
USE OF ST-TYPE LIPID COMPOUNDS IN PREPARATION OF NUCLEIC ACID DELIVERY REAGENT AND RELATED PRODUCT

FIELD

5 The present invention relates to the field of biology. Specifically, the present application relates to use of lipid compound for delivering nucleic acid, wherein the compound, or a plurality of combinations thereof, are capable of facilitating the absorption of a variety of nucleic acids via oral administration in vivo, into target sites in the body of a subject in need thereof, and into target cells. The present application
10 relates to these compounds which are extracted and found in traditional Chinese medicine, and which can also be obtained by synthetic methods.

BACKGROUND

Over the past few decades, the concept of using nucleic acid molecules as
15 therapeutic agents has evolved from theory to clinical reality. Indeed, nucleic acid molecules possess numerous attributes that render them suitable as therapeutic agents. They can fold into complex conformations, allowing them to interact with proteins, small molecules, or other nucleic acids, and some can even form catalytic centers. Nucleic acid drugs offer precise targeting and are poised to potentially alter the current
20 landscape of Western medicine dominated by compound and protein-based drugs, emerging as the third major type of therapeutic agents after small molecule drugs and antibody drugs. For instance, small interfering RNA (siRNA), as an effector molecule of RNA interference (RNAi), holds increasingly broad prospects as a therapeutic drug. Currently, 13 nucleic acid drugs have been approved globally, and various siRNA drugs
25 have entered clinical trials, indicating promising development prospects. Typically, people collectively refer to siRNA, microRNA (miRNA), and other non-coding small RNAs as small nucleic acids or small RNA (sRNA). In addition to small RNAs, nucleic acid molecules suitable as drugs include mRNA, antisense nucleic acids, and others. However, due to the inherent susceptibility of nucleic acid molecules, such as RNA, to
30 degradation and their relatively short half-life in the body, they are generally not

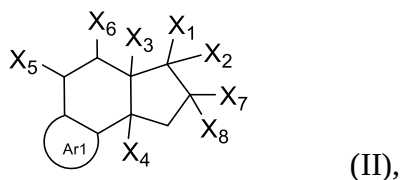
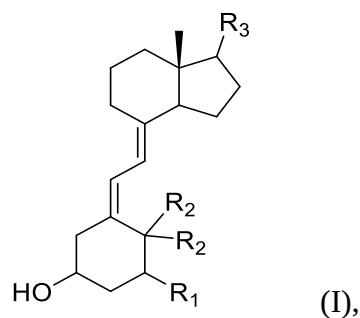
considered the optimal choice for therapeutic drugs. Therefore, the urgent challenge for professionals in this field is how to effectively deliver nucleic acid molecules, including small RNAs and mRNAs, to target organs and cells in the body, realizing their biological activity and therapeutic or preventive effects.

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SUMMARY OF THE INVENTION

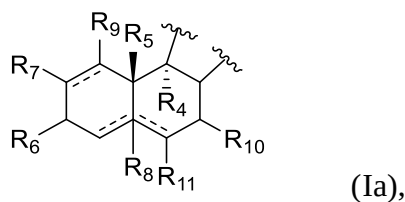
In one aspect, the present application provides use of a lipid composition in the manufacture of an agent for delivering nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:

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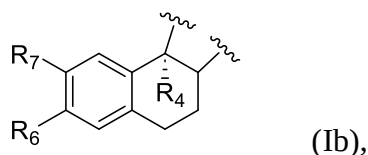


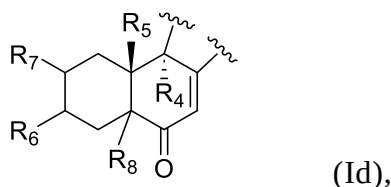
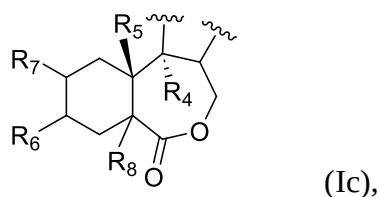
wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



15





wherein:

== is a carbon-carbon single bond or carbon-carbon double bond;

5 R_1 is hydrogen or hydroxyl;

each R_2 is hydrogen, or two R_2 together with the carbon atom to which they are attached form a straight or branched C_{2-20} alkenyl;

R_3 is straight or branched C_{1-20} alkyl optionally substituted by one or more hydroxyls, straight or branched C_{1-20} alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, straight or branched C_{2-20} alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C_{1-20} heteroalkyl optionally substituted by one or more hydroxyls;

R_4 is hydrogen, hydroxyl or halogen;

15 R_5 is hydrogen, hydroxyl, or straight or branched C_{1-20} alkyl optionally substituted by one or more hydroxyls;

R_6 is hydrogen, hydroxyl, oxo, $-OC(O)R'$, or $-O$ -heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C_{1-20} alkyl;

R_7 is hydrogen or hydroxyl;

R_8 is absent, hydrogen or hydroxyl;

20 R_9 , R_{10} and R_{11} are independently hydrogen, oxo or hydroxyl;

X_1 is hydrogen, oxo, hydroxyl, $-C(O)R'$, $-OC(O)R'$, C_{3-20} cycloalkenyl optionally substituted by oxo, C_{3-20} heterocycloalkenyl optionally substituted by oxo, or straight or branched C_{1-20} alkyl optionally substituted by one or more groups selected from hydroxyl, amino, $-COOH$ or $-C(O)N(R'')_2$;

X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;

X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

X₄ is hydrogen or hydroxyl;

5 X₅ is hydrogen, hydroxyl or oxo;

X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

10 R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;
each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

15 In some embodiments, salts of the compounds including pharmaceutically acceptable salts.

In another aspect, the present application provides use of a lipid composition in the manufacture of an agent for delivering nucleic acid, the lipid composition comprises one or more compounds selected from the group consisting of lipids 508,
20 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653 as shown in table below, or salts, hydrates or solvates thereof:

Lipid Compound No.	Product Name
508	Brassinolide
512	Vitamin D4
532	Fluoxymesterone
534	Fludrocortisone
538	Ponasterone A

539	Mestanolone
540	Maxacalcitol
545	Paricalcitol
546	Methyltestosterone
547	Methylprednisolone
548	5 α -androstanediol
549	Desoxycortisone
550	G Strophanin G
551	Cholestan-3,5, 6-triol
552	Glycodesoxycholic acid
553	Glycocholic acid
554	Calcipotriol
555	4-androstene-11 β - ol -3, 17-dione
556	17-valerate - β - estradiol ester
557	Medroxyprogesterone
558	Hecogenin
559	Digitoxigenin
560	Levonorgestrel
561	Dehydroepiandrosterone
562	Nandrolone
563	Androsterone
564	Prednisone
565	Cholesterol margarate
566	Hydrocortisone
567	19-hydroxy-androstane-4-ene-3, 17-dione
568	Testosterone propionate
569	Doxercalciferol
570	1 α , 25-dihydroxyvitamin D2
571	Calcifediol

575	Progesterone
576	Norethindrone
577	Lithocholic acid
579	Testosterone
580	Chenodeoxycholic acid
581	Deoxycholic acid
582	Hydrocortisone acetate
583	5 α -cholestan-3 β -ol
584	Cholesterol stearate
585	Cortisone acetate
586	3 α -hydroxy-7-oxo-5 β -cholanic acid
587	4-androstene-3, 17-diketone
588	Sodium deoxycholate
589	Diosgenin
590	Pregnenolone
591	Ethinylestradiol
592	Ursodesoxycholic acid
633	Estriol
653	5 α -cholestane

In some embodiments, the lipid composition or the agent may deliver the nucleic acid via oral administration, inhalation, or injection. In some embodiments, the lipid composition or the agent delivers the nucleic acid via oral administration. In some
5 embodiments, the delivery includes in vivo digestive tract delivery.

In some embodiments, the delivery includes in vitro cellular delivery.

In some embodiments, the lipid composition or the agent may be used to prepare a lipid nucleic acid mixture.

The lipid nucleic acid mixture may be prepared by appropriate methods,
10 including, but not limited to, heating, reverse-phase evaporation, or mixing.

In some embodiments, the heating method comprises adding an organic solvent solution of a lipid to an aqueous solution of a nucleic acid to obtain a mixture solution, and heating the mixture solution at a suitable temperature. In some embodiments, the heating method further comprises cooling the heated mixture solution to obtain a mixture of the lipid and the nucleic acid.

In some embodiments, the mixture solution is heated at a temperature selected from 25°C to 100°C, 30°C to 100°C, 40°C to 100°C, 50°C to 100°C, 60°C to 100°C, 70°C to 100°C, 80°C to 100°C, 90°C to 100°C, or 95°C to 100°C. In some embodiments, the mixture solution is heated at a temperature selected from 30°C, 35°C, 37°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C.

In some embodiments, the time for heating the mixture solution is about 5 minutes to about 24 hours, about 5 minutes to about 20 hours, about 5 minutes to about 16 hours, about 10 minutes to about 20 hours, about 10 minutes to about 16 hours, about 15 minutes to about 24 hours, about 15 minutes to about 20 hours, about 30 minutes to about 24 hours, about 30 minutes to about 20 hours, about 40 minutes to about 16 hours, about 50 minutes to about 12 hours, about 1 hour to about 8 hours, or about 2 hours to about 4 hours. In some embodiments, the time for heating the mixture solution is about 5 minutes to about 1 hour, about 5 minutes to about 30 minutes, about 5 minutes to about 15 minutes, or about 10 minutes to about 15 minutes. In some embodiments, the time for heating the mixture solution is about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, 40 minutes, 50 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12 hours, 16 hours, 20 hours, or 24 hours.

In some embodiments, the mixture solution is cooled at a temperature selected from 25°C to -80°C, 20°C to -80°C, 15°C to -80°C, 10°C to -80°C, 4°C to -80°C, 0°C to -80°C, -10°C to -80°C, -20°C to -80°C, -30°C to -80°C, or -40°C to -80°C. In some embodiments, the mixture solution is cooled at a temperature selected from 25°C, 20°C, 15°C, 10°C, 4°C, or 0°C.

In some embodiments, the reverse-phase evaporation method comprises mixing

an aqueous solution of a nucleic acid with an organic solvent solution of a lipid compound to obtain a mixture solution. In some embodiments, the reverse-phase evaporation method further comprises removing the organic solvent from the mixture solution followed by hydration to obtain a mixture of the lipid and the nucleic acid. In some embodiments, the mixture solution is ultrasonicated and/or evaporated to remove the organic solvent. In some embodiments, the step to remove the organic solvent from the mixture solution is conducted at a suitable temperature.

In some embodiments, the organic solvent in the mixture solution is removed at a temperature selected from about 25°C to about 70°C, 30°C to about 70°C, about 30°C to about 65°C, about 40°C to about 65°C, about 40°C to about 60°C, or about 50°C to about 60°C. In some embodiments, the organic solvent in the mixture solution is removed at a temperature selected from about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, or about 70°C.

In another aspect, the present application provides a method of delivering nucleic acid to an individual in need thereof, comprising administering a lipid composition and the nucleic acid to the individual orally, via inhalation or injection. In some embodiments, the lipid composition and the nucleic acid are administered in the form of a lipid nucleic acid mixture.

In some embodiments, the nucleic acid comprises DNA or RNA. In some embodiments, the DNA is non-coding DNA (such as antisense DNA) or coding DNA, among others. In some embodiments, the RNA is antisense RNA, mRNA, lncRNA, or small RNA (such as miRNA, siRNA, piRNA, snoRNA, tsRNA), among others.

In some embodiments, the nucleic acid comprises small nucleic acids having a length of 14-32bp, 16-28bp, or 18-24bp.

In certain embodiments, the nucleic acid is single-stranded or double-stranded.

In certain embodiments, the nucleic acid has a stem-loop structure.

In some embodiments, the nucleic acid is used for treating diseases.

In some embodiments, the nucleic acid is used for treating cancer, inflammation, fibrotic disease, autoimmune or autoinflammatory disease, bacterial infection, behavioral and psychiatric disorder, blood disease, chromosomal disease, congenital

and hereditary disease, connective tissue disease, digestive disease, ear nose throat disease, endocrine disease, environmental disease, eye disease, female reproductive disease, fungal infection, heart disease, hereditary cancer syndrome, disease of the immune system, kidney and urinary disease, lung disease, male reproductive disease, 5 metabolic disorder, mouth disease, musculoskeletal disease, myelodysplastic syndrome, neonatal screening, nutritional disease, parasitic disease, rare cancer, rare disease, skin disease, or viral infection.

In some embodiments, the nucleic acid is used for treating hepatocellular carcinoma, corneal neovascularization, recurrent or refractory anaplastic astrocytoma 10 (WHO Grade III), or secondary glioblastoma (WHO Grade IV), advanced squamous cell lung cancer, acromegaly, psoriasis, Duchenne muscular dystrophy, advanced non-small cell lung cancer, metastatic castration-resistant prostate cancer, cytomegalovirus retinitis, HIV infection, hepatitis B, hepatitis C, hyperlipoprotein disease, total knee replacement, type 2 diabetes, familial amyloid polyneuropathy (FAP), wet macular 15 degeneration (e.g., neovascular age-related macular degeneration, subfoveal neovascular age-related macular degeneration, exudative age-related macular degeneration), hypercholesterolemia, Crohn's disease, extensive liver fibrosis, infantile spinal muscular atrophy, melanoma, neonatal coronary artery disease, mild allergic asthma, chronic lymphocytic leukemia, and hypertriglyceridemia, small cell 20 obliterations of the liver with renal or lung dysfunction after hematopoietic stem cell transplantation, or hereditary transthyretin amyloidosis.

In another aspect, the present application also provides a pharmaceutical composition comprising a lipid composition and a nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or 25 pharmaceutically acceptable salts, hydrates or solvates thereof. In some embodiments, the lipid composition and the nucleic acid are present in the form of a lipid nucleic acid mixture.

In another aspect, the present application also provides a pharmaceutically composition comprising a lipid composition and a nucleic acid, wherein the lipid 30 composition comprises one or more compounds selected from the group consisting of

lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653, or salts, hydrates, or solvates thereof. In some embodiments, the
5 lipid composition and the nucleic acid are present in the form of a lipid nucleic acid mixture.

In another aspect, the present application also provides use of the pharmaceutical compositions of the present application in the manufacture of medicament for the prevention and/or treatment of diseases that can be prevented and/or treated with
10 nucleic acid, or for in vivo delivering nucleic acid to a subject in need thereof.

In another aspect, the present application also provides a kit comprising one or more compounds of Formula (I) or Formula (II), or pharmaceutically acceptable salts, hydrates or solvates thereof, positioned in a first container, and a nucleic acid positioned in a second container.

15 In another aspect, the present application also provides a kit comprising one or more compounds positioned or pharmaceutically acceptable salts, hydrates, or solvates thereof in a first container, and a nucleic acid positioned in a second container, wherein the one or more compounds are selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552,
20 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In another aspect, the present application provides the use of the kit of the present application in the manufacture of medicament for the prevention and/or
25 treatment of diseases that can be prevented and/or treated with nucleic acids, or for in vivo delivering nucleic acids to a subject in need thereof.

In another aspect, the present application provides a method of delivering a nucleic acid to a target cell, comprising administering to the target cell the pharmaceutical composition of the present application or a lipid nucleic acid mixture
30 formulated from the kit of the present application.

In another aspect, the present application provides a method of in vivo delivering nucleic acid to a subject in need thereof, comprising administering to the subject of the pharmaceutical composition of the present application or a lipid nucleic acid mixture formulated from the kit of the present application.

It should be understood that within the scope of the present disclosure, each above-mentioned technical feature of the present disclosure and each technical feature specifically described below (e.g., in Examples) can be combined with each other to form a new or preferred technical solution, the details of which will not be elaborated here one by one due to space limitations.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the results of blank group, free uptake group, and lipid 508 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), and blood (i) of mouse.

Figure 2 illustrates the results of blank group, free uptake group, and lipid 512 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), and blood (i) of mouse.

Figure 3 illustrates the results of the blank group, free uptake group, and lipid 532 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 4 illustrates the results of the blank group, free uptake group, and lipid 534 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 5 illustrates the results of the blank group, free uptake group, and lipid 538 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),

blood (i), and femur (j) of mouse.

Figure 6 illustrates the results of the blank group, free uptake group, and lipid 539 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
5 blood (i), and femur (j) of mouse.

Figure 7 illustrates the results of the blank group, free uptake group, and lipid 540 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

10 Figure 8 illustrates the results of the blank group, free uptake group, and lipid 545 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 9 illustrates the results of the blank group, free uptake group, and lipid 546
15 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 10 illustrates the results of the blank group, free uptake group, and lipid 547 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
20 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 11 illustrates the results of the blank group, free uptake group, and lipid 548 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
25 blood (i), and femur (j) of mouse.

Figure 12 illustrates the results of the blank group, free uptake group, and lipid 549 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

30 Figure 13 illustrates the results of the blank group, free uptake group, and lipid

550 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 14 illustrates the results of the blank group, free uptake group, and lipid
5 551 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 15 illustrates the results of the blank group, free uptake group, and lipid
552 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
10 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 16 illustrates the results of the blank group, free uptake group, and lipid
553 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
15 blood (i), and femur (j) of mouse.

Figure 17 illustrates the results of the blank group, free uptake group, and lipid
554 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

20 Figure 18 illustrates the results of the blank group, free uptake group, and lipid
555 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 19 illustrates the results of the blank group, free uptake group, and lipid
25 556 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 20 illustrates the results of the blank group, free uptake group, and lipid
557 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
30 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),

blood (i), and femur (j) of mouse.

Figure 21 illustrates the results of the blank group, free uptake group, and lipid
558 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
5 blood (i), and femur (j) of mouse.

Figure 22 illustrates the results of the blank group, free uptake group, and lipid
559 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
blood (i), and femur (j) of mouse.

10 Figure 23 illustrates the results of the blank group, free uptake group, and lipid
560 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
blood (i), and femur (j) of mouse.

Figure 24 illustrates the results of the blank group, free uptake group, and lipid
15 561 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
blood (i), and femur (j) of mouse.

Figure 25 illustrates the results of the blank group, free uptake group, and lipid
562 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
20 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
blood (i), and femur (j) of mouse.

Figure 26 illustrates the results of the blank group, free uptake group, and lipid
563 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
25 blood (i), and femur (j) of mouse.

Figure 27 illustrates the results of the blank group, free uptake group, and lipid
564 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
blood (i), and femur (j) of mouse.

30 Figure 29 illustrates the results of the blank group, free uptake group, and lipid

565 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 29 illustrates the results of the blank group, free uptake group, and lipid
5 566 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 30 illustrates the results of the blank group, free uptake group, and lipid
567 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
10 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 31 illustrates the results of the blank group, free uptake group, and lipid
568 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
15 blood (i), and femur (j) of mouse.

Figure 32 illustrates the results of the blank group, free uptake group, and lipid
569 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

20 Figure 33 illustrates the results of the blank group, free uptake group, and lipid 570 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 34 illustrates the results of the blank group, free uptake group, and lipid
25 571 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 35 illustrates the results of the blank group, free uptake group, and lipid
575 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
30 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),

blood (i), and femur (j) of mouse.

Figure 36 illustrates the results of the blank group, free uptake group, and lipid 576 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
5 blood (i), and femur (j) of mouse.

Figure 37 illustrates the results of the blank group, free uptake group, and lipid 577 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

10 Figure 38 illustrates the results of the blank group, free uptake group, and lipid 579 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 39 illustrates the results of the blank group, free uptake group, and lipid 580 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
15 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 40 illustrates the results of the blank group, free uptake group, and lipid 581 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
20 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 41 illustrates the results of the blank group, free uptake group, and lipid 582 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
25 blood (i), and femur (j) of mouse.

Figure 42 illustrates the results of the blank group, free uptake group, and lipid 583 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

30 Figure 43 illustrates the results of the blank group, free uptake group, and lipid

584 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 44 illustrates the results of the blank group, free uptake group, and lipid
5 585 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 45 illustrates the results of the blank group, free uptake group, and lipid
586 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
10 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 46 illustrates the results of the blank group, free uptake group, and lipid
587 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
15 blood (i), and femur (j) of mouse.

Figure 47 illustrates the results of the blank group, free uptake group, and lipid
588 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

20 Figure 48 illustrates the results of the blank group, free uptake group, and lipid 589 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 49 illustrates the results of the blank group, free uptake group, and lipid
25 590 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

Figure 50 illustrates the results of the blank group, free uptake group, and lipid
591 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c),
30 lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),

blood (i), and femur (j) of mouse.

Figure 51 illustrates the results of the blank group, free uptake group, and lipid 592 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h),
5 blood (i), and femur (j) of mouse.

Figure 52 illustrates the results of the blank group, free uptake group, and lipid 633 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

10 Figure 53 illustrates the results of the blank group, free uptake group, and lipid 653 for delivery of PGY-sRNA-26 into heart tissue (a), liver tissue (b), spleen tissue (c), lung tissue (d), kidney tissue (e), stomach tissue (f), intestine tissue (g), brain tissue (h), blood (i), and femur (j) of mouse.

15 DETAILED DESCRIPTION OF THE INVENTION

The present invention is based, at least in part, on the suprising discovery by the inventor of the present application after extensive experimentation that there are some lipid components in traditional Chinese medicine, and the lipids derived from extracts of traditional Chinese medicine can facilitate the absorption/entry of nucleic acids such
20 as small RNA into cells and/or in vivo target sites of a subject in need thereof. For the purposes of the present invention, these lipid components may also be synthetic.

The present application is described in detail below with reference to some embodiments of the present application which show the structure and formula in an exemplary way. Although the present application is described in conjunction with listed
25 embodiments, it should be understood that it is not intended to limit the present application to those embodiments described. Instead, the present application is intended to cover all alternatives, modifications and equivalents falling within the scope limited by the Claims. Those skilled in the art will recognize other methods and materials similar to or equivalent to those described herein that may be used to implement the

present application, and the present application is not limited in any way to the methods and materials described herein. Where the referenced literature and similar materials differ from or contradict the description of the present application (including limited terms, use of terms, techniques, etc.), the description of the present Application shall
5 prevail.

It should also be understood that certain features described in different embodiments may also be provided in combination in a single embodiment. Conversely, multiple features described in a single embodiment may also be provided separately or in any appropriate subcombination.

10 It should also be understood that the numerical points recorded herein are intended to include the numerical points themselves, as well as the numerical ranges between any two of the recorded points (as these numerical ranges have been listed separately).

Definition

As used herein, the following definitions shall apply unless otherwise stated. For
15 the purposes of the present application, chemical elements are identified according to the Periodic Table of Elements (CAS Edition) of the Handbook of Chemistry and Physics (75th Edition). In addition, the general principles of organic chemistry and specific functional parts and reactivity are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 1999 and “March's Advanced Organic
20 Chemistry,” 5th Ed., Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of which is incorporated by reference into the present application.

Linking substituents are described herein. When the structure clearly requires a linking group, it should be understood that the Markush variable listed for that group is a linking group. For example, if the structure requires a linking group and the definition
25 of a Markush group for that variable lists “alkyl”, it should be understood that “alkyl” means an alkylene linking group.

The term “substituted” as used herein, whether or not preceded by the term “optionally”, represents that one or more of the hydrogens in a given group are replaced by suitable substituents. Unless otherwise stated, the “substituted” group may have a
30 suitable substituent at each position of the group suitable for substitution, and the

substituent may be the same or different at each position when more than one position in any given structure can be substituted by more than one substituent selected from a particular group. The combinations of substituents contemplated by the present invention are preferably those resulting in the formation of stable or chemically viable compounds. The term “stable” as used herein refers to a compound that remains substantially unchanged when subjected to conditions that permit its production, detection, and (in some embodiments) its recovery, purification, and use for one or more of the purposes disclosed herein. Unless specifically referred to as “unsubstituted”, the chemical moieties described herein are to be understood to include substituents. For example, when referring to “aryl”, it includes substituted aryl and unsubstituted aryl.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, such substituent may be bonded via any atomic bond in such formula. Combinations of substituents and/or variables are permissible, but only if such combination results in a stable compound.

The term “C_{i-j}” as used herein indicates a range of the number of carbon atoms, where i and j are integers and j is greater than i, and the range of the number of carbon atoms includes the endpoints (i.e., i and j) and every integer point between the endpoints. For example, C₁₋₆ indicates a range of 1 to 6 carbon atoms, including 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, and 6 carbon atoms. In some embodiments, the term “C₁₋₁₂” indicates 1 to 12, particularly 1 to 10, particularly 1 to 8, particularly 1 to 6, particularly 1 to 5, particularly 1 to 4, particularly 1 to 3, or particularly 1 to 2 carbon atoms.

The term “alkyl” as used herein, whether as part of another term or used independently, refers to saturated straight or branched alkyl groups. The term “C_{i-j} alkyl” refers to alkyl having i to j carbon atoms. In some embodiments, alkyl contains 1 to 20 carbon atoms. In some embodiments, alkyl contains 5 to 20 carbon atoms. In some embodiments, alkyl contains 1 to 20 carbon atoms, 1 to 19 carbon atoms, 1 to 18 carbon atoms, 1 to 17 carbon atoms, 1 to 16 carbon atoms, 1 to 15 carbon atoms, 1 to

14 carbon atoms, 1 to 13 carbon atoms, 1 to 12 carbon atoms, 1 to 11 carbon atoms, 1 to 10 carbon atoms, 1 to 9 carbon atoms, 1 to 8 carbon atoms, 1 to 7 carbon atoms, 1 to 6 carbon atoms, 1 to 5 carbon atoms, 1 to 4 carbon atoms, 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, 1-propyl (n-propyl), 2-propyl (isopropyl), 1-butyl (n-butyl), 2-methyl-1-propyl (isobutyl), 2-butyl (neobutyl), 2-methyl-2-propyl (tert-butyl), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, 1-heptyl, 1-octyl, 1-nonyl, 1-decyl, etc. Examples of "C1-20 alkyl" include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and eicosyl.

The term "alkenyl" as used herein, whether as part of another term or used independently, refers to a straight or branched hydrocarbon radical having at least one carbon-carbon double bond, which may be optionally substituted independently by one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively "E" and "Z" orientations. In some embodiments, alkenyl contains 2 to 20 carbon atoms. In some embodiments, alkenyl contains 5 to 20 carbon atoms. In some embodiments, alkenyl contains 2 to 20 carbon atoms, 2 to 19 carbon atoms, 2 to 18 carbon atoms, 2 to 17 carbon atoms, 2 to 16 carbon atoms, 2 to 15 carbon atoms, 2 to 14 carbon atoms, 2 to 13 carbon atoms, 2 to 12 carbon atoms, 2 to 11 carbon atoms, 2 to 10 carbon atoms, 2 to 9 carbon atoms, 2 to 8 carbon atoms, 2 to 7 carbon atoms, 2 to 6 carbon atoms, 2 to 5 carbon atoms, 2 to 4 carbon atoms, or 2 to 3 carbon atoms. In some embodiments, alkenyl contains more than one carbon-carbon double bond. It should be understood that where alkenyl contains more than one carbon-carbon double bond, the double bonds may be separated from each other or conjugated. In some embodiments, alkenyl contains 5 carbon-carbon double bonds, 4 carbon-carbon double bonds, 3 carbon-carbon double bonds, 2 carbon-carbon double bonds, or 1 carbon-carbon double bond.

The term “alkynyl” as used herein, whether as part of another term or used independently, refers to a straight or branched hydrocarbon radical having at least one carbon-carbon triple bond, which may be optionally substituted independently by one or more substituents. In some embodiments, alkynyl contains 2 to 12 carbon atoms. In
5 some embodiments, alkynyl contains 2 to 11 carbon atoms. In some embodiments, alkynyl contains 2 to 11 carbon atoms, 2 to 10 carbon atoms, 2 to 9 carbon atoms, 2 to 8 carbon atoms, 2 to 7 carbon atoms, 2 to 6 carbon atoms, 2 to 5 carbon atoms, 2 to 4 carbon atoms, 2 to 3 carbon atoms. In some embodiments, alkynyl contains 2 carbon atoms. Examples of alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-
10 propynyl, etc.

The term “cycloalkyl” as used herein, whether as part of another term or used independently, refers to a saturated monocyclic and polycyclic ring system wherein all ring atoms are carbon, and which contains at least three ring-forming carbon atoms. In some embodiments, cycloalkyl may contain 3 to 20 ring-forming carbon atoms, 3 to 19
15 ring-forming carbon atoms, 3 to 18 ring-forming carbon atoms, 3 to 17 ring-forming carbon atoms, 3 to 16 ring-forming carbon atoms, 3 to 15 ring-forming carbon atoms, 3 to 14 ring-forming carbon atoms, 3 to 13 ring-forming carbon atoms, 3 to 12 ring-forming carbon atoms, 3 to 11 ring-forming carbon atoms, 3 to 10 ring-forming carbon atoms, 3 to 9 ring-forming carbon atoms, 3 to 8 ring-forming carbon atoms, 3
20 to 7 ring-forming carbon atoms, 3 to 6 ring-forming carbon atoms, 3 to 5 ring-forming carbon atoms, 4 to 20 ring-forming carbon atoms, 4 to 19 ring-forming carbon atoms, 4 to 18 ring-forming carbon atoms, 4 to 17 ring-forming carbon atoms, 4 to 16 ring-forming carbon atoms, 4 to 15 ring-forming carbon atoms, 4 to 14 ring-forming carbon atoms, 4 to 13 ring-forming carbon atoms, 4 to 12 ring-forming carbon atoms, 4 to 11
25 ring-forming carbon atoms, 4 to 10 ring-forming carbon atoms, 4 to 9 ring-forming carbon atoms, 4 to 8 ring-forming carbon atoms, 4 to 7 ring-forming carbon atoms, 4 to 6 ring-forming carbon atoms, or 4 to 5 ring-forming carbon atoms. Cycloalkyl may optionally be substituted at one or more ring positions by one or more substituents described herein. Cycloalkyl can be a monocyclic or polycyclic carbon ring system. In
30 some embodiments, cycloalkyl is a monocyclic system. In some embodiments,

cycloalkyl is a fused, spiro or bridged polycyclic ring system. The term "fused ring" as used herein refers to a ring system with two rings sharing two adjacent atoms, the term "spiro ring" as used herein refers to a ring system with two rings connected through one single common atom, and the term "bridged ring" as used herein refers to a ring system with two rings sharing three or more atoms. Cycloalkyl may be saturated, partially unsaturated, or fully unsaturated. In some embodiments, cycloalkyl may be a saturated cyclic alkyl. In some embodiments, cycloalkyl may be an unsaturated cyclic alkyl group containing at least one double or triple bond in the ring system.

The term "cycloalkenyl" as used herein, whether as part of another term or used independently, refers to a monocyclic and polycyclic ring system containing 3-20 ring-forming carbon atoms and at least one carbon-carbon double bond, wherein all ring atoms are carbon, provided that the size of the cycloalkenyl ring allows. In some embodiments, cycloalkenyl contains more than 1 carbon-carbon double bond. It should be understood that where the alkenyl group contains more than one carbon-carbon double bond, the double bonds may be separated from each other or conjugated. In some embodiments, cycloalkenyl contains 5 carbon-carbon double bonds, 4 carbon-carbon double bonds, 3 carbon-carbon double bonds, 2 carbon-carbon double bonds, or 1 carbon-carbon double bond.

As used herein, the term "heteroatom" refers to nitrogen, oxygen, sulfur or phosphorus and comprises any oxidized form of nitrogen or sulfur and any quaternized form of basic nitrogen.

The term "heteroalkyl" as used herein, whether as part of another term or used independently, refers to alkyl in which at least one carbon atom is substituted by a heteroatom selected from nitrogen, oxygen, sulfur or phosphorus, wherein the heteroatom may be placed either at the end or in the middle of the alkyl.

The term "heteroalkenyl" as used herein, whether as part of another term or used independently, refers to alkenyl in which at least one carbon atom is substituted by a heteroatom selected from nitrogen, oxygen, sulfur or phosphorus, wherein the heteroatom may be placed either at the end or in the middle of the alkenyl.

The term "heterocyclyl" as used herein refers to a cycloalkyl wherein one or more

(e.g., 1, 2, or 3) ring atoms are substituted by a heteroatom including, but not limited to, oxygen, sulfur, nitrogen, phosphorus, etc. Examples of heterocyclyl containing one heteroatom include pyrrolidine, tetrahydropyran, tetrahydrofuran and piperidine, and examples of a heterocyclyl containing two heteroatoms include morpholine and
5 piperazine.

The term “heterocycloalkenyl” as used herein refers to a cycloalkenyl wherein one or more (e.g., 1, 2 or 3) ring atoms are replaced by a heteroatom including, but not limited to, oxygen, sulfur, nitrogen, phosphorus, etc. Examples of heterocycloalkenyl containing one heteroatom include 1-pyrroline and 2,5-dihydrofuran.

10 The term “oxo” as used herein refers to =O.

The term “hydroxyl” as used herein refers to -OH.

The term “amine” as used herein refers to -NH₂.

The terms “halogen” as used herein refers to fluorine, chlorine, bromine and iodine.

As used herein, the term “pharmacologically acceptable salt” refers to a salt or
15 zwitterionic form of a compound described herein that is, within a reasonable medical judgment, suitable for use in contact with human or animal tissues without excessive toxicity, irritation, allergic reaction, or other problems, and that is commensurate with a reasonable benefit/risk ratio.

As used herein, the term “pharmaceutical composition” refers to a composition
20 comprising the lipid composition and nucleic acid as described in the present application, which may optionally further comprise a pharmaceutically acceptable carrier.

As used herein, the term “pharmaceutically acceptable” refers to a compound, material, composition and/or formulation that is, within a reasonable medical judgment,
25 is suitable for use in contact with human and animal tissues without excessive toxicity, irritation, allergic reaction or other problems or complications, and that is commensurate with a reasonable benefit/risk ratio. In some embodiments, a pharmaceutically acceptable compound, material, composition and/or formulation refers to those approved by a regulatory administration (e.g., the U.S. Food and Drug
30 Administration, the Chinese Food and Drug Administration, or the European Medicines

Agency) or generally listed in a publically recognized pharmacopoeia (e.g., the U.S. Pharmacopoeia, the Chinese Pharmacopoeia, or the European Pharmacopoeia).

As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid
5 filler, diluent, excipient, solvent or encapsulation material, which is involved carrying or delivering the compound provided herein from one location, body fluid, tissue, organ (internal or external) or part of the body to another location, body fluid, tissue, organ or part of the body. Pharmaceutically acceptable carriers may be vehicle, diluent, excipient, or other materials that can be used to contact animal tissues without excessive toxicity
10 or side effects. Examples of pharmaceutically acceptable carriers include sugar, starch, cellulose, malt, tragacanth, gelatin, Ringer's solution, alginic acid, isotonic saline, buffer, etc. Pharmaceutically acceptable carriers available for use in the present application include those commonly known in the art, such as those disclosed in “Remington Pharmaceutical Sciences”, Mack Pub. Co., New Jersey (1991), that is incorporated by
15 reference herein.

The term “deliver”, “delivery”, or “delivering” as used herein encompasses both topical and systematic delivery. “Topical delivery” refers to the direct delivery of a therapeutic agent to be delivered (such as nucleic acid) to a target site in the organism. For example, the agent can be locally delivered by direct injection into a target site
20 (such as a disease site, such as a tumor or inflammation site) or a target organ (such as the heart, spleen, lungs, kidneys, etc.). “Systematic delivery” is the delivery causing a therapeutic agent (such as nucleic acid) extensively biologically distributed within an organism, thereby exposing an effective amount of the therapeutic agent to most parts of the body. In order to achieve the extensive biological distribution, a lifetime in blood
25 is usually required such that the therapeutic agents are not degraded or cleared rapidly before reaching a target site far from the administration site. Systematic delivery of a lipid composition may be performed in any suitable way, including, for example, oral administration, inhalation administration, intralimentary administration, intravenous administration, subcutaneous administration, and intraperitoneal administration.

As used herein, the term “lipid” refers to a class of organic compounds that include,

but are not limited to, esters of fatty acids and are characterized as insoluble in water (e.g. solubility in water of less than about 0.01 % by weight) but soluble in many organic solvents. A lipid can be, for example, simple lipid (such as fat, oil, wax), compound lipid (such as phospholipid, glycolipid), and derived lipid (such as steroid).

5 The term "nucleic acid" as used herein refers to polymers containing at least two deoxyribonucleotides or ribonucleotides, which may be in single-stranded or double-stranded form. Nucleic acids may comprise natural ribonucleotides and deoxyribonucleotides, as well as non-natural ribonucleotides and deoxyribonucleotides. Natural ribonucleotides include, for example, adenosine, guanosine, cytidine, uridine,
10 pseudouridine, inosine, and xanthosine. Natural deoxyribonucleotides include, for example, deoxyadenosine, deoxyguanosine, deoxycytidine, and deoxythymidine. Non-natural ribonucleotides and deoxyribonucleotides typically have modified nucleic bases, modified ribose or deoxyribose, and/or modified phosphate ester linkages.

 "Nucleotide" comprises sugar (e.g., deoxyribose or ribose), a base, and a
15 phosphate group. Nucleotides are linked together by phosphate groups to form polymers. "Base" includes purines and pyrimidines, and further includes natural compounds such as adenine, thymine, guanine, cytosine, uracil, inosine, and natural analogs, as well as synthetic derivatives of purines and pyrimidines with modifications such as amine, alcohol, thiol, carboxyl, and alkyl halide. Nucleic acids in the present
20 application may also include nucleotide analogs or modified nucleotides, which can be synthetic, naturally occurring, or non-naturally occurring, with binding characteristics similar to natural nucleic acids. Examples of nucleotide analogs or modified nucleotides include, but are not limited to, nucleotides with thio-phosphate esters, amino-phosphate esters, methyl-phosphate esters, or chiral-methyl-phosphate esters, 2'-O-methyl
25 ribonucleotides, and peptide-nucleic acids (PNAs).

 Examples of nucleic acids include DNA or RNA. DNA includes coding DNA and non-coding DNA, examples of which include antisense DNA, plasmid DNA, preconcentrated DNA, PCR products, DNA vectors (P1, PAC, BAC, YAC, artificial chromosomes), expression cassettes, hybrid sequences, chromosomal DNA, or
30 derivatives and combinations thereof. Examples of RNA include antisense RNA,

siRNA, asymmetric interfering RNA (aiRNA), microRNA (miRNA), mRNA, tRNA, rRNA, viral RNA (vRNA), long non-coding RNA (lncRNA), Piwi-interacting RNA (piRNA), small nucleolar RNA (snoRNA), tRNA-derived small RNA (tsRNA), or their combinations.

5 Unless otherwise indicated, specific nucleic acid sequences inherently include their conservatively modified variants (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, complementary sequences, and explicitly indicated sequences. Specifically, degenerate codon substitutions can be achieved by generating sequences in which one or more selected (or all) codons at the third position are replaced with
10 mixed basic and/or deoxyadenosine residues (Batzer et al., *Nucleic Acid Res.*, 19:5081(1991); Ohtsuka et al., *J. Biol. Chem.*, 260:2605-2608(1985); Rossolini et al., *Mol. Cell. Probes*, 8:91-98(1994)).

The term "complementary" in the context of nucleotide pairing used herein includes classical Watson-Crick pairing, i.e., G-C, A-T, or A-U pairing. Classical
15 Watson-Crick pairing also includes situations in which one or two nucleotides have been modified (e.g., by ribose modification or phosphate ester backbone modification). The term "complementary" sequences as used herein may also include non-Watson-Crick base pairs and/or base pairs formed by non-natural and modified nucleotides.

As used herein, the term "treat", "treating", or "treatment" refers to eliminating,
20 reducing or improving a disease or condition, and/or related symptoms. Although not excluded, the treatment of a disease or condition does not require the complete elimination of the disease or condition, and/or related symptoms. The term "treat", "treating", or "treatment" as used herein may include "prophylaxis", which refers to reducing the possibility of recurrence of a disease or condition, or reducing the
25 possibility of recurrence of a previously controlled disease or condition, in a subject who is not subject to a disease or condition but is at risk or prone to the disease or condition or whose disease or condition is at risk or prone to recurrence. Within the meaning of the present invention, "treat", "treating", or "treatment" also includes relapse prevention or stage prevention, as well as treatment of acute or chronic signs,
30 symptoms and/or dysfunction. Treatment can be symptom-specific, for example, to

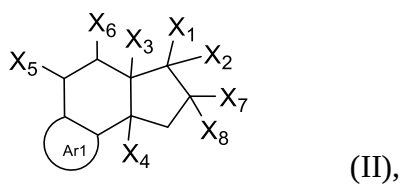
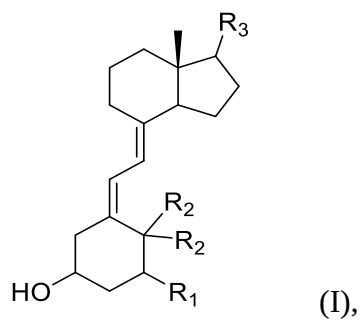
suppress symptoms. It can work for a short period of time, for a medium period, or it can be a long-term treatment, such as in the case of maintenance therapy.

As used herein, the term “subject” means any organism to which the lipid composition described herein may be administered for therapeutic purposes. In some embodiments, subject refers to primates (e.g., human), dogs, rabbits, guinea pigs, pigs, rats, and mice. In some embodiments, the subject is primates. In other embodiments, the subject is human.

Method and Use of Lipid Compounds for Delivering Nucleic Acid

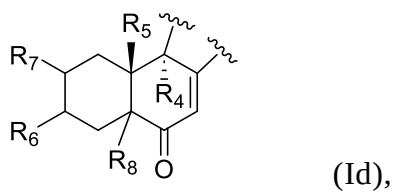
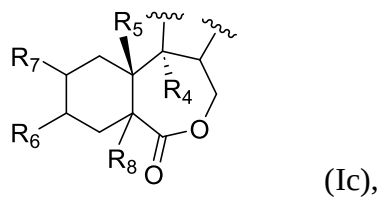
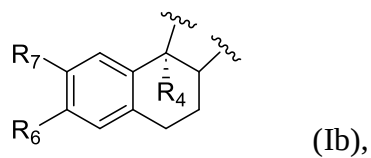
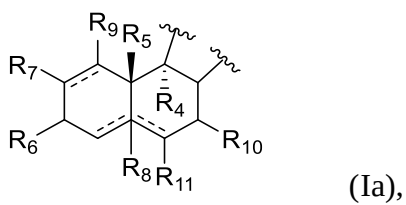
The present application provides method and use of lipid compounds for delivering nucleic acid. The present invention is at least partly based on the discovery of the remarkable effects of certain lipid compounds in nucleic acid delivery. The present application provides various lipid compounds, which have been found to form stable nucleic acid lipid mixture and effectively deliver nucleic acids into cells, particularly the in vivo cells. The lipid compounds provided herein can deliver nucleic acid molecules into the body and specific target organs within the body via oral administration, thereby achieving desirable therapeutic effects. Surprisingly, different lipid compounds exhibit varying effects in delivering nucleic acids to target organs, demonstrating different preferences for different target organs. Some lipid compounds show significant nucleic acid delivery effects for more than one target organ, and efficiently deliver nucleic acids to multiple target organs, thus having broad use in nucleic acid delivery. Certain lipid compounds exhibit particularly notable delivery effects for a specific target organ, making them suitable for delivering nucleic acids that act on such specific organ.

In one aspect, the present application provides use of a lipid composition in the manufacture of an agent for delivering nucleic acid, or a method of delivering nucleic acid, wherein the lipid composition in the manufacture of an agent for delivering nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:



wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



wherein:

10 $\equiv$ is a carbon-carbon single bond or carbon-carbon double bond;

R1 is hydrogen or hydroxyl;

-
- each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are attached form a straight or branched C₂₋₂₀ alkenyl;
- R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls, straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected
- 5 from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;
- R₄ is hydrogen, hydroxyl or halogen;
- R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by
- 10 one or more hydroxyls;
- R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;
- R₇ is hydrogen or hydroxyl;
- R₈ is absent, hydrogen or hydroxyl;
- 15 R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;
- X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl, amino, -COOH or -C(O)N(R'')₂;
- 20 X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;
- X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;
- X₄ is hydrogen or hydroxyl;
- X₅ is hydrogen, hydroxyl or oxo;
- 25 X₆ is hydrogen, oxo or hydroxyl;
- X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;

each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

In some embodiments, R₁ is hydrogen; in some embodiments, R₁ is hydroxyl.

In some embodiments, each R₂ is hydrogen; in some embodiments, two R₂ together with the carbon atom to which they are attached form a carbon-carbon double bond, or form a straight or branched C₂₋₂₀ alkenyl.

In some embodiments, R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls; in some embodiments, R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl; in some embodiments, R₃ is straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl; in some embodiments, R₃ is straight or branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls.

In some embodiments, R₄ is hydrogen; in some embodiments, R₄ is hydroxyl; in some embodiments, R₄ is halogen.

In some embodiments, R₅ is hydrogen; in some embodiments, R₅ is hydroxyl; in some embodiments, R₅ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls.

In some embodiments, R₆ is hydrogen; in some embodiments, R₆ is hydroxyl; in some embodiments, R₆ is oxo; in some embodiments, R₆ is -OC(O)R'; in some embodiments, R₆ is -O-heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl.

In some embodiments, R₇ is hydrogen; in some embodiments, R₇ is hydroxyl.

In some embodiments, R₈ is absent; in some embodiments, R₈ is hydrogen; in some embodiments, R₈ is hydroxyl.

In some embodiments, R₉ is hydrogen; in some embodiments, R₉ is oxo; in some embodiments, R₉ is hydroxyl.

In some embodiments, R₁₀ is hydrogen; in some embodiments, R₁₀ is oxo; in some embodiments, R₁₀ is hydroxyl.

In some embodiments, R₁₁ is hydrogen; in some embodiments, R₁₁ is oxo; in some embodiments, R₁₁ is hydroxyl.

5 In some embodiments, X₁ is hydrogen; in some embodiments, X₁ is oxo; in some embodiments, X₁ is hydroxyl; in some embodiments, X₁ is -C(O)R'; in some embodiments, X₁ is -OC(O)R'; in some embodiments, X₁ is C₃₋₂₀ cycloalkenyl optionally substituted by oxo; in some embodiments, X₁ is C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo; in some embodiments, X₁ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl, amino, -COOH or -C(O)N(R'')₂.

In some embodiments, X₂ is absent; in some embodiments, X₂ is hydrogen; in some embodiments, X₂ is hydroxyl; in some embodiments, X₂ is straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl.

15 In some embodiments, X₃ is hydrogen; in some embodiments, X₃ is straight or branched C₁₋₂₀ alkyl.

In some embodiments, X₄ is hydrogen; in some embodiments, X₄ is hydroxyl.

In some embodiments, X₅ is hydrogen; in some embodiments, X₅ is hydroxyl; in some embodiments, X₅ is oxo.

20 In some embodiments, X₆ is hydrogen; in some embodiments, X₆ is oxo; in some embodiments, X₆ is hydroxyl.

In some embodiments, X₇ is hydrogen.

In some embodiments, X₈ is hydrogen.

In some embodiments, X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl.

25 In some embodiments, R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R''; in some embodiments, R' is straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl.

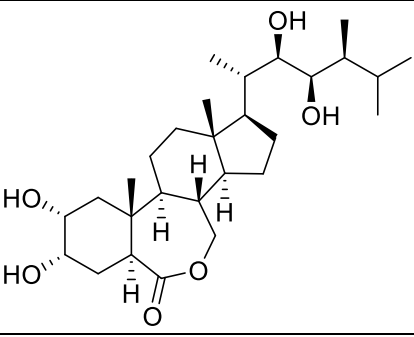
In some embodiments, each R'' is independently hydrogen.

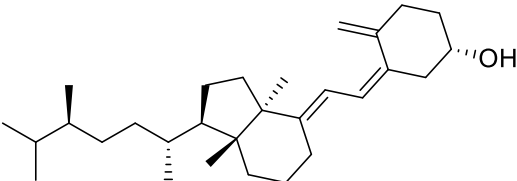
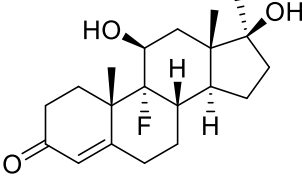
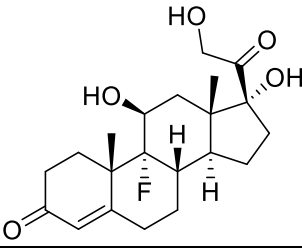
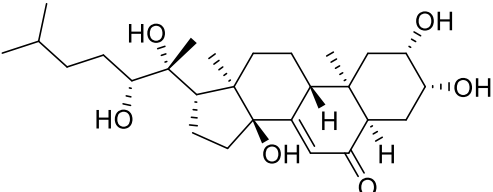
In some embodiments, R'' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

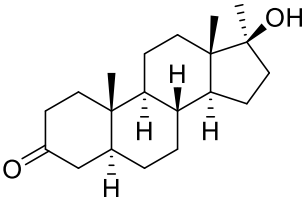
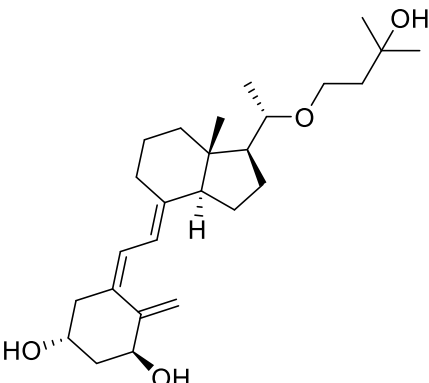
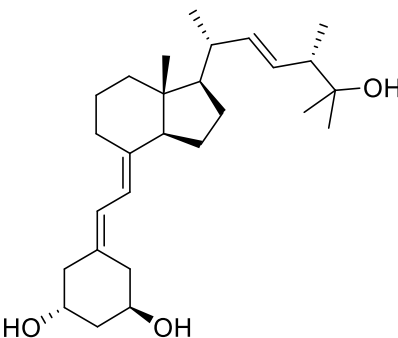
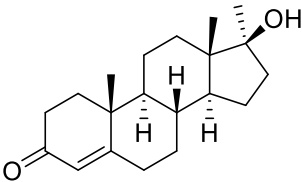
In some embodiments, the lipid composition comprises one or more compounds
 5 of Formula (I) or Formula (II) selected from the group consisting of lipids 508, 512,
 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556,
 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576,
 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and
 653, or salts, hydrates or solvates thereof, wherein the information of the lipid such as
 10 chemical name and chemical structure is presented in Table 1.

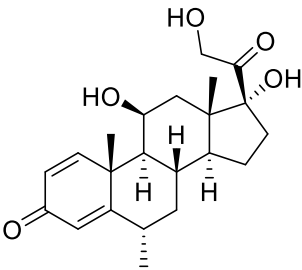
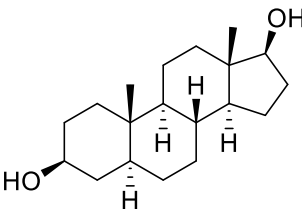
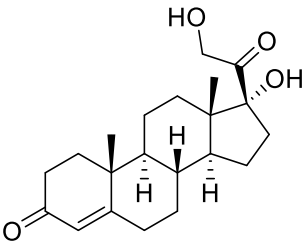
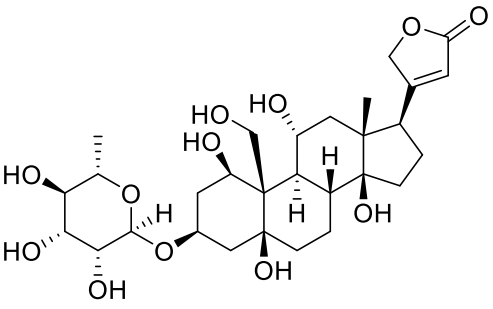
In another aspect, the present application also provides use of a lipid composition
 in the manufacture of an agent for delivering nucleic acid, or a method of delivering
 nucleic acid, wherein the lipid composition comprises one or more compounds
 selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545,
 15 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562,
 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583,
 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653, or salts, hydrates, or
 solvates thereof, wherein the information of the lipid such as chemical name and
 chemical structure is presented in Table 1.

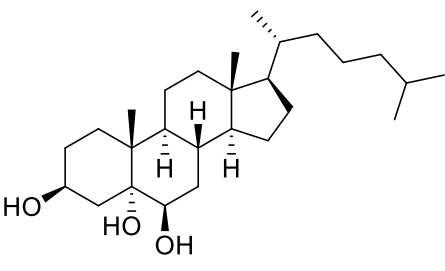
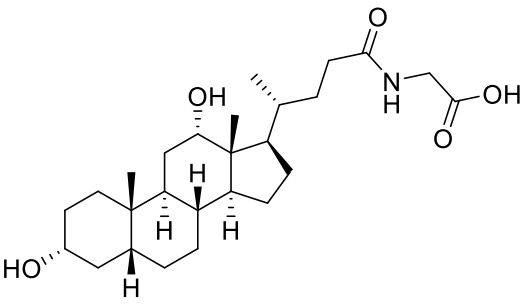
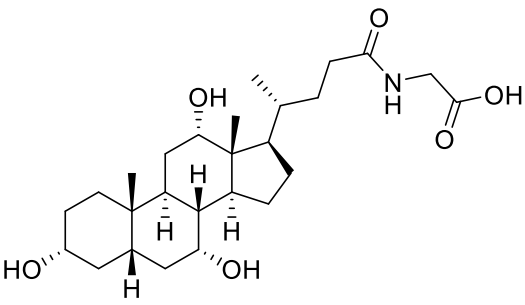
20 Table 1. Cas number, structure, and product name of Lipids 508-653

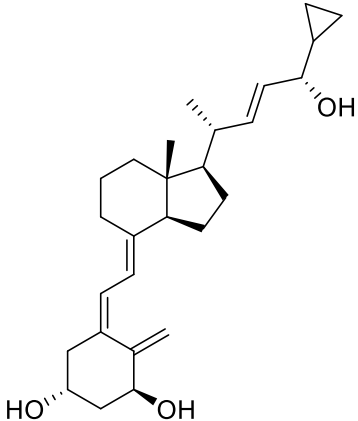
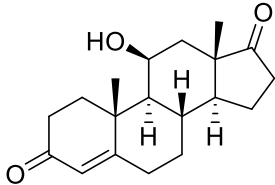
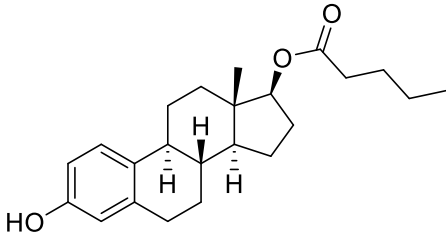
NO.	Cas number	Structure and product name
508	72962-43-7	
		Brassinolide (1R,3aS,3bS,6aS,8S,9R,10aR,10bS,12aS)-1- [(1S,2R,3R,4S)-2,3-Dihydroxy-1,4,5- trimethylhexyl]hexadecahydro-8,9-dihydroxy-10a,12a-

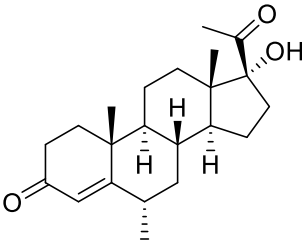
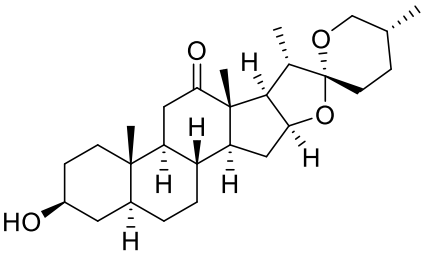
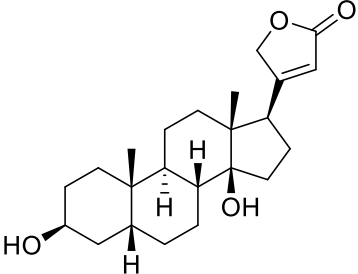
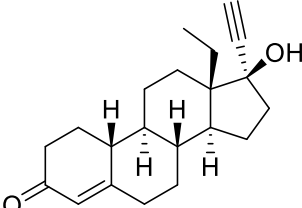
		dimethyl-6H-benz[c]indeno[5,4-e]oxepin-6-one
512	511-28-4	 Vitamin D4 (1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-1-[(2R,5S)-5,6-dimethylheptan-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol
532	76-43-7	 Fluoxymesterone (8S,9R,10S,11S,13S,14S,17S)-9-fluoro-11,17-dihydroxy-10,13,17-trimethyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one
534	127-31-1	 Fludrocortisone (8S,9R,10S,11S,13S,14S,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one
538	13408-56-5	 Ponasterone A (2S,3R,5R,9R,10R,13R,14S,17S)-17-[(2R,3R)-2,3-dihydroxy-6-methylheptan-2-yl]-2,3,14-trihydroxy-10,13-dimethyl-2,3,4,5,9,11,12,15,16,17-decahydro-1H-cyclopenta[a]phenanthren-6-one

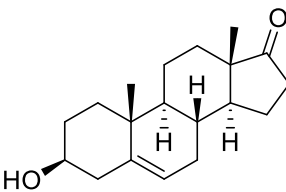
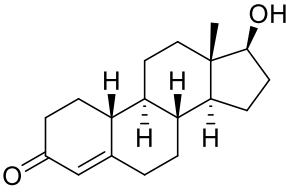
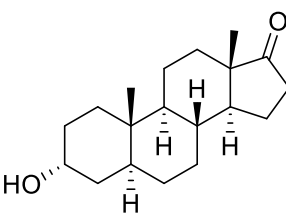
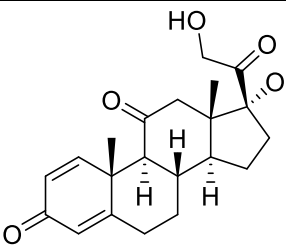
539	521-11-9	
		Mestanolone (5S,8R,9S,10S,13S,14S,17S)-17-hydroxy-10,13,17-trimethyl-2,4,5,6,7,8,9,11,12,14,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-3-one
540	103909-75-7	
		Maxacalcitol (1R,3S,5Z)-5-[(2E)-2-[(1S,3aS,7aS)-1-[(1S)-1-(3-hydroxy-3-methylbutoxy)ethyl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexane-1,3-diol
545	131918-61-1	
		Paricalcitol (1R,3R)-5-[(2E)-2-[(1R,3aS,7aR)-1-[(E,2R,5S)-6-hydroxy-5,6-dimethylhept-3-en-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]cyclohexane-1,3-diol
546	58-18-4	
		Methyltestosterone (8R,9S,10R,13S,14S,17S)-17-

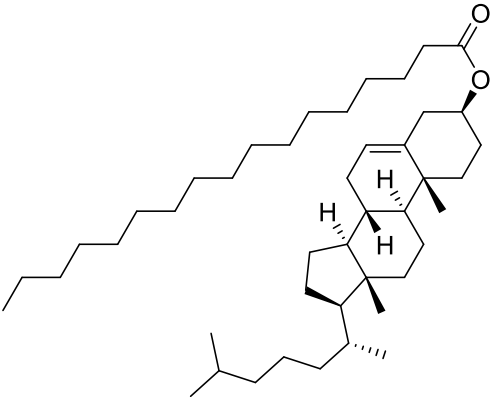
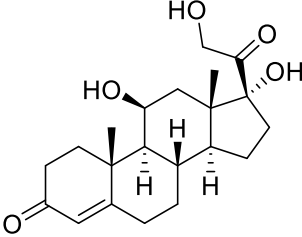
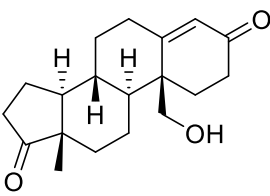
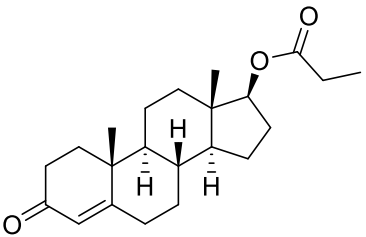
		hydroxy-10,13,17-trimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-3-one
547	83-43-2	
		Methylprednisolone (6S,8S,9S,10R,11S,13S,14S,17R)-11,17-dihydroxy-17-(2-hydroxyacetyl)-6,10,13-trimethyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthren-3-one
548	571-20-0	
		5α-androstanediol (3S,5S,8R,9S,10S,13S,14S,17S)-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3,17-diol
549	152-58-9	
		Desoxycortisone (8R,9S,10R,13S,14S,17R)-17-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-3-one
550	11018-89-6	 8 H₂O

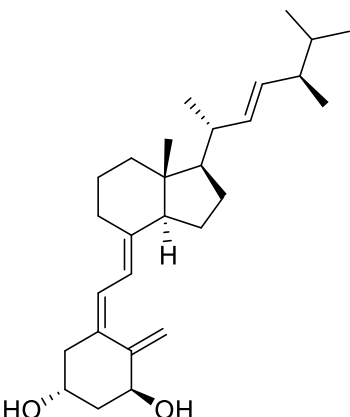
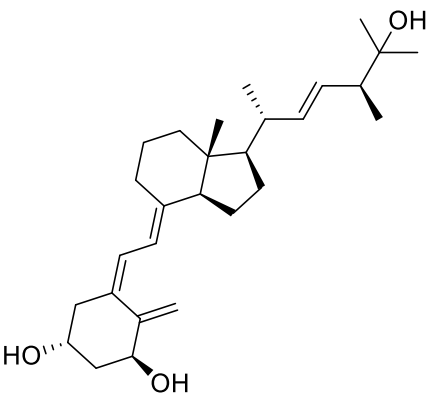
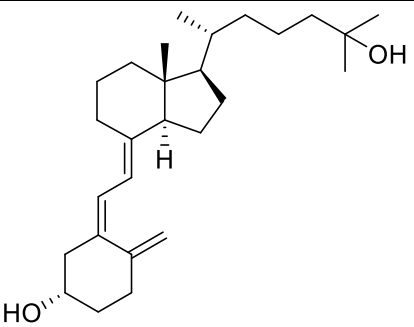
		Strophanin G 3- [(1R,3S,5S,8R,9S,10R,11R,13R,14S,17R)-1,5,11,14-tetrahydroxy-10-(hydroxymethyl)-13-methyl-3-[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-2,3,4,6,7,8,9,11,12,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl]-2H-furan-5-one;octahydrate
551	1253-84-5	 Cholestan-3,5,6-triol (3S,5R,6R,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl]-1,2,3,4,6,7,8,9,11,12,14,15,16,17-tetradecahydrocyclopenta[a]phenanthrene-3,5,6-triol
552	360-65-6	 Glycodesoxycholic acid 2-[[[(4R)-4-[(3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoyl]amino]acetic acid
553	475-31-0	 Glycocholic acid 2-[[[(4R)-4-

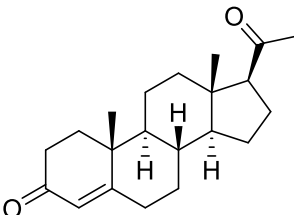
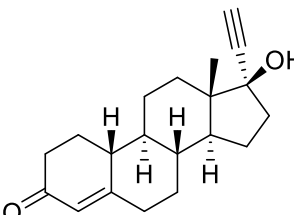
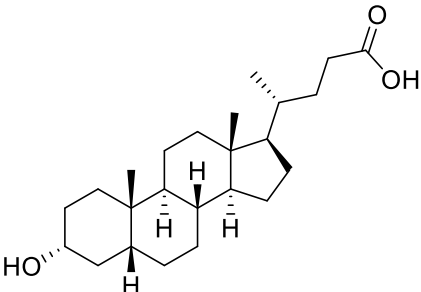
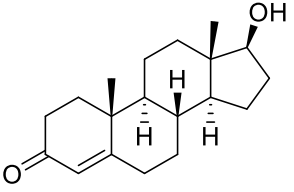
		[(3R,5S,7R,8R,9S,10S,12S,13R,14S,17R)-3,7,12-trihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoyl]amino]acetic acid
554	112965-21-6	 Calcipotriol (1R,3S,5Z)-5-[(2E)-2-[(1R,3aS,7aR)-1-[(E,2R,5S)-5-cyclopropyl-5-hydroxypent-3-en-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexane-1,3-diol
555	382-44-5	 4-androstene-11β-ol-3,17-dione (8S,9S,10R,11S,13S,14S)-11-hydroxy-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthrene-3,17-dione
556	979-32-8	 17-valerate-β-estradiol ester [(8R,9S,13S,14S,17S)-3-hydroxy-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthren-17-yl] pentanoate

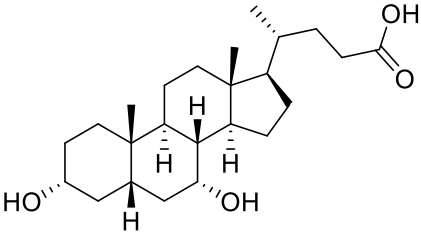
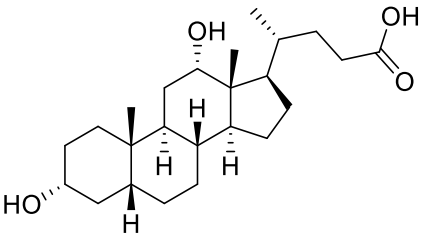
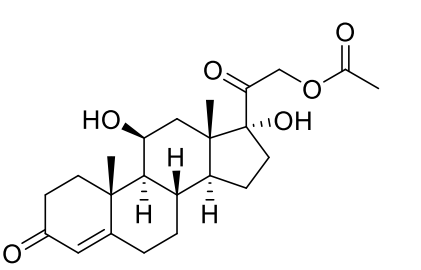
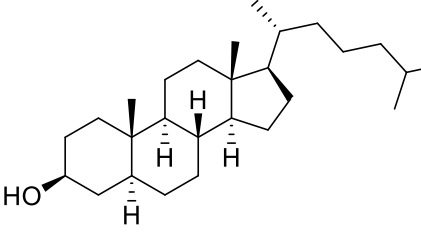
557	520-85-4	 Medroxyprogesterone (6S,8R,9S,10R,13S,14S,17R)-17-acetyl-17-hydroxy-6,10,13-trimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-3-one
558	467-55-0	 Hecogenin (1R,2S,4S,5'R,6R,7S,8R,9S,12S,13S,16S,18S)-16-hydroxy-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0.2.9.0.4]icosane-6,2'-oxane]-10-one
559	143-62-4	 Digitoxigenin 3-[(3S,5R,8R,9S,10S,13R,14S,17R)-3,14-dihydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-2H-furan-5-one
560	797-63-7	

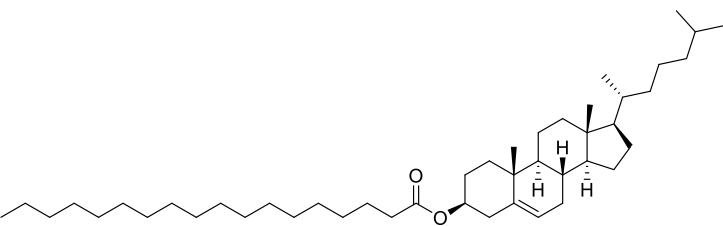
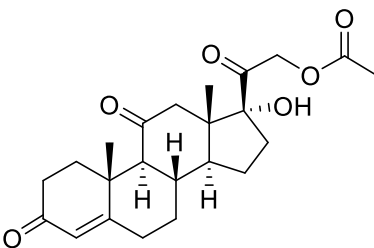
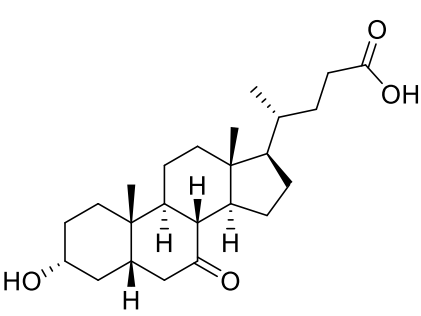
		Levonorgestrel (8R,9S,10R,13S,14S,17R)-13-ethyl-17-ethynyl-17-hydroxy-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-one
561	53-43-0	 Dehydroepiandrosterone (3S,8R,9S,10R,13S,14S)-3-hydroxy-10,13-dimethyl-1,2,3,4,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-one
562	434-22-0	 Nandrolone (8R,9S,10R,13S,14S,17S)-17-hydroxy-13-methyl-2,6,7,8,9,10,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-one
563	53-41-8	 Androsterone (3R,5S,8R,9S,10S,13S,14S)-3-hydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,14,15,16-tetradecahydrocyclopenta[a]phenanthren-17-one
564	53-03-2	 Prednisone (8S,9S,10R,13S,14S,17R)-17-hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,12,14,15,16-octahydrocyclopenta[a]phenanthrene-3,11-dione

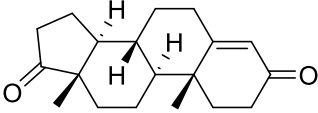
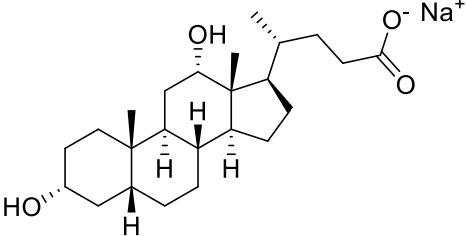
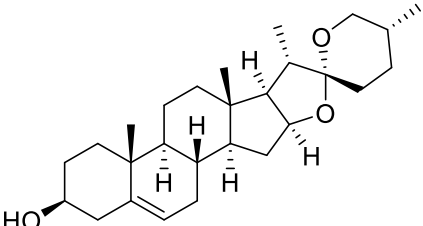
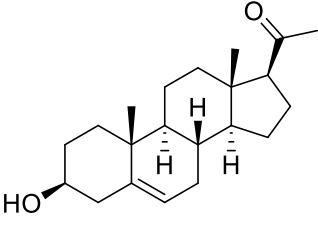
565	24365-37-5	 Cholesterol margarate [(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl] heptadecanoate
566	50-23-7	 Hydrocortisone (8S,9S,10R,11S,13S,14S,17R)-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-3-one
567	510-64-5	 19-hydroxy-androstane-4-ene-3, 17-dione (8R,9S,10S,13S,14S)-10-(hydroxymethyl)-13-methyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthrene-3,17-dione
568	57-85-2	 Testosterone propionate [(8R,9S,10R,13S,14S,17S)-

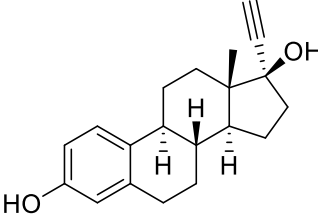
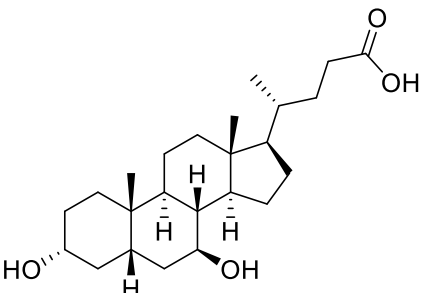
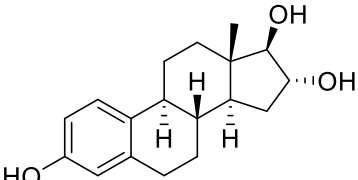
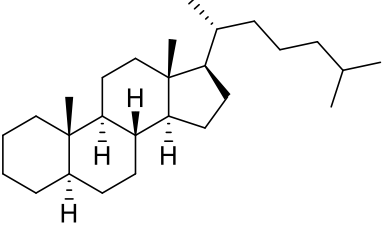
		10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl] propanoate
569	54573-75-0	 Doxercalciferol (1R,3S,5Z)-4-Methylene-5-[(2E)-2-[(1R,3aS,7aR)-octahydro-7a-methyl-1-[(1R,2E,4R)-1,4,5-trimethyl-2-hexen-1-yl]-4H-inden-4-ylidene]ethylidene]-1,3-cyclohexanediol
570	60133-18-8	 1α, 25-dihydroxyvitamin D2 (1R,3S,5Z)-5-[(2E)-2-[(1R,3aS,7aR)-1-[(E,2R,5S)-6-hydroxy-5,6-dimethylhept-3-en-2-yl]-7a-methyl-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylenecyclohexane-1,3-diol
571	19356-17-3	 Calcifediol (1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-1-[(2R)-6-hydroxy-6-methylheptan-2-yl]-7a-methyl-2,3,3a,5,6,7-

		hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol
575	57-83-0	 Progesterone (8S,9S,10R,13S,14S,17S)-17-acetyl-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one
576	68-22-4	 Norethindrone (8R,9S,10R,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-3-one
577	434-13-9	 Lithocholic acid (4R)-4-[(3R,5R,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid
579	58-22-0	 Testosterone (8R,9S,10R,13S,14S,17S)-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one

580	474-25-9	 Chenodeoxycholic acid (4R)-4- [(3R,5S,7R,8R,9S,10S,13R,14S,17R)-3,7-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid
581	83-44-3	 Deoxycholic acid (4R)-4- [(3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid
582	50-03-3	 Hydrocortisone acetate [2- [(8S,9S,10R,11S,13S,14S,17R)-11,17-dihydroxy-10,13-dimethyl-3-oxo-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate
583	80-97-7	 5α-cholestan-3β-ol (3S,5S,8R,9S,10S,13R,14S,17R)-

		10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol
584	35602-69-8	 Cholesterol stearate [(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl] octadecanoate
585	50-04-4	 Cortisone acetate [2-[(8S,9S,10R,13S,14S,17R)-17-hydroxy-10,13-dimethyl-3,11-dioxo-1,2,6,7,8,9,12,14,15,16-decahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] acetate)
586	4651-67-6	 3α-hydroxy-7-oxo-5β-cholanic acid (4R)-4-[(3R,5S,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethyl-7-oxo-1,2,3,4,5,6,8,9,11,12,14,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]pentanoic acid

587	63-05-8	 4-androstene-3, 17-diketone (8R,9S,10R,13S,14S)-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1H-cyclopenta[a]phenanthrene-3,17-dione
588	302-95-4	 Sodium deoxycholate sodium;(4R)-4-[(3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoate
589	512-04-9	 Diosgenin (1S,2S,4S,5'R,6R,7S,8R,9S,12S,13R,16S)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icos-18-ene-6,2'-oxane]-16-ol
590	145-13-1	 Pregnenolone 1-[(3S,8S,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl]ethanone

591	57-63-6	 Ethinyloestradiol (8R,9S,13S,14S,17R)-17-ethynyl-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diol
592	128-13-2	 Ursodesoxycholic acid (4R)-4-[(3R,5S,7S,8R,9S,10S,13R,14S,17R)-3,7-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid
633	50-27-1	 Estriol (8R,9S,13S,14S,16R,17R)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,16,17-triol
653	481-21-0	 5α-cholestane (5R,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene

In some embodiments, the compound is synthetic. The above compounds can be synthesized by means of chemical synthesis according to the chemical structure of the compounds. Alternatively, some of the compounds in the present application are commercially available.

5 In some embodiments, the compound derives from extracts of traditional Chinese medicine. "Extracts of traditional Chinese medicine" as used herein refers to extracts obtained from traditional Chinese medicinal materials or medicinal plants by suitable methods. The extracts of traditional Chinese medicine may be obtained using any suitable extraction method. As an example, the herbal decoction pieces (Yin Pian) of
10 traditional Chinese medicine can be soaked in water, followed by strong fire decoction and weak fire decoction in sequence. The decocted Chinese medicine liquid is concentrated, and then added chloroform-methanol, chloroform and water in sequence and mixed thoroughly, and the chloroform layer is taken to obtain the extracts of traditional Chinese medicine. In some embodiments, the compound
15 monomer may be further isolated or purified from the extracts of traditional Chinese medicine.

In some embodiments, the extracts of traditional Chinese medicine are obtained by Bligh&Dyer process (Bligh E.G. and Dyer, W. J., A rapid method for total lipid extraction and purification, Can. J. Biochem. Physiol., 1959, 37: 911-917) to extract
20 liposoluble components, or obtained by decoction and extraction of traditional Chinese medicine.

In some embodiments, the extracts of traditional Chinese medicine are obtained by decoction and extraction of traditional Chinese medicine.

In some embodiments, the extracts of traditional Chinese medicine are obtained
25 by soaking the traditional Chinese medicine in water, followed by strong fire decoction and weak fire decoction in sequence. The decocted Chinese medicine liquid is concentrated, and then added chloroform-methanol, chloroform and water in sequence and mixed, and the chloroform layer is taken and extracted.

Lipid composition

In some embodiments, the lipid composition provided herein comprises one or more compounds of the present application or salts, hydrates, or solvates thereof. The lipid composition may be one of the compounds provided herein or salts, hydrates, or solvates thereof, or may be a mixture of two or more of the compounds provided
5 herein.

In some embodiments, the lipid composition may also comprise one or more lipid compounds other than the compounds provided herein. These lipid compounds may be, for example, neutral lipids, charged lipids, steroid compounds, and polymer-conjugated lipids. “Neutral lipid” refers to a lipid compound that exists in an
10 uncharged or a neutral zwitterionic form at a selected pH value (e.g. physiological pH). “Charged lipid” refers to a lipid compound that exists in a positively or negatively charged form that is not limited by pH values in a useful physiological range (e.g., pH of about 3 to about 9).

In some embodiments, the lipid composition may further comprise one or more
15 solvents capable of mixing with the compound provided herein or salts, hydrates, or solvates thereof to form a homogeneous mixture.

The solvent comprised in the lipid composition may comprise organic solvent or solvent mixture, such as chloroform, dichloromethane, diethyl ether, cyclohexane, cyclopentane, benzene, toluene, methanol or other aliphatic alcohols, such as ethanol,
20 propanol, isopropanol, butanol, tert-butanol, isobutanol, pentanol, and hexanol. These solvents can be used alone, in combination and/or optionally together with suitable buffers as solvents in the lipid composition. The solvent can be selected depending on the polarity of the solvent, the ease for removing the solvent at a later stage in the formation of the lipid nucleic acid mixture, and/or pharmaceutically acceptable
25 properties. In some embodiments, the solvent is non-toxic, or pharmaceutically acceptable. Exemplary pharmaceutically acceptable solvents include lower alcohols (1-6 carbon atoms), such as methanol, ethanol, n-butanol, isobutanol, and n-butanol. In some embodiments, an appropriate amount of solvent may be used such that the nucleic acid and lipid form a clear single-phase mixture.

The lipid compositions provided herein can be used for delivering nucleic acids or preparing agents for delivering nucleic acid. In certain embodiments, the nucleic acids include DNA or RNA. In some embodiments, the nucleic acids may include coding DNA, non-coding DNA, antisense nucleic acids, messenger RNA (mRNA),
5 long non-coding RNA (lncRNA), and small RNA (such as microRNA (miRNA), small interfering RNA (siRNA), Piwi-interacting RNA (piRNA), small nucleolar RNA (snoRNA), tRNA-derived small RNA (tsRNA), and the like.

In some embodiments, the nucleic acids are single-stranded or double-stranded. Examples of single-stranded nucleic acids include miRNA, mRNA, antisense DNA,
10 antisense RNA, etc. Examples of double-stranded nucleic acids include siRNA, double-stranded DNA, double-stranded RNA, etc.

In some embodiments, the nucleic acids have a stem-loop structure. The term "stem-loop structure" refers to the presence of reverse complementary sequences in two parts of a single-stranded nucleic acid. Upon base pairing, these reverse
15 complementary sequences form a double-stranded structure, and the non-complementary portion between the two reverse complementary regions protrudes to form a loop structure. The stem-loop structure is also known as a hairpin structure.

In some embodiments, the nucleic acids include small nucleic acids. Small nucleic acids refer to nucleic acids with shorter lengths (e.g., less than 200
20 nucleotides). Small nucleic acids can be non-coding, such as small RNA (e.g., miRNA, siRNA, piRNA, snoRNA, tsRNA), and can be either single-stranded or double-stranded. In some embodiments, the nucleic acids are small nucleic acids having a length of 14-32bp, 16-28bp, or 18-24bp.

In some embodiments, the nucleic acids are nucleic acid drugs. Nucleic acid
25 drugs can belong to various categories, such as antisense nucleic acids, siRNA, CpG oligodeoxynucleotides, nucleic acid aptamers, mRNA or DNA encoding target proteins, miRNA, etc. Exemplary nucleic acid drugs include AEG35156, aganirsen, AP 12009, Apatorsen, ATL1103, AVT-02 UE, Bevasiranib Sodium, BMN 044, BMN 053, CpG 7909, Custirsen, Drisapersen, Eteplirsen, Fomivirsen, Pegaptanib,
30 Mipomersen, Defibrotide, Nusinersen, Patisiran, Tegsedi, and Fovista.

In some embodiments, the nucleic acid is used for treating diseases.

In some embodiments, the nucleic acid is used for treating cancer, inflammation, fibrotic disease, autoimmune disease or autoinflammatory disease, bacterial infection, behavioral and psychiatric disorder, blood disease, chromosomal disease, congenital
5 and hereditary disease, connective tissue disease, digestive disease, ear nose throat disease, endocrine disease, environmental disease, eye disease, female reproductive disease, fungal infection, heart disease, hereditary cancer syndrome, immune system disorder, kidney and urinary disease, lung disease, male reproductive disease, metabolic disorder, mouth disease, musculoskeletal disease, myelodysplastic
10 syndrome, neonatal screening, nutritional disease, parasitic disease, rare cancer, rare disease, skin disease, or viral infection.

In some embodiments, the nucleic acid is used for treating hepatocellular carcinoma, corneal neovascularization, recurrent or refractory anaplastic astrocytoma (WHO Grade III), or secondary glioblastoma (WHO Grade IV), advanced squamous
15 cell lung cancer, acromegaly, psoriasis, Duchenne muscular dystrophy, advanced non-small cell lung cancer, metastatic castration-resistant prostate cancer, cytomegalovirus retinitis, HIV infection, hepatitis B, hepatitis C, hyperlipoprotein disease, total knee replacement, type 2 diabetes, familial amyloid polyneuropathy (FAP), wet macular degeneration (e.g., neovascular age-related macular degeneration, subfoveal
20 neovascular age-related macular degeneration, exudative age-related macular degeneration), hypercholesterolemia, Crohn's disease, extensive liver fibrosis, infantile spinal muscular atrophy, melanoma, neonatal coronary artery disease, mild allergic asthma, chronic lymphocytic leukemia, and hypertriglyceridemia, small cell obliterans of the liver with renal or lung dysfunction after hematopoietic stem cell
25 transplantation, or hereditary transthyretin amyloidosis.

In some embodiments, the lipid composition can form a lipid nucleic acid mixture with nucleic acid. The nucleic acid can be delivered by the lipid nucleic acid mixture. “A lipid nucleic acid mixture” in the present application refers to a lipid-based mixture for delivering nucleic acid, such as liposomes. Examples of liposomes
30 include, for example, lipid particles or lipid vesicles that encapsulate nucleic acids.

The lipid nucleic acid mixture may be prepared by suitable methods, including, for example, mixing, heating, reverse-phase evaporation.

The mixing method includes the steps of mixing the compound provided herein or salts, hydrates, or solvates thereof with the nucleic acid to be delivered. In some embodiments, the mixing may be a direct mixing of the lipid composition provided herein with the nucleic acid to be delivered (for example, a mixture of dry powder of the lipid composition and the nucleic acid, followed by adding an appropriate solvent to form a lipid nucleic acid mixture with lipid encapsulating the nucleic acid). In some embodiments, the mixing may be conducted by mixing the lipid composition provided herein that is dissolved in an appropriate solvent with the nucleic acid, or mixing the nucleic acid dissolved in an appropriate solvent with the lipid composition provided herein, or mixing the lipid composition provided herein dissolved in an appropriate solvent with the nucleic acid dissolved in an appropriate solvent. Examples of suitable solvents that may be used for the lipid composition of the present application are described previously in the specification of the present application. Suitable solvents that may be used for the nucleic acid include water (DEPC treated water, double steamed water), buffers, saline, or glucose solutions, etc. The mixing step may be conducted with any suitable step, for example, nucleic acid (or its solution) may be added to a lipid composition (or its solution), or a lipid composition (or its solution) may be added to nucleic acid (or its solution). In some embodiments, the mixing may also include steps such as vortex, ultrasound, etc., to facilitate uniform mixing.

In some embodiments, the mixing method comprises adding an ethanol solution of the lipid composition of the present application to a suitable volume of the nucleic acid to be delivered in aqueous buffer, then mixing uniformly by vortex or ultrasonic, followed by incubating to obtain a lipid nucleic acid mixture. In some embodiments, the mixing method comprises combining an ethanol solution of the lipid compound of the present application with a suitable volume of an ethanol solution of the nucleic acid to be delivered, then mixing uniformly by vortex or ultrasonic, followed by incubating to obtain a lipid nucleic acid mixture, removing the ethanol, and re-suspending the resulting lipid nucleic acid mixture in an aqueous buffer.

In some embodiments, the nucleic acid and the lipid compound can be mixed at a certain ratio. The ratio depends on the nucleic acid to be delivered and the amount thereof, as well as the lipid compound to be used to achieve the effect of nucleic acid encapsulation. The ratio can be any ratio that meets the therapeutic needs, as long as a stable lipid nucleic acid mixture is formed and the required amount of nucleic acid is provided. In some embodiments, the ratio of nucleic acid to lipid compound can be, for example, 0.1nmol : 100μg to 10nmol : 100μg, 0.2nmol : 100μg to 10nmol : 100μg, 0.3nmol : 100μg to 10nmol : 100μg, 0.4 nmol : 100μg to 10nmol : 100μg, 0.5 nmol : 100μg to 10nmol : 100μg, 1nmol : 100μg to 10nmol : 100μg, 2nmol : 100μg to 10nmol : 100μg, 3nmol : 100μg to 10nmol : 100μg, 4nmol : 100μg to 10nmol : 100μg, 5nmol : 100μg to 10nmol : 100μg, 6nmol : 100μg to 10nmol, 7nmol : 100μg to 10nmol, 8nmol : 100μg to 10nmol, or 9nmol : 100μg to 10nmol : 100μg. In some embodiments, the ratio of nucleic acid to lipid compound can be 1nmol : 100μg, 2nmol : 100μg, 3nmol : 100μg, 4nmol : 100μg, 5nmol : 100μg, 6nmol : 100μg, 7nmol : 100μg, 8nmol : 100μg, 9nmol : 100μg, or 10nmol : 100μg. In some embodiments, the ratio of nucleic acid to lipid compound can be 10nmol : 100μg.

The mixing method can be conducted at any suitable temperature, as long as a lipid nucleic acid mixture capable of delivering nucleic acid can be formed. In some embodiments, the nucleic acid and the lipid compound can be mixed at a suitable temperature, for example, but not limited, of 0°C to 100°C, 4°C to 100°C, 10°C to 100°C, 15°C to 100°C, 20°C to 100°C, 25°C to 100°C, 30°C to 100°C, 35°C to 100°C, 40°C to 100°C, 45°C to 100°C, 50°C to 100°C, 55°C to 100°C, 60°C to 100°C, 65°C to 100°C, 70°C to 100°C, 75°C to 100°C, 80°C to 100°C, 85°C to 100°C, 90°C to 100°C, or 95°C to 100°C. In some embodiments, the temperature is 0°C, 4°C, 10°C, 20°C, 30°C, 40°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, or 90°C. In some embodiments, the temperature is 90°C.

In some embodiments, the lipid nucleic acid mixture is prepared by heating method. The heating method comprises mixing a solution of the compound provided herein or salts, hydrates, or solvates thereof dissolved in an appropriate solvent with an aqueous solution of the nucleic acid to be delivered to obtain a mixture solution,

and heating the mixture solution at a suitable temperature. In some embodiments, the step of heating the mixture solution is conducted at a temperature selected from 25°C to 100°C, 30°C to 100°C, 40°C to 100°C, 50°C to 100°C, 60°C to 100°C, 70°C to 100°C, 80°C to 100°C, 90°C to 100°C or 95°C to 100°C. In some embodiments, the step of heating the mixture solution is conducted at a temperature selected from about 30°C, about 35°C, about 37°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C. In some embodiments, the step of heating the mixture solution is conducted at 90°C.

10 In some embodiments, the heating method comprises heating the mixture solution for an appropriate amount of time. Those skilled of art can select an appropriate heating time according to the properties of the lipid compound and nucleic acid used and the desired lipid nucleic acid mixture. The heating time can be, for example, about 5 minutes to about 24 hours, about 5 minutes to about 20 hours, about 5 minutes to about 16 hours, about 10 minutes to about 20 hours, about 10 minutes to about 16 hours, about 15 minutes to about 24 hours, about 15 minutes to about 20 hours, about 30 minutes to about 24 hours, about 30 minutes to about 20 hours, about 40 minutes to about 16 hours, about 50 minutes to about 12 hours, about 1 hour to about 8 hours, or about 2 hours to about 4 hours. In some embodiments, the heating time can be, for example, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 40 minutes, about 50 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 12 hours, about 16 hours, about 20 hours, or about 24 hours. In some embodiments, the heating time is about 15 minutes.

In some embodiments, the heating method further comprises a cooling step. The cooling can be conducted after the step of heating the mixture solution at a suitable temperature, as long as the formed lipid nucleic acid mixture is not disrupted.

Exemplary cooling temperature includes, not limited to, 25°C to -80°C, 20°C to -80°C, 15°C to -80°C, 10°C to -80°C, 4°C to -80°C, 0°C to -80°C, -10°C to -80°C, -

20°C to -80°C, -30°C to -80°C, or -40°C to -80°C. In some embodiments, the mixture solution is cooled at room temperature (such as 25°C or 20°C) after the step of heating the mixture solution.

In some embodiments, the lipid nucleic acid mixture is prepared by reverse-phase evaporation method. The reverse-phase evaporation method comprises adding an aqueous solution of a nucleic acid to a solution of a lipid compound dissolved in an appropriate solvent, followed by removing the solvent via, e.g., ultrasonic or evaporation. In some embodiments, the reverse-phase evaporation method further comprises hydration after removal of the solvent to obtain a lipid nucleic acid mixture. In some embodiments, the hydration includes adding water or a suitable culture medium to the system. In some embodiments, the suitable culture medium is, for example, an OPTI-MEM culture medium.

In some embodiments, the solvent removal step is conducted at a suitable temperature, such as about 25°C to about 70°C, 30°C to about 70°C, about 30°C to about 65°C, about 40°C to about 65°C, about 40°C to about 60°C, or about 50°C to about 60°C. In some embodiments, the solvent removal step is conducted at about 25°C, 30°C, about 35°C, about 37°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, or about 70°C. In some embodiments, the solvent removal step is conducted at about 55°C.

In some embodiments, the nucleic acid delivery is a delivery via oral administration, inhalation or injection. In some embodiments, the nucleic acid delivery is delivered via oral administration. In some embodiments, the agent is used for delivering nucleic acid via oral administration. In some embodiments, the nucleic acid delivery is in vivo digestive tract delivery.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to a target organ or target tissue of interest of the individual.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the heart tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid

compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

5 In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the hepatic tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 10 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the splenic tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid 15 compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 567, 568, 569, 570, 571, 575, 576, 579, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally 20 administered to an individual, can deliver the nucleic acid to the lung tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 25 582, 588, 583, 585, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the renal tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 508, 512, 585, 532, 534, 538, 30 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559,

560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the gastric tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

10 In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the intestinal tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 15 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the brain tissue of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to blood of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 592, 633 and 653.

In some embodiments, the lipid nucleic acid mixture, after being orally administered to an individual, can deliver the nucleic acid to the thigh bone of the individual. In some embodiments, the lipid nucleic acid mixture comprises a lipid compound selected from the group consisting of lipids 562, 580, 584, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, after the lipid nucleic acid mixture is orally administered to an individual, the nucleic acid is delivered to two or more tissues.

In some embodiments, the nucleic acid delivery comprises in vitro cellular delivery. “In vitro” as used herein refers to outside a multicellular organism, such as a human or animal body. In vitro cells include such as in vitro cell cultures, in vitro tissues or cells. In vitro delivery comprises delivering nucleic acid into cells outside the body, for example, comprises contacting the lipid nucleic acid mixture with in vitro cells under the condition that allows the nucleic acid to enter the cell.

Pharmaceutical composition

In another aspect, the present application also provides a pharmaceutical composition comprising one or more compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, or solvates thereof. In some embodiments, the compounds are selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In another aspect, the present application also provides a pharmaceutical composition comprising a lipid composition and a nucleic acid, wherein the lipid composition comprises one or more compounds selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653, or salts, hydrates, or solvates thereof.

The pharmaceutical compositions provided in the present application may be in solid or liquid form, including semi-solid, semi-liquid, suspension and colloidal forms. Solid form can be, for example, tablet or powder. Liquid form can be, for example, an oral solution, an oral syrup, an injectable liquid, or an aerosol suitable for, for example, inhalation administration.

In some embodiments, the pharmaceutical composition is formulated to be administered orally, by inhalation, via the digestive tract, or via the respiratory tract. In some embodiments, the pharmaceutical composition is formulated to deliver the nucleic acid by in vivo digestive tract delivery. In some embodiments, the pharmaceutical composition is an oral pharmaceutical composition. When used for oral administration, the pharmaceutical composition is preferably in solid or liquid form.

As a solid pharmaceutical composition for oral administration, the pharmaceutical composition can be formulated in the form of powder, pellet, compressed tablet, pill, capsule, chewable gum, etc. Typically, such solid composition may also contain one or more inert diluents or edible carriers (such as starch, lactose, or dextrin) and one or more excipients selected from the group consisting of adhesive (e.g., carboxymethyl cellulose, ethyl cellulose, microcrystalline cellulose, tragacanth or gelatin), dissolver (e.g., alginate, sodium alginate, Primogel, cornstarch, etc.), lubricant (e.g., magnesium stearate or Sterotex), glidant (e.g., colloidal silica), sweetener (e.g., sucrose or saccharin), flavoring agent; and colorant.

As a liquid pharmaceutical composition for oral administration, the pharmaceutical composition may be formulated as, for example, elixir, syrup, solution, emulsion, or suspension. When used for oral administration, the liquid pharmaceutical composition contains one or more excipients selected from the group consisting of sweetener, preservatives, stain/colorant, and flavoring agent.

The pharmaceutical composition of the present disclosure can also be formulated to be administered by inhalation through the respiratory tract. An appropriate inhalation formulation may include formulation that can be administered as aerosol.

The aerosol can be delivered in single-phase, biphasic or three-phase systems. For

example, the aerosol can be delivered by liquefied gas and compressed gas, or by a suitable system wherein the active ingredient is dispersed. The delivery of the aerosol includes the necessary container, activator, valve, sub-container, etc., which together can form a kit.

5 In some embodiments, the pharmaceutical compositions of the present application may also be formulated to be administered parenterally, such as by injection. The liquid composition for injection may be a solution, suspension or injection powder and may comprise one or more of surfactant, preservatives, wetting agent, dispersant, suspension, buffer, stabilizer and isotonic agent.

10 In some embodiments, the pharmaceutical composition may also be used for delivery through in vitro cells.

 In some embodiments, the lipid composition and the nucleic acid are present at least partially or fully in the form of mixture in the pharmaceutical composition. In some embodiments, the mixture is prepared by heating method, reverse-phase
15 evaporation method, or mixing method.

 In another aspect, the present application also provides the use of the pharmaceutical compositions of the present application in the manufacture of a medicament for the prevention and/or treatment of diseases that can be prevented and/or treated with nucleic acid, or for in vivo delivering nucleic acid to a subject in
20 need thereof.

 The pharmaceutical composition provided in the present application can be used for the treatment of diseases that can be treated with nucleic acid. Common diseases for example, but not limited to, cancer, inflammation, fibrotic disease, autoimmune disease or autoinflammatory disease, bacterial infection, behavioral and psychiatric
25 disorder, blood disease, chromosomal disease, congenital and hereditary disease, connective tissue disease, digestive disease, ear nose throat disease, endocrine disease, environmental disease, eye disease, female reproductive disease, fungal infection, heart disease, hereditary cancer syndrome, immune system disorder, kidney and urinary disease, lung disease, male reproductive disease, metabolic disorder, mouth
30 disease, musculoskeletal disease, myelodysplastic syndrome, neonatal screening,

nutritional disease, parasitic disease, rare cancer, rare disease, skin disease, or viral infection.

Examples of cancers include, but are not limited to, stomach cancer, lung cancer, colorectal cancer, liver cancer, pancreatic cancer, cervical cancer, breast cancer, leukemia, multiple myeloma.

Examples of inflammation include, but are not limited to, pneumonia, myocarditis, acute and chronic gastritis, acute and chronic enteritis, acute and chronic hepatitis, acute and chronic nephritis, dermatitis, encephalitis, lymphadenitis, conjunctivitis, keratitis, iridocyclitis, otitis media, allergic rhinitis, asthma, pulmonary fibrosis, chronic obstructive pulmonary disease, atopic dermatitis, sickle cell disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis.

Known nucleic acid drugs may treat a variety of diseases. Indications for known nucleic acid drugs include, for example, hepatocellular carcinoma, corneal neovascularization, recurrent or refractory anaplastic astrocytoma (WHO Grade III), or secondary glioblastoma (WHO Grade IV), advanced squamous cell lung cancer, acromegaly, psoriasis, Duchenne muscular dystrophy, advanced non-small cell lung cancer, metastatic castration-resistant prostate cancer, cytomegalovirus retinitis, HIV infection, hepatitis B, hepatitis C, hyperlipoprotein disease, total knee replacement, type 2 diabetes, familial amyloid polyneuropathy (FAP), wet macular degeneration (e.g., neovascular age-related macular degeneration, subfoveal neovascular age-related macular degeneration, exudative age-related macular degeneration), hypercholesterolemia, Crohn's disease, extensive liver fibrosis, infantile spinal muscular atrophy, melanoma, neonatal coronary artery disease, mild allergic asthma, chronic lymphocytic leukemia, and hypertriglyceridemia, small cell obliterans of the liver with renal or lung dysfunction after hematopoietic stem cell transplantation, or hereditary transthyretin amyloidosis.

Kit

In another aspect, the present application also provides a kit comprising one or more compounds of Formula (I) or Formula (II), or pharmaceutically acceptable salts, hydrates, or solvates thereof, positioned in a first container, and a nucleic acid

positioned in a second container. In some embodiments, the compounds are selected from the group consisting of lipids.

In another aspect, the present application also provides a kit comprising one or more compounds or pharmaceutically acceptable salts, hydrates, or solvates thereof, positioned in a first container, and a nucleic acid positioned in a second container, wherein the one or more compounds are selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

In some embodiments, the lipid composition and the nucleic acid in the kit are formulated at least partially or fully as a lipid nucleic acid mixture before use. In some embodiments, the mixture is prepared by heating method, reverse-phase evaporation method, or mixing method.

In some embodiments, wherein the kit is formulated as an oral pharmaceutical composition.

In some embodiments, wherein the kit is formulated to be administered orally, by inhalation, through the digestive tract, or through the respiratory tract.

In some embodiments, wherein the kit is formulated to deliver the nucleic acid through in vitro cells delivery, or in vivo digestive tract delivery.

In another aspect, the present application provides the use of the kit in the manufacture of a medicament for the prevention and/or treatment of diseases that can be prevented and/or treated with nucleic acid, or for in vivo delivering nucleic acid to a subject in need thereof.

Method of delivering nucleic acid

In another aspect, the present application provides a method of delivering nucleic acid to a target cell, comprising administering to the target cell the pharmaceutical composition of the present application or a lipid nucleic acid mixture formulated from the kit of the present application.

In another aspect, the present application provides a method of in vivo delivering nucleic acid to a subject in need thereof, comprising administering to the subject the pharmaceutical composition of the present application or a lipid nucleic acid mixture formulated from the kit of the present application.

5 In some embodiments, the subject is human or an animal, such as a mammal.

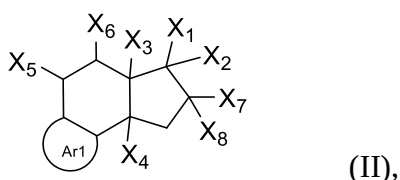
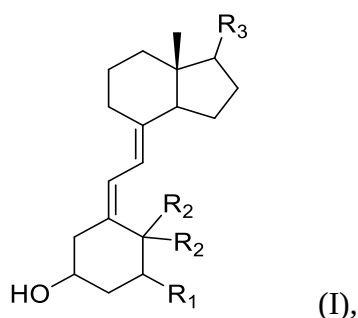
In some embodiments, the nucleic acid is in vivo delivered to the blood circulation or to the target tissue/cell of the subject.

In some embodiments, the method comprises administering the medicament by route of oral, inhalation, or injection.

10 In some embodiments, the method comprises administering the medicament through the digestive tract, or through the respiratory tract.

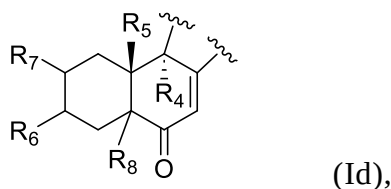
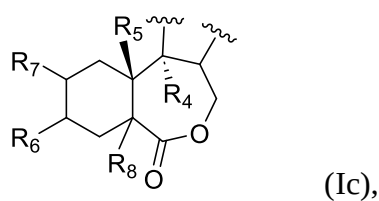
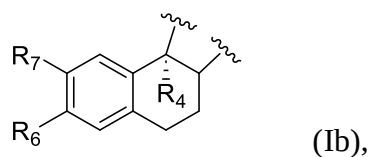
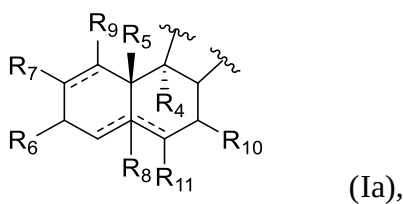
In some embodiments, the method comprises administering the medicament orally.

Item 1: use of a lipid composition in the manufacture of an agent for delivering
15 nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:



wherein

20 Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



5 wherein:

== is a carbon-carbon single bond or carbon-carbon double bond;

R₁ is hydrogen or hydroxyl;

each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are attached form a carbon-carbon double bond, or form a straight or branched C₂₋₂₀

10 alkenyl;

R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls, straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched

15 C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;

R₄ is hydrogen, hydroxyl or halogen;

R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls;

R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted

20 by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;

R₇ is hydrogen or hydroxyl;

R₈ is absent, hydrogen or hydroxyl;

R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;

X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally
5 substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight
or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from
hydroxyl, amino, -COOH or -C(O)N(R'')₂;

X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or
branched C₂₋₂₀ alkynyl;

10 X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

X₄ is hydrogen or hydroxyl;

X₅ is hydrogen, hydroxyl or oxo;

X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they
15 are attached form a heterocyclyl optionally substituted by one or more straight or
branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls
or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or
more groups selected from hydroxyl or cycloalkyl;

20 each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally
substituted by one or more -COOH.

Item 2: the use of item 1, wherein the lipid composition is used for delivering the
nucleic acid via oral administration, inhalation, or injection.

Item 3: the use of item 2, wherein the lipid composition is used for delivering the
25 nucleic acid via oral administration.

Item 4: the use of any one of the preceding items, wherein the delivery comprises
in vitro cells delivery, or in vivo digestive tract delivery.

Item 5: the use of any one of the preceding items, wherein the lipid composition
is mixed with the nucleic acid to prepare a lipid nucleic acid mixture, optionally, the

lipid nucleic acid mixture is prepared by heating method, reverse-phase evaporation method, or mixing method.

Item 6: the use of item 5, wherein the heating method comprises mixing the lipid composition with the nucleic acid to obtain a mixture, and heating the mixture at a temperature selected from 25°C to 100°C, 30°C to 100°C, 40°C to 100°C, 50°C to 100°C, 60°C to 100°C, 70°C to 100°C, 80°C to 100°C, 90°C to 100°C, or 95°C to 100°C.

Item 7: the use of item 6, wherein heating the mixture at a temperature selected from 30°C, 35°C, 37°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C.

Item 8: the use of any one of item 6 or 7, wherein mixing the lipid composition with the nucleic acid comprises adding an organic solvent solution of the lipid composition to an aqueous solution of the nucleic acid.

Item 9: the use of item 5, wherein the reverse-phase evaporation method comprises mixing an aqueous solution of the nucleic acid with an organic solvent solution of a lipid compound to obtain a mixture solution, and then removing the organic solvent from the mixture solution.

Item 10: the use of item 9, wherein the organic solvent in the mixture solution is removed at a temperature selected from about 25°C to about 70°C, 30°C to about 70°C, about 30°C to about 65°C, about 40°C to about 65°C, about 40°C to about 60°C, or about 50°C to about 60°C.

Item 11: the use of item 9, wherein mixing an aqueous solution of the nucleic acid with an organic solvent solution of a lipid compound comprises adding the aqueous solution of the nucleic acid into the organic solvent solution of the lipid compound.

Item 12: the use of any one of the preceding items, wherein R₁ is hydrogen.

Item 13: the use of any one of the preceding items, wherein R₁ is hydroxyl.

Item 14: the use of any one of the preceding items, wherein each R₂ is hydrogen.

Item 15: the use of any one of the preceding items, wherein two R₂ together with the carbon atom to which they are attached form a straight or branched C₂₋₂₀ alkenyl.

Item 16: the use of any one of the preceding items, wherein R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls.

Item 17: the use of any one of the preceding items, wherein R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from
5 hydroxyl or cycloalkyl.

Item 18: the use of any one of the preceding items, wherein R₃ is straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl.

Item 19: the use of any one of the preceding items, wherein R₃ is straight or
10 branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls.

Item 20: the use of any one of the preceding items, wherein R₄ is hydrogen.

Item 21: the use of any one of the preceding items, wherein R₄ is hydroxyl.

Item 22: the use of any one of the preceding items, wherein R₄ is halogen.

Item 23: the use of any one of the preceding items, wherein R₅ is hydrogen.

15 Item 24: the use of any one of the preceding items, wherein R₅ is hydroxyl.

Item 25: the use of any one of the preceding items, wherein R₅ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls.

Item 26: the use of any one of the preceding items, wherein R₆ is hydrogen.

Item 27: the use of any one of the preceding items, wherein R₆ is hydroxyl.

20 Item 28: the use of any one of the preceding items, wherein R₆ is oxo.

Item 29: the use of any one of the preceding items, wherein R₆ is -OC(O)R'.

Item 30: the use of any one of the preceding items, wherein R₆ is -O-heterocycl
optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl.

Item 31: the use of any one of the preceding items, wherein R₇ is hydrogen.

25 Item 32: the use of any one of the preceding items, wherein R₇ is hydroxyl.

Item 33: the use of any one of the preceding items, wherein R₈ is absent.

Item 34: the use of any one of the preceding items, wherein R₈ is hydrogen.

Item 35: the use of any one of the preceding items, wherein R₈ is hydroxyl.

Item 36: the use of any one of the preceding items, wherein R₉ is hydrogen.

30 Item 37: the use of any one of the preceding items, wherein R₉ is oxo.

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- Item 38: the use of any one of the preceding items, wherein R₉ is hydroxyl.
- Item 39: the use of any one of the preceding items, wherein R₁₀ is hydrogen.
- Item 40: the use of any one of the preceding items, wherein R₁₀ is oxo.
- Item 41: the use of any one of the preceding items, wherein R₁₀ is hydroxyl.
- 5 Item 42: the use of any one of the preceding items, wherein R₁₁ is hydrogen.
- Item 43: the use of any one of the preceding items, wherein R₁₁ is oxo.
- Item 44: the use of any one of the preceding items, wherein R₁₁ is hydroxyl.
- Item 45: the use of any one of the preceding items, wherein X₁ is hydrogen.
- Item 46: the use of any one of the preceding items, wherein X₁ is oxo.
- 10 Item 47: the use of any one of the preceding items, wherein X₁ is hydroxyl.
- Item 48: the use of any one of the preceding items, wherein X₁ is -C(O)R'.
- Item 49: the use of any one of the preceding items, wherein X₁ is -OC(O)R'.
- Item 50: the use of any one of the preceding items, wherein X₁ is C₃₋₂₀
cycloalkenyl optionally substituted by oxo.
- 15 Item 51: the use of any one of the preceding items, wherein X₁ is C₃₋₂₀
heterocycloalkenyl optionally substituted by oxo.
- Item 52: the use of any one of the preceding items, wherein X₁ is straight or
branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from
hydroxyl, amino, -COOH or -C(O)N(R'')₂.
- 20 Item 53: the use of any one of the preceding items, wherein X₂ is absent.
- Item 54: the use of any one of the preceding items, wherein X₂ is hydrogen.
- Item 55: the use of any one of the preceding items, wherein X₂ is hydroxyl.
- Item 56: the use of any one of the preceding items, wherein X₂ is straight or
branched C₁₋₂₀ alkyl.
- 25 Item 57: the use of any one of the preceding items, wherein X₂ is straight or
branched C₂₋₂₀ alkynyl.
- Item 58: the use of any one of the preceding items, wherein X₃ is hydrogen.
- Item 59: the use of any one of the preceding items, wherein X₃ is straight or
branched C₁₋₂₀ alkyl.
- 30 Item 60: the use of any one of the preceding items, wherein X₄ is hydrogen.

Item 61: the use of any one of the preceding items, wherein X₄ is hydroxyl.

Item 62: the use of any one of the preceding items, wherein X₅ is hydrogen.

Item 63: the use of any one of the preceding items, wherein X₅ is hydroxyl.

Item 64: the use of any one of the preceding items, wherein X₅ is oxo.

5 Item 65: the use of any one of the preceding items, wherein X₆ is hydrogen.

Item 66: the use of any one of the preceding items, wherein X₆ is oxo.

Item 67: the use of any one of the preceding items, wherein X₆ is hydroxyl.

Item 68: the use of any one of the preceding items, wherein X₇ is hydrogen.

Item 69: the use of any one of the preceding items, wherein X₈ is hydrogen.

10 Item 70: the use of any one of the preceding items, wherein X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl.

Item 71: the use of any one of items 29, 48, 49, wherein R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R''.

15 Item 72: the use of any one of items 29, 48, 49, wherein R' is straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl.

Item 73: the use of any one of items 52, 71, 72, wherein each R'' is independently hydrogen.

20 Item 74: the use of any one of items 52, 71, 72, wherein R'' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

Item 75: the use of any one of items 1-11, wherein the lipid composition comprises one or more compounds selected from the group consisting of

Lipid Compound No.	Product Name
508	Brassinolide
512	Vitamin D4
532	Fluoxymesterone
534	Fludrocortisone
538	Ponasterone A

539	Mestanolone
540	Maxacalcitol
545	Paricalcitol
546	Methyltestosterone
547	Methylprednisolone
548	5 α -androstanediol
549	Desoxycortisone
550	G Strophanin G
551	Cholestan-3,5, 6-triol
552	Glycodesoxycholic acid
553	Glycocholic acid
554	Calcipotriol
555	4-androstene-11 β - ol -3, 17-dione
556	17-valerate - β - estradiol ester
557	Medroxyprogesterone
558	Hecogenin
559	Digitoxigenin
560	Levonorgestrel
561	Dehydroepiandrosterone
562	Nandrolone
563	Androsterone
564	Prednisone
565	Cholesterol margarate
566	Hydrocortisone
567	19-hydroxy-androstane-4-ene-3, 17-dione
568	Testosterone propionate
569	Doxercalciferol
570	1 α , 25-dihydroxyvitamin D2
571	Calcifediol

575	Progesterone
576	Norethindrone
577	Lithocholic acid
579	Testosterone
580	Chenodeoxycholic acid
581	Deoxycholic acid
582	Hydrocortisone acetate
583	5 α -cholestan-3 β -ol
584	Cholesterol stearate
585	Cortisone acetate
586	3 α -hydroxy-7-oxo-5 β -cholan-ic acid
587	4-androstene-3, 17-diketone
588	Sodium deoxycholate
589	Diosgenin
590	Pregnenolone
591	Ethinylloestradiol
592	Ursodesoxycholic acid
633	Estriol
653	5 α -cholestane

or salts, hydrates or solvates thereof.

Item 76: the use of any one of the preceding items, wherein the salt is a pharmaceutically acceptable salt.

Item 77: the use of any one of the preceding items, wherein the compound
5 derives from extracts of traditional Chinese medicine.

Item 78: the use of item 77, wherein the extracts of traditional Chinese medicine are obtained by decoction, preparation, and extraction of traditional Chinese medicine.

Item 79: the use of item 78, wherein the extracts of traditional Chinese medicine are obtained by soaking the traditional Chinese medicine in water, followed by
10 decoction over high heat and low heat successively, concentrating the decocted

Chinese medicine liquid, adding chloroform-methanol, chloroform and water in sequence and mixing, and extracting the chloroform layer.

Item 80: the use of any one of the preceding items, wherein the nucleic acid comprises DNA or RNA, optionally, the DNA is selected from coding DNA or non-coding DNA, and the RNA is selected from antisense nucleic acids, mRNA, lncRNA, or small RNA.

Item 81: the use of item 80, wherein the nucleic acid comprises small nucleic acids having a length of 14-32bp, 16-28bp, or 18-24bp.

Item 82: the use of any one of the preceding items, wherein the nucleic acid is single-stranded or double-stranded.

Item 83: the use of any one of the preceding items, wherein the nucleic acid has a stem-loop structure.

Item 84: the use of any one of the preceding items, wherein the nucleic acid is used for treating diseases.

Item 85: the use of item 84, wherein the nucleic acid is used for treating cancer, inflammation, fibrotic disease, autoimmune or autoinflammatory disease, bacterial infection, behavioral and psychiatric disorder, blood disease, chromosomal disease, congenital and hereditary disease, connective tissue disease, digestive disease, ear nose throat disease, endocrine disease, environmental disease, eye disease, female reproductive disease, fungal infection, heart disease, hereditary cancer syndrome, disease of the immune system, kidney and urinary disease, lung disease, male reproductive disease, metabolic disorder, mouth disease, musculoskeletal disease, myelodysplastic syndrome, neonatal screening, nutritional disease, parasitic disease, rare cancer, rare disease, skin disease, or viral infection.

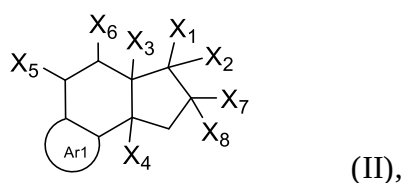
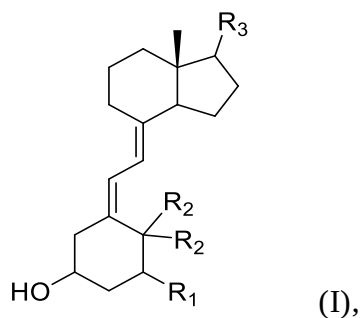
Item 86: the use of item 84, wherein the nucleic acid is used for treating hepatocellular carcinoma, corneal neovascularization, recurrent or refractory anaplastic astrocytoma (WHO Grade III), or secondary glioblastoma (WHO Grade IV), advanced squamous cell lung cancer, acromegaly, psoriasis, Duchenne muscular dystrophy, advanced non-small cell lung cancer, metastatic castration-resistant prostate cancer, cytomegalovirus retinitis, HIV infection, hepatitis B, hepatitis C,

hyperlipoprotein disease, total knee replacement, type 2 diabetes, familial amyloid polyneuropathy (FAP), wet macular degeneration (e.g., neovascular age-related macular degeneration, subfoveal neovascular age-related macular degeneration, exudative age-related macular degeneration), hypercholesterolemia, Crohn's disease,

5 extensive liver fibrosis, infantile spinal muscular atrophy, melanoma, neonatal coronary artery disease, mild allergic asthma, chronic lymphocytic leukemia, and hypertriglyceridemia, small cell obliterans of the liver with renal or lung dysfunction after hematopoietic stem cell transplantation, or hereditary transthyretin amyloidosis.

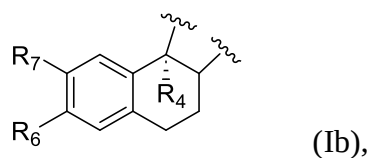
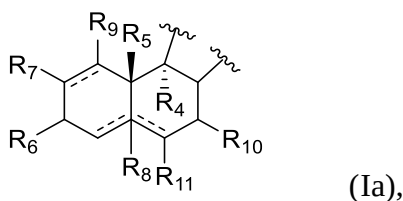
Item 87: A pharmaceutical composition comprising a lipid composition and a

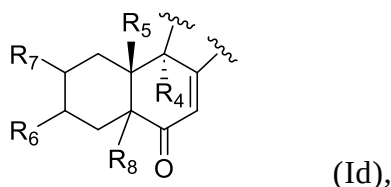
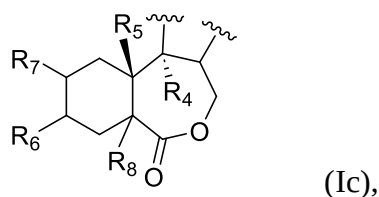
10 nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:



wherein

15 Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):





wherein:

== is a carbon-carbon single bond or carbon-carbon double bond;

5 R_1 is hydrogen or hydroxyl;

each R_2 is hydrogen, or two R_2 together with the carbon atom to which they are attached form a straight or branched C_{2-20} alkenyl;

R_3 is straight or branched C_{1-20} alkyl optionally substituted by one or more hydroxyls, straight or branched C_{1-20} alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, straight or branched C_{2-20} alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C_{1-20} heteroalkyl optionally substituted by one or more hydroxyls;

R_4 is hydrogen, hydroxyl or halogen;

15 R_5 is hydrogen, hydroxyl, or straight or branched C_{1-20} alkyl optionally substituted by one or more hydroxyls;

R_6 is hydrogen, hydroxyl, oxo, $-OC(O)R'$, or $-O$ -heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C_{1-20} alkyl;

R_7 is hydrogen or hydroxyl;

R_8 is absent, hydrogen or hydroxyl;

20 R_9 , R_{10} and R_{11} are independently hydrogen, oxo or hydroxyl;

X_1 is hydrogen, oxo, hydroxyl, $-C(O)R'$, $-OC(O)R'$, C_{3-20} cycloalkenyl optionally substituted by oxo, C_{3-20} heterocycloalkenyl optionally substituted by oxo, or straight or branched C_{1-20} alkyl optionally substituted by one or more groups selected from hydroxyl, amino, $-COOH$ or $-C(O)N(R'')_2$;

X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;

X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

X₄ is hydrogen or hydroxyl;

5 X₅ is hydrogen, hydroxyl or oxo;

X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

10 R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;
each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

15 Item 88: A pharmaceutical composition comprising a lipid composition and a nucleic acid, wherein the lipid composition comprises one or more compounds selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583,
20 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653, or salts, hydrates or solvates thereof.

Item 89: The pharmaceutical composition of item 87 or 88, wherein the pharmaceutical composition is formulated to be administered orally, by inhalation, through the digestive tract, or through the respiratory tract.

25 Item 90: The pharmaceutical composition of item 87 or 88, wherein the pharmaceutical composition is used for delivering the nucleic acid through in vitro cells delivery, or in vivo digestive tract delivery.

Item 91: The pharmaceutical composition of item 87 or 88, wherein the pharmaceutical composition is an oral pharmaceutical composition.

Item 92: The pharmaceutical composition of any one of item 87-91, wherein the lipid composition and the nucleic acid are present at least partially or wholly in the form of a lipid nucleic acid mixture.

Item 93: The pharmaceutical composition of item 92, wherein the lipid nucleic acid mixture is prepared by heating method, reverse-phase evaporation method, or mixing method.

Item 94: The pharmaceutical composition of item 93, wherein the heating method comprises mixing the lipid composition with the nucleic acid to obtain a mixture, and heating the mixture at a temperature selected from 25°C to 100°C, 50°C to 100°C, 80°C to 100°C, or 95°C to 100°C.

Item 95: The pharmaceutical composition of item 94, wherein heating the mixture at a temperature selected from 37°C, 60°C, 80°C, or 100°C.

Item 96: The pharmaceutical composition of item 95, wherein mixing the lipid composition with the nucleic acid comprises adding an organic solvent solution of the lipid composition to an aqueous solution of the nucleic acid.

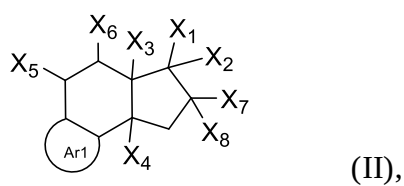
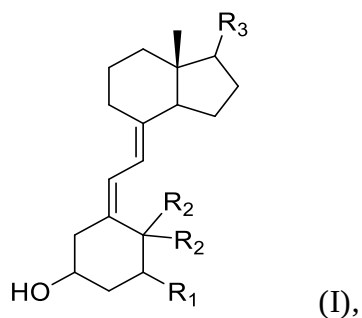
Item 97: The pharmaceutical composition of item 96, wherein the reverse-phase evaporation method comprises mixing an aqueous solution of the nucleic acid with an organic solvent solution of a lipid compound to obtain a mixture solution, and then removing the organic solvent from the mixture solution at 25°C to 70°C, 30°C to 65°C, or 40°C to 60°C.

Item 98: The pharmaceutical composition of item 97, wherein removing the organic solvent from the mixture solution at 55°C.

Item 99: The pharmaceutical composition of any one of items 93 and 97-98, wherein the reverse-phase evaporation method comprises adding the aqueous solution of the nucleic acid into the organic solvent solution of the lipid composition.

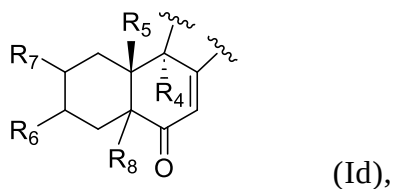
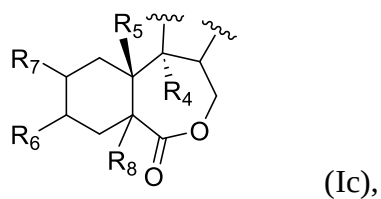
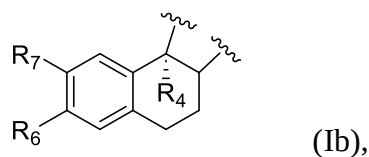
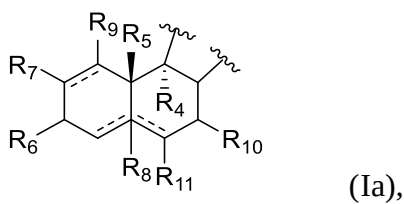
Item 100: Use of the pharmaceutical composition of any one of items 87-99 in the manufacture of medicament for preventing and/or treating diseases that can be prevented and/or treated with nucleic acid, or for in vivo delivering nucleic acid to a subject in need thereof.

Item 101: A kit comprising one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof positioned in a first container:



5 wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



10

and a nucleic acid positioned in a second container;

wherein:

--- is a carbon-carbon single bond or carbon-carbon double bond;

R₁ is hydrogen or hydroxyl;

each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are attached form a straight or branched C₂₋₂₀ alkenyl;

5 R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls, straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;

10 R₄ is hydrogen, hydroxyl or halogen;

R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls;

R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;

15 R₇ is hydrogen or hydroxyl;

R₈ is absent, hydrogen or hydroxyl;

R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;

X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight
20 or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl, amino, -COOH or -C(O)N(R'')₂;

X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;

X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

25 X₄ is hydrogen or hydroxyl;

X₅ is hydrogen, hydroxyl or oxo;

X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or

30 branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;

each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

Item 102: A kit, comprising:

one or more compounds or pharmaceutically acceptable salts, hydrates or solvates thereof positioned in a first container, and a nucleic acid positioned in a second container, wherein the one or more compounds selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.

Item 103: The kit of item 101 or 102, wherein the lipid composition and the nucleic acid are formulated at least partially or wholly a lipid nucleic acid mixture before use.

Item 104: the kit of item 103, wherein the lipid nucleic acid mixture is prepared by heating method, reverse-phase evaporation method, or mixing method.

Item 105: the kit of item 104, wherein the heating method is conducted at a temperature selected from 25°C to 100°C, 50°C to 100°C, 80°C to 100°C, or 95°C to 100°C.

Item 106: the kit of item 105, wherein the heating method is conducted at a temperature selected from 37°C, 60°C, 80°C, or 100°C.

Item 107: the kit any one of items 104-106, wherein the heating method comprises adding an organic solvent solution of the lipid composition to an aqueous solution of the nucleic acid.

Item 108: the kit of item 104, wherein the reverse-phase evaporation method is conducted at a temperature selected from 25°C to 70°C, 30°C to 65°C, or 40°C to 60°C.

Item 109: the kit of item 108, wherein the reverse-phase evaporation method is conducted at a temperature of 55°C.

Item 110: the kit of any one of items 104 and 108-109, wherein the reverse-phase evaporation method comprises adding an aqueous solution of the nucleic acid to an organic solvent solution of the lipid composition.

Item 111: the kit of any one of items 101-110, wherein the kit is formulated to be an oral pharmaceutical composition.

Item 112: the kit of any one of items 101-110, wherein the kit is formulated to be administered orally, by inhalation, through the digestive tract, or through the respiratory tract.

Item 113: the kit of any one of items 101-110, wherein the kit is formulated to deliver the nucleic acid through in vitro cells delivery, or in vivo digestive tract delivery.

Item 114: use of the kit in the manufacture of medicament of items 101-113 for the preventing and/or treating diseases that can be prevented and/or treated with nucleic acid, or for in vivo delivering nucleic acid to a subject in need thereof.

Item 115: a method of delivering nucleic acid to a target cell, comprising administering to the target cell the pharmaceutical composition of any one of items 87-99, or a lipid nucleic acid mixture formulated from the kit of any one of items 101-113.

Item 116: a method of in vivo delivering nucleic acid to a subject in need thereof, comprising administering to the subject in need the pharmaceutical composition of any one of items 87-99, or a lipid nucleic acid mixture formulated from the kit of any one of items 101-113.

Item 117: the method of item 116, wherein the subject is human or an animal, such as a mammal.

Item 118: the method of item 116 or 117, wherein the nucleic acid is in vivo delivered to the blood circulation or to the target tissue/cell of the subject.

Item 119: the method of item 118, wherein the target tissue is selected from heart, liver, spleen, lung, kidney, stomach, intestine, brain, blood and femur.

Item 120: the method of any one of items 116-118, wherein comprises administering the medication orally, by inhalation, or by injection.

Item 121: the method of any one of items 116-120, wherein comprises administering the medication through the digestive tract, or through the respiratory tract.

Item 122: the method of item 121, wherein the nucleic acid is in vivo delivered to the blood circulation or to the target tissue/cell of the subject.

The above technical solution provided in the present application can significantly improve the efficient targeted delivery of nucleic acid, and overcome the defects of prior art nucleic acid liposomes that need to be improved, such as low encapsulation rate, poor safety, poor stability, complex preparation process, inhomogeneous product, poor reproducibility, and poor targeting.

The above features mentioned in the present disclosure, or the features mentioned in examples, may be arbitrarily combined. All features disclosed in the specification of the present application may be used with any composition form, and each feature disclosed in the specification may be replaced by any alternative feature providing the same, equal or similar purpose. Thus, unless otherwise specified, the features disclosed are only general examples of equal or similar features.

The present disclosure is further described in combination with specific examples. It is understood that these examples are used only to illustrate the present disclosure and not to limit the scope of the present disclosure.

Example 1: Extraction, Identification, and Synthesis of Lipids Derived from Traditional Chinese Medicine Sources

1.1 Preparation of Traditional Chinese Medicine Decoction

1) 100g of traditional Chinese medicine decoction pieces (purchased from Beijing Tong Ren Tang Pharmacy) were added 1000mL ddH₂O and soaked for 30 minutes.

2) The traditional Chinese medicine was decocted in a decoction pot over high

heat for 15 minutes followed by decoction over low heat for 20 minutes.

3) 400mL of the decocted medicinal liquid was added to a rotary evaporator, and concentrate at 60°C, 60rpm for 30 minutes to 100mL.

1.2 Extraction of Lipids from Traditional Chinese Medicine

5 1) 600mL of chloroform-methanol mixture (chloroform: methanol=1: 2, v/v) was added to 160mL of the decoction obtained in above 1.1 (rotary evaporator concentrated) such that chloroform: methanol: water=1:2:0.8, and stirred for 10-15 minutes.

2) 200mL of chloroform was added to a conical flask, and stirred for 10 minutes.

10 3) 200mL of ddH₂O was added to the conical flask such that chloroform: methanol:water=2: 2:1.8, and stirred for 10 minutes.

4) The upper layer liquid and insoluble substances in the middle layer were removed, the bottom chloroform layer was collected, and stored at -40°C.

1.3 Identification of Lipids from Traditional Chinese Medicine

15 HPLC-MS/MS was used to identify lipid components from traditional Chinese medicine.

Instrument Conditions

1) Chromatography Conditions:

Instrument: Ultimate 3000; Column: Kinetex C18 (100×2.1mm, 1.9μm); Column Temperature: 45°C; Mobile Phase: A: acetonitrile:water (V/V, 60:40) with 10 mmol/L ammonium formate, Mobile Phase B: acetonitrile:isopropanol (10:90, V/V) with 10 mmol/L ammonium formate and 0.1% formic acid. Flow Rate: 0.4 mL/min; Injection Volume: 4 μL.

2) Mass Spectrum Parameters:

25 a) Positive Mode: Heater Temperature 300°C, Sheath Gas Flow Rate 45 arb, Aux Gas Flow Rate 15 arb, Sweep Gas Flow Rate 1 arb, Nozzle Voltage 3.0 KV, Capillary

Temperature 350°C, S-Lens RF Level 30%. Scan Range: 200-1500.

b) Negative Mode: Heater Temperature 300°C, Sheath Gas Flow Rate 45 arb, Aux Gas Flow Rate 15 arb, Sweep Gas Flow Rate 1 arb, Nozzle Voltage 2.5KV, Capillary Temperature 350°C, S-Lens RF Level 60%. Scan Range: 200-1500.

5 **1.4 Acquisition of Lipids**

The 53 fatty acid (ST) lipid compounds used in the following examples were purchased from Aladdin and Macklin.

Example 2: Preparation of Lipid-Nucleic Acid Mixture (Heating Method):

The concentration of the lipid chloroform solution is 10 mg/ml (stock solution).

10 The solutions were grouped according to the lipid compound numbers.

10 nmol of small RNA (as shown in Table 2) was dissolved in 400 µl of DEPC-treated water in a glass tube, 10 µl of the corresponding lipid stock solution was added such that the lipid mass in the system was 100 µg. The mixture was mixed thoroughly, heated in a 90°C water bath for 15 minutes, and then cooled naturally to obtain the lipid
15 nucleic acid mixture of lipid and small RNA.

Table 2. Small RNA Sequence Information (purchased from General Biol Co., Ltd.)

Name	Sequence	Modification
PGY-sRNA-26	TCCGGAATGATTGGGCGTAAAGCGT (SEQ ID No. 1)	3'-2-O-methyl
PGY-sRNA-26 Reverse Transcription Primer	GTCGTATCCAGTGCACGCTCCGAGGTATTCTG CACTGGATACGACACGCTT (SEQ ID No. 2)	
PGY-sRNA-26 Forward Primer	TCGCGCTCCGGAATGATTGGG (SEQ ID No. 3)	
PGY-sRNA-26	GTGCACGCTCCGAGGT (SEQ ID No. 4)	

Reverse Primer		
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Example 3: In Vivo Delivery Study of Lipid-Nucleic Acid Mixture

1. Experimental Animals:

C57BL/6 male mice, approximately 6 weeks old, weighing 20-24g, were obtained
 5 from Beijing Vital River Laboratory Animal Technology Co., Ltd. The mice were housed in the SPF-grade animal facility at the Animal Center of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. The mice were fasted for 12 hours before gavage administration.

2. Preparation of Lipid-Small RNA Complex:

10 The lipid nucleic acid mixture was prepared following the method described in Example 2. The resultant lipid nucleic acid mixture was orally administered to each mouse at a dose of 100 µg lipid:10 nmol single-stranded 3'-methylated small RNA PGY-sRNA-26.

3. Detection of Relative Entry Amount:

15 3.1 Experimental Groups:

1) Blank group (n=4): mice were administered with 500 µl saline by gavage, this group served as a blank control;

2) Free uptake group (n=4): mice were directly administered with small RNA PGY-sRNA-26 solution (10 nmol/mouse, 500 µl) by gavage, this group served as a
 20 negative control;

3) Lipid-treated group (n=4): mice were administered with 500 µl lipid nucleic acid mixture prepared in step 2 by gavage.

3.2 Tissue Sampling and RNA Extraction:

After 12 hours of gavage administration, 500 µl blood from the eyeball of each
 25 mouse was sampled, added to 1.5 ml Trizol Reagent LS (purchased from Invitrogen),

thoroughly mixed for lysis. 3 ml of Trizol Reagent LS was added to tissue samples and homogenized for complete lysis, wherein the sampled tissues include heart, liver, spleen, lung, kidney, stomach, intestine, brain, blood, femur. RNA was extracted from 1ml of the blood or the tissue lysate following the steps below:

5 - Centrifuge at 4°C, 12,000rpm for 5 min, discard the precipitate, transfer Trizol to a new centrifuge tube;

 - Add chloroform at 200µL chloroform /mL Trizol, shake well, stand at room temperature for 5 min;

 - Centrifuge at 4°C, 12,000rpm for 15 min;

10 - Take the upper aqueous phase to another centrifuge tube, add isopropanol at 0.4 mL isopropanol /mL Trizol, mix well, and stand at low temperature for 10-20 min;

 - Centrifuge at 4°C, 12,000 rpm for 15 min, discard the supernatant, RNA precipitated at the bottom of the tube;

15 - Add 1 mL of 75% ethanol, gently shake the centrifuge tube, suspend the precipitate;

 - Centrifuge at 4°C, 12,000 rpm for 15 min, discard the supernatant, add 1 mL of 75% ethanol, gently shake the centrifuge tube, suspend the precipitate;

20 - Centrifuge at 4°C, 12,000rpm for 15min, discard the supernatant, air-dry at room temperature, dissolve RNA samples in 50 µL RNase-free H₂O, measure OD value to quantify RNA concentration.

3.3 Reverse Transcription of sRNA to cDNA:

sRNA was reverse transcribed to cDNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, cat. no. 4368813) by stem-loop method (see, e.g., "Real-time quantification of microRNAs by stem-loop RT-PCR, Nucleic Acids Res. 2005 Nov 27;33(20):e179", incorporated herein by reference). The reverse
25 transcription system is as follows: Template RNA (200 ng/µL) 10 µL, 10X RT Buffer

2.0 μ L, 25X dNTP Mix (100 mM) 0.8 μ L, U6 RT stem-loop primer (10 μ M) 2.0 μ L, PGY-sRNA-26 RT stem-loop primer (10 μ M) 2.0 μ L, MultiScribeTM Reverse Transcriptase (50 U/ μ L) 1.0 μ L, RNase Inhibitor (40 U/ μ L) 1.0 μ L, nuclease-free H₂O 1.2 μ L. After transient centrifugation, the reverse transcription system was placed in a PCR machine with the following reaction conditions: (1) 25°C, 10 min; (2) 37°C, 120 min; (3) 85°C, 5 min; (4) 4°C, stop reaction. After the reaction, add 20 μ L RNase-free ddH₂O, adjust the final volume to 40 μ L. The stem-loop primers used in this reverse transcription process were synthesized by Beijing Tianyi Huiyuan Biotechnology Co., Ltd. (U6 was used as a standard reference gene to calculate its relative expression, because U6 RT primer was used as a reference gene in relative quantification of RT-qPCR reactions for small RNA):

U6 RT stem-loop primer:

GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAAAATA
TG (SEQ ID No. 5);

PGY-sRNA-26 RT stem-loop primer:

GTCGTATCCAGTGCACGCTCCGAGGTATTCGCACTGGATACGACACGCTT
(SEQ ID No. 2).

3.4 Quantitative PCR Amplification Reaction:

The qPCR reaction system has a total volume of 10 μ L, including: 5 μ L 2 $\times$ SYBR Green Master Mix, 0.5 μ L forward primer (10 μ M), 0.5 μ L reverse primer (10 μ M), 1 μ L cDNA obtained from reverse transcription, and 3 μ L RNase-free ddH₂O. LightCycler 480 Fluorescent Quantitative PCR Instrument was used with the PCR reaction conditions as follows: 95°C, 5 min for initial denaturation, followed by entering the PCR amplification cycle: (1) 95°C, 10 s; (2) 55°C, 10 s; (3) 72°C, 20 s; a total of 40 cycles; finally, a cooling step at 40°C for 10 s. The forward and reverse primers for the amplification reaction were designed and synthesized by Beijing Tianyi Huiyuan Biotechnology Co., Ltd. (U6 F primer: GCGCGTCGTGAAGCGTTC (SEQ ID No. 6), U6 R primer: GTGCAGGGTCCGAGGT (SEQ ID No. 7); PGY-sRNA-26 forward

primer: TCGCGCTCCGGAATGATTGGG (SEQ ID No. 3), reverse primer miR all rev: GTGCACGCTCCGAGGT (SEQ ID No. 4)).

3.5 Calculation of Relative Expression Using the 2- Δ Ct Method.

4. The experimental results are illustrated in figures.

5 Conclusion:

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse heart tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse liver tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 567, 568, 569, 570, 571, 575, 576, 579, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse spleen tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 588, 583, 585, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse lung tissue.

Lipids 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse

kidney tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse stomach tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse intestinal tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 586, 587, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse brain tissue.

Lipids 562, 580, 584, 508, 512, 585, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 587, 588, 589, 590, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse blood.

Lipids 562, 580, 584, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 581, 582, 583, 585, 586, 588, 589, 590, 591, 592, 633 and 653 can effectively orally deliver single-stranded sRNA nucleic acids into mouse femur.

For the 9 tissues and blood tested in the experiments, various lipid monomers delivered nucleic acids into heart and stomach tissues the most efficiently. More lipids efficiently entered into heart and stomach tissues, followed by intestinal tissues, and blood.

Lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552,

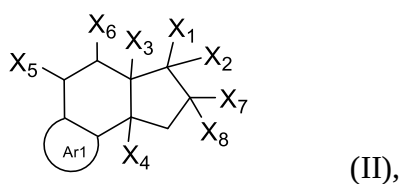
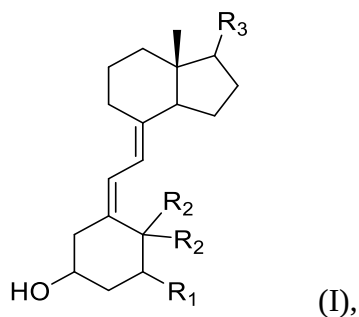
553, 554, 555, 556, 557, 558, 559, 560, 563, 567, 568, 569, 570, 575, 581, 582, 588, 589, 590, 592, 633 and 653 exhibited the best delivery efficacy, effectively delivering nucleic acids into each tissue and blood tested, suggesting their potential as a broad-spectrum nucleic acid delivery carrier.

- 5 All references mentioned in this invention are cited as references in this application, just as each reference is cited individually. Additionally, it should be understood that, after reading the teachings of this invention, those skilled in the art can make various changes or modifications, and such equivalent forms are also within the scope defined by the claims attached to this application.

WHAT IS CLAIMED IS:

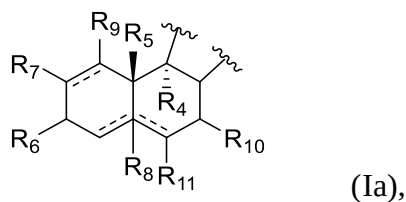
1. Use of a lipid composition in the manufacture of an agent for delivering nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:

5

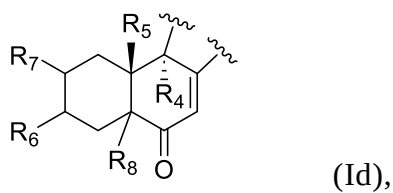
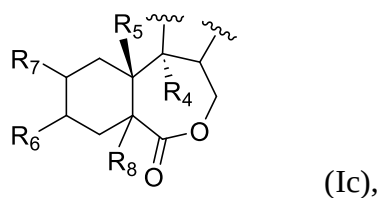
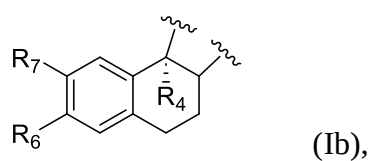


wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



10



wherein:

== is a carbon-carbon single bond or carbon-carbon double bond;

R₁ is hydrogen or hydroxyl;

each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are
5 attached form a carbon-carbon double bond, or form a straight or branched C₂₋₂₀
alkenyl;

R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls,
straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected
from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted
10 by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched
C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;

R₄ is hydrogen, hydroxyl or halogen;

R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by
one or more hydroxyls;

15 R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted
by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;

R₇ is hydrogen or hydroxyl;

R₈ is absent, hydrogen or hydroxyl;

R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;

20 X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally
substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight
or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from
hydroxyl, amino, -COOH or -C(O)N(R'')₂;

X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or
25 branched C₂₋₂₀ alkynyl;

X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

X₄ is hydrogen or hydroxyl;

X₅ is hydrogen, hydroxyl or oxo;

X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;

each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

2. The use of claim 1, wherein the lipid composition comprises one or more

10 compounds selected from the group consisting of:

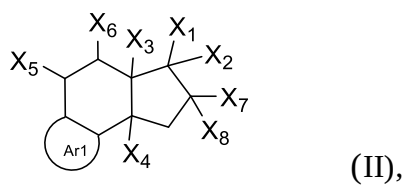
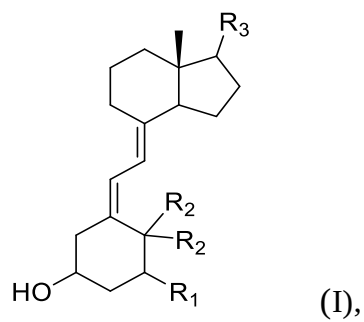
Lipid Compound No.	Product Name
508	Brassinolide
512	Vitamin D4
532	Fluoxymesterone
534	Fludrocortisone
538	Ponasterone A
539	Mestanolone
540	Maxacalcitol
545	Paricalcitol
546	Methyltestosterone
547	Methylprednisolone
548	5 α -androstanediol
549	Desoxycortisone
550	G Strophanin G
551	Cholestan-3,5, 6-triol
552	Glycodesoxycholic acid
553	Glycocholic acid
554	Calcipotriol
555	4-androstene-11 β - ol -3, 17-dione

556	17-valerate - β - estradiol ester
557	Medroxyprogesterone
558	Hecogenin
559	Digitoxigenin
560	Levonorgestrel
561	Dehydroepiandrosterone
562	Nandrolone
563	Androsterone
564	Prednisone
565	Cholesterol margarate
566	Hydrocortisone
567	19-hydroxy-androstane-4-ene-3, 17-dione
568	Testosterone propionate
569	Doxercalciferol
570	1 α , 25-dihydroxyvitamin D2
571	Calcifediol
575	Progesterone
576	Norethindrone
577	Lithocholic acid
579	Testosterone
580	Chenodeoxycholic acid
581	Deoxycholic acid
582	Hydrocortisone acetated
583	5 α -cholestan-3 β -ol
584	Cholesterol stearate
585	Cortisone acetate
586	3 α -hydroxy-7-oxo-5 β -cholanic acid
587	4-androstene-3, 17-diketone
588	Sodium deoxycholate

589	Diosgenin
590	Pregnenolone
591	Ethinylestradiol
592	Ursodesoxycholic acid
633	Estriol
653	5 α -cholestane

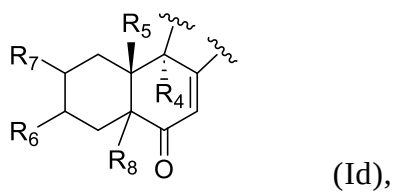
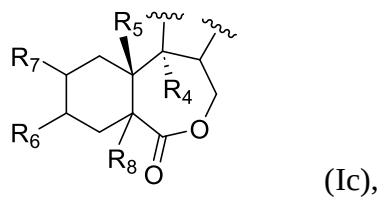
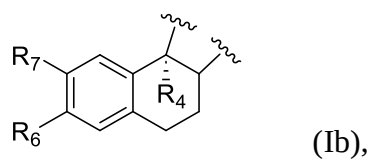
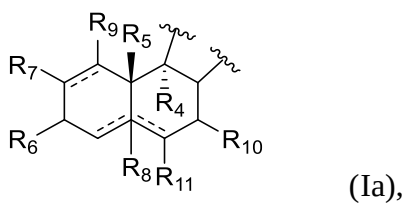
or salts, hydrates or solvates thereof.

3. The use of any one of the preceding claims, wherein the compound derives from extracts of traditional Chinese medicine.
4. The use of any one of the preceding claims, wherein the nucleic acid comprises
- 5 DNA or RNA, optionally, the DNA is selected from coding DNA or non-coding DNA, the RNA is selected from antisense nucleic acid, mRNA, lncRNA or small RNA.
5. The use of any one of the preceding claims, wherein the nucleic acid is used for treating disease.
- 10 6. The use of claim 5, wherein the nucleic acid is used for treating cancer, inflammation, fibrotic disease, autoimmune or autoinflammatory disease, bacterial infection, behavioural and psychiatric disorder, blood disease, chromosomal disease, congenital and hereditary diseases, connective tissue disease, digestive disease, ear nose throat disease, endocrine disease, environmental disease, eye disease, female
- 15 reproductive disease, fungal infection, heart disease, hereditary cancer syndrome, disease of the immune system, kidney and urinary disease, lung disease, male reproductive disease, metabolic disorder, mouth disease, musculoskeletal disease, myelodysplastic syndrome, neonatal screening, nutritional disease, parasitic disease, rare cancer, rare disease, skin disease or viral infection.
- 20 7. A pharmaceutical composition comprising a lipid composition and a nucleic acid, wherein the lipid composition comprises one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof:



wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):



wherein:

10 $\equiv$ is a carbon-carbon single bond or carbon-carbon double bond;

R₁ is hydrogen or hydroxyl;

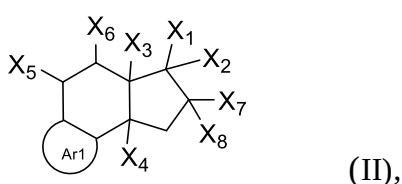
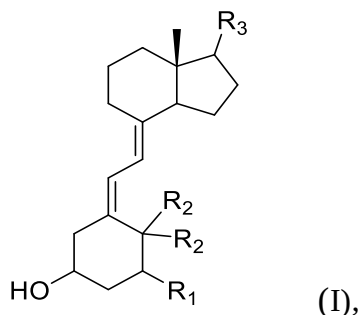
-
- each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are attached form a straight or branched C₂₋₂₀ alkenyl;
- R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls, straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected
- 5 from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;
- R₄ is hydrogen, hydroxyl or halogen;
- R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by
- 10 one or more hydroxyls;
- R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;
- R₇ is hydrogen or hydroxyl;
- R₈ is absent, hydrogen or hydroxyl;
- 15 R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;
- X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl, amino, -COOH or -C(O)N(R'')₂;
- 20 X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;
- X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;
- X₄ is hydrogen or hydroxyl;
- X₅ is hydrogen, hydroxyl or oxo;
- 25 X₆ is hydrogen, oxo or hydroxyl;
- X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;

each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

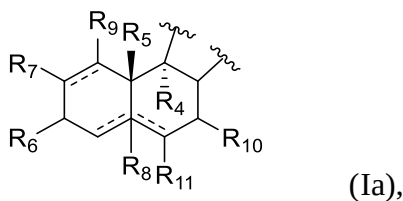
8. A pharmaceutical composition comprising a lipid composition and a nucleic acid, wherein the lipid composition comprises one or more compounds selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653, or salts, hydrates or solvates thereof.

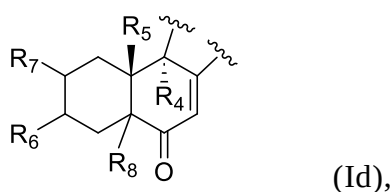
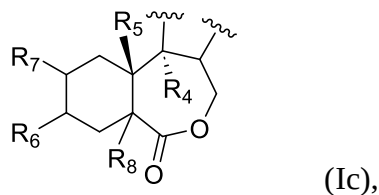
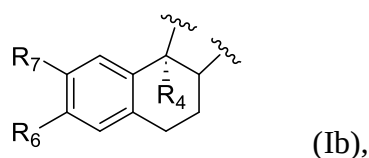
9. A kit comprising one or more compounds of Formula (I) or Formula (II), or salts, hydrates or solvates thereof positioned in a first container:



wherein

Ar1 is selected from Formula (Ia), Formula (Ib), Formula (Ic) or Formula (Id):





and a nucleic acid positioned in a second container;

5 wherein:

== is a carbon-carbon single bond or carbon-carbon double bond;

R₁ is hydrogen or hydroxyl;

each R₂ is hydrogen, or two R₂ together with the carbon atom to which they are attached form a straight or branched C₂₋₂₀ alkenyl;

10 R₃ is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls, straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl, or straight or branched C₁₋₂₀ heteroalkyl optionally substituted by one or more hydroxyls;

15 R₄ is hydrogen, hydroxyl or halogen;

R₅ is hydrogen, hydroxyl, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls;

R₆ is hydrogen, hydroxyl, oxo, -OC(O)R', or -O-heterocyclyl optionally substituted by one or more groups selected from hydroxyl or C₁₋₂₀ alkyl;

20 R₇ is hydrogen or hydroxyl;

R₈ is absent, hydrogen or hydroxyl;

R₉, R₁₀ and R₁₁ are independently hydrogen, oxo or hydroxyl;

X₁ is hydrogen, oxo, hydroxyl, -C(O)R', -OC(O)R', C₃₋₂₀ cycloalkenyl optionally substituted by oxo, C₃₋₂₀ heterocycloalkenyl optionally substituted by oxo, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more groups selected from hydroxyl, amino, -COOH or -C(O)N(R'')₂;

5 X₂ is absent, hydrogen, hydroxyl, straight or branched C₁₋₂₀ alkyl or straight or branched C₂₋₂₀ alkynyl;

X₃ is hydrogen or straight or branched C₁₋₂₀ alkyl;

X₄ is hydrogen or hydroxyl;

X₅ is hydrogen, hydroxyl or oxo;

10 X₆ is hydrogen, oxo or hydroxyl;

X₇ and X₈ are hydrogen, or X₁ and X₇ together with the carbon atoms to which they are attached form a heterocyclyl optionally substituted by one or more straight or branched C₁₋₂₀ alkyl;

R' is straight or branched C₁₋₂₀ alkyl optionally substituted by one or more hydroxyls

15 or -OC(O)R'', or straight or branched C₂₋₂₀ alkenyl optionally substituted by one or more groups selected from hydroxyl or cycloalkyl;

each R'' is independently hydrogen, or straight or branched C₁₋₂₀ alkyl optionally substituted by one or more -COOH.

10. A kit, comprising:

20 one or more compounds or pharmaceutically acceptable salts, hydrates or solvates thereof positioned in a first container, and a nucleic acid positioned in a second container, wherein the one or more compounds selected from the group consisting of lipids 508, 512, 532, 534, 538, 539, 540, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 25 571, 575, 576, 577, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 633 and 653.