Claims

1. A method of synthesising an ionisable lipid of Formula (I), or a pharmaceutically acceptable salt, solvate or stereoisomer thereof:



(I)

wherein

each R_1 is independently oxo, optionally substituted oxyacyl, optionally substituted acyloxyl, optionally substituted silyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

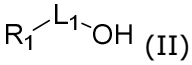
each L_1 is independently optionally substituted alkylene, optionally substituted heterocyclylene, or optionally substituted arylene;

R_2 is independently H, halo, oxo, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted oxy, optionally substituted oxyacyl, optionally substituted acyloxyl, or optionally substituted silyl; and

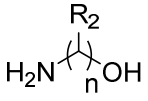
n is an integer selected from 1 to 10;

the method comprising:

N-alkylating at least two molar equivalence of alcohols of Formula (II) with 1 molar equivalence of amino alcohol of Formula (III) in the presence of a hydrogen borrowing catalyst;



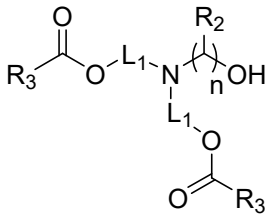
(II)



(III)

wherein the hydrogen borrowing catalyst is an iridium catalyst.

2. The method according to claim 1, wherein the ionisable lipid of Formula (I) is an ionisable lipid of Formula (Ia), or a pharmaceutically acceptable salt, solvate or stereoisomer thereof:



(Ia)

wherein

each R_3 is independently optionally substituted alkyl, optionally substituted heterocyclyl, or optionally substituted aryl;

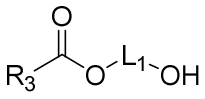
each L_1 is independently optionally substituted alkylene, optionally substituted heterocyclylene, or optionally substituted arylene;

R_2 is independently H, halo, oxo, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted oxy, optionally substituted oxyacyl, optionally substituted acyloxyl, or optionally substituted silyl; and

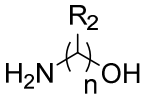
n is an integer selected from 1 to 10;

the method comprising:

N-alkylating at least two molar equivalence of acyloxy-substituted alkyl alcohols of Formula (IIa) with 1 molar equivalence of amino alcohol of Formula (III) in the presence of a hydrogen borrowing catalyst;



(IIa)



(III)

wherein the hydrogen borrowing catalyst is an iridium catalyst.

3. The method of claim 1 or 2, wherein the hydrogen borrowing catalyst is a cyclopentadienyl iridium complex, wherein the cyclopentadienyl is optionally substituted.

4. The method of any one of claims 1 to 3, wherein the hydrogen borrowing catalyst is cyclopentadienyl iridium dichloride dimer ($[Cp^*IrCl_2]_2$), wherein the cyclopentadienyl is optionally substituted.

5. The method of any one of claims 1 to 4, wherein the hydrogen borrowing catalyst is added at a concentration of about 1 mol% to about 5 mol% relative to the hydroxyl-substituted alkyl amine.

6. The method of any one of claims 1 to 5, wherein each R_1 is independently C_{10}-C_{24} alkyl, optionally substituted with halo.

7. The method of any one of claims 1 to 6, wherein each L_1 is independently C_1-C_{10} alkylene, optionally substituted with halo.

8. The method of any one of claims 1 to 7, wherein n is an integer selected from 1 to 5.

9. The method of any one of claims 1 to 8, further comprising a step of protecting the hydroxyl moiety on the amino alcohol;
wherein the hydroxyl moiety is protected with a protecting group selected from 2-tetrahydropyranyl (THP), benzyl or dimethyl-tert-butylsilyl (TBS), tert-butyldiphenylsilyl (TBDPS), optionally substituted benzyl ether or other ethers such as methoxymethyl ether (MOM), P-methoxybenzyl (PMB).

10. The method of any one of claims 1 to 9, wherein the molar ratio of the amino alcohol to the alcohol is about 1:2 to about 1:20.

11. The method of any one of claims 1 to 10, wherein the N-alkylation step is performed in the presence of $NaHCO_3$ and toluene.

12. The method of any one of claims 1 to 11, wherein the N-alkylation step is performed at a temperature of about 80°C to about 110°C, and/or for about 16 hr to about 24 hr.

13. The method of any one of claims 1 to 12, further comprising a step of purifying the ionisable lipid from the amino alcohol and/or the alcohol, preferably using column chromatography in the presence of dichloromethane, methanol and ammonia, and in the presence of magnesium silicate (Florisil) or silica gel.

14. The method of any one of claims 1 to 13, further comprising a step of purifying the ionisable lipid from the hydrogen borrowing catalyst in the presence of a metal scavenger.

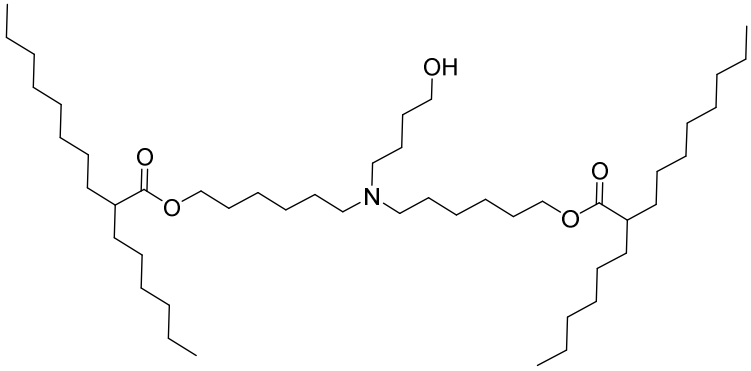
15. The method of any one of claims 1 to 14, further comprising a step of deprotecting the hydroxyl moiety on the ionisable lipid, preferably in the presence of hydrochloric acid and methanol.

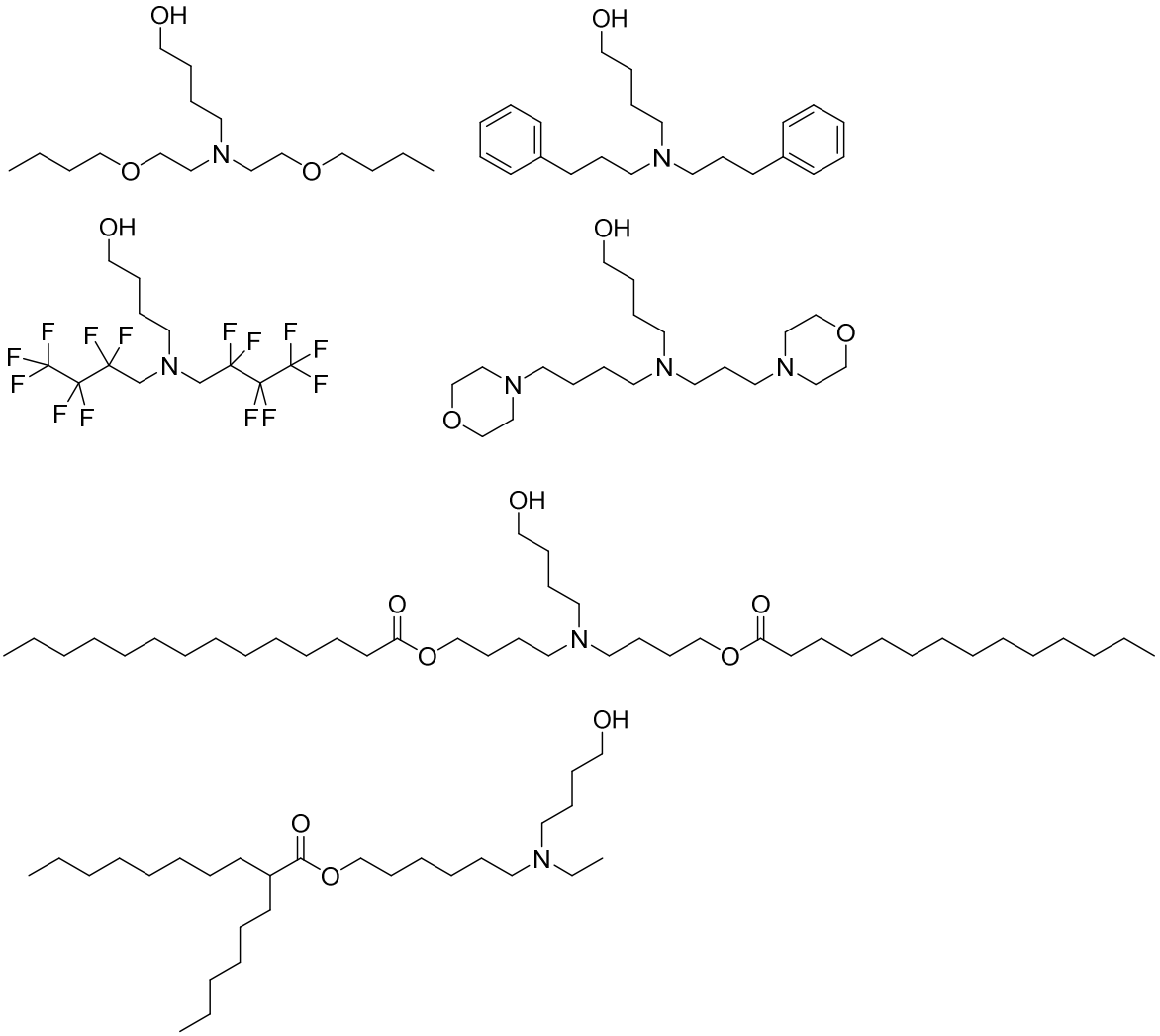
16. The method of any one of claims 1 to 16, further comprising a step of isolating a

free amine form of the ionisable lipid, preferably in the presence of ammonia, methanol and ethyl acetate, or in the presence of diethyl ether, water, and sodium carbonate.

17. The method of any one of claims 1 to 16, wherein the method further comprising a step of deprotecting the hydroxyl moiety on the ionisable lipid and a step of isolating a free amine form of the ionisable lipid, wherein the deprotection step and isolation step are performed sequentially in a reaction vessel after the N-alkylation step.

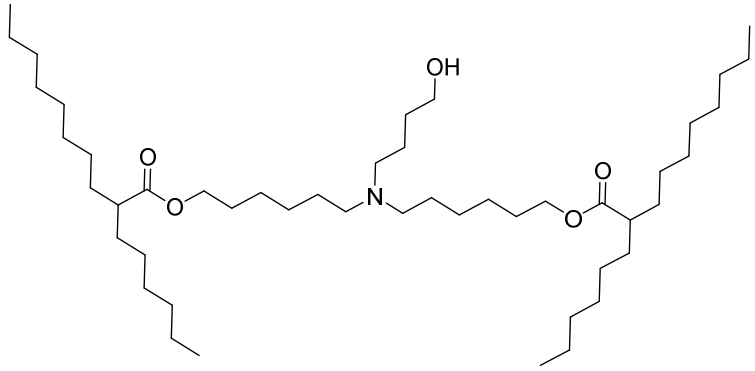
18. The method of any one of claims 1 to 17, wherein the ionisable lipid of Formula (I) is selected from:





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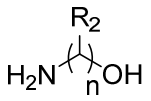
19. A method of synthesising ALC-0315, or a pharmaceutically acceptable salt, solvate or isomer thereof:



(ALC-0315)

the method comprising:

N-alkylating 1 molar equivalence of amino alcohol of Formula (III)

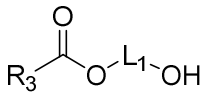


(III)

wherein R_2 is independently H; and

n is 4;

with at least two molar equivalence of acyloxy-substituted alkyl alcohols of Formula (IIa)



(IIa)

wherein R_3 is independently C_{15} alkyl bonded to the acyl moiety at a C7 position; and

L_1 is independently C_6 alkylene;

in the presence of a cyclopentadienyl iridium dichloride dimer ($[Cp^*IrCl_2]_2$) catalyst.

20. The method of claim 19, wherein the hydroxyl moiety on the amino alcohol is protected with a 2-tetrahydropyranyl (THP) group.