NANOMATERIALS

RELATED APPLICATION INFORMATION

[0001] This application claims priority to U.S. Provisional Application No. 62/958,876, filed January 9, 2020, which is hereby incorporated herein by reference in its entirety.

BACKGROUND

Field

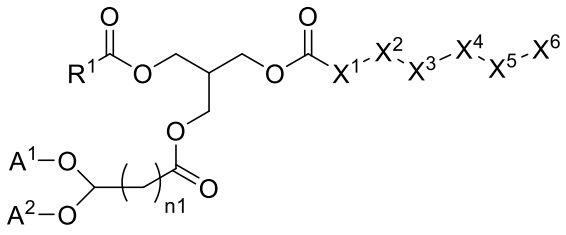
[0002] The present application relates to the fields of chemistry, biology, and medicine. Disclosed herein are drug delivery systems and methods of their use. More particularly, disclosed herein are nanoparticle compositions for delivery of nucleic acids to cells.

Description

[0003] Hepatocytes help maintain homeostasis and produce many secreted proteins and, thus, are implicated in many genetic diseases. While nanoparticles carrying RNA have been directed to hepatocytes, systemic delivery to hepatocytes without targeting ligands remains challenging.

SUMMARY

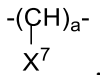
[0004] One aspect described herein relates to a compound of Formula (I):



(I)

[0005] wherein:

[0006] R^1 is C_9-C_{20} alkyl or C_9-C_{20} alkenyl with 1-3 units of unsaturation;

[0007] X^1 and X^2 are each independently absent or selected from –O–, NR^2-, and , wherein each R^2 is independently hydrogen or C_1-C_6 alkyl;

[0008] each a is independently an integer between 1 and 6;

[0009] X^3 and X^4 are each independently absent or selected from the group consisting of: 4- to 8-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 5- to 6-membered heteroaryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 5- to 6-membered aryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, 4- to 7-membered cycloalkyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, –O– and –NR^3–, wherein each R^3 is independently a hydrogen atom or C_1-C_6 alkyl and wherein X^1-X^2-X^3-X^4 does not contain any oxygen-oxygen, oxygen-nitrogen or nitrogen-nitrogen bonds;

[0010] X^5 is –$(CH_2)_b$–, wherein b is an integer between 0 and 6;

[0011] X^6 is hydrogen, C_1-C_6 alkyl, 5- to 6-membered heteroaryl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, or –NR^4R^5, wherein R^4 and R^5 are each independently hydrogen or C_1-C_6 alkyl; or alternatively R^4 and R^5 join together with the nitrogen to which they are bound to form a 4- to 7-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, wherein the heterocyclyl optionally includes an additional heteroatom selected from oxygen, sulfur, and nitrogen;

[0012] each X^7 is independently hydrogen, hydroxyl or –NR^6R^7, wherein R^6 and R^7 are each independently hydrogen or C_1-C_6 alkyl; or alternatively R^6 and R^7 join together with the nitrogen to which they are bound to form a 4- to 7-membered heterocyclyl optionally substituted with 1 or 2 C_1-C_6 alkyl groups, wherein the heterocyclyl optionally includes an additional heteroatom selected from oxygen, sulfur, and nitrogen;

[0013] at least one of X^1, X^2, X^3, X^4, and X^5 is present;

[0014] A^1 and A^2 are each independently selected from the group consisting of: C_5-C_{12} haloalkyl, C_5-C_{12} alkenyl, C_5-C_{12} alkynyl, (C_5-C_{12} alkoxy)-$(CH_2)_{n2}$–, (C_5-C_{10} aryl)-$(CH_2)_{n3}$– optionally ring substituted with one or two halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy groups, and (C_3-C_8 cycloalkyl)-$(CH_2)_{n4}$– optionally ring substituted with 1 or 2 C_1-C_6 alkyl groups; or alternatively A^1 and A^2 join together with the atoms to which they are bound to form a 5- to 6-membered cyclic acetal substituted with 1 or 2 C_4-C_{10} alkyl groups;

[0015] n1, n2 and n3 are each individually an integer between 1 and 4; and

[0016] n4 is an integer between zero and 4.

[0017] There is also provided a lipid nanoparticle composition comprising: an ionizable lipid as described herein; a phospholipid; a polyethylene glycol-lipid; a cholesterol; and optionally a nucleic acid. Another aspect described herein relates to a lipid nanoparticle composition comprising: an ionizable lipid that comprises a compound as described herein, optionally wherein the amount of the ionizable lipid is present in a range of about 35 to 65 mole percent, based on total moles; a phospholipid, optionally wherein the phospholipid is DSPC or DMPC; a polyethylene glycol-lipid; a cholesterol; and optionally a nucleic acid. Another aspect described herein relates to a method of delivering a nucleic acid to a subject in need thereof, comprising administering to the subject in need the lipid nanoparticle composition as described herein.

[0018] These and other examples are described in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] **FIG. 1** illustrates a reaction scheme for preparing compounds of the Formula (I).

[0020] **FIG. 2** summarizes the structures of the compounds of Examples 1-148.

DETAILED DESCRIPTION

Definitions

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0022] As used herein, any "R" or “X” group(s) such as, without limitation, R^1, R^2, R^3, R^4, R^5, R^6, R^7, X^1, X^2, X^3, X^4, X^5, X^6, X^7, A^1 and A^2 represent substituents that can be attached to the indicated atom(s). Such R, X and A groups may be referred to herein in a general way as “R” groups. An R group may be substituted or unsubstituted. If two "R" groups are said to "join together" it will be understood that the R groups and the atoms to which they are bound can form a cyclic structure such as a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an $NR^a R^b$ group are indicated to "join together," it means that they are covalently bonded to one another to form a ring: