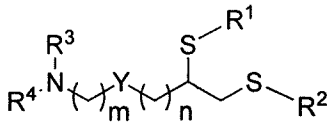
hydrocarbyl group, or R^3 and R^4 may join to form an optionally substituted heterocyclic ring of 3 to 10 atoms and 1 to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

R^5 is either absent or is hydrogen or C_1-C_{12} alkyl to provide a quaternary amine,

m is an integer from 1 to 12 and n is an integer from 2 to 12.

In a preferred embodiment of the invention, R^1 and R^2 are the same or different and independently C_6-C_{24} alkyl, more preferred, R^1 and R^2 are the same C_6-C_{18} alkyl.

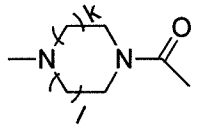
Also, the present invention provides amino lipids of the general formula (II):



(II)

R^1 and R^2 are the same C_6-C_{18} alkyl

Y is either an amide, an ester or a heterocyclic amide of the formula



wherein k and l are integers from 0 to 2,

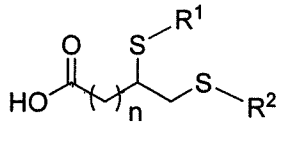
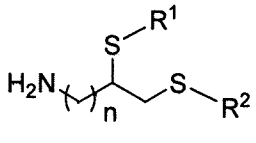
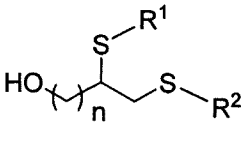
R^3 and R^4 are either the same or different C_1-C_{12} alkyls, wherein alkyl may be optionally substituted with a C_1-C_6 hydrocarbyl group, or R^3 and R^4 may join to form an optionally substituted heterocyclic ring of 3 to 10 atoms and 1 to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

m is an integer from 1 to 12 and n is an integer from 2 to 12

In another preferred embodiment of the invention Y is an amide.

In a preferred embodiment of the compounds according to the formulas (I) or (II),

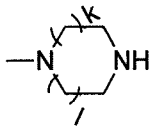
n and m are independently integers 2 or 3.


(Va),

(Vb),

(Vc)

wherein n, R^1 and R^2 are defined as above,,

This reaction is conducted via a radical mechanism. Chemical radical sources can be added to start the reaction or it can be simply conducted under sunlight. In a preferred embodiment the reaction is started by UV irradiation.

The second step is a condensation reaction of the product of the first step (formula Va) with an amine or alcohol of the general formula $(R^3R^4R^5N)(CH_2)_mZ$, with m as an integer from 1 to 12, wherein Z is NH_2, OH, or a secondary heterocyclic amine of the formula,

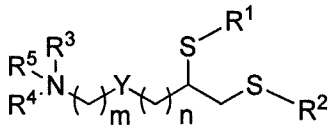

, wherein k and l are integers from 0 to 2,

Or condensation reaction of the product of the first step (formula Vb or Vc) with carboxylic acid of the general formula $(R^3R^4R^5N)(CH_2)_mZ$, with m as an integer from 1 to 12, wherein Z is COOH.

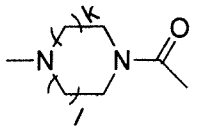
R^3 and R^4 are either the same or different and independently C_1-C_{12} alkyl, C_1-C_{12} alkenyl, or C_1-C_{12} alkynyl, which may be optionally substituted with a C_1-C_6 hydrocarbyl group, or R^3 and R^4 may join to form a ring of 3 to 10 carbon atoms and ~~1θ~~ 1 to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

R^5 is either absent or is hydrogen or C_1-C_{12} alkyl to provide a quaternary amine,

to yield a compound of the general formula (VI)


(VI),

Y being either an amide, an ester or a heterocyclic amide of the formula


wherein k and l are integers from 0 to 2,

wherein n, m, Y, R^1, R^2, R^3, R^4 and R^5 are defined as above.

In a most preferred embodiment, the bioactive agent is a nucleic acid. In another preferred embodiment said bioactive agent is a member optionally selected from the group consisting of: an antineoplastic agent, an antibiotic, an immunomodulator, an anti-inflammatory agent, an agent acting on the central nervous system, a polypeptide or a polypeptoid.

In yet another embodiment the lipid particle or liposome further contains at least one polyethylene glycol (PEG)-lipid. PEG lipids help to protect the particles and their cargo from degradation in-vitro and in-vivo. Moreover, PEG form a protective layer over the liposome surface and increase the circulating time in vivo. It can be used in liposome drug delivery (PEG-liposome).

Lipid particles or liposomes containing a bioactive agent can be used to deliver any of a variety of therapeutic agents into cells. The present invention encompasses the use of lipid particles, especially liposomes, as described above for the manufacture of a medicament for delivering a bioactive agent into a cell.

Preferably said bioactive agent is a nucleic acid, including but not limited to, RNA, antisense oligonucleotide, a DNA, a plasmid, a ribosomal RNA (rRNA), a micro RNA (miRNA), transfer RNA (tRNA), a small inhibitory RNA (siRNA) or small nuclear RNA (snRNA). The bioactive agent may also be an antineoplastic agent, an antibiotic, an immunomodulator, an anti-inflammatory agent, an agent acting on the central nervous system, antigens or fragments thereof, proteins, peptides, polypeptoid, vaccines and small-molecules or mixtures thereof.

As has been set out above, lipid particles or liposomes containing amino lipids as defined in the present invention are suitable to deliver bioactive agents into cells. The wide variety of different amino lipids which can be synthesised by the mentioned versatile synthesis method can be screened for

for which vaccines derived from natural sources are too dangerous for human use and recombinant vaccines *are* not always effective, for example, hepatitis B virus, human immunodeficiency virus (HIV), hepatitis C virus (HCV) and herpes simplex virus.

Targets for anti-sense therapy are also known. Further targets for gene therapy and anti-sense therapy are being proposed as knowledge of the genetic basis of disease increases, as are further targets for gene vaccination.

A lipid particle of the invention may be used in vaccination. Thus, a lipid particle or liposome of the invention may be used to deliver an antigen or a nucleic acid encoding an antigen. These techniques are familiar to a person skilled in the art. Examples for liposome vaccines are described in Butts C, et al. Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV Non-Small-Cell Lung Cancer. Journal of Clinical Oncology. 2005, 23:6674-6681 and in U'Ren L, et al. Vaccination with liposome-DNA complexes elicits enhanced antitumor immunity. Cancer Gene Therapy. 2006, 13:1033-1044.

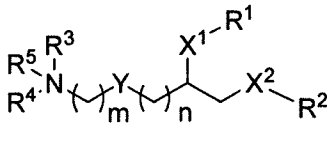
A lipid particle of the invention may be used to elicit an immune response against a wide variety of antigens for the treatment and/or prevention of a number of conditions including, but not limited to, cancer, allergies, toxicity and infection by pathogens such as viruses, bacteria, fungi, and other pathogenic organisms.

In a preferred embodiment of the invention said lipid particle or liposome can be used ~~as a medicament~~ in treatment of a viral infection, a liver disease or disorder, or cancer. On liver diseases, liposomes can be captured by the cells of the reticulo-endothelial system, which are primarily situated in the liver. The liposomes will be accumulated there.

A lipid particle of the invention may be used for the manufacture of a medicament to treat a viral infection, a liver disease or disorder, or cancer.

Claims

1. Amino lipids with the following formula (I):

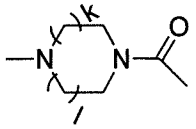


(I)

wherein R^1 and R^2 are the same or different and independently C_6-C_{24} alkyl, C_6-C_{24} alkenyl, C_6-C_{24} alkynyl, or C_6-C_{24} acyl, which can be optionally substituted with a C_1-C_6 hydrocarbyl group,

X^1 and X^2 are the same or different, either S or S=O or $S(=O)_2$,

Y is either an amide, an ester or a heterocyclic amide of the formula



wherein k and l are integers from 0 to 2,

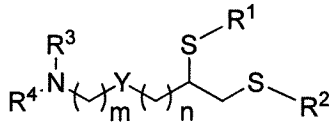
R^3 and R^4 are either the same or different and independently C_1-C_{12} alkyl, C_1-C_{12} alkenyl, or C_1-C_{12} alkynyl, wherein alkyl, alkenyl or alkynyl may be optionally substituted with a C_1-C_6 hydrocarbyl group, or R^3 and R^4 may join to form an optionally substituted heterocyclic ring of 3 to 10 atoms and ~~1~~0 to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

R^5 is either absent or is hydrogen or C_1-C_{12} alkyl to provide a quaternary amine,

m is an integer from 1 to 12 and n is an integer from 2 to 12.

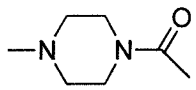
2. The amino lipids of claim 1, wherein R^1 and R^2 are the same or different and independently C_6-C_{24} alkyl, which can be optionally substituted with a C_1-C_6 hydrocarbyl group.

3. The amino lipid of claim 1 or 2, having the structure of formula (II)



(II) R^1 and R^2 are the same C_6-C_{18} alkyl

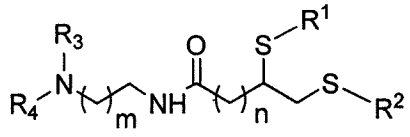
Y is either an amide, an ester or a heterocyclic amide of the formula



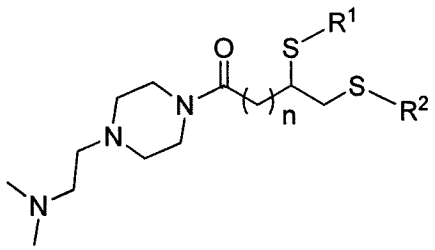
R^3 and R^4 are either the same or different C_1-C_{12} alkyls, wherein alkyl may be optionally substituted with a C_1-C_6 hydrocarbyl group, or R^3 and R^4 may join to form an optionally substituted heterocyclic ring of 3 to 10 atoms and 1~~0~~ to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

m is an integer from 1 to 12, n is an integer from 2 to 12.

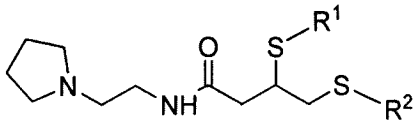
4. The amino lipid of claims 1 to 3, having the structure of formula (IIIa), (IIIb) or (IIIc)



(IIIa),



(IIIb), or



(IIIc),

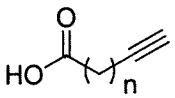
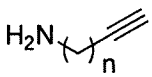
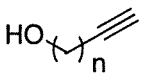
wherein R^1 and R^2 are the same C_{11}-C_{12} alkyls,

R^3 and R^4 are the same C_1-C_2 alkyls,

m is an integer from 1 to 2, n is an integer from 2 to 3.

5. A method to synthesize an amino lipid as defined in claims 1 to 4 comprising the following steps:

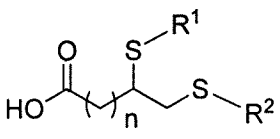
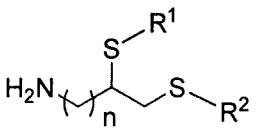
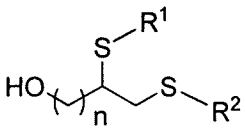
a) reaction of alkynes of the general formula (IVa), (IVb) or (IVc),


(IVa),

(IVb), or

(IVc)

wherein n is an integer from 2 to 12,

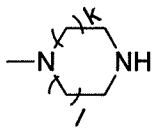
with compounds of the general formula, HS-R^1 and HS-R^2,

wherein R^1 and R^2 are the same or different and independently C_6-C_{24} alkyl, C_6-C_{24} alkenyl, C_6-C_{24} alkynyl, or C_6-C_{24} acyl, which can be optionally substituted with a C_1-C_6 hydrocarbyl group, under either UV-irradiation or using a radical initiator, to yield a compound of the general formula (Va), (Vb) or (Vc),


(Va),

(Vb),

(Vc)

wherein n, R^1 and R^2 are defined as above,

b) condensation reaction of the product of step a) of the formula Va with an amine or alcohol of the general formula $(R^3R^4R^5N)(CH_2)_mZ$, with m as an integer from 1 to 12, wherein Z is NH_2, OH, or a secondary heterocyclic amine of the formula



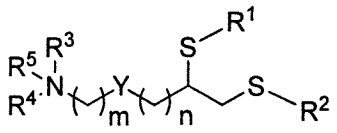
, wherein k and l are integers from 0 to 2,

or condensation reaction of the product of step a) of the formula Vb and Vc with carboxylic acid of the general formula $(R^3R^4R^5N)(CH_2)_mZ$, with m as an integer from 1 to 12, wherein Z is COOH.

R^3 and R^4 are either the same or different and independently C_1-C_{12} alkyl, C_1-C_{12} alkenyl, or C_1-C_{12} alkynyl, which may be optionally substituted with a C_1-C_6 hydrocarbyl group, or R^3 and R^4 may join to form a ring of 3 to 10 carbon atoms and 1~~0~~ to 6 heteroatoms chosen from nitrogen, thiol and oxygen,

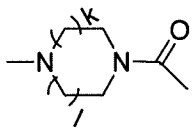
R^5 is either absent or is hydrogen or C_1-C_{12} alkyl to provide a quaternary amine,

to yield a compound of the general formula (VI)



(VI),

Y being either an amide, an ester or a heterocyclic amide of the formula



wherein k and l are integers from 0 to 2,

~~,~~ wherein n, m, Y, R^1, R^2, R^3, R^4 and R^5 are defined as above.

6. Method according to claim 5, comprising an optional step c) oxidation of the thioethers of the general formula

(VI) (product of step b) into sulfoxide (S=0) and/or sulfone ($S(=0)_2$) using an oxidation reagent.

7. A lipid particle containing an amino lipid of one of the claims 1 to 4.

8. A lipid particle according to claim 7, wherein said lipid particle is a liposome.

9. The lipid particle according to one of the claims 7 or 8, further containing a non-cationic lipid.

10. A lipid particle according to one of the claims 7 to 9, further containing a sterol.

11. A lipid particle according to one of the claims 7 to 10, further containing a bioactive agent.

12. A lipid particle according to claim 11, wherein said bioactive agent is a member optionally selected from the group consisting of: a nucleic acid, an antineoplastic agent, an antibiotic, an immunomodulator, an anti-inflammatory agent, an agent acting on the central nervous system, a polypeptide or a polypeptoid.

13. Use of a lipid particle according to one of the claims 7 to 12 for the manufacture of a medicament for delivering a bioactive agent into a cell.

14. Lipid particle according to one of the claims 7 to 12 for use as a medicament.

15. Lipid particle according to one of the claims 7 to 12 for use in treatment of a viral infection, a liver disease or disorder, or cancer.

16. Use of a lipid particle according to one of claims 7 to 12 for the manufacture of a medicament to treat a viral infection, a liver disease or disorder, or cancer.