	700	AS284	cacugagaauacug ucccuua	DS671	0.919	0.847
960	S283	gcuuaaaagggaca guauucu	684	AS285	ugaauacuguccu uuuaagcaagc	DS681	0.884	0.961

The results showed that the 5' or 3' end of the sense and antisense strands of RNA inhibitors can differ by 1, 2 or even 3 nucleotides, and the activities of RNA inhibitors are not significantly affected.

Example 11 Investigation of the effect of different modifications at 2' position of nucleotide glycosyls on RNA inhibitor activity

Investigated the effect on the activity of RNA inhibitors of fluorine modification at 2' position of nucleotide glycosyls at different positions starting from the 5' end of the sense strand, and fluorine modification at 2' position of nucleotide glycosyls at different positions starting from the 5' end of the antisense strand.

Transfected RNA inhibitor into HepG2 cells, and measured APOC3 mRNA level by qRT-PCR. Compared with the supernatant of HepG 2 cells without intervention, the average expression level of APOC3 mRNA in the intervention group was calibrated, and the inhibition rate was calculated. The test results were shown in Table 35 and Figure 3.

Table 35 The inhibition rate of APOC3 mRNA after RNA inhibitor intervention

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strands code	Average Inhibition	
							1nM	0.1nM
1112	S541	AsAsGGfGfCfA fGUAUUCTCAG UsGsU	1142	AS520	AsCsACUGfAGA AUfACfUGUCCC sUsU	DS201	0.4396 8408	0
1113	S542	GsAsGGfGfCfA GUAUUCUCAG UsGsU	1143	AS521	AsCsACUGfAGA AUfACfUGUCCC sUsC	DS211	0.5320 4033	0.2090 261
1114	S543	CsAsGGfGfCfA fGUAUUCUCAG UsGsU	1144	AS522	AsCsACUGfAGA AUfACfUGUCCC sUsG	DS221	0.6190 0211	0
1115	S544	GsGsGAfCAfGfU fAUUCUCAGUG CsUsA	1145	AS523	GsCsACUGfAGA AUfACfUGUCCC sUsU	DS231	0.8282 0992	0.8646 5283
1116	S545	GsAsGGfGfCfA fGUAUUCUCAG UsGsU	1146	AS524	AsCsACUGfAGA AUfACfUGUCCC sUsC	DS241	0.4761 101	0
1117	S546	GsAsGCfGAfCfA fGUAUUCTCAG UsGsU	1147	AS525	AsCsACUGfAGA AUfACfUGUCGC sUsC	DS251	0.4664 62	0
1118	S547	UsAsGGfGfCfA fGUAUUCTCAG UsGsU	1148	AS526	AsCsACUGfAGA AUfACfUGUCCC sUsA	DS261	0.9014 1965	0.8086 2764
1119	S548	AsUsGGfGfCfA fGUAUUCTCAG UsGsU	1149	AS527	AsCsACUGfAGA AUfACfUGUCCC sAsU	DS271	0.4232 252	0.1985 1928

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strand code	Average Inhibition	
							1nM	0.1nM
1120	S549	AsGsGGfACfAfG fUAUUCUCAGU GsUsA	1150	AS528	UsCsACUGfAGA AUfACfUGUCCC sUsU	DS281	0.8809 7941	0.6891 1395
1121	S550	AsAsGGfGfAfCfA fGUAUUCUCAG UsGsA	1151	AS529	UsCsACUGfAGA AUfACfUGUCCC sUsU	DS291	0.7345 9528	0.7086 7407
1122	S551	GsCsUUfAAfAfA fGGGACAGUAU UsCsA	1152	AS530	UsGsAAUAfCUG UCfCCfUUUUA sGsC	DS301	0	0.2302 3379
1123	S552	GsCsUUAAAAfG fGfGACAGUAU UsCsA	1153	AS531	UsfGsAfAUfACf UGfUCfCCfUUfU UfAAsGsC	DS311	0.9420 0427	0.8751 5849
1124	S553	GsCsUUfAAfAfA fGGGACAGUAU UsCsU	1154	AS532	AsAsUACUfGUC CCfUUfUUAAGC sAsA	DS421	0.5039 7905	0.0169 2893
1125	S554	GsCsUUfAAfAfA AfGGfGfCAfG UAUUsCsU	1155	AS533	AsfAsUfACfUGf UCCCUUfUUfAA GCsAsA	DS431	0.9205 1393	0.1046 0114
1126	S555	CsUsUAfAAfAfG fGGACAGUAUU CsUsC	1156	AS534	GsAsAUACfUGU CCfCUfUUUAAG sCsA	DS441	0.2717 1299	0
1127	S556	CsUsfUAfAAfAf GfGGfACfAGfU AUUCsUsC	1157	AS535	GsfAsAfUAfCUf GUCCCUfUUfUA AGsCsA	DS451	0.8492 3242	0.2706 6857

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strands code	Average Inhibition	
							1nM	0.1nM
1128	S557	UsUsAAfAAfGfGfGACAGUAUUCUsCsA	1158	AS536	AsGsAAUafCUGUCfCCfUUUUAAsGsC	DS461	0.8739331	0.8306664
1129	S558	UsUsfAAfAAfGfGfGfGfCAfGUfAUUCUsCsA	1159	AS537	AsfGsAfAUfACfUGUCCCCfUUfUUAAsGsC	DS471	0.95089087	0.79315352
1130	S559	UsAsAAfAGfGfGfACAGUAUUCUCsAsG	1160	AS538	GsAsGAAUfACUGUfCCfCUUUUAAsAsG	DS481	0.50444347	0.3883753
1131	S560	UsAsfAAfAGfGfGfGfACfAGfUAfUUCUCsAsG	1161	AS539	GsfAsGfAAfUAfCUGUCCfCUfUUAAsAsG	DS491	0.75282363	0.39360064
1132	S561	AsAsAAfGGfGfAfCAGUAUUCUCAsGsC	1162	AS540	UsGsAGAAfUACUGfUCfCCUUUUsAsA	DS501	0.54418952	0.72684271
1133	S562	AsAsfAAfGGfGfAfCAfGUfAUfUUCUCAsGsC	1163	AS541	UsfGsAfGAfAUfACUGUCfCCfUUAUsAsA	DS511	0.93540529	0.989981452
1134	S563	AsAsAGfGGfAfCfAGUAUUCUCAGsUsG	1164	AS542	CsfUsGfAGfAAfUACUGUfCCfCUUUsUsA	DS521	0.91358498	0.98440306
1135	S564	AsAsAfGGfGfAfCfAfGUfAUfUcUUCAGsUsG	1165	AS543	CsfUsGfAGfAAfUACUGUfCCfCUUUsUsA	DS531	0.93393405	0.90155531

SEQ ID NO.	sense strand code	sense strand sequence 5'→3'	SEQ ID NO.	antisense strand code	antisense strand sequence 5'→3'	Double strand code	Average Inhibition	
							1nM	0.1nM
1136	S565	AsAsGGfGAfCfA fGUAUUCUCAG UsGsC	1166	AS544	AsCsUGAGfAAU ACfUGfUCCCUU sUsA	DS541	0.9308 5339	0.9814 1713
1137	S566	AsAsfGGfGAfCf AfGUfAUfUCfUC AGUsGsC	1167	AS545	AsfCsUfGAfGAf AUACUGfUCfCC UUsUsA	DS551	0.9723 2923	0.9250 3153
1138	S567	AsGsGGfACfAfG fUAUUCUCAGU GsCsU	1168	AS546	CsAsCUGAfGAA UAfCUfGUCCCU sUsA	DS561	0.5341 0452	0.7224 1722
1139	S568	AsGsGGfACfAf GfUAfUfCUfCA GUGsCsU	1169	AS547	CsfAsCfUGfAGf AAUACUfGUfCC CUUsUsA	DS571	0.8624 7604	0.9514 6775
1140	S569	GsCsUUfAAfAfA fGGGACAGUAU UsCsA	1170	AS548	UsAsAUfCUGU CfCCfUUUUAAG CsAsA	DS581	0.4202 7334	0.5183 2601
1141	S570	GsCsUUAAAAfG fGfGACAGUAU UsCsA	1171	AS549	UsAsfAUfACfUG fUCfCCfUfUfUf AAGCsAsA	DS591	0.9088 6421	0.8420 9032

According to the test results, the modification mode is sequence-specific. The ideal ones for the fluorine modification at 2'-position of the nucleotide glycosyls at positions 5, 7, 8, and 9 starting from 5' end of the sense chain, and the fluorine modification at 2'-position of the nucleotide glycosyls at positions 7, 14, and 16 starting from the 5' end of the antisense chain are DS231, DS261, DS281 and DS311.

DS541 and DS551 have the same sequence, and the 2' positions of the nucleotide glycosyls at

positions 5, 7, 8, and 9 starting from the 5' end of the sense chain are fluorinated, and the 2' positions of the nucleotide glycosyls at positions 7, 14, and 16 starting from the 5' end of the antisense chain are fluorinated, or the 2' positions of the nucleotide glycosyls at positions 3, 5, 7, 8, 9, 11, 13, and 15 starting from the 5' end of the sense chain are fluorinated, and the 2' positions of the nucleotide glycosyls at positions 2, 4, 6, 8, 14, and 16 starting from the 5' end of the antisense chain are fluorinated, the RNA inhibitors maintain good activity.

DS571 has fluorine modification at 2' positions of nucleotide glycosyls at positions 3, 5, 7, 8, 9, 11, 13, and 15 starting from the 5' end of the sense strand, and fluorine modification at 2' positions of nucleotide glycosyls at positions 2, 4, 6, 8, 14, and 16 starting from the 5' end of the antisense strand, the effect is satisfactory.

DS591 has fluorine modification at 2' positions of nucleotide glycosyls at positions 9, 10 and 11 starting from the 5' end of the sense strand, and fluorine modification at 2' positions of nucleotide glycosyls at positions 2, 4, 6, 8, 14, and 16 starting from the 5' end of the antisense strand, the effect is satisfactory.

Example 12 Evaluation of the effect of 5'MVIP09/3'MVIP09 combination on RNA inhibitor delivery using PHH screening

Primary human hepatocytes (PHH) were used to evaluate the in vitro activity of the RNA inhibitors in Table 16. Thawed frozen PHH and adjusted the cell density to 6×10^5 cells per ml. Took from the dilution plate the prepared RNA inhibitors and added it to a 96-well cell culture plate (10 μ L/well), and added 90 μ L/well of cells to the 96-well plate, with a final volume of 100 μ L per well. The RNA inhibitors were diluted 10-fold starting from 500 nM, with a total of 3 concentration points and triplicate wells. After addition, the cells were placed in a 5% CO₂, 37°C incubator for 48 hours. Extracted RNA from cells and then reverse transcribed it into cDNA. Detected target gene cDNA using qPCR. GAPDH was used as an internal reference gene and qPCR was performed in a 384-well plate. The qPCR reaction program was: 95°C for 10 minutes; then 95°C for 15 seconds and 60°C for 1 minute for 40 cycles. The relative expression level of APOC3 mRNA was detected and the inhibition rate was calculated. The results are shown in Table 36 and Figure 4.

Table 36 Inhibition rate of APOC3 mRNA after RNA inhibitor intervention

sense strand code	sense strand sequence 5' strand sequence	antisense strand code	antisense strand sequence 5'→3'	RNA inhibitor	Average Inhibition		
					500 nM	100nM	10nM
S313'	5'MVIP09-GsGsGAfCAfGfUfAUUCUCAGUGCsUsA	AS316'	GsCsACUGfAGA AUfACfUGUCCC sUsU-3'MVIP09	Kylo-12-DS2311	0.8121	0.5954	0.4321
S314'	5'MVIP09-UsAsGGfGAfCfAfGUAUUCTCAGUsGsU	AS317'	AsCsACUGfAGA AUfACfUGUCCC sUsA-3'MVIP09	Kylo-12-DS2611	0.7926	0.61235	0.4021
S315'	5'MVIP09-AsAsGGfGAfCfAfGUAUUCUCAGUsGsA	AS318'	UsCsACUGfAGA AUfACfUGUCCC sUsU-3'MVIP09	Kylo-12-DS2911	0.8033	0.6791	0.5017
S316'	5'MVIP09-AsAsGGfGAfCfAfGUAUUCUCAGUsGsC	AS319'	AsCsUGAGfAAU ACfUGfUCCCCUUsUsA-3'MVIP09	Kylo-12-DS5411	0.7922	0.6316	0.5391
S317'	5'MVIP09-AsAsfGGfGAfCfAfGUfAUfUCfUCAGUsGsC	AS320'	AsfCsUfGAfGAfAUACUGfUCfCCUUsUsA-3'MVIP09	Kylo-12-DS5511	0.7781	0.6973	0.5239
S318'	5'MVIP09-AsGsGfGGfACfAfGfUAfUfUCfCfAGUGsCsU	AS321'	CsfAsCfUGfAGfAAUACUfGUfCCCUsUsA-3'MVIP09	Kylo-12-DS5711	0.8126	0.6185	0.4756
S319'	5'MVIP09-GsCsUUAAAFGfGfGACAGUAUUsCsA	AS322'	AsfAUfACfUGfUCfCCfUfUfUfAA GCsAsA-3'MVIP09	Kylo-12-DS5911	0.8253	0.6011	0.5530
S320'	5'MVIP09-GsCsUUAAAFG	AS323'	UsfGsAfAUfACfUGfUCfCCfUfUfU	Kylo-12-DS3111	0.7797	0.6374	0.5321

sense strand code	sense strand sequence 5' strand sequence	antisense strand code	antisense strand sequence 5'→3'	RNA inhibitor	Average Inhibition		
					500 nM	100nM	10nM
	fGfGACAGUAU UsCsA		fAAsGsC- 3'MVIP09				

The test results showed that the RNA inhibitor formed by the modified sense strand and antisense strand conjugating to carrier 5'MVIP09/3'MVIP09 can be freely taken up into PHH cells, inhibiting APOC3 mRNA in PHH cells and showing significant dose-effect effect.

Example 13 Evaluation of the activity of RNA inhibitors using transgenic mouse model

Examined the in vivo activity of the RNA inhibitors in Table 36. Selected APOC3 Tg mouse model of appropriate age for experimental evaluation. Administered 3mg/kg by subcutaneous injection on Day0. Collected blood on days 8, 15, 22, 29, 35 and 42 after administration, measured TG and APOC3 levels. After RNA inhibitor intervention, the normalized average APOC3 levels in serum were shown in Table 37 and Figure 5.

Table 37 Average APOC3 level in serum after normalization

RNA inhibitor	d0	d8	d15	d22	d29	d35	d42
Saline group	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Kylo-12-DS2311	1.000	0.219	0.161	0.234	0.199	0.267	0.299
Kylo-12-DS2611	1.000	0.209	0.178	0.157	0.246	0.278	0.300
Kylo-12-DS2911	1.000	0.159	0.169	0.210	0.269	0.250	0.289
Kylo-12-DS5911	1.000	0.189	0.193	0.225	0.253	0.320	0.35

Note: Normalization is to divide the APOC3 level of an animal at a time point by the APOC3 level of the animal on Day 0 to obtain a ratio A1, and to divide the average level of the control group at a time point by the average level of the control group on Day 0 to obtain a ratio A2. A1 divided by A2 is the normalized average APOC3 level in serum.

After RNA inhibitor intervention, the results of the normalized average TG levels in serum were shown in Table 38 and Figure 6:

Table 38 Normalized average TG level in serum

RNA inhibitor	d0	d8	d15	d22	d29	d35	d42
Saline group	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Kylo-12-DS2311	1.000	0.356	0.307	0.389	0.394	0.450	0.560
Kylo-12-DS2611	1.000	0.289	0.297	0.322	0.398	0.411	0.460
Kylo-12-DS2911	1.000	0.199	0.213	0.278	0.321	0.345	0.384
Kylo-12-DS5911	1.000	0.201	0.267	0.293	0.307	0.323	0.360

Note: Normalization is to divide the TG level of an animal at a time point by the TG level of the animal on Day 0 to obtain a ratio A1, and to divide the average level of the control group at a time point by the average level of the control group on Day 0 to obtain a ratio A2. A1 divided by A2 is the normalized average TG level in serum.

Example 14 Evaluation of the activity of RNA inhibitors using transgenic mouse model

Examined the in vivo activity of the RNA inhibitors in Table 22-1. Took hAPOC3 Tg mouse model of appropriate age for experimental evaluation. Selected 55 6~8-week-old male hAPOC3 Tg mouse and divided into administration group (Ky-12-DS23001, Ky-12-DS25001, Ky-12-DS25401, Ky-12-DS29701, Ky-12-DS29801, Ky-12-DS31705, Ky-12-DS33001 and Ky-12-DS31701) and saline group. The mice were fasted after adaptive feeding for 2-3 days. Fasting blood collection was performed to separate serum to determine hAPOC3 protein, TG, TC and LDL-c levels. The mice were randomly divided into groups according to TG indexes, with 5 mice in each group. The day of administration was defined as day0. For Ky-12-DS31701, investigated 3 dosage groups. On Day0, administered 1 mg/kg, 3 mg/kg, and 6 mg/kg by subcutaneous injection. For the other groups, administered 3 mg/kg by subcutaneous injection. Collected blood on Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70 and 77, measured hAPOC3, TC, TG and LDL-c levels and normalized the results (the calculation method is shown in Example 13). The normalized interference effects of hAPOC3, TC, TG and LDL-c were shown in Figures 7, 8, 9 and 10.

The test results showed that these RNA inhibitors investigated in this example have varying degrees of effects on hAPOC3 expression, TC, TG and LDL-c levels in the serum of hAPOC3 Tg mice, among which the hAPOC3 expression and TG levels were significantly and sustainedly affected. At the dose of 3 mg/kg: by day 35, the reduction rate of Ky-12-DS25401 on TG level could be as high as 89.89%. by day 77, the reduction rate of each RNA inhibitor on TG level remains above 50%. This example also examined the dose-effect relationship of the RNA inhibitor Ky-12-DS31701 on hAPOC3 expression,

TC, TG and LDL-c levels. The test results showed that the effect of the RNA inhibitor on TG levels have a significant dose-effect relationship: by Day 14, 1mg/kg, 3mg/kg and 6mg/kg can reduce TG level by 84.21%, 88.98% and 95.06% respectively.

Example 15 Evaluation of the activity of RNA inhibitors using cynomolgus monkey model

Hyperlipidemia cynomolgus monkeys, male, 15, 3 in each group, administration group (Ky-12-DS31701, Ky-12-DS31712, Ky-12-DS31711 and Ky-12-DS33001) and saline group. The monkeys were randomly divided into groups according to TG level after 2 weeks of adaptive feeding. Administered subcutaneously at 4 mg/kg on the day of grouping. Collected blood from the saphenous vein or cephalic vein at the following time points: day 0 and days 7, 14, 21, 28, 35, 42, 49, 56 and 63 after administration. Measured APOC3, TC, TG, HDL-c and LDL-c levels and normalized the results. The normalized interference effects of APOC3, TG, HDL-c, LDL-c and TC were shown in Figures 11, 12, 13, 14 and 15. On day 28 and day 63, performed additional liver biopsies on the cynomolgus monkeys in Ky-12-DS31701 administration group respectively. Extracted liver tissue, measured APOC3 mRNA level in the liver of cynomolgus monkeys by RT-qPCR, and normalized the results.

The test results showed that the RNA inhibitors Ky-12-DS31701, Ky-12-DS31712, Ky-12-DS31711, and Ky-12-DS33001 all had significant inhibitory effect on APOC3 expression in serum of cynomolgus monkeys, among which Ky-12-DS31701 and Ky-12-DS33001 reduced TG level by 84.01% and 81.15% respectively, both TC and LDL-c levels were reduced to varying degrees, and HDL-c level was significantly increased. The above-mentioned compounds had significant and sustained inhibitory effects on APOC3 expression and TG level. Among them, the reduction level of TG by Ky-12-DS31701 could still reach 75.48% on day 63. On day 28 and day 63, performed liver biopsies on the cynomolgus monkeys in Ky-12-DS31701 administration group respectively. Extracted liver tissue, measured APOC3 mRNA level in the liver of cynomolgus monkeys by RT-qPCR, and normalized the results. The normalization calculation method was shown in Example 13. The test results showed that the inhibition rates of Ky-12-DS31701 on APOC3 mRNA level in cynomolgus monkeys were 91.65% and 87.23% respectively, and the highest individual inhibition rate was 95%.

The basic principles, main features and advantages of the present invention have been shown and described above. Those skilled in the art should understand that the above examples do not limit the present application in any way, and all technical solutions obtained by equivalent replacement or equivalent transformation shall fall within the scope of protection of the invention.

Claims

1. An RNA inhibitor for inhibiting the expression of APOC3 gene or pharmaceutically acceptable salt thereof, characterized in that the RNA inhibitor is formed by base pairing of a sense strand and an antisense strand with chain length of 15-30 nucleotides each independently, wherein the chain length is preferably 19-23 nucleotides each independently, and at least 80% of the bases between the sense strand and the antisense strand are complementary.

2. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 1, characterized in that the antisense strand is selected from a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b): 5' uugguggcgugcucauguaatt 3' (SEQ ID NO. 212), 5' uaaccugcaugaagcugagatt 3' (SEQ ID NO. 216), 5' uaaacggugcuccaguagucutt 3' (SEQ ID NO. 224), 5' cagagaacuuguccuuaacggtt 3' (SEQ ID NO. 225), 5' uauugaggucucaggcagccatt 3' (SEQ ID NO. 241), 5' ugaaguuggucugaccucaggtt 3' (SEQ ID NO. 255), 5' gcacugagaaucuguccuuuu 3' (SEQ ID NO. 256), 5' gcacugagaaucuguccuu3' (SEQ ID NO. 459), 5' acacugagaaucuguccua 3' (SEQ ID NO. 461), 5' ugaauacuguccuuuuuagc 3' (SEQ ID NO. 465), 5' cugagaaucuguccuuuuu 3' (SEQ ID NO. 471), 5' acugagaaucuguccuuua 3' (SEQ ID NO. 472), 5' uaauacuguccuuuuuagcaa 3' (SEQ ID NO. 438), 5' ugaggucucaggcagccacgg3' (SEQ ID NO. 600), 5' uggauaggcagguggacuugg3' (SEQ ID NO. 620), 5' caggauggauaggcaggugga3' (SEQ ID NO. 624), 5' gagcacugagaaucugucc3' (SEQ ID NO. 668), 5' acacugagaaucugucgcuc3' (SEQ ID NO. 687), 5' acacugagaaucugucguu3' (SEQ ID NO. 700), 5' ucacugagaaucuguccuu 3' (SEQ ID NO. 519);

wherein, g= guanylate, a= adenylate, u= uridylate, c= cytidylate, t= thymidylate.

3. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 1, characterized in that the sense strand and antisense strand are selected from a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b), the sequences combination of the sense strand and the antisense strand is as follows:

SEQ ID NO.	single strand code	sense strand 5'→3'	SEQ ID NO.	single strand code	antisense strand 5'→3'
161	S58	uuacaugaagcacgccaccaatt	212	AS58	uugguggcgugcuucauguaatt
165	S62	ucucagcuucaugcaggguuat t	216	AS62	uaaccugcaugaagcugagatt
173	S70	agacuacuggagcacccguuaat t	224	AS70	uuaacggugcuccaguagucutt
174	S71	ccguuaaggacaaguucucugt t	225	AS71	cagagaacuuguccuuaacggtt
190	S87	uggcugccugagaccucaauat t	241	AS87	uauugaggucucaggcagccatt
204	S101	ccugaggucagaccaacuucacat t	255	AS10 1	ugaaguuggucugaccucaggtt
205	S102	aaggacaguuucucagugct t	256	AS10 2	gcacugagaauacuguccuuuu
440	S268	gggacaguuucucagugcua	459	AS27 0	gcacugagaauacuguccuu
442	S270	uaggacaguuuctcagugu	461	AS27 2	acacugagaauacuguccua
446	S274	gcuuaaaaggacaguuuca	465	AS27 6	ugaauacuguccuuuaagc
452	S280	aaaggacaguuucucagug	471	AS28 2	cugagaauacuguccuuua
453	S281	aaggacaguuucucagugc	472	AS28 3	acugagaauacuguccuuua
702	S194	gcuuaaaaggacaguuuca	438	AS19 4	uaauacuguccuuuaagcaa
864	S356	guggcugccugagaccucaau	600	AS35 6	ugaggucucaggcagccacgg
884	S376	aaguccaccugccuauccauc	620	AS37 6	uggauaggcagguggacuugg
888	S380	caccugccuauccauccugaa	624	AS38 0	caggauggauaggcaggugga

931	S423	gggacagauuucucagugcuu	667	AS42 3	gcacugagaauacuguccuu
932	S424	gacagauuucucagugcucu	668	AS42 4	gagcacugagaauacugucc
951	S443	gagcgacagauuucucagugu	687	AS44 3	acacugagaauacugucguc
964	S456	aagcgacagauuucucagugu	700	AS45 6	acacugagaauacugucgcu
781	S273	aaggacagauuucucaguga	519	AS27 5	ucacugagaauacuguccuu

wherein, g= guanylate, a= adenylate, u= uridylate, c= cytidylate, t= thymidylate.

4. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 1, characterized in that the sense strand and/or antisense strand comprises at least one 2'-modified nucleotide, the 2'-modified nucleotide includes: 2'-O-methyl nucleotide, 2'-deoxy-2'-fluoro nucleotide, 2'-deoxy nucleotide, 2'-methoxyethyl nucleotide, 2'-amino nucleotide or 2'-alkyl nucleotide.

5. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 4, characterized in that the sense strand and/or antisense strand comprises at least one 2'-O-methyl nucleotide or 2'-deoxy-2'-fluoro nucleotide.

6. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 5, characterized in that the phosphate bonds among three adjacent nucleotides at at least one of the ends of the sense strand and/or antisense strand could be thiolated.

7. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 5, characterized in that the sense strand and the antisense strand are selected from: a) the following sequences, b) sequences having at least 15 consecutive nucleotides identical to those in a), and c) sequences having no more than 3 nucleotides different from those in a) and b):

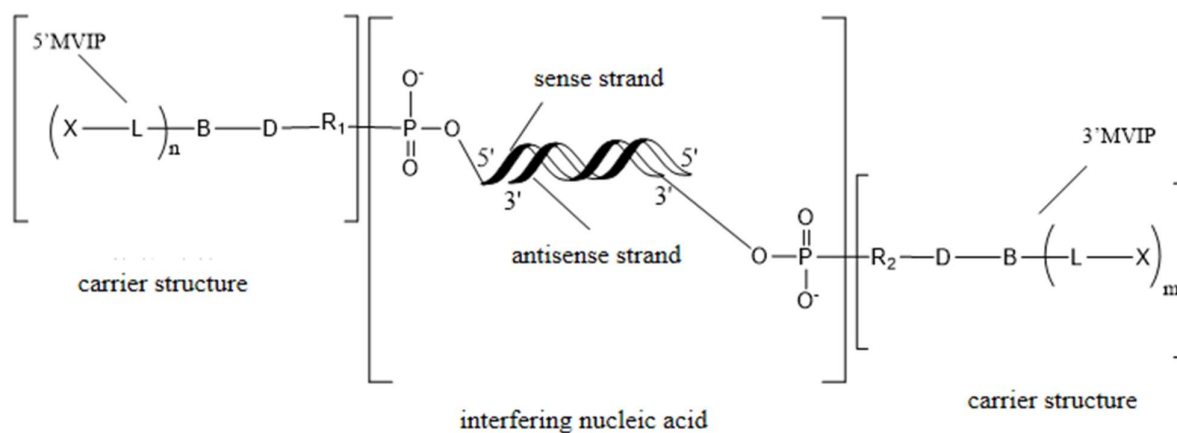
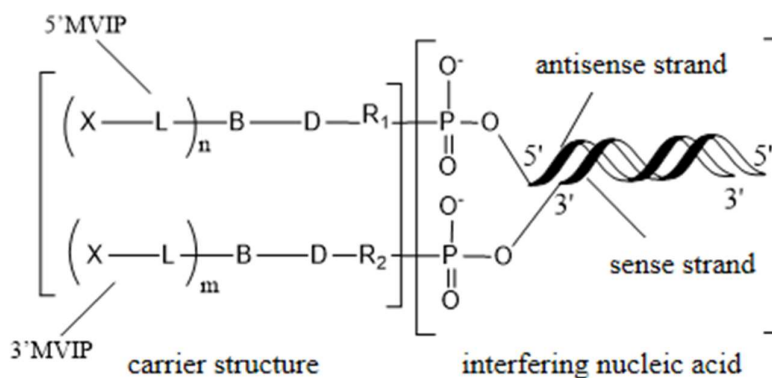
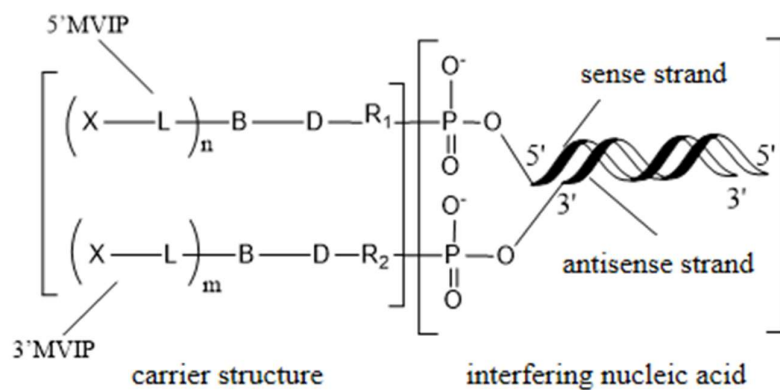
SE Q ID NO.	single strand code	sense strand 5'→3'	SE Q ID NO.	single strand code	antisense strand sequence 5'→3'
411	S16 7	UsUsACAUGAfAfGfCACGCC ACCsAsA	381	AS16 7	UsfUsGfGUfGGfCGUGCUfUCfA UGUsAsA
412	S16 8	UsCsUCAGCUfUfCfAUGCAG GGUsUsA	382	AS16 8	UsfAsAfCCfCUfGCAUGAfAGfC UGAsGsA
417	S17 3	AsGsACUACUfGfGfAGCACC GUUsAsA	387	AS17 3	UsfUsAfACfGGfUGCUCcfAGfU AGUsCsU
418	S17 4	CsCsGUUAAGfGfAfCAAGU UCUCsUsG	388	AS17 4	CsfAsGfAGfAAfCUUGUCfCUfU AACsGsG
428	S18 4	UsGsGCUGCCfUfGfAGACCU CAAsUsA	398	AS18 4	UsfAsUfUGfAGfGUCUCAfGGfC AGCsCsA
435	S19 1	CsCsUGAGGUfCfAfGACCAA CUUsCsA	405	AS19 1	UsfGsAfAGfUfGGUCUGfACfC UCAsGsG
436	S19 2	AsAsGGGACAfGfUfAUUCU CAGUsGsC	406	AS19 2	GsfCsAfCUfGAfGAAUACfUGfU CCCUUsUsU
478	S28 7	GsGsGAfCAfGfUfAUUCUCA GUGCsUsA	507	AS28 9	GsCsACUGfAGAAUfACfUGUCC CsUsU
481	S29 0	UsAsGGfGAfCfAfGUUUUCT CAGUsGsU	510	AS29 2	AsCsACUGfAGAAUfACfUGUCC CsUsA
486	S29 5	GsCsUUAAAAfGfGfGACAG UAUUsCsA	515	AS29 7	UsfGsAfAUfACfUGfUCfCCfUUF UUFAsGsC
497	S30 6	AsAsAGfGGfAfCfAGUAUUC UCAGsUsG	526	AS30 8	CsfUsGfAGfAAfUACUGUfCCfC UUUsUsA
499	S30 8	AsAsGGfGAfCfAfGUUUUCU CAGUsGsC	527	AS30 9	AsCsUGAGfAAUACfUGfUCCCCU UsUsA
486	S29 5	GsCsUUAAAAfGfGfGACAG UAUUsCsA	532	AS31 4	UsAsfAUfACfUGfUCfCCfUUFU fAAGCsAsA

SE	Q	single strand	sense strand 5'→3'	SE	Q	single strand	antisense strand sequence 5'→3'
ID				ID			
NO.	code			NO.	code		
102	S45	GsUsGGCUGCfCfUfGAGACC		AS45	UsfGsAfGGfUCfUCAGGCfAGfC		
8	7	UCAsAsU		965	7	CfACsfGsG	
102	S45	AsAsGUCCACfCfUfGCCUAU		AS45	UsfGsGfAUfAGfGCAGGUfGGfA		
9	8	CCAsUsC		966	8	CfUUsfGsG	
103	S45	CsAsCCUGCCCfUfAfUCCAUC		AS45	CsfAsGfGAfUGfGAUAGGfCAfG		
0	9	CUGsAsA		967	9	GfUGsfGsA	
103	S46	GsGsGACAGUfAfUfUCUCA		AS46	GsfCsAfCUfGAfGAAUACfUGfU		
1	0	GUGCsUsU		968	0	CfCCsfUsU	
103	S46	GsAsCAGUAUfUfCfUCAGU		AS46	GsfAsGfCAfCUfGAGAAUfACfU		
2	1	GCUCsUsU		969	1	GfUCsfCsC	
103	S46	GsAsGCGACAfGfUfAUUCU		970	AS46	AsfCsAfCUfGAfGAAUACfUGfU	
3	2	CAGUsGsU		2	CfGCsfUsC		
103	S46	GsAsGCGAfCAfGfUfAUUCU		AS46	AsfCsAfCUfGAfGAfAUACfUGfU		
9	8	CAGUsGsU		976	8	CfGCsUsC	
111	S53	AsAsGCGACAfGfUfAUUCU		102	AS51	AsfCsAfCUfGAfGAAUACfUGfU	
0	9	CAGUsGsU		4	6	CfGCsfUsU	
112	S55	AsAsGGfGAfCfAfGUAAUUCU		115	AS52	UsCsACUGfAGAAUfACfUGUCC	
1	0	CAGUsGsA		1	9	CsUsU	

wherein, G=2'-O-methylguanylate, A=2'-O-methyladenylate, U=2'-O-methyluridylate, C=2'-O-methylcytidylate; fG=2'-fluoroguanlylate, fA=2'-fluoroadenylate, fU=2'-fluorouridylate, fC=2'-fluorocytidylate, Gs=2'-O-methyl-3'-thioguanlylate, As=2'-O-methyl-3'-thioadenylate, Us=2'-O-methyl-3'-thiouridylate, Cs=2'-O-methyl-3'-thiocytidylate, fGs=2'-fluoro-3'-thioguanlylate, fAs=2'-fluoro-3'-thioadenylate, fUs=2'-fluoro-3'-thiouridylate, fCs=2'-fluoro-3'-thiocytidylate, T=thymidylate.

8. The RNA inhibitor or pharmaceutically acceptable salt thereof according to any of claims 1-7,

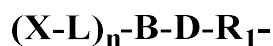
characterized in that the RNA inhibitor further contains a carrier structure, and has the structure as shown in Formula Ia, Ib or Ic:



wherein,

the carrier structure includes a 5'MVIP and a 3'MVIP;

the 5'MVIP is composed of a transition point R_1 , a linking chain D, a linker B, a branched chain L and a liver targeting specific ligand X and is connected with 5' end of the sense strand or 5' end of the antisense strand through the transition point R_1 , has the structure as shown in the formula I:



I

the 3'MVIP is composed of a transition point R_2 , a linking chain D, a linker B, a branched chain L and a liver targeting specific ligand X and is connected with 3' end of the sense strand or 3' end of the antisense strand through the transition point R_2 , has the structure as shown in the formula II:

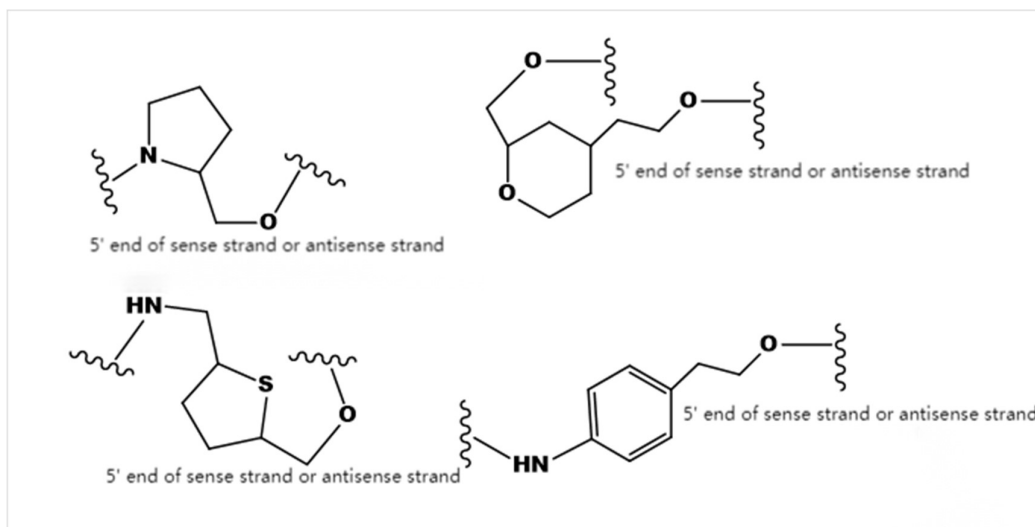


II

wherein,

n and m are each independently any integer of 0-4, each independently preferably an integer of 1-3, and $n+m$ = an integer of 2-6, preferably $n+m=2, 3$ or 4, more preferably 4,

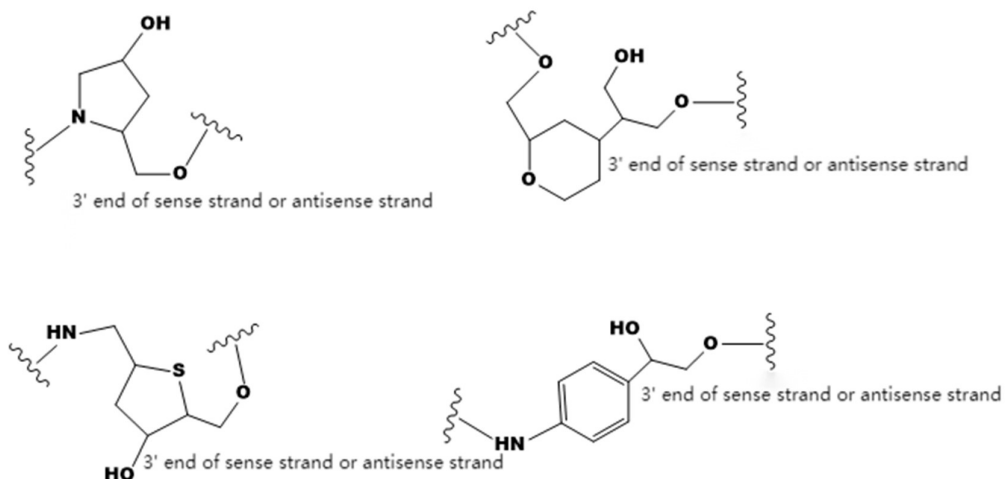
the transition point R_1 is a heterocyclic or carbocyclic structure containing N, S or O as shown below,



alternatively, R_1 is $-NH(CH_2)_xCH_2O-$, wherein x is any integer of 3-12, preferably any integer of 4-

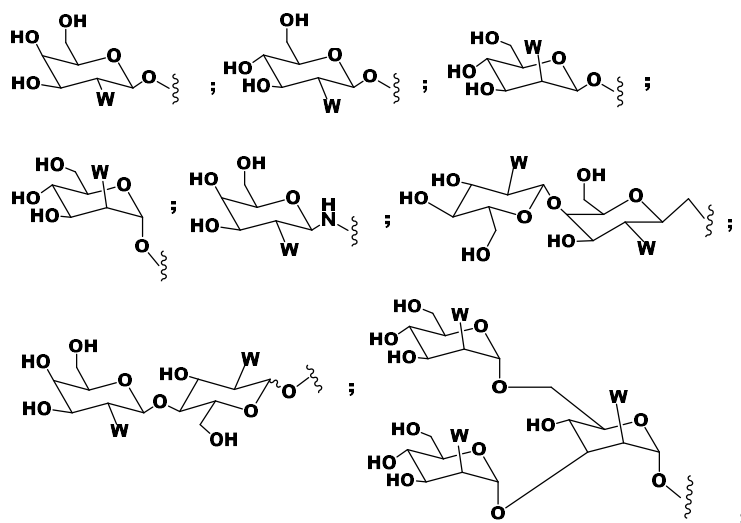
6;

the transition point R₂ is a heterocyclic or carbocyclic structure containing N, S or O as shown below,



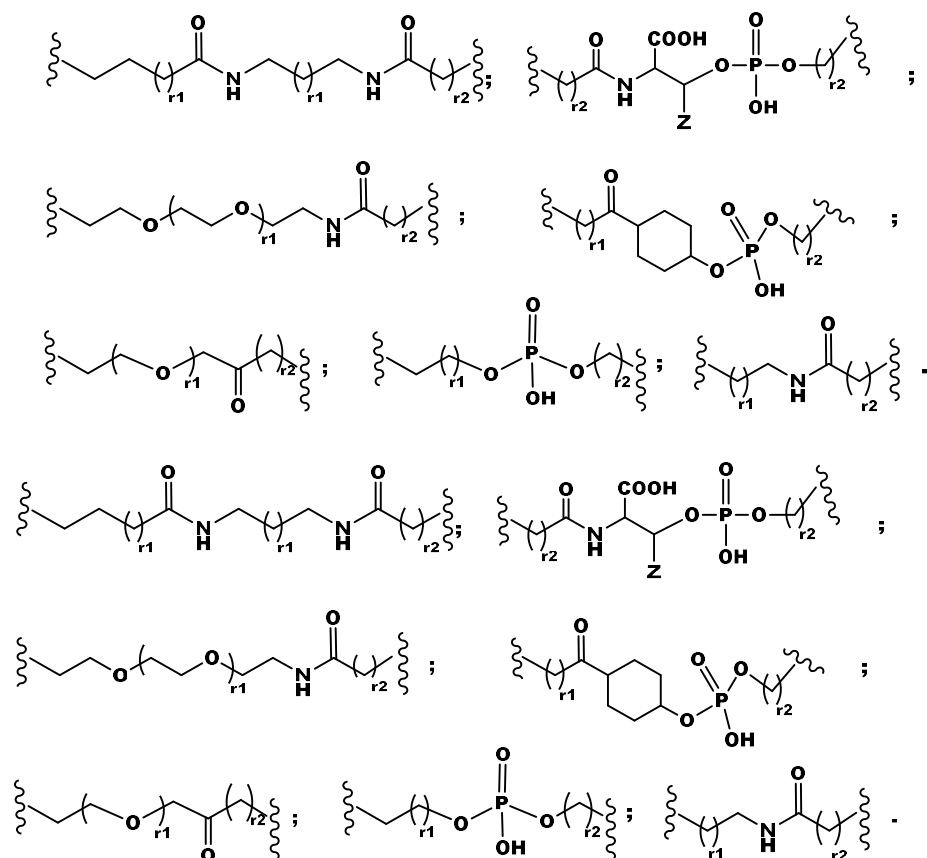
alternatively, the transition point R₂ is -NH(CH₂)_{x1}CH(OH)(CH₂)_{x2}CH₂O-, wherein x₁ is any integer of 1-4, and x₂ is any integer of 0-4;

the liver targeting specific ligand X may be the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, and is selected from monosaccharides and their derivatives, preferably selected from N-acetylgalactosamine and their derivatives, and more preferably selected from the following structures::



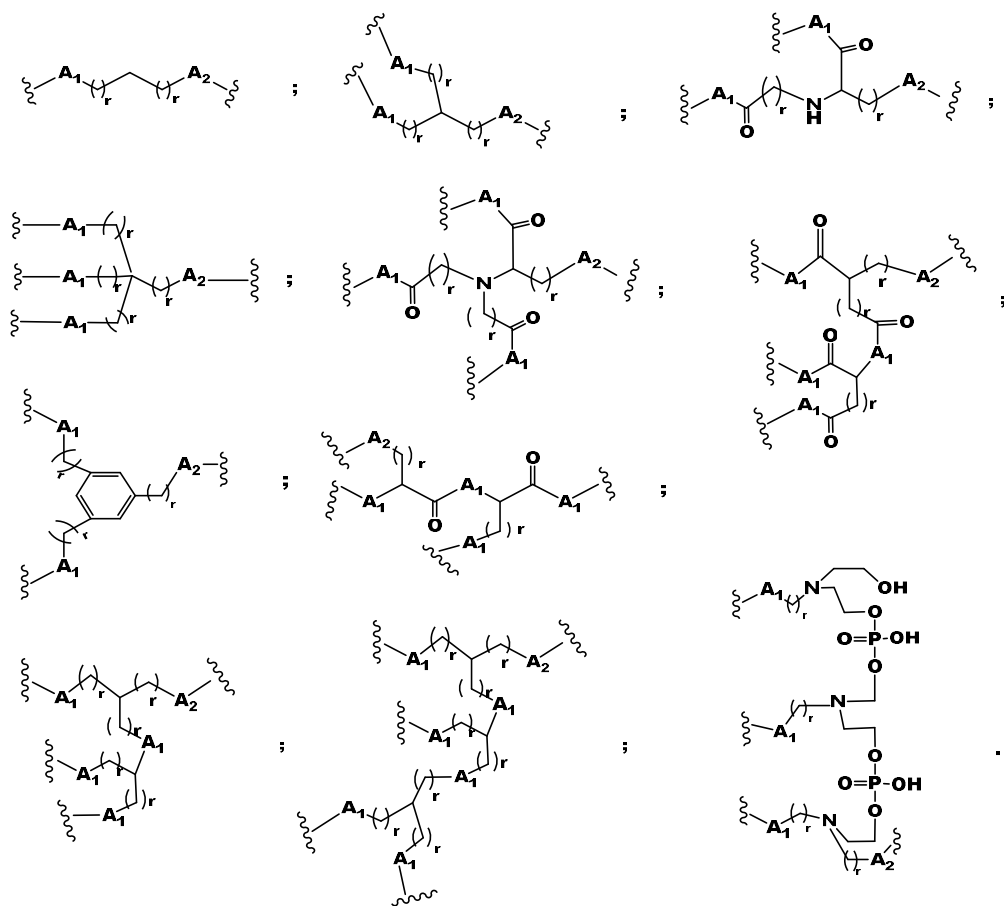
wherein, W is selected from one or two of -OH, -NHCOOH and -NHCO(CH₂)_qCH₃, wherein q is an integer of 0-4.;

the branch chain L is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from one or more of the following structures:



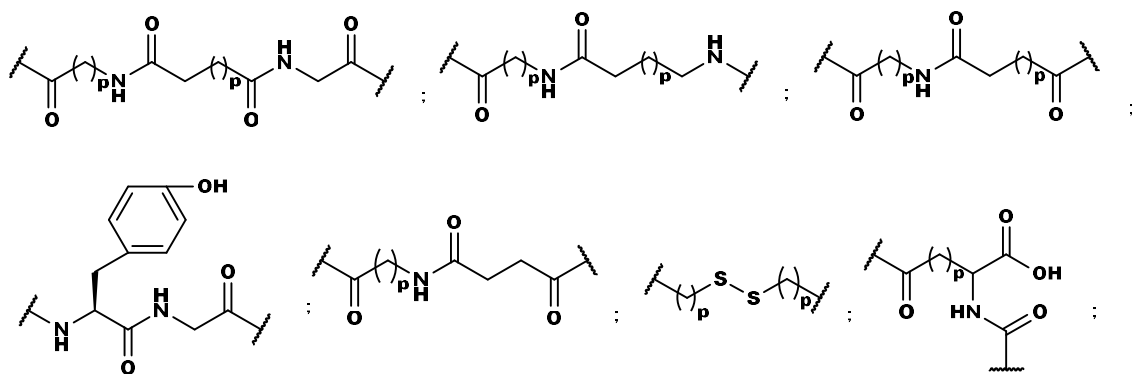
wherein, r1 is any integer of 1-12, r2 is any integer of 0-20, and Z is H, alkyl or amido, alkyl is, for example, C₁-C₅ alkyl;

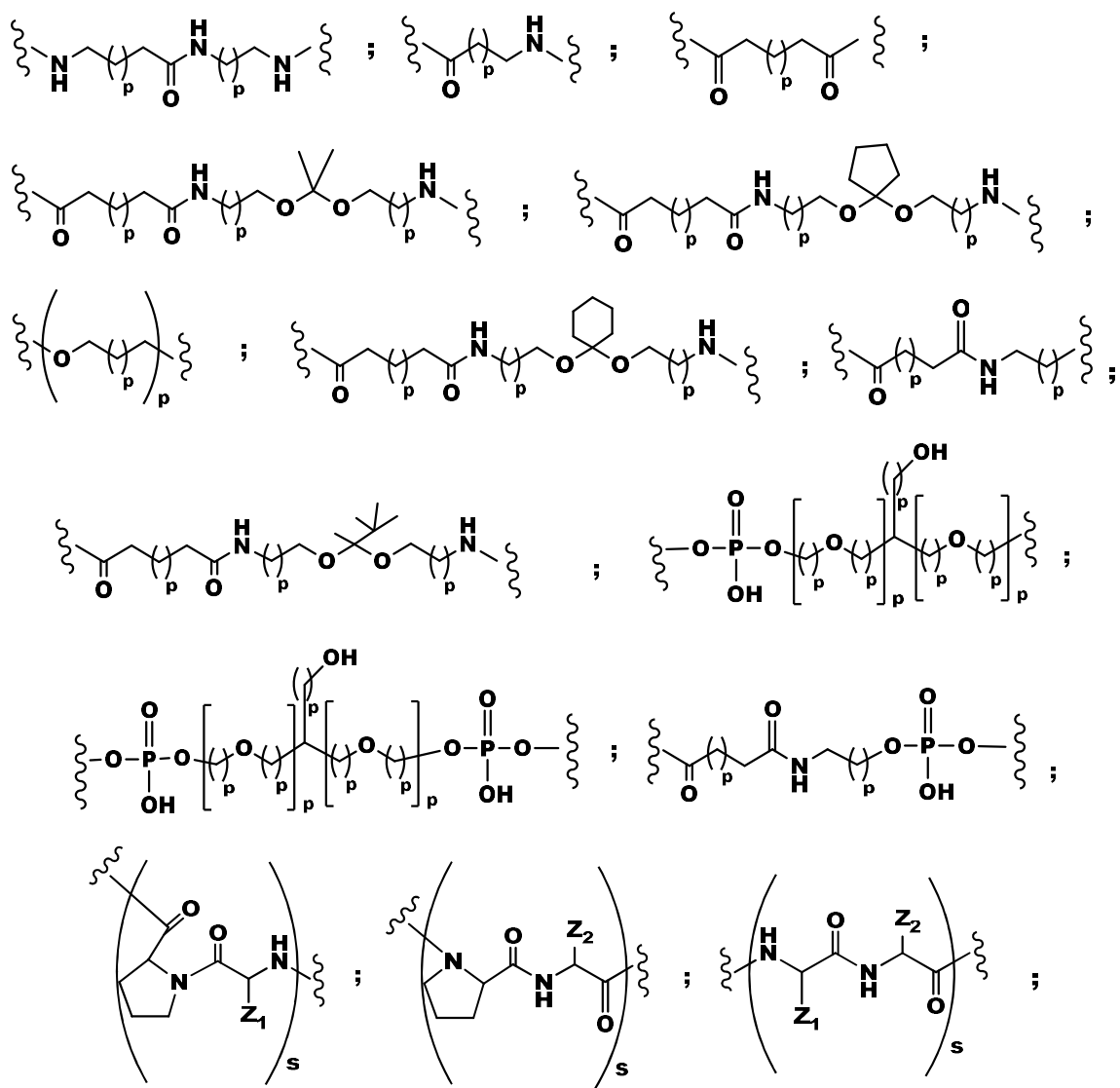
the linker B is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from the following structures:

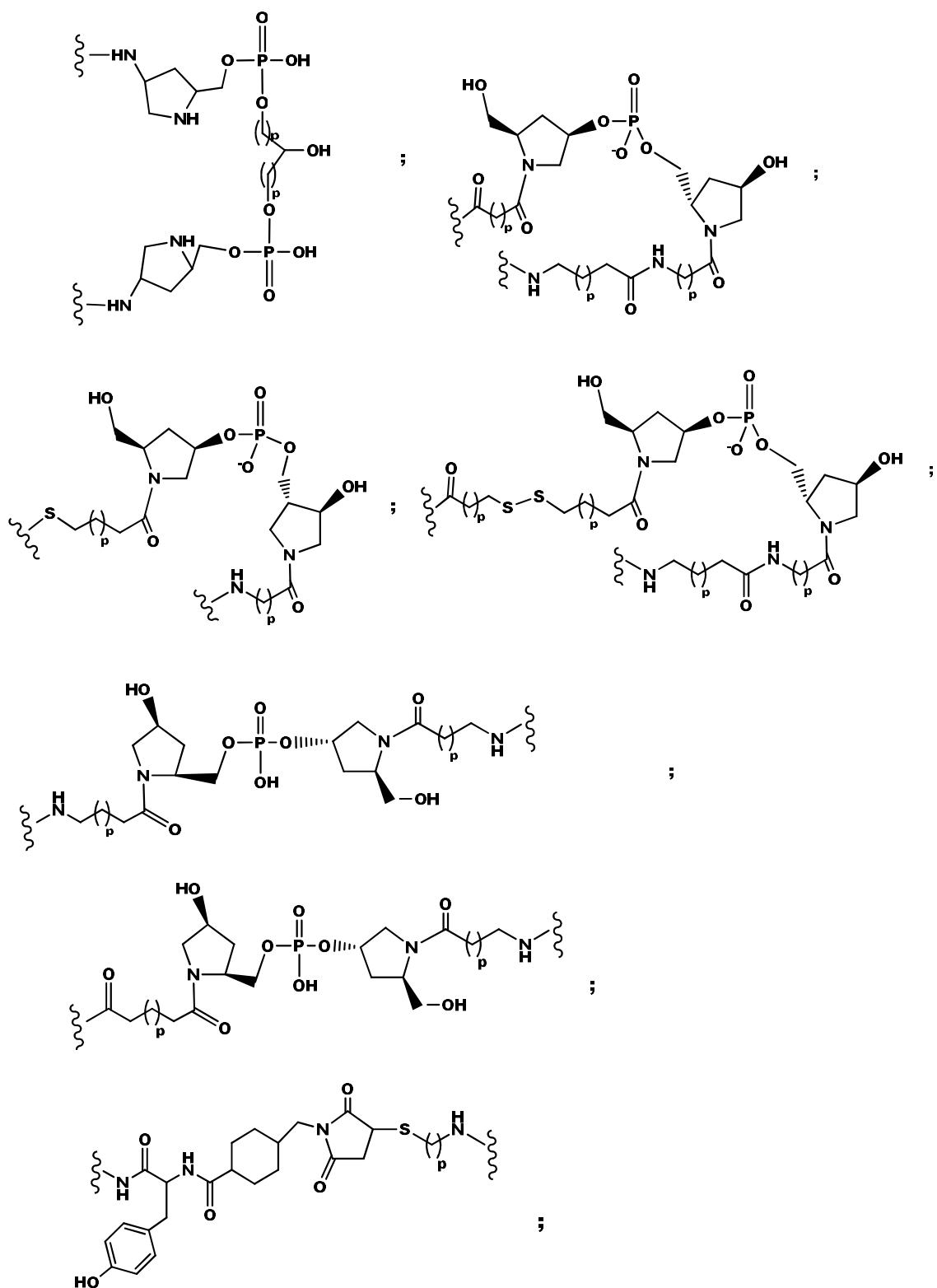


wherein, A₁ and A₂ are each independently C, O, S, -NH-, carbonyl, amido, phosphoryl or thiophosphoryl, and r is any integer of 0-4;

the linking chain D is the same or different within each of 5'MVIP and 3'MVIP or between 5'MVIP and 3'MVIP, which is selected from the following structures:



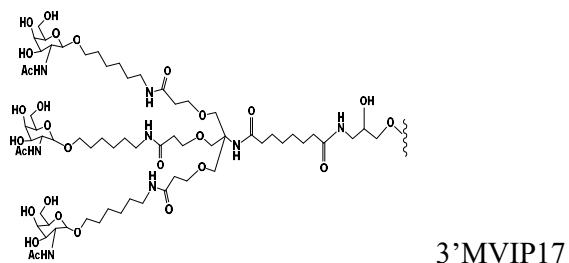
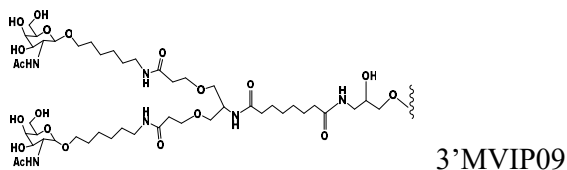
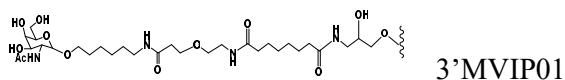
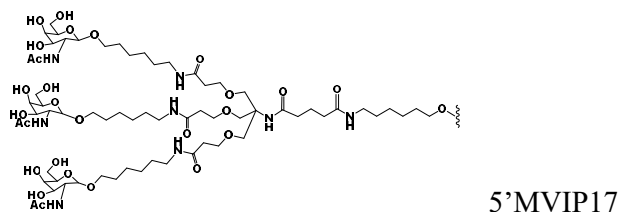
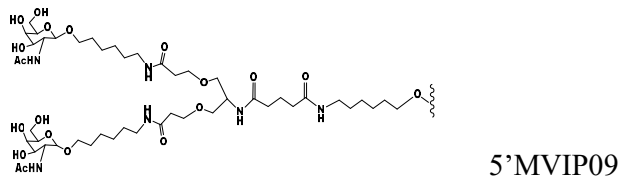
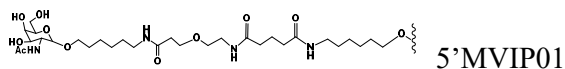




wherein, each p is independently any integer of 1-20; s is any integer of 2-13; Z_1 and Z_2 are the same or different substituent groups.

9. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 8,

characterized in that the 5'MVIP is 5'MVIP01, 5'MVIP09 or 5'MVIP17 as shown below, and the 3'MVIP is 3'MVIP01, 3'MVIP09 or 3'MVIP17 as shown below:



10. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 9, characterized in that the carrier structure at 5' end of the sense strand is 5'MVIP17, the carrier structure at 3' end of the sense strand is 3'MVIP17, the combination of the sense strand 5'MVIP and the antisense strand 3'MVIP is 5'MVIP01/3'MVIP01, 5'MVIP01/3'MVIP17, 5'MVIP17/3'MVIP01 or 5'MVIP09/3'MVIP09, or the combination of the sense strand 5'MVIP and the antisense strand 3'MVIP is 5'MVIP01/3'MVIP09, 5'MVIP09/3'MVIP01 or 5'MVIP01/3'MVIP01.

11. The RNA inhibitor or pharmaceutically acceptable salt thereof according to claim 9,

characterized in that the RNA inhibitor is selected from Ky-12-DS23001, Ky-12-DS25001, Ky-12-DS25401, Ky-12-DS29701, Ky-12-DS29801, Ky-12-DS31701, Ky-12-DS31702, Ky-12-DS31703, Ky-12-DS31704, Ky-12-DS31705, Ky-12-DS31706, Ky-12-DS31707, Ky-12-DS31708, Ky-12-DS31709, Ky-12-DS31711, Ky-12-DS31712, Ky-12-DS31713, Ky-12-DS33001, Ky-12-DS33006, Kylo-12-DS1071, Kylo-12-DS1081, Kylo-12-DS1131, Kylo-12-DS1141, Kylo-12-DS1241, Kylo-12-DS1311, Kylo-12-DS1321, Kylo-12-DS5911, Kylo-12-DS2911, Kylo-12-DS2611, Kylo-12-DS2311, Kylo-12-DS3111 and Kylo-12-DS5411.

12. Use of the RNA inhibitor or pharmaceutically acceptable salt thereof according to any of claims 1-11 in the preparation of a drug for treating and/or preventing a disease associated with an elevated APOC3 level, characterized in that the disease associated with an elevated APOC3 level includes hepatic diseases, which comprise inflammatory, cardiovascular and cerebrovascular and metabolic diseases, wherein the cardiovascular and cerebrovascular diseases include hyperlipidemia, stroke, atherosclerosis, thrombosis, coronary heart disease, aortic valve stenosis, hypertriglyceridemia (HTG), severe hypertriglyceridemia (sHTG) or familial chylomicronemia syndrome (FCS).

13. A pharmaceutical composition, characterized in that the composition comprises the APOC3 inhibitor or pharmaceutically acceptable salt thereof according to any of claims 1-11 and pharmaceutically acceptable excipients, wherein the pharmaceutical composition is an oral preparation, an intravenous injection, or a subcutaneous or intramuscular injection, preferably a subcutaneous injection.