

Description

Title of Invention: IONIZABLE LIPIDS AND LIPID NANOPARTICLES FOR RNA DELIVERY

FIELD OF THE INVENTION

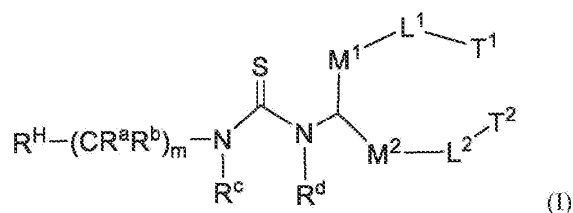
- [0001] Provided herein is a novel ionizable cationic lipid compound that can be assembled with other helper lipids, such as phospholipids, structural lipids, and polymer conjugated lipids capable of reducing aggregation, to form lipid nanoparticles for delivery of therapeutic and/or prophylactics nucleic acids (e.g., RNA) both in vitro and in vivo.

BACKGROUND OF THE INVENTION

- [0002] Lipid nanoparticle compositions, including cationic and/or ionizable lipids, phospholipids, PEG lipids, and structural lipids, have proven effective as transport vehicles for delivering biologically active substances including small molecule drugs, proteins, and nucleic acids into cells and/or intracellular compartments. However, the effective targeted delivery of nucleic acids remains a persistent medical challenge since delivering nucleic acids to cells is hindered by their inherent instability and limited ability to permeate cell membranes.
- [0003] Therefore, there is a need to develop novel ionizable lipids with improved safety, efficacy, and specificity in nucleic acid delivery.

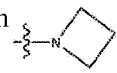
SUMMARY OF THE INVENTION

- [0004] Provided herein is a novel ionizable cationic lipid compound or a pharmaceutically acceptable salt thereof, or a stereoisomer, a tautomer or a geometric isomer thereof, which can be used alone or in combination with other lipid components such as other helper lipids, such as phospholipids, structural lipids, and polymer conjugated lipids to form lipid nanoparticles (LNP) for the delivery of therapeutic and/or prophylactics agents, e.g., therapeutic nucleic acids. Provided herein is also a method for delivering nucleic acids such as antisense oligonucleotides, small interfering RNA and/or messenger RNA via lipid nanoparticles comprising ionizable cationic lipid compounds and a method for the use of such lipid nanoparticles for the treatment and prophylaxis of various diseases or conditions.
- [0005] The embodiment comprises the following aspects:
- [0006] In some embodiments, provided herein is a compound of Formula (I) :

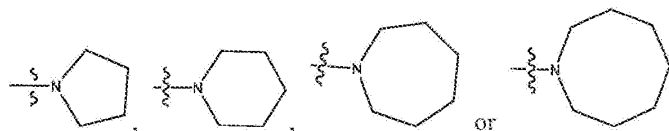


- [0007] or a pharmaceutically acceptable salt thereof, or a stereoisomer, a tautomer or a geometric isomer thereof,
- [0008] R^H is -N(R^1R^2), cycloalkyl, aryl, heteroaryl, or heterocyclyl, wherein each of said cycloalkyl, aryl, heteroaryl, or heterocyclyl is independently unsubstituted or substituted with one, two or three substituents R^{Ha} ;
- [0009] R^{Ha} is C_{1-12} alkyl, or -OH; wherein said C_{1-12} alkyl is independently unsubstituted or substituted with F, -OR, -CO₂R, -SR, or -C₁₋₆alkyl;
- [0010] R^1 and R^2 are each independently H or C_{1-12} alkyl or R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4-to 9-membered heterocyclyl comprising 0 or 1 heteroatom selected from oxygen, nitrogen or sulfur, or a 5-to 9-membered heteroaryl comprising 0, 1, or 2 heteroatom selected from oxygen, nitrogen or sulfur; and
- [0011] each R^a is independently selected from H or C_{1-6} alkyl;
- [0012] each R^b is independently selected from H or C_{1-6} alkyl;
- [0013] m is an integer ranging from 1 to 15;
- [0014] R^c and R^d are each independently selected from H or C_{1-6} alkyl; each of said C_{1-6} alkyl is independently substituted with one, two or three R^M ;
- [0015] M^1 and M^2 are each independently a single bond, C_{1-18} alkylene or C_{2-18} alkenylene; wherein one or two methylene units of the C_{1-18} alkylene or C_{2-18} alkenylene are optionally and independently replaced by L^{m1} or L^{m2} ; wherein each of said C_{1-18} alkylene or C_{2-18} alkenylene is independently unsubstituted or substituted with one, two or three R^M ;
- [0016] L^1 and L^2 are independently selected from a single bond, -C(=O)O-, -OC(=O)O-, -OC(=O)C(=O)O-, -C(=O)S-, -C(=S)O-, -C(=S)S-, -OC(=O)-, -OC(=S)-, -SC(=O)-, -SC(=S)-, -C(=O)-, -C(=S)-, -O-, -S-, -NR^L-, -C(=O)NR^L-, -C(=S)NR^L-, -NR^LC(=O)-, -NR^LC(=S)-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -OC(=O)NR^L-, -OC(=S)NR^L-, -SC(=S)NR^L-, -SC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=S)O-, -NR^LC(=S)S-, -NR^LC(=O)S-, -CH(OH)-, -CH(SH)-, -P(=O)(OR^L)O-, -S(O)-, -S(O)₂-, -S-S-, a cycloalkylene group, an arylene group, a heteroarylene group and a heterocyclylene group;
- [0017] R^L is H or C_{1-12} alkyl; and

- [0018] T^1 and T^2 are each independently C_{1-24} alkyl, C_{2-24} alkenyl or C_{2-24} alkynyl; wherein one or two methylene units of the C_{1-24} alkyl, C_{2-24} alkenyl or C_{2-24} alkynyl are optionally and independently replaced by L^{m1} or L^{m2} ; wherein each of said C_{1-24} alkyl, C_{2-24} alkenyl or C_{2-24} alkynyl is independently substituted with one, two or three R^M ;
- [0019] L^{m1} and L^{m2} are independently selected from a single bond, $-C(=O)O-$, $-OC(=O)-$, $O-$, $-OC(=O)C(=O)O-$, $-C(=O)S-$, $-C(=S)O-$, $-C(=S)S-$, $-OC(=O)-$, $-OC(=S)-$, $-SC(=O)-$, $-SC(=S)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-S-$, $-NR^{mL}-$, $-C(=O)NR^{mL}-$, $-C(=S)NR^{mL}-$, $-NR^{mL}C(=O)-$, $-NR^{mL}C(=S)-$, $-NR^{mL}C(=O)NR^{mL}-$, $-NR^{mL}C(=S)NR^{mL}-$, $-OC(=O)NR^{mL}-$, $-OC(=S)NR^{mL}-$, $-SC(=S)NR^{mL}-$, $-SC(=O)NR^{mL}-$, $-NR^{mL}C(=O)O-$, $-NR^{mL}C(=S)O-$, $-NR^{mL}C(=S)S-$, $-NR^{mL}C(=O)S-$, $-CH(OH)-$, $-CH(SH)-$, $-P(=O)(OR^{mL})O-$, $-S(O)-$, $-S(O)_2-$, $-S-S-$, a cycloalkylene group, an arylene group, a heteroarylene group and a heterocyclylene group;
- [0020] R^{mL} is H or C_{1-12} alkyl,
- [0021] R^M is F, $-OR$, $-CO_2R$, $-SR$, $-C_{1-6}$ alkyl, cycloalkyl, or heterocyclyl;
- [0022] R is hydrogen, or C_{1-6} alkyl optionally substituted with one, two or three selected from F, cycloalkyl, or heterocyclyl.
- [0023] In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently H or C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl or t-butyl). In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl or t-butyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently methyl, or ethyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently methyl.
- [0024] In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4-to 8-membered heterocyclyl comprising 0 or 1 heteroatom selected from oxygen, nitrogen or sulfur. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4-, 5-, 6-, 7- or 8-membered heterocyclyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form

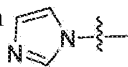


In some embodiments,



R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 5-to 8-membered heteroaryl comprising 0, 1, or 2 heteroatom selected from oxygen, nitrogen or sulfur. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 ,

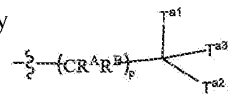
together with the nitrogen atom to which they attach, form a 5-, 6-, 7- or 8-membered heteroaryl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form



- [0025] In some embodiments, R^a and R^b are each H. In some embodiments, m is 2 or 3 and R^a and R^b are each H. In some embodiments, the moiety $-(CR^aR^b)_m$ -is $-(CH_2-CR^aR^b)$ -, $-(CR^aR^b-CH_2)$ -, $-(CH_2-CH_2-CR^aR^b)$ -, $-(CH_2-CR^aR^b-CH_2)$ -or- $-(CR^aR^b-CH_2-CH_2)$ -, wherein R^a and R^b are H or C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl) and R^a and R^b are not both H. In some embodiments, the moiety $-(CR^aR^b)_m$ -is $-(CH_2-CR^aR^b)$ -, $-(CR^aR^b-CH_2)$ -, $-(CH_2-CH_2-CR^aR^b)$ -, $-(CH_2-CR^aR^b-CH_2)$ -or- $-(CR^aR^b-CH_2-CH_2)$ -, wherein R^a and R^b are H or C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl). In some embodiments, the moiety $-(CR^aR^b)_m$ -is $-(CH_2-CR^aR^b)$ -, $-(CR^aR^b-CH_2)$ -, $-(CH_2-CH_2-CR^aR^b)$ -, $-(CH_2-CR^aR^b-CH_2)$ -or- $-(CR^aR^b-CH_2-CH_2)$ -, wherein R^a and R^b are H, methyl or ethyl. In some embodiments, the moiety $-(CR^aR^b)_m$ -is $-(CH_2-CR^aR^b)$ -, $-(CR^aR^b-CH_2)$ -, $-(CH_2-CH_2-CR^aR^b)$ -, $-(CH_2-CR^aR^b-CH_2)$ -or- $-(CR^aR^b-CH_2-CH_2)$ -, wherein R^a and R^b are H or methyl.
- [0026] In some embodiments, R^c is H or C_{1-4} alkyl. In some embodiments, R^c is H, methyl, or ethyl.
- [0027] In some embodiments, R^d is H or C_{1-4} alkyl. In some embodiments, R^d is H, methyl, or ethyl.
- [0028] In some embodiments, M^1 and M^2 are each independently C_{4-12} alkylene or C_{4-12} alkenylene. In some embodiments, M^1 and M^2 are each independently C_4 alkylene, C_5 alkylene, C_6 alkylene, C_7 alkylene, C_8 alkylene, C_9 alkylene, C_{10} alkylene, C_{11} alkylene, C_{12} alkylene, C_4 alkenylene, C_5 alkenylene, C_6 alkenylene, C_7 alkenylene, C_8 alkenylene, C_9 alkenylene, C_{10} alkenylene, C_{11} alkenylene, C_{12} alkenylene, C_5 alkadienylene, C_6 alkadienylene, C_7 alkadienylene, C_8 alkadienylene, C_9 alkadienylene, C_{10} alkadienylene, C_{11} alkadienylene, or C_{12} alkadienylene.
- [0029] In some embodiments, L^1 and L^2 are independently selected from a single bond, $-C(=O)O-$, $-C(=O)S-$, $-C(=S)O-$, $-C(=S)S-$, $-OC(=O)-$, $-OC(=S)-$, $-SC(=O)-$, $-SC(=S)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-S-$, $-OC(=O)O-$, $-OC(=O)C(=O)O-$, $-P(=O)(ORL)O-$, or $-S-S-$. In some embodiments, L^1 and L^2 are independently a single bond. In some embodiments, L^1 and L^2 are independently $-C(=O)O-$, or $-OC(=O)-$.
- [0030] In some embodiments, T^1 and T^2 are each independently C_{6-12} alkyl or C_{6-12} alkenyl. In some embodiments, T^1 and T^2 are each independently C_6 alkyl, C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_6 alkenyl, C_7 alkenyl, C_8 alkenyl, C_9 alkenyl,

C₁₀alkenyl, C₁₁alkenyl, C₁₂alkenyl, C₆alkadienyl, C₇alkadienyl, C₈alkadienyl, C₉alkadienyl, C₁₀alkadienyl, C₁₁alkadienyl, or C₁₂alkadienyl.

[0031] In some embodiments, T¹ and T² are each independently



[0032] wherein

[0033] R^A and R^B are each independently selected from H or C₁₋₆alkyl;

[0034] p is an integer ranging from 0 to 12;

[0035] T^{a1} is H or C₁₋₆alkyl;

[0036] T^{a2} and T^{a3} are each independently C₁₋₁₂alkyl, C₂₋₁₂alkenyl or C₂₋₁₂alkynyl;

[0037] provided that the variables R^A, R^B, p, T^{a1}, T^{a2}, and T^{a3} are each selected such that T¹ and T² are each independently C₆₋₂₄alkyl, C₆₋₂₄alkenyl, or C₆₋₂₄alkynyl.

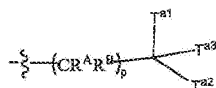
[0038] In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, T^{a1} is H and T^{a2} and T^{a3} are each independently C₄₋₁₂alkyl or C₄₋₁₂alkenyl. In some embodiments, T^{a1} is H and T^{a2} and T^{a3} are each independently C₄₋₁₂alkyl or C₄₋₁₂alkadienyl. In some embodiments, T^{a1} is H, T^{a2} is C₃₋₁₂alkyl and T^{a3} is C₃₋₁₂alkenyl. In some embodiments, T^{a1} is H, T^{a2} is C₃₋₁₂alkyl and T^{a3} is C₃₋₁₂alkadienyl.

[0039] In some embodiments, M¹ and M² are each independently C₃₋₁₂alkylene or C₃₋₁₂alkenylene; L¹ and L² are independently a single bond; and T¹ and T² are each independently C₆₋₁₂alkyl or C₆₋₁₂alkenyl; in some embodiments, M¹ and M² are each independently C₄alkylene, C₅alkylene, C₆alkylene, C₇alkylene, C₈alkylene, C₉alkylene, C₁₀alkylene, C₁₁alkylene, C₁₂alkylene, C₄alkenylene, C₅alkenylene, C₆alkenylene, C₇alkenylene, C₈alkenylene, C₉alkenylene, C₁₀alkenylene, C₁₁alkenylene, C₁₂alkenylene, C₅alkadienylene, C₆alkadienylene, C₇alkadienylene, C₈alkadienylene, C₉alkadienylene, C₁₀alkadienylene, C₁₁alkadienylene, or C₁₂alkadienylene; and in some embodiments, T¹ and T² are each independently C₆alkyl, C₇alkyl, C₈alkyl, C₉alkyl, C₁₀alkyl, C₁₁alkyl, C₁₂alkyl, C₆alkenyl, C₇alkenyl, C₈alkenyl, C₉alkenyl, C₁₀alkenyl, C₁₁alkenyl, C₁₂alkenyl, C₆alkadienyl, C₇alkadienyl, C₈alkadienyl, C₉alkadienyl, C₁₀alkadienyl, C₁₁alkadienyl, or C₁₂alkadienyl.

[0040] In some embodiments, M¹ and M² are each independently C₃₋₁₂alkylene or C₃₋₁₂alkenylene; L¹ and L² are independently -C(=O)O-, or -OC(=O)-; and T¹ and T² are each independently C₆₋₁₂alkyl or C₆₋₁₂alkenyl; in some embodiments, M¹ and M² are each independently C₄alkylene, C₅alkylene, C₆alkylene, C₇alkylene, C₈alkylene, C₉alkylene, C₁₀alkylene, C₁₁alkylene, C₁₂alkylene, C₄alkenylene, C₅alkenylene, C₆alkenylene, C₇alkenylene, C₈alkenylene, C₉alkenylene, C₁₀alkenylene, C₁₁alkenylene, C₁₂alkenylene, C₅alkadienylene, C₆alkadienylene, C₇alkadienylene,

C₈alkadienylene, C₉alkadienylene, C₁₀alkadienylene, C₁₁alkadienylene, or C₁₂alkadienylene; and in some embodiments, T¹ and T² are each independently C₆alkyl, C₇alkyl, C₈alkyl, C₉alkyl, C₁₀alkyl, C₁₁alkyl, C₁₂alkyl, C₆alkenyl, C₇alkenyl, C₈alkenyl, C₉alkenyl, C₁₀alkenyl, C₁₁alkenyl, C₁₂alkenyl, C₆alkadienyl, C₇alkadienyl, C₈alkadienyl, C₉alkadienyl, C₁₀alkadienyl, C₁₁alkadienyl, or C₁₂alkadienyl.

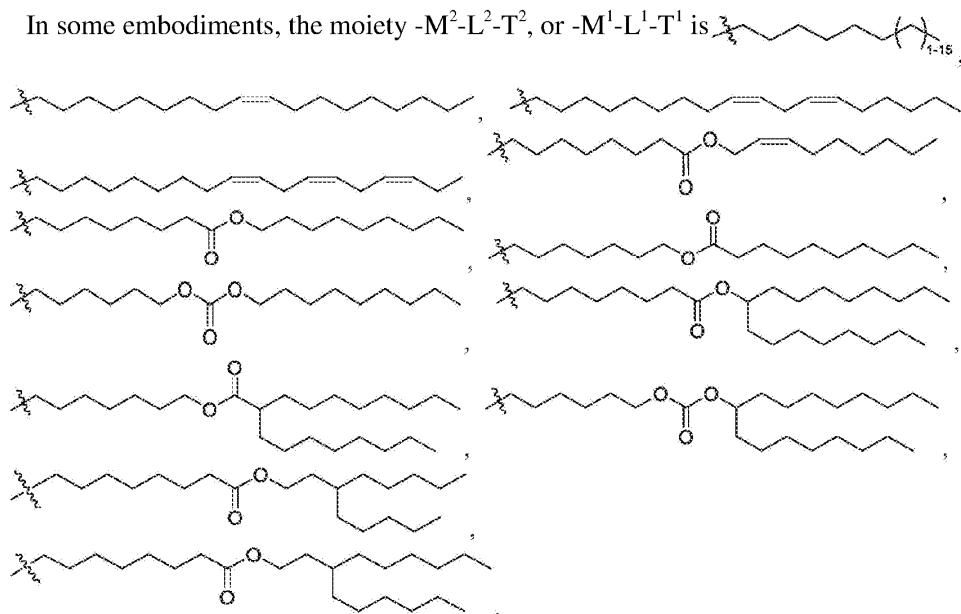
- [0041] In some embodiments, M¹ and M² are each independently C₄₋₁₂alkylene or C₄₋₁₂alkenylene; L¹ and L² are independently -C(=O)O-, or -OC(=O)-; and T¹ and T² are each independently

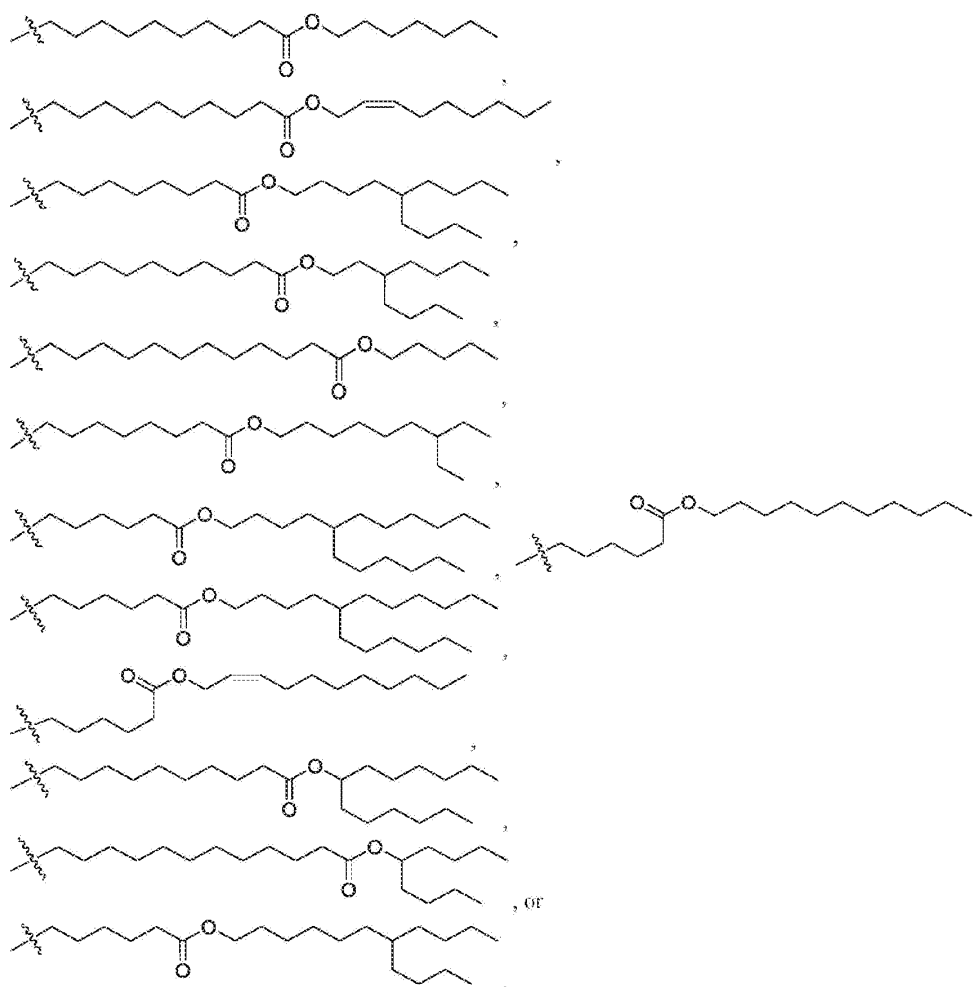


- [0042] In some embodiments, the moiety -M²-L²-T², or -M¹-L¹-T¹ is decanyl, undecanyl, dodecanyl, tridecanyl, tetradecanyl, heptadecanyl, octadecanyl, decenyl, decadienyl, undecenyl, undecadienyl, dodecenyl, dodecadienyl, tridecanyl, tridecenyl, tridecedienyl, tetradecenyl, tetradecadienyl, heptadecenyl, heptadecadienyl, octadecaenyl, or octadecadienyl.

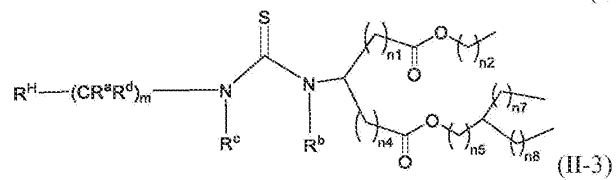
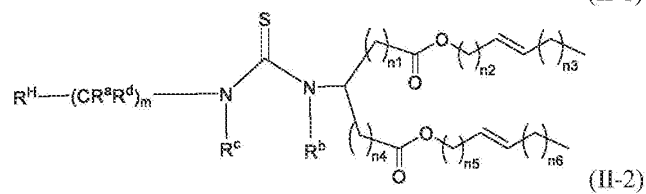
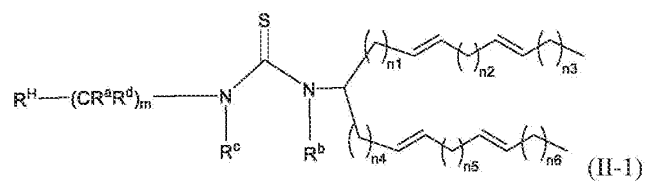
- [0043] In some embodiments, the moiety -M²-L²-T², or -M¹-L¹-T¹ is decan-2-yl, undecan-3-yl, dodecan-4-yl, tridecan-5-yl, tetradecan-6-yl, 2-methylundecan-3-yl, 2-methyldodecan-2-yl, 3-methylundecan-3-yl, 4-methyldodecan-4-yl, or heptadeca-9-yl.

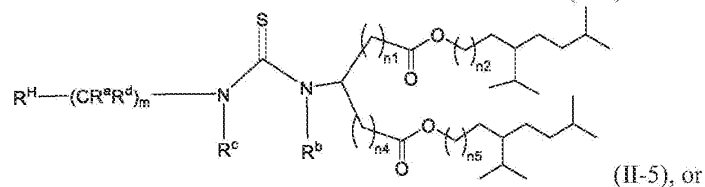
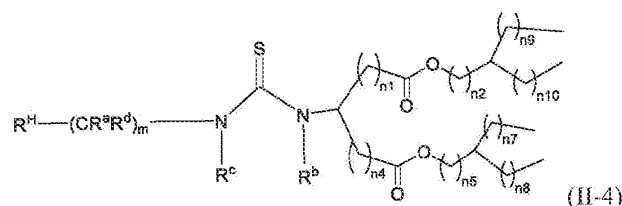
- [0044] In some embodiments, the moiety -M²-L²-T², or -M¹-L¹-T¹ is



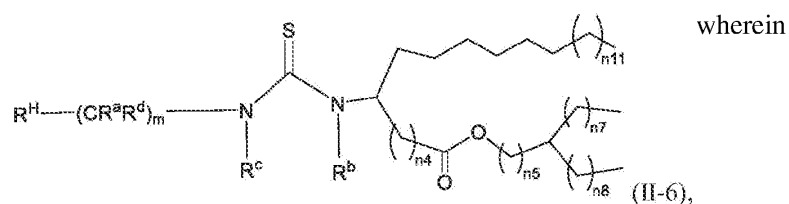


[0045] In some embodiments, a compound of Formula (II-1) - (II-6) :





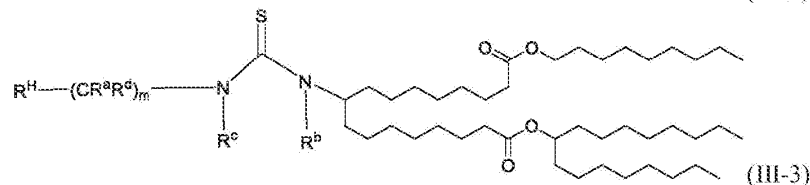
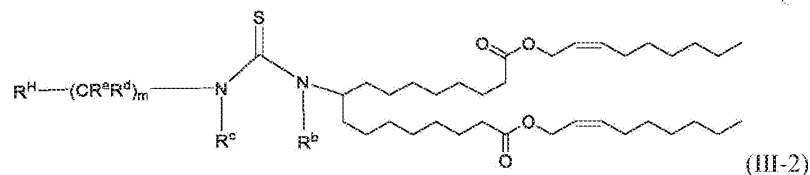
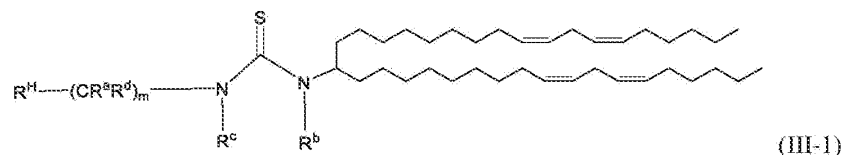
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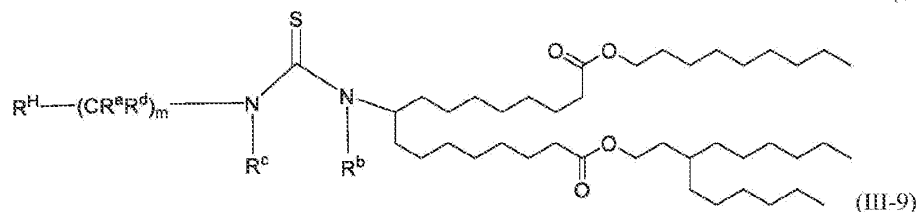
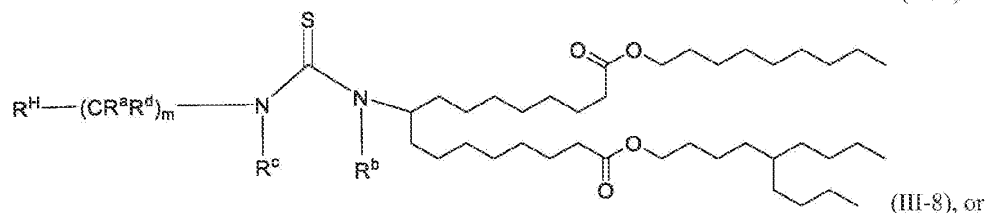
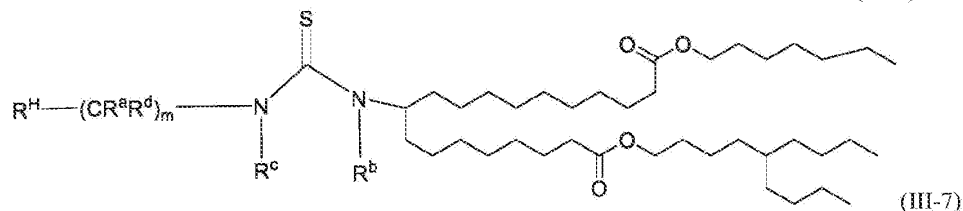
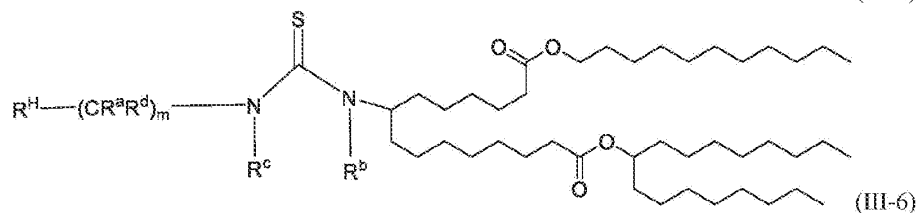
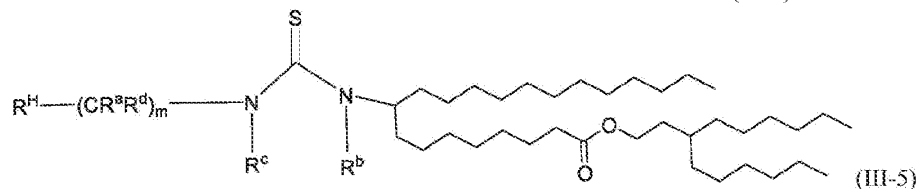
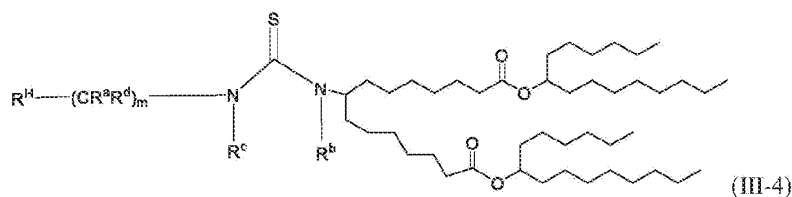


wherein

[0047] m is an integer ranging from 1 to 15;[0048] $n1, n2, n3, n4, n5, n6, n7, n8, n9, n10,$ and $n11$ are each independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18.[0049] In some embodiments, a compound of Formula (II-3), $n1$ is selected from 5, 7, or 9; $n2$ is selected from 7, 9, or 11; $n4$ is selected from 5, 7, or 9; $n5$ is selected from 0, 2, or 4; $n7$ is selected from 4, 6, or 8.[0050] In some embodiments, a compound of Formula (II-6), $n11$ is 5; $n4$ is selected from 5, 7, or 9; $n5$ is selected from 0, 2, or 4; $n7$ is selected from 4, 6, or 8.

[0051] In some embodiments, a compound selected from Formula (III-1) - (III-9) :



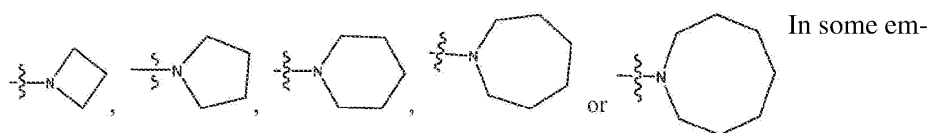


[0052] wherein m , R^H , R^a , R^b , R^c , and R^d are defined as above.

[0053] In some embodiments, a compound of Formula (II-1) - (II-6), (III-1) - (III-9), R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently H or C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl or t-butyl). In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl or t-butyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are each independently methyl, or ethyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 are

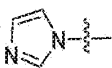
methyl. In some embodiments, R^a and R^b are each H. In some embodiments, m is 2 or 3 and R^a and R^b are each H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl) and R^a and R^b are not both H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl). In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl or ethyl. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl. In some embodiments, R^c is H or C_{1-4} alkyl. In some embodiments, R^c is H, methyl, or ethyl. In some embodiments, R^c is H. In some embodiments, R^d is H or C_{1-4} alkyl. In some embodiments, R^d is H, methyl, or ethyl. In some embodiments, R^d is H.

[0054] In some embodiments, a compound of Formula (III-1) - (III-9), R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4- to 8-membered heterocyclyl comprising 0 or 1 additional heteroatom selected from oxygen, nitrogen or sulfur. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4-, 5-, 6-, 7- or 8-membered heterocyclyl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form



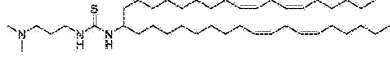
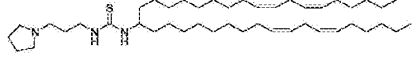
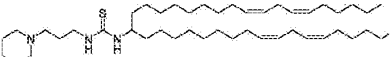
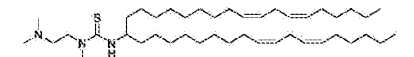
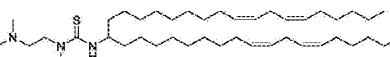
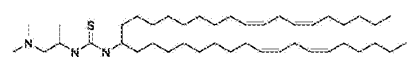
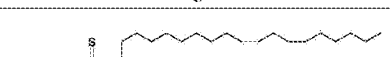
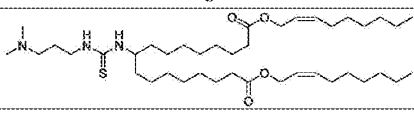
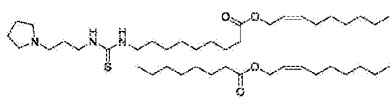
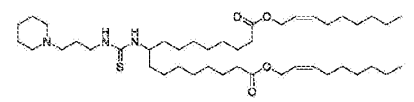
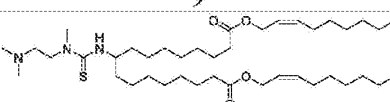
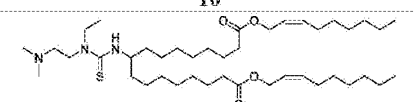
bodiments, R^a and R^b are each H. In some embodiments, m is 2 or 3 and R^a and R^b are each H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl) and R^a and R^b are not both H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl). In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl or ethyl. In some

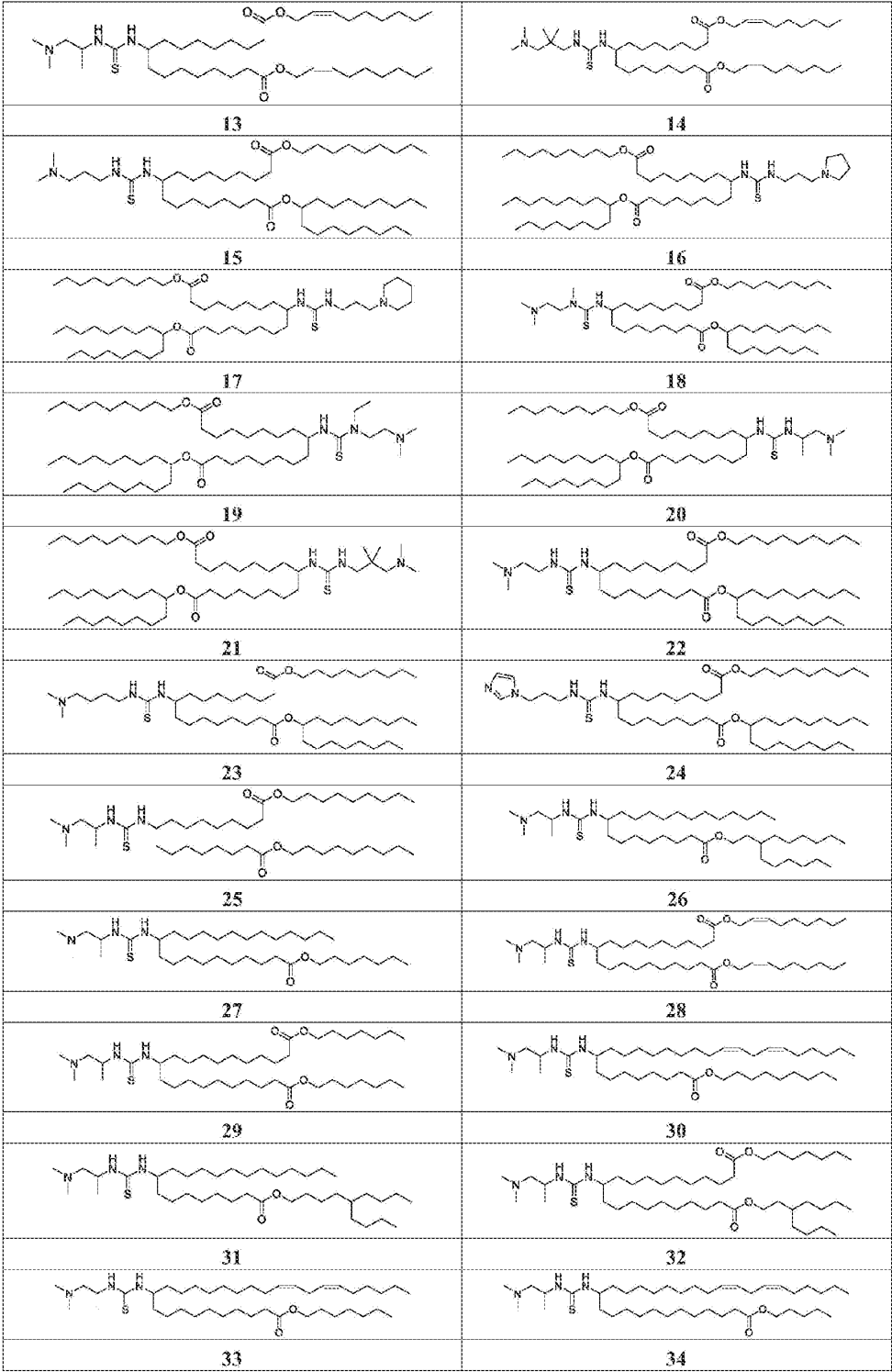
embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl. In some embodiments, R^c is H or C_{1-4} alkyl. In some embodiments, R^c is H, methyl, or ethyl. In some embodiments, R^c is H. In some embodiments, R^d is H or C_{1-4} alkyl. In some embodiments, R^d is H, methyl, or ethyl. In some embodiments, R^d is H.

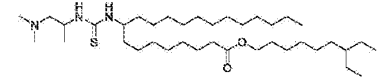
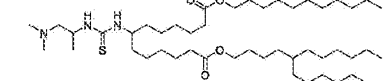
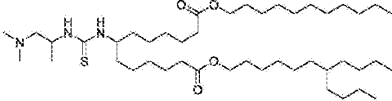
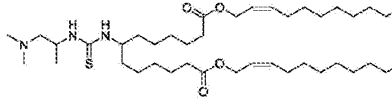
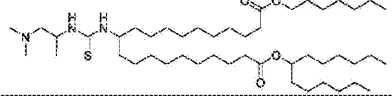
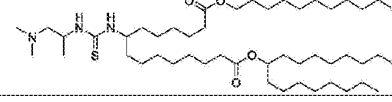
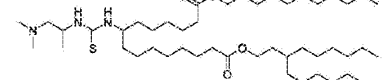
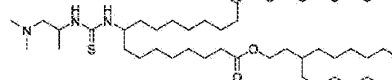
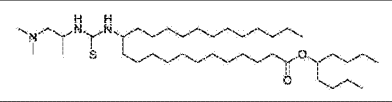
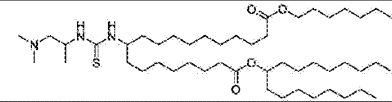
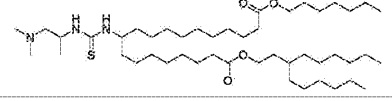
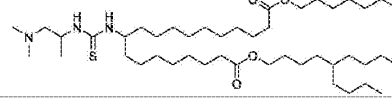
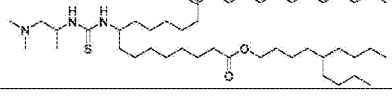
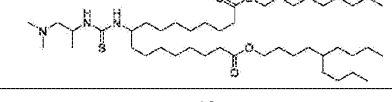
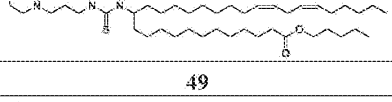
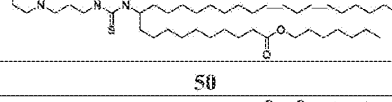
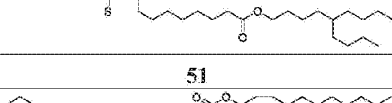
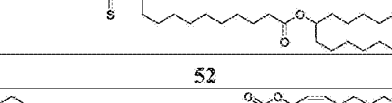
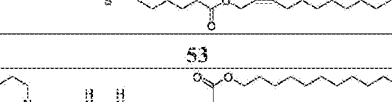
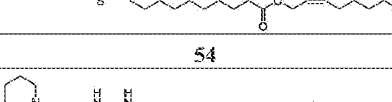
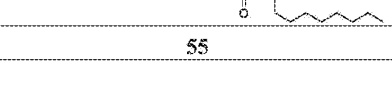
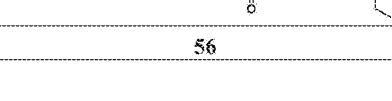
[0055] In some embodiments, a compound of Formula (III-1) - (III-9), R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 5- to 8-membered heteroaryl comprising 0, 1, or 2 additional heteroatom selected from oxygen, nitrogen or sulfur. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 5-, 6-, 7- or 8-membered heteroaryl. In some embodiments, R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form . In some embodiments, R^a and R^b

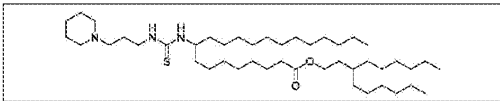
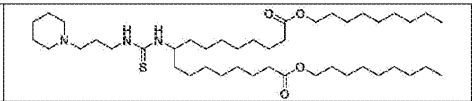
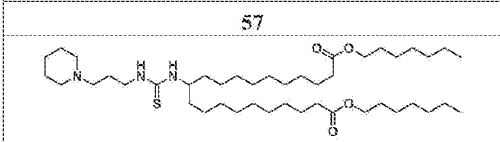
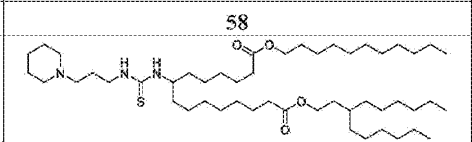
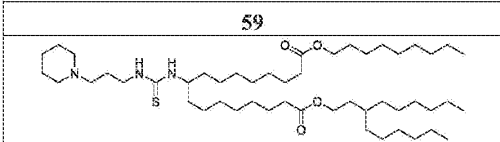
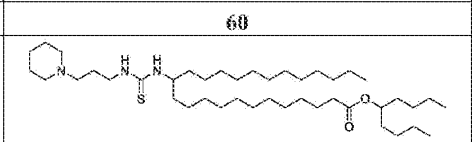
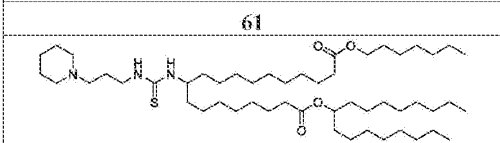
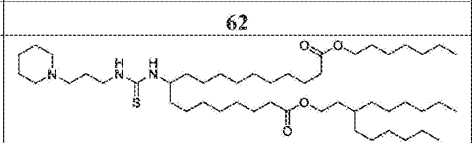
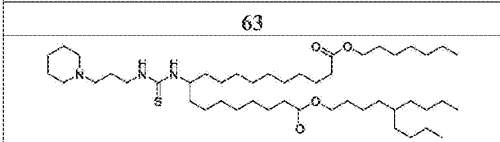
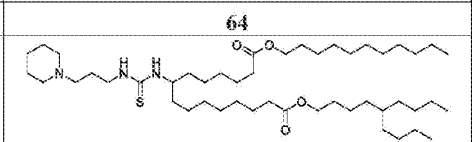
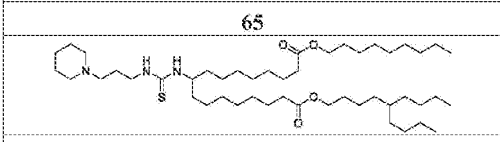
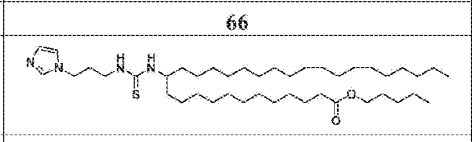
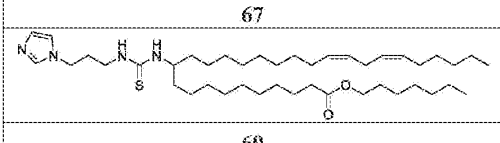
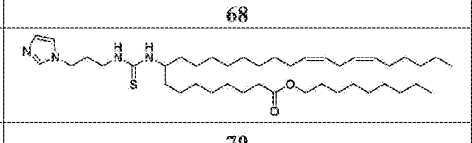
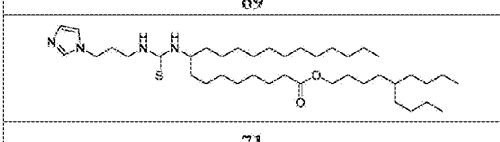
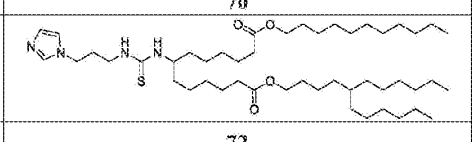
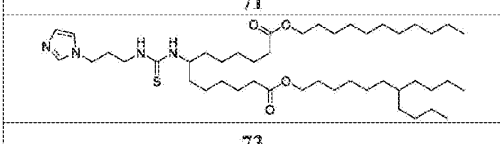
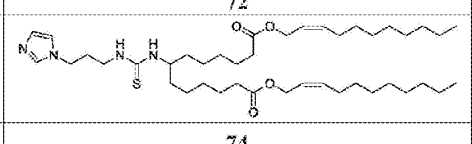
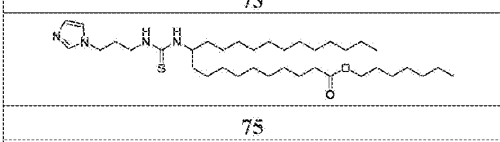
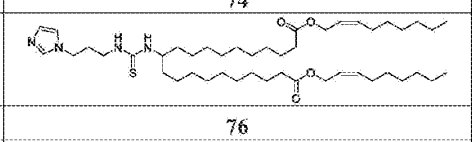
are each H. In some embodiments, m is 2 or 3 and R^a and R^b are each H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl) and R^a and R^b are not both H. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are C_{1-6} alkyl (e.g., C_{1-4} alkyl, C_{1-3} alkyl or C_{1-2} alkyl). In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl or ethyl. In some embodiments, the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are methyl. In some embodiments, R^c is H or C_{1-4} alkyl. In some embodiments, R^c is H, methyl, or ethyl. In some embodiments, R^c is H. In some embodiments, R^d is H or C_{1-4} alkyl. In some embodiments, R^d is H, methyl, or ethyl. In some embodiments, R^d is H.

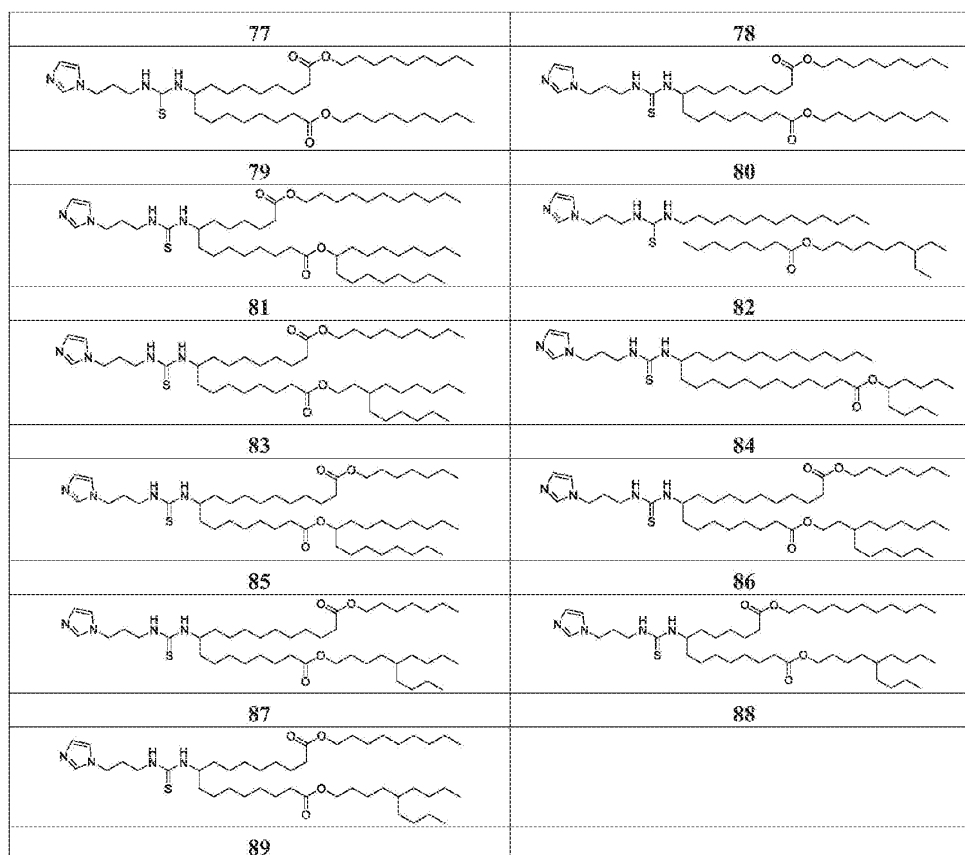
[0056] In some embodiments, the compound provided herein is selected from the group consisting of:

 1	 2
 3	 4
 5	 6
 7	 8
 9	 10
 11	 12



	
35	36
	
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73	74
	
75	76



[0057] Provided herein are pharmaceutical compositions comprising the compounds of formula (I) and a therapeutic agent. In some embodiments, the pharmaceutical compositions further comprise one or more components selected from phospholipids, structural lipids, and polymer conjugated lipids to form lipid nanoparticles (LNP) for the delivery of the therapeutic and/or prophylactics agent. In some embodiments, the therapeutic and/or prophylactics agent is a nucleic acid. In some embodiments, the pharmaceutical compositions comprise the compounds of formula (I), a therapeutic agent, phospholipids, steroids, and polymer conjugated lipids to form lipid nanoparticles (LNP) for the delivery of the therapeutic and/or prophylactics agent; the ionizable lipids comprise from about 20 mol% to about 85 mol% of total lipids; the phospholipids comprise from about 4 mol% to about 50 mol% of total lipids; the structural lipids comprise from about 20 mol% to about 45 mol% of total lipids; the polymer lipids comprise from about 0.5 mol% to about 5 mol% of total lipids; the total lipids are composed of phospholipids, structural lipids, and polymer conjugated lipids. In some embodiments, the pharmaceutical compositions comprise the compounds of formula (I), a therapeutic agent, phospholipids, steroids, and polymer conjugated lipids to form lipid nanoparticles (LNP) for the delivery of the therapeutic and/or pro-

phylactics agent; the ionizable lipids comprise from about 20 mol% to about 85 mol % of total lipids; the phospholipids comprise from about 4 mol% to about 30 mol% of total lipids; the structural lipids comprise from about 20 mol% to about 45 mol% of total lipids; the polymer lipids comprise from about 0.5 mol% to about 5 mol% of total lipids; the total lipids are composed of phospholipids, structural lipids, and polymer conjugated lipids.

[0058] Provided here is a method for administering a therapeutic agent to a patient in need thereof, the method comprising preparing a composition of lipid nanoparticles comprising the compound of formula (I) and a therapeutic and/or prophylactics agent and delivering the composition to the patient. In some embodiments, the therapeutic and/or prophylactics agent is a nucleic acid. In some embodiments, the therapeutic and/or prophylactic agent is mRNA vaccine.

[0059] BRIEF DESCRIPTION OF THE DRAWING

[0060] Figs. 1-3 shown the particle sizes, size polydispersity, Zeta potential of the LNP provided herein.

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[0061] Fig. 4 shows the relative luminescence intensity ratio of the LNP provided herein compare to lipofectamine.

[0062] Fig. 5 depicts the relative T-cell responses (ELISpot) ratio of the LNP provided herein compare to benchmark LNP SM 102.

DETAILED DESCRIPTION OF THE INVENTION

[0063] The following terms have the indicated meanings throughout the specification:

[0064] As used herein, including the appended Aspects, the singular forms of words such as "a", "an", and "the", include their corresponding plural references unless the context clearly dictates otherwise.

[0065] The term "or" is used to mean, and is used interchangeably with, the term "and/or" unless the context clearly dictates otherwise.

[0066] The term "ionizable lipid" includes lipids that assume a positive charge on pH decrease, and any of a number of lipid species that carry a net positive charge at a selective pH, such as physiological pH.

[0067] The term "nucleic acid" refers to a polymer containing at least two deoxyribonucleotides or ribonucleotides in either single- or double-stranded form and includes DNA, RNA, and hybrids thereof. DNA may be in the form of antisense molecules, plasmid DNA, cDNA, PCR products, or vectors. RNA may be in the form of small hairpin RNA (shRNA), circular RNA, antisense oligonucleotides (ASO), small interfering RNA (siRNA), self-amplification RNA (saRNA), messenger RNA (mRNA), antisense RNA, miRNA, micRNA, multivalent RNA, dicer substrate RNA or viral RNA (vRNA), and combinations thereof. Nucleic acids include nucleic acids

containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, and which have similar binding properties as the reference nucleic acid. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2'-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs). Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid.

[0068] The term “lipid nanoparticle” refers to particles having at least one dimension on the order of nanometers (e.g., 1-1,000 nm) which include one or more of the compounds of Formula (I) or other specified cationic lipids. Such lipid nanoparticles typically comprise a compound of Formula (I) and/or other cationic or ionizable cationic lipid compound and one or more excipient selected from structural lipid such as cholesterol, phospholipids such as 1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and polymer conjugated lipids such as PEG lipid and zwitterionic polymer lipids. In some embodiments, lipid nanoparticles are included in a formulation that can be used to deliver an active agent or therapeutic agent, such as a nucleic acid (e.g., mRNA) to a target site of interest (e.g., cell, tissue, organ, tumor, and the like). In some embodiments, the nucleic acid can be partially or completely encapsulated in the lipid portion of the lipid nanoparticle, thereby protecting it from enzymatic degradation or other undesirable effects induced by the mechanisms of the host organism or cells e.g., an adverse immune response.

[0069] The term “alkyl” refers to a hydrocarbon group selected from linear and branched saturated monovalent hydrocarbon groups comprising from 1 to 24, such as from 1 to 18, from 1 to 16, from 1 to 12, further such as from 1 to 10, more further such as from 1 to 8, or from 1 to 6, or from 1 to 4, carbon atoms. In some embodiments, the alkyl is linear alkyl or branched alkyl. For example, C₈₋₁₈alkyl comprises octanyl, nonanyl, decanyl, undecanyl, dodecanyl, tridecanyl, tetradecanyl, heptadecanyl, and octadecanyl. Examples of alkyl groups comprising from 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) include, but not limited to, methyl, ethyl, 1-propyl or n-propyl (“n-Pr”), 2-propyl or isopropyl (“i-Pr”), 1-butyl or n-butyl (“n-Bu”), 2-methyl-1-propyl or isobutyl (“i-Bu”), 1-methylpropyl or s-butyl (“s-Bu”), 1, 1-dimethylethyl or t-butyl (“t-Bu”), 1-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, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2, 3-dimethyl-2-butyl and 3, 3-dimethyl-2-butyl groups. A linear or branched alkyl, such as a “linear or branched C₁₋₁₈ alkyl,” “linear or branched C₁₋₁₂ alkyl,” or “linear or

branched C₁₋₈ alkyl” means that the saturated monovalent hydrocarbon group is a linear or branched chain.

[0070] The term “alkenyl” or “alkenyl group” means a linear or branched hydrocarbon including at least one double bond and two or more carbon atoms (e.g, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, or more carbon atoms) and comprising from 2 to 24, such as from 2 to 18, from 2 to 16, from 2 to 12, further such as from 2 to 10, more further such as from 2 to 8, or from 2 to 6, or from 2 to 4, carbon atoms. An alkenyl group may include one, two, three, four, or more carbon-carbon double bonds. In some embodiments, the alkenyl is linear alkenyl or branched alkenyl. For example, Cisalkenyl may include one or more double bonds. A C₁₈ alkenyl group including two double bonds. Examples of an alkenyl group include decenyl, decadienyl, undecenyl, undecadienyl, dodecenyl, dodecadienyl, tridecanyl, tridecenyl, tridecedienyl, tetradecenyl, tetradecadienyl, heptadecenyl, heptadecadienyl, octadecaenyl, or octadecadienyl.

[0071] The terms “branched alkyl”, “branched alkenyl” and “branched alkynyl” refer to an alkyl, alkenyl, or alkynyl group in which one carbon atom in the group is bound to at least two other carbon atoms, or is bound to at least three other carbon atoms, and is not a ring atom of a cyclic group. For example,  is a branched alkyl.

[0072] The term “alkylene” as used herein refers to a saturated divalent hydrocarbon radical of 1 to 20 carbon atoms (i.e., C₁₋₂₀ alkylene), examples of which include, but are not limited to, those having the same core structures of the alkyl groups as exemplified above. “Divalent” means that the alkylene has two points of attachment to the remainder of the molecule. In one embodiment, the alkylene has 1 to 12 carbon atoms (i.e., C₁₋₁₂ alkylene) or 1 to 10 carbon atoms (i.e., C₁₋₁₀ alkylene). In one embodiment, the alkylene has 1 to 8 carbon atoms (i.e., C₁₋₈ alkylene), 1 to 7 carbon atoms (i.e., C₁₋₇ alkylene), 1 to 6 carbon atoms (i.e., C₁₋₆ alkylene), 1 to 4 carbon atoms (i.e., C₁₋₄ alkylene), 1 to 3 carbon atoms (i.e., C₁₋₃ alkylene), ethylene, or methylene. A linear or branched alkylene, such as a “linear or branched C₁₋₆ alkylene,” “linear or branched C₁₋₄ alkylene,” or “linear or branched C₁₋₃ alkylene” means that the saturated divalent hydrocarbon radical is a linear or branched chain.

[0073] The term “alkenylene” as used herein refers to aliphatic divalent hydrocarbon radical of 1 to 20 carbon atoms (i.e., C₂₋₂₀ alkenylene) with one or two carbon-carbon double bonds, wherein the alkenylene radical includes radicals having “cis” and “trans” orientations, or by an alternative nomenclature, “E” and “Z” orientations. “Divalent” means that alkenylene has two points of attachment to the remainder of the molecule. In one embodiment, the alkenylene has 2 to 12 carbon atoms (i.e., C₂₋₁₂ alkenylene),

2 to 10 carbon atoms (i.e., C_{2-10} alkenylene). In one embodiment, the alkenylene has 2 to four carbon atoms (C_{2-4}). Examples include, but are not limited to, ethylenylene or vinylene ($-CH=CH-$), allyl ($-CH_2CH=CH-$), and the like. A linear or branched alkenylene, such as a “linear or branched C_{2-6} alkenylene,” “linear or branched C_{2-4} alkenylene,” or “linear or branched C_{2-3} alkenylene” means that the unsaturated divalent hydrocarbon radical is a linear or branched chain.

- [0074] The term “cycloalkyl” refers to a hydrocarbon group selected from saturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups including fused, bridged or spiro cycloalkyl. For example, the cycloalkyl group may comprise from 3 to 12, such as from 3 to 10, further such as 3 to 8, further such as 3 to 6, 3 to 5, or 3 to 4 carbon atoms. Even further for example, the cycloalkyl group may be selected from monocyclic group comprising from 3 to 12, such as from 3 to 10, further such as 3 to 8, 3 to 6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. In particular, examples of the saturated monocyclic cycloalkyl group, e.g., C_{3-8} cycloalkyl, include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In a preferred embodiment, the cycloalkyl is a monocyclic ring comprising 3 to 6 carbon atoms (abbreviated as C3-6 cycloalkyl), including but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.
- [0075] The term “aryl” used alone or in combination with other terms refers to a group selected from:
- [0076] (i) 5- and 6-membered carbocyclic aromatic rings, e.g., phenyl;
- [0077] (ii) bicyclic ring systems such as 7- to 12-membered bicyclic ring systems, wherein at least one ring is carbocyclic and aromatic, e.g., naphthyl and indanyl; and,
- [0078] (iii) tricyclic ring systems such as 10- to 15-membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, e.g., fluorenyl.
- [0079] The term “heteroaryl” refers to a group selected from:
- [0080] (i) 5-, 6- or 7-membered aromatic, monocyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, in some embodiments, from 1 to 2, heteroatoms, selected from nitrogen (N), sulfur (S) and oxygen (O), with the remaining ring atoms being carbon;
- [0081] (i) 7- to 12-membered bicyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and

- [0082] (i) 11-to 14-membered tricyclic rings comprising at least one heteroatom, for example, from 1 to 4, or in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.
- [0083] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring (s) of the heteroaryl group can be oxidized to form N-oxides. The term “C-linked heteroaryl” as used herein means that the heteroaryl group is connected to the core molecule by a bond from a C-atom of the heteroaryl ring.
- [0084] The terms “aromatic heterocyclic ring” and “heteroaryl” are used interchangeable throughout the disclosure herein. In some embodiments, a monocyclic or bicyclic aromatic heterocyclic ring has 5-, 6-, 7-, 8-, 9- or 10-ring forming members with 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O) and the remaining ring members being carbon. In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is a monocyclic or bicyclic ring comprising 1 or 2 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O). In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is a 5-to 6-membered heteroaryl ring, which is monocyclic and which has 1 or 2 heteroatom ring members independently selected from nitrogen (N), sulfur (S) and oxygen (O). In some embodiments, the monocyclic or bicyclic aromatic heterocyclic ring is an 8-to 10-membered heteroaryl ring, which is bicyclic and which has 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.
- [0085] “Heterocyclyl”, “heterocycle” or “heterocyclic” are interchangeable and refer to a non-aromatic heterocyclyl group comprising one or more heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon, including monocyclic, fused, bridged, and spiro ring, i.e., containing monocyclic heterocyclyl, bridged heterocyclyl, spiro heterocyclyl, and fused heterocyclic groups. The term “optionally oxidized sulfur” used herein refers to S, SO or SO₂. Exemplary heterocyclyl groups include, but not limited to, monocyclic 4 to 9-membered heterocyclyl, such as pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 2,

5-piperazinyl, pyranyl, morpholinyl, morpholino, morpholin-2-yl, morpholin-3-yl, oxiranyl, aziridin-1-yl, aziridin-2-yl, azocan-1-yl, azocan-2-yl, azocan-3-yl, azocan-4-yl, azocan-5-yl, thiiranyl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, oxetanyl, thietanyl, 1, 2-dithietanyl, 1, 3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, oxepanyl, thiepanyl, 1, 4-oxathianyl, 1, 4-dioxepanyl, 1, 4-oxathiepanyl, 1, 4-oxaazepanyl, 1, 4-dithiepanyl, 1, 4-thiazepanyl and 1, 4-diazepanyl, 1, 4-dithianyl, 1, 4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1, 4-dioxanyl, 1, 3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinyl, imidazoliny, pyrimidinonyl, or 1, 1-dioxo-thiomorpholinyl.

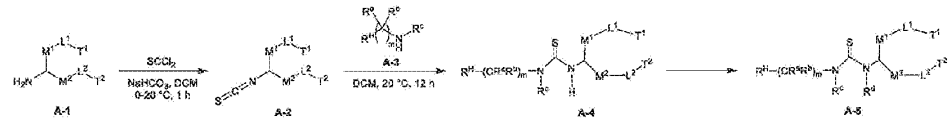
- [0086] Compounds disclosed herein may contain an asymmetric center and may thus exist as enantiomers. "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. Where the compounds disclosed herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds disclosed herein and / or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, the reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.
- [0087] When compounds disclosed herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.
- [0088] It may be advantageous to separate reaction products from one another and /or from starting materials. The desired product of each step or series of steps is separated and /or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

- [0089] “Diastereomers” refers to stereoisomers of a compound with two or more chiral centers but which are not mirror images of one another. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher’s acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.
- [0090] “Pharmaceutically acceptable salts” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A pharmaceutically acceptable salt may be prepared in situ during the final isolation and purification of the compounds disclosed herein, or separately by reacting the free base function with a suitable organic acid or by reacting the acidic group with a suitable base.
- [0091] A “pharmaceutical composition” refers to a formulation of a compound provided herein and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.
- [0092] In addition, if a compound disclosed herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and/or water and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.
- [0093] The terms “administration”, “administering”, “treating” and “treatment” herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, mean contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as the contact of a reagent to a fluid, where the fluid is in contact with the cell. The term “administration” and “treatment” also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell.
- [0094] The term “patient” as used herein refers to human.

- [0095] The term "effective amount" or "therapeutically effective amount" refers to an amount of the active ingredient, such as a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The "therapeutically effective amount" can vary with the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In some embodiments, "therapeutically effective amount" is an amount of at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof disclosed herein effective to "treat" as defined above, a disease or disorder in a subject. In the case of combination therapy, the "therapeutically effective amount" refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.
- [0096] Throughout this specification, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising" are intended to specify the presence of the features thereafter, but do not exclude the presence or addition of one or more other features. When used herein the term "comprising" can be substituted with the term "containing", "including" or sometimes "having".
- [0097] Throughout this specification, the term " C_{n-m} " indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-8} , C_{1-6} , and the like.
- [0098] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.
- [0099] General Synthesis
- [0100] Compounds disclosed herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.
- [0101] The reaction for preparing compounds disclosed herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials, the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's boiling temperature. A given reaction can be carried out in one solvent or mixture of solvents.
- [0102] The selection of an appropriate protecting group can be readily determined by one skilled in the art.

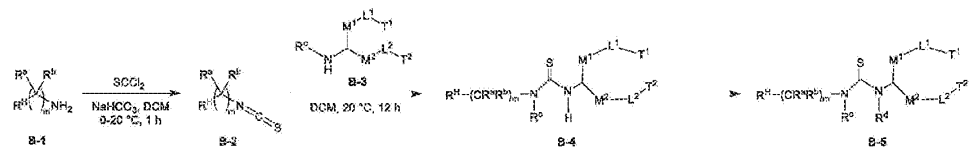
[0103] Reactions can be monitored according to any suitable method known in the art, such as NMR, UV, HPLC, LC-MS and TLC. Compounds can be purified by a variety of methods, including HPLC and normal phase silica chromatography.

[0104] Scheme I



[0105] Embodiments of the compound of Formula (I) (e.g., compound Example 4) can be synthesized according to Scheme I (“Method A”). R^H , R^a , R^b , R^c , R^d , M^1 , M^2 , L^1 , L^2 , T^1 , T^2 and m in general reaction Scheme I are as defined herein. A-1 are prepared according to methods known in the art. A solution of A-1 is treated with isosulfide hydrogenation reagent (e.g., thiophosgene) under alkaline conditions to obtain A-2 after any necessary work up. A solution of A-2 is treated with amine A-3 to obtain A-4 after any necessary work up and purification. A-5 is obtained by further modification with R^d .

[0106] Scheme II



[0107] Embodiments of the compound of Formula (I) (e.g., compound Example 11) can be synthesized according to Scheme II (“Method B”). R^H , R^a , R^b , R^c , R^d , M^1 , M^2 , L^1 , L^2 , T^1 , T^2 and m in general reaction Scheme I are as defined herein. B-1 are prepared according to methods known in the art. A solution of B-1 is treated with isosulfide hydrogenation reagent (e.g., thiophosgene) under alkaline conditions to obtain B-2 after any necessary work up. A solution of B-2 is treated with amine B-3 to obtain B-4 after any necessary work up and purification. B-5 is obtained by further modification with R^d .

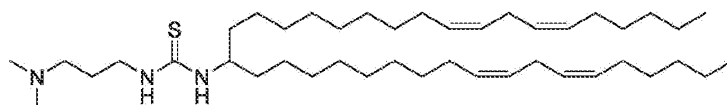
[0108] ABBREVIATIONS

(Boc) ₂ O	di-tert-butyl dicarbonate
Ac ₂ O	Acetic anhydride
AcOH	Acetic Acid
DCM	dichloromethane
DIEA	diisopropylethylamine

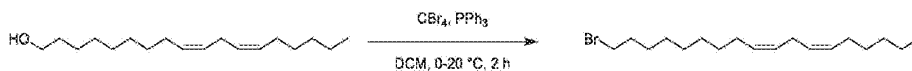
DMAP	4-dimethylaminopyridine
DCM	Dichloromethane
CBr ₄	Carbon tetrabromide
PPh ₃	Triphenylphosphine
EA, EtOAc	Ethyl acetate
PE	Petroleum ether
CDCl ₃	Chloroform-d
Mg	Magnesium
I ₂	Iodine
THF	Tetrahydrofuran
H ₂ SO ₄	Sulfuric acid
Na ₂ SO ₄	Sodium sulfate
EtOH	Ethanol
KOH	Potassium hydroxide
HCl	Hydrochloric acid
PCC	Pyridinium chlorochromate
Na ₂ CO ₃	Sodium carbonate
MeOH	Methanol
NaBH ₄	Sodium borohydride
NH ₄ OH	Ammonium hydroxide
SCCl ₂	Thiophosgene
NaHCO ₃	Sodium bicarbonate
DMSO- <i>d</i> ₆	Dimethyl sulfoxide- <i>d</i> ₆
DMAP	4-dimethylaminopyridine
TBDPSCI	<i>tert</i> -Butylchlorodiphenylsilane
CH ₃ CN	Acetonitrile
RuCl ₃	Ruthenium(III) chloride hydrate
N ₂	Nitrogen
NaIO ₄	Sodium periodate
EDCI	N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
TBAF	Tetrabutylammonium fluoride
DIAD	Diisopropyl azodicarboxylate
DPPA	Diphenylphosphoryl azide
TLC	thin-layer chromatography
<i>prep</i> -TLC	Preparative thin-layer chromatography
rt	room temperature

[0109] Examples

[0110] Example 1: 1- (3- (dimethylamino) propyl) -3- ((6Z, 9Z, 28Z, 31Z) -hepta-
triaconta-6, 9, 28, 31-tetraen-19-yl) thiourea

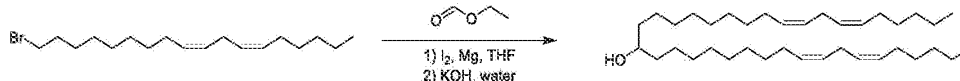


[0111] Step1: (6Z, 9Z) -18-bromooctadeca-6, 9-diene



[0112] To a mixture of (9Z, 12Z) -octadeca-9, 12-dien-1-ol (60 g, 225 mmol) and CBr_4 (134 g, 405 mmol) in DCM (600 mL), the solution of PPh_3 (119 g, 455 mmol) in DCM (500 mL) was added at 0 °C, then the mixture was stirred at 20 °C for 2 hours. TLC showed (9Z, 12Z) -octadeca-9, 12-dien-1-ol was consumed and one major new spot with lower polarity was detected. The mixture was filtered, the filter cake was washed with water (300 mL) and concentrated under reduced pressure to give a residue. After the residue was triturated with PE/EtOAc (1000 mL, 5/1) for 2 hours, the mixture was filtered, the filter cake was washed with PE/EtOAc (500 mL, 5/1), then the collected filtrate was concentrated to give the crude product. The crude was purified by column chromatography (SiO_2 , PE) to give (6Z, 9Z) -18-bromooctadeca-6, 9-diene (68 g, 91.7% yield). ^1H NMR (400 MHz, CDCl_3) δ 5.46-5.27 (m, 4H), 3.42 (t, J = 6.8 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.11-2.01 (m, 4H), 1.88-1.85 (m, 2H), 1.43 (m, 2H), 1.39-1.28 (m, 14H), 0.95-0.84 (m, 3H).

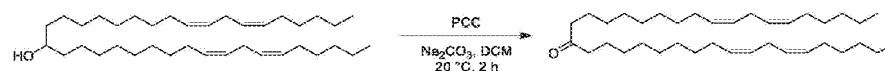
[0113] Step 2: (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-ol



[0114] To a flame dried 250 mL three-neck flask, Mg (3.69 g, 152 mmol) and I_2 (77.1 mg, 304 μmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser. Then 80 mL of THF was added to the flask and the solution of (6Z, 9Z) -18-bromooctadeca-6, 9-diene (10 g, 30.4 mmol) in THF (40 mL) was added slowly to the flask at 20 °C, then the mixture was stirred at 20 °C for 1 hour. Then the mixture was cooled to 0 °C, the solution of ethyl formate (1.01 g, 13.7 mmol, 1.10 mL) in THF (20 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 12 hours. TLC showed (6Z, 9Z) -18-bromooctadeca-6, 9-diene was consumed and one major new spot with lower polarity was detected. The reaction was quenched by adding 2 mL of acetone dropwise followed by ice cold water (20 mL). The reaction mixture was treated with aq. H_2SO_4 (10 % by volume, 30 mL) until the solution became homogeneous and the layers were separated. The mixture was extracted with EtOAc (2×100 mL). The combined ether layers were dried with Na_2SO_4 and concentrated to get the crude product. The crude was stirred with a mixture of EtOH (15 mL), water (2 mL) and KOH (0.56 g) for 1.5 hours. The

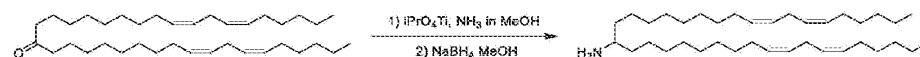
EtOH was evaporated under reduced pressure and the residue treated with EtOAc (50 mL). 5 N HCl (7 mL) was added via dropping funnel. The organic phase was washed with water (2×50 mL), dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0/1 to 3/50) to give (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-ol (2.5 g, 34.6%yield). ¹H NMR (500 MHz, CDCl₃) δ 5.46 -5.30 (m, 8H), 3.60 -3.58 (m, 1H), 2.78 (t, J = 6.5 Hz, 4H), 2.08 -2.03 (m, 8H), 1.47 -1.43 (m, 4H), 1.40 -1.29 (m, 36H), 0.90 (t, J = 7.0 Hz, 6H).

[0115] Step 3: (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-one



[0116] To a solution of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-ol (2.6 g, 4.92 mmol) in DCM (50 mL), PCC (2.65 g, 12.3 mmol) and Na₂CO₃ (261 mg, 2.46 mmol) was added. The mixture was stirred at 20 °C for 2 hours. TLC showed (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-ol was consumed and one major new spot with lower polarity was detected. The mixture was diluted with water (50 mL) and filtered, the filter cake was washed with DCM (100 mL), the filtrate was extracted with DCM (100 mL×3). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0/1 to 1/25) to give (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-one (2.12 g, 81.9%yield). ¹H NMR (400 MHz, CDCl₃) δ 5.47 -5.29 (m, 8H), 2.78 (t, J = 6.4 Hz, 4H), 2.39 (t, J = 7.45 Hz, 4H), 2.12 -1.99 (m, 8H), 1.62 -1.55 (m, 4H), 1.39 -1.27 (m, 32H), 0.90 (t, J = 6.8 Hz, 6H).

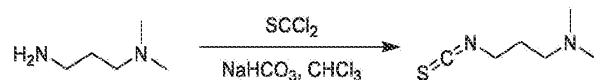
[0117] Step 4: (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine



[0118] Tetraisopropoxytitanium (2.27 g, 7.97 mmol, 2.35 mL) and NH₃/MeOH (12 mL) were added to a solution of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-one (2.1 g, 3.99 mmol) in MeOH (30 mL). After the mixture was stirred at 20 °C for 6 hours, NaBH₄ (302 mg, 7.97 mmol) was added to the mixture at 20 °C, then the mixture was stirred at 20 °C for 16 hours. TLC showed (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-one was consumed and one major new spot with lower polarity was detected. The mixture was quenched with 10%NH₄OH (50 mL) and diluted with EtOAc (50 mL). The mixture was filtered, and the filter cake was washed with EtOAc (2×100 mL). The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography

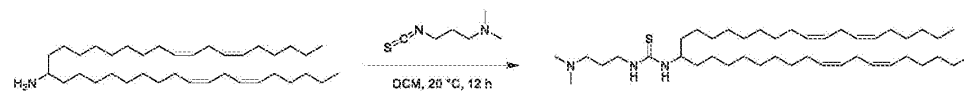
(SiO₂, MeOH: DCM = 0/1 to 3/50) to give (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (1.2 g, 57.0%yield) . ¹H NMR (500 MHz, CDCl₃) δ 5.44 -5.27 (m, 8H) , 2.89 -2.82 (m, 1H) , 2.78 (t, J= 6.5 Hz, 4H) , 2.06 (q, J= 7.5 Hz, 8H) , 1.53 -1.41 (m, 4H) , 1.38 -1.26 (m, 36H) , 0.90 (t, J= 7.0 Hz, 6 H) .

[0119] Step 5: 3-isothiocyanato-N, N-dimethylpropan-1-amine



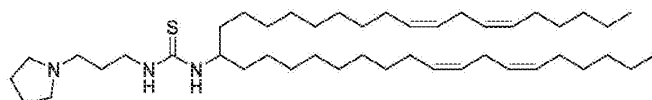
[0120] To a solution of N¹, N¹-dimethylpropane-1, 3-diamine (1 g, 9.79 mmol, 1.22 mL) in DCM (100 mL) , the solution of NaHCO₃ (5.76 g, 68.5 mmol) in water (100 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCl₂ (1.46 g, 12.7 mmol, 975 μL) was added to the mixture, then the mixture was stirred at 20°C for 1 hour. TLC showed N¹, N¹-dimethylpropane-1, 3-diamine was consumed and one major new spot with lower polarity was detected. The mixture was extracted with DCM (100 mL) . The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The solvent was evaporated to give 3-isothiocyanato-N, N-dimethylpropan-1-amine (300 mg, 21.2%yield) . ¹H NMR (400 MHz, CDCl₃) δ 3.61 (t, J= 6.4 Hz, 2H) , 2.42 (t, J= 6.8 Hz, 2H) , 2.26 (s, 6H) , 1.87 (quin, J= 6.8 Hz, 2H) .

[0121] Step 6: 1- (3- (dimethylamino) propyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea

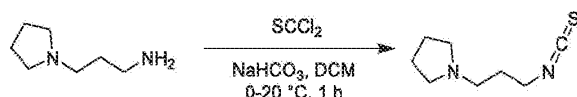


[0122] The mixture of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (230 mg, 436 μmol) and 3-isothiocyanato-N, N-dimethylpropan-1-amine (81.7 mg, 566 μmol) in DCM (5 mL) was stirred at 20 °C for 12 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with aq. HCl (1 N, 10 mL) and sat. NaHCO₃ (20 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, MeOH: DCM = 0/1 to 3/50) to give 1- (3- (dimethylamino) propyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea (148.6 mg, 50.8%yield) . ¹H NMR (400 MHz, DMSO-d₆) δ 7.18 (s, 1 H) , 5.40 -5.24 (m, 8H) , 4.24 (s, 1H) , 3.39 (s, 2H) , 2.73 (t, J= 6.0 Hz, 4H) , 2.48-2.33 (m, 9H) , 2.01 (q, J = 6.4 Hz, 8H) , 1.72 (s, 2H) , 1.38 (s, 4H) , 1.34 -1.21 (m, 36H) , 0.86 (t, J = 6.8 Hz, 6H) . LCMS showed the purity is 100%, Rt = 3.786 min; MS Calcd. : 671.6, MS Found: 673.6 [M+H]⁺ .

- [0123] Example 2: 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (pyrrolidin-1-yl) propyl) thiourea

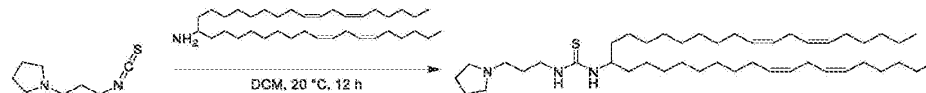


- [0124] Step 1: 1- (3-isothiocyanatopropyl) pyrrolidine



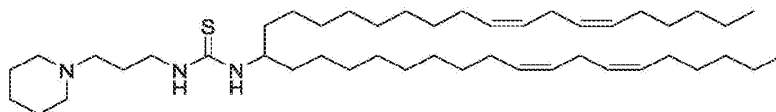
- [0125] To a solution of 3- (pyrrolidin-1-yl) propan-1-amine (500 mg, 3.90 mmol) in DCM (50 mL) , the solution of NaHCO_3 (2.29 g, 27.3 mmol) in H_2O (50 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCCl_2 (583 mg, 5.07 mmol, 389 μL) was added to the mixture, then the mixture was stirred at 20 °C for 1 h. TLC showed 3- (pyrrolidin-1-yl) propan-1-amine was consumed and one major new spot with lower polarity was detected. The mixture was extracted with DCM (100 mL) . The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The solvent was evaporated to give 1- (3-isothiocyanatopropyl) pyrrolidine (300 mg, 45.2% yield) . ^1H NMR (400 MHz, CDCl_3) δ 3.66 (t, J = 6.4 Hz, 2H) , 2.73 (s, 6H) , 2.07 -1.95 (m, 2H) , 1.94 -1.82 (m, 4H) .

- [0126] Step 2: 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (pyrrolidin-1-yl) propyl) thiourea

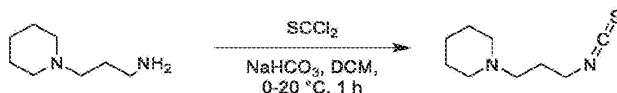


- [0127] The mixture of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (200 mg, 379 μmol) and 1- (3-isothiocyanatopropyl) pyrrolidine (83.9 mg, 492 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with aq. HCl (1 N, 10 mL) and sat. NaHCO_3 (20 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO_2 , MeOH: DCM = 0/1 to 1/20) to give 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (pyrrolidin-1-yl) propyl) thiourea (102 mg, 38.7% yield) . ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.19 (s, 1H) , 7.47 -7.30 (m, 1H) , 5.40 -5.23 (m, 8H) , 4.23 (d, J = 6.8 Hz, 1 H) , 3.43 (s, 2H) , 3.32 (s, 2H) , 3.25 -3.10 (m, 2H) , 3.03 (s, 3H) , 2.73 (t, J = 6.0 Hz, 4H) , 2.01 (q, J = 6.4 Hz, 8H) , 1.94 -1.79 (m, 6H) , 1.41 -1.21 (m, 40H) , 0.86 (t, J = 6.8 Hz, 6H) . LCMS showed the purity is 98.4%, R_t = 4.411 min; MS Calcd. : 697.6, MS Found: 698.7 [$\text{M} + \text{H}$] $^+$.

[0128] Example 3: 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (piperidin-1-yl) propyl) thiourea

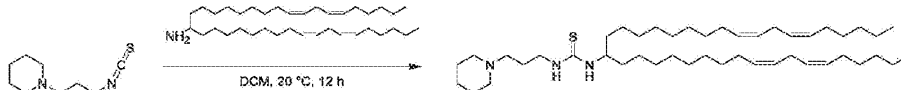


[0129] Step 1: 1- (3-isothiocyanatopropyl) piperidine



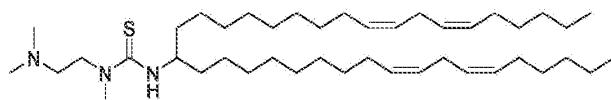
[0130] To a solution of 3- (piperidin-1-yl) propan-1-amine (500 mg, 3.52 mmol) in DCM (50 mL) , the solution of NaHCO₃ (2.07 g, 24.6 mmol) in H₂O (50 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCl₂ (525 mg, 4.57 mmol, 350 μL) was added to the mixture, then the mixture was stirred at 20 °C for 1 h. TLC showed 3- (piperidin-1-yl) propan-1-amine was consumed and one major new spot with lower polarity was detected. The mixture was extracted with DCM (100 mL) . The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The solvent was evaporated to give 1- (3-isothiocyanatopropyl) piperidine (300 mg, 46.3% yield) . ¹H NMR (400 MHz, CDCl₃) δ 3.64 (t, J= 6.4 Hz, 2H) , 2.60 (s, 6H) , 2.07 -1.97 (m, 2H) , 1.74 (s, 4H) , 1.51 (s, 2H) .

[0131] Step 2: 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (piperidin-1-yl) propyl) thiourea

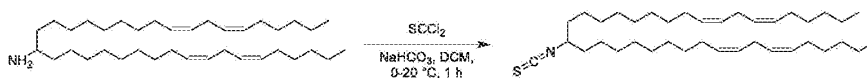


[0132] The mixture of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (200 mg, 379 μmol) and 1- (3-isothiocyanatopropyl) piperidine (90.8 mg, 492 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with aq. HCl (1N, 10 mL) and sat. NaHCO₃ (20 mL) , dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, MeOH: DCM = 0/1 to 1/20) to give 1- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -3- (3- (piperidin-1-yl) propyl) thiourea (82 mg, 30.4% yield) . ¹H NMR (400 MHz, DMSO-d₆) δ 7.36 (s, 1H) , 5.42 -5.24 (m, 8H) , 4.22 (s, 1H) , 3.42 (s, 4H) , 3.00 (s, 2H) , 2.86 (s, 2H) , 2.73 (t, J= 6.0 Hz, 4H) , 2.53 (s, 1H) , 2.47 -2.44 (m, 2H) , 2.01 (q, J= 6.8 Hz, 8H) , 1.91 -1.71 (m, 4H) , 1.67 (s, 2H) , 1.40 -1.22 (m, 40H) , 0.86 (t, J= 6.8 Hz, 6H) . LCMS showed the purity is 100%, Rt = 4.450 min; MS Calcd. : 711.6, MS Found: 712.6 [M+H]⁺.

- [0133] Example 4: 1- (2- (dimethylamino) ethyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -1-methylthiourea

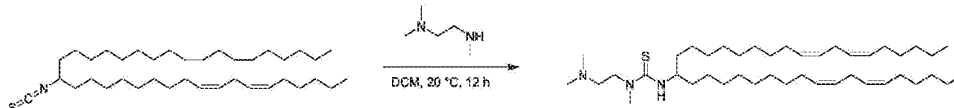


- [0134] Step 1: (6Z, 9Z, 28Z, 31Z) -19-isothiocyanatoheptatriaconta-6, 9, 28, 31-tetraene



- [0135] To a solution of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (600 mg, 1.14 mmol) in DCM (50 mL) , the solution of NaHCO₃ (668 mg, 7.96 mmol) in H₂O (50 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCl₂ (170 mg, 1.48 mmol, 113 μL) was added to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 h. TLC showed (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine was consumed and one major new spot with lower polarity was detected. The mixture was extracted with DCM (100 mL) . The combined organic layer was washed with brine (100 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The solvent was evaporated to give (6Z, 9Z, 28Z, 31Z) -19-isothiocyanatoheptatriaconta-6, 9, 28, 31-tetraene (600 mg, 92.6%yield) . ¹H NMR (500 MHz, CDCl₃) δ 5.45 -5.29 (m, 8H) , 3.67 -3.58 (m, 1H) , 2.79 (t, J= 6.5 Hz, 4H) 2.06 (q, J= 7.0 Hz, 8 H) , 1.67 -1.58 (m, 2H) , 1.52 -1.43 (m, 2H) , 1.40-1.27 (m, 36H) , 0.90 (t, J= 7.0 Hz, 6H) .

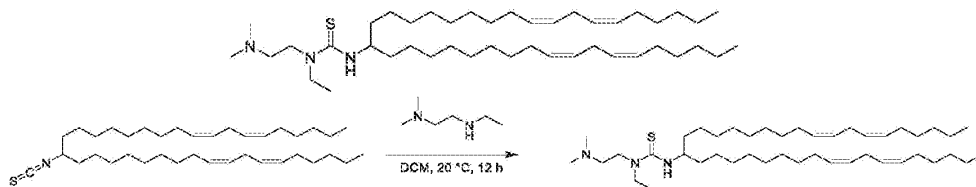
- [0136] Step 2: 1- (2- (dimethylamino) ethyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -1-methylthiourea



- [0137] The mixture of (6Z, 9Z, 28Z, 31Z) -19-isothiocyanatoheptatriaconta-6, 9, 28, 31-tetraene (300 mg, 526 μmol) and N¹, N¹, N²-trimethylethane-1, 2-diamine (69.9 mg, 684 μmol, 88.9 μL) in DCM (10 mL) was stirred at 20 °C for 12 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with aq. HCl (1N, 10 mL) and sat. NaHCO₃ (20 mL) , dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, MeOH: DCM = 0/1 to 1/20) to give 1- (2- (dimethylamino) ethyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) -1-methylthiourea (129 mg, 36.4%yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H) , 5.49 -5.23 (m, 8H) , 4.56 -4.28 (m, 1H) , 3.50 -3.41 (m, 2H) , 3.32 (s, 3H) , 2.78 (t, J= 6.4Hz, 4H) , 2.55 (s, 2H) , 2.36 -2.19 (m, 6H) , 2.10 -1.99

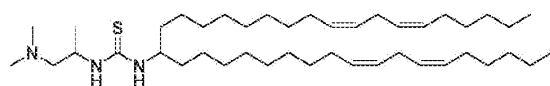
(m, 8H) , 1.59-1.50 (m, 2H) , 1.48 -1.40 (m, 2H) , 1.37 -1.23 (m, 36H) , 0.89 (t, J= 6.8 Hz, 6H) . LCMS showed the purity is 100%, Rt = 3.125 min; MS Calcd. : 671.6, MS Found: 672.7 [M+H]⁺.

[0138] Example 5: 1- (2- (dimethylamino) ethyl) -1-ethyl-3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea

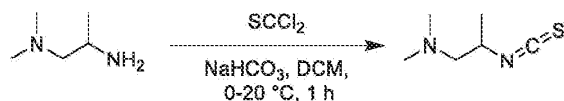


[0139] A mixture of (6Z, 9Z, 28Z, 31Z) -19-isothiocyanatoheptatriaconta-6, 9, 28, 31-tetraene (300 mg, 526 μ mol) and N¹-ethyl-N², N²-dimethylethane-1, 2-diamine (79.5 mg, 684 μ mol, 108 μ L) in DCM (10 mL) was stirred at 20 °C for 12 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with aq. HCl (1N, 10 mL) and sat. NaHCO₃ (20 mL) , dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, MeOH: DCM = 0/1 to 1/20) to give 1- (2- (dimethylamino) ethyl) -1-ethyl-3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea (141 mg, 39.1%yield) . ¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1 H) , 5.46 -5.27 (m, 8H) , 4.52 -4.37 (m, 1H) , 3.85 (d, J= 6.8 Hz, 2H) , 3.51 -3.30 (m, 2H) , 2.78 (t, J= 6.4 Hz, 4H) , 2.53 (s, 2H) , 2.30 (s, 6H) , 2.10 -1.96 (m, 8H) , 1.60 -1.50 (m, 2H) , 1.45 (d, J=6.8 Hz, 2H) , 1.39 -1.26 (m, 36H) , 1.22 (t, J= 7.2 Hz, 3H) , 0.90 (t, J= 6.8 Hz, 6H) . LCMS showed the purity is 100%, Rt = 4.437 min; MS Calcd. : 685.6, MS Found: 686.7 [M+H]⁺.

[0140] Example 6: 1- (1- (dimethylamino) propan-2-yl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea



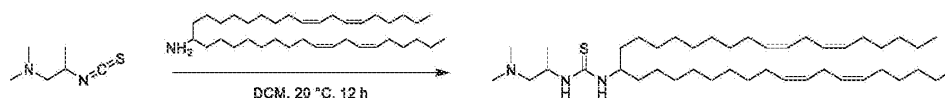
[0141] Step 1: 2-isothiocyanato-N, N-dimethylpropan-1-amine



[0142] To a mixture of N¹, N¹-dimethylpropane-1, 2-diamine (300 mg, 2.94 mmol) in DCM (25 mL) , the solution of NaHCO₃ (1.73 g, 20.5 mmol) in H₂O (25 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCl₂ (439 mg, 3.82 mmol, 293 μ L) was added to the mixture, then the mixture was stirred at 20°C for 1 h. TLC showed N¹, N¹-dimethylpropane-1, 2-diamine was consumed and one major new spot with lower

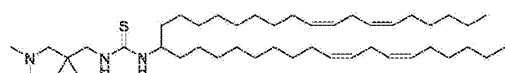
polarity was detected. The mixture was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The solvent was evaporated to give 2-isothiocyanato-N, N-dimethylpropan-1-amine (190 mg, 44.9% yield). ^1H NMR (400 MHz, CDCl_3) δ 3.93 -3.80 (m, 1H), 2.55 (m, 1H), 2.41 -2.32 (m, 1H), 2.30 (s, 6H), 1.35 (d, J = 6.4 Hz, 3H).

[0143] Step 2: 1- (1- (dimethylamino) propan-2-yl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea

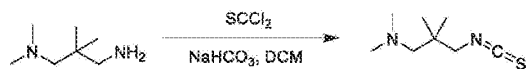


[0144] A mixture of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (200 mg, 379 μmol) and 2-isothiocyanato-N, N-dimethylpropan-1-amine (71.0 mg, 492 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours, then the mixture was stirred at 40 °C for 5 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL), washed with aq. HCl (1 N, 10 mL) and sat. NaHCO_3 (20 mL), dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO_2 , MeOH: DCM = 0/1 to 1/20) to give 1- (1- (dimethylamino) propan-2-yl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea (126 mg, 49.3% yield). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.32 (s, 1H), 6.96 (s, 1H), 5.39 -5.28 (m, 8H), 4.30 -4.19 (m, 1H), 2.74 (t, J = 6.5 Hz, 4H), 2.53 (d, J = 2.0 Hz, 2H), 2.48 -2.10 (m, 7H), 2.02 (q, J = 7.0 Hz, 8H), 1.46 -1.35 (m, 4H), 1.35 -1.23 (m, 36H), 1.08 (d, J = 6.5 Hz, 3H), 0.86 (t, J = 7.0 Hz, 6H). LCMS showed the purity is 98.2%, R_t = 4.393 min; MS Calcd.: 671.6, MS Found: 672.7 $[\text{M}+\text{H}]^+$.

[0145] Example 7: 1- (3- (dimethylamino) -2, 2-dimethylpropyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea



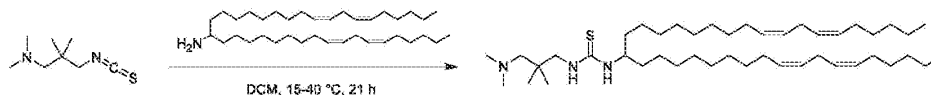
[0146] Step 1: 3-isothiocyanato-N, N, 2, 2-tetramethylpropan-1-amine



[0147] To a mixture of N^1 , N^1 , 2, 2-tetramethylpropane-1, 3-diamine (500 mg, 3.84 mmol, 610 μL) in DCM (50 mL), the solution of NaHCO_3 (2.26 g, 26.9 mmol) in H_2O (50 mL) was added. After the mixture was stirred at 0 °C for 0.1 h, SCl_2 (574 mg, 4.99 mmol, 383 μL) was added to the mixture, then the mixture was stirred at 20 °C for 1 h. TLC showed N^1 , N^1 , 2, 2-tetramethylpropane-1, 3-diamine was consumed and one

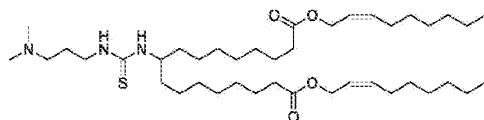
major new spot with lower polarity was detected. The mixture was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The solvent was evaporated to give 3-isothiocyanato-N, N, 2, 2-tetramethylpropan-1-amine (560 mg, 84.7% yield). ^1H NMR (400 MHz, CDCl_3) δ 3.42 (s, 2H), 2.32 (s, 6H), 2.20 (s, 2H), 0.96 (s, 6H).

[0148] Step 2: 1- (3- (dimethylamino) -2, 2-dimethylpropyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea

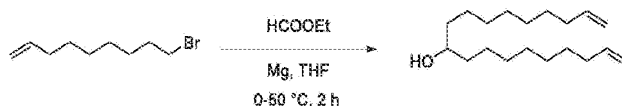


[0149] A mixture of (6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-amine (200 mg, 379 μmol) and 3-isothiocyanato-N, N, 2, 2-tetramethylpropan-1-amine (84.9 mg, 492 μmol) in DCM (10 mL) was stirred at 15 °C for 12 hours. LCMS showed that desired mass was detected, starting material remained. Another 50 mg of 3-isothiocyanato-N, N, 2, 2-tetramethylpropan-1-amine was added. The mixture was stirred at 15 °C for 8 hours and 40 °C for 1 hour. LCMS showed that desired mass was detected, starting material was consumed completely. TLC showed that one main spot was observed. The mixture was quenched with aq. HCl (1 N, 15 mL) and extracted with DCM (30 mL $\times$ 2). The combined organic phase was washed with sat. NaHCO_3 (20 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO_2 , MeOH: DCM = 0/1 to 1/16) to 1- (3- (dimethylamino) -2, 2-dimethylpropyl) -3- ((6Z, 9Z, 28Z, 31Z) -heptatriaconta-6, 9, 28, 31-tetraen-19-yl) thiourea (155.7 mg, 59% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.03 (br s, 1H), 5.69 (br s, 1H), 5.45-5.27 (m, 8H), 3.69-3.16 (m, 3H), 2.78 (t, J = 6.4 Hz, 4H), 2.31 (br s, 8H), 2.13-2.01 (m, 8H), 1.57-1.48 (m, 4H), 1.41-1.27 (m, 36H), 0.98 (s, 6H), 0.90 (t, J = 6.8 Hz, 6H). LCMS showed the purity is 100.00%, R_t = 4.534 min; MS Calcd.: 699.7, MS Found: 700.8 $[\text{M}+\text{H}]^+$.

[0150] Example 8: di ((Z) -non-2-en-1-yl) 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate

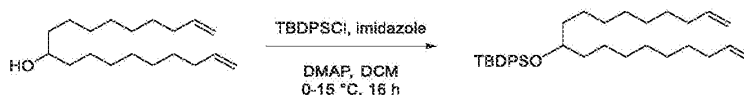


[0151] Step 1: nonadeca-1, 18-dien-10-ol



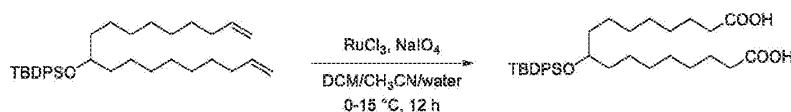
- [0152] To a flame dried 500 mL three-neck bottle, freshly activated Mg (14.2 g, 585 mmol) and I₂ (10.0 mg, 39.4 μmol) were added, and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, and flushed with N₂. THF (30 mL) was added to the flask via syringe. 9-bromonon-1-ene (40.0 g, 195 mmol) was dissolved in THF (100 mL) and added to the addition funnel. About 10 mL of this above solution was added to the Mg turnings while stirring vigorously. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux. After the completion of the addition the reaction mixture was kept at 50 °C for 1 h and then cooled in ice-bath. Ethyl formate (6.50 g, 87.8 mmol, 7.06 mL) in THF (100 mL) transferred to the addition funnel and added dropwise to the reaction mixture with stirring at 0 °C. An exothermic reaction was observed. After the initiation of the reaction the rest of the solution of ethyl formate was quickly added as a stream and the reaction mixture was stirred for 1 h at 50 °C to give a brown suspension. TLC showed that one main spot was observed. The reaction was quenched by adding acetone (50 mL) under ice-bath. The reaction mixture was treated with aq. H₂SO₄ (10 % by volume, 400 mL) slowly until the solution became homogeneous and the layers were separated. The aqueous phase was extracted with EtOAc (300 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo to give nonadeca-1, 18-dien-10-ol (24 g, crude). The crude was used into next step directly. ¹H NMR (400 MHz, CDCl₃) δ5.88-5.76 (m, 2H), 5.12-4.90 (m, 4H), 3.62-3.55 (m, 1H), 2.11-2.00 (m, 4H), 1.49-1.28 (m, 24H).

- [0153] Step 2: tert-butyl (nonadeca-1, 18-dien-10-yloxy) diphenylsilane



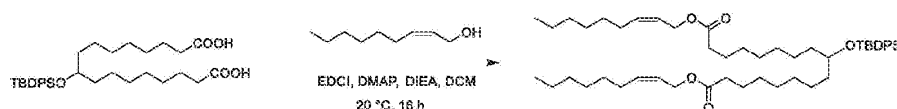
- [0154] To a solution of nonadeca-1, 18-dien-10-ol (22.0 g, 78.4 mmol) in DCM (200 mL), imidazole (21.4 g, 314 mmol), DMAP (1.92 g, 15.7 mmol) and TBDPSCl (43.1 g, 157 mmol) was added at 0 °C. The resulting reaction mixture was stirred at 15 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with saturated NaHCO₃ (400 mL) and diluted with DCM (200 mL). The organic phase was separated and washed with brine (200 mL), dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 19: 1) to give tert-butyl (nonadeca-1, 18-dien-10-yloxy) diphenylsilane (44 g, crude). ¹H NMR (500 MHz, CDCl₃) δ7.70-7.66 (m, 4H), 7.43-7.34 (m, 6H), 5.88-5.76 (m, 2H), 5.05-4.91 (m, 4H), 3.74-3.68 (m, 1H), 2.05-2.00 (m, 4H), 1.44-1.33 (m, 8H), 1.25-1.10 (m, 16H), 1.06 (s, 9H).

[0155] Step 3: 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioic acid



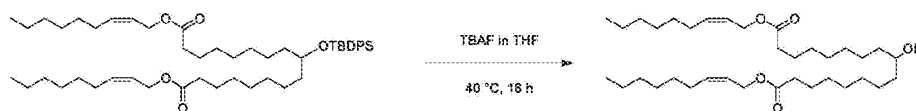
[0156] To a mixture of tert-butyl (nonadeca-1, 18-dien-10-yloxy) diphenylsilane (11.0 g, 21.2 mmol) in DCM (250 mL) and CH₃CN (300 mL), RuCl₃ (879 mg, 4.24 mmol) under N₂ atmosphere was added, then a solution of NaIO₄ (45.3 g, 212 mmol) in water (300 mL) was added to the mixture dropwise at 0 °C. The resulting reaction mixture was stirred at 15 °C for 12 hours. TLC showed that starting material was consumed completely. The reaction mixture was diluted with brine (200 mL) and treated with 1 N HCl aqueous solution until pH = 6. Then the mixture was extracted with DCM (500 mL × 3). The combined organic phase was washed with brine (500 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 1: 1) to give 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioic acid (10.0 g, 85% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.71 -7.63 (m, 4H), 7.45 -7.33 (m, 6H), 3.74 -3.67 (m, 1H), 2.34 (t, J = 7.2 Hz, 4H), 1.68 -1.56 (m, 4H), 1.46 -1.34 (m, 4H), 1.31 -1.09 (m, 16H), 1.05 (s, 9H).

[0157] Step 4: di ((Z)-non-2-en-1-yl) 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate



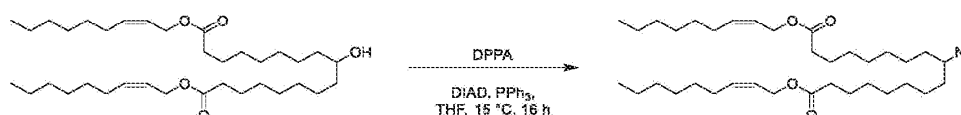
[0158] To a solution of 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioic acid (7.5 g, 13.5 mmol) in DCM (100 mL), (Z)-non-2-en-1-ol (3.85 g, 27.0 mmol), DMAP (6.61 g, 54.1 mmol) and EDCI (10.4 g, 54.1 mmol) was added. The mixture was stirred at 20 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was diluted with saturated NaHCO₃ (80 mL). The mixture was extracted with DCM (80 mL × 3). The combined organic phase was washed with brine (60 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 10: 1) to give di ((Z)-non-2-en-1-yl) 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (3.8 g, 35% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.69 -7.65 (m, 4H), 7.44 -7.33 (m, 6H), 5.70 -5.61 (m, 2H), 5.57 -5.50 (m, 2H), 4.63 (d, J = 7.0 Hz, 4H), 3.74 -3.66 (m, 1H), 2.28 (t, J = 7.5 Hz, 4H), 2.11 (q, J = 7.5 Hz, 4H), 1.63 -1.57 (m, 4H), 1.42 -1.09 (m, 36H), 1.05 (s, 9H), 0.92 -0.86 (m, 6H).

[0159] Step 5: di ((Z)-non-2-en-1-yl) 9-hydroxyheptadecanedioate



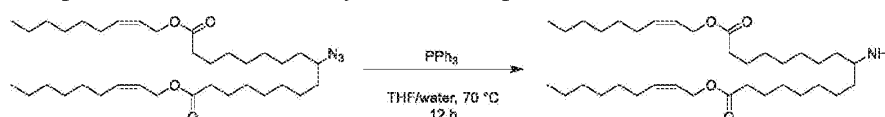
- [0160] To a solution of di ((Z) -non-2-en-1-yl) 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (3.4 g, 4.23 mmol) in THF (20 mL) , 21.2 mL of TBAF (1 M) was added. The mixture was stirred at 40 °C for 16 hours. TLC showed that one new spot was observed. The mixture was diluted with water (100 mL) and extracted with PE (100 mL × 2) . The combined organic phase was dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 5: 1) to give di ((Z) -non-2-en-1-yl) 9-hydroxyheptadecanedioate (1.44 g, 60%yield) . ¹H NMR (400 MHz, CDCl₃) δ5.71 -5.60 (m, 2H) , 5.59 -5.49 (m, 2H) , 4.63 (d, J = 6.8 Hz, 4H) , 3.62 -3.54 (m, 1H) , 2.31 (t, J = 8.0 Hz, 4H) , 2.14 -2.06 (m, 4H) , 1.69-1.58 (m, 4H) , 1.50 -1.24 (m, 36H) , 0.96 -0.86 (m, 6H) .

- [0161] Step 6: di ((Z) -non-2-en-1-yl) 9-azidoheptadecanedioate



- [0162] To a solution of di ((Z) -non-2-en-1-yl) 9-hydroxyheptadecanedioate (840 mg, 1.49 mmol) in THF (30 mL) , PPh₃ (780 mg, 2.97 mmol) and DIAD (601 mg, 2.97 mmol, 577 μL) was added at 15 °C under N₂ atmosphere. After stirring at 15 °C for 10 min, DPPA (818 mg, 2.97 mmol, 642 μL) was added. The mixture was stirred at 15 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 10: 1) to give di ((Z) -non-2-en-1-yl) 9-azidoheptadecanedioate (470 mg, 54%yield) . ¹H NMR (500 MHz, CDCl₃) δ5.70-5.62 (m, 2H) , 5.57 -5.50 (m, 2H) , 4.63 (d, J = 6.5 Hz, 4H) , 3.25 -3.18 (m, 1H) , 2.32 (t, J = 7.0 Hz, 4H) , 2.11 (q, J=6.8 Hz, 4H) , 1.69 -1.59 (m, 4H) , 1.53 -1.47 (m, 4H) , 1.40 -1.24 (m, 32H) , 0.92 -0.86 (m, 6H) .

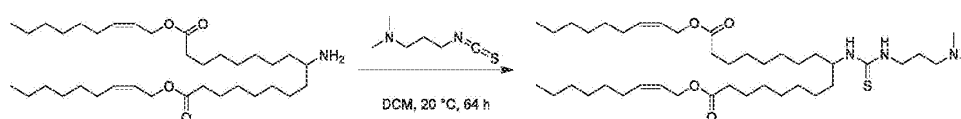
- [0163] Step 7: di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate



- [0164] To a mixture of di ((Z) -non-2-en-1-yl) 9-azidoheptadecanedioate (530 mg, 898 μmol) in THF (20 mL) and water (5 mL) , PPh₃ (353 mg, 1.35 mmol) was added under N₂ atmosphere. The mixture was stirred at 70 °C for 12 hours. TLC showed that starting material was consumed completely. The reaction mixture was diluted

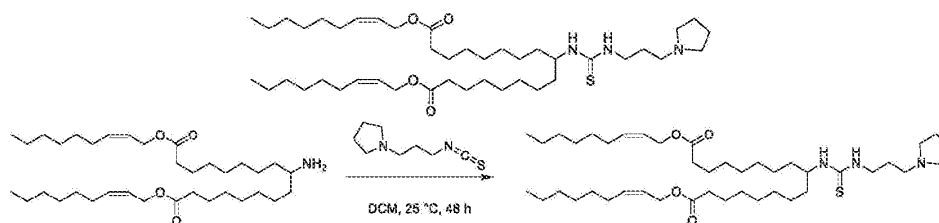
with water (50 mL) and extracted with EtOAc (80 mL $\times$ 2). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO_2 , PE: EtOAc = 1: 0 to 1: 1) to give di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate (280 mg, 55%yield). ^1H NMR (400 MHz, CDCl_3) δ 5.69-5.61 (m, 2H), 5.57-5.49 (m, 2H), 4.63 (d, J = 6.8 Hz, 4H), 2.66 (br s, 1H), 2.31 (t, J = 7.6 Hz, 4H), 2.10 (q, J = 7.2 Hz, 4H), 1.68-1.58 (m, 4H), 1.43-1.16 (m, 36H), 0.89 (t, J = 6.8 Hz, 6H).

[0165] Step 8: di ((Z) -non-2-en-1-yl) 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate



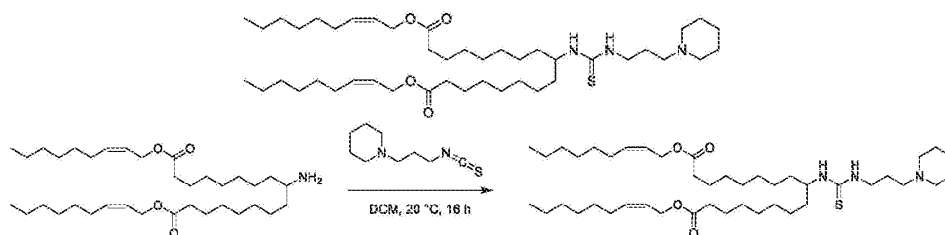
[0166] A mixture of di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate (140 mg, 248.27 μmol) and 3-isothiocyanato-N, N-dimethyl-propan-1-amine (71.6 mg, 497 μmol) in DCM (5 mL) was stirred at 20 °C for 48 hours. LCMS showed that desired mass was detected but starting material remained. 50 mg of 3-isothiocyanato-N, N-dimethyl-propan-1-amine was added. The mixture was stirred at 20 °C for another 16 hours. LCMS showed that desired mass was detected. The mixture was quenched with aq. HCl (1 N, 3 mL) and diluted with water (20 mL). Then the mixture was extracted with DCM (50 mL $\times$ 2). The combined organic phase was washed with saturated NaHCO_3 (20 mL), brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z) -non-2-en-1-yl) 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate (66.9 mg, 38%yield). ^1H NMR (400 MHz, CDCl_3) δ 5.72-5.58 (m, 2H), 5.58-5.48 (m, 2H), 4.63 (d, J = 6.8 Hz, 4H), 4.05-3.6 (m, 3H), 2.58 (br s, 2H), 2.42-2.22 (m, 10H), 2.10 (q, J = 7.2 Hz, 4H), 1.82 (s, 2H), 1.62 (t, J = 7.2 Hz, 4H), 1.52-1.17 (m, 36H), 0.99-0.79 (m, 6H). LCMS showed the purity is 99.50%, R_t = 5.165 min; MS Calcd.: 707.6, MS Found: 708.4 $[\text{M}+\text{H}]^+$.

[0167] Example 9: di ((Z) -non-2-en-1-yl) 9- (3- (3- (pyrrolidin-1-yl) propyl) thioureido) heptadecanedioate



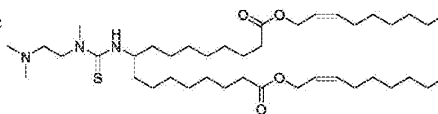
[0168] A mixture of di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate (120 mg, 213 μ mol) and 1- (3-isothiocyanatopropyl) -pyrrolidine (72.5 mg, 426) in DCM (5 mL) was stirred at 20 °C for 48 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The mixture was quenched with 1 N HCl (2 mL) and diluted with water (20 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO₃ (20 mL) , brine (50 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z) -non-2-en-1-yl) 9- (3- (3- (pyrrolidin-1-yl) propyl) thioureido) heptadecanedioate (89.1 mg, 57%yield) . ¹H NMR (400MHz, CDCl₃) δ 5.69 -5.61 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.62 (d, J = 6.8 Hz, 4H) , 4.01 -3.25 (m, 3H) , 2.95 -2.62 (m, 6H) , 2.30 (t, J = 7.6 Hz, 4H) , 2.10 (q, J = 7.2 Hz, 4H) , 1.93 (s, 6H) , 1.69 -1.57 (m, 4H) , 1.55 -1.21 (m, 36H) , 0.96 -0.84 (m, 6H) . LCMS showed the purity is 100.00%, Rt = 4.831 min; MS Calcd. : 733.6, MS Found: 734.5 [M+H]⁺.

[0169] Example 10: di ((Z) -non-2-en-1-yl) 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate

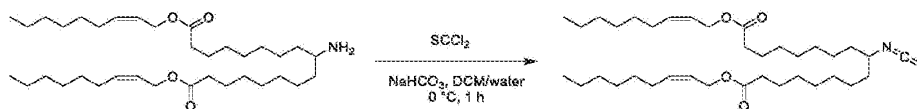


[0170] A mixture of di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate (150 mg, 266 μ mol) and 1- (3-isothiocyanatopropyl) piperidine (73.5 mg, 399 μ mol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed desired mass was detected. The mixture was diluted with DCM (20 mL) , washed with HCl (1 N, 10 mL) and saturated NaHCO₃ (20 mL) , dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, MeOH: DCM = 0/1 to 3/50) to give di ((Z) -non-2-en-1-yl) 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate (149 mg, 75%yield) . ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H) , 6.78 (s, 1H) , 5.67 -5.61 (m, 2H) , 5.56 -5.48 (m, 2H) , 4.62 (d, J= 6.8 Hz, 4H) , 4.45 -4.05 (m, 1H) , 3.76 (s, 2H) , 2.98 (s, 6H) , 2.29 (t, J= 7.6 Hz, 4H) , 2.10 (q, J= 7.2 Hz, 6H) , 2.00 (d, J= 12.4 Hz, 4H) , 1.64-1.57 (m, 4H) , 1.53 -1.24 (m, 38H) , 0.92 -0.84 (m, 6H) . LCMS showed the purity is 99.89%, Rt = 1.349 min; MS Calcd. : 747.6, MS Found: 748.5 [M+H]⁺.

[0171] Example 11: di ((Z) -non-2-en-1-yl) 9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate

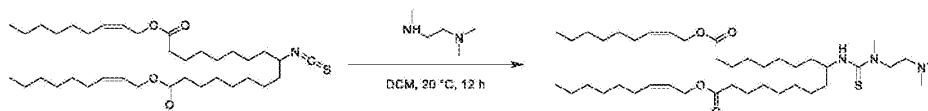


[0172] Step 1: di ((Z) -non-2-en-1-yl) 9-isothiocyanatoheptadecanedioate



[0173] To a solution of di ((Z) -non-2-en-1-yl) 9-aminoheptadecanedioate (100 mg, 177 μ mol) in DCM (10 mL) , a solution of NaHCO_3 (104 mg, 1.24 mmol) in water (5 mL) was added, then thiocarbonyl dichloride (408 mg, 355 μ mol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. TLC showed that starting material was consumed completely. Then the reaction mixture was extracted with DCM (30 mL $\times$ 2) . The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The solvent was concentrated in vacuo to give di ((Z) -non-2-en-1-yl) 9-isothiocyanatoheptadecanedioate (107 mg, crude) . The crude product was used into next step directly. ^1H NMR (400MHz, CDCl_3) δ 5.70-5.61 (m, 2H) , 5.58 -5.51 (m, 2H) , 4.63 (d, J = 6.4 Hz, 4H) , 3.66 -3.57 (m, 1H) , 2.32 (t, J = 7.6 Hz, 4H) , 2.11 (q, J = 7.2 Hz, 4H) , 1.69 -1.54 (m, 4H) , 1.53 -1.19 (m, 36H) , 0.97 -0.81 (m, 6H) .

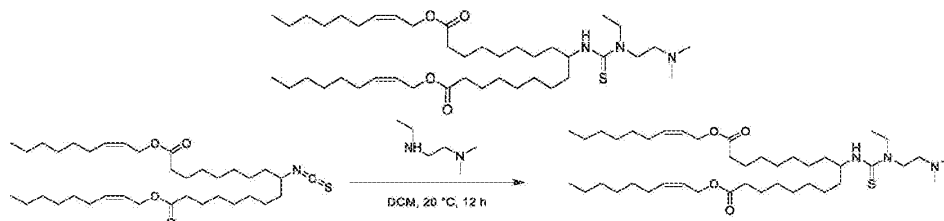
[0174] Step 2: di ((Z) -non-2-en-1-yl) 9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate



[0175] A mixture of di ((Z) -non-2-en-1-yl) 9-isothiocyanatoheptadecanedioate (107 mg, 177 μ mol) and N, N', N'-trimethylethane-1, 2-diamine (36.1 mg, 353 μ mol) in DCM (5 mL) was stirred at 20 °C for 12 hours. TLC showed that several spots were observed. The mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z) -non-2-en-1-yl) 9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate (144.8 mg, 79%yield) . ^1H NMR (400 MHz, CDCl_3) δ 8.91 (br s, 1H) , 5.70 -5.60 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.62 (d, J = 6.8 Hz, 4H) , 4.48 -4.31 (m, 1H) , 3.43 (br s, 2H) , 3.32 (s, 3H) , 2.52 (br s, 2H) , 2.37 -2.24 (m, 10H) , 2.10 (q, J = 7.2 Hz,

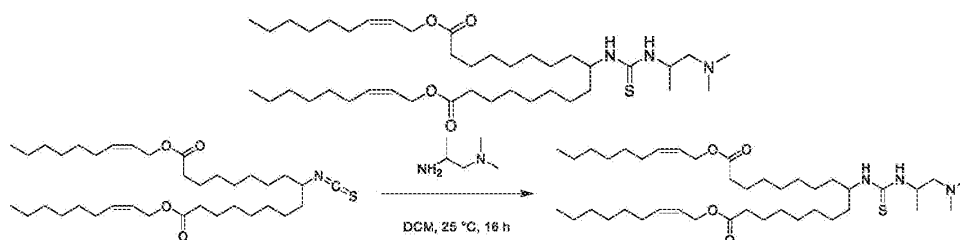
4H) , 1.67 -1.58 (m, 4H) , 1.56 -1.50 (m, 2H) , 1.46 -1.21 (m, 34H) , 0.97 -0.80 (m, 6H) . LCMS showed the purity is 100.00%, Rt = 5.167 min; MS Calcd. : 707.6, MS Found: 708.5 [M+H]⁺.

[0176] Example 12: di ((Z) -non-2-en-1-yl) 9- (3- (2- (dimethylamino) ethyl) -3-ethylthioureido) heptadecanedioate



[0177] A mixture of di ((Z) -non-2-en-1-yl) 9-isothiocyanatoheptadecanedioate (160 mg, 264 μ mol) and N-ethyl-N', N'-dimethyl-ethane-1, 2-diamine (61.4 mg, 528 μ mol) in DCM (5 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The mixture was quenched with 1 N HCl (3 mL) and diluted with water (20 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO₃ (20 mL) and brine (50 mL) , dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z) -non-2-en-1-yl) 9- (3- (2- (dimethylamino) ethyl) -3-ethylthioureido) heptadecanedioate (126.6 mg, 66%yield) . ¹H NMR (400 MHz, CDCl₃) δ 9.14 (br s, 1H) , 5.71 -5.60 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.62 (d, J = 6.8 Hz, 4H) , 4.46 -4.35 (m, 1H) , 3.86 (q, J = 7.2 Hz, 2H) , 3.42 -3.33 (m, 2H) , 2.55 -2.46 (m, 2H) , 2.33 -2.23 (m, 10H) , 2.10 (q, J = 7.2 Hz, 4H) , 1.68 -1.59 (m, 4H) , 1.55 -1.49 (m, 2H) , 1.45 -1.26 (m, 34H) , 1.22 (t, J = 7.2 Hz, 3H) , 0.92 -0.85 (m, 6H) . LCMS showed the purity is 100.00%, Rt = 4.832 min; MS Calcd. : 721.6, MS Found: 722.5 [M+H]⁺.

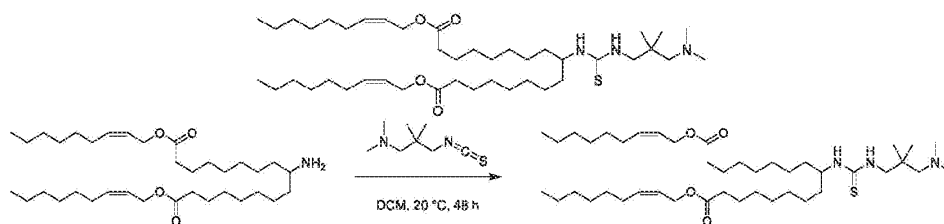
[0178] Example 13: di ((Z) -non-2-en-1-yl) 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate



[0179] A mixture of di ((Z) -non-2-en-1-yl) 9-isothiocyanatoheptadecanedioate (118 mg, 195 μ mol) and N¹, N¹-dimethylpropane-1, 2-diamine (39.8 mg, 389 μ mol) in DCM (5 mL) was stirred at 25 °C for 16 hours. LCMS showed that desired mass was

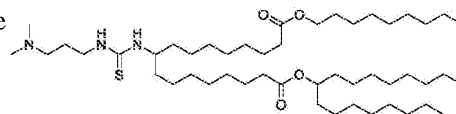
detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (3 mL) and diluted with water (30 mL). Then the mixture was extracted with DCM (50 mL $\times$ 2). The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z)-non-2-en-1-yl) 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate (94.7 mg, 69% yield). ^1H NMR (400 MHz, CDCl_3) δ 10.04 (br s, 1H), 5.74 (br s, 1H), 5.69-5.61 (m, 2H), 5.57-5.48 (m, 2H), 4.63 (d, J = 6.8 Hz, 4H), 4.25 (br s, 1H), 3.64 (br s, 1H), 2.55 (br s, 1H), 2.36-2.25 (m, 10H), 2.25-2.20 (m, 1H), 2.10 (q, J = 7.2 Hz, 4H), 1.69-1.57 (m, 4H), 1.56-1.44 (m, 2H), 1.41-1.24 (m, 34H), 1.21 (d, J = 6.8 Hz, 3H), 0.92-0.86 (m, 6H). LCMS showed the purity is 100.00%, R_t = 5.498 min; MS Calcd.: 707.6, MS Found: 708.5 $[\text{M}+\text{H}]^+$.

[0180] Example 14: di ((Z)-non-2-en-1-yl) 9- (3- (3- (dimethylamino) -2, 2-dimethylpropyl) thioureido) heptadecanedioate

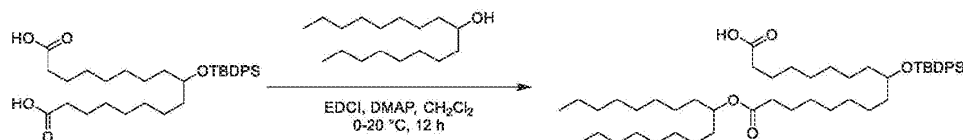


[0181] A mixture of di ((Z)-non-2-en-1-yl) 9-aminoheptadecanedioate (140 mg, 248 μmol) and 3-isothiocyanato-N, N, 2, 2-tetramethyl-propan-1-amine (85.6 mg, 497 μmol) in DCM (5 mL) was stirred at 20 °C for 48 hours. TLC showed that several spots were observed. The mixture was quenched with 1 N HCl (3 mL) and diluted with water (20 mL). Then the mixture was extracted with DCM (50 mL $\times$ 2). The combined organic phase was washed with saturated NaHCO_3 (20 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give di ((Z)-non-2-en-1-yl) 9- (3- (3- (dimethylamino) -2, 2-dimethylpropyl) thioureido) heptadecanedioate (118.1 mg, 65% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.04 (br s, 1H), 5.70-5.60 (m, 2H), 5.58-5.47 (m, 4H), 4.62 (d, J = 6.8 Hz, 4H), 3.66-3.16 (m, 3H), 2.37-2.26 (m, 12H), 2.10 (q, J = 7.2 Hz, 4H), 1.67-1.48 (m, 4H), 1.46-1.22 (m, 36H), 0.98 (s, 6H), 0.92-0.86 (m, 6H). LCMS showed the purity is 100.0%, R_t = 5.291 min; MS Calcd.: 735.6, MS Found: 736.6 $[\text{M}+\text{H}]^+$.

- [0182] Example 15: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate

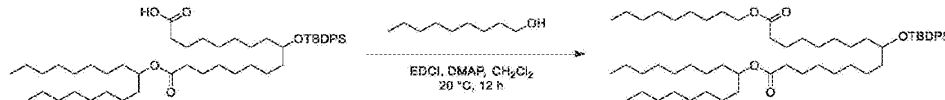


- [0183] Step 1: 9- ((tert-butyldiphenylsilyl) oxy) -17- (heptadecan-9-yloxy) -17-oxoheptadecanoic acid



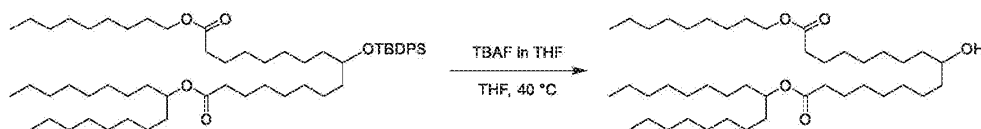
- [0184] To a mixture of 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioic acid (9 g, 16.2 mmol) , EDCI (2.24 g, 11.7 mmol) and DMAP (1.43 g, 11.7 mmol) in DCM (200 mL) , a solution of heptadecan-9-ol (2 g, 7.80 mmol, 1 eq) in DCM (100 mL) was added at 0 °C dropwise. The mixture was stirred at 20 °C for 12 hours. TLC showed that one new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 4: 1) to give 9- ((tert-butyldiphenylsilyl) oxy) -17- (heptadecan-9-yloxy) -17-oxoheptadecanoic acid (3.8 g, 61% yield) . ¹H NMR (400MHz, CDCl₃) δ7.71-7.64 (m, 4H) , 7.46 -7.31 (m, 6H) , 4.91 -4.83 (m, 1H) , 3.74 -3.66 (m, 1H) , 2.33 (t, J = 7.2 Hz, 2H) , 2.26 (t, J = 7.6 Hz, 2H) , 1.62 -1.55 (m, 4H) , 1.654 -1.47 (m, 4H) , 1.44 -1.36 (m, 4H) , 1.32 -1.10 (m, 40H) , 1.05 (s, 9H) , 0.88 (t, J = 6.8 Hz, 6H) .

- [0185] Step 2: 1- (heptadecan-9-yl) 17-nonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate



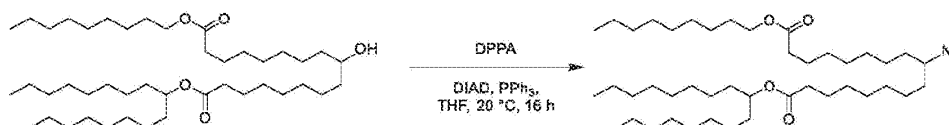
- [0186] A mixture of 9- ((tert-butyldiphenylsilyl) oxy) -17- (heptadecan-9-yloxy) -17-oxoheptadecanoic acid (3 g, 3.78 mmol) , nonan-1-ol (1.09 g, 7.56 mmol) , EDCI (1.45 g, 7.56 mmol) and DMAP (924 mg, 7.56 mmol) in DCM (50 mL) was stirred at 20 °C for 12 hours. TLC showed that one new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 10: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (3.2 g, 92% yield) . ¹H NMR (400 MHz, CDCl₃) δ7.72-7.64 (m, 4H) , 7.45 -7.32 (m, 6H) , 4.90 -4.83 (m, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 3.73 -3.66 (m, 1H) , 2.29 -2.23 (m, 4H) , 1.68 -1.58 (m, 4H) , 1.55 -1.48 (m, 4H) , 1.44 -1.09 (m, 58H) , 1.05 (s, 9H) , 0.92-0.84 (m, 9H) .

- [0187] Step 3: 1- (heptadecan-9-yl) 17-nonyl 9-hydroxyheptadecanedioate



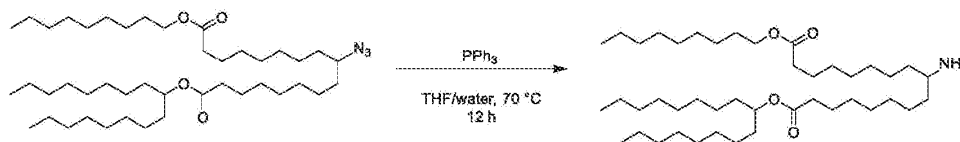
- [0188] To a solution of 1- (heptadecan-9-yl) 17-nonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (3.2 g, 3.48 mmol) in THF (50 mL) , 17.4 mL of TBAF (1 M) was added. Then the mixture was stirred at 40 °C for 36 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with water (50 mL) and saturated NaHCO_3 (50 mL) . Then the mixture was extracted with EtOAc (150 mL $\times$ 2) . The combined organic phase was washed with brine (80 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO_2 , PE: EtOAc = 1: 0 to 4: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9-hydroxyheptadecanedioate (2.3 g, 97%yield) . ^1H NMR (400 MHz, CDCl_3) δ 4.91 -4.83 (m, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 3.58 (br s, 1H) , 2.33 -2.25 (m, 4H) , 1.68 -1.58 (m, 6H) , 1.54 -1.48 (m, 4H) , 1.46 -1.20 (m, 56H) , 0.92 -0.84 (m, 9H) .

- [0189] Step 4: 1- (heptadecan-9-yl) 17-nonyl 9-azidoheptadecanedioate



- [0190] To a solution of give 1- (heptadecan-9-yl) 17-nonyl 9-hydroxyheptadecanedioate (2.3 g, 3.38 mmol) in THF (80 mL) , PPh_3 (1.77 g, 6.75 mmol) and DIAD (1.37 g, 6.75 mmol, 1.3 mL) was added. After stirring at 20 °C for 10 min, DPPA (1.86 g, 6.75 mmol, 1.5 mL) was added and the mixture was stirred at 20 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2 , PE: EtOAc = 1: 0 to 4: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9-azidoheptadecanedioate (1.6 g, 67%yield) . ^1H NMR (400 MHz, CDCl_3) δ 4.92 -4.83 (m, 1H) , 4.07 (t, J = 6.8 Hz, 2H) , 3.26 -3.18 (m, 1H) , 2.33 -2.25 (m, 4H) , 1.67-1.58 (m, 6H) , 1.54 -1.47 (m, 8H) , 1.38 -1.22 (m, 52H) , 0.91 -0.87 (m, 9H) .

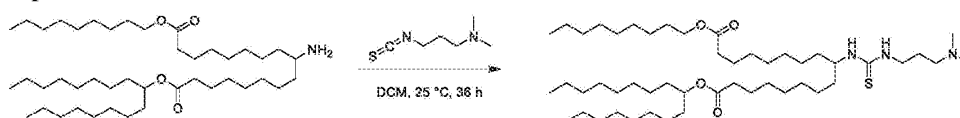
- [0191] Step 5: 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate



- [0192] To a mixture of 1- (heptadecan-9-yl) 17-nonyl 9-azidoheptadecanedioate (1.6 g, 2.27 mmol) in THF (50 mL) and water (10 mL) , PPh_3 (1.19 g, 4.53 mmol) was added under N_2 atmosphere. Then the mixture was stirred at 70 °C for 12 hours. TLC showed

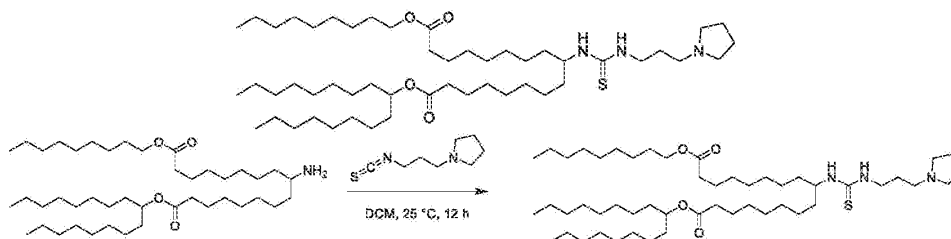
that starting material was consumed completely. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (80 mL $\times$ 2). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO_2 , PE: EtOAc = 1: 0 to 1: 1) to give pure 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (800 mg, 52% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.91 -4.83 (m, 1H), 4.06 (t, J = 6.8 Hz, 2H), 2.70 -2.63 (m, 1H), 2.33 -2.25 (m, 4H), 1.69 -1.57 (m, 6H), 1.55 -1.41 (m, 8H), 1.41 -1.22 (m, 52H), 0.92 -0.83 (m, 9H).

[0193] Step 6: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate



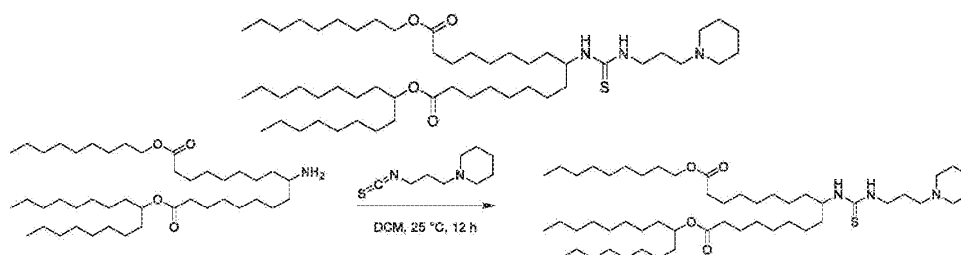
[0194] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (110 mg, 162 μmol) and 3-isothiocyanato-N, N-dimethyl-propan-1-amine (46.7 mg, 323 μmol) in DCM (5 mL) was stirred at 25 $^\circ\text{C}$ for 36 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL). Then the mixture was extracted with DCM (50 mL $\times$ 2). The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL), then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 25/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (dimethylamino) propyl) thioureido) heptadecanedioate (75.4 mg, 57% yield). ^1H NMR (400 MHz, CDCl_3) δ 4.91 -4.83 (m, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.96 -3.30 (m, 3H), 2.57 (br s, 2H), 2.44 -2.20 (m, 10H), 1.90 -1.74 (m, 2H), 1.67 -1.57 (m, 6H), 1.54 -1.40 (m, 8H), 1.39 -1.21 (m, 52H), 0.89 (s, 9H). LCMS showed the purity is 100.0%, R_t = 4.987 min; MS Calcd. : 823.7, MS Found: 824.5 $[\text{M}+\text{H}]^+$.

[0195] Example 16: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (pyrrolidin-1-yl) propyl) thioureido) heptadecanedioate



[0196] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (170 mg, 250 μ mol) and 1- (3-isothiocyanatopropyl) -pyrrolidine (85.1 mg, 500 μ mol) in DCM (5 mL) was stirred at 25 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (pyrrolidin-1-yl) propyl) thioureido) heptadecanedioate (84.0 mg, 40%yield) . ^1H NMR (400 MHz, CDCl_3) δ 8.13 (br s, 1H) , 6.21 -5.50 (m, 1H) , 6.17 -5.43 (m, 1H) , 4.93 -4.82 (m, 1H) , 4.05 (t, J = 6.8 Hz, 2H) , 3.92 -3.50 (m, 3H) , 3.40 -2.69 (m, 6H) , 2.35 -2.22 (m, 4H) , 2.06 (br s, 6H) , 1.67 -1.56 (m, 6H) , 1.55 -1.41 (m, 8H) , 1.38 -1.23 (m, 52H) , 0.94 -0.81 (m, 9H) . LCMS showed the purity is 100.0%, Rt = 4.793 min; MS Calcd. : 849.7, MS Found: 850.6 $[\text{M}+\text{H}]^+$.

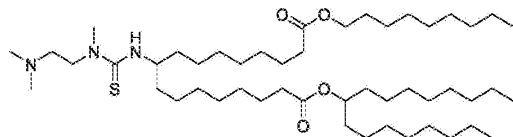
[0197] Example 17: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate



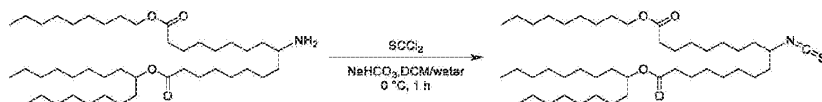
[0198] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (150 mg, 250 μ mol) and 1- (3-isothiocyanatopropyl) -piperidine (81.3 mg, 441 μ mol) in DCM (5 mL) was stirred at 25 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate (82.3 mg, 43%yield) . ^1H NMR (400 MHz, CDCl_3) δ 7.95 (s, 1H) , 6.67 -5.71 (m, 1H) , 4.91 -4.83 (m, 1H) , 4.05 (t, J = 6.8 Hz, 2H) , 3.85 -3.30 (m, 3H) , 3.12 -2.40 (m, 6H) , 2.33 -2.21 (m, 4H) , 2.10 -1.68 (m, 8H) , 1.65 -1.58 (m, 6H) , 1.55 -1.40 (m, 8H) , 1.39 -1.13 (m, 52H) , 0.88 (t, J = 6.8

Hz, 9H) . LCMS showed the purity is 100.0%, Rt = 4.875 min; MS Calcd. : 863.8, MS Found: 864.6 [M+H]⁺.

[0199] Example 18: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate

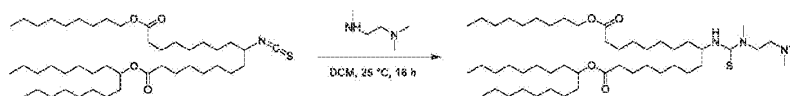


[0200] Step 1: 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate



[0201] To a mixture of 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (330 mg, crude) , NaHCO₃ (285 mg, 3.40 mmol) in water (10 mL) and DCM (20 mL) , thionyl chloride (112 mg, 970 μmol) was added at 0 °C. Then the mixture was stirred at 0 °C for 1 h. TLC showed that starting material was consumed completely. Then the reaction mixture was extracted with DCM (30 mL × 2) . The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by flash column chromatography (SiO₂, PE: EtOAc = 1: 0 to 19: 1) to give pure 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (260 mg, 74%yield) . ¹H NMR (400 MHz, CDCl₃) δ4.94-4.81 (m, 1H) , 4.07 (t, J = 6.8 Hz, 2H) , 3.68 -3.56 (m, 1H) , 2.32 -2.25 (m, 4H) , 1.69 -1.54 (m, 6H) , 1.53 -1.46 (m, 8H) , 1.39 -1.23 (m, 52H) , 0.94 -0.86 (m, 9H) .

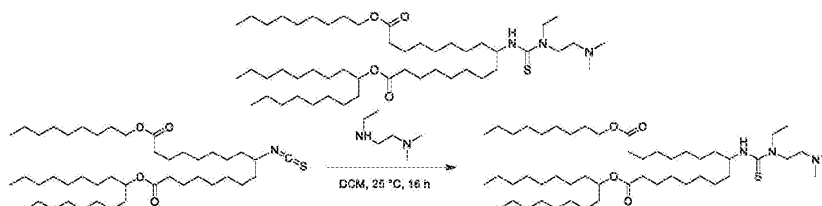
[0202] Step 2: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate



[0203] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (130 mg, 180 μmol) and N, N', N'-trimethylethane-1, 2-diamine (36.8 mg, 360 μmol) in DCM (5 mL) was stirred at 25 °C for 16 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL × 2) . The combined organic phase was washed with saturated NaHCO₃ (30 mL) and brine (50 mL) , then dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give 1- (heptadecan-9-yl) 17-nonyl

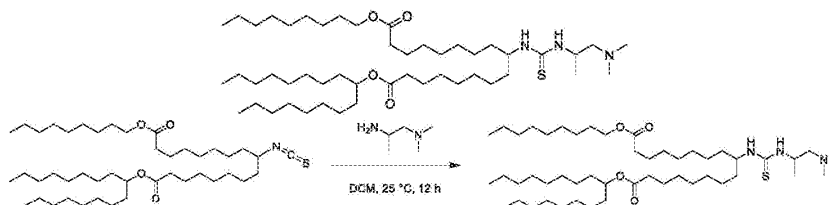
9- (3- (2- (dimethylamino) ethyl) -3-methylthioureido) heptadecanedioate (61.4 mg, 41%yield) . ^1H NMR (400 MHz, CDCl_3) δ 9.00-8.76 (m, 1H) , 4.95 -4.80 (m, 1H) , 4.46 -4.34 (m, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 3.42 (br s, 2H) , 3.32 (s, 3H) , 2.58 -2.45 (m, 2H) , 2.35 -2.18 (m, 10H) , 1.67 -1.58 (m, 6H) , 1.55 -1.39 (m, 8H) , 1.38 -1.18 (m, 52H) , 0.94 -0.78 (m, 9H) . LCMS showed the purity is 100.0%, R_t = 4.813 min; MS Calcd. : 823.7, MS Found: 824.7 $[\text{M}+\text{H}]^+$.

[0204] Example 19: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) -3-ethylthioureido) heptadecanedioate



[0205] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (130 mg, 180 μmol) and N-ethyl-N', N'-dimethyl-ethane-1, 2-diamine (41.8 mg, 360 μmol) in DCM (5 mL) was stirred at 25 $^{\circ}\text{C}$ for 16 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) -3-ethylthioureido) heptadecanedioate (56.7 mg, 38%yield) . ^1H NMR (400 MHz, CDCl_3) δ 9.11 (s, 1H) , 4.89-4.81 (m, 1H) , 4.49 -4.36 (m, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 3.87 (q, J = 7.2 Hz, 2H) , 3.42 -3.32 (m, 2H) , 2.56 -2.46 (m, 2H) , 2.33 -2.23 (m, 10H) , 1.66 -1.59 (m, 6H) , 1.55 -1.47 (m, 8H) , 1.37 -1.19 (m, 55H) , 0.92 -0.85 (m, 9H) . LCMS showed the purity is 100.0%, R_t = 4.813 min; MS Calcd. : 837.7, MS Found: 838.7 $[\text{M}+\text{H}]^+$.

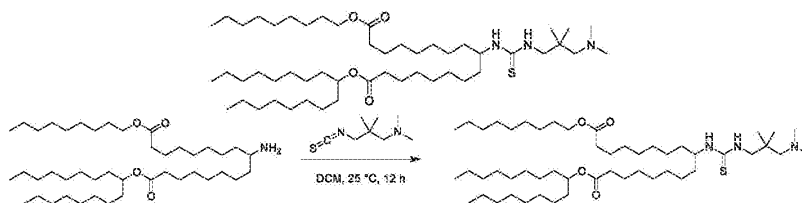
[0206] Example 20: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate



[0207] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (210 mg, 291 μmol) and N¹, N¹-dimethylpropane-1, 2-diamine (59.4 mg, 582 μmol)

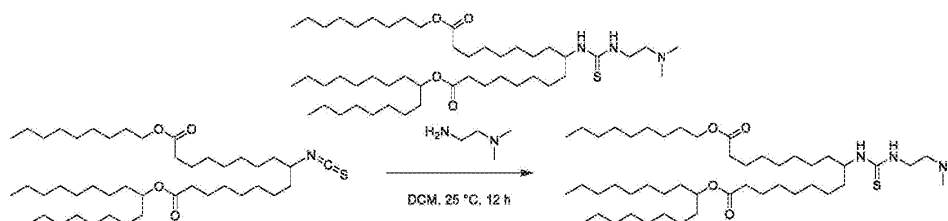
in DCM (5 mL) was stirred at 25 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL × 2) . The combined organic phase was washed with saturated NaHCO₃ (30 mL) and brine (50 mL) , then dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 20/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate (107.2 mg, 45%yield) . ¹H NMR (400 MHz, CDCl₃) δ 10.02 (br s, 1H) , 5.80 (br s, 1H) , 4.91 -4.82 (m, 1H) , 4.25 (br s, 1H) , 4.05 (t, J = 6.8 Hz, 2H) , 3.91 -3.54 (m, 1H) , 2.60 (br s, 1H) , 2.46 -2.12 (m, 11H) , 1.74 -1.56 (m, 6H) , 1.54 -1.45 (m, 8H) , 1.40 -1.16 (m, 55H) , 0.88 (t, J = 6.4 Hz, 9H) . LCMS showed the purity is 100.0%, Rt = 5.299 min; MS Calcd. : 823.7, MS Found: 824.6 [M+H]⁺.

[0208] Example 21: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (dimethylamino) -2, 2-dimethylpropyl) thioureido) heptadecanedioate



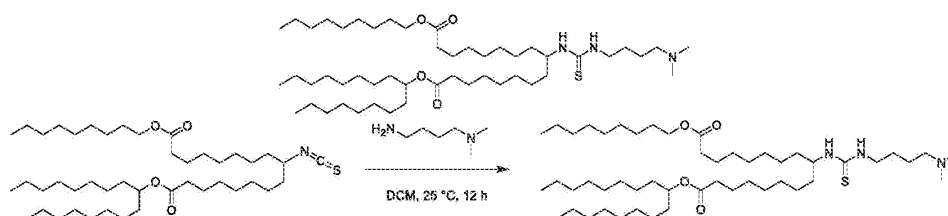
[0209] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-aminoheptadecanedioate (150 mg, 221 μmol) and 3-isothiocyanato-N, N, 2, 2-tetramethyl-propan-1-amine (76.0 mg, 441 μmol) in DCM (5 mL) was stirred at 25 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL ×2) . The combined organic phase was washed with saturated NaHCO₃ (30 mL) and brine (50 mL) , then dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by prep-TLC (DCM/MeOH = 25/1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (dimethylamino) -2, 2-dimethylpropyl) thioureido) heptadecanedioate (91.7 mg, 49%yield) . ¹H NMR (400MHz, CDCl₃) δ 9.04 (br s, 1H) , 5.67 (br s, 1H) , 4.90 -4.82 (m, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 3.80 -3.41 (m, 2H) , 3.28 (br s, 1H) , 2.34 -2.25 (m, 12H) , 1.66 -1.60 (m, 6H) , 1.55 -1.42 (m, 8H) , 1.35 -1.22 (m, 52H) , 1.00 -0.94 (m, 6H) , 0.88 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 100.0%, Rt = 4.771 min; MS Calcd. : 851.8, MS Found: 852.6 [M+H]⁺.

- [0210] Example 22: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) thioureido) heptadecanedioate



- [0211] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (240 mg, 332 μmol) and N^1, N^1 -dimethylethane-1, 2-diamine (58.6 mg, 665 μmol , 73 μL) in DCM (5 mL) was stirred at 25 $^{\circ}\text{C}$ for 12 hours. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO_2 , DCM: MeOH = 1: 0 to 19: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (2- (dimethylamino) ethyl) thioureido) heptadecanedioate (231.0 mg, 86%yield) . ^1H NMR (400 MHz, CDCl_3) δ 6.24 (br s, 1H) , 4.92 -4.81 (m, 1H) , 4.49 -3.66 (m, 3H) , 3.74 -3.15 (m, 2H) , 2.61 -2.46 (m, 2H) , 2.36 -2.20 (m, 10H) , 1.79 -1.60 (m, 6H) , 1.56 -1.40 (m, 8H) , 1.43 -1.20 (m, 52H) , 0.88 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 100.0%, Rt = 5.133 min; MS Calcd. : 809.7, MS Found: 810.5 $[\text{M}+\text{H}]^+$.

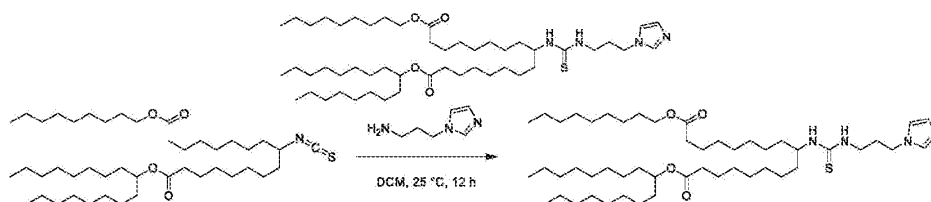
- [0212] Example 23: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (4- (dimethylamino) butyl) thioureido) heptadecanedioate



- [0213] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (240 mg, 332 μmol) and N^1, N^1 -dimethylbutane-1, 4-diamine (77.2 mg, 665 μmol) in DCM (5 mL) was stirred at 25 $^{\circ}\text{C}$ for 12 hours. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl(4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL $\times$ 2) . The combined organic phase was washed with saturated NaHCO_3 (30 mL) and brine (50 mL) , then dried over anhydrous Na_2SO_4 . The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography

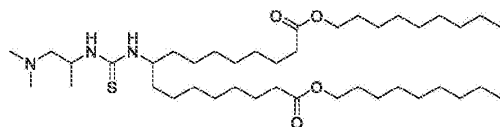
(SiO₂, DCM: MeOH = 1: 0 to 19: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (4- (dimethylamino) butyl) thioureido) heptadecanedioate (126.7 mg, 45%yield) . ¹H NMR (400 MHz, CDCl₃) δ 7.02 (br s, 1H) , 5.79 (br s, 1H) , 4.90 -4.81 (m, 1H) , 4.52 -3.87 (m, 3H) , 3.52 (br s, 2H) , 2.58 (s, 2H) , 2.44 (s, 6H) , 2.33 -2.17 (m, 4H) , 1.80 -1.67 (m, 4H) , 1.66 -1.56 (m, 6H) , 1.55 -1.40 (m, 8H) , 1.37 -1.19 (m, 52H) , 0.88 (t, J= 6.8 Hz, 9H) . LCMS showed the purity is 100.0%, Rt = 4.418 min; MS Calcd. : 837.7, MS Found: 838.6 [M+H]⁺ .

[0214] Example 24: 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate

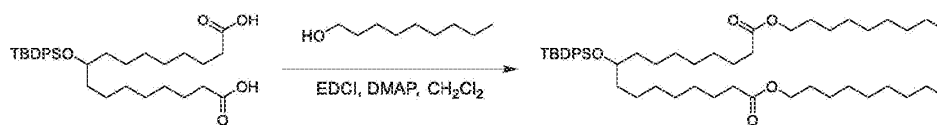


[0215] A mixture of 1- (heptadecan-9-yl) 17-nonyl 9-isothiocyanatoheptadecanedioate (240 mg, 332 μmol) and 3- (1H-imidazol-1-yl) propan-1-amine (83.2 mg, 665 μmol, 79 μL) in DCM (5 mL) was stirred at 25 °C for 12 hours. TLC showed that several spots were observed. The reaction mixture was quenched with 1 N HCl (4 mL) and diluted with water (30 mL) . Then the mixture was extracted with DCM (50 mL × 2) . The combined organic phase was washed with saturated NaHCO₃ (30 mL) and brine (50 mL) , then dried over anhydrous Na₂SO₄. The solid was filtered. The residue was obtained upon evaporation of the solvent and purified by column chromatography (SiO₂, DCM: MeOH = 1: 0 to 19: 1) to give 1- (heptadecan-9-yl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate (225.1 mg, 80%yield) . ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H) , 7.24 (br s, 1H) , 7.15 (s, 1H) , 7.07 (br s, 1H) , 6.88 (s, 1H) , 4.77 (s, 1H) , 4.26 (br s, 1H) , 4.05 -3.89 (m, 4H) , 3.36 -3.34 (m, 2H) , 2.28 -2.20 (m, 4H) , 1.96-1.86 (m, 2H) , 1.58 -1.43 (m, 10H) , 1.38 (br s, 4H) , 1.22 (br s, 52) , 0.90 -0.80 (m, 9H) . LCMS showed the purity is 100.0%, Rt = 4.790 min; MS Calcd. : 846.7, MS Found: 847.5 [M+H]⁺ .

[0216] Example 25: dinonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate

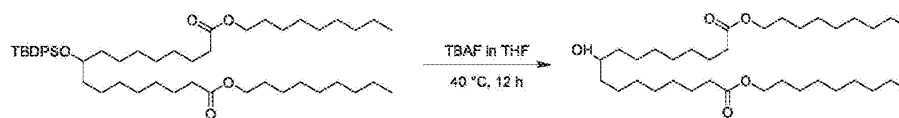


[0217] Step1: dinonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate



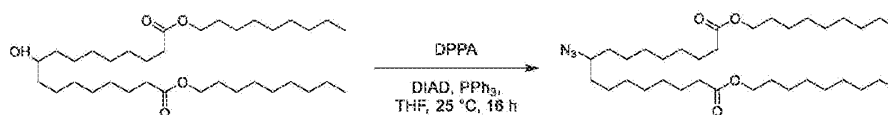
- [0218] To a mixture of 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioic acid (7.0 g, 12.6 mmol) in DCM (100 mL), DMAP (6.17 g, 50.5 mmol) and EDCI (9.67 g, 50.5 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 10 min, then nonan-1-ol (5.46 g, 37.85 mmol, 3 eq) was added. Then the mixture was stirred at 25 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was diluted with saturated NaHCO₃ (80 mL). The mixture was extracted with DCM (100 mL × 3). The combined organic phase was washed with brine (120 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, PE: EtOAc = 1: 0 to 10: 1) to give dinonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (7.2 g, 71%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ7.69 -7.65 (m, 4H), 7.46 -7.32 (m, 6H), 4.06 (t, J= 6.8 Hz, 4H), 3.70 (t, J= 5.6 Hz, 1H), 2.27 (t, J= 7.6 Hz, 4H), 1.71 -1.56 (m, 8H), 1.46 -1.08 (m, 44H), 1.05 (s, 9H), 0.94 -0.86 (m, 6H).

- [0219] Step 2: dinonyl 9-hydroxyheptadecanedioate



- [0220] To a mixture of dinonyl 9- ((tert-butyldiphenylsilyl) oxy) heptadecanedioate (7.2 g, 8.92 mmol) in THF (100 mL), TBAF (1 M, 44.59 mL) was added under N₂ atmosphere. The mixture was stirred at 40 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with saturated NaHCO₃ (100 mL) and extracted with EtOAc (100 mL × 2). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, PE: EtOAc = 1: 0 to 10: 1) to give dinonyl 9-hydroxyheptadecanedioate (4.2 g, 83%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ4.06 (t, J= 6.8 Hz, 4H), 3.65 (t, J= 6.0 Hz, 1H), 3.58 (br s, 1H), 2.29 (t, J= 7.6 Hz, 4H), 1.67 -1.55 (m, 8H), 1.39 -1.27 (m, 44H), 0.92 -0.87 (m, 6H).

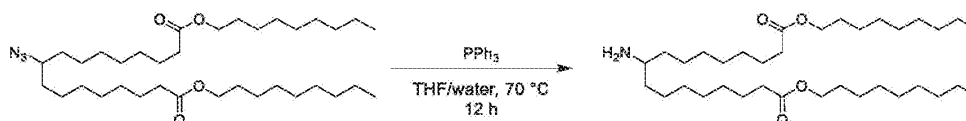
- [0221] Step 3: dinonyl 9-azidoheptadecanedioate



- [0222] To a mixture of dinonyl 9-hydroxyheptadecanedioate (4.2 g, 7.38 mmol) in THF (100 mL), PPh₃ (3.87 g, 14.8 mmol) and DIAD (2.99 g, 14.8 mmol) were added at 0

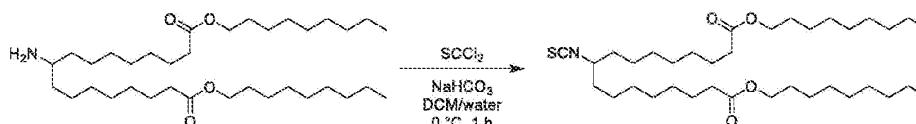
°C under N₂ atmosphere. The mixture was stirred at 25 °C for 10 min, then DPPA (4.06 g, 14.8 mmol, 3.19 mL) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, PE: EtOAc = 1: 0 to 4: 1) to give dinonyl 9-azidoheptadecanedioate (3.0 g, 68%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ4.06 (t, J= 6.8 Hz, 4H) , 3.24 -3.18 (m, 1H) , 2.30 (t, J= 7.6 Hz, 4H) , 1.65 -1.58 (m, 8H) , 1.53 -1.47 (m, 4H) , 1.35 -1.25 (m, 40H) , 0.91 -0.87 (m, 6H) .

[0223] Step 4: dinonyl 9-aminoheptadecanedioate



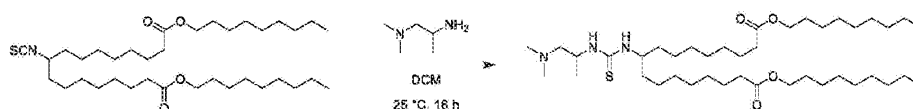
[0224] To a mixture of dinonyl 9-azidoheptadecanedioate (3.0 g, 5.05 mmol) in THF (80 mL) and water (16 mL) , PPh₃ (2.65 g, 10.1 mmol) was added under N₂ atmosphere. The mixture was stirred at 70 °C for 12 hours. TLC showed that starting material was consumed completely. The reaction mixture was diluted with water (50 mL) , extracted with EtOAc (80 mL × 2) . The combined organic phase was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, PE: EtOAc = 1: 0 to 1: 1) to give dinonyl 9-aminoheptadecanedioate (2.7 g, crude) as a light-yellow solid. ¹H NMR (400 MHz, CDCl₃) δ4.06 (t, J= 6.8 Hz, 4H) , 2.66 (br s, 1H) , 2.29 (t, J= 7.6 Hz, 4H) , 1.67 -1.57 (m, 8H) , 1.48 -1.21 (m, 44H) , 0.92 -0.84 (m, 6H) .

[0225] Step 5: dinonyl 9-isothiocyanatoheptadecanedioate



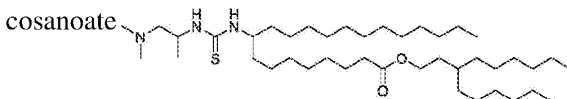
[0226] To a mixture of dinonyl 9-aminoheptadecanedioate (300 mg, 528 μmol) in DCM (20 mL) , asolution of NaHCO₃ (311 mg, 3.70 mmol) in water (5 mL) and thiocarbonyl dichloride (121 mg, 1.06 mmol) were added in sequence at 0 °C. The mixture was stirred at 0 °C for 1 hour. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (20 mL) and water (30 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, PE:EtOAc = 1: 0 to 19: 1) to give dinonyl 9-isothiocyanatoheptadecanedioate (240 mg, 74%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ4.06 (t, J= 6.8 Hz, 4H) , 3.66 -3.58 (m, 1H) , 2.30 (t, J= 7.4 Hz, 4H) , 1.66 -1.59 (m, 8H) , 1.56 -1.22 (m, 44H) , 0.92 -0.85 (m, 6H) .

[0227] Step 6: dinonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate

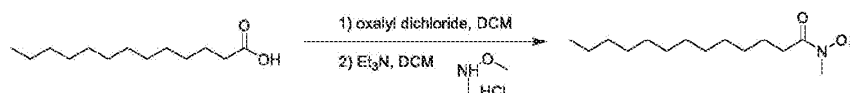


[0228] A mixture of dinonyl 9-isothiocyanoheptadecanedioate (240 mg, 393 μmol), N^1 , N^1 -dimethylpropane-1, 2-diamine (138 mg, 787 μmol , 2HCl) and Et_3N (159 mg, 1.57 mmol, 219 μL) in DCM (10 mL) was stirred at 25 °C for 16 hours to give a yellow solution. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was diluted with EtOAc (150 mL), washed with 1 N HCl (50 mL $\times$ 2), saturated NaHCO_3 (50 mL $\times$ 2), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , DCM: MeOH = 1: 0 to 19: 1) to give dinonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate (135.2 mg, 48% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 9.99 (br s, 1H), 5.79 (br s, 1H), 4.32-4.16 (m, 1H), 4.06 (t, J = 6.8 Hz, 4H), 3.80-3.55 (m, 1H), 2.62-2.51 (m, 1H), 2.36-2.19 (m, 11H), 1.70-1.42 (m, 12H), 1.38-1.25 (m, 40H), 1.21 (d, J = 6.8 Hz, 3H), 0.93-0.84 (m, 6H). LCMS showed the purity is 100.0%, R_t = 2.767 min; MS Calcd.: 711.6, MS Found: 712.6 $[\text{M}+\text{H}]^+$.

[0229] Example 26: 3-hexylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heneicosanoate



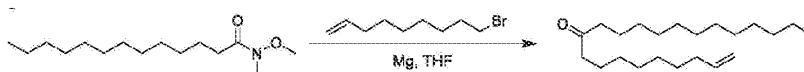
[0230] Step1: N-methoxy-N-methyltridecanamide



[0231] To a mixture of tridecanoic acid (50.0 g, 233 mmol) in DCM (300 mL), DMF (one drop, catalytic amount) and oxalyl dichloride (44.4 g, 350 mmol, 31 mL) were added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 hour and 25 °C for 30 min. TLC showed that tridecanoic acid was consumed completely. The mixture was concentrated in vacuo. The residue was dissolved with DCM (400 mL), N, O-dimethylhydroxylamine hydrochloride (27.3 g, 280 mmol) and Et_3N (47.2 g, 467 mmol, 65 mL) were added at 0 °C. The mixture was allowed to warm to 25 °C and stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with saturated NaHCO_3 (150 mL) and diluted with water (300 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (100 mL). The combined organic phase was washed with brine (350 mL), dried

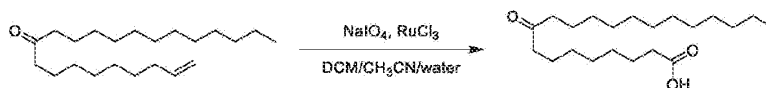
over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give N-methoxy-N-methyltridecanamide (51 g, 85% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.69 (s, 3H) , 3.18 (s, 3H) , 2.41 (t, J= 7.6 Hz, 2H) , 1.69 -1.58 (m, 2H) , 1.35 -1.23 (m, 18H) , 0.89 (t, J= 7.6 Hz, 3H) .

[0232] Step 2: docos-1-en-10-one



[0233] To a drying three-neck bottle, freshly activated Mg (14.5 g, 594 mmol) and I_2 (10 mg) were added. The flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, and flushed with N_2 . THF (70 mL) was added to the flask via syringe. The 9-bromonon-1-ene (61.0 g, 297 mmol) was dissolved in THF (250 mL) and added to the addition funnel. About 60 mL of this above solution was added to the Mg turnings while stirring vigorously and heating by high gun. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux. After the completion of the addition, the reaction mixture was kept at 50 $^\circ\text{C}$ for 1 h and then cooled in ice-bath. N-methoxy-N-methyltridecanamide (51.0 g, 198 mmol) in THF (250 mL) transferred to the addition funnel and added dropwise to the reaction mixture with stirring at 0 $^\circ\text{C}$. The reaction mixture was stirred at 25 $^\circ\text{C}$ for another 12 hours. TLC showed that one main spot was observed. The reaction was quenched by adding saturated NH_4Cl (200 mL) slowly under ice bath. The reaction mixture was treated with aqueous H_2SO_4 (10% by volume, 300 mL) slowly until the solution became homogeneous and the layers were separated. The aqueous phase was extracted with EtOAc (2 $\times$ 300 mL) . The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give docos-1-en-10-one (63 g, crude) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 5.88-5.75 (m, 1H) , 5.06 -4.88 (m, 2H) , 2.39 (t, J= 7.6 Hz, 4H) , 2.07 -1.99 (m, 2H) , 1.63 -1.52 (m, 4H) , 1.41 -1.23 (m, 26H) , 0.89 (t, J= 6.8 Hz, 3H) .

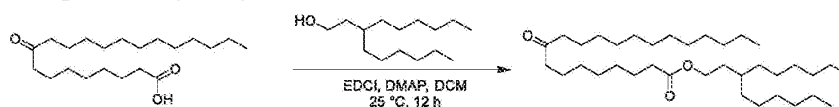
[0234] Step 3: 9-oxohenicosanoic acid



[0235] To a mixture of docos-1-en-10-one (63.0 g, 195 mmol) in DCM (500 mL) and CH_3CN (500 mL) , RuCl_3 (4.05 g, 19.5 mmol) was added under N_2 atmosphere. Then a solution of NaIO_4 (167 g, 781 mmol) in water (500 mL) was added dropwise at 0 $^\circ\text{C}$. The mixture was stirred at 25 $^\circ\text{C}$ for 12 hours. TLC showed that starting material was

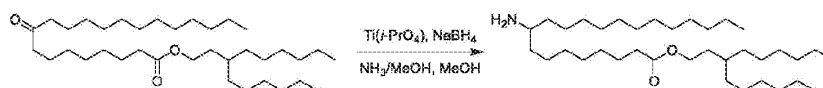
consumed completely. The reaction mixture was diluted with brine (500 mL). The mixture was adjusted with 1N HCl to pH = 6. The mixture was extracted with DCM (500 mL×2). The combined organic phase was washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM/MeOH = 1: 0 to 10: 1) to give 9-oxohenicosanoic acid (34 g, 51%yield) as a gray solid. ¹H NMR (400 MHz, CDCl₃) δ= 2.43 -2.31 (m, 6H), 1.68 -1.61 (m, 2H), 1.59 -1.51 (m, 4H), 1.39 -1.21 (m, 24H), 0.92 -0.84 (m, 3H).

[0236] Step 4: 3-hexylnonyl 9-oxohenicosanoate



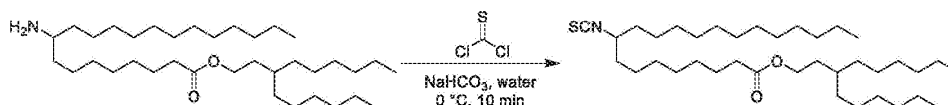
[0237] To a mixture of 9-oxohenicosanoic acid (8.0 g, 23.5 mmol) and 3-hexylnonan-1-ol (6.44 g, 28.2 mmol) in DCM (150 mL), EDCI (9.01 g, 47.0 mmol) and DMAP (5.74 g, 47.0 mmol) were added. The mixture was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give 3-hexylnonyl 9-oxohenicosanoate (7 g, 54%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ4.08 (t, J= 7.2 Hz, 2H), 2.38 (t, J= 7.2 Hz, 4H), 2.28 (t, J= 7.6 Hz, 2H), 1.65-1.52 (m, 8H), 1.40 (br s, 1H), 1.35 -1.23 (m, 44H), 0.89 (t, J= 6.8 Hz, 9H).

[0238] Step 5: 3-hexylnonyl 9-aminohenicosanoate



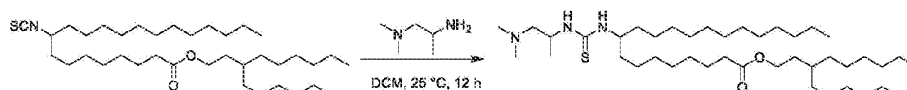
[0239] To a mixture of 3-hexylnonyl 9-oxohenicosanoate (10.0 g, 18.2 mmol) in MeOH (150 mL) and NH₃/MeOH (7 M, 75 mL), tetraisopropoxytitanium (10.3 g, 36.3 mmol, 10.7 mL) was added. The mixture was stirred 25 °C for 4 hours. Then NaBH₄ (1.37 g, 36.3 mmol) was added. The mixture was stirred at 25 °C for another 12 hours. TLC showed that that 3-hexylnonyl 9-oxohenicosanoate was consumed completely and two main spots were observed. The mixture was quenched with water (50 mL) and diluted with ethyl acetate (150 mL). The reaction mixture was filtered, and the filter cake was washed with ethyl acetate (2×300 mL). The three batches filtrate were combined and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc= 1: 0 to 3: 2, then DCM/MeOH = 1: 0 to 10: 1) to give 3-hexylnonyl 9-aminohenicosanoate (14 g, 47%yield) as a colorless oil in total. ¹H NMR (400 MHz, CDCl₃) δ4.09 (t, J= 7.2 Hz, 2H), 2.69 (br s, 1H), 2.29 (t, J= 7.6 Hz, 2H), 1.71 -1.52 (m, 4H), 1.46 -1.19 (m, 53H), 0.98 -0.79 (m, 9H).

[0240] Step 6: 3-hexylnonyl 9-isothiocyanatohenicosanoate



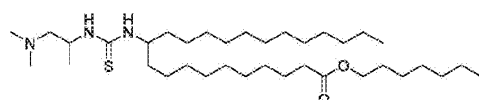
[0241] To a mixture of 3-hexylnonyl 9-aminohenicosanoate (14.0 g, 25.4 mmol) in DCM (150 mL), a solution of NaHCO_3 (14.9 g, 178 mmol) in water (100 mL) and thionyl chloride (5.83 g, 50.7 mmol, 3.89 mL) were added at 0 °C. The mixture was stirred at 0 °C for 10 min. TLC showed that one main spot was observed. The organic phase was separated, the aqueous phase extracted with DCM (100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , PE: EtOAc = 1: 0 to 19: 1) to give 3-hexylnonyl 9-isothiocyanatohenicosanoate (13.8 g, 92% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.09 (t, J = 7.2 Hz, 2H), 3.66-3.58 (m, 1H), 2.35-2.24 (m, 2H), 1.72-1.58 (m, 6H), 1.50-1.19 (m, 51H), 0.89 (t, J = 6.8 Hz, 9H).

[0242] Step 7: 3-hexylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate

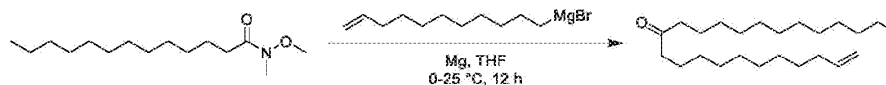


[0243] A mixture of 3-hexylnonyl 9-isothiocyanatohenicosanoate (300 mg, 505 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (77.4 mg, 758 μmol) in DCM (10 mL) was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL). The organic phase was washed with saturated NaHCO_3 (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , DCM: MeOH = 1: 0 to 19: 1) to give 3-hexylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate (285.2 mg, 81% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 10.33-9.82 (m, 1H), 5.86-5.59 (m, 1H), 4.37-4.15 (m, 1H), 4.08 (t, J = 7.2 Hz, 2H), 3.75-3.52 (m, 1H), 2.59-2.49 (m, 1H), 2.38-2.15 (m, 9H), 1.66-1.45 (m, 6H), 1.44-1.23 (m, 51H), 1.20 (d, J = 6.8 Hz, 3H), 0.92-0.85 (m, 9H). LCMS showed the purity is 100%, R_t = 5.003 min; MS Calcd.: 695.6, MS Found: 696.6 $[\text{M}+\text{H}]^+$.

[0244] Example 27: heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) tri-cosanoate

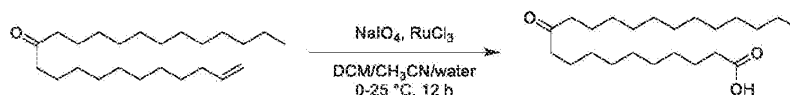


[0245] Step1: tetracos-1-en-12-one



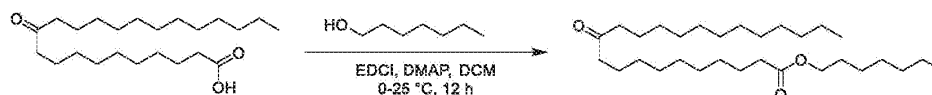
[0246] To a mixture of N-methoxy-N-methyltridecanamide (15 g, 58.3 mmol) in THF (100 mL), a solution of undec-10-en-1-ylmagnesium bromide (18.0 g, 69.9 mmol) (80 mL in THF) was added at 0 °C under N₂ atmosphere. The mixture was allowed to warm to 25 °C and stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction was quenched by adding saturated NH₄Cl (50 mL) under ice-bath. The aqueous phase was extracted with EtOAc (100 mL × 2). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give tetracos-1-en-12-one (17.7 g, 87% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.87-5.75 (m, 1H), 5.04-4.87 (m, 2H), 2.39 (t, J= 7.6 Hz, 4H), 2.09-1.99 (m, 2H), 1.59-1.51 (m, 4H), 1.41-1.24 (m, 30H), 0.92-0.86 (m, 3H).

[0247] Step 2: 11-oxotricosanoic acid



[0248] To a mixture of tetracos-1-en-12-one (17.7 g, 50.5 mmol) in DCM (300 mL) and CH₃CN (300 mL), RuCl₃ (1.05 g, 5.05 mmol) was added under N₂ atmosphere. Then a solution of NaIO₄ (54.0 g, 252 mmol) in water (300 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hours. TLC showed that starting material was consumed completely. The reaction mixture was diluted with brine (500 mL). The mixture was adjusted with 1 N HCl to pH = 6. The mixture was extracted with DCM (500 mL × 2). The combined organic phase was washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give 11-oxotricosanoic acid (11 g, 59% yield) as a black solid. The product was used into next step directly. ¹H NMR (500 MHz, CDCl₃) δ 2.42-2.33 (m, 6H), 1.67-1.61 (m, 2H), 1.60-1.52 (m, 4H), 1.37-1.23 (m, 28H), 0.89 (t, J= 7.0 Hz, 3H).

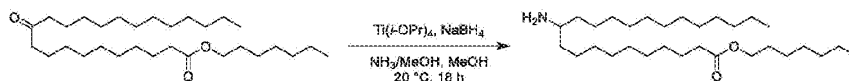
[0249] Step 3: heptyl 11-oxotricosanoate



[0250] To a mixture of 11-oxotricosanoic acid (4 g, 10.9 mmol) in DCM (100 mL), EDCI (4.16 g, 21.7 mmol) and DMAP (2.65 g, 21.7 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 10 min, then heptan-1-ol (2.52 g, 21.7 mmol) was added. The mixture was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with saturated NaHCO₃ (80 mL). The

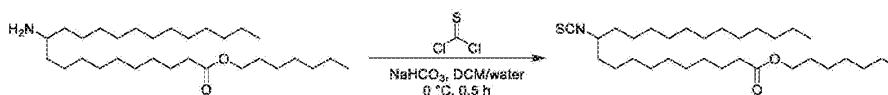
mixture was extracted with DCM (80 mL). The combined organic phase was washed with brine (120 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give heptyl 11-oxotricosanoate (4.9 g, 97% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.6 Hz, 4H), 2.29 (t, J = 7.8 Hz, 2H), 1.66 -1.59 (m, 4H), 1.58 -1.50 (m, 2H), 1.40 -1.21 (m, 38H), 0.92 -0.85 (m, 6H).

[0251] Step 4: heptyl 11-aminotricosanoate



[0252] To a mixture of heptyl 11-oxotricosanoate (2.9 g, 6.21 mmol) in MeOH (40 mL) and NH_3/MeOH (7 M, 16 mL), tetraisopropoxytitanium (3.53 g, 12.4 mmol) was added. The mixture was stirred 20 °C for 6 hours. Then NaBH_4 (470 mg, 12.4 mmol) was added. The mixture was stirred at 20 °C for another 12 hours. TLC showed that heptyl 11-oxotricosanoate was consumed completely and two main spots were detected. The mixture was quenched with water (100 mL) and diluted with ethyl acetate (150 mL). The aqueous phase was extracted with ethyl acetate (100 mL $\times$ 2). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 1: 1) to give heptyl 11-aminotricosanoate (470 mg, 16% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 2H), 2.71 (br s, 1H), 2.29 (t, J = 7.6 Hz, 2H), 1.62 (q, J = 6.8 Hz, 4H), 1.49 -1.25 (m, 44H), 0.94 -0.85 (m, 6H).

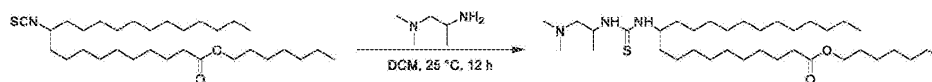
[0253] Step 5: heptyl 11-isothiocyanatotricosanoate



[0254] To a mixture of heptyl 11-aminotricosanoate (470 mg, 1.00 mmol) in DCM (10 mL), a solution of NaHCO_3 (591 mg, 7.03 mmol) in water (5 mL) was added. Then thiocarbonyl dichloride (231 mg, 2.01 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (20 mL) and water (30 mL). The organic phase was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give heptyl 11-isothiocyanatotricosanoate (330 mg, 64% yield) as a yellow oil. ^1H NMR (400

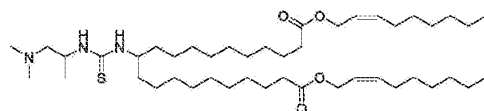
MHz, CDCl₃) δ 4.06 (t, J= 6.8 Hz, 2H) , 3.66 -3.57 (m, 1H) , 2.30 (t, J= 7.6 Hz, 2H) , 1.69-1.58 (m, 6H) , 1.54 -1.23 (m, 42H) , 0.92 -0.84 (m, 6H) .

[0255] Step 6: heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) tricosanoate

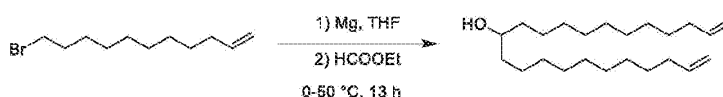


[0256] A mixture of heptyl 11-isothiocyanatotricosanoate (200 mg, 392 μ mol) and N¹, N¹-dimethylpropane-1, 2-diamine (160 mg, 1.57 mmol) in DCM (10 mL) was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL) . The organic phase was washed with saturated NaHCO₃ (50 mL) , brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give the crude product, which was further purified by prep-TLC (DCM/MeOH = 25: 1) , and purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) tricosanoate (77.1 mg, 32%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.93 (br s, 1H) , 5.83 (br s, 1H) , 4.25 (br s, 1H) , 4.06 (t, J= 6.8 Hz, 2H) , 3.69 (br s, 1H) , 2.69 -2.52 (m, 1H) , 2.41-2.20 (m, 9H) , 1.69 -1.59 (m, 4H) , 1.56 -1.24 (m, 44H) , 1.21 (d, J= 6.8 Hz, 3H) , 0.96 -0.83 (m, 6H) . LCMS showed the purity is 100%, Rt = 2.542 min; MS Calcd. : 611.5, MS Found: 612.5 [M+H]⁺.

[0257] Example 28: di ((Z) -non-2-en-1-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) hencosanedioate



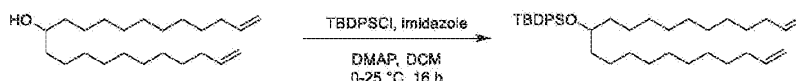
[0258] Step 1: tricos-1, 22-dien-12-ol



[0259] To a drying three-neck bottle, freshly activated Mg (8.34 g, 343 mmol) and I₂ (11.00 mg) were added. The flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, and flushed with N₂. THF (60 mL) was added to the flask via syringe. The 11-bromoundec-1-ene (50 g, 214 mmol) was dissolved in THF (100 mL) and added to the addition funnel. About 10 mL of this above solution was added to the Mg turnings while stirring vigorously and heating by high temperature gun. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle

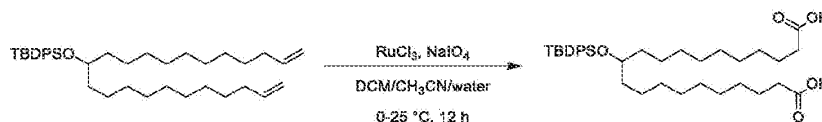
reflux. After the completion of the addition the reaction mixture was kept at 50 °C for 1 hour (80 mL of the solution was used into next step) . After cooled in ice bath, ethyl formate (5.07 g, 68.38 mmol, 5.5 mL) in THF (100 mL) was transferred to the addition funnel and was added dropwise to the reaction mixture with stirring at 0 °C. The reaction mixture was stirred for 12 h at 25 °C. showed that one main spot was observed. The reaction was quenched by adding acetone (50 mL) under ice-bath. The reaction mixture was treated with H₂SO₄ (10% by volume, 200 mL) slowly until the solution became homogeneous and the layers were separated. The aqueous phase was extracted with EtOAc (100 mL × 2) . The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give tricos-1, 22-dien-12-ol (14 g, 61% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.88 -5.77 (m, 2H) , 5.07 -4.90 (m, 4H) , 3.59 (br s, 1H) , 2.05 (q, J= 6.8 Hz, 4H) , 1.29 (br s, 32H) .

[0260] Step 2: tert-butyldiphenyl (tricos-1, 22-dien-12-yloxy) silane



[0261] To a mixture of tricos-1, 22-dien-12-ol (14 g, 41.6 mmol) in DCM (200 mL) , imidazole (11.3 g, 166 mmol) and DMAP (1.02 g, 8.32 mmol) were added, then TBDPSCl (22.9 g, 83.2 mmol, 21.3 mL) was added at 0 °C. The mixture was stirred at 25 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with saturated NaHCO₃ (400 mL) , diluted with DCM (200 mL) . The organic phase was separated and washed with brine (200 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give tert-butyldiphenyl (tricos-1, 22-dien-12-yloxy) silane (21 g, 88% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.74 -7.66 (m, 4H) , 7.48 -7.31 (m, 6H) , 5.89 -5.76 (m, 2H) , 5.07 -4.89 (m, 4H) , 3.71 (q, J= 5.6 Hz, 1H) , 2.05 (q, J= 7.2 Hz, 4H) , 1.48 -1.35 (m, 8H) , 1.32-1.12 (m, 24H) , 1.06 (s, 9H) .

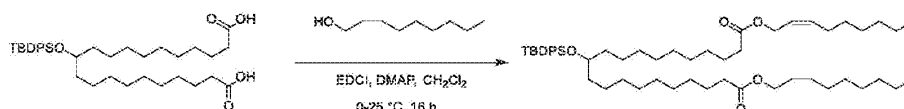
[0262] Step 3: 11- ((tert-butyldiphenylsilyl) oxy) heneicosanedioic acid



[0263] To a mixture of tert-butyldiphenyl (tricos-1, 22-dien-12-yloxy) silane (21 g, 36.5 mmol) in DCM (500 mL) and CH₃CN (500 mL) , RuCl₃ (1.52 g, 7.30 mmol) was added. Then a solution of NaIO₄ (78.1 g, 365 mmol) in water (500 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with brine (200 mL) . The

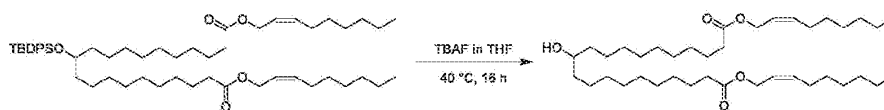
mixture was adjusted with 1 N HCl to pH =6. The mixture was extracted with DCM (500 mL $\times$ 3). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 1: 1) to give 11-((tert-butyldiphenylsilyl) oxy) henicosanedioic acid (16 g, 72% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 -7.65 (m, 4H), 7.45 -7.33 (m, 6H), 3.71 (q, J= 5.6 Hz, 1H), 2.36 (t, J= 7.2 Hz, 4H), 1.68 -1.57 (m, 4H), 1.45 -1.15 (m, 28H), 1.05 (s, 9H).

[0264] Step 4: di ((Z)-non-2-en-1-yl) 11-((tert-butyldiphenylsilyl) oxy) henicosanedioate



[0265] To a mixture of 11-((tert-butyldiphenylsilyl) oxy) henicosanedioic acid (5.0 g, 8.18 mmol) in DCM (100 mL), EDCI (6.28 g, 32.7 mmol) and DMAP (4.00 g, 32.7 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 10 min, then (Z)-non-2-en-1-ol (2.33 g, 16.4 mmol) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was diluted with saturated NaHCO₃ (80 mL). The mixture was extracted with DCM (80 mL). The combined organic phase was washed with brine (120 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give di((Z)-non-2-en-1-yl) 11-((tert-butyldiphenylsilyl) oxy) henicosanedioate (3.2 g, 46% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 -7.65 (m, 4H), 7.44 -7.32 (m, 6H), 5.69 -5.60 (m, 2H), 5.57 -5.49 (m, 2H), 4.63 (d, J= 6.8 Hz, 4H), 3.70 (q, J= 5.6 Hz, 1H), 2.31 (t, J= 7.6 Hz, 4H), 2.11 (q, J= 7.2 Hz, 4H), 1.66 -1.58 (m, 4H), 1.40 -1.12 (m, 44H), 1.05 (s, 9H), 0.91 -0.86 (m, 6H).

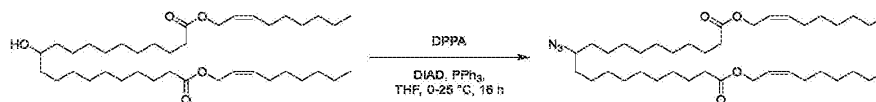
[0266] Step 5: di ((Z)-non-2-en-1-yl) 11-hydroxyhenicosanedioate



[0267] To a mixture of di((Z)-non-2-en-1-yl) 11-((tert-butyldiphenylsilyl) oxy) henicosanedioate (5.2 g, 6.05 mmol) in THF (80 mL) was added TBAF (1 M, 30 mL). The mixture was stirred at 40 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with water (50 mL). The mixture was extracted with EtOAc (100 mL $\times$ 2). The combined organic phase was washed with brine (80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give di((Z)-non-2-en-1-yl) 11-hydroxyhenicosanedioate (3 g, 80% yield)

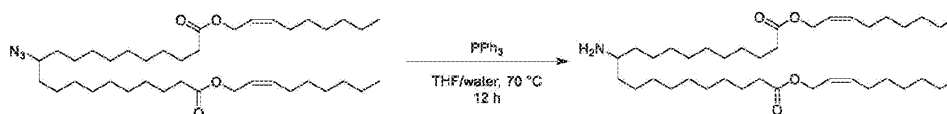
as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.71 -5.61 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.63 (d, J = 6.8 Hz, 4H) , 3.59 (br s, 1H) , 2.31 (t, J = 7.6 Hz, 4H) , 2.21 (br s, 1H) , 2.11 (q, J = 7.2 Hz, 4H) , 1.68 -1.60 (m, 4H) , 1.49 -1.24 (m, 44H) , 0.93 -0.86 (m, 6H) .

[0268] Step 6: di ((Z) -non-2-en-1-yl) 11-azidohenicosanedioate



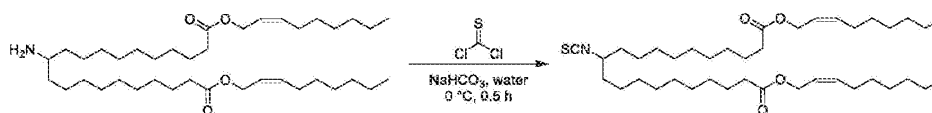
[0269] To a mixture of di ((Z) -non-2-en-1-yl) 11-hydroxyhenicosanedioate (3 g, 4.83 mmol) in THF (80 mL) was added PPh_3 (2.53 g, 9.66 mmol) and DIAD (1.95 g, 9.66 mmol, 1.87 mL) at 0 °C. The mixture was stirred at 25 °C for 10 min, then DPPA (2.66 g, 9.66 mmol, 2.09 mL) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give di ((Z) -non-2-en-1-yl) 11-azidohenicosanedioate (2.0 g, 64% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.71 -5.60 (m, 2H) , 5.58 -5.48 (m, 2H) , 4.63 (d, J = 6.8 Hz, 4H) , 3.22 (q, J = 6.4 Hz, 1H) , 2.31 (t, J = 7.6 Hz, 4H) , 2.10 (q, J = 7.2 Hz, 4H) , 1.63 (t, J = 7.2 Hz, 4H) , 1.53 -1.47 (m, 4H) , 1.40 -1.24 (m, 40H) , 0.92 -0.87 (m, 6H) .

[0270] Step 7: di ((Z) -non-2-en-1-yl) 11-aminohenicosanedioate



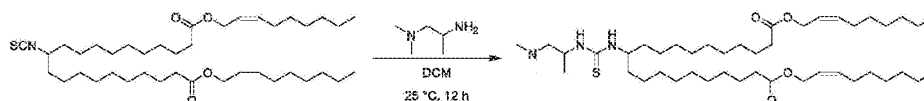
[0271] A mixture of di ((Z) -non-2-en-1-yl) 11-azidohenicosanedioate (2 g, 3.10 mmol) and PPh_3 (1.62 g, 6.19 mmol) in THF (80 mL) and water (16 mL) was stirred at 70 °C for 12 hours under N_2 atmosphere. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 1: 1) to give di ((Z) -non-2-en-1-yl) 11-aminohenicosanedioate (3 g, crude) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.61 -5.53 (m, 2H) , 5.50 -5.40 (m, 2H) , 4.55 (d, J = 6.8 Hz, 4H) , 2.59 (br s, 1H) , 2.23 (t, J = 7.6 Hz, 4H) , 2.03 (q, J = 7.2 Hz, 4H) , 1.60 -1.49 (m, 4H) , 1.39 -1.13 (m, 44H) , 0.84 -0.76 (m, 6H) .

[0272] Step 8: di ((Z) -non-2-en-1-yl) 11-isothiocyanatohenicosanedioate



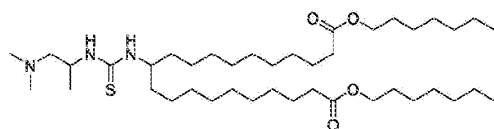
[0273] To a mixture of di ((Z) -non-2-en-1-yl) 11-aminohenicosanedioate (1 g, crude, 1.03 mmol) in DCM (20 mL) was added a solution of NaHCO_3 (607 mg, 7.23 mmol) in water (10 mL), then thiocarbonyl dichloride (237 mg, 2.06 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (20 mL) and water (30 mL). The organic phase was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give di ((Z) -non-2-en-1-yl) 11-isothiocyanatohenicosanedioate (680 mg, 99%yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.70 -5.61 (m, 2H), 5.57 -5.49 (m, 2H), 4.63 (d, J= 6.8 Hz, 4H), 3.66 -3.68 (m, 1H), 2.31 (t, J= 7.6 Hz, 4H), 2.10 (q, J= 7.2 Hz, 4H), 1.67 -1.58 (m, 6H), 1.52 -1.24 (m, 42H), 0.92 -0.86 (m, 6H).

[0274] Step 9: di ((Z) -non-2-en-1-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate

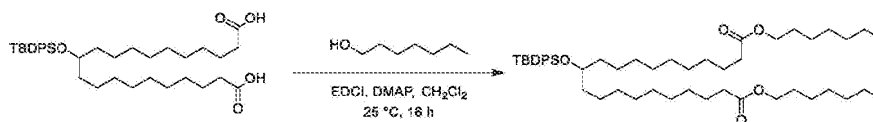


[0275] A mixture of di ((Z) -non-2-en-1-yl) 11-isothiocyanatohenicosanedioate (350 mg, 529 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (216 mg, 2.11 mmol) in DCM (10 mL) was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with HCl (1 N, 20 mL) and DCM (100 mL). The organic phase was washed with saturated NaHCO_3 (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give the crude product, which was further purified by prep-TLC (DCM/MeOH = 25: 1) and purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give di ((Z) -non-2-en-1-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate (166.6 mg, 41%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 10.00 (br s, 1H), 5.77 (br s, 1H), 5.69 -5.60 (m, 2H), 5.57 -5.48 (m, 2H), 4.62 (d, J= 6.8 Hz, 4H), 4.25 (br s, 1H), 3.65 (br s, 1H), 2.56 (t, J= 10.0 Hz, 1H), 2.37 -2.22 (m, 11H), 2.10 (q, J= 7.2 Hz, 4H), 1.68 -1.58 (m, 4H), 1.56 -1.23 (m, 44H), 1.20 (d, J= 6.8 Hz, 3H), 0.92 -0.85 (m, 6H). LCMS showed the purity is 100.0%, R_t = 5.719 min; MS Calcd. : 763.6, MS Found: 764.6 $[\text{M}+\text{H}]^+$.

[0276] Example 29: diheptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate

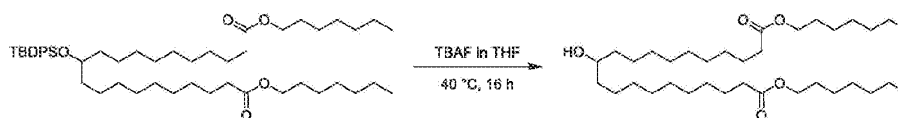


[0277] Step 1: diheptyl 11-((tert-butyldiphenylsilyl)oxy)henicosanedioate



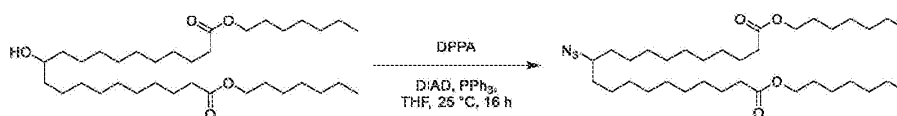
[0278] To a mixture of 11-((tert-butyldiphenylsilyl)oxy)henicosanedioic acid (5.0 g, 8.18 mmol) in DCM (100 mL) was added EDCI (6.28 g, 32.7 mmol) and DMAP (4.00 g, 32.7 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, then heptan-1-ol (1.90 g, 16.4 mmol, 2.31 mL) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was diluted with saturated NaHCO_3 (80 mL). The mixture was extracted with DCM (100 mL $\times$ 3). The combined organic phase was washed with brine (120 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give diheptyl 11-((tert-butyldiphenylsilyl)oxy)henicosanedioate (2.2 g, 33% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.77 -7.61 (m, 4H), 7.45 -7.30 (m, 6H), 4.07 (t, J = 6.8 Hz, 4H), 3.70 (q, J = 6.0 Hz, 1H), 2.29 (t, J = 7.6 Hz, 4H), 1.67 -1.60 (m, 8H), 1.41 -1.09 (m, 44H), 1.05 (s, 9H), 0.91 -0.87 (m, 6H).

[0279] Step 2: diheptyl 11-hydroxyhenicosanedioate



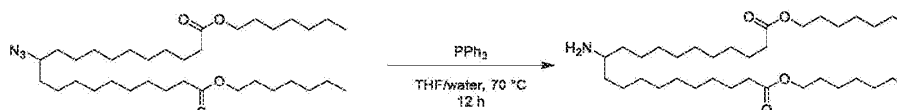
[0280] To a mixture of diheptyl 11-((tert-butyldiphenylsilyl)oxy)henicosanedioate (2.2 g, 2.73 mmol) in THF (30 mL) was added TBAF (1 M, 13.6 mL). The mixture was stirred at 40 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with water (50 mL). The mixture was extracted with EtOAc (100 mL $\times$ 2). The combined organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give diheptyl 11-hydroxyhenicosanedioate (1.2 g, 77% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 4H), 3.62 -3.54 (m, 1H), 2.29 (t, J = 7.6 Hz, 4H), 1.69 -1.55 (m, 8H), 1.47 -1.24 (m, 44H), 0.91 -0.87 (m, 6H).

[0281] Step 3: diheptyl 11-azidoheicosanedioate



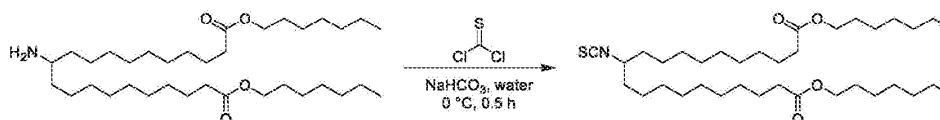
[0282] To a mixture of diheptyl 11-hydroxyhenicosanedioate (1.2 g, 2.11 mmol) in THF (30 mL) was added PPh_3 (1.11 g, 4.22 mmol) and DIAD (853.04 mg, 4.22 mmol) at 0 °C. The mixture was stirred at 25 °C for 10 min, then DPPA (1.16 g, 4.22 mmol) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give diheptyl 11-azidohenicosanedioate (920 mg, 73% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 4H), 3.22 (q, J = 6.4 Hz, 1H), 2.30 (t, J = 7.2 Hz, 4H), 1.68 - 1.59 (m, 8H), 1.49 (t, J = 6.8 Hz, 4H), 1.38 - 1.26 (m, 40H), 0.92 - 0.86 (m, 6H).

[0283] Step 4: diheptyl 11-aminohenicosanedioate



[0284] A mixture of diheptyl 11-azidohenicosanedioate (920 mg, 1.55 mmol) and PPh_3 (813 mg, 3.10 mmol) in THF (30 mL) and water (6 mL) was stirred at 70 °C for 12 hours under N_2 atmosphere. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 0: 1) to give diheptyl 11-aminohenicosanedioate (1.1 g, crude) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 4H), 2.67 (br s, 1H), 2.29 (t, J = 7.6 Hz, 4H), 1.62 (q, J = 6.8 Hz, 8H), 1.51 (br s, 2H), 1.42 - 1.26 (m, 42H), 0.93 - 0.85 (m, 6H).

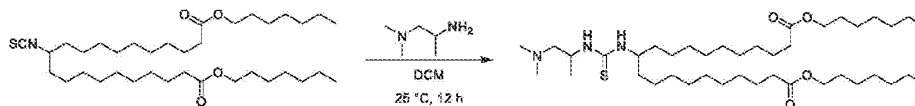
[0285] Step 5: diheptyl 11-isothiocyanatohenicosanedioate



[0286] To a mixture of diheptyl 11-aminohenicosanedioate (600 mg, crude, 665.58 μmol) in DCM (20 mL) was added a solution of NaHCO_3 (391 mg, 4.66 mmol) in water (10 mL), then thiocarbonyl dichloride (153 mg, 1.33 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (20 mL) and water (30 mL). The organic phase was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give diheptyl

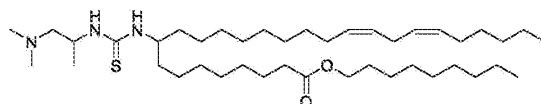
11-isothiocyanatohenicosanedioate (400 mg, 99%yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 4H) , 3.66 -3.57 (m, 1H) , 2.30 (t, J = 7.6 Hz, 4H) , 1.68 -1.58 (m, 10H) , 1.40 -1.23 (m, 42H) , 0.93 -0.86 (m, 6H) .

[0287] Step 6: diheptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate

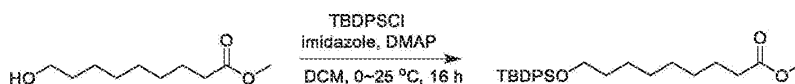


[0288] A mixture of diheptyl 11-isothiocyanatohenicosanedioate (250 mg, 410 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (168 mg, 1.64 mmol) in DCM (10 mL) was stirred at 25 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL) . The organic phase was washed with saturated NaHCO_3 (50 mL) , brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give the crude product, which was further purified by prep-TLC (DCM/MeOH = 25: 1) , and purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give diheptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate (126.4 mg, 43%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.93 (br s, 1H) , 5.78 (br s, 1H) , 4.36 -4.16 (m, 1H) , 4.06 (t, J = 6.8 Hz, 4H) , 3.69 (br s, 1H) , 2.63 -2.52 (m, 1H) , 2.39 -2.20 (m, 11H) , 1.68 -1.58 (m, 8H) , 1.54 -1.23 (m, 44H) , 1.21 (d, J = 6.8 Hz, 3H) , 0.93 -0.85 (m, 6H) . LCMS showed the purity is 100.00%, Rt = 5.196 min; MS Calcd. : 711.6, MS Found: 712.6 $[\text{M}+\text{H}]^+$.

[0289] Example 30: nonyl (18Z, 21Z) -9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptacos-18, 21-dienoate



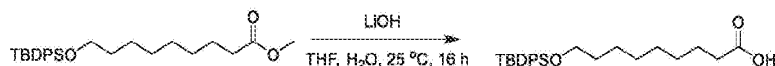
[0290] Step 1: methyl 9- ((tert-butyl diphenylsilyl) oxy) nonanoate



[0291] To a mixture of methyl 9-hydroxynonanoate (2.0 g, 10.6 mmol) , imidazole (2.89 g, 42.5 mmol) , DMAP (260 mg, 2.12 mmol) in DCM (30 mL) was added TBDPSCl (5.84 g, 21.3 mmol, 5.44 mL) at 0 °C, then the mixture was stirred at 25 °C for 16 hours. TLC showed methyl 9-hydroxynonanoate was consumed and one major new spot was detected. The reaction mixture was quenched with saturated NaHCO_3 (100 mL) , extracted with DCM (80 mL $\times$ 2) . The organic phase was separated and washed

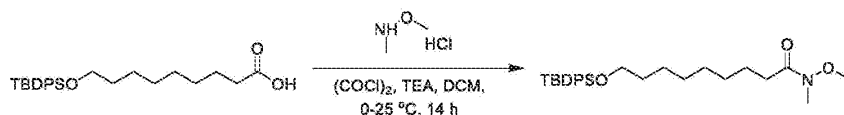
with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 2/25) to give methyl 9-((tert-butyldiphenylsilyl)oxy)nonanoate (3.8 g, 83.8% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.65 (m, 4H), 7.44-7.37 (m, 6H), 3.71-3.59 (m, 5H), 2.31 (t, J = 7.6 Hz, 2H), 1.67-1.51 (m, 6H), 1.39-1.28 (m, 6H), 1.05 (s, 9H).

[0292] Step 2: 9-((tert-butyldiphenylsilyl)oxy)nonanoic acid



[0293] A mixture of methyl 9-((tert-butyldiphenylsilyl)oxy)nonanoate (2 g, 4.69 mmol), LiOH·H₂O (590 mg, 14.1 mmol) in THF (20 mL) and H₂O (5 mL) was stirred at 25 °C for 16 hours. TLC showed methyl 9-((tert-butyldiphenylsilyl)oxy)nonanoate was consumed and one major new spot was detected. The mixture was diluted with HCl (1 N, 2 mL) and H₂O (30 mL) and extracted with EtOAc (30 mL × 2), the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/5) to give 9-((tert-butyldiphenylsilyl)oxy)nonanoic acid (1.55 g, 80.1% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.76-7.65 (m, 4H), 7.46-7.34 (m, 6H), 3.66 (t, J = 6.4 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 1.66-1.52 (m, 4H), 1.39-1.26 (m, 8H), 1.07-1.04 (m, 9H).

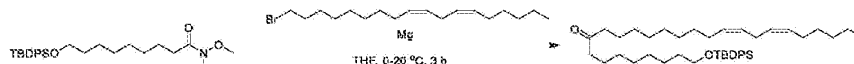
[0294] Step 3: 9-((tert-butyldiphenylsilyl)oxy)-N-methoxy-N-methylnonanamide



[0295] To a mixture of 9-((tert-butyldiphenylsilyl)oxy)nonanoic acid (1.35 g, 3.27 mmol) and DMF (23.9 mg, 327 μmol , 25.1 μL) in DCM (20 mL) was added $(\text{COCl})_2$ (623 mg, 4.91 mmol, 430 μL) at 0 °C, then the mixture was stirred at 25 °C for 2 hours, then the mixture was concentrated to give a residue. The residue in DCM (5 mL) was added into the solution of N-methoxymethanamine (638 mg, 6.54 mmol, HCl), TEA (993 mg, 9.81 mmol, 1.37 mL) in DCM (20 mL) at 0 °C, then the solution was stirred at 25 °C for 12 hours. TLC showed one major new spot was detected. The mixture was diluted with HCl (1 N, 2 mL) and H₂O (30 mL) and extracted with DCM (30 mL × 2), the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 3/20) to give 9-((tert-butyldiphenylsilyl)oxy)-N-methoxy-N-methylnonanamide (1.1 g, 73.8% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.62 (m, 4H), 7.46

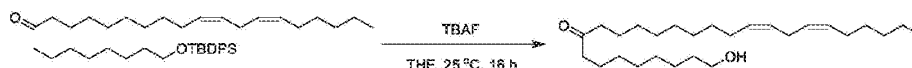
-7.35 (m, 6H) , 3.75 -3.56 (m, 5H) , 3.19 (s, 3H) , 2.41 (t, J= 7.6 Hz, 2H) , 1.68 -1.59 (m, 2H) , 1.55 (d, J= 7.6 Hz, 2H) , 1.40 -1.27 (m, 8H) , 1.05 (s, 9H) .

[0296] Step 4: (18Z, 21Z) -1- ((tert-butyldiphenylsilyl) oxy) heptacos-18, 21-dien-9-one



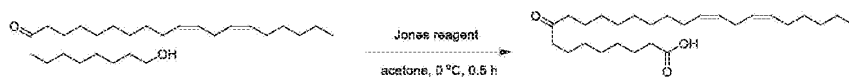
[0297] To a drying 250 mL three-neck flask, Mg (1.85 g, 75.9 mmol) and I₂ (385 mg, 1.52 mmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, then THF (10 mL) was added in the flask and the solution of (6Z, 9Z) -18-bromooctadeca-6, 9-diene (5.0 g, 15.2 mmol) in THF (40 mL) was added slowly to the flask at 20 °C, then the mixture was stirred at 20 °C for 2 hours. Then the mixture was added into the solution of 9- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methylnonanamide (1.0 g, 2.19 mmol) in THF (10 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 hour. The reaction was quenched with saturated NH₄Cl (40 mL) at 0 °C, then the mixture was warmed to 20 °C and extracted with EtOAc (2 × 30 mL) . The combined organic layers were washed brine (30 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to get residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/20) to give (18Z, 21Z) -1- ((tert-butyldiphenylsilyl) oxy) heptacos-18, 21-dien-9-one (1.37 g, 96.5%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.75 -7.63 (m, 4H) , 7.50 -7.34 (m, 6H) , 5.47 -5.26 (m, 4H) , 3.65 (t, J= 6.4 Hz, 2H) , 2.78 (t, J= 6.4 Hz, 2H) , 2.43 -2.33 (m, 4H) , 2.12 -1.99 (m, 4H) , 1.57 (s, 2H) , 1.55-1.51 (m, 2H) , 1.39 -1.24 (m, 26H) , 1.05 (s, 9H) , 0.92 -0.88 (m, 3H) .

[0298] Step 5: (18Z, 21Z) -1-hydroxyheptacos-18, 21-dien-9-one



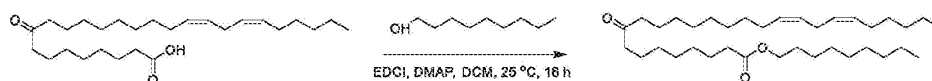
[0299] To a mixture of (18Z, 21Z) -1- ((tert-butyldiphenylsilyl) oxy) heptacos-18, 21-dien-9-one (1.37 g, 2.12 mmol) in THF (20 mL) was added TBAF (1 M, 10.6 mL) under N₂ atmosphere. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO₃ (50 mL) , extracted with EtOAc (100 mL × 2) , the combined organic layers were washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 4/25) to give (18Z, 21Z) -1-hydroxyheptacos-18, 21-dien-9-one (750 mg, 86.8%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.48 -5.25 (m, 4H) , 3.64 (s, 2H) , 2.78 (t, J= 6.4 Hz, 2H) , 2.39 (t, J= 7.6 Hz, 4H) , 2.10 -2.02 (m, 4H) , 1.56 (d, J= 6.4 Hz, 4H) , 1.41 -1.25 (m, 26H) , 0.95 -0.86 (m, 3H) .

[0300] Step 6: (18Z, 21Z) -9-oxoheptacos-18, 21-dienoic acid



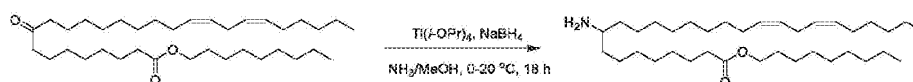
- [0301] To a mixture of (18Z, 21Z) -1-hydroxyheptacos-18, 21-dien-9-one (750 mg, 1.84 mmol) in acetone (15 mL) was added Jones reagent (2.5 M, 1.48 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (1 mL) , diluted with H₂O (20 mL) and extracted with EtOAc (30 mL× 3) , the combined organic layers were washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give (18Z, 21Z) -9-oxoheptacos-18, 21-dienoic acid (540 mg, 69.6%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.44 -5.27 (m, 4H) , 2.78 (t, J= 6.4 Hz, 2H) , 2.42 -2.32 (m, 6H) , 2.07 -2.04 (m, 4H) , 1.68 -1.60 (m, 4H) , 1.41 -1.27 (m, 24H) , 0.91 -0.87 (m, 3H) .

- [0302] Step 7: nonyl (18Z, 21Z) -9-oxoheptacos-18, 21-dienoate



- [0303] A mixture of (18Z, 21Z) -9-oxoheptacos-18, 21-dienoic acid (540 mg, 1.28 mmol) , nonan-1-ol (370 mg, 2.57 mmol) , EDCI (492 mg, 2.57 mmol) , DMAP (157 mg, 1.28 mmol) in DCM (10 mL) was stirred at 25 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give nonyl (18Z, 21Z) -9-oxoheptacos-18, 21-dienoate (600 mg, 85.5%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.46 -5.27 (m, 4H) , 4.06 (t, J= 6.8 Hz, 2H) , 2.78 (t, J= 6.4 Hz, 2H) , 2.38 (t, J= 7.6 Hz, 4H) , 2.29 (t, J= 7.6 Hz, 2H) , 2.10 -2.01 (m, 4H) , 1.69 -1.60 (m, 4H) , 1.59 -1.55 (m, 4H) , 1.40 -1.27 (m, 34H) , 0.92 -0.87 (m, 6H) .

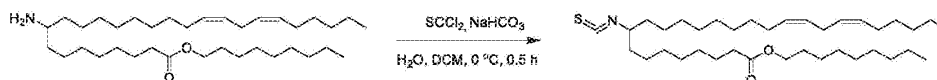
- [0304] Step 8: nonyl (18Z, 21Z) -9-aminoheptacos-18, 21-dienoate



- [0305] A mixture of nonyl (18Z, 21Z) -9-oxoheptacos-18, 21-dienoate (600 mg, 1.10 mmol) , iPrO₄Ti (624 mg, 2.19 mmol, 648 μL) in MeOH (10 mL) and NH₃/MeOH (4 mL) , then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (83.0 mg, 2.19 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20°C for 12 hours. The mixture was quenched with H₂O (5 mL) and diluted with ethyl acetate (30 mL) . The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 30 mL) , the combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/2) to give nonyl (18Z, 21Z) -9-aminoheptacos-18, 21-dienoate (270 mg, 44.9%yield) as a light-yellow

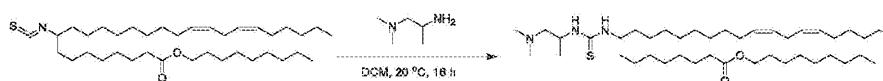
oil. ^1H NMR (400 MHz, CDCl_3) δ 5.48 -5.28 (m, 4H) , 4.06 (t, J = 6.8 Hz, 2H) , 2.78 (t, J =6.4 Hz, 2H) , 2.67 (d, J = 2.4 Hz, 1H) , 2.30 (t, J = 7.6 Hz, 2H) , 2.10 -2.01 (m, 4H) , 1.62 (quin, J = 7.2 Hz, 4H) , 1.37 -1.18 (m, 42H) , 0.93 -0.86 (m, 6H) .

[0306] Step 9: nonyl (18Z, 21Z) -9-isothiocyanatoheptacos-18, 21-dienoate



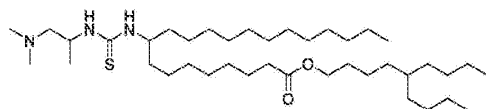
[0307] To a mixture of nonyl (18Z, 21Z) -9-aminoheptacos-18, 21-dienoate (270 mg, 493 μmol) and NaHCO_3 (290 mg, 3.45 mmol) in DCM (15 mL) and H_2O (15 mL) was added SCCl_2 (73.7 mg, 641 μmol , 49.1 μL) at $0\text{ }^\circ\text{C}$, then the mixture was stirred at $0\text{ }^\circ\text{C}$ for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc : PE = 0 to 1/20) to give nonyl (18Z, 21Z) -9-isothiocyanatoheptacos-18, 21-dienoate (278 mg, 95.6%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.48 -5.29 (m, 4H) , 4.07 (t, J = 6.8 Hz, 2H) , 3.70 -3.55 (m, 1H) , 2.78 (t, J = 6.4 Hz, 2H) , 2.30 (t, J = 7.6 Hz, 2H) , 2.06 (q, J = 6.8 Hz, 4H) , 1.65 -1.60 (m, 4H) , 1.55 -1.41 (m, 4H) , 1.41 -1.25 (m, 38H) , 0.95 -0.83 (m, 6H) .

[0308] Step 10: nonyl (18Z, 21Z) -9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptacos-18, 21-dienoate

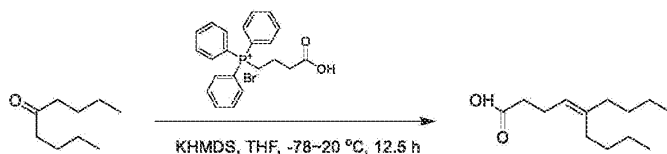


[0309] A mixture of nonyl (18Z, 21Z) -9-isothiocyanatoheptacos-18, 21-dienoate (278 mg, 471 μmol) , N^1, N^1 -dimethylpropane-1, 2-diamine (96.3 mg, 942 μmol) in DCM (5 mL) was stirred at $20\text{ }^\circ\text{C}$ for 16 hours. The mixture was diluted with DCM (50 mL) , washed with HCl (1N, 10 mL) , saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc/PE =0 to 3/5, MeOH/DCM =0 to 1/20) to give the crude, the crude was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 55%-85%B over 20 min) to give nonyl (18Z, 21Z) -9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptacos-18, 21-dienoate (76.1 mg, 23.3%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.47 -5.22 (m, 4H) , 4.38 -4.17 (m, 1H) , 4.06 (t, J = 6.8 Hz, 3H) , 2.78 (t, J = 6.8 Hz, 3H) , 2.66 -2.21 (m, 9H) , 2.09 -2.01 (m, 4H) , 1.64 -1.60 (m, 4H) , 1.55 -1.50 (m, 2H) , 1.39 -1.23 (m, 43H) , 0.94 -0.84 (m, 6H) . LCMS showed the purity is 100%, Rt = 2.491 min; MS Calcd. : 691.6, MS Found: 692.6 $[\text{M}+\text{H}]^+$.

[0310] Example 31: 5-butylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate

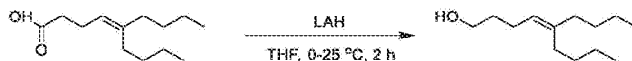


[0311] Step 1: 5-butylnon-4-enoic acid



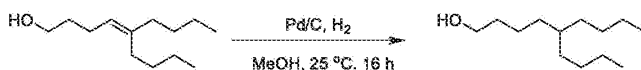
[0312] To a mixture of (3-carboxypropyl) triphenylphosphonium bromide (30.18 g, 70.3 mmol) in THF (100 mL) was added KHMDS (1 M, 141 mL) at -78 °C, then the mixture was stirred at 20 °C for 0.5 hour, then the solution of nonan-5-one (5 g, 35.2 mmol) in THF (20 mL) at -78 °C, then the mixture was stirred at 25 °C for 12 hours. The reaction was quenched with H₂O (50 mL) at 0 °C. The two layers were separated, and the aqueous layer was acidified with 10% HCl to pH = 2. The aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/25) to give 5-butylnon-4-enoic acid (5 g, crude) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.16-5.05 (m, 1H), 2.38-2.28 (m, 4H), 2.04-1.94 (m, 4H), 1.37-1.32 (m, 8H), 0.93 (s, 6H).

[0313] Step 2: 5-butylnon-4-en-1-ol



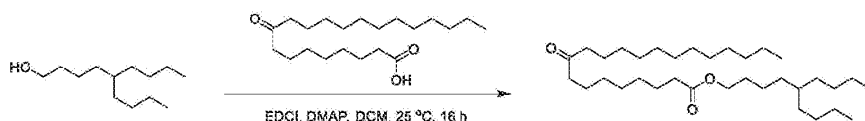
[0314] To a mixture of 5-butylnon-4-enoic acid (5 g, crude) in THF (50 mL) was added LiAlH₄ (2.5 M, 14.1 mL) at 0 °C under N₂ atmosphere. The mixture was allowed warm to 25 °C and stirred at 25 °C for 2 hours N₂ atmosphere. Then, the reaction mixture was cooled to 0 °C by ice-bath. Then Na₂SO₄·10H₂O (30 g) was added slowly. The mixture was stirred at 25 °C for 1 hour, then filtered and the filter cake was washed with EtOAc (50 mL × 3). The filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 4/25) to give 5-butylnon-4-en-1-ol (1 g, 21.4% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.12 (t, J = 7.2 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 2.10 (q, J = 7.2 Hz, 2H), 2.04-1.94 (m, 4H), 1.68-1.60 (m, 2H), 1.38-1.29 (m, 8H), 0.94-0.89 (m, 6H).

[0315] Step 3: 5-butylnonan-1-ol



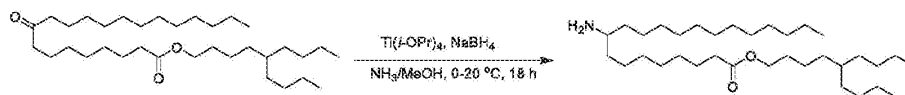
[0316] A mixture of 5-butylnon-4-en-1-ol (1 g, 5.04 mmol), Pd/C (1 g, 10% purity) in MeOH (20 mL) under N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (30 psi) at 25 °C for 16 hours. The reaction mixture was filtered, the filter cake was washed with MeOH (20 mL × 3) and the filter was concentrated to give 5-butylnonan-1-ol (800 mg, 79.2% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.66 (t, J = 6.8 Hz, 2H), 1.58 - 1.52 (m, 2H), 1.36 - 1.23 (m, 17H), 0.90 (t, J = 6.8 Hz, 6H).

[0317] Step 4: 5-butylnonyl 9-oxohenicosanoate



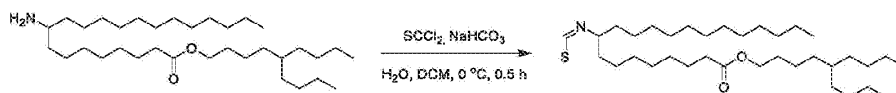
[0318] A mixture of 9-oxohenicosanoic acid (1.50 g, 4.39 mmol), 5-butylnonan-1-ol (800 mg, 3.99 mmol), EDCI (1.53 g, 7.99 mmol), DMAP (488 mg, 3.99 mmol) in DCM (20 mL) was stirred at 25 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 5-butylnonyl 9-oxohenicosanoate (1.6 g, 76.6% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.07 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.6 Hz, 4H), 2.33 - 2.26 (m, 2H), 1.65 - 1.58 (m, 4H), 1.57 - 1.49 (m, 4H), 1.38 - 1.15 (m, 41H), 0.92 - 0.86 (m, 9H).

[0319] Step 5: 5-butylnonyl 9-aminohenicosanoate



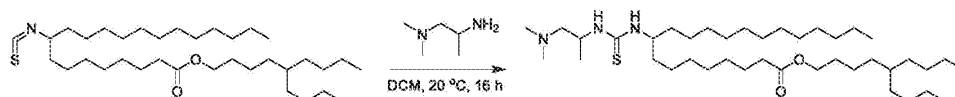
[0320] A mixture of 5-butylnonyl 9-oxohenicosanoate (1.5 g, 2.87 mmol), iPrO₄Ti (1.63 g, 5.74 mmol, 1.69 mL) in MeOH (20 mL) and NH₃/MeOH (7 M, 8 mL), then mixture was stirred at 20 °C for 6 hours, then NaBH₄ (217. mg, 5.74 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20 °C for 12 hours. The mixture was quenched with H₂O (10 mL) and diluted with ethyl acetate (30 mL). The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 50 mL), the combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/2) to give 5-butylnonyl 9-aminohenicosanoate (670 mg, 44.6% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.07 (t, J = 6.8 Hz, 2H), 2.67 (d, J = 2.8 Hz, 1H), 2.35 - 2.25 (m, 2H), 1.66 - 1.56 (m, 4H), 1.38 (d, J = 6.4 Hz, 4H), 1.33 - 1.23 (m, 45H), 0.92 - 0.87 (m, 9H).

[0321] Step 6: 5-butylnonyl 9-isothiocyanatohenicosanoate

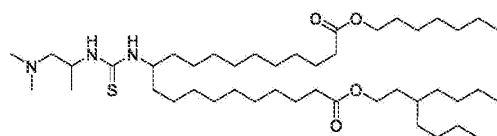


- [0322] To a mixture of 5-butylnonyl 9-aminohenicosanoate (300 mg, 573 μ mol) and NaHCO_3 (337 mg, 4.01 mmol) in DCM (15 mL) and H_2O (15 mL) was added SCCl_2 (85.6 mg, 744 μ mol, 57.1 μ L) at 0 $^\circ\text{C}$, then the mixture was stirred at 0 $^\circ\text{C}$ for 0.5 hour. The mixture was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/20) to give 5-butylnonyl 9-isothiocyantohenicosanoate (300 mg, 92.6% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.07 (t, J = 6.8 Hz, 2H), 3.67 -3.56 (m, 1H), 2.36 -2.25 (m, 2H), 1.66 -1.57 (m, 6H), 1.56 -1.50 (m, 2H), 1.44 -1.19 (m, 45H), 0.93 -0.86 (m, 9H).

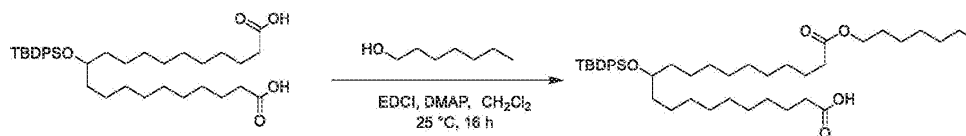
- [0323] Step 7: 5-butylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate



- [0324] A mixture of 5-butylnonyl 9-isothiocyantohenicosanoate (300 mg, 530 μ mol), N^1 , N^1 -dimethylpropane-1, 2-diamine (108 mg, 1.06 mmol) in DCM (5 mL) was stirred at 20 $^\circ\text{C}$ for 16 hours. The mixture was diluted with DCM (50 mL), washed with HCl (1 N, 10 mL), saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc/PE=0 to 3/5, MeOH/DCM=0 to 1/20) to give the crude, the crude was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μ m; mobile phase: [water (FA) -ACN]; gradient: 55%-85%B over 20 min) to give 5-butylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate (104.5 mg, 29.4% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.38 -4.12 (m, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.97 -3.64 (m, 1H), 2.75 -2.59 (m, 1H), 2.47 -2.19 (m, 9H), 1.67 -1.44 (m, 8H), 1.35 -1.17 (m, 48H), 0.96 -0.83 (m, 9H). LCMS showed the purity is 99.79%, R_t = 3.185 min; MS Calcd.: 667.6, MS Found: 668.6 $[\text{M}+\text{H}]^+$.
- [0325] Example 32: 1- (3-butylheptyl) 21-heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate

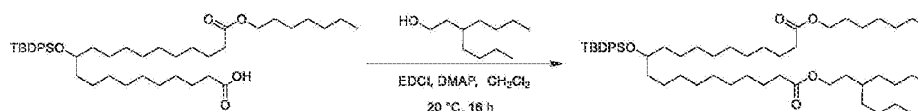


- [0326] Step 1: 11- ((tert-butylidiphenylsilyl) oxy) -21- (heptyloxy) -21-oxohenicosanoic acid



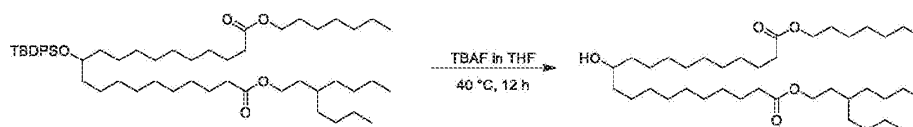
- [0327] To a mixture of 11- ((tert-butylidiphenylsilyl) oxy) henicosanedioic acid (8.0 g, 13.1 mmol) in DCM (50 mL) was added EDCI (3.01 g, 15.7 mmol) and DMAP (1.92 g, 15.7 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, then heptan-1-ol (1.37 g, 11.8 mmol) in DCM (20 mL) was added. The mixture was stirred at 25 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was diluted with saturated NaHCO₃ (80 mL). The mixture was extracted with DCM (80 mL). The combined organic phase was washed with brine (120 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 11- ((tert-butylidiphenylsilyl) oxy) -21- (heptyloxy) -21-oxohenicosanoic acid (3.5 g, 38% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.71 -7.65 (m, 4H), 7.45 -7.32 (m, 6H), 4.07 (t, J= 6.8 Hz, 2H), 3.70 (q, J= 5.6 Hz, 1H), 2.35 (t, J= 7.6 Hz, 2H), 2.30 (t, J= 7.6 Hz, 2H), 1.69 -1.57 (m, 6H), 1.46 -1.09 (m, 36H), 1.05 (s, 9H), 0.92-0.86 (m, 3H).

- [0328] Step 2: 1- (3-butylheptyl) 21-heptyl 11- ((tert-butylidiphenylsilyl) oxy) henicosanedioate



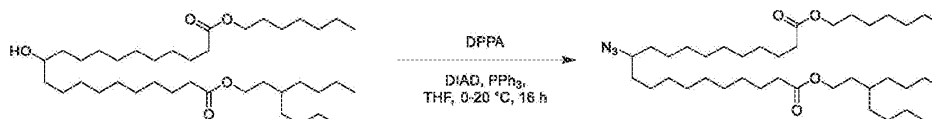
- [0329] To a mixture of 11- ((tert-butylidiphenylsilyl) oxy) -21- (heptyloxy) -21-oxohenicosanoic acid (3.5 g, 4.94 mmol) in DCM (50 mL) was added EDCI (1.89 g, 9.87 mmol) and DMAP (1.21 g, 9.87 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, then 3-butylheptan-1-ol (1.02 g, 5.92 mmol) was added. The mixture was stirred at 20 °C for 16 hours. TLC showed that one new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1- (3-butylheptyl) 21-heptyl 11- ((tert-butylidiphenylsilyl) oxy) henicosanedioate (2.8 g, 66% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.71 -7.64 (m, 4H), 7.47 -7.32 (m, 6H), 4.12 -4.04 (m, 4H), 3.70 (q, J= 5.6 Hz, 1H), 2.29 (dt, J= 2.4, 7.6 Hz, 4H), 1.68 -1.57 (m, 8H), 1.43 -1.13 (m, 49H), 1.05 (s, 9H), 0.92 -0.87 (m, 9H).

- [0330] Step 3: 1- (3-butylheptyl) 21-heptyl 11-hydroxyhenicosanedioate



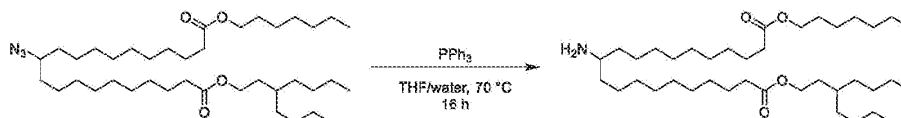
[0331] To a mixture of 1- (3-butylheptyl) 21-heptyl 11- ((tert-butyldiphenylsilyl) oxy) henicosanedioate (2.8 g, 3.24 mmol) in THF (50 mL) was added TBAF (1 M, 16.2 mL) . The mixture was stirred at 40 °C for 12 hours under N₂ atmosphere. TLC showed that one new spot was observed. The reaction mixture was diluted with water (100 mL) , extracted with EtOAc (100 mL × 2) . The combined organic phase was washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 1- (3-butylheptyl) 21-heptyl 11-hydroxyhenicosanedioate (1.7 g, crude) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.04 -3.96 (m, 4H) , 3.55 -3.47 (m, 1H) , 2.21 (dt, J= 2.4, 7.6 Hz, 4H) , 1.61 -1.48 (m, 8H) , 1.28-1.14 (m, 49H) , 0.85 -0.78 (m, 9H) .

[0332] Step 4: 1- (3-butylheptyl) 21-heptyl 11-azidohenicosanedioate



[0333] To a mixture of 1- (3-butylheptyl) 21-heptyl 11-hydroxyhenicosanedioate (1.7 g, crude, 2.72 mmol) in THF (50 mL) was added PPh₃ (1.43 g, 5.44 mmol) and DIAD (1.10 g, 5.44 mmol, 1.05 mL) at 0 °C. The mixture was stirred at 20 °C for 10 min, then DPPA (1.50 g, 5.44 mmol, 1.17 mL) was added. The mixture was stirred at 20 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1- (3-butylheptyl) 21-heptyl 11-azidohenicosanedioate (1.3 g, crude) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.11 -4.04 (m, 4H) , 3.27 -3.18 (m, 1H) , 2.32-2.24 (m, 4H) , 1.69 -1.58 (m, 8H) , 1.52 -1.47 (m, 2H) , 1.36 -1.22 (m, 47H) , 0.92 -0.85 (m, 9H) .

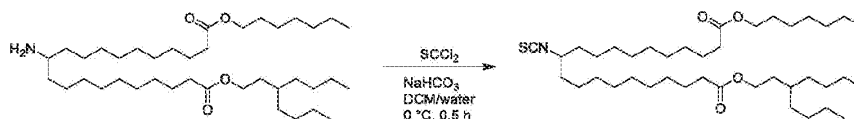
[0334] Step 5: 1- (3-butylheptyl) 21-heptyl 11-aminohenicosanedioate



[0335] A mixture of 1- (3-butylheptyl) 21-heptyl 11-azidohenicosanedioate (1.3 g, crude, 2.00 mmol) and PPh₃ (1.05 g, 4.00 mmol) in THF (40 mL) and water (8 mL) was stirred at 70 °C for 16 hours under N₂ atmosphere. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 0: 1) to give 1- (3-

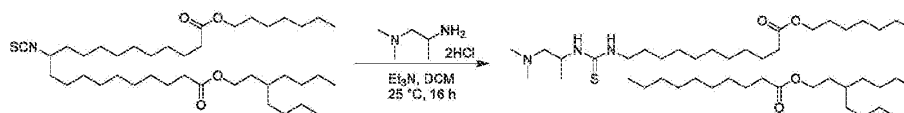
butylheptyl) 21-heptyl 11-aminohenicosanedioate (630 mg, crude) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.14 -4.02 (m, 4H) , 2.71 (br s, 1H) , 2.29 (dt, J = 2.4, 7.6 Hz, 4H) , 1.66 -1.53 (m, 8H) , 1.44 -1.20 (m, 49H) , 0.97 -0.83 (m, 9H) .

[0336] Step 6: 1- (3-butylheptyl) 21-heptyl 11-isothiocyanatohenicosanedioate



[0337] To a mixture of 1- (3-butylheptyl) 21-heptyl 11-aminohenicosanedioate (630 mg, crude, 1.01 mmol) in DCM (20 mL) was added a solution of NaHCO_3 (594 mg, 7.07 mmol) in water (10 mL) , then thiocarbonyl dichloride (232 mg, 2.02 mmol) was added at $0\text{ }^\circ\text{C}$. The mixture was stirred at $0\text{ }^\circ\text{C}$ for 0.5 hour. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (20 mL) and water (30 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1- (3-butylheptyl) 21-heptyl 11-isothiocyanatohenicosanedioate (200 mg, 30%yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.12 -4.04 (m, 4H) , 3.67 -3.57 (m, 1H) , 2.30 (dt, J = 2.4, 7.6 Hz, 4H) , 1.68 -1.58 (m, 9H) , 1.41 -1.22 (m, 48H) , 0.93 -0.85 (m, 9H) .

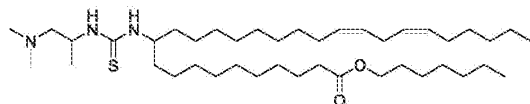
[0338] Step 7: 1- (3-butylheptyl) 21-heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate



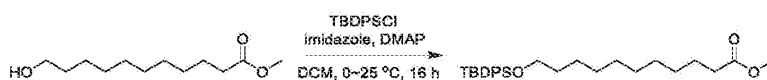
[0339] A mixture of 1- (3-butylheptyl) 21-heptyl 11-isothiocyanatohenicosanedioate (200 mg, 300 μmol) , N^1 , N^1 -dimethylpropane-1, 2-diamine (105 mg, 601 μmol , 2HCl) and Et_3N (122 mg, 1.20 mmol) in DCM (5 mL) was stirred at $25\text{ }^\circ\text{C}$ for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL) . The organic phase was washed with saturated NaHCO_3 (50 mL) , brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 50%-80%B over 20 min) to give 1- (3-butylheptyl) 21-heptyl 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate (56.4 mg, 24%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.92 (br s, 1H) , 5.94 (br s, 1H) , 4.36 -4.11 (m, 1H) , 4.05 -3.95 (m, 4H) , 3.88 -3.47 (m, 1H) , 2.64 -2.46 (m, 1H) , 2.38 -2.13 (m, 11H) , 1.63 -1.40 (m, 8H) ,

1.36 -1.09 (m, 49H) , 1.14 (d, J= 6.8 Hz, 3H) , 0.89 -0.75 (m, 9H) . LCMS showed the purity is 100.00%, Rt = 3.728 min; MS Calcd. : 767.7, MS Found: 768.6 [M+H]⁺.

[0340] Example 33: heptyl (20Z, 23Z) -11- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonacosa-20, 23-dienoate

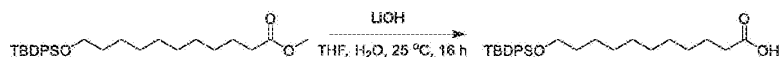


[0341] Step 1: methyl 11- ((tert-butyldiphenylsilyl) oxy) undecanoate



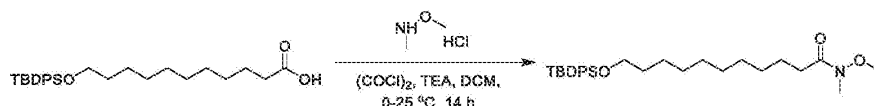
[0342] To a mixture of methyl 11-hydroxyundecanoate (5 g, 23.1 mmol) , imidazole (6.29 g, 92.5 mmol) , DMAP (565 mg, 4.62 mmol) in DCM (100 mL) was added TBDPSCl (12.71 g, 46.2 mmol, 11.8 mL) at 0 °C, then the mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO₃ (100 mL) , extracted with DCM (100 mL × 2) . The organic phase was separated and washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 2/25) to give methyl 11- ((tert-butyldiphenylsilyl) oxy) undecanoate (10 g, 95.1%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.71 -7.62 (m, 4H) , 7.44 -7.38 (m, 6H) , 3.71 -3.61 (m, 5H) , 2.31 (t, J= 7.6 Hz, 2H) , 1.67 -1.56 (m, 6H) , 1.36 -1.26 (m, 10H) , 1.06 (s, 9H) .

[0343] Step 2: 11- ((tert-butyldiphenylsilyl) oxy) undecanoic acid



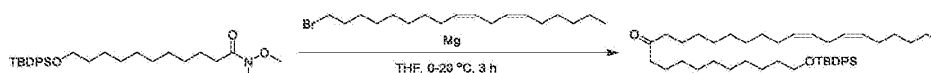
[0344] A mixture of 11- ((tert-butyldiphenylsilyl) oxy) undecanoate (10 g, 22.0 mmol) , LiOH. H₂O (2.77 g, 66.0 mmol) in THF (50 mL) and H₂O (10 mL) was stirred at 25 °C for 16 hours. The mixture was diluted with HCl (1 N, 50 mL) and H₂O (30 mL) and extracted with EtOAc (100 mL × 2) , the combined organic layers were washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give 11- ((tert-butyldiphenylsilyl) oxy) undecanoic acid (9.5 g, 98.0%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 -7.65 (m, 4H) , 7.43 -7.38 (m, 6H) , 3.66 (t, J= 6.4 Hz, 2H) , 2.36 (t, J= 7.6 Hz, 2H) , 1.67 -1.62 (m, 2H) , 1.58 -1.54 (m, 2H) , 1.38 -1.26 (m, 12H) , 1.05 (s, 9H) .

[0345] Step 3: 11- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methylundecanamide



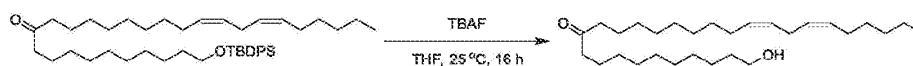
[0346] To a mixture of 11-((tert-butyldiphenylsilyl)oxy)undecanoic acid (9.5 g, 21.6 mmol) and DMF (158 mg, 2.16 mmol, 166 μ L) in DCM (80 mL) was added (COCl)₂ (4.10 g, 32.3 mmol, 2.83 mL) at 0 °C, then the mixture was stirred at 25 °C for 2 hours, then the mixture was concentrated to give a residue. The residue in DCM (40 mL) was added into the solution of N-methoxymethanamine (4.21 g, 43.1 mmol, HCl), TEA (6.54 g, 64.7 mmol, 9.00 mL) in DCM (80 mL) at 0 °C, then the solution was stirred at 25 °C for 12 hours. TLC showed one major new spot was detected. The mixture was diluted with HCl (1 N, 10 mL) and H₂O (50 mL) and extracted with DCM (60 mL $\times$ 2), the combined organic layers were washed with saturated NaHCO₃ (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 3/20) to give 11-((tert-butyldiphenylsilyl)oxy)-N-methoxy-N-methylundecanamide (5.2 g, 49.9% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.71 -7.64 (m, 4H), 7.46 -7.35 (m, 6H), 3.75 -3.62 (m, 5H), 3.19 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H), 1.62 (d, J = 7.2 Hz, 2H), 1.57 -1.52 (m, 2H), 1.38 -1.25 (m, 12H), 1.05 (s, 9H).

[0347] Step 4: (20Z, 23Z)-1-((tert-butyldiphenylsilyl)oxy)nonacosa-20, 23-dien-11-one



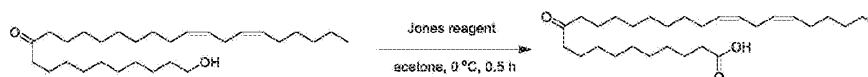
[0348] To a drying 250 mL three-neck flask, Mg (1.85 g, 75.9 mmol) and I₂ (385 mg, 1.52 mmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, then THF (10 mL) was added in the flask and the solution of (6Z, 9Z)-18-bromooctadec-6, 9-diene (5 g, 15.2 mmol) in THF (40 mL) was added slowly to the flask at 20 °C, then the mixture was stirred at 20 °C for 2 hours. Then the mixture was added into the solution of 11-((tert-butyldiphenylsilyl)oxy)-N-methoxy-N-methylundecanamide (2 g, 4.13 mmol) in THF (10 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 hour. The reaction was quenched with saturated NH₄Cl (40 mL) at 0 °C, then the mixture was warmed to 20 °C and extracted with EtOAc (2 $\times$ 30 mL). The combined organic layers were washed brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to get residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/20) to give (20Z, 23Z)-1-((tert-butyldiphenylsilyl)oxy)nonacosa-20, 23-dien-11-one (2.5 g, 89.9% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.67 -7.54 (m, 4H), 7.38 -7.24 (m, 6H), 5.38 -5.19 (m, 4H), 3.58 (t, J = 6.4 Hz, 2H), 2.70 (t, J = 6.4 Hz, 2H), 2.31 (t, J = 7.6 Hz, 4H), 2.05 -1.93 (m, 4H), 1.50 (s, 2H), 1.47 -1.44 (m, 2H), 1.31 -1.16 (m, 30H), 0.97 (s, 9H), 0.84 -0.80 (m, 3H).

[0349] Step 5: (20Z, 23Z)-1-hydroxynonacosa-20, 23-dien-11-one



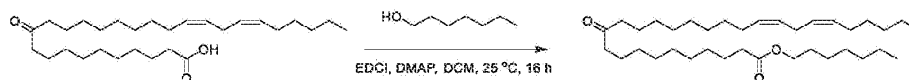
[0350] To a mixture of (20Z, 23Z)-1-(tert-butyldiphenylsilyl oxy) nonacos-20, 23-dien-11-one (2.5 g, 3.71 mmol) in THF (40 mL) was added TBAF (1 M, 18.6 mL) under N₂ atmosphere. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO₃ (50 mL), extracted with EtOAc (50 mL × 2), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give (20Z, 23Z)-1-hydroxynonacos-20, 23-dien-11-one (1.5 g, 92.9% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.47-5.24 (m, 4H), 3.70-3.59 (m, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 7.6 Hz, 4H), 2.10-1.98 (m, 4H), 1.59-1.54 (m, 4H), 1.41-1.25 (m, 30H), 0.93-0.87 (m, 3H).

[0351] Step 6: (20Z, 23Z)-11-oxononacos-20, 23-dienoic acid



[0352] To a mixture of (20Z, 23Z)-1-hydroxynonacos-20, 23-dien-11-one (1.5 g, 3.45 mmol) in acetone (30 mL) was added Jones reagent (2.5 M, 2.76 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (1 mL), diluted with H₂O (30 mL) and extracted with EtOAc (50 mL × 3), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give (20Z, 23Z)-11-oxononacos-20, 23-dienoic acid (1.2 g, 77.5% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.38-5.35 (m, 4H), 2.78 (s, 2H), 2.45-2.30 (m, 6H), 2.05 (d, J = 2.4 Hz, 4H), 1.68-1.58 (m, 4H), 1.37-1.29 (m, 28H), 0.90 (s, 3H).

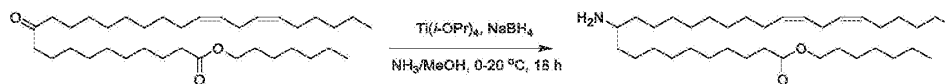
[0353] Step 7: heptyl (20Z, 23Z)-11-oxononacos-20, 23-dienoate



[0354] A mixture of (20Z, 23Z)-11-oxononacos-20, 23-dienoic acid (1.2 g, 2.67 mmol), heptan-1-ol (622 mg, 5.35 mmol, 756 μL), EDCI (1.03 g, 5.35 mmol), DMAP (327 mg, 2.67 mmol) in DCM (20 mL) was stirred at 25 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give heptyl (20Z, 23Z)-11-oxononacos-20, 23-dienoate (1.29 g, 88.2% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.45-5.29 (m, 4H), 4.06 (t, J = 6.8 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.38 (t, J = 7.6 Hz,

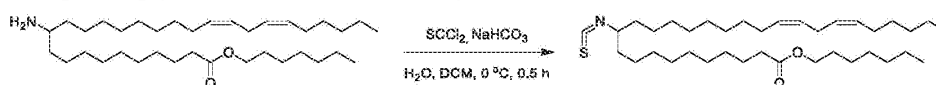
4H) , 2.29 (t, J= 7.6 Hz, 2H) , 2.10 -2.01 (m, 4H) , 1.66 -1.59 (m, 4H) , 1.54 (s, 4H) , 1.39 -1.27 (m, 34H) , 0.93 -0.86 (m, 6H) .

[0355] Step 8: heptyl (20Z, 23Z) -11-aminononacosa-20, 23-dienoate



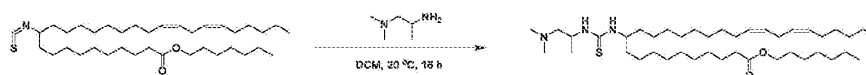
[0356] A mixture of heptyl (20Z, 23Z) -11-oxononacosa-20, 23-dienoate (1.2 g, 2.19 mmol) , Ti (i-PrO) ₄ (1.25 g, 4.39 mmol, 1.30 mL) in MeOH (25 mL) and NH₃/MeOH (7 M, 10 mL) , then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (166 mg, 4.39 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20°C for 12 hours. The mixture was quenched with H₂O (5 mL) and diluted with ethyl acetate (30 mL) . The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 30 mL) , the combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/2) to give heptyl (20Z, 23Z) -11-aminononacosa-20, 23-dienoate (1.1 g, 91.5%yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.47 -5.28 (m, 4H) , 4.06 (t, J= 6.8 Hz, 2H) , 2.78 (t, J = 6.4 Hz, 3H) , 2.29 (t, J= 7.6 Hz, 2H) , 2.06 (q, J= 6.8 Hz, 4H) , 1.66 -1.58 (m, 4H) , 1.42 -1.23 (m, 42H) , 0.95 -0.84 (m, 6H) .

[0357] Step 9: heptyl (20Z, 23Z) -11-isothiocyanatononacosa-20, 23-dienoate



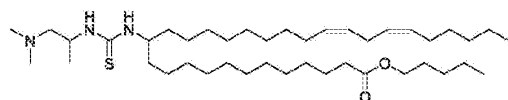
[0358] To a mixture of heptyl (20Z, 23Z) -11-aminononacosa-20, 23-dienoate (300 mg, 548 μmol) and NaHCO₃ (322 mg, 3.83 mmol) in DCM (15 mL) and H₂O (15 mL) was added SCl₂ (81.8 mg, 712 μmol, 54.6 μL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/20) to give heptyl (20Z, 23Z) -11-isothiocyanatononacosa-20, 23-dienoate (280 mg, 86.7%yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.43 -5.31 (m, 4H) , 4.07 (t, J= 7.0 Hz, 2H) , 3.65-3.59 (m, 1H) , 2.78 (t, J= 6.5 Hz, 2H) , 2.34 -2.28 (m, 2H) , 2.06 (q, J = 7.0 Hz, 4H) , 1.66 -1.56 (m, 8H) , 1.40 -1.28 (m, 38H) , 0.92 -0.88 (m, 6H) .

[0359] Step 10: heptyl (20Z, 23Z) -11- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonacosa-20, 23-dienoate

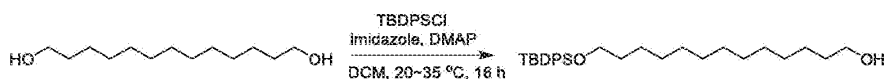


[0360] A mixture of heptyl (20Z, 23Z) -11-isothiocyanatononacos-20, 23-dienoate (280 mg, 475 μ mol), N^1, N^1 -dimethylpropane-1, 2-diamine (97 mg, 949 μ mol) in DCM (5 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with DCM (50 mL), washed with HCl (1 N, 10 mL), saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μ m; mobile phase: [water (FA) -ACN]; gradient: 55%-85%B over 20 min) to give heptyl (20Z, 23Z) -11- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonacos-20, 23-dienoate (124.8 mg, 38.0%yield) as light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.45 -5.27 (m, 4H), 4.37 -4.14 (m, 1H), 4.06 (t, J = 6.8 Hz, 3H), 2.85 -2.64 (m, 3H), 2.57 -2.25 (m, 9H), 2.06 (q, J = 6.8 Hz, 4H), 1.67 -1.59 (m, 4H), 1.56 -1.49 (m, 2H), 1.39-1.22 (m, 43H), 0.95 -0.84 (m, 6H). LCMS showed the purity is 100%, R_t = 3.171 min; MS Calcd.: 691.6, MS Found: 692.6 $[\text{M}+\text{H}]^+$.

[0361] Example 34: pentyl (22Z, 25Z) -13- (3- (1- (dimethylamino) propan-2-yl) thioureido) hentriaconta-22, 25-dienoate

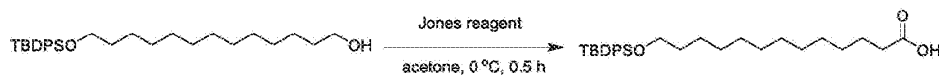


[0362] Step 1: 13- ((tert-butyldiphenylsilyl) oxy) tridecan-1-ol



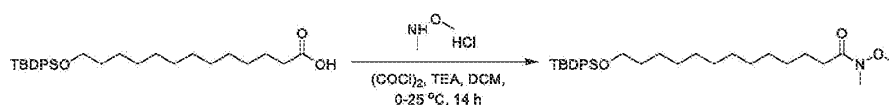
[0363] To a mixture of tridecane-1, 13-diol (10 g, 46.2 mmol), imidazole (6.29 g, 92.4 mmol), DMAP (565 mg, 4.62 mmol) in DCM (150 mL) was added the solution TBDPSCI (11.4 g, 41.6 mmol, 10.7 mL) in DCM (40 mL) at 35 °C, then the mixture was stirred at 20 °C for 16hours. TLC showed the starting material was remained and two major new spots were detected. The reaction mixture was quenched with saturated NaHCO_3 (200 mL), extracted with DCM (100 mL $\times$ 2). The organic phase was separated and washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/4) to give 13- ((tert-butyldiphenylsilyl) oxy) tridecan-1-ol (10.6 g, 50.4%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 -7.66 (m, 4H), 7.45 -7.36 (m, 6H), 3.70 -3.61 (m, 4H), 1.62 -1.57 (m, 2H), 1.39 -1.23 (m, 20H), 1.05 (s, 9H).

[0364] Step 2: 13- ((tert-butyldiphenylsilyl) oxy) tridecanoic acid



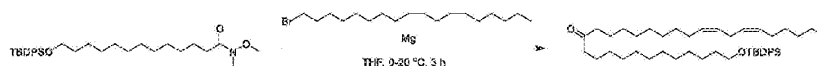
[0365] A mixture of 13- ((tert-butyldiphenylsilyl) oxy) tridecan-1-ol (10.6 g, 23.3 mmol) in acetone (100 mL) was added Jones reagent (2.5 M, 18.7 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (10 mL) , diluted with H₂O (100 mL) and extracted with EtOAc (100 mL × 3) , the combined organic layer was washed with brine (100 mL) and dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/3) to give 13- ((tert-butyldiphenylsilyl) oxy) tridecanoic acid (10 g, 91.5%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 -7.65 (m, 4H) , 7.44 -7.37 (m, 6H) , 3.66 (t, J= 6.4 Hz, 2H) , 2.36 (t, J= 7.6 Hz, 2H) , 1.68 -1.62 (m, 2H) , 1.59 -1.53 (m, 2H) , 1.39 -1.25 (m, 16H) , 1.06 (s, 9H) .

[0366] Step 3: 13- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methyltridecanamide



[0367] To a mixture of 13- ((tert-butyldiphenylsilyl) oxy) tridecanoic acid (10 g, 21.3 mmol) and DMF (156 mg, 2.13 mmol, 164 μL) in DCM (80 mL) was added (COCl)₂ (4.06 g, 32.0 mmol, 2.80 mL) at 0 °C, then the mixture was stirred at 25 °C for 2 hours, then the mixture was concentrated to give a residue. The residue in DCM (40 mL) was added into the solution of N-methoxymethanamine (4.16 g, 42.7 mmol, HCl) , TEA (6.48 g, 64.0 mmol, 8.91 mL) in DCM (80 mL) at 0 °C, then the solution was stirred at 25 °C for 12 hours. TLC showed one major new spot was detected. The mixture was diluted with HCl (1 N, 10 mL) and H₂O (50 mL) and extracted with DCM (60 mL × 2) , the combined organic layers were washed with saturated NaHCO₃ (50 mL) and brine (50 mL) , dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 3/20) to give 13- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methyltridecanamide (4.5 g, 41.2%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.74 -7.62 (m, 4H) , 7.46 -7.34 (m, 6H) , 3.72 -3.60 (m, 5H) , 3.19 (s, 3H) , 2.42 (t, J= 7.6 Hz, 2H) , 1.70 -1.61 (m, 2H) , 1.58 -1.52 (m, 2H) , 1.39 -1.25 (m, 16H) , 1.05 (s, 9H) .

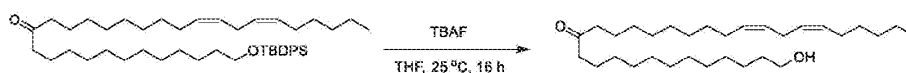
[0368] Step 4: (22Z, 25Z) -1- ((tert-butyldiphenylsilyl) oxy) hentriaconta-22, 25-dien-13-one



[0369] To a drying 250 mL three-neck flask, Mg (1.85 g, 75.9 mmol) and I₂ (385 mg, 1.52 mmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, then THF (10 mL) was added in the flask and the solution of (6Z, 9Z) -18-bromooctadeca-6, 9-diene (5.0 g, 15.2 mmol) in THF (40 mL) was added slowly to the flask at 20 °C, then the mixture was stirred at 20 °C for 2

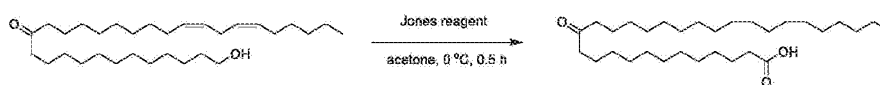
hours. Then the mixture was added into the solution of 13- ((tert-butylidiphenylsilyl) oxy) -N-methoxy-N-methyltridecanamide (2 g, 3.90 mmol) in THF (10 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 hour. The reaction was quenched with saturated NH₄Cl (40 mL) at 0 °C, then the mixture was warmed to 20 °C and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to get residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/20) to give (22Z, 25Z) -1- ((tert-butylidiphenylsilyl) oxy) hentriaconta-22, 25-dien-13-one (2.1 g, 76.8%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.74 -7.62 (m, 4H), 7.50 -7.34 (m, 6H), 5.44 -5.29 (m, 4H), 3.66 (t, J= 6.4 Hz, 2H), 2.78 (t, J= 6.4 Hz, 2H), 2.39 (t, J= 7.6 Hz, 4H), 2.10 -2.00 (m, 4H), 1.61 -1.58 (m, 2H), 1.55 -1.52 (m, 2H), 1.39 -1.24 (m, 34H), 1.05 (s, 9H), 0.90 (t, J= 6.8 Hz, 3H).

[0370] Step 5: (22Z, 25Z) -1-hydroxyhentriaconta-22, 25-dien-13-one



[0371] To a mixture of (22Z, 25Z) -1- ((tert-butylidiphenylsilyl) oxy) hentriaconta-22, 25-dien-13-one (3.18 g, 4.54 mmol) in THF (50 mL) was added TBAF (1 M, 22.7 mL) under N₂ atmosphere. The mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO₃ (50 mL), extracted with EtOAc (50 mL × 2), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give (22Z, 25Z) -1-hydroxyhentriaconta-22, 25-dien-13-one (2 g, 95.3%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.48 -5.24 (m, 4H), 3.65 (t, J= 6.8 Hz, 2H), 2.78 (t, J= 6.4 Hz, 2H), 2.39 (t, J= 7.6 Hz, 4H), 2.11 -2.00 (m, 4H), 1.60 -1.58 (m, 2H), 1.56 (s, 2H), 1.41 -1.25 (m, 34H), 0.90 (t, J= 6.8 Hz, 3H).

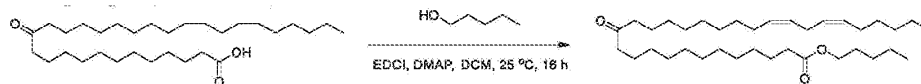
[0372] Step 6: (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoic acid



[0373] To a mixture of (22Z, 25Z) -1-hydroxyhentriaconta-22, 25-dien-13-one (2.0 g, 4.32 mmol) in acetone (40 mL) was added Jones reagent (2.5 M, 3.46 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (1 mL), diluted with H₂O (30 mL) and extracted with EtOAc (50 mL × 3), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/5) to give (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoic acid (2 g, 97.1%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 5.44

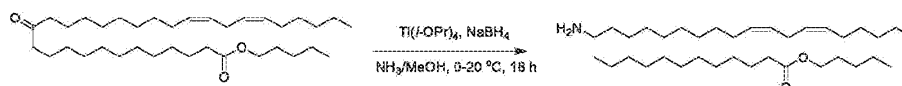
-5.26 (m, 4H) , 2.78 (t, J= 6.8 Hz, 2H) , 2.42 -2.34 (m, 6H) , 2.09 -2.02 (m, 4H) , 1.66 -1.61 (m, 2H) , 1.55 (d, J= 6.8 Hz, 2H) , 1.39 -1.26 (m, 32H) , 0.90 (t, J= 6.8 Hz, 3H) .

[0374] Step 7: pentyl (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoate



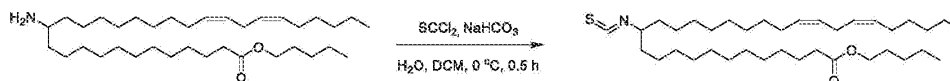
[0375] A mixture of (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoic acid (2 g, 4.19 mmol) , pentan-1-ol (740 mg, 8.39 mmol, 912 μ L) , EDCI (1.61 g, 8.39 mmol) , DMAP (512 mg, 4.19 mmol) in DCM (30 mL) was stirred at 25 $^{\circ}$ C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give pentyl (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoate (1.9 g, 82.8%yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 5.42 -5.28 (m, 4H) , 4.07 (t, J= 6.8 Hz, 2H) , 2.78 (t, J= 6.0 Hz, 2H) , 2.39 (t, J= 7.6 Hz, 4H) , 2.30 (t, J= 7.6 Hz, 2H) , 2.10 -2.01 (m, 4H) , 1.67 -1.56 (m, 8H) , 1.38 -1.26 (m, 34H) , 0.93 -0.88 (m, 6H) .

[0376] Step 8: pentyl (22Z, 25Z) -13-aminohentriaconta-22, 25-dienoate



[0377] A mixture of pentyl (22Z, 25Z) -13-oxohentriaconta-22, 25-dienoate (1.9 g, 3.47 mmol) , $\text{Ti}(\text{i-OPr})_4$ (1.97 g, 6.95 mmol, 2.05 mL) in MeOH (30 mL) and NH_3/MeOH (7 M, 10 mL) , then the mixture was stirred at 20 $^{\circ}$ C for 6 hours, then NaBH_4 (263 mg, 6.95 mmol) was added the mixture at 0 $^{\circ}$ C, then the mixture was stirred at 20 $^{\circ}$ C for 12 hours. The mixture was quenched with H_2O (20 mL) and diluted with ethyl acetate (50 mL) . The inorganic solids were filtered and the aqueous phase was washed with ethyl acetate (2 $\times$ 30 mL) , the combined organic layer was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/1) to give pentyl (22Z, 25Z) -13-aminohentriaconta-22, 25-dienoate (1.5 g, 78.8%yield) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 5.45 -5.27 (m, 4H) , 4.05 (t, J= 6.5 Hz, 2H) , 2.83 -2.67 (m, 3H) , 2.28 (t, J= 7.5 Hz, 2H) , 2.05 (q, J= 7.0 Hz, 4H) , 1.68 -1.57 (m, 4H) , 1.46-1.25 (m, 42H) , 0.94 -0.84 (m, 6H) .

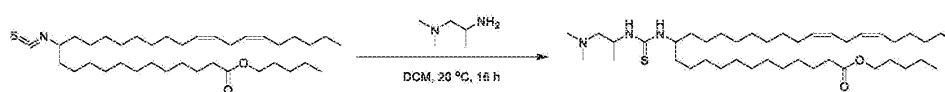
[0378] Step 9: pentyl (22Z, 25Z) -13-isothiocyanatohentriaconta-22, 25-dienoate



[0379] To a mixture of pentyl (22Z, 25Z) -13-aminohentriaconta-22, 25-dienoate (300 mg, 548 μ mol) and NaHCO_3 (322 mg, 3.83 mmol) in DCM (15 mL) and H_2O (15 mL) was added SCCl_2 (81.8 mg, 712 μ mol, 54.6 μ L) at 0 $^{\circ}$ C, then the mixture was stirred at 0 $^{\circ}$ C

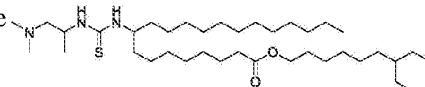
for 0.5 hour. The mixture was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/20) to give pentyl (22Z, 25Z) -13-isothiocyanatohentriaconta-22, 25-dienoate (320 mg, 99.1% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.48 -5.26 (m, 4H), 4.07 (t, J = 6.8 Hz, 2H), 3.66 -3.58 (m, 1H), 2.78 (t, J = 6.8 Hz, 2H), 2.35 -2.25 (m, 2H), 2.06 (q, J = 6.8 Hz, 4H), 1.68 -1.58 (m, 6H), 1.54 -1.46 (m, 2H), 1.42 -1.25 (m, 38H), 0.97 -0.85 (m, 6H).

[0380] Step 10: pentyl (22Z, 25Z) -13- (3- (1- (dimethylamino) propan-2-yl) thioureido) hentriaconta-22, 25-dienoate

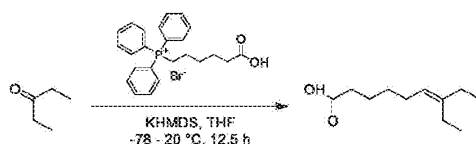


[0381] A mixture of pentyl (22Z, 25Z) -13-isothiocyanatohentriaconta-22, 25-dienoate (320 mg, 542 μmol), N^1 , N^1 -dimethylpropane-1, 2-diamine (111 mg, 1.08 mmol) in DCM (5 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with DCM (50 mL), washed with HCl (1 N, 10 mL), saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN]; gradient: 55%-85%B over 20 min) to give pentyl (22Z, 25Z) -13- (3- (1- (dimethylamino) propan-2-yl) thioureido) hentriaconta-22, 25-dienoate (183 mg, 48.8% yield) as light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.45 -5.27 (m, 4H), 4.35 -4.15 (m, 1H), 4.11 -3.58 (m, 3H), 2.78 (t, J = 6.4 Hz, 2H), 2.71 -2.57 (m, 1H), 2.47 -2.20 (m, 9H), 2.06 (q, J = 6.8 Hz, 4H), 1.67 -1.52 (m, 6H), 1.42 -1.21 (m, 43H), 0.90 (q, J = 6.8 Hz, 6H). LCMS showed the purity is 100%, R_t = 3.317 min; MS Calcd.: 691.6, MS Found: 692.6 $[\text{M}+\text{H}]^+$.

[0382] Example 35: 7-ethylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) hentriaconoate



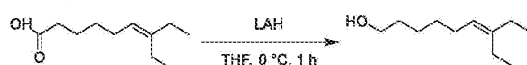
[0383] Step 1: 7-ethylnon-6-enoic acid



[0384] To a mixture of (5-carboxypentyl) triphenylphosphonium bromide (53.1 g, 116 mmol) in THF (150 mL) was added KHMDS (1 M, 232 mL) at -78 °C. The mixture was stirred at 20 °C for 0.5 hour, then the solution of pentan-3-one (5.0 g, 58.1 mmol) in THF (20 mL) at -78 °C. The resulting reaction mixture was stirred at 20 °C for

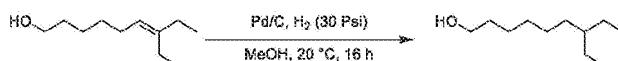
12 hours. TLC showed that one new spot was observed. The reaction was quenched with H₂O (80 mL) at 0 °C. The two layers were separated, and the aqueous layer was acidified with 10% HCl to pH = 2. The aqueous layer was extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 3: 1) to give 7-ethylnon-6-enoic acid (9.8 g, crude) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.06 (t, J = 7.2 Hz, 1H), 2.37 (t, J = 7.6 Hz, 2H), 2.10 - 1.94 (m, 6H), 1.70 - 1.59 (m, 2H), 1.47 - 1.35 (m, 2H), 1.02 - 0.92 (m, 6H).

[0385] Step 2: 7-ethylnon-6-en-1-ol



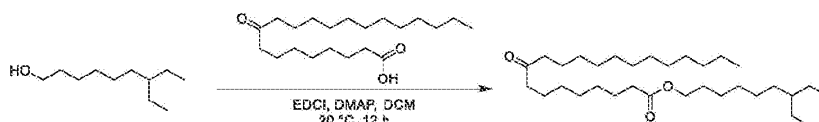
[0386] To a mixture 7-ethylnon-6-enoic acid (9.8 g, crude, 53.2 mmol) in THF (150 mL) was added LAH (2.5 M, 19.2 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 1 hour under N₂ atmosphere. TLC showed that one new spot was observed. The reaction mixture was cooled to 0 °C by ice-bath, Na₂SO₄·10H₂O (50 g) was added slowly. The mixture was stirred at 25 °C for 1 hour, then filtered and the filter cake was washed with EtOAc (50 mL × 3). The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 3: 1) to give 7-ethylnon-6-en-1-ol (3.0 g, 33% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.07 (t, J = 6.8 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 2.09 - 1.96 (m, 6H), 1.64 - 1.54 (m, 2H), 1.45 - 1.34 (m, 5H), 1.03 - 0.92 (m, 6H).

[0387] Step 3: 7-ethylnonan-1-ol



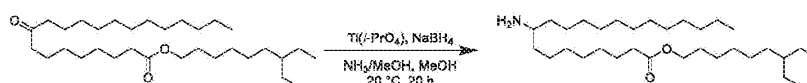
[0388] To a mixture of 7-ethylnon-6-en-1-ol (3.0 g, 17.6 mmol) in MeOH (50 mL) was added Pd/C (1 g, 10% purity) under N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (30 psi) at 20 °C for 16 hours. The reaction mixture was filtered through a celite, the filter cake was washed with MeOH (50 mL × 3) and the filter was concentrated in vacuo to give 7-ethylnonan-1-ol (3.0 g, 99% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, J = 6.4 Hz, 2H), 1.61 - 1.53 (m, 2H), 1.44 - 1.20 (m, 12H), 1.18 - 1.11 (m, 1H), 0.84 (t, J = 7.6 Hz, 6H).

[0389] Step 4: 7-ethylnonyl 9-oxohenicosanoate



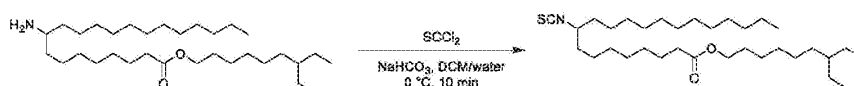
[0390] To a mixture of 9-oxohenicosanoic acid (3.0 g, 8.81 mmol) and 7-ethylnonan-1-ol (1.52 g, 8.81 mmol) in DCM (50 mL) was added EDCI (3.38 g, 17.6 mmol) and DMAP (2.15 g, 17.6 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 7-ethylnonyl 9-oxohenicosanoate (2.4 g, 55%yield) as a colorless oil. ¹H NMR (400MHz, CDCl₃) δ 4.06 (t, J= 6.8 Hz, 2H) , 2.38 (t, J= 7.2 Hz, 4H) , 2.29 (t, J= 7.6 Hz, 2H) , 1.65 -1.59 (m, 4H) , 1.57 -1.50 (m, 4H) , 1.36 -1.18 (m, 37H) , 0.91 -0.80 (m, 9H) .

[0391] Step 5: 7-ethylnonyl 9-aminohenicosanoate



[0392] To a mixture of 7-ethylnonyl 9-oxohenicosanoate (2.4 g, 4.85 mmol) in MeOH (50 mL) and NH₃/MeOH (7 M, 20 mL) was added tetraisopropoxytitanium (2.76 g, 9.70 mmol, 2.86 mL) . The mixture was stirred 20 °C for 4 hours. Then NaBH₄ (366.99 mg, 9.70 mmol, 2 eq) was added slowly. The mixture was stirred at 20 °C for another 16 hours. TLC showed that one main spot was detected. The mixture was quenched with water (100 mL) and diluted with DCM (150 mL) . The mixture was filtered through a celite. The aqueous phase was extracted with DCM (100 mL × 2) . The combined organic layer was washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 10: 1) to give 7-ethylnonyl 9-aminohenicosanoate (1.17 g, 49%yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.06 (t, J= 6.5 Hz, 2H) , 2.80 (br s, 1H) , 2.29 (t, J= 7.5 Hz, 2H) , 1.68 -1.57 (m, 4H) , 1.53 -1.21 (m, 44H) , 1.18 -1.12 (m, 1H) , 0.89 (t, J= 7.0 Hz, 3H) , 0.84 (t, J= 7.5 Hz, 6H) .

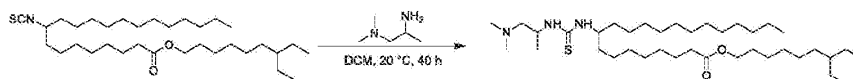
[0393] Step 6: 7-ethylnonyl 9-isothiocyanatohenicosanoate



[0394] To a mixture of 7-ethylnonyl 9-aminohenicosanoate (370 mg, 746 μmol) in DCM (20 mL) and water (10 mL) was added NaHCO₃ (439 mg, 5.22 mmol) and thiocarbonyl dichloride (172 mg, 1.49 mmol) . The mixture was stirred at 0 °C for 10 min. TLC showed that one main spot was observed. The reaction mixture was diluted with DCM (30 mL) and water (20 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to 7-ethylnonyl 9-isothiocyanatohenicosanoate (350 mg, 87%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.07 (t, J= 6.8 Hz, 2H) , 3.67 -3.58 (m, 1H) ,

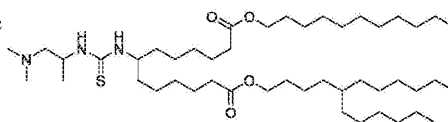
2.30 (t, J= 7.6 Hz, 2H) , 1.67 -1.58 (m, 6H) , 1.40 -1.22 (m, 42H) , 1.18 -1.11 (m, 1H) , 0.92 -0.81 (m, 9H) .

[0395] Step 7: 7-ethylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate

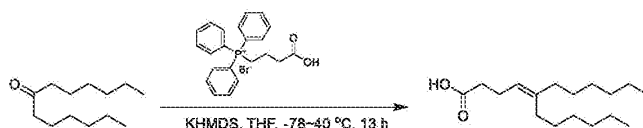


[0396] A mixture of 7-ethylnonyl 9-isothiocyanatohenicosanoate (350 mg, 651 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (133 mg, 1.30 mmol) in DCM (10 mL) was stirred at 20 °C for 40 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was diluted with EtOAc (100 mL) and HCl (1 N, 20 mL) . The organic phase was separated and washed with saturated NaHCO_3 (50 mL) , brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 50%-80%B over 20 min) to give 7-ethylnonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanoate (193.0 mg, 46%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 9.60 (br s, 1H) , 6.07 (br s, 1H) , 4.26 (br s, 1H) , 4.06 (t, J= 6.4 Hz, 2H) , 3.97-3.68 (m, 1H) , 2.82 -2.60 (m, 1H) , 2.46 -2.24 (m, 9H) , 1.70-1.55 (m, 4H) , 1.45 -1.19 (m, 47H) , 1.18-1.11 (m, 1H) , 0.98-0.77 (m, 9H) . LCMS showed the purity is 100%, R_t = 3.181 min; MS Calcd. : 639.6, MS Found: 640.5 $[\text{M}+\text{H}]^+$.

[0397] Example 36: 1- (5-hexylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate



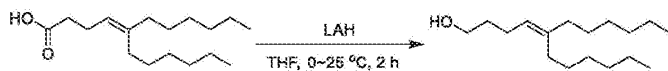
[0398] Step 1: 5-hexylundec-4-enoic acid



[0399] To a mixture of (3-carboxypropyl) triphenylphosphonium bromide (21.6 g, 50.4 mmol) in THF (100 mL) was added KHMDS (1 M, 101 mL) at -78 °C, then the mixture was stirred at 40 °C for 1 hour, then the solution of tridecan-7-one (5 g, 25.2 mmol) in THF (10 mL) at -78 °C, then the mixture was stirred at 25 °C for 12 hours. The reaction was quenched with H_2O (50 mL) at 0 °C. The two layers were separated, and the aqueous layer was acidified with 10% HCl to pH = 2. The aqueous layer was extracted with EtOAc (2 $\times$ 200 mL) . The combined organic layer was washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a

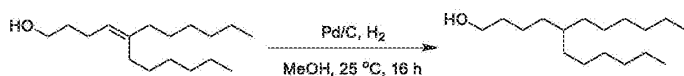
residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/2) to give 5-hexylundec-4-enoic acid (0.9 g, 13.3%yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.08 (t, J = 6.4 Hz, 1H) , 2.44 -2.33 (m, 4H) , 2.04 -1.94 (m, 4H) , 1.41 -1.27 (m, 16H) , 0.91 -0.87 (m, 6H) .

[0400] Step 2: 5-hexylundec-4-en-1-ol



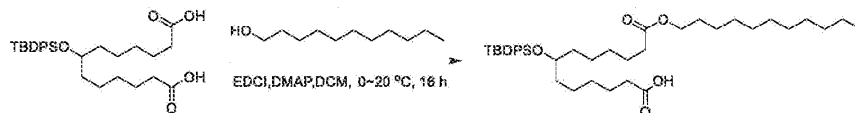
[0401] To a mixture of 5-hexylundec-4-enoic acid (900 mg, 3.35 mmol) in THF (10 mL) was added LiAlH_4 (2.5 M, 2.01 mL) at 0 °C under N_2 atmosphere. The mixture was allowed warm to 25 °C and stirred at 25 °C for 2 hours N_2 atmosphere. After completely, the reaction mixture was cooled to 0 °C by ice-bath. Then $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (5 g) was added slowly. The mixture was stirred at 25 °C for 1 hour, then filtered and the filter cake was washed with EtOAc (50 mL $\times$ 3) . The filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/20) to give 5-hexylundec-4-en-1-ol (430 mg, 50.4%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.12 (t, J = 7.2 Hz, 1H) , 3.66 (t, J = 6.8 Hz, 2H) , 2.14 -2.05 (m, 2H) , 2.04 -1.92 (m, 4H) , 1.63 (quin, J = 6.8 Hz, 2H) , 1.38 -1.26 (m, 16H) , 0.93 -0.86 (m, 6H) .

[0402] Step 3: 5-hexylundecan-1-ol



[0403] A mixture of 5-hexylundec-4-en-1-ol (430 mg, 1.69 mmol) , Pd/C (300 mg, 10%purity) in MeOH (10 mL) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (30 psi) at 25 °C for 16 hours. The reaction mixture was filtered, the filter cake was washed with MeOH (50 mL $\times$ 3) and the filter was concentrated to give 5-hexylundecan-1-ol (380 mg, 87.7%yield) as colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.66 (t, J = 6.8 Hz, 2H) , 1.59 -1.52 (m, 2H) , 1.39 -1.22 (m, 26H) , 0.89 (t, J = 6.8 Hz, 6H) .

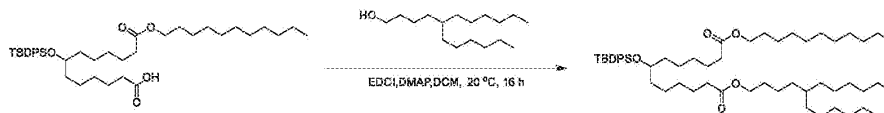
[0404] Step 4: 7- ((tert-butyl) diphenylsilyl oxy) -13-oxo-13- (undecyloxy) tridecanoic acid



[0405] To a mixture of 7- ((tert-butyl) diphenylsilyl oxy) tridecanedioic acid (6.8 g, 13.6 mmol) and EDCI (2.61 g, 13.6 mmol) , DMAP (1.67 g, 13.6 mmol) in DCM (100 mL) was added the solution of undecan-1-ol (1.88 g, 10.9 mmol) in DCM (50 mL) at 0 °C, then the mixture was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc:

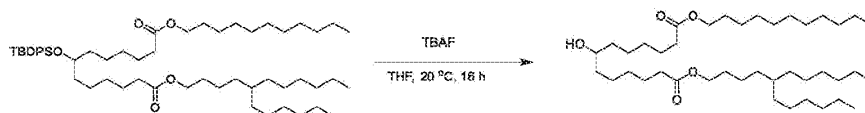
PE = 0 to 1/5) to give 7- ((tert-butyldiphenylsilyl) oxy) -13-oxo-13-(undecyloxy) tridecanoic acid (2 g, 22.5%yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 -7.64 (m, 4H) , 7.45 -7.33 (m, 6H) , 4.06 (t, J= 6.8 Hz, 2H) , 3.70 (t, J= 5.6 Hz, 1H) , 2.32 -2.18 (m, 4H) , 1.66 -1.58 (m, 2H) , 1.57 -1.48 (m, 4H) , 1.45 -1.37 (m, 4H) , 1.33 -1.12 (m, 24H) , 1.05 (s, 9H) , 0.92 -0.86 (m, 3H) .

[0406] Step 5: 1- (5-hexylundecyl) 13-undecyl 7- ((tert-butyldiphenylsilyl) oxy) tridecanedioate



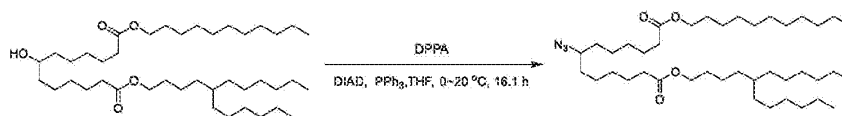
[0407] A mixture of 7- ((tert-butyldiphenylsilyl) oxy) -13-oxo-13- (undecyloxy) tridecanoic acid (1 g, 1.53 mmol) , 5-hexylundecan-1-ol (380 mg, 1.48 mmol) , EDCI (284 mg, 1.48 mmol) , DMAP (181 mg, 1.48 mmol) in DCM (10 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give 1- (5-hexylundecyl) 13-undecyl 7- ((tert-butyldiphenylsilyl) oxy) tridecanedioate (900 mg, 68.1%yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.69 -7.64 (m, 4H) , 7.44 -7.34 (m, 6H) , 4.10 -4.02 (m, 4H) , 3.70 (quin, J= 5.6 Hz, 1H) , 2.26 -2.18 (m, 4H) , 1.67 -1.58 (m, 4H) , 1.55 -1.48 (m, 4H) , 1.44 -1.37 (m, 4H) , 1.34 -1.19 (m, 45H) , 1.18 -1.12 (m, 4H) , 1.05 (s, 9H) , 0.92 -0.87 (m, 9H) .

[0408] Step 6: 1- (5-hexylundecyl) 13-undecyl 7-hydroxytridecanedioate



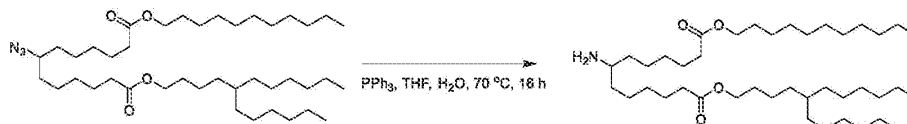
[0409] To a mixture of 1- (5-hexylundecyl) 13-undecyl 7- ((tert-butyldiphenylsilyl) oxy) tridecanedioate (900 mg, 1.01 mmol) in THF (10 mL) was added TBAF (1 M, 5.05 mL) at 20 °C, then the mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (50 mL) , extracted with EtOAc (2 $\times$ 50 mL) . The combined organic phase was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/5) to give 1- (5-hexylundecyl) 13-undecyl 7-hydroxytridecanedioate (600 mg, 91.0%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.11 -4.02 (m, 4H) , 3.58 (d, J= 3.6 Hz, 1H) , 2.31 (t, J= 7.6 Hz, 4H) , 1.69 -1.58 (m, 8H) , 1.50 -1.22 (m, 53H) , 0.93-0.85 (m, 9H) .

[0410] Step 7: 1- (5-hexylundecyl) 13-undecyl 7-azidotridecanedioate



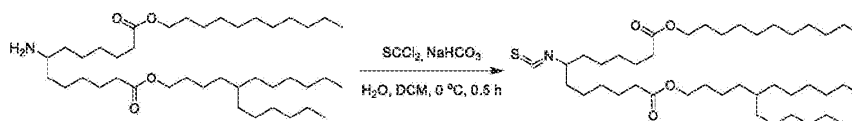
[0411] To a mixture of 1- (5-hexylundecyl) 13-undecyl 7-hydroxytridecanedioate (600 mg, 918 μ mol) in THF (10 mL) was added PPh₃ (482 mg, 1.84 mmol) , DIAD (372 mg, 1.84 mmol, 356 μ L) at 0 °C, then the mixture was stirred at 20 °C for 0.1 hour, then DPPA (506 mg, 1.84 mmol, 396 μ L) was added into the mixture, then the mixture was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 1- (5-hexylundecyl) 13-undecyl 7-azidotridecanedioate (600 mg, 96.3%yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.10 -4.04 (m, 4H) , 3.23 (t, J= 6.0 Hz, 1H) , 2.31 (t, J= 7.6 Hz, 4H) , 1.70 -1.59 (m, 8H) , 1.50 (s, 2H) , 1.40 -1.19 (m, 51H) , 0.91 -0.87 (m, 9H) .

[0412] Step 8: 1- (5-hexylundecyl) 13-undecyl 7-aminotridecanedioate



[0413] A mixture of 1- (5-hexylundecyl) 13-undecyl 7-azidotridecanedioate (600 mg, 885 μ mol) , PPh₃ (464 mg, 1.77 mmol) in THF (20 mL) and H₂O (4 mL) was stirred at 70 °C under N₂ atmosphere for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 1- (5-hexylundecyl) 13-undecyl 7-aminotridecanedioate (510 mg, 88.4%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.59 -8.11 (m, 2H) , 4.11 -4.01 (m, 4H) , 3.28 -3.09 (m, 1H) , 2.37 -2.25 (m, 4H) , 1.80 -1.60 (m, 10H) , 1.53 -1.18 (m, 51H) , 0.89 (t, J= 6.8 Hz, 9H) .

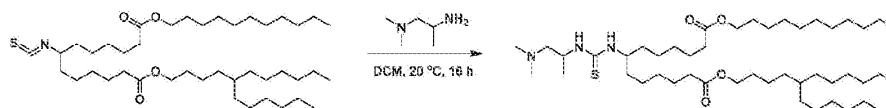
[0414] Step 9: 1- (5-hexylundecyl) 13-undecyl 7-isothiocyanatotridecanedioate



[0415] To a mixture of 1- (5-hexylundecyl) 13-undecyl 7-aminotridecanedioate (300 mg, 460 μ mol) and NaHCO₃ (271 mg, 3.22 mmol) in DCM (15 mL) and H₂O (15 mL) was added SCl₂ (68.8 mg, 598 μ mol, 45.9 μ L) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 7/100) to give 1- (5-hexylundecyl) 13-undecyl 7-isothiocyanatotride-

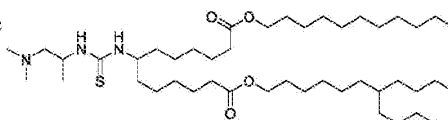
canedioate (270 mg, 84.6%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.11 -4.03 (m, 4H) , 3.68 -3.57 (m, 1H) , 2.32 (t, J = 7.6 Hz, 4H) , 1.70 -1.59 (m, 10H) , 1.53 -1.14 (m, 51H) , 0.94 -0.85 (m, 9H) .

[0416] Step 10: 1- (5-hexylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate

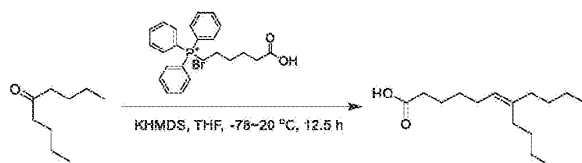


[0417] A mixture of 1- (5-hexylundecyl) 13-undecyl 7-isothiocyanatotrilecanedioate (270 mg, 389 μmol) , N^1 , N^1 -dimethylpropane-1, 2-diamine (79.5 mg, 778 μmol) in DCM (8 mL) was stirred at 20 $^\circ\text{C}$ for 16 hours. The mixture was diluted with DCM (50 mL) , washed with HCl (1 N, 10 mL) , saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 20 min) to give 1- (5-hexylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate (142.8 mg, 44.8%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.38 -4.21 (m, 1H) , 4.13 -4.02 (m, 4H) , 2.78 -2.57 (m, 1H) , 2.43 -2.22 (m, 10H) , 1.69-1.52 (m, 10H) , 1.49 -1.20 (m, 56H) , 0.89 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 97.22%, Rt = 4.822 min; MS Calcd. : 795.7, MS Found: 796.6 $[\text{M}+\text{H}]^+$.

[0418] Example 37: 1- (7-butylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate



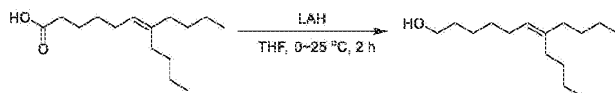
[0419] Step 1: 7-butylundec-6-enoic acid



[0420] To a mixture of (5-carboxypentyl) triphenylphosphonium bromide (32.2 g, 70.3 mmol) in THF (100 mL) was added KHMDS (1 M, 141 mL) at -78 $^\circ\text{C}$, then the mixture was stirred at 20 $^\circ\text{C}$ for 0.5 hour, then the solution of nonan-5-one (5 g, 35.2 mmol) in THF (20 mL) at -78 $^\circ\text{C}$, then the mixture was stirred at 25 $^\circ\text{C}$ for 12 hours. The reaction was quenched with H_2O (50 mL) at 0 $^\circ\text{C}$. The two layers were separated, and the aqueous layer was acidified with 10%HCl to pH = 2. The aqueous layer was extracted with EtOAc (2 $\times$ 200 mL) . The combined organic layer was washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a

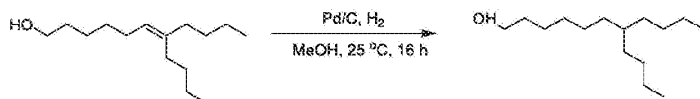
residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/2) to give 7-butylundec-6-enoic acid (8.2 g, 97.0%yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.08 (t, J= 7.2 Hz, 1H) , 2.36 (t, J= 7.6 Hz, 2H) , 2.05 -1.92 (m, 6H) , 1.65 (quin, J= 7.6 Hz, 2H) , 1.45 -1.27 (m, 10H) , 0.93 -0.88 (m, 6H) .

[0421] Step 2: 7-butylundec-6-en-1-ol



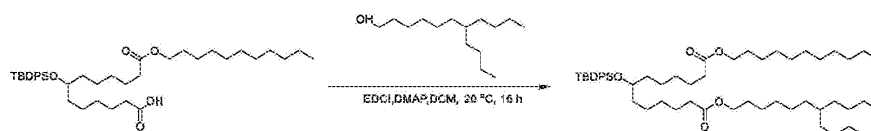
[0422] To a mixture of 7-butylundec-6-enoic acid (8.2 g, 34.11 mmol) in THF (100 mL) was added LiAlH₄ (2.5 M, 17.7 mL) at 0 °C under N₂ atmosphere. The mixture was allowed warm to 25 °C and stirred at 25 °C for 2 hours N₂ atmosphere. After completely, the reaction mixture was cooled to 0 °C by ice-bath. Then Na₂SO₄·10H₂O (30 g) was added slowly. The mixture was stirred at 25 °C for 1 hour, then filtered and the filter cake was washed with EtOAc (50 mL × 3) . The filtrate was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/20) to give 7-butylundec-6-en-1-ol (3.86 g, 50.0%yield) as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.10 (t, J= 7.0 Hz, 1H) , 3.65 (t, J= 6.5 Hz, 2H) , 2.03 -1.94 (m, 6H) , 1.62 -1.55 (m, 2H) , 1.38 -1.25 (m, 12H) , 0.94 -0.88 (m, 6H) .

[0423] Step 3: 7-butylundecan-1-ol



[0424] A mixture of 7-butylundec-6-en-1-ol (3.86 g, 17.1 mmol) , Pd/C (1.0 g, 10%purity) in MeOH (40 mL) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (30 psi) at 25°C for 16 hours. The reaction mixture was filtered, the filter cake was washed with MeOH (50 mL × 3) , and the filter was concentrated to give 7-butylundecan-1-ol (3.5 g, 89.9%yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, J= 6.8 Hz, 2H) , 1.63 -1.53 (m, 2H) , 1.40 -1.18 (m, 21H) , 0.90 (t, J= 6.8 Hz, 6H) .

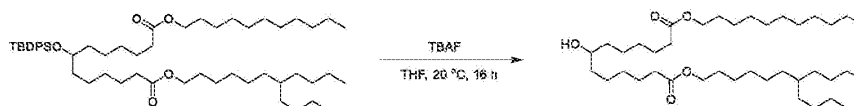
[0425] Step 4: 1- (7-butylundecyl) 13-undecyl 7- ((tert-butyl diphenylsilyl) oxy) tridecanoate



[0426] A mixture of 7- ((tert-butyl diphenylsilyl) oxy) -13-oxo-13- (undecyloxy) tridecanoic acid (1 g, 1.53 mmol) , 7-butylundecan-1-ol (420 mg, 1.84 mmol) , EDCI (294 mg, 1.53 mmol) , DMAP (187 mg, 1.53 mmol) in DCM (10 mL) was stirred at 20 °C for

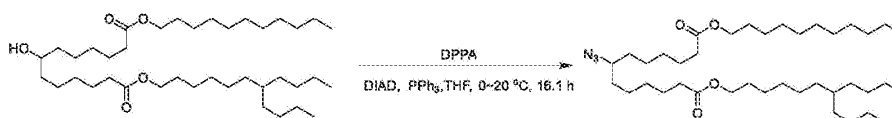
16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give 1- (7-butylundecyl) 13-undecyl 7- ((tert-butyl) diphenylsilyl) oxy) tridecanedioate (1.2 g, 90.8% yield) as yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.69 -7.63 (m, 4H) , 7.44 -7.34 (m, 6H) , 4.05 (t, J = 7.0 Hz, 4H) , 3.70 (quin, J = 5.5 Hz, 1H) , 2.22 (t, J = 7.6 Hz, 4H) , 1.65 -1.58 (m, 4H) , 1.54 -1.48 (m, 4H) , 1.43 -1.37 (m, 4H) , 1.35 -1.21 (m, 4H) , 1.18 -1.12 (m, 4H) , 1.05 (s, 9H) , 0.92 -0.88 (m, 9H) .

[0427] Step 5: 1- (7-butylundecyl) 13-undecyl 7-hydroxytridecanedioate



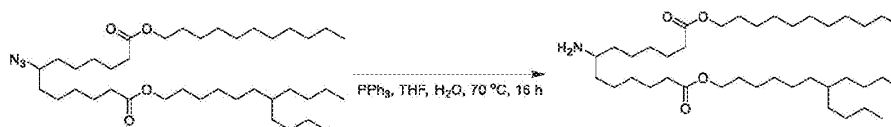
[0428] To a mixture of 1- (7-butylundecyl) 13-undecyl 7- ((tert-butyl) diphenylsilyl) oxy) tridecanedioate (1.2 g, 1.39 mmol) in THF (15 mL) was added TBAF (1 M, 6.95 mL) at 20 °C, then the mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (50 mL) , extracted with EtOAc (2x50 mL) . The combined organic phase was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/5) to give 1- (7-butylundecyl) 13-undecyl 7-hydroxytridecanedioate (780 mg, 89.8% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 4H) , 3.58 (d, J = 3.2 Hz, 1H) , 2.31 (t, J = 7.6 Hz, 4H) , 1.68 -1.59 (m, 8H) , 1.48 -1.22 (m, 49H) , 0.93-0.86 (m, 9H) .

[0429] Step 6: 1- (7-butylundecyl) 13-undecyl 7-azidotridecanedioate



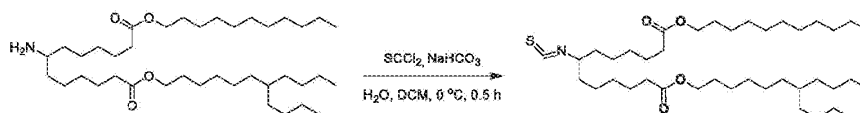
[0430] To a mixture of 1- (7-butylundecyl) 13-undecyl 7-hydroxytridecanedioate (780 mg, 1.25 mmol) in THF (15 mL) was added PPh_3 (655 mg, 2.50 mmol) , DIAD (505 mg, 2.50 mmol, 484 μL) at 0 °C, then the mixture was stirred at 20 °C for 0.1 hour, then DPPA (687 mg, 2.50 mmol, 539 μL) was added into the mixture, then the mixture was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give 1- (7-butylundecyl) 13-undecyl 7-azidotridecanedioate (740 mg, 91.2% yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.07 (t, J = 6.8 Hz, 4H) , 3.23 (t, J = 6.0 Hz, 1H) , 2.31 (t, J = 7.6 Hz, 4H) , 1.69 -1.59 (m, 8H) , 1.51 -1.49 (m, 2H) , 1.41 -1.18 (m, 47H) , 0.94 -0.86 (m, 9H) .

[0431] Step 7: 1- (7-butylundecyl) 13-undecyl 7-aminotridecanedioate



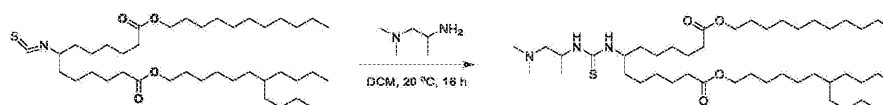
[0432] A mixture of 1- (7-butylundecyl) 13-undecyl 7-azidotridecanedioate (740 mg, 1.14 mmol) , PPh₃ (597 mg, 2.28 mmol) in THF (20 mL) and H₂O (4 mL) was stirred at 70 °C under N₂ for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 1- (7-butylundecyl) 13-undecyl 7-aminotridecanedioate (630 mg, 88.7%yield) as light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.48 -8.20 (m, 2H) , 4.06 (q, J= 6.8 Hz, 4H) , 3.27-3.08 (m, 1H) , 2.31 (t, J= 7.6 Hz, 4H) , 1.80 -1.61 (m, 10H) , 1.52 -1.16 (m, 47H) , 0.94 -0.85 (m, 9H) .

[0433] Step 8: 1- (7-butylundecyl) 13-undecyl 7-isothiocyanatotridecanedioate



[0434] To a mixture of 1- (7-butylundecyl) 13-undecyl 7-aminotridecanedioate (300 mg, 481 μmol) and NaHCO₃ (283 mg, 3.37 mmol) in DCM (15 mL) and H₂O (15 mL) was added SOCl₂ (71.9 mg, 625 μmol, 47.9 μL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 7/100) to give 1- (7-butylundecyl) 13-undecyl 7-isothiocyanatotridecanedioate (310 mg, 96.8%yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.07 (t, J= 6.8 Hz, 4H) , 3.69 -3.55 (m, 1H) , 2.32 (t, J= 7.6 Hz, 4H) , 1.67 -1.58 (m, 10H) , 1.52 -1.20 (m, 47H) , 0.92 -0.87 (m, 9H) .

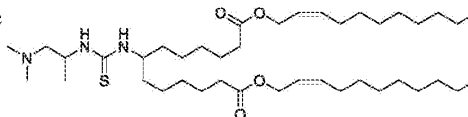
[0435] Step 9: 1- (7-butylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate



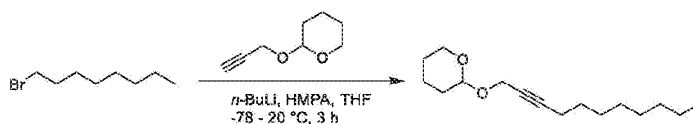
[0436] A mixture of 1- (7-butylundecyl) 13-undecyl 7-isothiocyanatotridecanedioate (310 mg, 465 μmol) , N¹, N¹-dimethylpropane-1, 2-diamine (95.11 mg, 930.81 μmol) in DCM (8 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with DCM (50 mL) , washed with HCl (1 N, 10 mL) , saturated NaHCO₃ (30 mL) and brine (30 mL) , dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm; mobile phase: [water (FA) -ACN] ; gradient: 55%-85%B over 20 min) to give 1-

(7-butylundecyl) 13-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate (191.1 mg, 53.5% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.43 -4.20 (m, 1H) , 4.05 (t, J = 6.8 Hz, 4H) , 4.03 -3.48 (m, 1H) , 2.92 -2.64 (m, 1H) , 2.63 -2.08 (m, 11H) , 1.72 -1.45 (m, 12H) , 1.40 -1.17 (m, 48H) , 0.99 -0.80 (m, 9H) . LCMS showed the purity is 100%, R_t = 3.825 min; MS Calcd. : 767.7, MS Found: 768.7 $[\text{M}+\text{H}]^+$.

[0437] Example 38: di ((Z) -undec-2-en-1-yl) 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate

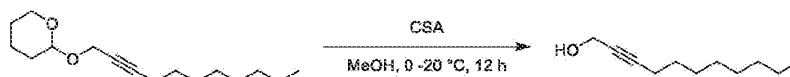


[0438] Step 1: 2- (undec-2-yn-1-yloxy) tetrahydro-2H-pyran



[0439] To a mixture of 2- (prop-2-yn-1-yloxy) tetrahydro-2H-pyran (36.3 g, 259 mmol, 36.4 mL) in THF (400 mL) was added *n*-BuLi (2.5 M, 113.9 mL) at -78°C under N_2 atmosphere. The mixture was stirred at -78°C for 1 hour. Then 1-bromooctane (50 g, 259 mmol, 45.1 mL) in HMPA (50.0 g, 279 mmol, 48.8 mL) was added dropwise. The mixture was allowed to warm up to 20°C and stirred at 20°C for 2 hours under N_2 atmosphere. TLC showed that one main spot was observed. The mixture was cooled to 0°C , then quenched with saturated NH_4Cl (200 mL) . The aqueous phase was separated and extracted with EtOAc (100 mL $\times$ 2) . The combined organic layers were washed with brine (250 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 2- (undec-2-yn-1-yloxy) tetrahydro-2H-pyran (43 g, crude) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.83 (q, J = 3.6 Hz, 1H) , 4.34 -4.21 (m, 2H) , 3.90 -3.83 (m, 1H) , 3.59 -3.50 (m, 1H) , 2.25 -2.18 (m, 2H) , 1.92 -1.81 (m, 2H) , 1.67 -1.48 (m, 6H) , 1.33 -1.25 (m, 10H) , 0.92 -0.77 (m, 3H) .

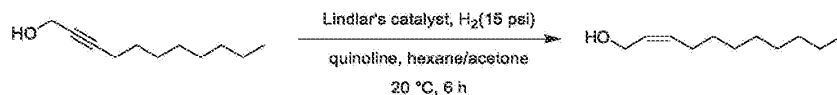
[0440] Step 2: undec-2-yn-1-ol



[0441] To a mixture of 2- (undec-2-yn-1-yloxy) tetrahydro-2H-pyran (37 g, crude, 147 mmol) in MeOH (500 mL) was added [rac- (1R, 4S) -7, 7-dimethyl-2-oxo-norbornan-1-yl] methanesulfonic acid (CSA) (1.70 g, 7.33 mmol) at 0°C . The mixture was stirred at 20°C for 12 hours. TLC showed that several spots were observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give undec-2-yn-1-ol (5.0

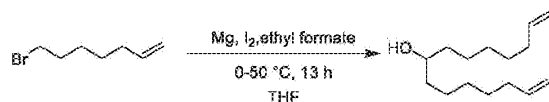
g, 20% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.26 (t, $J = 2.4$ Hz, 2H), 2.24 -2.18 (m, 2H), 1.54 -1.46 (m, 2H), 1.42 -1.24 (m, 10H), 0.92 -0.86 (m, 3H).

[0442] Step 3: (Z) -undec-2-en-1-ol



[0443] To a mixture of undec-2-yn-1-ol (5.7 g, 33.9 mmol) in Hexane (200 mL) and acetone (40 mL) was added quinoline (57 mL) and Lindlar's catalyst (285 mg) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 6 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with 1 M HCl to pH = 6. The mixture was extracted with EtOAc (200 mL $\times$ 2), The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 5: 1) to give (Z) -undec-2-en-1-ol (5.7 g, 99% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.64 -5.51 (m, 2H), 4.20 (d, $J = 6.0$ Hz, 2H), 2.12 -2.02 (m, 2H), 1.39 -1.21 (m, 13H), 0.93 -0.85 (m, 3H).

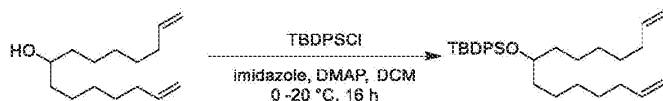
[0444] Step 4: pentadeca-1, 14-dien-8-ol



[0445] To a drying 1 L three-neck bottle, freshly activated Mg (13.7 g, 565 mmol) and I_2 (14.5 mg, cat.) were added and the flask was equipped with a magnetic stir bar, an addition funnel, and a reflux condenser, and flushed with N_2 atmosphere and THF (60 mL) was added to the flask via syringe. The 7-bromohept-1-ene (50.0 g, 282 mmol) was dissolved in THF (100 mL) and added to the addition funnel. About 30 mL of this above solution was added to the Mg turnings while stirring vigorously and heating by high gun. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux. After the completion of the addition the reaction mixture was kept at 50 °C for 1 hour. After cooled in ice bath, ethyl formate (9.41 g, 127 mmol, 10.2 mL) in THF (100 mL) was transferred to the addition funnel and was added dropwise to the reaction mixture with stirring at 0 °C. The reaction mixture was stirred at 25 °C for 12 hours under N_2 atmosphere. TLC showed that one main spot was observed. The reaction was quenched by adding acetone (50 mL) under ice-bath. The reaction mixture was treated with aq. H_2SO_4 (10 % by volume, 200 mL) slowly until the solution became homogeneous and the layers were separated. The aqueous phase was extracted with EtOAc (100 mL $\times$ 2). The combined organic layers were dried

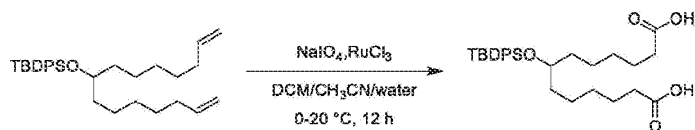
over anhydrous Na_2SO_4 and concentrated in vacuo to give pentadeca-1, 14-dien-8-ol (28.5 g, crude) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.88 -5.75 (m, 2H) , 5.06 -4.88 (m, 4H) , 3.59 (br s, 1H) , 2.11 -2.01 (m, 4H) , 1.52 -1.29 (m, 16H) .

[0446] Step 5: tert-butyl (pentadeca-1, 14-dien-8-yloxy) diphenylsilane



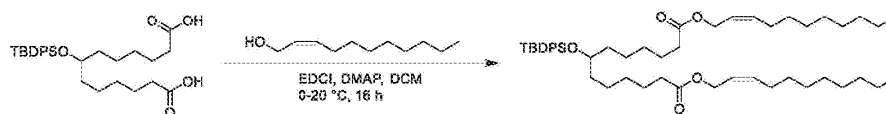
[0447] To a mixture of pentadeca-1, 14-dien-8-ol (28.5 g, crude, 127 mmol) in DCM (400 mL) was added imidazole (34.6 g, 508 mmol) and DMAP (3.10 g, 25.4 mmol) . Then TBDPSCI (69.9 g, 254 mmol, 65 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 16 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with saturated NaHCO_3 (400 mL) , diluted with DCM (200 mL) . The organic phase was separated and washed with brine (200 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give tert-butyl (pentadeca-1, 14-dien-8-yloxy) diphenylsilane (58.0 g, 99%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.75 -7.63 (m, 4H) , 7.46 -7.33 (m, 6H) , 5.84 -5.72 (m, 2H) , 5.01 -4.87 (m, 4H) , 3.71 (q, J= 5.2 Hz, 1H) , 1.98 (q, J= 7.2 Hz, 4H) , 1.42 -1.37 (m, 4H) , 1.33 -1.10 (m, 12H) , 1.06 (s, 9H) .

[0448] Step 6: 7- ((tert-butyl)diphenylsilyl oxy) tridecanedioic acid



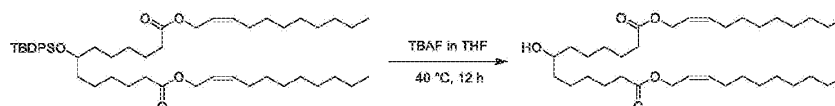
[0449] To a mixture of tert-butyl (pentadeca-1, 14-dien-8-yloxy) diphenylsilane (28 g, 60.5 mmol) in CH_3CN (300 mL) and DCM (300 mL) was added RuCl_3 (2.51 g, 12.1 mmol) and a solution of NaIO_4 (129 g, 605 mmol) in water (300 mL) dropwise under N_2 atmosphere at 0 °C. The mixture was stirred at 20 °C for 12 hours under N_2 atmosphere. TLC showed that starting material was consumed completely. The reaction mixture was diluted with brine (200 mL) . The mixture was adjusted with 1 N HCl to pH = 6. The mixture was extracted with DCM (500 mL $\times$ 3) . The combined organic phase was washed with brine (500 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 1: 1) to give 7- ((tert-butyl)diphenylsilyl oxy) tridecanedioic acid (20.0 g, 66%yield) as a brown gum. ^1H NMR (400 MHz, CDCl_3) δ 7.71 -7.64 (m, 4H) , 7.46 -7.33 (m, 6H) , 3.71 (q, J= 5.6 Hz, 1H) , 2.33 -2.23 (m, 4H) , 1.53 (q, J= 7.6 Hz, 4H) , 1.46 -1.37 (m, 4H) , 1.27 -1.13 (m, 8H) , 1.05 (s, 9H) .

[0450] Step 7: di ((Z) -undec-2-en-1-yl) 7- ((tert-butyl)diphenylsilyl oxy) tridecanedioate



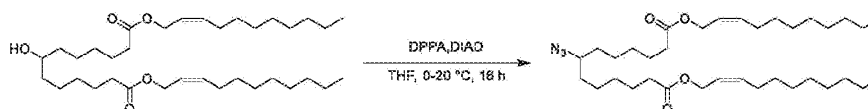
[0451] To a mixture of 7- ((tert-butylidiphenylsilyl) oxy) tridecanedioic acid (4.0 g, 8.02 mmol) and (Z) -undec-2-en-1-ol (2.73 g, 16.0 mmol) in DCM (100 mL) was added EDCI (6.15 g, 32.1 mmol) and DMAP (3.92 g, 32.1 mmol) at 0 °C. The mixture was stirred at 20 °C for 16 hours. TLC showed that one main spot was observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give di ((Z) -undec-2-en-1-yl) 7- ((tert-butylidiphenylsilyl) oxy) tridecanedioate (4.3 g, 67%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.69-7.64 (m, 4H) , 7.46 -7.32 (m, 6H) , 5.69 -5.60 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.62 (d, J= 6.8 Hz, 4H) , 3.69 (q, J= 5.6 Hz, 1H) , 2.23 (t, J= 7.6 Hz, 4H) , 2.13 -2.01 (m, 4H) , 1.59 -1.47 (m, 4H) , 1.46 -1.14 (m, 36H) , 1.05 (s, 9H) , 0.93 -0.82 (m, 6H) .

[0452] Step 8: di ((Z) -undec-2-en-1-yl) 7-hydroxytridecanedioate



[0453] To a mixture of di ((Z) -undec-2-en-1-yl) 7- ((tert-butylidiphenylsilyl) oxy) tridecanedioate (4.3 g, 5.35 mmol) in THF (50 mL) was added TBAF (1 M, 21 mL) . The mixture was stirred at 40 °C for 12 hours. TLC showed that one new spot was observed. The reaction mixture was quenched with water (80 mL) . The mixture was extracted with EtOAc (100 mL $\times$ 2) . The combined organic phase was washed with brine (80 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 4: 1) to give di ((Z) -undec-2-en-1-yl) 7-hydroxytridecanedioate (2.3 g, 76%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.69-5.47 (m, 4H) , 4.63 (d, J= 6.8 Hz, 4H) , 3.64 -3.52 (m, 1H) , 2.32 (t, J= 7.6 Hz, 4H) , 2.16 -2.06 (m, 4H) , 1.69 -1.60 (m, 4H) , 1.52 -1.24 (m, 36H) , 0.92 -0.85 (m, 6H) .

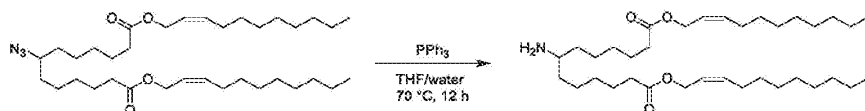
[0454] Step 9: di ((Z) -undec-2-en-1-yl) 7-azidotridecanedioate



[0455] To a mixture of di ((Z) -undec-2-en-1-yl) 7-hydroxytridecanedioate (2.3 g, 4.07 mmol) in THF (50 mL) was added PPh_3 (2.14 g, 8.14 mmol) and DIAD (1.65 g, 8.14 mmol, 1.58 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 10 min. Then DPPA (2.24 g, 8.14 mmol, 1.76 mL) was added at 0 °C. The mixture was stirred at 20 °C for 16 hours. TLC showed that one main spot was observed. The

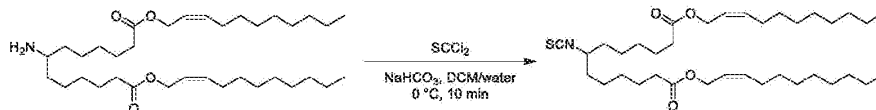
reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give di ((Z) -undec-2-en-1-yl) 7-azidotridecanedioate (3.2 g, crude) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.70 -5.61 (m, 2H) , 5.58-5.47 (m, 2H) , 4.63 (d, J= 6.8 Hz, 4H) , 3.28 -3.17 (m, 1H) , 2.32 (t, J= 7.6 Hz, 4H) , 2.10 (q, J= 7.2 Hz, 4H) , 1.65 (q, J= 7.2 Hz, 4H) , 1.53 -1.47 (m, 4H) , 1.40 -1.22 (m, 32H) , 0.93 -0.85 (m, 6H) .

[0456] Step 10: di ((Z) -undec-2-en-1-yl) 7-aminotridecanedioate



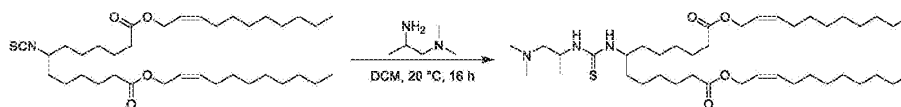
[0457] A mixture of di ((Z) -undec-2-en-1-yl) 7-azidotridecanedioate (3.2 g, crude, 4.07 mmol) and PPh₃ (2.13 g, 8.14 mmol) in THF (40 mL) and water (8 mL) was stirred at 70 °C for 12 hours under N₂ atmosphere. TLC showed that several spots were observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 15: 1) to give di ((Z) -undec-2-en-1-yl) 7-aminotridecanedioate (2.9 g, crude) as a white semisolid. ¹H NMR (400 MHz, CDCl₃) δ 5.70 -5.59 (m, 2H) , 5.55 -5.47 (m, 2H) , 4.62 (d, J= 6.8 Hz, 4H) , 2.70 (br s, 1H) , 2.31 (t, J= 7.6 Hz, 4H) , 2.16 -2.02 (m, 4H) , 1.64 (q, J= 7.2 Hz, 4H) , 1.45 -1.19 (m, 36H) , 0.88 (t, J= 6.8 Hz, 6H) .

[0458] Step 11: di ((Z) -undec-2-en-1-yl) 7-isothiocyanatotridecanedioate



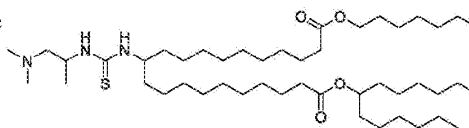
[0459] To a mixture of di ((Z) -undec-2-en-1-yl) 7-aminotridecanedioate (1 g, crude, 1.33 mmol) in DCM (50 mL) and water (20 mL) was added NaHCO₃ (782mg, 9.31 mmol) and thiocarbonyl dichloride (306 mg, 2.66 mmol) . The mixture was stirred at 0 °C for 10 min. TLC showed that starting material was consumed completely. The organic phase was separated and washed with brine (30 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give di ((Z) -undec-2-en-1-yl) 7-isothiocyanatotridecanedioate (400 mg, 49%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.70 -5.61 (m, 2H) , 5.57 -5.48 (m, 2H) , 4.63 (d, J= 6.8 Hz, 4H) , 3.66 -3.57 (m, 1H) , 2.33 (t, J= 7.6 Hz, 4H) , 2.11 (q, J= 7.2 Hz, 4H) , 1.71 -1.58 (m, 8H) , 1.44 -1.22 (m, 32H) , 0.92 -0.84 (m, 6H) .

[0460] Step 12: di ((Z) -undec-2-en-1-yl) 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate

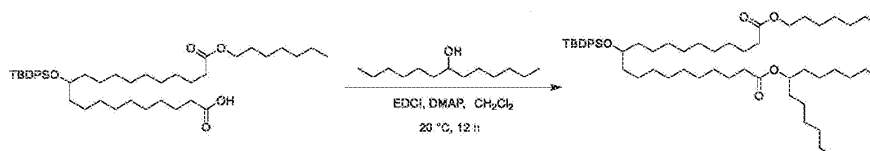


- [0461] A mixture of di ((Z) -undec-2-en-1-yl) 7-isothiocyanatotridecanedioate (200 mg, 330 μ mol) and N¹, N¹-dimethylpropane-1, 2-diamine (67.5 mg, 660 μ mol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL) . The organic phase was washed with saturated NaHCO₃ (50 mL) , brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μ m; mobile phase: [water (FA) -ACN] ; gradient: 45%-75%B over 20 min) to give di ((Z) -undec-2-en-1-yl) 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) tridecanedioate (97.2 mg, 42%yield, 100%purity) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.69 -5.59 (m, 2H) , 5.57 -5.45 (m, 2H) , 4.62 (d, J= 6.8 Hz, 4H) , 4.48 -3.98 (m, 2H) , 3.11-2.88 (m, 1H) , 2.80 -2.40 (m, 6H) , 2.37 -2.25 (m, 5H) , 2.10 (q, J= 7.2 Hz, 4H) , 1.70 -1.59 (m, 4H) , 1.51 -1.21 (m, 39H) , 0.96 -0.78 (m, 6H) . LCMS showed the purity is 100%, Rt = 1.995 min; MS Calcd. : 707.6, MS Found: 708.5 [M+H]⁺.

- [0462] Example 39: 1-heptyl 21- (tridecan-7-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate



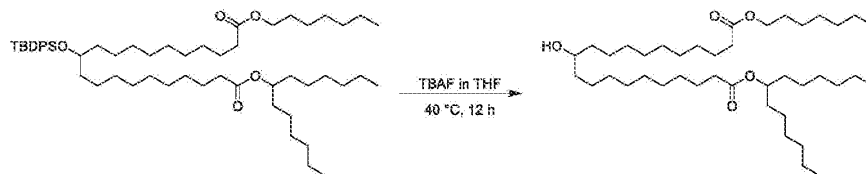
- [0463] Step 1: 1-heptyl 21- (tridecan-7-yl) 11- ((tert-butyldiphenylsilyl) oxy) henicosanedioate



- [0464] To a mixture of 11- ((tert-butyldiphenylsilyl) oxy) -21- (heptyloxy) -21-oxohenicosanoic acid (4.1 g, 5.78 mmol) in DCM (50 mL) was added EDCI (2.22 g, 11.56 mmol) and DMAP (1.41 g, 11.56 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, then tridecan-7-ol (1.39 g, 6.94 mmol) was added. The mixture was stirred at 20 °C for 12 hours. TLC showed that one new spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1-heptyl 21- (tridecan-7-yl) 11- ((tert-butyldiphenylsilyl) oxy) henicosanedioate (4.3 g, 83%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 -7.65 (m, 4H) , 7.44 -7.33 (m, 6H) , 4.88 (q, J= 6.0 Hz, 1H) , 4.07 (t, J= 6.8 Hz, 2H) , 3.70 (q, J= 5.6 Hz, 1H) , 2.33 -2.25 (m, 4H) , 1.67

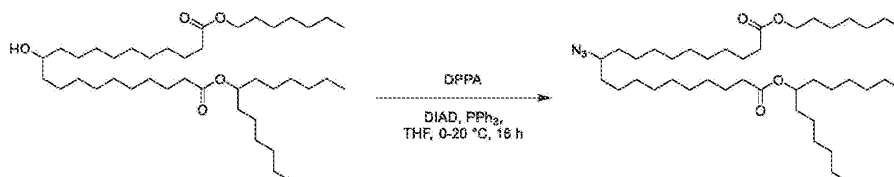
-1.58 (m, 6H) , 1.54 -1.48 (m, 4H) , 1.43 -1.09 (m, 52H) , 1.05 (s, 9H) , 0.92 -0.85 (m, 9H) .

[0465] Step 2: 1-heptyl 21- (tridecan-7-yl) 11-hydroxyhenicosanedioate



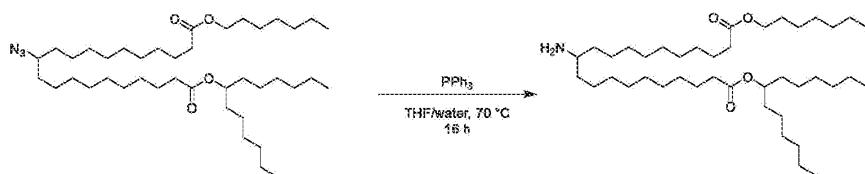
[0466] To a mixture of 1-heptyl 21- (tridecan-7-yl) 11- ((tert-butyldiphenylsilyl) oxy) henicosanedioate (4.3 g, 4.82 mmol) in THF (50 mL) was added TBAF (1 M, 24 mL) . The mixture was stirred at 40 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with water (80 mL) . The mixture was extracted with EtOAc (100 mL × 2) . The combined organic phase was washed with brine (80 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 4: 1) to give 1-heptyl 21- (tridecan-7-yl) 11-hydroxyhenicosanedioate (2.7 g, crude) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.88 (t, J= 6.0 Hz, 1H) , 4.06 (t, J= 6.4 Hz, 2H) , 3.64 -3.53 (m, 1H) , 2.36 -2.24 (m, 4H) , 1.68-1.57 (m, 6H) , 1.55 -1.47 (m, 4H) , 1.46 -1.39 (m, 4H) , 1.29 (br s, 48H) , 0.92 -0.83 (m, 9H) .

[0467] Step 3: 1-heptyl 21- (tridecan-7-yl) 11-azidohehenicosanedioate



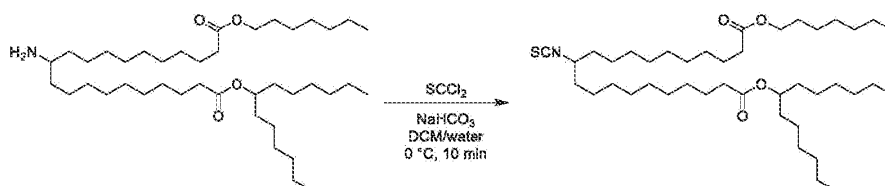
[0468] To a mixture of 1-heptyl 21- (tridecan-7-yl) 11-hydroxyhenicosanedioate (2.7 g, crude, 4.13 mmol) in THF (80 mL) was added PPh₃ (2.17 g, 8.27 mmol) and DIAD (1.67 g, 8.27 mmol, 1.60 mL) at 0 °C. The mixture was stirred at 20 °C for 10 min, then DPPA (2.28 g, 8.27 mmol, 1.78 mL) was added. The mixture was stirred at 20°C for 16 hours. TLC showed that one main spot was observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1-heptyl 21- (tridecan-7-yl) 11-azidohehenicosanedioate (2.0 g, 71%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.88 (q, J= 6.4 Hz, 1H) , 4.07 (t, J= 6.8 Hz, 2H) , 3.22 (q, J= 6.0 Hz, 1H) , 2.33 -2.23 (m, 4H) , 1.62 (q, J= 7.2 Hz, 6H) , 1.55 -1.47 (m, 8H) , 1.38 -1.20 (m, 48H) , 0.94 -0.84 (m, 9H) .

[0469] Step 4: 1-heptyl 21- (tridecan-7-yl) 11-aminohehenicosanedioate



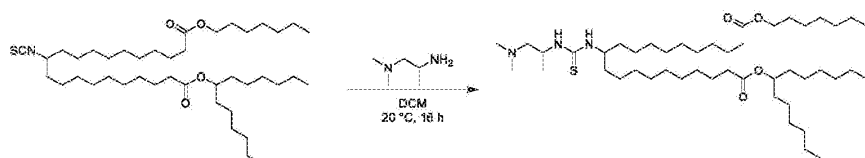
[0470] A mixture of 1-heptyl 21- (tridecan-7-yl) 11-azidohenicosanedioate (2.0 g, 2.95 mmol) and PPh_3 (1.55 g, 5.90 mmol) in THF (50 mL) /water (10 mL) was stirred at 70°C for 16 hours under N_2 atmosphere. TLC showed that several spots were observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 15: 1) to give 1-heptyl 21- (tridecan-7-yl) 11-aminohenicosanedioate (2.4 g, 80%yield, 64%purity) as a white semisolid. ^1H NMR (400 MHz, CDCl_3) δ 4.87 (q, $J=6.0$ Hz, 1H) , 4.06 (t, $J=6.4$ Hz, 2H) , 2.73 (br s, 1H) , 2.33 -2.23 (m, 4H) , 1.68 -1.55 (m, 6H) , 1.54 -1.48 (m, 4H) , 1.43 -1.17 (m, 52H) , 0.91 -0.84 (m, 9H) .

[0471] Step 5: 1-heptyl 21- (tridecan-7-yl) 11-isothiocyanatohenicosanedioate



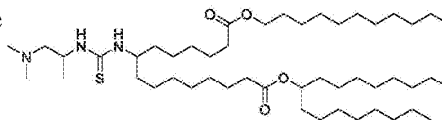
[0472] To a mixture of 1-heptyl 21- (tridecan-7-yl) 11-aminohenicosanedioate (1.4 g, 1.37 mmol, 64%purity) in DCM (50 mL) and water (20 mL) was added NaHCO_3 (808 mg, 9.62 mmol) and thiocarbonyl dichloride (316 mg, 2.75 mmol) at 0°C . The mixture was stirred at 0°C for 10 min. TLC showed that one main spot was observed. The reaction mixture was diluted with DCM (30 mL) and water (20 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give 1-heptyl 21- (tridecan-7-yl) 11-isothiocyanatohenicosanedioate (600 mg, 63%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.88 (q, $J=6.0$ Hz, 1H) , 4.07 (t, $J=6.8$ Hz, 2H) , 3.66 -3.57 (m, 1H) , 2.34 -2.25 (m, 4H) , 1.67 -1.58 (m, 8H) , 1.53 -1.47 (m, 6H) , 1.39 -1.23 (m, 48H) , 0.92 -0.86 (m, 9H) .

[0473] Step 6: 1-heptyl 21- (tridecan-7-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate

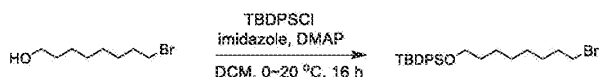


[0474] A mixture of 1-heptyl 21- (tridecan-7-yl) 11-isothiocyanatohenicosanedioate (200 mg, 288 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (58.9 mg, 576 μmol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 75%-98%B over 13 min) to give 1-heptyl 21- (tridecan-7-yl) 11- (3- (1- (dimethylamino) propan-2-yl) thioureido) henicosanedioate (128.4 mg, 56% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.89 (br s, 1H) , 5.82 (br s, 1H) , 4.87 (t, $J=6.0$ Hz, 1H) , 4.24 (br s, 1H) , 4.06 (t, $J=6.8$ Hz, 2H) , 3.68 (br s, 1H) , 2.67 -2.51 (m, 1H) , 2.41 -2.22 (m, 11H) , 1.67 -1.57 (m, 6H) , 1.56-1.46 (m, 6H) , 1.40 -1.17 (m, 53H) , 0.95 -0.83 (m, 9H) . LCMS showed the purity is 100.00%, $R_t = 6.231$ min; MS Calcd. : 795.7, MS Found: 796.9 $[\text{M}+\text{H}]^+$.

[0475] Example 40: 15- (heptadecan-9-yl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate

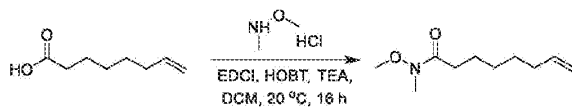


[0476] Step 1: ((8-bromooctyl) oxy) (tert-butyl) diphenylsilane



[0477] To a mixture of 8-bromooctan-1-ol (10 g, 47.8 mmol, 8.20 mL) , imidazole (13.0 g, 191 mmol) , DMAP (1.17 g, 9.56 mmol) in DCM (150 mL) was added TBDPSCI (26.3 g, 95.6 mmol, 24.5 mL) at 0 °C, then the mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (100 mL) , extracted with DCM (100 mL $\times$ 2) . The organic phase was separated and washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/50) to give ((8-bromooctyl) oxy) (tert-butyl) diphenylsilane (17.1 g, 79.9% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.75 -7.62 (m, 4H) , 7.47 -7.34 (m, 6H) , 3.66 (t, $J=6.4$ Hz, 2H) , 3.41 (t, $J=6.8$ Hz, 2H) , 1.91 -1.80 (m, 2H) , 1.61 -1.55 (m, 2H) , 1.47 -1.27 (m, 8H) , 1.06 (s, 9H) .

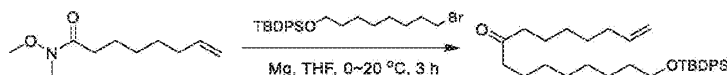
[0478] Step 2: N-methoxy-N-methyloct-7-enamide



[0479] A mixture of oct-7-enoic acid (5.0 g, 35.2 mmol) , N-methoxymethanamine; hydrochloride (5.14 g, 52.7 mmol) , EDCI (13.5 g, 70.3 mmol) , HOBt (9.50 g, 70.3 mmol) , TEA (14.2 g, 141 mmol, 19.6 mL) in DCM (100 mL) was stirred at 20 °C

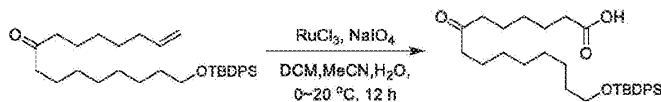
for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (100 mL) and extracted with DCM (80 mL $\times$ 2). The organic phase was separated and washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/5) to give N-methoxy-N-methyloct-7-enamide (6.3 g, 96.7% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.90-5.70 (m, 1H), 5.08-4.88 (m, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H), 2.12-2.02 (m, 2H), 1.69-1.61 (m, 2H), 1.48-1.31 (m, 4H).

[0480] Step 3: 16-((tert-butyldiphenylsilyl)oxy) hexadec-1-en-8-one



[0481] To a drying 250 mL three-neck flask, Mg (2.72 g, 111 mmol) and I_2 (28.4 mg, 112 μmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, then THF (10 mL) was added in the flask and the solution of ((8-bromooctyl)oxy)(tert-butyl)diphenylsilane (5.0 g, 11.2 mmol) in THF (40 mL) was added slowly to the flask at 20 °C, then the mixture was stirred at 20 °C for 2 hours. Then the mixture was added into the solution of N-methoxy-N-methyloct-7-enamide (1.7 g, 9.18 mmol) in THF (10 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 hour. The reaction was quenched with saturated NH_4Cl (40 mL) at 0 °C, then the mixture was warmed to 20 °C and extracted with EtOAc (2 $\times$ 40 mL). The combined organic layers were washed brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to get residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 7/100) to give 16-((tert-butyldiphenylsilyl)oxy) hexadec-1-en-8-one (3.96 g, 87.7% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.69-7.66 (m, 4H), 7.44-7.35 (m, 6H), 5.90-5.71 (m, 1H), 5.09-4.88 (m, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.46-2.30 (m, 4H), 2.05 (q, J = 7.2 Hz, 2H), 1.62-1.57 (m, 2H), 1.55-1.51 (m, 2H), 1.45-1.37 (m, 2H), 1.34-1.30 (m, 2H), 1.30-1.24 (m, 8H), 1.06 (s, 9H), 0.92-0.83 (m, 2H).

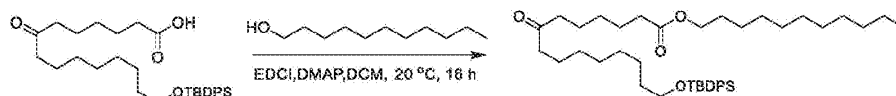
[0482] Step 4: 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoic acid



[0483] To a mixture of 16-((tert-butyldiphenylsilyl)oxy) hexadec-1-en-8-one (3.4 g, 6.90 mmol) in DCM (50 mL) and MeCN (50 mL) was added RuCl_3 (143 mg, 690 μmol). Then a solution of NaIO_4 (7.38 g, 34.5 mmol) in H_2O (50 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 12 hours. The reaction mixture was diluted with brine (100 mL). The mixture was adjusted with 1 N HCl to pH = 6. The mixture

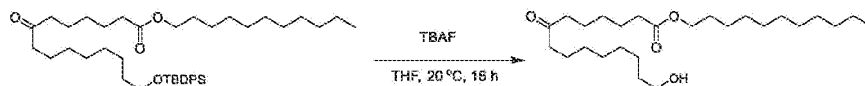
was filtered, the filter cake was washed with DCM (100 mL), the filtrate extracted with DCM (3 × 80 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/2) to give 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoic acid (1.78 g, 50.4% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.65 (m, 4H), 7.46-7.35 (m, 6H), 3.66 (t, J = 6.4 Hz, 2H), 2.44-2.32 (m, 6H), 1.72-1.51 (m, 8H), 1.39-1.31 (m, 4H), 1.29-1.24 (m, 6H), 1.06 (s, 9H).

[0484] Step 5: undecyl 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoate



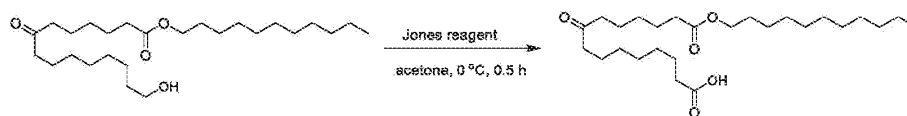
[0485] A mixture of 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoic acid (1.78 g, 3.48 mmol), undecan-1-ol (1.20 g, 6.97 mmol), EDCI (668 mg, 3.48 mmol), DMAP (426 mg, 3.48 mmol) in DCM (20 mL) was stirred at 20 °C for 16 hours. The reaction was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give undecyl 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoate (2.1 g, 90.6% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.62 (m, 4H), 7.47-7.32 (m, 6H), 4.06 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 2.44-2.34 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 1.70-1.56 (m, 8H), 1.55-1.51 (m, 2H), 1.37-1.24 (m, 26H), 1.05 (s, 9H), 0.89 (t, J = 6.8 Hz, 3H).

[0486] Step 6: undecyl 15-hydroxy-7-oxopentadecanoate



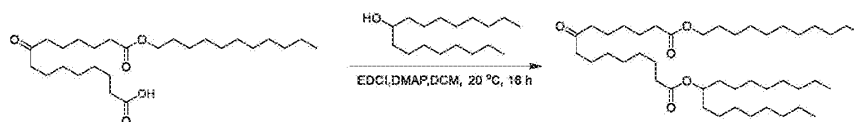
[0487] To a mixture of undecyl 15-((tert-butyldiphenylsilyl)oxy)-7-oxopentadecanoate (1.37 g, 2.12 mmol) in THF (20 mL) was added TBAF (1 M, 10.6 mL) under N₂ atmosphere. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO₃ (50 mL), extracted with EtOAc (100 mL × 2), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 4/25) to give undecyl 15-hydroxy-7-oxopentadecanoate (750 mg, 86.8% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.06 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 2.39 (q, J = 7.2 Hz, 4H), 2.30 (t, J = 7.6 Hz, 2H), 1.68-1.56 (m, 10H), 1.38-1.26 (m, 26H), 0.92-0.86 (m, 3H).

[0488] Step 7: 9, 15-dioxo-15-(undecyloxy) pentadecanoic acid



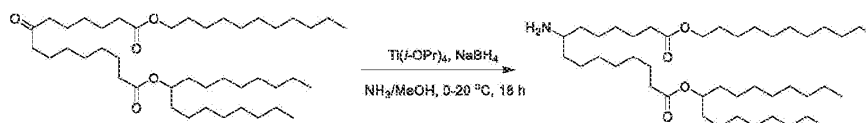
[0489] To a mixture of undecyl 15-hydroxy-7-oxopentadecanoate (1.25 g, 2.93 mmol) in acetone (50 mL) was added Jones reagent (2.5 M, 2.34 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (3 mL), diluted with H₂O (30 mL) and extracted with EtOAc (50 mL × 3), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give 9, 15-dioxo-15- (undecyloxy) pentadecanoic acid (1.25 g, 96.8%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.06 (t, J= 6.8 Hz, 2H), 2.48 -2.23 (m, 8H), 1.69 -1.53 (m, 10H), 1.38 -1.24 (m, 24H), 0.89 (t, J= 6.8 Hz, 3H).

[0490] Step 8: 15- (heptadecan-9-yl) 1-undecyl 7-oxopentadecanedioate



[0491] To a mixture of 9, 15-dioxo-15- (undecyloxy) pentadecanoic acid (1.39 g, 3.15 mmol), heptadecan-9-ol (1.62 g, 6.31 mmol) in DCM (20 mL) was added EDCI (605 mg, 3.15 mmol), DMAP (385 mg, 3.15 mmol), then the mixture was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 15- (heptadecan-9-yl) 1-undecyl 7-oxopentadecanedioate (2 g, 93.4%yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 4.93 -4.79 (m, 1H), 4.05 (t, J= 6.8 Hz, 2H), 2.39 (q, J= 7.2 Hz, 4H), 2.33 -2.24 (m, 4H), 1.68 -1.56 (m, 10H), 1.31 -1.25 (m, 52H), 0.90 -0.87 (m, 9H).

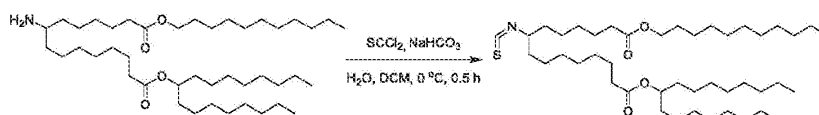
[0492] Step 9: 15- (heptadecan-9-yl) 1-undecyl 7-aminopentadecanedioate



[0493] A mixture of 15- (heptadecan-9-yl) 1-undecyl 7-oxopentadecanedioate (2.0 g, 2.95 mmol) and Ti (i-OPr)₄ (1.67 g, 5.89 mmol, 1.74 mL) in MeOH (30 mL) and NH₃/MeOH (15 mL), then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (223 mg, 5.89 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20 °C for 12 hours. The mixture was quenched with H₂O (20 mL) and diluted with ethyl acetate (50 mL). The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 50 mL), the combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The

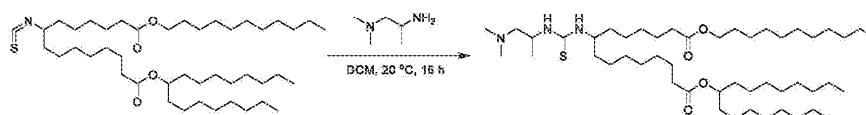
residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 15- (heptadecan-9-yl) 1-undecyl 7-aminopentadecanedioate (1.24 g, 61.9% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.87 (quin, J = 6.0 Hz, 1H) , 4.06 (t, J = 6.8 Hz, 2H) , 2.94 -2.80 (m, 1H) , 2.35 -2.24 (m, 4H) , 1.69 -1.57 (m, 6H) , 1.54 -1.39 (m, 10H) , 1.37 -1.22 (m, 50H) , 0.92 -0.85 (m, 9H) .

[0494] Step 10: 15- (heptadecan-9-yl) 1-undecyl 7-isothiocyanatopentadecanedioate



[0495] To a mixture of 15- (heptadecan-9-yl) 1-undecyl 7-aminopentadecanedioate (600 mg, 882 μmol) and NaHCO₃ (519 mg, 6.18 mmol) in DCM (20 mL) and H₂O (20 mL) was added SCl₂ (132 mg, 1.15 mmol, 87.9 μL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 7/100) to give 15- (heptadecan-9-yl) 1-undecyl 7-isothiocyanatopentadecanedioate (600 mg, 94.2% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.87 (quin, J = 6.4 Hz, 1H) , 4.07 (t, J = 6.8 Hz, 2H) , 3.67 -3.57 (m, 1H) , 2.35 -2.25 (m, 4H) , 1.70 -1.57 (m, 10H) , 1.54 -1.46 (m, 6H) , 1.42 -1.19 (m, 50H) , 0.89 (t, J = 6.8 Hz, 9H) .

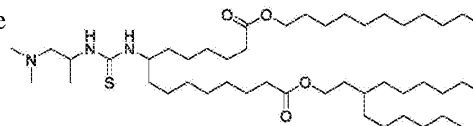
[0496] Step 11: 15- (heptadecan-9-yl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate



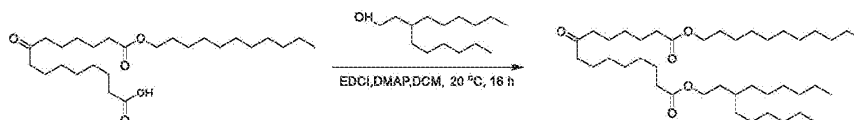
[0497] A mixture 15- (heptadecan-9-yl) 1-undecyl 7-isothiocyanatopentadecanedioate (200 mg, 277 μmol) , N¹, N¹-dimethylpropane-1, 2-diamine (56.6 mg, 554 μmol) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with HCl (1N, 5 mL) and H₂O (30 mL) and extracted with DCM (2 × 30 mL) , the combined organic layers were washed with saturated NaHCO₃ (30 mL) and brine (30 mL) , dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm; mobile phase: [water (FA) -MeOH] ; gradient: 65%-95%B over 20 min) to give 15- (heptadecan-9-yl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate (81.9 mg, 35.9% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.87 (quin, J = 6.4 Hz, 1H) , 4.39 -4.17 (m, 1H) , 4.05 (t, J = 6.8 Hz, 2H) , 3.97 -3.59 (m, 1H) , 2.84-2.55 (m, 1H) , 2.54 -2.07 (m, 11H) , 1.65 -1.57 (m, 6H) , 1.51 (d, J = 5.6 Hz, 6H) , 1.40

-1.21 (m, 57H) , 0.89 (t, J= 6.8 Hz, 9H) . LCMS showed the purity is 100%, Rt = 5.093 min; MS Calcd. : 823.7, MS Found: 824.7 [M+H]⁺.

[0498] Example 41: 15- (3-hexylnonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate

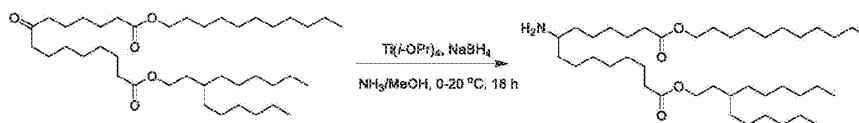


[0499] Step 1: 15- (3-hexylnonyl) 1-undecyl 7-oxopentadecanedioate



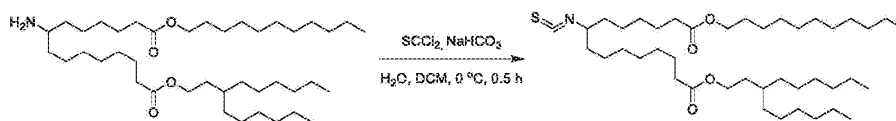
[0500] A mixture of 9, 15-dioxo-15- (undecyloxy) pentadecanoic acid (1.5 g, 3.40 mmol) , 3-hexylnonan-1-ol (933 mg, 4.08 mmol) , EDCI (653 mg, 3.40 mmol) , DMAP (416 mg, 3.40 mmol) in DCM (20 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 15- (3-hexylnonyl) 1-undecyl 7-oxopentadecanedioate (2 g, 90.2%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.11 -4.03 (m, 4H) , 2.39 (q, J= 7.2 Hz, 4H) , 2.29 (q, J= 7.2 Hz, 4H) , 1.65 -1.56 (m, 12H) , 1.30 -1.25 (m, 45H) , 0.90-0.86 (m, 9H) .

[0501] Step 2: 15- (3-hexylnonyl) 1-undecyl 7-aminopentadecanedioate



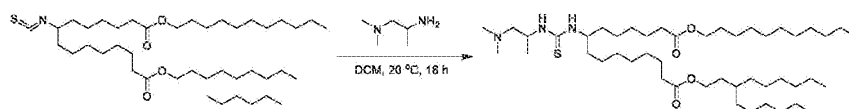
[0502] A mixture of 15- (3-hexylnonyl) 1-undecyl 7-oxopentadecanedioate (2 g, 3.07 mmol) and Ti (i-OPr)₄ (1.75 g, 6.14 mmol, 1.81 mL) in MeOH (30 mL) and NH₃/MeOH (7 M, 15 mL) , then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (340 mg, 8.99 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20°C for 12 hours. The mixture was quenched with H₂O (30 mL) and diluted with ethyl acetate (50 mL) . The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 100 mL) , the combined organic layer was washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 15- (3-hexylnonyl) 1-undecyl 7-aminopentadecanedioate (1.54 g, 76.9%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.12 -4.02 (m, 4H) , 2.75 (d, J= 2.8 Hz, 1H) , 2.30 (q, J= 7.2 Hz, 4H) , 1.66 -1.55 (m, 10H) , 1.46 -1.39 (m, 4H) , 1.37 -1.24 (m, 47H) , 0.89 (t, J= 6.8 Hz, 9H) .

[0503] Step 3: 15- (3-hexylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate



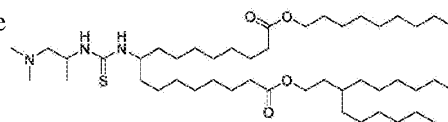
[0504] To a mixture of 15- (3-hexylnonyl) 1-undecyl 7-aminopentadecanedioate (400 mg, 613 μmol) and NaHCO_3 (258 mg, 3.07 mmol) in DCM (20 mL) and H_2O (20 mL) was added SCCl_2 (84.6 mg, 736 μmol , 56.4 μL) at 0 $^\circ\text{C}$, then the mixture was stirred at 0 $^\circ\text{C}$ for 0.5 hour. The mixture was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc : PE = 0 to 7/100) to give 15- (3-hexylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (420 mg, 98.6% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.16 -3.99 (m, 4H), 3.67 -3.56 (m, 1H), 2.31 (q, J = 7.8 Hz, 4H), 1.70 -1.57 (m, 10H), 1.49 (s, 4H), 1.42 -1.21 (m, 47H), 0.92 -0.86 (m, 9H).

[0505] Step 4: 15- (3-hexylnonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate

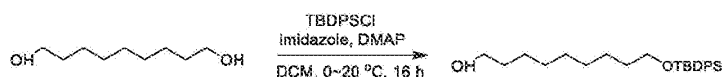


[0506] A mixture 15- (3-hexylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (210 mg, 303 μmol), N^1, N^1 -dimethylpropane-1, 2-diamine (61.8 mg, 605 μmol) in DCM (8 mL) was stirred at 20 $^\circ\text{C}$ for 16 hours. The mixture was diluted with HCl (1N, 5 mL) and H_2O (30 mL) and extracted with DCM (2 $\times$ 30 mL), the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 $\times$ 30 $\times$ 10 μm ; mobile phase: [water (FA) -ACN]; gradient: 73%-98%B over 13 min) to give 15- (3-hexylnonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate (109.2 mg, 45.3% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.39 -4.18 (m, 1H), 4.12 -4.02 (m, 4H), 4.00 -3.64 (m, 1H), 2.82 -2.57 (m, 1H), 2.46 -2.20 (m, 11H), 1.68 -1.52 (m, 10H), 1.40 -1.19 (m, 54H), 0.89 (t, J = 6.8 Hz, 9H). LCMS showed the purity is 100%, Rt = 4.627 min; MS Calcd.: 795.7, MS Found: 796.7 $[\text{M}+\text{H}]^+$.

[0507] Example 42: 1- (3-hexylnonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate

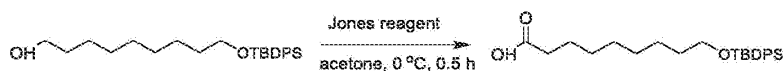


[0508] Step 1: 9- ((tert-butyl) diphenylsilyl) oxy) nonan-1-ol



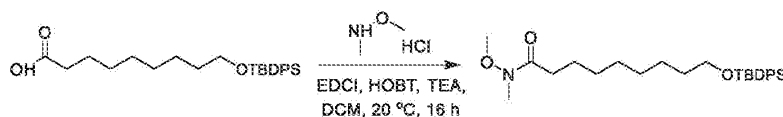
- [0509] To a mixture of nonane-1, 9-diol (10 g, 62.4 mmol) , imidazole (8.50 g, 125 mmol) , DMAP (762 mg, 6.24 mmol) in DCM (150 mL) was added the solution TBDPSCI (15.4 g, 56.2 mmol, 14.4 mL) in DCM (50 mL) at 35 °C, then the mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (200 mL) and extracted with DCM (100 mL $\times$ 2) . The organic phase was separated and washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/4) to give 9- ((tert-butyldiphenylsilyl) oxy) nonan-1-ol (12.6 g, 50.8%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.72 -7.65 (m, 4H) , 7.45 -7.34 (m, 6H) , 3.72 -3.59 (m, 4H) , 1.62 -1.52 (m, 4H) , 1.41 -1.27 (m, 10H) , 1.06 (s, 9H) .

- [0510] Step 2: 9- ((tert-butyldiphenylsilyl) oxy) nonanoic acid



- [0511] To a mixture of 9- ((tert-butyldiphenylsilyl) oxy) nonan-1-ol (12.6 g, 31.7 mmol) in acetone (100 mL) was added Jones reagent (2.5 M, 19.0 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (10 mL) , diluted with H_2O (100 mL) and extracted with EtOAc (100 mL $\times$ 3) , the combined organic layer was washed with brine (100 mL) and dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/3) to give 9- ((tert-butyldiphenylsilyl) oxy) nonanoic acid (11 g, 84.1%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 -7.66 (m, 4H) , 7.46 -7.37 (m, 6H) , 3.67 (t, J = 6.4 Hz, 2H) , 2.37 (t, J = 7.6 Hz, 2H) , 1.72 -1.54 (m, 4H) , 1.40 -1.29 (m, 8H) , 1.07 (s, 9H) .

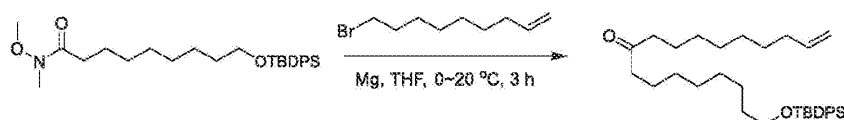
- [0512] Step 3: 9- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methylnonanamide



- [0513] A mixture of 9- ((tert-butyldiphenylsilyl) oxy) nonanoic acid (14.5 g, 35.1 mmol) , N-methoxymethanamine; hydrochloride (5.14 g, 52.7 mmol) , EDCI (13.5 g, 70.3 mmol) , HOBT (9.50 g, 70.3 mmol) , TEA (14.2 g, 141 mmol, 19.6 mL) in DCM (100 mL) was stirred at 20 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (100 mL) and extracted with DCM (80 mL $\times$ 2) . The organic phase was separated and washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chro-

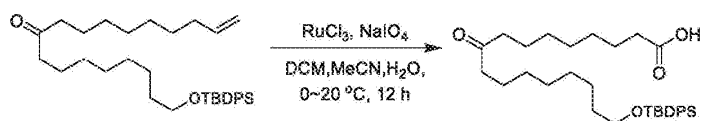
matography (SiO₂, EtOAc: PE = 0 to 1/5) to give 9- ((tert-butyldiphenylsilyl) oxy) - N-methoxy-N-methylnonanamide (12.2 g, 26.7 mmol, 76.1%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J= 6.4 Hz, 4H) , 7.46 -7.34 (m, 6H) , 3.77 -3.61 (m, 5H) , 3.19 (s, 3H) , 2.41 (t, J= 7.6 Hz, 2H) , 1.64 -1.54 (m, 4H) , 1.40 -1.27 (m, 8H) , 1.05 (s, 9H) .

[0514] Step 4: 1- ((tert-butyldiphenylsilyl) oxy) octadec-17-en-9-one



[0515] To a drying 250 mL three-neck flask, Mg (2.85 g, 117 mmol) and I₂ (334 mg, 1.32 mmol) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, then THF (10 mL) was added in the flask and the solution of 9-bromonon-1-ene (5.4 g, 26.3 mmol) in THF (40 mL) was added slowly to the flask at 20°C, then the mixture was stirred at 20 °C for 2 hours. Then the mixture was added into the solution of 9- ((tert-butyldiphenylsilyl) oxy) -N-methoxy-N-methylnonanamide (6.0 g, 13.2 mmol) in THF (20 mL) was added slowly to the mixture at 0 °C, then the mixture was stirred at 20 °C for 1 hour. The reaction was quenched with saturated NH₄Cl (40 mL) at 0 °C, then the mixture was warmed to 20 °C and extracted with EtOAc (2 × 50 mL) . The combined organic layers were washed brine (150 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 7/100) to give 1- ((tert-butyldiphenylsilyl) oxy) octadec-17-en-9-one (6.6 g, 96.2%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.76 -7.58 (m, 4H) , 7.49 -7.34 (m, 6H) , 5.92 -5.72 (m, 1H) , 5.10 -4.83 (m, 2H) , 3.66 (t, J= 6.4 Hz, 2H) , 2.43 -2.33 (m, 4H) , 2.09 -2.01 (m, 2H) , 1.63 -1.57 (m, 2H) , 1.55 -1.51 (m, 2H) , 1.42 -1.24 (m, 18H) , 1.05 (s, 9H) .

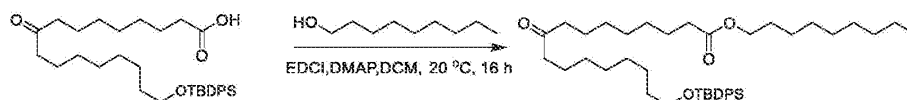
[0516] Step 5: 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoic acid



[0517] To a mixture of 1- ((tert-butyldiphenylsilyl) oxy) octadec-17-en-9-one (6.6 g, 12.7 mmol) in DCM (100 mL) and MeCN (100 mL) was added RuCl₃ (263 mg, 1.27 mmol) . Then a solution of NaIO₄ (13.6 g, 63.4 mmol) in H₂O (50 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 12 hours. The reaction mixture was diluted with brine (200 mL) . The mixture was adjusted with 1 N HCl to pH = 6. The mixture was filtered, the filter cake was washed with DCM (200 mL) , the filtrate extracted with DCM (3 × 100 mL) . The combined organic phase was washed with

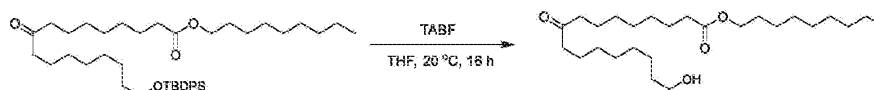
brine (100 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/2) to give 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoic acid (4.9 g, 71.8%yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.73 -7.60 (m, 4H), 7.48 -7.33 (m, 6H), 3.65 (t, J = 6.4 Hz, 2H), 2.44 -2.32 (m, 6H), 1.69 -1.51 (m, 8H), 1.36 -1.24 (m, 14H), 1.05 (s, 9H).

[0518] Step 6: nonyl 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoate



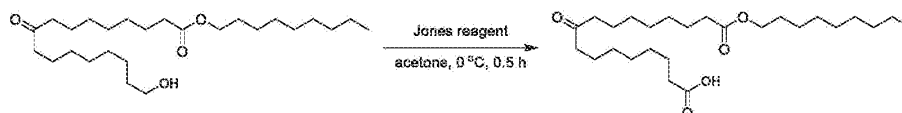
[0519] A mixture of 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoic acid (4.90 g, 9.09 mmol), nonan-1-ol (2.62 g, 18.2 mmol), EDCI (1.74 g, 9.09 mmol), DMAP (1.11 g, 9.09 mmol) in DCM (100 mL) was stirred at 20°C for 16 hours. The reaction was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give nonyl 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoate (5.28 g, 87.3%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.72 -7.64 (m, 4H), 7.46 -7.35 (m, 6H), 4.06 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 2.44-2.33 (m, 4H), 2.29 (t, J = 7.6 Hz, 2H), 1.67 -1.57 (m, 6H), 1.56 -1.51 (m, 4H), 1.37 -1.25 (m, 26H), 1.05 (s, 9H), 0.91 -0.87 (m, 3H).

[0520] Step 7: nonyl 17-hydroxy-9-oxoheptadecanoate



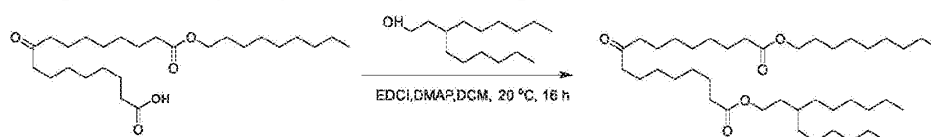
[0521] To a mixture of nonyl 17- ((tert-butyldiphenylsilyl) oxy) -9-oxoheptadecanoate (5.28 g, 7.94 mmol) in THF (100 mL) was added TBAF (1 M, 39.7 mL) under N_2 atmosphere. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with saturated NaHCO_3 (100 mL), extracted with EtOAc (100 mL $\times$ 2), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/3) to give nonyl 17-hydroxy-9-oxoheptadecanoate (3.3 g, 97.4%yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J = 6.8 Hz, 2H), 3.64 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.6 Hz, 4H), 2.29 (t, J = 7.6 Hz, 2H), 1.64 -1.54 (m, 10H), 1.37 -1.26 (m, 26H), 0.92 -0.87 (m, 3H).

[0522] Step 8: 17- (nonyloxy) -9, 17-dioxoheptadecanoic acid



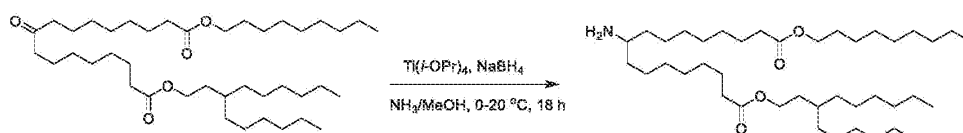
[0523] To a mixture of nonyl 17-hydroxy-9-oxoheptadecanoate (3.30 g, 7.73 mmol) in acetone (100 mL) was added Jones reagent (2.5 M, 6.19 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with i-PrOH (3 mL), diluted with H₂O (100 mL) and extracted with EtOAc (100 mL × 3), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give 17- (nonyloxy) -9, 17-dioxoheptadecanoic acid (3.10 g, 91.0%yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 4.06 (t, J= 6.8 Hz, 2H), 2.44 -2.24 (m, 8H), 1.69 -1.52 (m, 10H), 1.40 -1.22 (m, 24H), 0.91 -0.86 (m, 3H).

[0524] Step 9: 1- (3-hexylnonyl) 17-nonyl 9-oxoheptadecanedioate



[0525] To a mixture of 17- (nonyloxy) -9, 17-dioxoheptadecanoic acid (1.5 g, 3.40 mmol), 3-hexylnon-1-ol (933 mg, 4.08 mmol) EDCI (653 mg, 3.40 mmol) and DMAP (416 mg, 3.40 mmol) in DCM (20 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 1- (3-hexylnonyl) 17-nonyl 9-oxoheptadecanedioate (1.78 g, 80.3%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.11 -4.03 (m, 4H), 2.38 (t, J= 7.6 Hz, 4H), 2.32 -2.23 (m, 4H), 1.65 -1.54 (m, 12H), 1.35 -1.22 (m, 45H), 0.89 (t, J= 6.8 Hz, 9H).

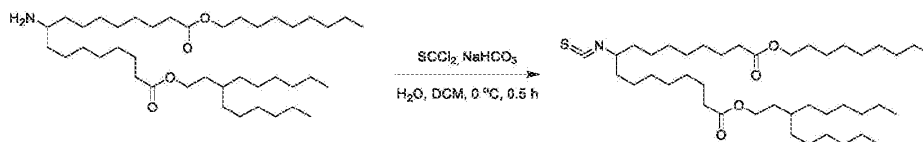
[0526] Step 10: 1- (3-hexylnonyl) 17-nonyl 9-aminoheptadecanedioate



[0527] A mixture of 1- (3-hexylnonyl) 17-nonyl 9-oxoheptadecanedioate (1.78 g, 2.73 mmol) and Ti (i-OPr)₄ (1.55 g, 5.47 mmol, 1.61 mL) in MeOH (30 mL) and NH₃/MeOH (7 M, 15 mL), then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (220 mg, 5.82 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20 °C for 12 hours. The mixture was quenched with H₂O (20 mL) and diluted with ethyl acetate (50 mL). The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 100 mL), the combined organic layer was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 1- (3-hexylnonyl) 17-nonyl 9-aminoheptadecanedioate (1.25 g, 70.1%yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.15 -4.00 (m, 4H), 2.73

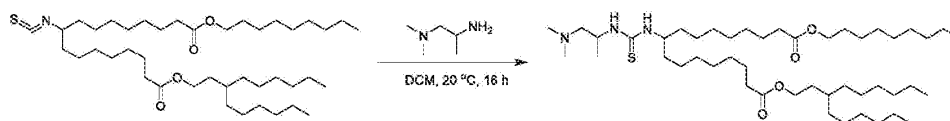
(s, 1H) , 2.34 -2.20 (m, 4H) , 1.66 -1.55 (m, 8H) , 1.46 -1.24 (m, 53H) , 0.89 (t, J= 6.8 Hz, 9H) .

[0528] Step 11: 1- (3-hexylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate



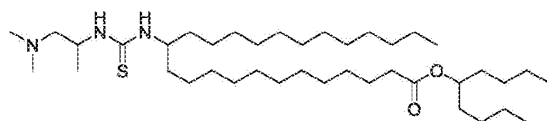
[0529] To a mixture of 1- (3-hexylnonyl) 17-nonyl 9-aminoheptadecanedioate (500 mg, 767 μmol) and NaHCO_3 (322 mg, 3.83 mmol) in DCM (20 mL) and H_2O (20 mL) was added SCCl_2 (106 mg, 920 μmol , 70.5 μL) at $0\text{ }^\circ\text{C}$, then the mixture was stirred at $0\text{ }^\circ\text{C}$ for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc : PE = 0 to 7/100) to give 1- (3-hexylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (520 mg, 97.7%yield) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 4.15 -4.00 (m, 4H) , 3.65 -3.57 (m, 1H) , 2.36-2.25 (m, 4H) , 1.67 -1.57 (m, 10H) , 1.53 -1.22 (m, 51H) , 0.89 (t, J= 7.0 Hz, 9H) .

[0530] Step 12: 1- (3-hexylnonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate

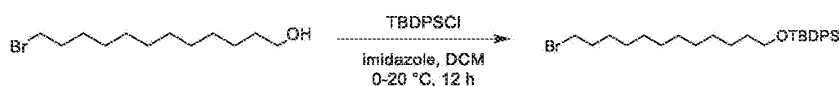


[0531] A mixture of 1- (3-hexylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (200 mg, 288 μmol) , N^1 , N^1 -dimethylpropane-1, 2-diamine (58.9 mg, 576 μmol) in DCM (6 mL) was stirred at $20\text{ }^\circ\text{C}$ for 16 hours. The mixture was diluted with HCl (1N, 5 mL) and H_2O (30 mL) and extracted with DCM (2 $\times$ 30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 $\times$ 30 $\times$ 10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 70%-98%B over 13 min) to give 1- (3-hexylnonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate (127.5 mg, 55.6%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.36 -4.14 (m, 1H) , 4.12 -4.00 (m, 4H) , 3.96 -3.60 (m, 1H) , 2.74 -2.55 (m, 1H) , 2.43 -2.22 (m, 11H) , 1.67 -1.49 (m, 10H) , 1.41 -1.19 (m, 54H) , 0.89 (t, J= 6.8 Hz, 9H) . LCMS showed the purity is 100%, Rt = 3.566 min; MS Calcd. : 795.7, MS Found: 796.7 $[\text{M}+\text{H}]^+$.

[0532] Example 43: nonan-5-yl 13- (3- (1- (dimethylamino) propan-2-yl) thioureido) penta-cosanoate

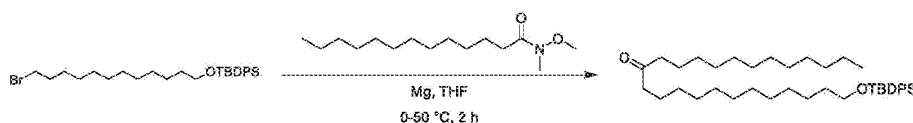


[0533] Step 1: ((12-bromododecyl) oxy) (tert-butyl) diphenylsilane



[0534] To a mixture of 12-bromododecan-1-ol (10 g, 37.7 mmol) in DCM (100 mL) was added imidazole (10.3 g, 151 mmol) and DMAP (921 mg, 7.54 mmol) at 0 °C. Then TBDPSCI (20.7 g, 75.4 mmol) was added. The mixture was stirred at 20 °C for 12 hours. TLC showed that one new spot was observed. The mixture was quenched with saturated NaHCO_3 (100 mL). The mixture was extracted with DCM (100 mL $\times$ 2). The combined organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (PE/EtOAc=1: 0 to 9: 1) to give ((12-bromododecyl) oxy) (tert-butyl) diphenylsilane (16.3 g, 86% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 -7.65 (m, 4H), 7.42 -7.35 (m, 6H), 3.66 (t, J = 6.4 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 1.92 -1.80 (m, 2H), 1.59 -1.52 (m, 2H), 1.48 -1.39 (m, 2H), 1.37 -1.22 (m, 14H), 1.06 (s, 9H).

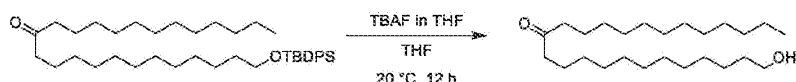
[0535] Step 2: 1- ((tert-butyldiphenylsilyl) oxy) pentacosan-13-one



[0536] To a drying 250 mL three-neck bottle, freshly activated Mg (1.93 g, 79.4 mmol) and I_2 (one grain, catalytic amount) were added. The flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, and flushed with N_2 and THF (20 mL) was added to the flask via syringe. The ((12-bromododecyl) oxy) (tert-butyl) diphenylsilane (11.7 g, 23.3 mmol) was dissolved in THF (50 mL) and added to the addition funnel. This above solution was added to the Mg turnings while stirring vigorously and heating by high gun. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux. After the completion of the addition the reaction mixture was kept at 50 °C for 1 hour. The mixture was cooled into ice-bath. N-methoxy-N-methyltridecanamide (4 g, 15.5 mmol) in THF (50 mL) transferred to the addition funnel and added dropwise to the reaction mixture with stirring at 0 °C. The reaction mixture was stirred at 50 °C for 1 hour. TLC showed that one main spot was observed. The reaction was quenched by adding saturated NH_4Cl (50 mL) under ice-bath. The reaction mixture was extracted with EtOAc (100 mL $\times$ 2). The combined

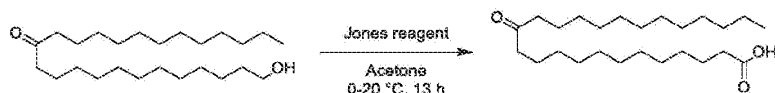
organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1-((tert-butyldiphenylsilyl)oxy)pentacosan-13-one (9.65 g, crude, theoretical quantity). The crude was used into next step directly. ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.65 (m, 4H), 7.45-7.32 (m, 6H), 3.66 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 7.6 Hz, 2H), 1.62-1.51 (m, 4H), 1.38-1.21 (m, 38H), 1.05 (s, 9H), 0.89 (t, J = 6.8 Hz, 3H).

[0537] Step 3: 1-hydroxypentacosan-13-one



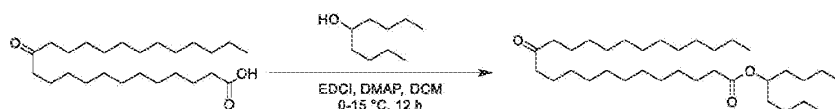
[0538] To a mixture of 1-((tert-butyldiphenylsilyl)oxy)pentacosan-13-one (9.65 g, 15.5 mmol) in THF (30 mL) was added TBAF (1 M in THF, 47 mL). The mixture was stirred at 20 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was quenched with water (100 mL) and diluted with EtOAc (100 mL). A precipitate was collected by filtration and the filter cake was dried in vacuo to give 1-hydroxypentacosan-13-one (5.0 g, 84% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 3.65 (t, J = 6.4 Hz, 2H), 2.39 (t, J = 7.6 Hz, 4H), 1.62-1.55 (m, 5H), 1.39-1.21 (m, 36H), 0.89 (t, J = 6.8 Hz, 3H).

[0539] Step 4: 13-oxopentacosanoic acid



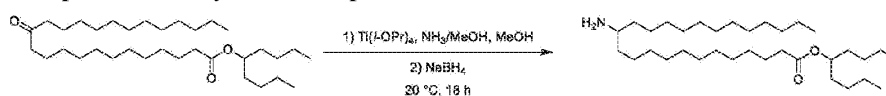
[0540] To a mixture of 1-hydroxypentacosan-13-one (5.0 g, 13.1 mmol) in acetone (300 mL) was added Jones reagent (2.5 M, 15.7 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 hour. TLC showed that one new spot was observed. The mixture was quenched with *i*-PrOH (50 mL) at 0 °C. The mixture was diluted with water (300 mL), stirred at 0 °C for 30 min. The mixture was filtered. The filter cake was washed with water (100 mL $\times$ 2) and dried in vacuo to give the crude product. HNMR showed that part of starting material remained. The crude product was diluted with acetone (300 mL), Jones reagent (2.5 M, 15 mL) was added to the mixture. The mixture was stirred at 20 °C for 12 hours. The mixture was quenched with *i*-PrOH (100 mL) at 0 °C. The mixture was diluted with water (400 mL), stirred at 20 °C for 30 min. The mixture was filtered, and the filter cake was washed with water (100 mL $\times$ 2) and dried in vacuo to give 13-oxopentacosanoic acid (4.2 g, 81% yield) as a white solid. The product was used into next step without purification. ^1H NMR (400 MHz, CDCl_3) δ 2.39 (br s, 6H), 1.71-1.48 (m, 6H), 1.27 (br s, 32H), 0.89 (br s, 3H).

[0541] Step 5: nonan-5-yl 13-oxopentacosanoate



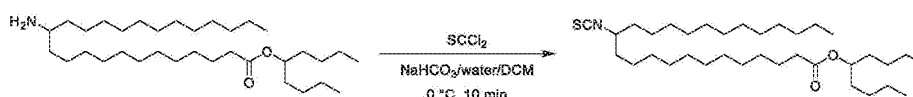
[0542] To a mixture of 13-oxopentacosanoic acid (4.2 g, 10.6 mmol) and nonan-5-ol (2.29 g, 15.9 mmol) in DCM (100 mL) was added DMAP (2.59 g, 21.2 mmol) and EDCI (4.06 g, 21.2 mmol) at 0 °C. The mixture was stirred at 15 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 9: 1) to give nonan-5-yl 13-oxopentacosanoate (5.0 g, 90%yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ4.88 (q, J= 6.0 Hz, 1H) , 2.38 (t, J= 7.5 Hz, 4H) , 2.28 (t, J= 7.5 Hz, 2H) , 1.69 -1.45 (m, 10H) , 1.36 -1.20 (m, 40H) , 0.92 -0.86 (m, 9H) .

[0543] Step 6: nonan-5-yl 13-aminopentacosanoate



[0544] To a mixture of nonan-5-yl 13-oxopentacosanoate (5.0 g, 9.56 mmol) in MeOH (70 mL) and NH₃/MeOH (7 M, 30 mL) was added tetrakisopropoxytitanium (5.44 g, 19.1 mmol) under N₂ atmosphere. The mixture was stirred 20 °C for 6 hours. Then NaBH₄ (724 mg, 19.1 mmol) was added slowly. The mixture was stirred at 20 °C for another 12 hours under N₂ atmosphere. The mixture was quenched with water (200 mL) and diluted with ethyl acetate (300 mL) . The mixture was filtered through a celite. The aqueous phase was extracted with ethyl acetate (100 mL × 2) . The combined organic layer was washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 10: 1) to give nonan-5-yl 13-aminopentacosanoate (3.2 g, 64%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ4.88 (q, J= 6.0 Hz, 1H) , 2.76 (br s, 1H) , 2.29 (t, J= 7.6 Hz, 2H) , 1.66 -1.58 (m, 2H) , 1.56 -1.50 (m, 4H) , 1.47 -1.22 (m, 48H) , 0.93 -0.84 (m, 9H) .

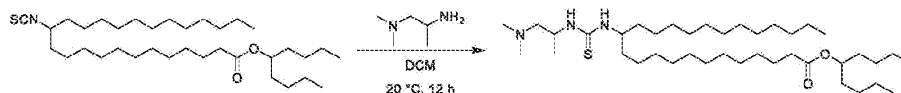
[0545] Step 7: nonan-5-yl 13-isothiocyanatopentacosanoate



[0546] To a mixture of nonan-5-yl 13-aminopentacosanoate (1.0 g, 1.91 mmol) and NaHCO₃ (1.12 g, 13.4 mmol,) in DCM (50 mL) and water (20 mL) was added thio-carbonyl dichloride (439 mg, 3.82 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. TLC showed that starting material was consumed completely. The reaction mixture was diluted with DCM (30 mL) and water (20 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give nonan-5-yl 13-isothiocyanatopenta-

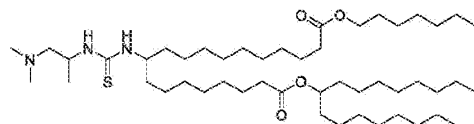
cosanoate (620 mg, 57%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.88 (q, $J = 6.4$ Hz, 1H) , 3.68 -3.57 (m, 1H) , 2.29 (t, $J = 7.6$ Hz, 2H) , 1.67 -1.58 (m, 4H) , 1.54 -1.48 (m, 4H) , 1.38 -1.20 (m, 46H) , 0.92 -0.87 (m, 9H) .

[0547] Step 8: nonan-5-yl 13- (3- (1- (dimethylamino) propan-2-yl) thioureido) penta-cosanoate

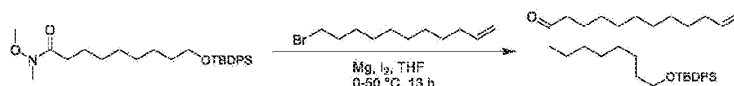


[0548] A mixture of nonan-5-yl 13-isothiocyanatopentacosanoate (200 mg, 353 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (72.2 mg, 707 μmol) in DCM (8 mL) was stirred at 20 $^\circ\text{C}$ for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 68%-98%B over 13 min) to give nonan-5-yl 13- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentacosanoate (121.7 mg, 52%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.57 (s, 1H) , 6.21 (br s, 1H) , 4.88 (t, $J = 6.4$ Hz, 1H) , 4.42 -4.06 (m, 1H) , 4.02 -3.64 (m, 1H) , 2.77 -2.59 (m, 1H) , 2.46 -2.21 (m, 9H) , 1.68 -1.46 (m, 8H) , 1.38 -1.20 (m, 49H) , 0.92 -0.82 (m, 9H) . LCMS showed the purity is 100%, $R_t = 6.242$ min; MS Calcd. : 667.6, MS Found: 668.6 $[\text{M}+\text{H}]^+$.

[0549] Example 44: 1- (heptadecan-9-yl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate



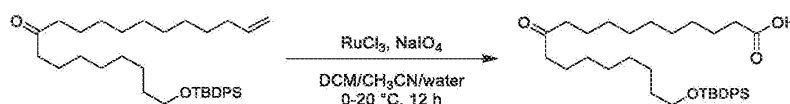
[0550] Step 1: 1- ((tert-butyldiphenylsilyl) oxy) icos-19-en-9-one



[0551] To a drying 250 mL three-neck bottle, freshly activated Mg (1.60 g, 65.8 mmol) and I_2 (one grain, catalytic amount) were added. The flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser, and flushed with N_2 and THF (20 mL) was added to the flask via syringe. The 11-bromoundec-1-ene (6.14 g, 26.3 mmol) was dissolved in THF (40 mL) and added to the addition funnel. This above solution was added to the Mg turnings while stirring vigorously and heating by high gun. An exothermic reaction was noticed and the THF started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux. After the completion of the addition the reaction mixture was kept at 50 $^\circ\text{C}$ for 1 hour. The mixture was cooled in ice-bath. 9- ((tert-butyldiphenylsilyl) oxy) -N-

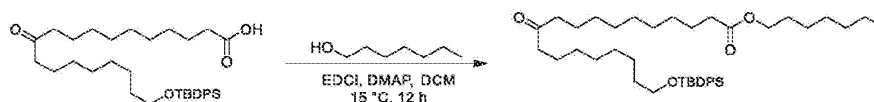
methoxy-N-methylnonanamide (6.0 g, 13.2 mmol) in THF (30 mL) transferred to the addition funnel and added dropwise to the reaction mixture with stirring at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours. TLC showed that one main spot was observed. The reaction was quenched by adding saturated NH_4Cl (50 mL) under ice-bath. The reaction mixture was extracted with EtOAc (100 mL $\times$ 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 19: 1) to give 1- ((tert-butyldiphenylsilyl) oxy) icos-19-en-9-one (6.0 g, 83%yield) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, J = 7.0 Hz, 4H) , 7.46 -7.36 (m, 6H) , 5.88 -5.76 (m, 1H) , 5.04 -4.92 (m, 2H) , 3.65 (t, J = 6.5 Hz, 2H) , 2.38 (dt, J = 2.0, 7.5 Hz, 4H) , 2.04 (q, J = 7.0 Hz, 2H) , 1.59-1.51 (m, 4H) , 1.41 -1.24 (m, 22H) , 1.05 (s, 9H) .

[0552] Step 2: 19- ((tert-butyldiphenylsilyl) oxy) -11-oxononadecanoic acid



[0553] To a mixture of 1- ((tert-butyldiphenylsilyl) oxy) icos-19-en-9-one (6.0 g, 10.9 mmol) in DCM (150 mL) and CH_3CN (150 mL) was added $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (572 mg, 2.19 mmol) under N_2 atmosphere. Then a solution of NaIO_4 (11.7 g, 54.7 mmol) in water (100 mL) was added dropwise at 0 °C. The mixture was stirred at 20 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with brine (200 mL) . The mixture was adjusted with 1 N HCl to pH = 6. The mixture was filtered, the filter cake was washed with DCM (200 mL) , then the filtrate extracted with DCM (100 mL $\times$ 3) . The combined organic phase was washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 1: 1) to give 19- ((tert-butyldiphenylsilyl) oxy) -11-oxononadecanoic acid (5.7 g, 92%yield) as a light-yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.67 (dd, J = 1.5, 7.5 Hz, 4H) , 7.46 -7.35 (m, 6H) , 3.65 (t, J = 6.5 Hz, 2H) , 2.42 -2.33 (m, 6H) , 1.67 -1.62 (m, 2H) , 1.59 -1.53 (m, 6H) , 1.39 -1.23 (m, 18H) , 1.05 (s, 9H) .

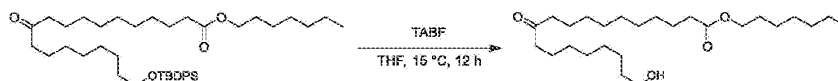
[0554] Step 3: heptyl 19- ((tert-butyldiphenylsilyl) oxy) -11-oxononadecanoate



[0555] To a mixture of 19- ((tert-butyldiphenylsilyl) oxy) -11-oxononadecanoic acid (5.7 g, 10.1 mmol) and heptan-1-ol (1.40 g, 12.1 mmol) in DCM (60 mL) was added DMAP (2.46 g, 20.1 mmol) and EDCI (3.86 g, 20.1 mmol) at 0 °C. The mixture was stirred at 15 °C for 12 hours. TLC showed that one main spot was observed. The

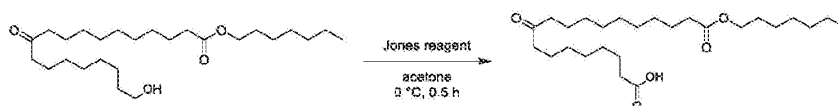
reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 9: 1) to give heptyl 19- ((tert-butylidiphenylsilyl) oxy) -11-oxononadecanoate (5.0 g, 75%yield) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.69-7.66 (m, 4H) , 7.45 -7.36 (m, 6H) , 4.06 (t, J= 7.0 Hz, 2H) , 3.65 (t, J= 6.5 Hz, 2H) , 2.41 -2.34 (m, 4H) , 2.32 -2.26 (m, 2H) , 1.66 -1.59 (m, 4H) , 1.56 -1.52 (m, 4H) , 1.39 -1.22 (m, 28H) , 1.05 (s, 9H) , 0.92 -0.86 (m, 3H) .

[0556] Step 4: heptyl 19-hydroxy-11-oxononadecanoate



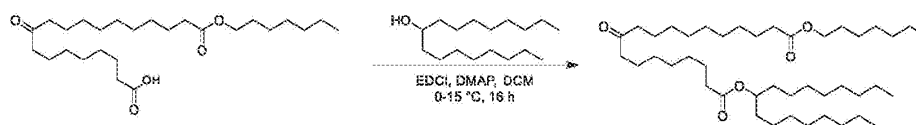
[0557] To a mixture of 19- ((tert-butylidiphenylsilyl) oxy) -11-oxononadecanoate (5.0 g, 7.52 mmol) in THF (50 mL) was added TBAF (1 M, 38 mL) . The mixture was stirred at 15 °C for 12 hours. TLC showed that one main spot was observed. The reaction mixture was diluted with saturated NaHCO_3 (100 mL) , extracted with EtOAc (100 mL $\times$ 2) . The combined organic phase was washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 9: 1) to give heptyl 19-hydroxy-11-oxononadecanoate (2.5 g, 78%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (t, J= 6.8 Hz, 2H) , 3.64 (t, J= 6.8 Hz, 2H) , 2.44 -2.35 (m, 4H) , 2.29 (t, J= 7.6 Hz, 2H) , 1.68 -1.50 (m, 8H) , 1.39 -1.25 (m, 28H) , 0.89 (t, J= 7.2 Hz, 3H) .

[0558] Step 5: 19- (heptyloxy) -9, 19-dioxononadecanoic acid



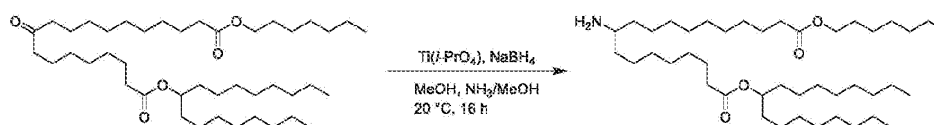
[0559] To a mixture of heptyl 19-hydroxy-11-oxononadecanoate (2.5 g, 5.86 mmol) in acetone (80 mL) was added Jones reagent (2.5 M, 4.69 mL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. TLC showed that one main spot was observed. The reaction mixture was quenched with i-PrOH (20 mL) under ice-bath, the mixture was stirred at 0 °C for 10 min. The mixture was diluted with water (150 mL) , extracted with EtOAc (150 mL $\times$ 2) . The combined organic phase washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give 19- (heptyloxy) -9, 19-dioxononadecanoic acid (2.50 g, crude) as a gray solid. The product was used into next step directly without further purification. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (br s, 2H) , 2.53 -2.17 (m, 8H) , 1.87 -1.47 (m, 10H) , 1.29 (br s, 24H) , 0.89 (br s, 3H) .

[0560] Step 6: 1- (heptadecan-9-yl) 19-heptyl 9-oxononadecanedioate



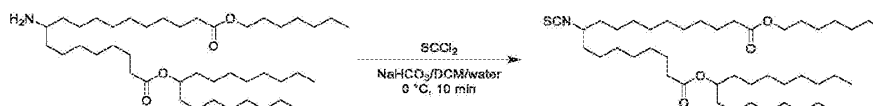
- [0561] To a mixture of 19- (heptyloxy) -9, 19-dioxononadecanoic acid (800 mg, 1.82 mmol) and heptadecan-9-ol (559 mg, 2.18 mmol) in DCM (30 mL) was added EDCI (696mg, 3.63 mmol) and DMAP (443.58 mg, 3.63 mmol) at 0 °C. The mixture was stirred at 15 °C for 16 hours. TLC showed that one main spot was observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 1- (heptadecan-9-yl) 19-heptyl 9-oxononadecanedioate (1 g, crude) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ4.87 (q, J= 6.4 Hz, 1H) , 4.06 (t, J= 6.8 Hz, 2H) , 2.42 -2.35 (m, 4H) , 2.32 2.25 (m, 4H) , 1.66 -1.47 (m, 12H) , 1.33 -1.28 (m, 50H) , 0.92 -0.85 (m, 9H) .

- [0562] Step 7: 1- (heptadecan-9-yl) 19-heptyl 9-aminononadecanedioate



- [0563] To a mixture of 1- (heptadecan-9-yl) 19-heptyl 9-oxononadecanedioate (1 g, 1.47 mmol) in MeOH (15 mL) and NH₃/MeOH (7 M, 6 mL) was added tetraisopropoxytitanium (837 mg, 2.95 mmol) under N₂ atmosphere. The mixture was stirred 20 °C for 4 hours. Then NaBH₄ (167 mg, 4.42 mmol) was added slowly. The mixture was stirred at 20 °C for another 12 hours under N₂ atmosphere. The mixture was quenched with brine (15 mL) and diluted with ethyl acetate (150 mL) . The mixture was filtered, and the filter cake was washed with EtOAc (50 mL × 2) . The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 9: 1) to give 1- (heptadecan-9-yl) 19-heptyl 9-aminononadecanedioate (500 mg, 50%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ4.87 (t, J= 6.4 Hz, 1H) , 4.06 (t, J= 6.8 Hz, 2H) , 3.17 -3.06 (m, 1H) , 2.28 (q, J= 7.2 Hz, 4H) , 1.76 -1.56 (m, 8H) , 1.54 -1.41 (m, 6H) , 1.36 -1.22 (m, 52H) , 0.93 -0.85 (m, 9H) .

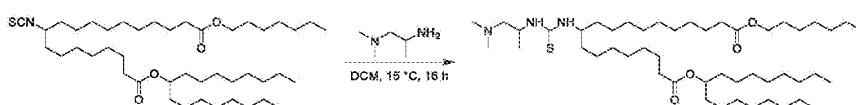
- [0564] Step 8: 1- (heptadecan-9-yl) 19-heptyl 9-isothiocyanatononadecanedioate



- [0565] To a mixture of 1- (heptadecan-9-yl) 19-heptyl 9-aminononadecanedioate (500 mg, 735 μmol) in DCM (30 mL) and water (10 mL) was added NaHCO₃ (432mg, 5.15 mmol) and thiocarbonyl dichloride (169mg, 1.47 mmol) . The mixture was stirred at 0 °C for 10 min. TLC showed that one main spot was observed. The reaction mixture

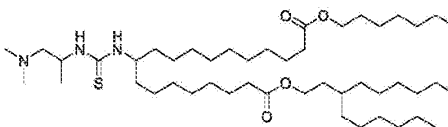
was diluted with DCM (30 mL) and water (20 mL). The organic phase was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give 1- (heptadecan-9-yl) 19-heptyl 9-isothiocyanatononadecanedioate (420 mg, 79%yield) as a light-yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 4.87 (q, J = 6.0 Hz, 1H), 4.06 (t, J = 7.0 Hz, 2H), 3.65 -3.29 (m, 1H), 2.32 -2.27 (m, 4H), 1.67 -1.58 (m, 8H), 1.53 -1.47 (m, 6H), 1.39 -1.21 (m, 52H), 0.92 -0.83 (m, 9H).

[0566] Step 9: 1- (heptadecan-9-yl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate

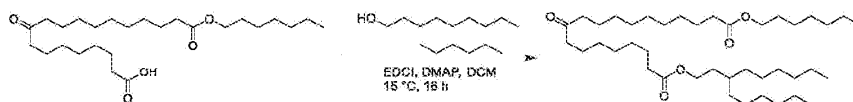


[0567] A mixture of 1- (heptadecan-9-yl) 19-heptyl 9-isothiocyanatononadecanedioate (150 mg, 208 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (42.4 mg, 415 μmol) in DCM (5 mL) was stirred at 15 $^\circ\text{C}$ for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN]; gradient: 75%-100%B over 13 min) to give 1- (heptadecan-9-yl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate (93.5 mg, 53%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 10.01 (br s, 1H), 5.78 (br s, 1H), 4.86 (q, J = 6.0 Hz, 1H), 4.25 (br s, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.67 (br s, 1H), 2.60 (br s, 1H), 2.45 -2.19 (m, 11H), 1.65 -1.58 (m, 6H), 1.55 -1.43 (m, 6H), 1.38 -1.20 (m, 57H), 0.91 -0.86 (m, 9H). LCMS showed the purity is 96.45%, R_t = 4.553 min; MS Calcd.: 823.7, MS Found: 824.7 $[\text{M}+\text{H}]^+$.

[0568] Example 45: 19-heptyl 1- (3-hexylnonyl) 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate



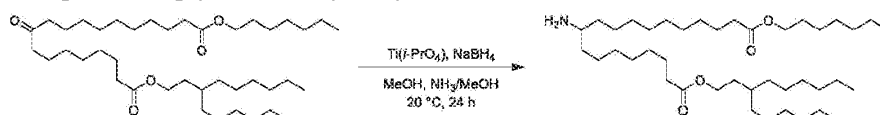
[0569] Step 1: 19-heptyl 1- (3-hexylnonyl) 9-oxononadecanedioate



[0570] To a mixture of 19- (heptyloxy) -9, 19-dioxononadecanoic acid (800 mg, 1.82 mmol) and 3-hexylnonan-1-ol (415 mg, 1.82 mmol) in DCM (50 mL) was added EDCI (696 mg, 3.63 mmol) and DMAP (444 mg, 3.63 mmol) at 0 $^\circ\text{C}$. The mixture was stirred at 15 $^\circ\text{C}$ for 16 hours. TLC showed that one main spot was observed. The mixture was

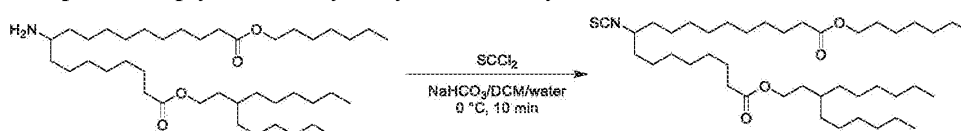
concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 19-heptyl 1- (3-hexylnonyl) 9-oxononadecanedioate (620 mg 52%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.12-4.02 (m, 4H) , 2.38 (t, J = 7.6 Hz, 4H) , 2.32 -2.26 (m, 4H) , 1.67 -1.58 (m, 8H) , 1.56 -1.51 (m, 4H) , 1.43 -1.22 (m, 45H) , 0.89 (t, J = 6.8 Hz, 9H) .

[0571] Step 2: 19-heptyl 1- (3-hexylnonyl) 9-aminononadecanedioate



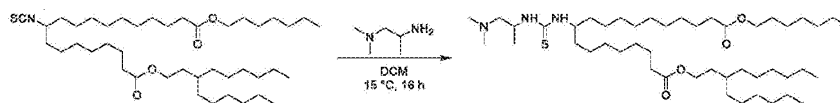
[0572] To a mixture of 19-heptyl 1- (3-hexylnonyl) 9-oxononadecanedioate (620 mg, 952 μmol) in MeOH (15 mL) and NH_3/MeOH (7 M, 6 mL) was added tetraisopropoxytitanium (541 mg, 1.90 mmol) under N_2 atmosphere. The mixture was stirred 20 $^\circ\text{C}$ for 12 hours. Then NaBH_4 (108 mg, 2.86 mmol) was added. The mixture was stirred at 20 $^\circ\text{C}$ for another 12 hours under N_2 atmosphere. The mixture was quenched with brine (30 mL) and diluted with ethyl acetate (200 mL) . The mixture was filtered, and the filter cake was washed with EtOAc (20 mL $\times$ 3) . The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 10: 1) to give 19-heptyl 1- (3-hexylnonyl) 9-aminononadecanedioate (550 mg, 88%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (br s, 2H) , 4.07 (q, J = 6.8 Hz, 4H) , 3.11 (br s, 1H) , 2.33 -2.23 (m, 4H) , 1.75 -1.54 (m, 12H) , 1.48 -1.22 (m, 49H) , 0.89 (t, J = 6.8 Hz, 9H) .

[0573] Step 3: 19-heptyl 1- (3-hexylnonyl) 9-isothiocyanatononadecanedioate



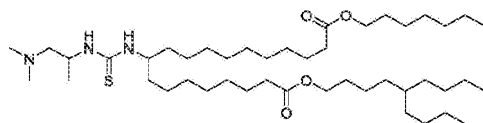
[0574] To a mixture of 19-heptyl 1- (3-hexylnonyl) 9-aminononadecanedioate (550 mg, 843 μmol , 1 eq) in DCM (30 mL) and water (10 mL) was added NaHCO_3 (496 mg, 5.90 mmol) and thiocarbonyl dichloride (194 mg, 1.69 mmol) . The mixture was stirred at 0 $^\circ\text{C}$ for 10 min. TLC showed that one main spot was observed. The reaction mixture was diluted with DCM (30 mL) and water (20 mL) . The organic phase was separated and washed with brine (20 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give 19-heptyl 1- (3-hexylnonyl) 9-isothiocyanatononadecanedioate (470 mg, 80%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.12-4.04 (m, 4H) , 3.65 -3.58 (m, 1H) , 2.30 (t, J = 7.6 Hz, 4H) , 1.67 -1.57 (m, 10H) , 1.53 -1.23 (m, 51H) , 0.89 (t, J = 6.8 Hz, 9H) .

- [0575] Step 4: 19-heptyl 1- (3-hexylnonyl) 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate

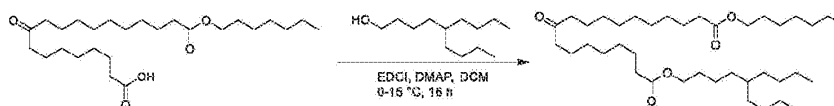


- [0576] A mixture of 19-heptyl 1- (3-hexylnonyl) 9-isothiocyanatononadecanedioate (155 mg, 223 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (43.9 mg, 429 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xlimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 69%-99%B over 13 min) to give 19-heptyl 1- (3-hexylnonyl) 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate (99.7 mg, 58%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.94 (s, 1H) , 5.84 (br s, 1H) , 4.24 (br s, 1H) , 4.11 -4.02 (m, 4H) , 3.70 (br s, 1H) , 2.62 (br s, 1H) , 2.42 -2.20 (m, 11H) , 1.69 -1.46 (m, 12H) , 1.41 -1.19 (m, 52H) , 0.89 (t, J = 6.7 Hz, 9H) . LCMS showed the purity is 100%, R_t = 3.600 min; MS Calcd. : 795.7, MS Found: 796.7 $[\text{M}+\text{H}]^+$.

- [0577] Example 46: 1- (5-butylnonyl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate

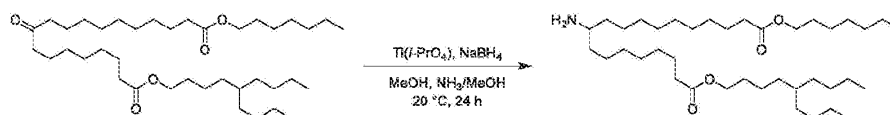


- [0578] Step 1: 1- (5-butylnonyl) 19-heptyl 9-oxononadecanedioate



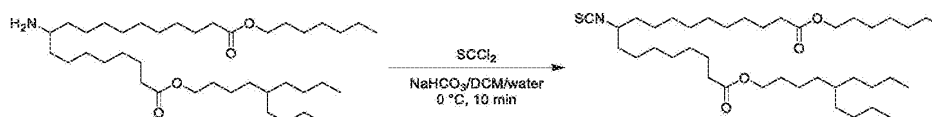
- [0579] To a mixture of 19- (heptyloxy) -9, 19-dioxononadecanoic acid (800 mg, 1.82 mmol) and 5-butylnonanol-1-ol (364 mg, 1.82 mmol) in DCM (30 mL) was added EDCI (696 mg, 3.63 mmol) and DMAP (444 mg, 3.63 mmol) at 0 °C. The mixture was stirred at 15 °C for 16 hours. TLC showed that one main spot was observed. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 10: 1) to give 1- (5-butylnonyl) 19-heptyl 9-oxononadecanedioate (680 mg, 60%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.06 (dt, J = 1.6, 6.8 Hz, 4H) , 2.38 (t, J = 7.6 Hz, 4H) , 2.29 (t, J = 7.6 Hz, 4H) , 1.67 -1.51 (m, 12H) , 1.39 -1.20 (m, 41H) , 0.94 -0.84 (m, 9H) .

- [0580] Step 2: 1- (5-butylnonyl) 19-heptyl 9-aminononadecanedioate



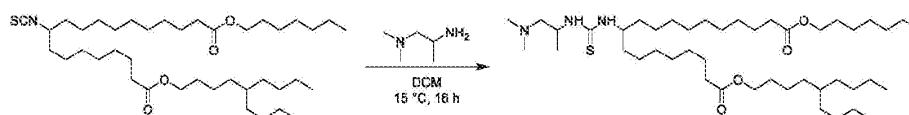
[0581] To a mixture of 1- (5-butylnonyl) 19-heptyl 9-oxononadecanedioate (680 mg, 1.09 mmol) in MeOH (15 mL) and NH_3/MeOH (7 M, 6 mL) was added tetraisopropoxytitanium (620 mg, 2.18 mmol) under N_2 atmosphere. The mixture was stirred at 20 °C for 12 hours. Then NaBH_4 (108 mg, 2.86 mmol) was added. The mixture was stirred at 20 °C for another 12 hours under N_2 atmosphere. The mixture was quenched with brine (30 mL) and diluted with ethyl acetate (200 mL). The mixture was filtered, and the filter cake was washed with EtOAc (20 mL $\times$ 3). The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 10: 1) to give 1- (5-butylnonyl) 19-heptyl 9-aminononadecanedioate (510 mg, 75%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (br s, 2H), 4.06 (t, J = 6.8 Hz, 4H), 3.12 (br s, 1H), 2.29 (t, J = 7.2 Hz, 4H), 1.78 -1.52 (m, 12H), 1.51 -1.19 (m, 45H), 0.93 -0.85 (m, 9H).

[0582] Step 3: 1- (5-butylnonyl) 19-heptyl 9-isothiocyanatononadecanedioate



[0583] To a mixture of 1- (5-butylnonyl) 19-heptyl 9-aminononadecanedioate (510 mg, 817 μmol) in DCM (30 mL) and water (10 mL) was added NaHCO_3 (481 mg, 5.72 mmol) and thiocarbonyl dichloride (188 mg, 1.63 mmol). The mixture was stirred at 0 °C for 10 min. TLC showed that one main spot was observed. The reaction mixture was diluted with DCM (30 mL) and water (20 mL). The organic phase was separated and washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 1: 0 to 15: 1) to give 1- (5-butylnonyl) 19-heptyl 9-isothiocyanatononadecanedioate (510 mg, 94% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.11 -4.02 (m, 4H), 3.66 -3.57 (m, 1H), 2.34 -2.26 (m, 4H), 1.68 -1.58 (m, 10H), 1.53 -1.18 (m, 47H), 0.94 -0.83 (m, 9H).

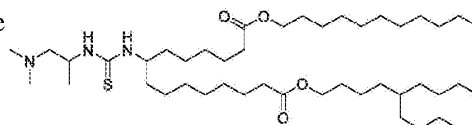
[0584] Step 4: 1- (5-butylnonyl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate



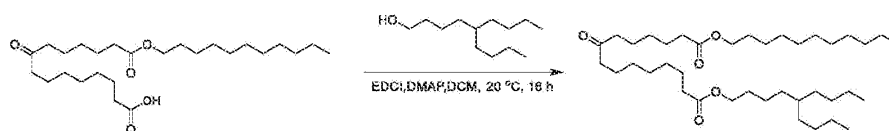
[0585] A mixture of 1- (5-butylnonyl) 19-heptyl 9-isothiocyanatononadecanedioate (170 mg, 255 μmol) and N^1, N^1 -dimethylpropane-1, 2-diamine (52.2 mg, 510 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA)

-ACN] ; gradient: 66%-96%B over 13 min) to give 1- (5-butylonyl) 19-heptyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) nonadecanedioate (75.8 mg, 39%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 9.96 (s, 1H) , 5.85 (br s, 1H) , 4.24 (br s, 1H) , 4.06 (t, J= 6.8 Hz, 4H) , 3.72 (br s, 1H) , 2.59 (br s, 1H) , 2.49 -2.15 (m, 11H) , 1.67 -1.56 (m, 10H) , 1.40 -1.18 (m, 50H) , 0.94 -0.84 (m, 9H) . LCMS showed the purity is 100%, R_t = 1.960 min; MS Calcd. : 767.7, MS Found: 768.7 $[\text{M}+\text{H}]^+$.

[0586] Example 47: 15- (5-butylonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate

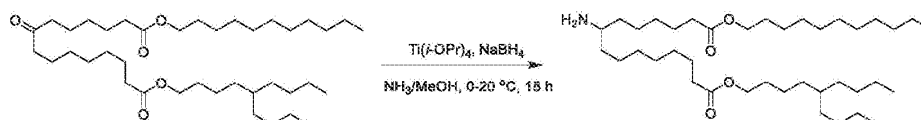


[0587] Step 1: 15- (5-butylonyl) 1-undecyl 7-oxopentadecanedioate



[0588] A mixture of 9, 15-dioxo-15- (undecyloxy) pentadecanoic acid (1.8 g, 4.08 mmol) , 5-butylnonan-1-ol (982 mg, 4.90 mmol) , EDCI (783 mg, 4.08 mmol) , DMAP (499 mg, 4.08 mmol) in DCM (30 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 1/10) to give 15- (5-butylonyl) 1-undecyl 7-oxopentadecanedioate (2.4 g, 94.3%yield) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 4.09 -4.02 (m, 4H) , 2.39 (q, J= 8.0 Hz, 4H) , 2.34 -2.26 (m, 4H) , 1.67 -1.63 (m, 2H) , 1.62 -1.51 (m, 10H) , 1.35 -1.21 (m, 41H) , 0.92 -0.87 (m, 9H) .

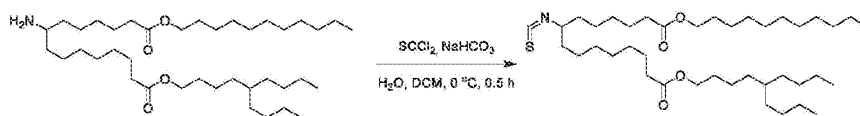
[0589] Step 2: 15- (5-butylonyl) 1-undecyl 7-aminopentadecanedioate



[0590] A mixture of 15- (5-butylonyl) 1-undecyl 7-oxopentadecanedioate (2.4 g, 3.85 mmol) and Ti (i-OPr)_4 (2.19 g, 7.70 mmol, 2.27 mL) in MeOH (30 mL) and NH_3/MeOH (7 M, 15 mL) , then the mixture was stirred at 20 °C for 6 hours, then NaBH_4 (330 mg, 8.72 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20°C for 12 hours. The mixture was quenched with H_2O (30 mL) and diluted with ethyl acetate (50 mL) . The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2×100 mL) , the combined organic layer was washed with brine (100 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , MeOH: DCM = 0 to 1/10) to give 15- (5-butylonyl) 1-undecyl 7-aminopentadecanedioate (1.6 g,

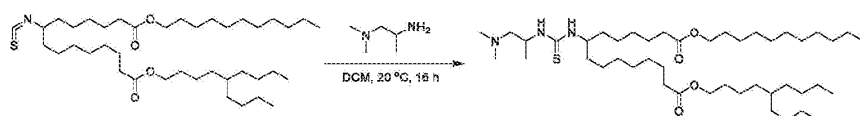
66.6%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.11 -4.03 (m, 4H) , 2.78 (s, 1H) , 2.35 -2.26 (m, 4H) , 1.68 -1.58 (m, 8H) , 1.44 -1.21 (m, 49H) , 0.94 -0.84 (m, 9H) .

[0591] Step 3: 15- (5-butylonyl) 1-undecyl 7-isothiocyanatopentadecanedioate



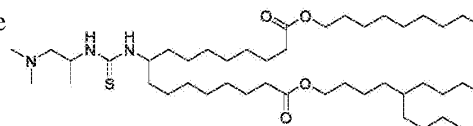
[0592] To a mixture of 15- (5-butylonyl) 1-undecyl 7-aminopentadecanedioate (500 mg, 801 μmol) and NaHCO_3 (337 mg, 4.01 mmol) in DCM (20 mL) and H_2O (20 mL) was added SCCl_2 (111 mg, 961 μmol , 73.7 μL) at $0\text{ }^\circ\text{C}$, then the mixture was stirred at $0\text{ }^\circ\text{C}$ for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc : PE = 0 to 2/25) to give 15- (5-butylonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (520 mg, 97.4%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.12 -4.02 (m, 4H) , 3.69 -3.54 (m, 1H) , 2.40 -2.24 (m, 4H) , 1.70 -1.57 (m, 12H) , 1.41 -1.19 (m, 45H) , 0.92 -0.87 (m, 9H) .

[0593] Step 4: 15- (5-butylonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate

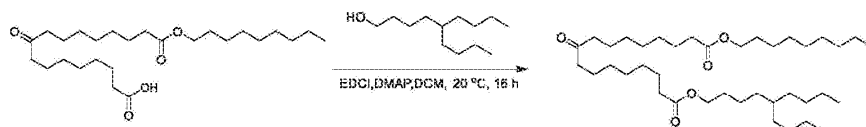


[0594] A mixture of 15- (5-butylonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (200 mg, 300 μmol) , $\text{N,N}'\text{-dimethylpropane-1,2-diamine}$ (61.4 mg, 601 μmol) in DCM (6 mL) was stirred at $20\text{ }^\circ\text{C}$ for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 13 min) to give 15- (5-butylonyl) 1-undecyl 7- (3- (1- (dimethylamino) propan-2-yl) thioureido) pentadecanedioate (92.1 mg, 39.9%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.40 -4.15 (m, 1H) , 4.10 -3.71 (m, 5H) , 2.80-2.58 (m, 1H) , 2.54 -2.14 (m, 11H) , 1.64 -1.45 (m, 10H) , 1.39 -1.15 (m, 50H) , 0.96 -0.84 (m, 9H) . LCMS showed the purity is 100%, Rt = 3.035 min; MS Calcd. : 767.7, MS Found: 768.7 $[\text{M}+\text{H}]^+$.

[0595] Example 48: 1- (5-butylonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate

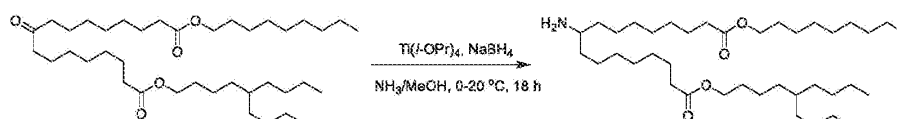


[0596] Step 1: 1- (5-butylonyl) 17-nonyl 9-oxoheptadecanedioate



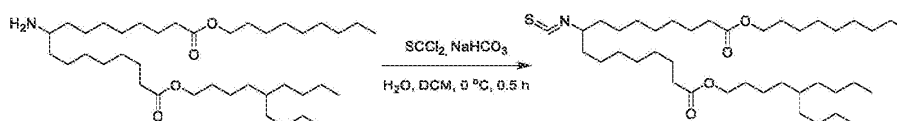
[0597] A mixture of 17- (nonyloxy) -9, 17-dioxoheptadecanoic acid (1.5 g, 3.40 mmol) , 5-butylnonan-1-ol (818 mg, 4.08 mmol) , EDCI (653 mg, 3.40 mmol) , DMAP (416 mg, 3.40 mmol) in DCM (20 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, EtOAc: PE = 0 to 1/10) to give 1- (5-butylnonyl) 17-nonyl 9-oxoheptadecanedioate (2 g, 94.3%yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.10 -4.04 (m, 4H) , 2.38 (t, J= 7.6 Hz, 4H) , 2.29 (t, J= 7.6 Hz, 4H) , 1.67 -1.57 (m, 10H) , 1.36 -1.20 (m, 43H) , 0.92 -0.87 (m, 9H) .

[0598] Step 2: 1- (5-butylnonyl) 17-nonyl 9-aminoheptadecanedioate



[0599] A mixture of 1- (5-butylnonyl) 17-nonyl 9-oxoheptadecanedioate (2 g, 3.21 mmol) and Ti (i-OPr)₄ (1.82 g, 6.42 mmol, 1.89 mL) in MeOH (30 mL) and NH₃/MeOH (7 M, 15 mL) , then the mixture was stirred at 20 °C for 6 hours, then NaBH₄ (190 mg, 5.02 mmol) was added the mixture at 0 °C, then the mixture was stirred at 20 °C for 12 hours. The mixture was quenched with H₂O (30 mL) and diluted with ethyl acetate (50 mL) . The inorganic solids were filtered, and the aqueous phase was washed with ethyl acetate (2 × 100 mL) , the combined organic layer was washed with brine (100 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, MeOH: DCM = 0 to 1/10) to give 1- (5-butylnonyl) 17-nonyl 9-aminoheptadecanedioate (1.3 g, 64.9%yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.11 -4.01 (m, 4H) , 2.96 -2.75 (m, 1H) , 2.29 (t, J= 7.6 Hz, 4H) , 1.67 -1.57 (m, 10H) , 1.37 -1.18 (m, 47H) , 0.95 -0.85 (m, 9H) .

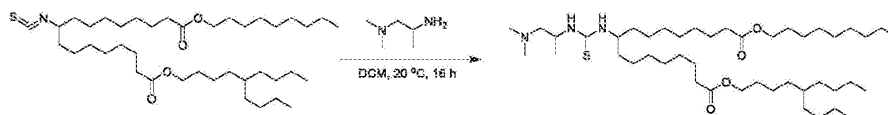
[0600] Step 3: 1- (5-butylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate



[0601] To a mixture of 1- (5-butylnonyl) 17-nonyl 9-aminoheptadecanedioate (500 mg, 801 μmol) , NaHCO₃ (337 mg, 4.01 mmol) in DCM (20 mL) and H₂O (20 mL) was added SOCl₂ (111 mg, 961 μmol, 73.7 μL) at 0 °C, then the mixture was stirred at 0 °C for 0.5 hour. The mixture was extracted with DCM (50 mL) . The combined organic layer was washed with brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated

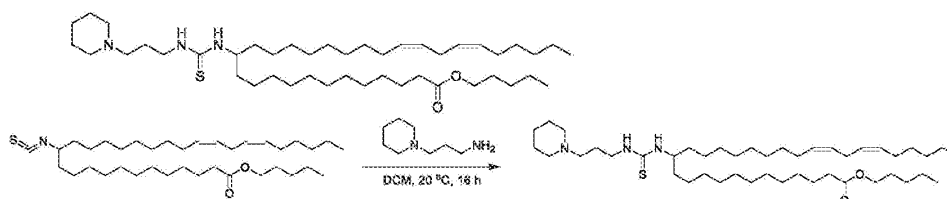
to give a residue. The residue was purified by column chromatography (SiO_2 , EtOAc: PE = 0 to 2/25) to give 1- (5-butylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (490 mg, 91.8%yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.12 -4.00 (m, 4H) , 3.66 -3.53 (m, 1H) , 2.35-2.25 (m, 4H) , 1.68 -1.56 (m, 10H) , 1.49 -1.42 (m, 2H) , 1.41 -1.17 (m, 45H) , 0.94 -0.84 (m, 9H) .

[0602] Step 4: 1- (5-butylnonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate



[0603] A mixture of 1- (5-butylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (190 mg, 285 μmol) , N^1 , N^1 -dimethylpropane-1, 2-diamine (58.3 mg, 570 μmol) in DCM (6 mL) was stirred at 20 $^\circ\text{C}$ for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 63%-93%B over 13 min) to give 1- (5-butylnonyl) 17-nonyl 9- (3- (1- (dimethylamino) propan-2-yl) thioureido) heptadecanedioate (126.6 mg, 57.8%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 10.71 -9.37 (m, 1H) , 6.16 -5.48 (m, 1H) , 4.36 -4.18 (m, 1H) , 4.14 -3.99 (m, 4H) , 3.88 -3.49 (m, 1H) , 2.69 -2.52 (m, 1H) , 2.45 -2.11 (m, 11H) , 1.69 -1.46 (m, 12H) , 1.37 -1.21 (m, 48H) , 0.94 -0.86 (m, 9H) . LCMS showed the purity is 100%, Rt = 3.429 min; MS Calcd. : 767.7, MS Found: 768.7 $[\text{M}+\text{H}]^+$.

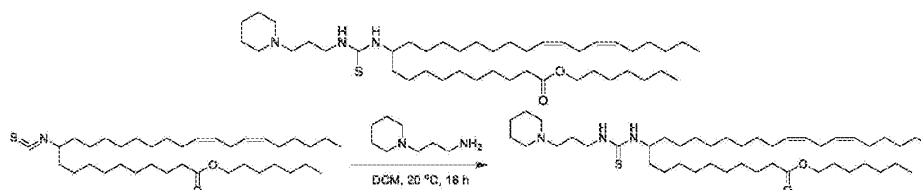
[0604] Example 49: pentyl (22Z, 25Z) -13- (3- (3- (piperidin-1-yl) propyl) thioureido) hentriaconta-22, 25-dienoate



[0605] A mixture of pentyl (22Z, 25Z) -13-isothiocyanatohentriaconta-22, 25-dienoate (300 mg, 508 μmol) , 3- (1-piperidyl) propan-1-amine (145 mg, 1.02 mmol) in DCM (8 mL) was stirred at 20 $^\circ\text{C}$ for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 55%-85%B over 20 min) to give pentyl (22Z, 25Z) -13- (3- (3- (piperidin-1-yl) propyl) thioureido) hentriaconta-22, 25-dienoate (110.1

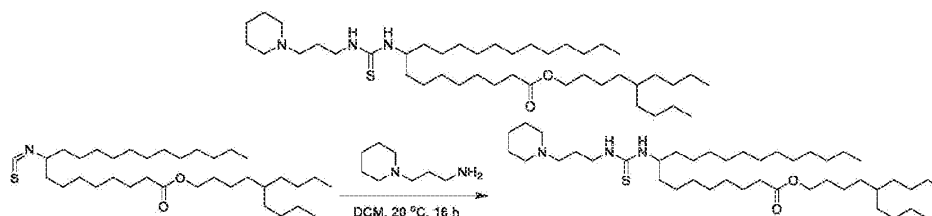
mg, 29.6%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.09 -7.57 (m, 1H) , 6.27 -5.81 (m, 1H) , 5.55 -5.16 (m, 4H) , 4.06 (t, J = 6.8 Hz, 3H) , 3.80 -3.49 (m, 2H) , 2.91 -2.40 (m, 8H) , 2.29 (t, J = 7.6 Hz, 2H) , 2.06 (q, J = 6.8 Hz, 4H) , 1.91 (s, 2H) , 1.76 (s, 4H) , 1.67 -1.50 (m, 8H) , 1.46 -1.21 (m, 40H) , 0.91 (q, J = 6.8 Hz, 6H) . LCMS showed the purity is 100%, R_t = 6.131 min; MS Calcd. : 731.6, MS Found: 732.8 $[\text{M}+\text{H}]^+$.

[0606] Example 50: heptyl (20Z, 23Z) -11- (3- (3- (piperidin-1-yl) propyl) thioureido) nonacosa-20, 23-dienoate



[0607] A mixture of heptyl (20Z, 23Z) -11-isothiocyanatononacosa-20, 23-dienoate (250 mg, 424 μmol) , 3- (1-piperidyl) propan-1-amine (121 mg, 847 μmol) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. LCMS showed Lipid 113 was detected. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN] ; gradient: 55%-85%B over 20 min) to give heptyl (20Z, 23Z) -11- (3- (3- (piperidin-1-yl) propyl) thioureido) nonacosa-20, 23-dienoate (95.0 mg, 30.6%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.37 -7.61 (m, 1H) , 6.48 -5.83 (m, 1H) , 5.46 -5.27 (m, 4H) , 4.34 -3.84 (m, 3H) , 3.80 -3.53 (m, 2H) , 3.05 -2.45 (m, 8H) , 2.29 (t, J = 7.6 Hz, 2H) , 2.10 -1.95 (m, 6H) , 1.91 -1.75 (m, 4H) , 1.67 -1.50 (m, 8H) , 1.43 -1.24 (m, 40H) , 0.94 -0.85 (m, 6H) . LCMS showed the purity is 100%, R_t = 6.143 min; MS Calcd. : 731.6, MS Found: 733.1 $[\text{M}+\text{H}]^+$.

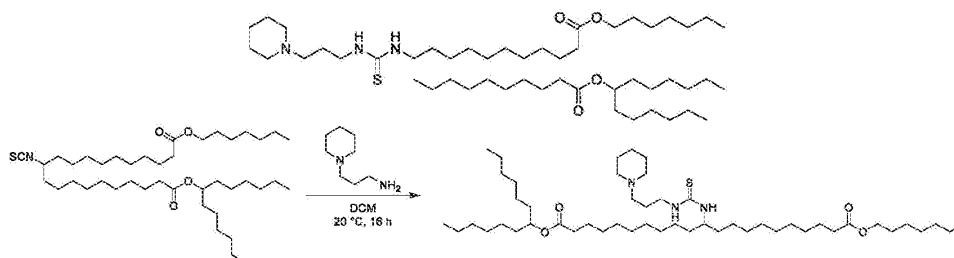
[0608] Example 51: 5-butylonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosa-9-enoate



[0609] A mixture of 5-butylonyl 9-isothiocyanatohenicosa-9-enoate (200 mg, 353 μmol) , 3- (1-piperidyl) propan-1-amine (101 mg, 707 μmol) in DCM (8 mL) was stirred at 20

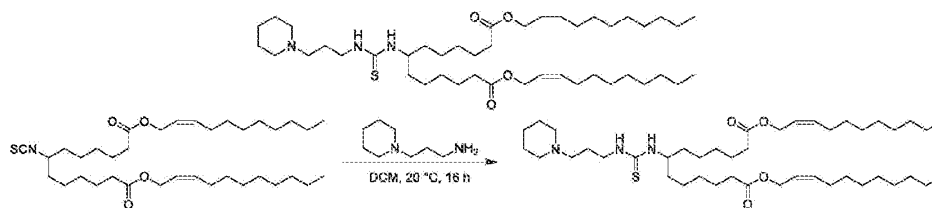
°C for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H₂O (30 mL) and extracted with DCM (2 × 30 mL), the combined organic layers were washed with saturated NaHCO₃ (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue, the residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 µm; mobile phase: [water (FA) -ACN]; gradient: 57%-87%B over 20 min) to give 5-butylonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanoate (85.1 mg, 34.0%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.06 (t, J= 6.8 Hz, 3H), 3.81 -3.59 (m, 2H), 3.10 -2.44 (m, 6H), 2.29 (t, J= 7.6 Hz, 2H), 2.05 -1.78 (m, 6H), 1.63 -1.56 (m, 8H), 1.44 (d, J = 5.6 Hz, 2H), 1.31 -1.21 (m, 45H), 0.91 -0.87 (m, 9H). LCMS showed the purity is 100%, Rt = 6.338 min; MS Calcd.: 707.6, MS Found: 708.8 [M+H]⁺.

[0610] Example 52: 1-heptyl 21- (tridecan-7-yl) 11- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanedioate



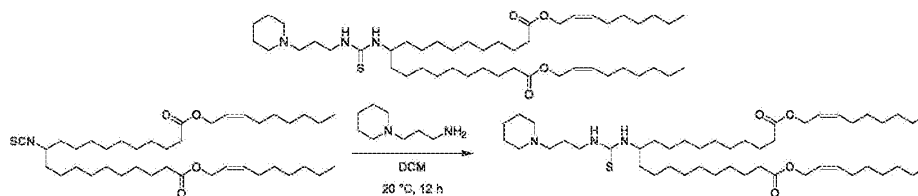
[0611] A mixture of 1-heptyl 21- (tridecan-7-yl) 11-isothiocyanatohenicosanedioate (200 mg, 288 µmol) and 3- (1-piperidyl) propan-1-amine (82.0 mg, 576 µmol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 µm; mobile phase: [water (FA) -ACN]; gradient: 75%-98%B over 13 min) to give 1-heptyl 21- (tridecan-7-yl) 11- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanedioate (123.2 mg, 51%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.70 (br s, 1H), 5.92 (br s, 1H), 4.87 (t, J= 6.0 Hz, 1H), 4.35 -3.82 (m, 3H), 3.60 (br s, 2H), 2.52 (br s, 6H), 2.33 -2.25 (m, 4H), 1.80 (br s, 2H), 1.69 -1.57 (m, 10H), 1.56 -1.46 (m, 8H), 1.41-1.20 (m, 50H), 0.94 -0.84 (m, 9H). LCMS showed the purity is 100.00%, Rt = 6.302 min; MS Calcd.: 835.7, MS Found: 836.7 [M+H]⁺.

[0612] Example 53: di ((Z) -undec-2-en-1-yl) 7- (3- (3- (piperidin-1-yl) propyl) thioureido) tridecanedioate



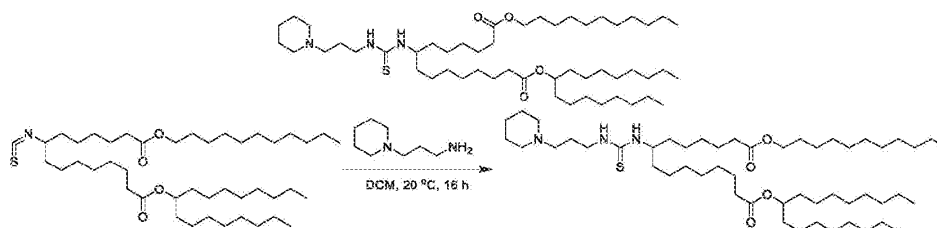
- [0613] A mixture of di ((Z)-undec-2-en-1-yl) 7-isothiocyanatotridecanedioate (200 mg, 330 μ mol) and 3- (1-piperidyl) propan-1-amine (93.9 mg, 660 μ mol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μ m; mobile phase: [water (FA) - ACN] ; gradient: 65%-85%B over 13 min) to give di ((Z)-undec-2-en-1-yl) 7- (3- (piperidin-1-yl) propyl) thioureido) tridecanedioate (105.5 mg, 42%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.70 (br s, 1H) , 5.94 (br s, 1H) , 5.69 -5.60 (m, 2H) , 5.56 -5.47 (m, 2H) , 4.62 (d, J= 6.8 Hz, 4H) , 4.05 (br s, 1H) , 3.56 (br s, 2H) , 2.50 (br s, 6H) , 2.30 (t, J= 7.6 Hz, 4H) , 2.10 (q, J= 7.2 Hz, 4H) , 1.79 (br s, 2H) , 1.69 -1.57 (m, 8H) , 1.56 -1.21 (m, 38H) , 0.88 (t, J= 6.8 Hz, 6H) . LCMS showed the purity is 99.30%, Rt = 5.356 min; MS Calcd. : 747.6, MS Found: 748.6 [M +H] $^+$.

- [0614] Example 54: di ((Z)-non-2-en-1-yl) 11- (3- (3- (piperidin-1-yl) propyl) thioureido) heneicosanedioate



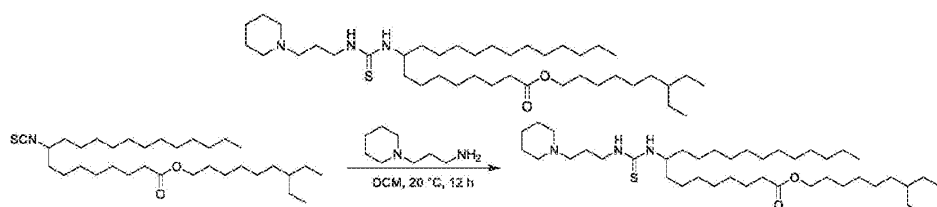
- [0615] A mixture of di ((Z)-non-2-en-1-yl) 11-isothiocyanatoheneicosanedioate (120 mg, 181 μ mol) and 3- (1-piperidyl) propan-1-amine (51.6 mg, 363 μ mol) in DCM (5 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μ m; mobile phase: [water (FA) - ACN] ; gradient: 63%-93%B over 13 min) to give di ((Z)-non-2-en-1-yl) 11- (3- (3- (piperidin-1-yl) propyl) thioureido) heneicosanedioate (29.7 mg, 20%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (br s, 1H) , 5.92 (br s, 1H) , 5.70 -5.60 (m, 2H) , 5.58 -5.49 (m, 2H) , 4.62 (d, J= 6.4 Hz, 4H) , 3.95 (s, 1H) , 3.59 (br s, 2H) , 2.53 (br s, 6H) , 2.31 (t, J= 7.2 Hz, 4H) , 2.10 (q, J= 7.2 Hz, 4H) , 1.81 (br s, 2H) , 1.70 -1.60 (m, 8H) , 1.56 -1.25 (m, 46H) , 0.95 -0.85 (m, 6H) . LCMS showed the purity is 96.24%, Rt = 5.929 min; MS Calcd. : 803.7, MS Found: 804.7 [M+H] $^+$.

- [0616] Example 55: 15- (heptadecan-9-yl) 1-undecyl 7- (3- (3- (piperidin-1-yl) propyl) thioureido) pentadecanedioate



- [0617] A mixture 15- (heptadecan-9-yl) 1-undecyl 7-isothiocyanatopentadecanedioate (200 mg, 277 μmol), 3- (1-piperidyl) propan-1-amine (78.8 mg, 554 μmol) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H₂O (30 mL) and extracted with DCM (2 $\times$ 30 mL), the combined organic layers were washed with saturated NaHCO₃ (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 $\times$ 40 mm $\times$ 5 μm ; mobile phase: [water (FA) -MeOH]; gradient: 65%-95%B over 20 min) to give 15- (heptadecan-9-yl) 1-undecyl 7- (3- (3- (piperidin-1-yl) propyl) thioureido) pentadecanedioate (93.2 mg, 38.9% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.21 -7.45 (m, 1H), 6.35 -5.65 (m, 1H), 4.86 (quin, J= 6.4 Hz, 1H), 4.23 -3.82 (m, 3H), 3.76 -3.45 (m, 2H), 2.82 -2.34 (m, 6H), 2.28 (q, J= 7.2 Hz, 4H), 1.84 (s, 2H), 1.69 (s, 2H), 1.64 -1.58 (m, 6H), 1.56 -1.42 (m, 10H), 1.39 -1.18 (m, 54H), 0.88 (t, J= 6.8 Hz, 9H). LCMS showed the purity is 100%, Rt = 4.951 min; MS Calcd.: 863.8, MS Found: 864.8 [M+H]⁺.

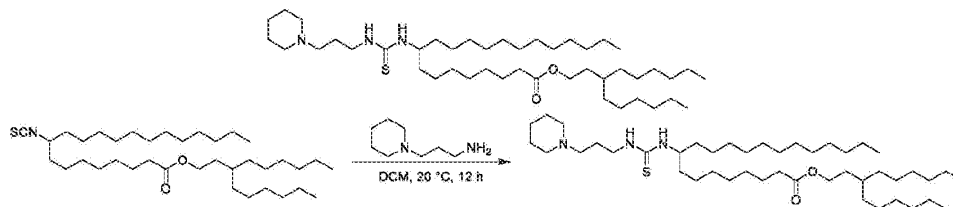
- [0618] Example 56: 7-ethylnonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanoate



- [0619] A mixture of 7-ethylnonyl 9-isothiocyanatohenicosanoate (200 mg, 372 μmol) and 3- (1-piperidyl) propan-1-amine (106 mg, 744 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 $\times$ 30 $\times$ 10 μm ; mobile phase: [water (FA) -ACN]; gradient: 64%-94%B over 13 min) to give 7-ethylnonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanoate (70.8 mg, 28% yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.62 (br s, 1H), 5.92 (br s, 1H), 4.21 -3.76 (m, 3H), 3.71-3.42 (m, 2H), 2.50 (br s, 6H), 2.29 (t,

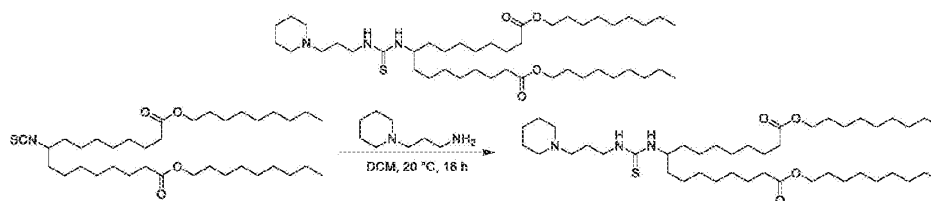
$J = 7.6$ Hz, 2H), 1.79 (br s, 2H), 1.69 -1.41 (m, 12H), 1.39 -1.21 (m, 42H), 1.18 -1.10 (m, 1H), 0.93 -0.77 (m, 9H). LCMS showed the purity is 100%, $R_t = 5.863$ min; MS Calcd.: 679.6, MS Found: 680.8 $[M+H]^+$.

[0620] Example 57: 3-hexylnonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanoate



[0621] A mixture of 3-hexylnonyl 9-isothiocyanatohenicosanoate (4.8 g, 8.08 mmol) and 3- (1-piperidyl) propan-1-amine (2.30 g, 16.2 mmol) in DCM (80 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate (200 mL) and washed with HCl (1 N, 50 mL), saturated NaHCO_3 (80 mL) and brine (80 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1 : 0 to 19 : 1) to give the crude product, which was further purified by prep-HPLC (column: C8 70 × 40 mm; mobile phase: [water (FA) -ACN]; gradient: 80%-99%B over 10 min) to give 3-hexylnonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanoate (2555.2 mg, 43% yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.64 (br s, 1H), 5.85 (br s, 1H), 4.35 -3.80 (m, 3H), 3.57 (br s, 2H), 2.59 -2.34 (m, 6H), 2.30 (t, $J = 7.6$ Hz, 2H), 1.80 -1.71 (m, 2H), 1.69 -1.53 (m, 12H), 1.51 -1.20 (m, 51H), 0.90 (t, $J = 6.8$ Hz, 9H). LCMS showed the purity is 100%, $R_t = 3.279$ min; MS Calcd.: 735.7, MS Found: 736.6 $[M+H]^+$.

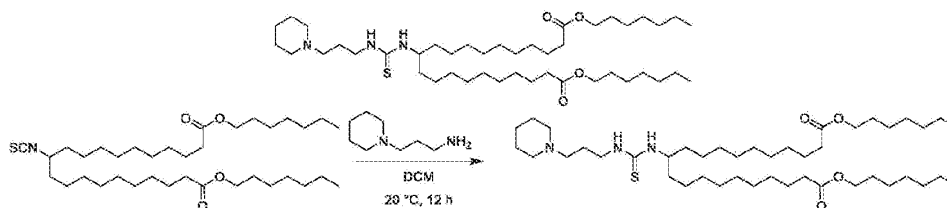
[0622] Example 58: dinonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate



[0623] A mixture of dinonyl 9-isothiocyanatoheptadecanedioate (200 mg, 328 μmol) and 3- (1-piperidyl) propan-1-amine (93.3 mg, 656 μmol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN]; gradient:

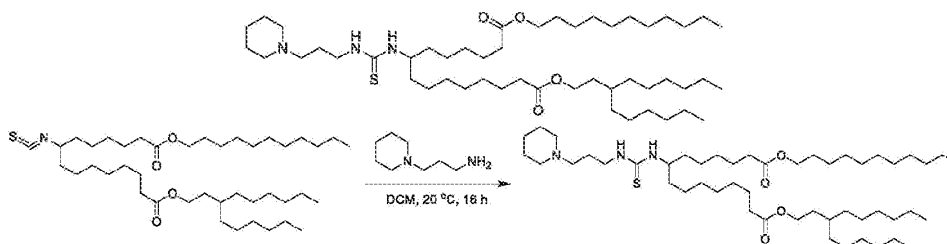
62%-92%B over 13 min) to give dinonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate (130.8 mg, 53%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.60 (br s, 1H) , 5.85 (br s, 1H) , 4.32 -3.81 (m, 5H) , 3.55 (br s, 2H) , 2.65 -2.35 (m, 6H) , 2.29 (t, J = 7.6 Hz, 4H) , 1.81 -1.72 (m, 2H) , 1.66 -1.41 (m, 18H) , 1.40 -1.22 (m, 40H) , 0.92 -0.85 (m, 6H) . LCMS showed the purity is 100.0%, R_t = 5.310 min; MS Calcd. : 751.6, MS Found: 752.8 $[\text{M}+\text{H}]^+$.

[0624] Example 59: diheptyl 11- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanedioate



[0625] A mixture of diheptyl 11-isothiocyanatohenicosanedioate (150 mg, 246 μmol) and 3- (1-piperidyl) propan-1-amine (70.0 mg, 492 μmol) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 61%-91%B over 13 min) to give diheptyl 11- (3- (3- (piperidin-1-yl) propyl) thioureido) henicosanedioate (136.0 mg, 73%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.63 (br s, 1H) , 5.87 (br s, 1H) , 4.23 -3.67 (m, 5H) , 3.57 (br s, 2H) , 2.49 (d, J = 5.2 Hz, 6H) , 2.29 (t, J = 7.6 Hz, 4H) , 1.78 (d, J = 4.4 Hz, 2H) , 1.69 -1.42 (m, 18H) , 1.39 -1.15 (m, 40H) , 0.95 -0.76 (m, 6H) . LCMS showed the purity is 99.59%, R_t = 5.440 min; MS Calcd. : 751.6, MS Found: 753.6 $[\text{M}+\text{H}]^+$.

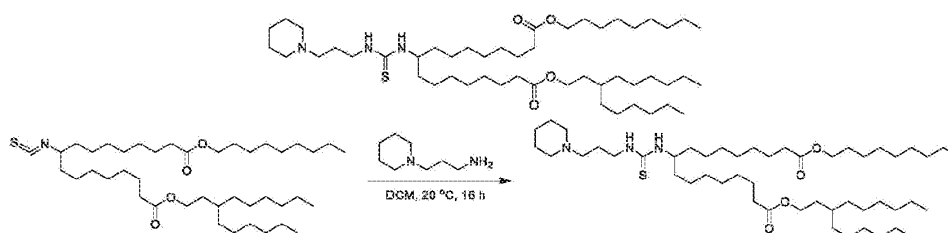
[0626] Example 60: 15- (3-hexylnonyl) 1-undecyl 7- (3- (3- (piperidin-1-yl) propyl) thioureido) pentadecanedioate



[0627] A mixture 15- (3-hexylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (210 mg, 302 μmol) , 3- (1-piperidyl) propan-1-amine (86.1. mg, 605 μmol) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2 $\times$ 30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous

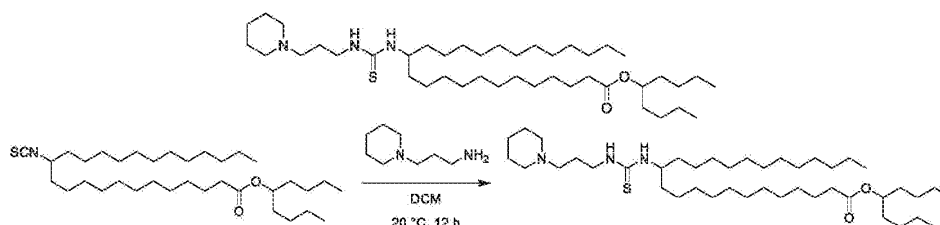
Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) - ACN] ; gradient: 70%-98%B over 13 min) to give 15- (3-hexylnonyl) 1-undecyl 7- (3- (3- (piperidin-1-yl) propyl) thioureido) pentadecanedioate (121.4 mg, 48.0%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.36 -3.93 (m, 5H) , 3.81 -3.60 (m, 2H) , 3.28 -2.50 (m, 6H) , 2.33 -2.24 (m, 4H) , 2.07 (s, 2H) , 1.92 (s, 4H) , 1.66 -1.53 (m, 10H) , 1.49 -1.20 (m, 53H) , 0.89 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 100%, R_t = 3.926 min; MS Calcd. : 835.7, MS Found: 836.7 $[\text{M}+\text{H}]^+$.

[0628] Example 61: 1- (3-hexylnonyl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate



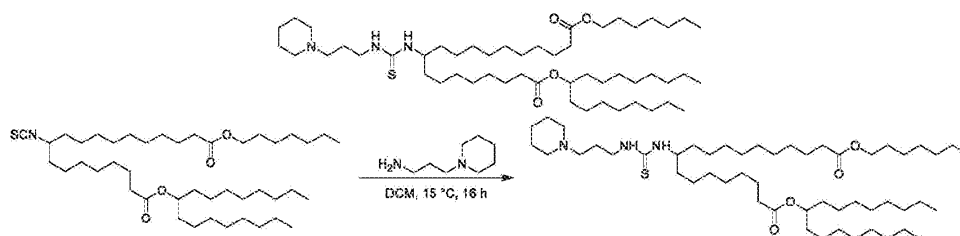
[0629] A mixture 1- (3-hexylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (200 mg, 288 μmol) , 3- (1-piperidyl) propan-1-amine (82.0 mg, 576 μmol) in DCM (6 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2 $\times$ 30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) - ACN] ; gradient: 70%-98%B over 13 min) to give 1- (3-hexylnonyl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate (121.1 mg, 50.3%yield) as a light-yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 4.18 -3.79 (m, 5H) , 3.77 -3.41 (m, 2H) , 2.92 -2.33 (m, 6H) , 2.32 -2.25 (m, 4H) , 1.90 -1.77 (m, 2H) , 1.64 -1.39 (m, 16H) , 1.38 -1.12 (m, 51H) , 0.88 (t, J = 7.0 Hz, 9H) . LCMS showed the purity is 100%, R_t = 3.792 min; MS Calcd. : 835.7, MS Found: 836.7 $[\text{M}+\text{H}]^+$.

[0630] Example 62: nonan-5-yl 13- (3- (3- (piperidin-1-yl) propyl) thioureido) pentacosanoate



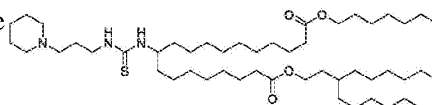
[0631] A mixture of nonan-5-yl 13-isothiocyanatopentacosanoate (200 mg, 353 μmol) and 3- (1-piperidyl) propan-1-amine (101 mg, 707 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 66%-96%B over 13 min) to give nonan-5-yl 13- (3- (3- (piperidin-1-yl) propyl) thioureido) pentacosanoate (155.8 mg, 62%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (br s, 1H) , 5.99 (br s, 1H) , 4.88 (t, J= 6.4 Hz, 1H) , 4.28 -3.30 (m, 3H) , 2.58 (br s, 6H) , 2.28 (t, J= 7.6 Hz, 2H) , 1.84 (br s, 2H) , 1.74 -1.40 (m, 12H) , 1.37 -1.18 (m, 48H) , 0.93 -0.83 (m, 9H) . LCMS showed the purity is 99.72%, R_t = 6.210 min; MS Calcd. : 707.6, MS Found: 708.6 $[\text{M}+\text{H}]^+$.

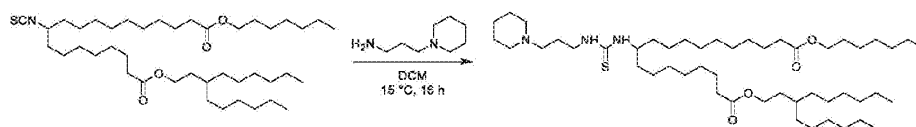
[0632] Example 63: 1- (heptadecan-9-yl) 19-heptyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) nonadecanedioate



[0633] A mixture of 1- (heptadecan-9-yl) 19-heptyl 9-isothiocyanatononadecanedioate (150 mg, 208 μmol) and 3- (1-piperidyl) propan-1-amine (59.1 mg, 415 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 73%-98%B over 13 min) to give 1- (heptadecan-9-yl) 19-heptyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) nonadecanedioate (97.5 mg, 54%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.68 (s, 1H) , 5.86 (br s, 1H) , 4.87 (t, J= 6.0 Hz, 1H) , 4.36 -3.75 (m, 3H) , 3.88 -3.44 (m, 2H) , 2.59 -2.39 (m, 6H) , 2.28 (q, J= 7.2 Hz, 4H) , 1.85 -1.74 (m, 2H) , 1.69 -1.57 (m, 10H) , 1.56 -1.41 (m, 10H) , 1.37 -1.22 (m, 52H) , 0.92 -0.82 (m, 9H) . LCMS showed the purity is 100%, R_t = 4.392 min; MS Calcd. : 863.8, MS Found: 864.8 $[\text{M}+\text{H}]^+$.

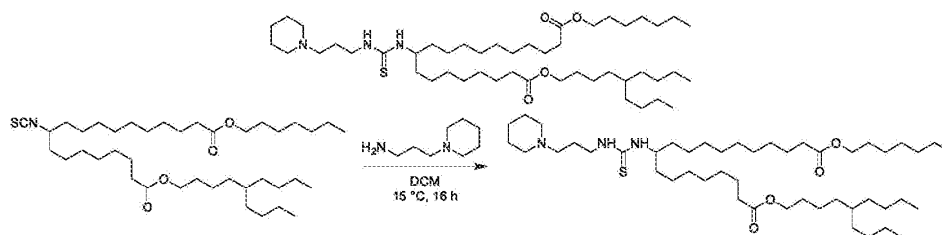
[0634] Example 64: 19-heptyl 1- (3-hexylnonyl) 9- (3- (3- (piperidin-1-yl) propyl) thioureido) nonadecanedioate





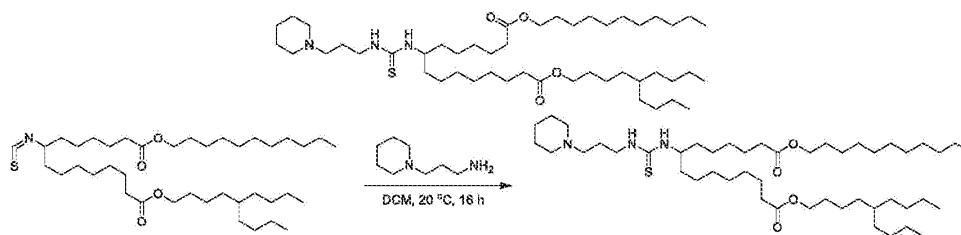
[0635] A mixture of 19-heptyl 1-(3-hexylnonyl) 9-isothiocyanatononadecanedioate (155 mg, 223 μmol) and 3-(piperidin-1-yl)propan-1-amine (63.5 mg, 447 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 68%-98%B over 13 min) to give 19-heptyl 1-(3-hexylnonyl) 9-(3-(3-(piperidin-1-yl)propyl)thioureido)nonadecanedioate (115.1 mg, 61%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (br s, 1H) , 6.02 (br s, 1H) , 4.24 -3.82 (m, 5H) , 3.77 -3.46 (m, 2H) , 2.99 -2.38 (m, 6H) , 2.32 -2.25 (m, 4H) , 1.94 -1.83 (m, 2H) , 1.76 -1.48 (m, 14H) , 1.46 -1.19 (m, 53H) , 0.89 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 100%, R_t = 3.092 min; MS Calcd. : 835.7, MS Found: 836.7 $[\text{M}+\text{H}]^+$.

[0636] Example 65: 1-(5-butylnonyl) 19-heptyl 9-(3-(3-(piperidin-1-yl)propyl)thioureido)nonadecanedioate



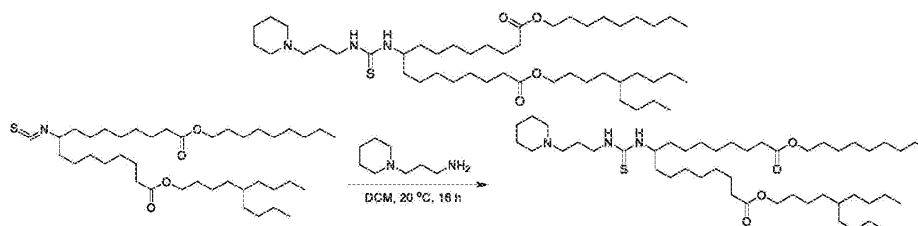
[0637] A mixture of 1-(5-butylnonyl) 19-heptyl 9-isothiocyanatononadecanedioate (170 mg, 255 μmol) and 3-(piperidin-1-yl)propan-1-amine (72.6 mg, 510 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 13 min) to give 1-(5-butylnonyl) 19-heptyl 9-(3-(3-(piperidin-1-yl)propyl)thioureido)nonadecanedioate (92.5 mg, 45%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (br s, 1H) , 5.94 (br s, 1H) , 4.43 -3.80 (m, 5H) , 3.60 (br s, 2H) , 2.57 (br s, 6H) , 2.29 (t, J = 7.6 Hz, 4H) , 1.84 (br s, 2H) , 1.72 -1.41 (m, 18H) , 1.39 -1.19 (m, 45H) , 1.01 -0.77 (m, 9H) . LCMS showed the purity is 100%, R_t = 1.874 min; MS Calcd. : 807.7, MS Found: 808.7 $[\text{M}+\text{H}]^+$.

[0638] Example 66: 15-(5-butylnonyl) 1-undecyl 7-(3-(3-(piperidin-1-yl)propyl)thioureido)pentadecanedioate



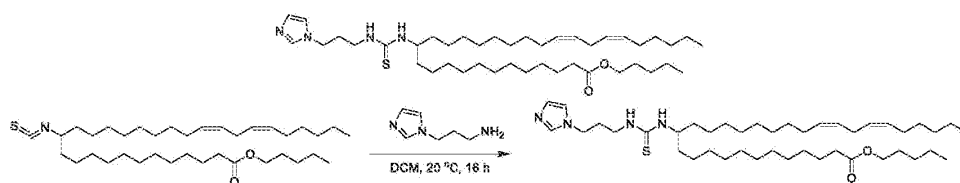
[0639] A mixture of 15- (5-butylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (200 mg, 300 μ mol) , 3- (1-piperidyl) propan-1-amine (85.4 mg, 601 μ mol) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μ m; mobile phase: [water (FA) -ACN] ; gradient: 63%-93%B over 13 min) to give 15- (5-butylnonyl) 1-undecyl 7- (3- (3- (piperidin-1-yl) propyl) thioureido) pentadecanedioate (63.5 mg, 26.2%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.24 -3.91 (m, 5H) , 3.73 -3.46 (m, 2H) , 2.85 -2.36 (m, 6H) , 2.29 (t, J= 7.6 Hz, 4H) , 1.86 (s, 2H) , 1.70 (s, 4H) , 1.66 -1.42 (m, 15H) , 1.38 -1.22 (m, 44H) , 0.95 -0.85 (m, 9H) . LCMS showed the purity is 100%, Rt = 2.629 min; MS Calcd. : 807.7, MS Found: 808.7 $[\text{M}+\text{H}]^+$.

[0640] Example 67: 1- (5-butylnonyl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate



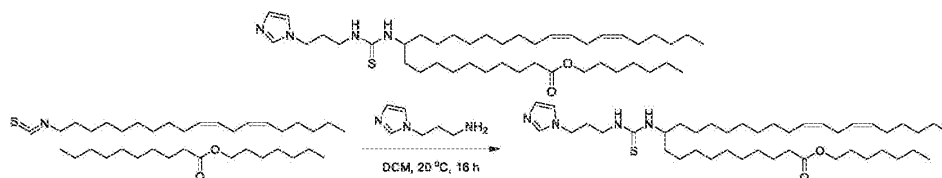
[0641] A mixture of 1- (5-butylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (190 mg, 285 μ mol) , 3- (1-piperidyl) propan-1-amine (81.2 mg, 570 μ mol) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μ m; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 13 min) to give 1- (5-butylnonyl) 17-nonyl 9- (3- (3- (piperidin-1-yl) propyl) thioureido) heptadecanedioate (86.7 mg, 37.6%yield) as a light-yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.15 -7.40 (m, 1H) , 6.20 -5.59 (m, 1H) , 4.25 -3.81 (m, 5H) , 3.73 -3.35 (m, 2H) , 2.68 -2.33 (m, 6H) , 2.29 (t, J= 7.6 Hz, 4H) , 1.79 (s, 2H) , 1.69-1.42 (m, 18H) , 1.37 -1.21 (m, 45H) , 0.94 -0.85 (m, 9H) . LCMS showed the purity is 100%, Rt = 2.541 min; MS Calcd. : 807.7, MS Found: 808.7 $[\text{M}+\text{H}]^+$.

[0642] Example 68: pentyl (22Z, 25Z) -13- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) hentriaconta-22, 25-dienoate



- [0643] A mixture pentyl (22Z, 25Z) -13-isothiocyanatohentriaconta-22, 25-dienoate (320 mg, 542 μmol), 3-imidazol-1-ylpropan-1-amine (136 mg, 1.08 mmol, 129 μL) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. LCMS showed Lipid 99 was detected. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL), the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN]; gradient: 50%-80%B over 20 min) to give pentyl (22Z, 25Z) -13- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) hentriaconta-22, 25-dienoate (137.3 mg, 35.4%yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.32-7.20 (m, 1H), 7.15 (s, 1H), 7.13-7.01 (m, 1H), 6.88 (s, 1H), 5.40-5.22 (m, 4H), 4.38-4.13 (m, 1H), 4.05-3.89 (m, 4H), 2.73 (t, $J = 6.0$ Hz, 2H), 2.26 (t, $J = 7.2$ Hz, 2H), 2.06-1.97 (m, 4H), 1.91 (quin, $J = 6.8$ Hz, 2H), 1.59-1.45 (m, 4H), 1.42-1.18 (m, 44H), 0.90-0.80 (m, 6H). LCMS showed the purity is 100%, $R_t = 5.839$ min; MS Calcd.: 714.6, MS Found: 715.6 $[\text{M} + \text{H}]^+$.

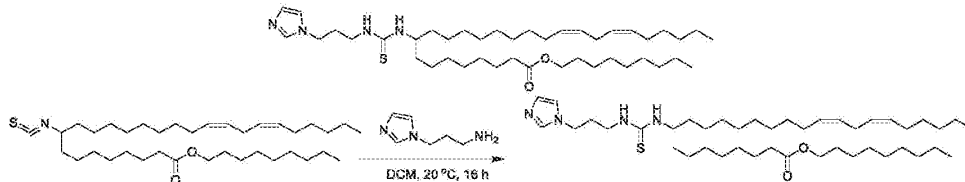
- [0644] Example 69: heptyl (20Z, 23Z) -11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonacosa-20, 23-dienoate



- [0645] A mixture of heptyl (20Z, 23Z) -11-isothiocyanatononacosa-20, 23-dienoate (260 mg, 441 μmol), 3-imidazol-1-ylpropan-1-amine (110 mg, 881 μmol , 105 μL) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL), the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN]; gradient: 55%-85%B over 20 min) to give heptyl (20Z, 23Z) -11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonacosa-20, 23-dienoate (102.3 mg, 32.5%yield) as light-yellow oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.33

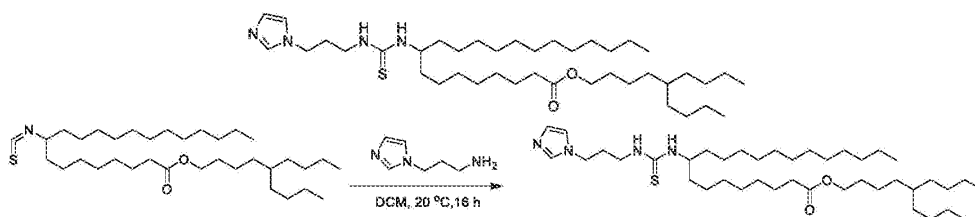
-7.19 (m, 1H) , 7.15 (s, 1H) , 7.12 -7.02 (m, 1H) , 6.88 (s, 1H) , 5.41 -5.24 (m, 4H) , 4.35 -4.18 (m, 1H) , 4.05 -3.91 (m, 4H) , 2.73 (t, J= 6.5 Hz, 2H) , 2.26 (t, J= 7.5 Hz, 2H) , 2.05 -1.98 (m, 4H) , 1.95 -1.87 (m, 2H) , 1.58 -1.47 (m, 4H) , 1.38 (s, 4H) , 1.34 -1.21 (m, 40H) , 0.89 -0.83 (m, 6H) . LCMS showed the purity is 100%, Rt = 6.127 min; MS Calcd. : 714.6, MS Found: 715.6 [M+H]⁺.

[0646] Example 70: nonyl (18Z, 21Z) -9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptacos-18, 21-dienoate



[0647] A mixture of nonyl (18Z, 21Z) -9-isothiocyanatoheptacos-18, 21-dienoate (120 mg, 203 μ mol) , 3-imidazol-1-ylpropan-1-amine (50.9 mg, 407 μ mol, 48.5 μ L) in DCM (5 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with DCM (50 mL) , washed with HCl (1 N, 10 mL) , saturated NaHCO₃ (30 mL) and brine (30 mL) , dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μ m; mobile phase: [water (FA) -ACN] ; gradient: 52%-82%B over 20 min) to give nonyl (18Z, 21Z) -9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptacos-18, 21-dienoate (31.6 mg, 21.7%yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H) , 7.31 -7.19 (m, 1H) , 7.15 (s, 1H) , 7.13 -7.00 (m, 1H) , 6.87 (s, 1H) , 5.39-5.25 (m, 4H) , 4.38 -4.09 (m, 1H) , 4.03 -3.90 (m, 4H) , 2.72 (t, J= 6.0 Hz, 2H) , 2.25 (t, J= 7.2 Hz, 2H) , 2.06 -1.96 (m, 4H) , 1.95 -1.87 (m, 2H) , 1.58 -1.46 (m, 4H) , 1.37 (d, J= 4.4 Hz, 4H) , 1.32 -1.20 (m, 40H) , 0.85 (t, J= 6.8 Hz, 6H) . LCMS showed the purity is 100%, Rt = 6.184 min; MS Calcd. : 714.6, MS Found: 715.6 [M+H]⁺.

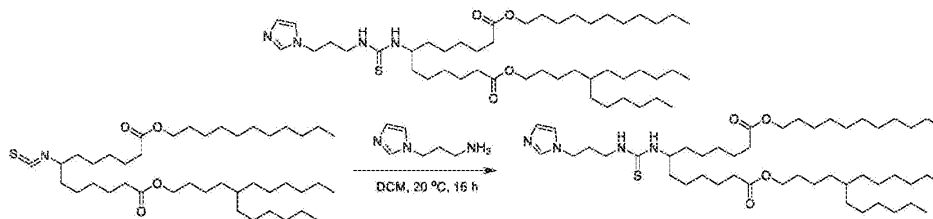
[0648] Example 71: 5-butylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henic-
cosanoate



[0649] A mixture of 5-butylnonyl 9-isothiocyanatohenicosanoate (310 mg, 548 μ mol) , 3-imidazol-1-ylpropan-1-amine (137 mg, 1.10 mmol, 131 μ L) in DCM (8 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H₂O (30 mL) and extracted with DCM (2 $\times$ 30 mL) , the combined organic layers were

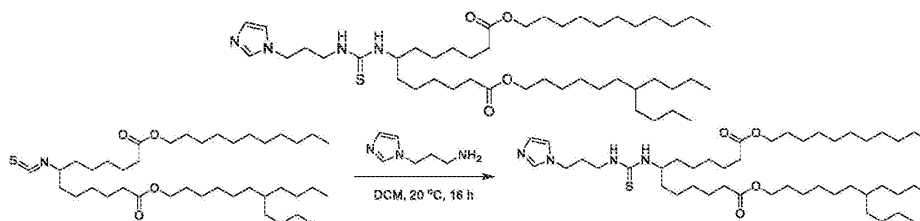
washed with sat. NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue, the residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN]; gradient: 60%-90%B over 20 min) to give 5-butylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanoate (115.3 mg, 30.5% yield) as a light-yellow oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.31 -7.19 (m, 1H), 7.15 (s, 1H), 7.11 -7.02 (m, 1H), 6.88 (s, 1H), 4.41 -4.16 (m, 1H), 4.05 -3.87 (m, 4H), 2.25 (t, $J=7.5$ Hz, 2H), 1.96 -1.84 (m, 2H), 1.58 -1.46 (m, 4H), 1.38 (s, 4H), 1.28 -1.18 (m, 47H), 0.88 -0.83 (m, 9H). LCMS showed the purity is 100%, $R_t = 6.190$ min; MS Calcd.: 690.6, MS Found: 691.6 $[\text{M}+\text{H}]^+$.

[0650] Example 72: 1- (5-hexylundecyl) 13-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) tridecanedioate



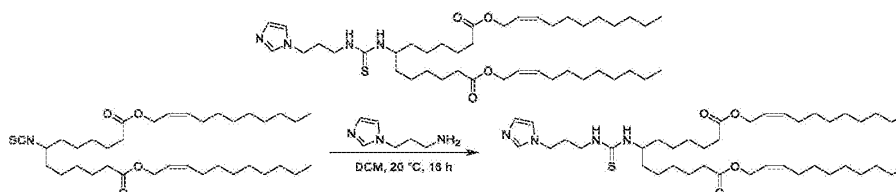
[0651] A mixture of 1- (5-hexylundecyl) 13-undecyl 7-isothiocyanatotridecanedioate (200 mg, 288 μmol), 3-imidazol-1-ylpropan-1-amine (72.1 mg, 576 μmol , 68.8 μL) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL), the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -ACN]; gradient: 65%-95%B over 20 min) to give 1- (5-hexylundecyl) 13-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) tridecanedioate (61.6 mg, 26.1% yield) as light-yellow oil. ^1H NMR (500 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.36 -7.22 (m, 1H), 7.15 (s, 1H), 7.13 -7.03 (m, 1H), 6.88 (s, 1H), 4.34 -4.14 (m, 1H), 4.06 -3.94 (m, 6H), 2.25 (t, $J=7.5$ Hz, 4H), 1.96 -1.88 (m, 2H), 1.58 -1.47 (m, 8H), 1.38 (s, 4H), 1.30 -1.18 (m, 51H), 0.88 -0.83 (m, 9H). LCMS showed the purity is 100%, $R_t = 6.711$ min; MS Calcd.: 818.7, MS Found: 819.7 $[\text{M}+\text{H}]^+$.

[0652] Example 73: 1- (7-butylundecyl) 13-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) tridecanedioate



- [0653] A mixture of 1-(7-butylundecyl) 13-undecyl 7-isothiocyanatotrilecanedioate (300 mg, 450 μ mol), 3-imidazol-1-ylpropan-1-amine (113 mg, 901 μ mol, 107 μ L) in DCM (8 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with HCl (1 N, 5 mL) and H₂O (30 mL) and extracted with DCM (2 $\times$ 30 mL), the combined organic layers were washed with saturated NaHCO₃ (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 $\times$ 40 mm $\times$ 5 μ m; mobile phase: [water (FA) -ACN]; gradient: 60%-90%B over 20 min) to give 1-(7-butylundecyl) 13-undecyl 7-(3-(3-(1H-imidazol-1-yl) propyl) thioureido) tridecanedioate (93.4 mg, 26.2% yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H), 7.32 (s, 1H), 7.18-7.14 (m, 1H), 7.01 (s, 1H), 6.90-6.85 (m, 1H), 4.37-4.15 (m, 1H), 4.01-3.94 (m, 6H), 2.25 (t, J = 7.2 Hz, 4H), 1.98-1.86 (m, 2H), 1.56-1.46 (m, 8H), 1.42-1.34 (m, 4H), 1.29-1.18 (m, 47H), 0.88-0.83 (m, 9H). LCMS showed the purity is 100%, Rt = 6.394 min; MS Calcd.: 790.6, MS Found: 791.6 [M+H]⁺.

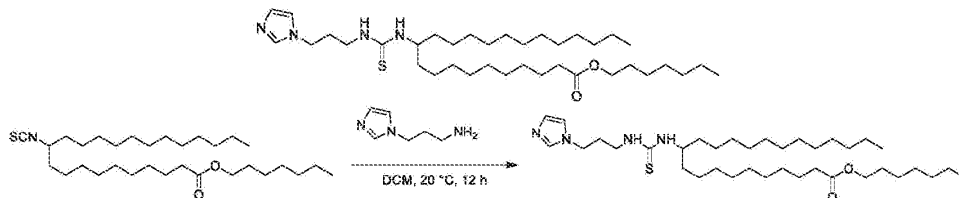
- [0654] Example 74: di ((Z)-undec-2-en-1-yl) 7-(3-(3-(1H-imidazol-1-yl) propyl) thioureido) tridecanedioate



- [0655] A mixture of di ((Z)-undec-2-en-1-yl) 7-isothiocyanatotrilecanedioate (200 mg, 330 μ mol) and 3-imidazol-1-ylpropan-1-amine (82.6 mg, 660 μ mol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL). The organic phase was washed with saturated NaHCO₃ (50 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 $\times$ 40 mm $\times$ 5 μ m; mobile phase: [water (FA) -ACN]; gradient: 45%-75%B over 20 min) to give di ((Z)-undec-2-en-1-yl) 7-(3-(3-(1H-imidazol-1-yl) propyl) thioureido) tridecanedioate (154.8 mg, 64% yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H), 7.29 (br s, 1H), 7.19-7.04 (m, 2H), 6.88 (s, 1H), 5.65-5.55 (m, 2H), 5.53-5.43 (m, 2H),

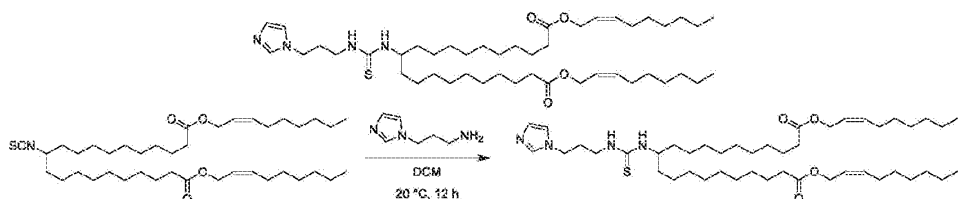
4.55 (d, $J = 6.8$ Hz, 4H), 4.25 (br s, 1H), 3.96 (t, $J = 7.2$ Hz, 2H), 3.46-3.34 (m, 2H), 2.26 (t, $J = 7.2$ Hz, 4H), 2.05 (q, $J = 7.2$ Hz, 4H), 1.97-1.87 (m, 2H), 1.54-1.45 (m, 4H), 1.42-1.16 (m, 36H), 0.85 (t, $J = 7.2$ Hz, 6H). LCMS showed the purity is 100%, $R_t = 5.113$ min; MS Calcd.: 730.5, MS Found: 731.5 $[M+H]^+$.

[0656] Example 75: heptyl 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) tricosanoate



[0657] A mixture of heptyl 11-isothiocyanatotricosanoate (130 mg, 255 μ mol) and 3-imidazol-1-ylpropan-1-amine (63.8 mg, 510 μ mol) in DCM (5 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL). The organic phase was washed with saturated NaHCO_3 (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μ m; mobile phase: [water (FA) - ACN]; gradient: 45%-75%B over 20 min) to give heptyl 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) tricosanoate (61.8 mg, 38% yield) as a light-yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.60 (s, 1H), 7.26 (br s, 1H), 7.15 (s, 1H), 7.09 (br s, 1H), 6.88 (s, 1H), 4.36-4.14 (m, 1H), 4.03-3.93 (m, 4H), 2.25 (t, $J = 7.2$ Hz, 2H), 1.97-1.87 (m, 2H), 1.58-1.46 (m, 4H), 1.38 (br s, 4H), 1.31-1.17 (m, 42H), 0.90-0.80 (m, 6H). LCMS showed the purity is 100%, $R_t = 1.770$ min; MS Calcd.: 634.5, MS Found: 635.5 $[M+H]^+$.

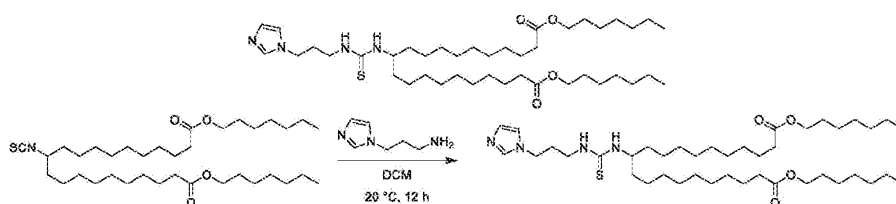
[0658] Example 76: di ((Z) -non-2-en-1-yl) 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heneicosanedioate



[0659] A mixture of di ((Z) -non-2-en-1-yl) 11-isothiocyanatoheneicosanedioate (210 mg, 317 μ mol) and 3-imidazol-1-ylpropan-1-amine (79.4 mg, 634 μ mol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with 1 N HCl (20 mL) and DCM (100 mL). The organic phase was washed with saturated NaHCO_3 (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified

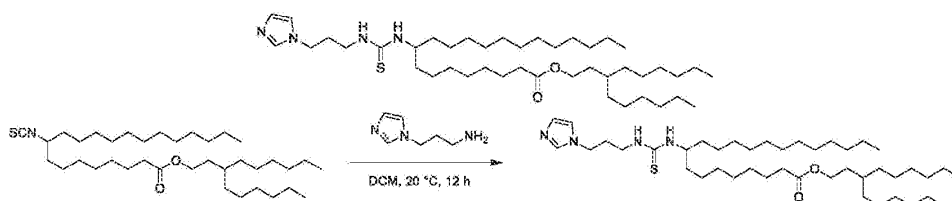
by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 um; mobile phase: [water (FA) -ACN] ; gradient: 50%-80%B over 20 min) to give di ((Z) -non-2-en-1-yl) 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanedioate (129.0 mg, 52%yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H) , 7.28 (br s, 1H) , 7.15 (s, 1H) , 7.13 -7.04 (m, 1H) , 6.88 (s, 1H) , 5.66 -5.56 (m, 2H) , 5.54 -5.45 (m, 2H) , 4.56 (d, J= 6.8 Hz, 4H) , 4.25 (br s, 1H) , 3.97 (t, J= 6.8 Hz, 2H) , 2.27 (t, J= 7.2 Hz, 4H) , 2.07 (q, J= 7.2 Hz, 4H) , 1.96 -1.88 (m, 2H) , 1.50 (t, J= 6.8 Hz, 4H) , 1.41 -1.19 (m, 44H) , 0.89 -0.83 (m, 6H) . LCMS showed the purity is 100.0%, Rt = 5.621 min; MS Calcd. : 786.6, MS Found: 787.6 [M+H]⁺.

[0660] Example 77: diheptyl 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanedioate



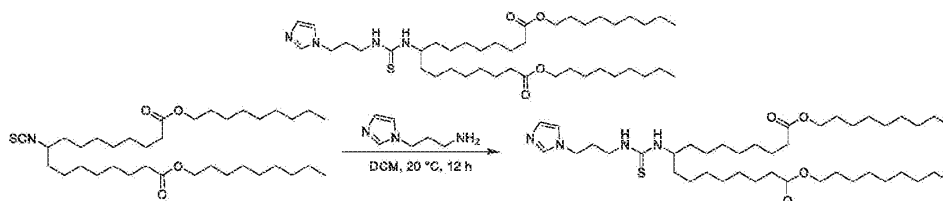
[0661] A mixture of diheptyl 11-isothiocyanatohenicosanedioate (150 mg, 245.91 μmol, 1 eq) and 3-imidazol-1-ylpropan-1-amine (61.6 mg, 491 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with HCl (1 N, 20 mL) and DCM (100 mL) . The organic phase was washed with saturated NaHCO₃ (50 mL) , brine (50 mL) , dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 um; mobile phase: [water (FA) -ACN] ; gradient: 45%-75%B over 20 min) to give diheptyl 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanedioate (76.8 mg, 42%yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H) , 7.25 (br s, 1H) , 7.15 (s, 1H) , 7.12 -6.99 (m, 1H) , 6.88 (s, 1H) , 4.26 (br s, 1H) , 4.03 -3.91 (m, 6H) , 2.25 (t, J= 7.2 Hz, 4H) , 1.91 (q, J= 6.8 Hz, 2H) , 1.59 -1.46 (m, 8H) , 1.42 -1.15 (m, 44H) , 0.88 -0.82 (m, 6H) . LCMS showed the purity is 99.21%, Rt = 5.163 min; MS Calcd. : 734.6, MS Found: 735.6 [M+H]⁺.

[0662] Example 78: 3-hexylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanoate



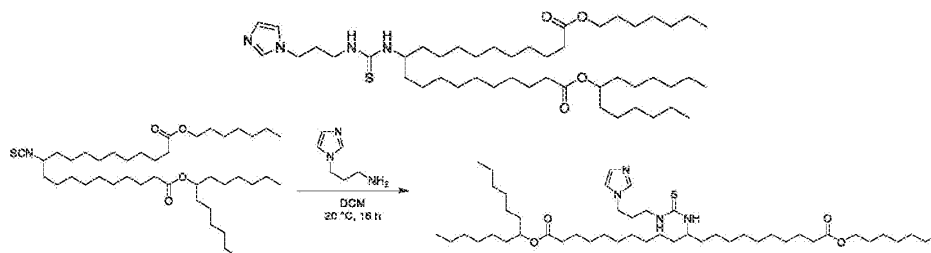
[0663] A mixture of 3-hexylnonyl 9-isothiocyanatoheptacosanoate (4.8 g, 8.08 mmol) and 3-imidazol-1-ylpropan-1-amine (2.02 g, 16.2 mmol) in DCM (80 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. TLC showed that several spots were observed. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with HCl (1 N, 50 mL), saturated NaHCO₃ (80 mL) and brine (80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 1: 0 to 19: 1) to give the crude product, which was further purified by prep-HPLC (column: C8 70 × 40 mm; mobile phase: [water (FA) -ACN]; gradient: 80%-99%B over 10 min) to give 3-hexylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptacosanoate (3642.0 mg, 62%yield) as a light-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 7.06 (s, 1H), 6.97 (s, 1H), 6.21 -5.98 (m, 1H), 5.94 -5.75 (m, 1H), 4.38 -3.79 (m, 5H), 3.57 (br s, 2H), 2.28 (t, J= 7.6 Hz, 2H), 2.14 (q, J= 6.8 Hz, 2H), 1.64 -1.54 (m, 4H), 1.53 -1.37 (m, 5H), 1.34 -1.19 (m, 48H), 0.89 (t, J= 6.8 Hz, 9H). LCMS showed the purity is 100%, Rt = 3.619 min; MS Calcd.: 718.6, MS Found: 719.6 [M+H]⁺.

[0664] Example 79: dinonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate



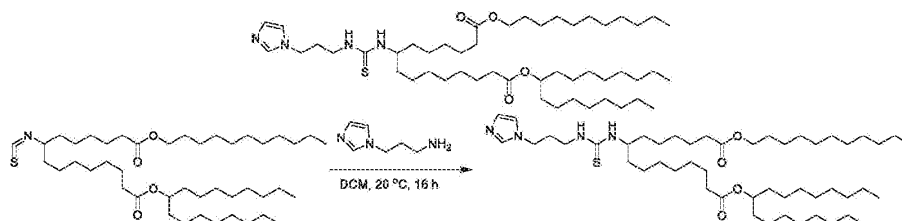
[0665] A mixture of dinonyl 9-isothiocyanatoheptadecanedioate (200 mg, 328 μmol) and 3-imidazol-1-ylpropan-1-amine (82.1 mg, 656 μmol) in DCM (8 mL) was stirred at 20 °C for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was diluted with HCl (1 N, 20 mL) and DCM (100 mL). The organic phase was washed with NaHCO₃ (50 mL), brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5μm; mobile phase: [water (FA) -ACN]; gradient: 45%-75%B over 20 min) and lyophilized to give dinonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate (117.5 mg, 49%yield) as a light brown oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H), 7.26 (br s, 1H), 7.15 (s, 1H), 7.09 (br s, 1H), 6.88 (s, 1H), 4.42 -4.14 (m, 1H), 4.02 -3.90 (m, 6H), 2.25 (t, J= 7.2 Hz, 4H), 1.96 -1.87 (m, 2H), 1.59 -1.45 (m, 8H), 1.43 -1.17 (m, 46H), 0.88 -0.81 (m, 6H). LCMS showed the purity is 100.0%, Rt = 5.432 min; MS Calcd.: 734.6, MS Found: 735.6 [M+H]⁺.

[0666] Example 80: 1-heptyl 21- (tridecan-7-yl) 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanedioate



[0667] A mixture of 1-heptyl 21- (tridecan-7-yl) 11-isothiocyanatohenicosanedioate (200 mg, 288 μmol) and 3-imidazol-1-ylpropan-1-amine (72.1 mg, 576 μmol) in DCM (8 mL) was stirred at 20 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) - ACN] ; gradient: 75%-98%B over 13 min) to give 1-heptyl 21- (tridecan-7-yl) 11- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosanedioate (102.9 mg, 44%yield) as a light-yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.60 (s, 1H) , 7.27 (br s, 1H) , 7.17 -7.02 (m, 2H) , 6.88 (s, 1H) , 4.78 (q J= 6.4 Hz, 1H) , 4.25 (br s, 1H) , 4.02 -3.92 (m, 4H) , 2.28 -2.20 (m, 4H) , 1.91 (q, J= 7.2 Hz, 2H) , 1.59 -1.42 (m, 10H) , 1.38 (br s, 4H) , 1.32 -1.15 (m, 48H) , 0.89 -0.80 (m, 9H) . LCMS showed the purity is 100.00%, R_t = 6.138 min; MS Calcd. : 818.7, MS Found: 820.7 $[\text{M}+\text{H}]^+$.

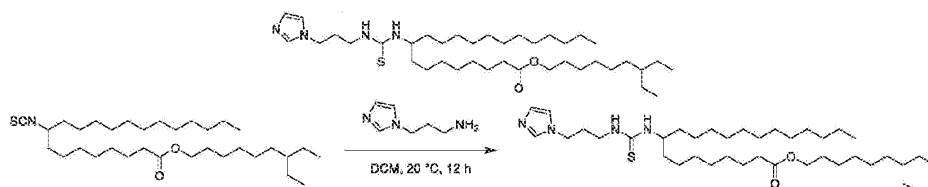
[0668] Example 81: 15- (heptadecan-9-yl) 1-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentadecanedioate



[0669] A mixture 15- (heptadecan-9-yl) 1-undecyl 7-isothiocyanatopentadecanedioate (200 mg, 277 μmol) , 3-imidazol-1-ylpropan-1-amine (69.3 mg, 554 μmol , 66.1 μL) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was diluted with HCl (1N, 5 mL) and H_2O (30 mL) and extracted with DCM (2×30 mL) , the combined organic layers were washed with saturated NaHCO_3 (30 mL) and brine (30 mL) , dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C8 50 *40 mm *5 μm ; mobile phase: [water (FA) -MeOH] ; gradient: 65%-95%B over 20 min) to give 15- (heptadecan-9-yl) 1-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentadecanedioate (79.7

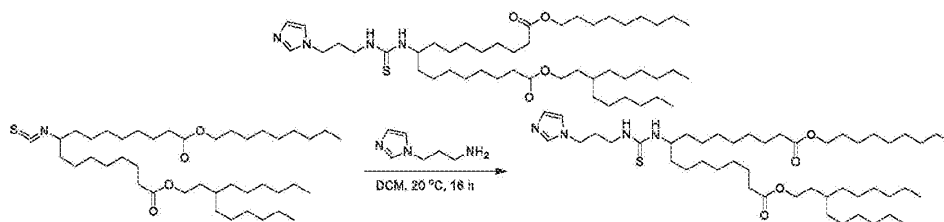
mg, 34.0% yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.38 -7.21 (m, 1H), 7.18 -7.13 (m, 1H), 7.13 -6.98 (m, 1H), 6.91 -6.84 (m, 1H), 4.83 -4.70 (m, 1H), 4.47 -4.19 (m, 1H), 4.06 -3.89 (m, 4H), 2.28 -2.21 (m, 4H), 1.96 -1.86 (m, 2H), 1.58 -1.42 (m, 12H), 1.42 -1.36 (m, 4H), 1.30 -1.20 (m, 52H), 0.87 -0.81 (m, 9H). LCMS showed the purity is 100%, R_t = 4.595 min; MS Calcd.: 846.7, MS Found: 847.7 $[\text{M}+\text{H}]^+$.

[0670] Example 82: 7-ethylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosoanoate



[0671] A mixture of 7-ethylnonyl 9-isothiocyanatohenicosoanoate (200 mg, 372 μmol) and 3-imidazol-1-ylpropan-1-amine (93.1 mg, 744 μmol) in DCM (8 mL) was stirred at 20 $^{\circ}\text{C}$ for 12 hours. LCMS showed that desired mass was detected. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN]; gradient: 65%-95%B over 13 min) to give 7-ethylnonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) henicosoanoate (190.7 mg, 77% yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.38 -7.23 (m, 1H), 7.19 -7.01 (m, 2H), 6.88 (s, 1H), 4.24 (br s, 1H), 4.02 -3.93 (m, 4H), 3.57 -3.34 (m, 2H), 2.25 (t, J = 7.2 Hz, 2H), 1.91 (q, J = 6.8 Hz, 2H), 1.59 -1.45 (m, 4H), 1.38 (br s, 4H), 1.32 -1.09 (m, 41H), 0.88 -0.76 (m, 9H). LCMS showed the purity is 100%, R_t = 5.524 min; MS Calcd.: 662.6, MS Found: 663.5 $[\text{M}+\text{H}]^+$.

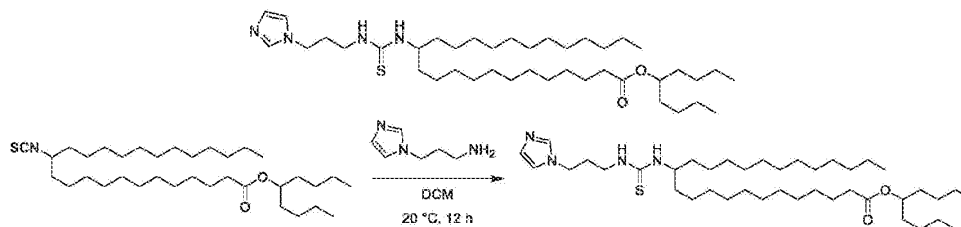
[0672] Example 83: 1- (3-hexylnonyl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate



[0673] A mixture 1- (3-hexylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (120 mg, 173 μmol), 3-imidazol-1-ylpropan-1-amine (43.3 mg, 346 μmol , 41.3 μL) in DCM (5 mL) was stirred at 20 $^{\circ}\text{C}$ for 16 hours. LCMS showed Lipid 137 was detected. The mixture was diluted with HCl (1 N, 5 mL) and H_2O (30 mL) and extracted with DCM (2 $\times$ 30 mL), the combined organic layers were washed with saturated NaHCO_3 (30

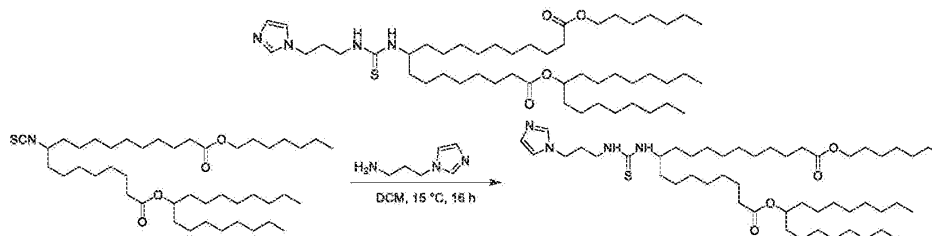
mL) and brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 68%-98%B over 13 min) to give 1- (3-hexylnonyl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate (84.2 mg, 59.5% yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H), 7.31 -7.18 (m, 1H), 7.15 (s, 1H), 7.11 -6.99 (m, 1H), 6.88 (s, 1H), 4.43 -4.13 (m, 1H), 4.10 -3.90 (m, 6H), 2.29 -2.19 (m, 4H), 1.91 (quin, $J=6.8$ Hz, 2H), 1.58 -1.45 (m, 8H), 1.43 -1.09 (m, 55H), 0.91 -0.79 (m, 9H). LCMS showed the purity is 100%, $R_t = 2.987$ min; MS Calcd.: 818.7, MS Found: 819.7 $[\text{M} + \text{H}]^+$.

[0674] Example 84: nonan-5-yl 13- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentacosanoate



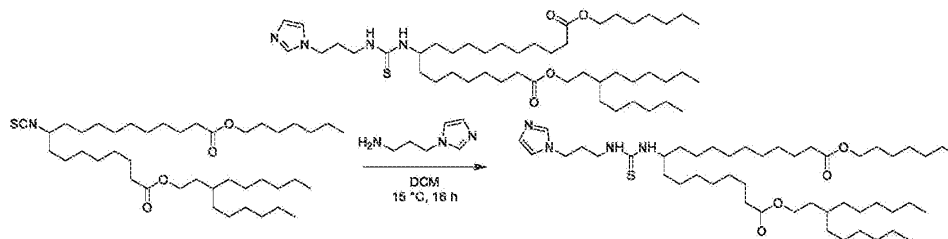
[0675] A mixture of nonan-5-yl 13-isothiocyanatopentacosanoate (200 mg, 353 μmol) and 3-imidazol-1-ylpropan-1-amine (88.5 mg, 707 μmol) and in DCM (8 mL) was stirred at 20 $^\circ\text{C}$ for 12 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 66%-96%B over 13 min) to give nonan-5-yl 13- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentacosanoate (139.1 mg, 57% yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.30 -7.22 (m, 1H), 7.17 -7.02 (m, 2H), 6.88 (s, 1H), 4.83 -4.72 (m, 1H), 4.23 (br s, 1H), 3.96 (t, $J=7.2$ Hz, 2H), 2.25 (t, $J=7.2$ Hz, 2H), 1.91 (q, $J=7.2$ Hz, 2H), 1.56 -1.34 (m, 10H), 1.30 -1.16 (m, 46H), 0.88 -0.80 (m, 9H). LCMS showed the purity is 99.75%, $R_t = 5.863$ min; MS Calcd.: 690.6, MS Found: 691.6 $[\text{M} + \text{H}]^+$.

[0676] Example 85: 1- (heptadecan-9-yl) 19-heptyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonadecanedioate



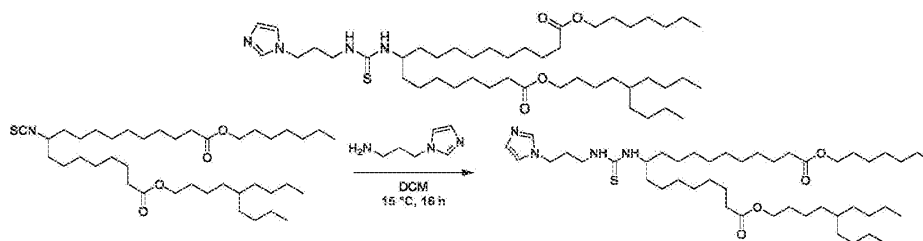
[0677] A mixture of 1- (heptadecan-9-yl) 19-heptyl 9-isothiocyanatononadecanedioate (120 mg, 166 μmol) and 3-imidazol-1-ylpropan-1-amine (41.6 mg, 332 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) - ACN] ; gradient: 85%-100%B over 13 min) to give 1- (heptadecan-9-yl) 19-heptyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonadecanedioate (40.9 mg, 29%yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 1H) , 7.27 (br s, 1H) , 7.17 -7.03 (m, 2H) , 6.89 (s, 1H) , 4.82 -4.74 (m, 1H) , 4.35 -4.19 (m, 1H) , 4.03 -3.94 (m, 4H) , 2.30 -2.22 (m, 4H) , 1.99 -1.83 (m, 2H) , 1.61 -1.43 (m, 10H) , 1.42 -1.35 (m, 4H) , 1.23 (br s, 54H) , 0.89 -0.83 (m, 9H) . LCMS showed the purity is 100%, R_t = 3.842 min; MS Calcd. : 846.7, MS Found: 847.7 $[\text{M}+\text{H}]^+$.

[0678] Example 86: 19-heptyl 1- (3-hexylnonyl) 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonadecanedioate



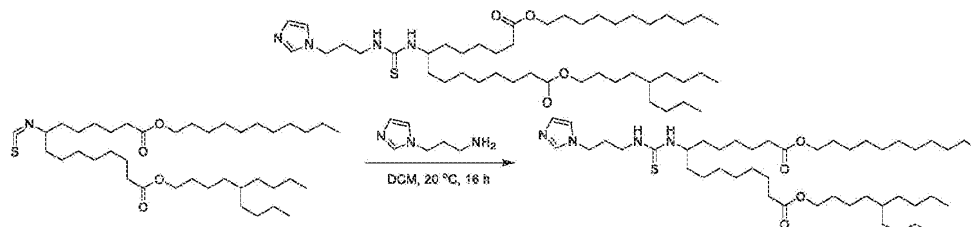
[0679] A mixture of 19-heptyl 1- (3-hexylnonyl) 9-isothiocyanatononadecanedioate (155 mg, 223 μmol) and 3- (1H-imidazol-1-yl) propan-1-amine (55.9 mg, 447 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 68%-98%B over 13 min) to give 19-heptyl 1- (3-hexylnonyl) 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonadecanedioate (92.9 mg, 51%yield) as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H) , 7.26 (br s, 1H) , 7.17 -7.02 (m, 2H) , 6.88 (s, 1H) , 4.25 (br s, 1H) , 4.06-3.92 (m, 6H) , 2.28 -2.21 (m, 4H) , 1.95 -1.85 (m, 2H) , 1.58 -1.45 (m, 8H) , 1.38 (br s, 4H) , 1.22 (br s, 51H) , 0.85 (t, J = 6.8 Hz, 9H) . LCMS showed the purity is 100%, R_t = 2.353 min; MS Calcd. : 818.7, MS Found: 819.7 $[\text{M}+\text{H}]^+$.

[0680] Example 87: 1- (5-butylnonyl) 19-heptyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) nonadecanedioate



[0681] A mixture of 1- (5-butylnonyl) 19-heptyl 9-isothiocyanatopentadecanedioate (170 mg, 255 μmol) and 3- (1H-imidazol-1-yl) propan-1-amine (63.9 mg, 510 μmol) in DCM (5 mL) was stirred at 15 °C for 16 hours. LCMS showed that desired mass was detected. The reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 13 min) to give 1- (5-butylnonyl) 19-heptyl 9-(3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentadecanedioate (81.9 mg, 41%yield) as a light-yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.60 (s, 1H) , 7.26 (br s, 1H) , 7.18 -7.01 (m, 2H) , 6.88 (s, 1H) , 4.24 (br s, 1H) , 4.04-3.89 (m, 6H) , 2.25 (t, J = 7.2 Hz, 4H) , 1.91 (q, J = 6.8 Hz, 2H) , 1.58 -1.45 (m, 8H) , 1.38 (br s, 4H) , 1.31-1.16 (m, 47H) , 0.89 -0.82 (m, 9H) . LCMS showed the purity is 100%, R_t = 5.951 min; MS Calcd. : 790.6, MS Found: 791.6 $[\text{M}+\text{H}]^+$.

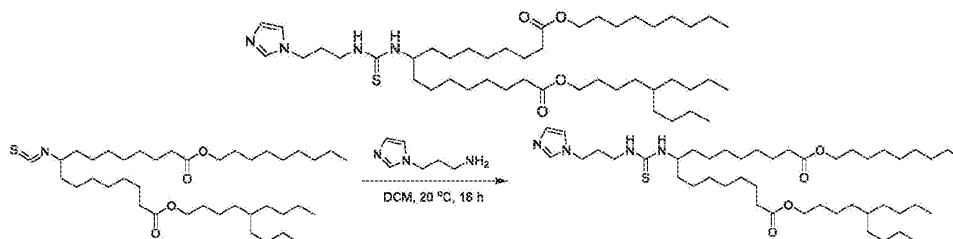
[0682] Example 88: 15- (5-butylnonyl) 1-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentadecanedioate



[0683] A mixture of 15- (5-butylnonyl) 1-undecyl 7-isothiocyanatopentadecanedioate (120 mg, 180 μmol) , 3-imidazol-1-ylpropan-1-amine (45.1 mg, 360 μmol , 43.0 μL) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xltime C4 100 *30 *10 μm ; mobile phase: [water (FA) -ACN] ; gradient: 65%-95%B over 13 min) to give 15- (5-butylnonyl) 1-undecyl 7- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) pentadecanedioate (60.4 mg, 42.4%yield) as a light-yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.60 (s, 1H) , 7.30-7.18 (m, 1H) , 7.15 (s, 1H) , 7.12 -7.02 (m, 1H) , 6.88 (s, 1H) , 5.75 (s, 1H) , 4.35 -4.10 (m, 1H) , 4.04 -3.91 (m, 6H) , 2.25 (t, J = 7.2 Hz, 4H) , 1.91 (quin, J = 6.8 Hz, 2H) , 1.59 -1.44 (m, 8H) , 1.43 -1.33 (m, 4H) , 1.31 -1.14

(m, 47H) , 0.89 -0.82 (m, 9H) . LCMS showed the purity is 100%, Rt = 2.093 min; MS Calcd. : 790.6, MS Found: 791.7 [M+H]⁺.

[0684] Example 89: 1- (5-butylnonyl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate



[0685] A mixture of 1- (5-butylnonyl) 17-nonyl 9-isothiocyanatoheptadecanedioate (110 mg, 165 μ mol) , 3-imidazol-1-ylpropan-1-amine (41.3 mg, 330 μ mol, 39.4 μ L) in DCM (6 mL) was stirred at 20 °C for 16 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C4 100 *30 *10 μ m; mobile phase: [water (FA) -ACN] ; gradient: 60%-90%B over 13 min) to give 1- (5-butylnonyl) 17-nonyl 9- (3- (3- (1H-imidazol-1-yl) propyl) thioureido) heptadecanedioate (62.5 mg, 47.8%yield) as a light-yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H) , 7.31 -7.19 (m, 1H) , 7.15 (s, 1H) , 7.12 -6.98 (m, 1H) , 6.88 (s, 1H) , 4.37 -4.10 (m, 1H) , 4.05 -3.90 (m, 6H) , 2.25 (t, J= 7.2 Hz, 4H) , 1.97 -1.86 (m, 2H) , 1.58 -1.45 (m, 8H) , 1.38 (s, 4H) , 1.31 -1.13 (m, 47H) , 0.89 -0.81 (m, 9H) . LCMS showed the purity is 100%, Rt = 5.987 min; MS Calcd. : 790.6, MS Found: 792.6 [M+H]⁺.

[0686] Preparation of lipid nanoparticle (LNP)

[0687] The LNPs were prepared at an ionizable lipid amine to RNA phosphate (N: P) molar ratio of 6: 1. Ionizable lipid, DSPC, cholesterol and DMG-PEG2000 were solubilized in EtOH at a molar ratio of 50:10: 38.5: 1.5. The luciferase (Luc) or Ovalbumin (OVA) -mRNA produced according to the protocol of HiScribe™ T7 High Yield RNA Synthesis Kit (NEW ENGLAND BioLabs® Inc.) , was diluted to 0.12 mg/mL in 50 mM citrate buffer, pH 4. The LNPs were prepared by microfluidic mixing of the ethanolic lipid solution and the mRNA aqueous solution at a volume ratio of 1: 3 using the Precision Nanosystems NanoAssemblr™ Ignite Benchtop Instrument with a total flow rate of 12 mL/min. Then the ethanol was removed, and the buffer was replaced with 25mM Tris buffer (pH 7.4) by dialysis overnight at 4°C using a 10 kDa Slide-a-Lyzer™ G2 Dialysis Cassette (ThermoFisher Scientific) . The resulting LNPs were filtered through a 220nm pore sterile filter and stored at 2-8°C. The isolated LNPs were separately characterized to determine the average particle size, polydispersity index (PDI) , zeta potential, encapsulation efficiency and pKa as described below.

- [0688] Characterization/Efficacy of lipid nanoparticle

[0689] Average particle size, PDI and zeta potential were measured by Zetasizer Ultra instrument (Malvern instrument) . The LNP samples were diluted 100*in 10 mM HEPES buffer (pH 7.4) prior to being measured by the Zetasizer Ultra instrument and the results were shown in FIGs. 1-3 and Table 1. LNP size was approximately 70-200 nm.

[0690] The QUANT-IT™ RIBOGREEN RNA assay (ThermoFisher SCIENTIFIC) was used to evaluate total mRNA concentration and encapsulation efficiency (EE) . LNP samples were diluted 100×with 1× TE buffer to be within the liner range of RiboGreen® agent. 50 μL of diluted LNP samples were mixed with either 50 μL 1× TE buffer or 0.2%Triton X-100 solution of 1× TE buffer in duplicate. The mixtures were incubated at 37°C for 15 minutes. The RiboGreen® agent was diluted 100× with 1× TE buffer and 100 μL of diluted solution was then added to each sample. The luminescence intensity was measured by a luminescence plate reader (SYNERGY neo2, BioTek) at an excitation wavelength of 480 nm and an emission wavelength of 520 nm. The percentage of free mRNA was determined by dividing the luminescence intensity of intact LNP sample by the luminescence intensity of disrupted LNP sample.

[0691] The apparent pKa of LNP samples were measured by the luminescence of 2- (p-toluidino) -6-napthalene sulfonic acid (TNS) assay. LNP comprising of ionizable lipid/DSPC/cholesterol/PEG-lipid (50/10/38.5/1.5) in 25mM Tris buffer (pH 7.4) was prepared at a concentration of ~4 mM total lipid. TNS was prepared as a 100 μM stock solution in distilled water. LNP samples were diluted to 100 μM lipid in 2 mL of buffered solutions containing, 10 mM HEPES, 10 mM MES, 10 mM ammonium acetate, 130 mM NaCl, where the pH ranged from 2.5 to 11. An aliquot of the TNS solution was added to give a final concentration of 1 μM and following vortex mixing luminescence intensity was measured at room temperature in a luminescence plate reader (SYNERGY neo2, BioTek) using excitation and emission wavelengths of 321 nm and 445 nm. A sigmoidal best fit analysis was applied to the luminescence data and the pKa was measured as the pH giving rise to half-maximal luminescence intensity.

[0692] The values of EE (encapsulation efficiency) and LNP's apparent pKa are shown in Table 1. mRNA encapsulation efficiency was mostly above 95%.

[0693] Table 1
- Rule 26,
27.12.2024

Lipid	Size (nm)	PDI	EE (%)	pKa
Example 1	100	0.12	97.99	8.06
Example 2	92	0.07	98.50	8.41
Example 3	89	0.04	97.79	7.88
Example 4	102	0.08	95.86	6.23
Example 5	70	0.11	95.04	5.36
Example 6	97	0.06	96.48	6.61
Example 7	77	0.03	95.24	5.69
Example 8	156	0.22	97.42	9.29
Example 9	188	0.25	98.30	9.04
Example 10	176	0.22	98.64	8.40
Example 13	197	0.21	95.42	7.96
Example 14	181	0.25	92.43	7.34
Example 15	115	0.07	98.56	8.24
Example 16	100	0.09	98.50	8.73

Example 17	137	0.18	98.57	8.12
Example 18	130	0.11	94.41	6.05
Example 19	108	0.18	93.49	5.52
Example 20	137	0.19	95.84	6.71
Example 21	119	0.12	91.93	5.89
Example 22	124	0.20	97.31	6.70
Example 23	101	0.14	98.86	8.25
Example 24	84	0.16	88.24	6.48
Example 25	136	0.08	76.40	7.2
Example 26	119	0.10	98.80	7.02
Example 27	112	0.05	95.50	6.9
Example 28	123	0.04	98.80	7.14
Example 29	149	0.02	89.70	7.05
Example 30	110	0.05	90.30	7.08
Example 31	116	0.11	99.10	7.1
Example 32	118	0.03	98.10	7.41
Example 33	126	0.07	96.60	7.23
Example 34	119	0.06	98.30	6.87
Example 35	115	0.06	86.13	7.4
Example 36	108	0.06	99.24	7.93
Example 37	92	0.02	97.85	7.62
Example 38	124	0.06	94.55	8.3
Example 39	92	0.01	95.57	6.56
Example 40	96	0.09	89.26	6.58
Example 41	99	0.09	93.09	6.64
Example 42	95	0.02	92.55	6.88
Example 43	102	0.04	91.70	5.91
Example 44	92	0.01	95.66	6.07
Example 45	94	0.09	95.60	6.21
Example 46	106	0.03	93.70	7.26
Example 47	96	0.06	94.72	7.37
Example 48	102	0.04	89.51	7.27
Example 49	87	0.02	96.18	8.1
Example 50	84	0.05	96.60	8.14
Example 51	86	0.04	97.21	8.17
Example 52	88	0.02	96.47	7.93
Example 53	115	0.03	97.24	8.88
Example 54	96	0.05	96.46	8.23
Example 55	82	0.02	97.82	8.32
Example 56	91	0.02	96.84	8.8
Example 57	76	0.05	97.41	8.13
Example 58	100	0.04	96.99	8.53
Example 59	101	0.03	96.50	8.25
Example 60	82	0.04	97.60	8.3

Example 61	81	0.05	97.69	8.42
Example 62	81	0.05	96.20	8.15
Example 63	79	0.05	97.19	8.11
Example 64	81	0.04	97.48	8.31
Example 65	87	0.03	97.21	8.12
Example 66	90	0.04	97.24	8.51
Example 67	88	0.05	97.28	8.24
Example 68	75	0.07	95.15	NA
Example 69	73	0.05	95.58	—
Example 70	78	0.06	95.90	—
Example 71	67	0.06	97.06	—
Example 72	73	0.05	96.64	—
Example 73	89	0.18	97.03	—
Example 74	89	0.03	95.78	—
Example 75	72	0.05	95.79	—
Example 76	78	0.06	94.01	—
Example 77	83	0.06	94.72	—
Example 78	70	0.10	97.05	—
Example 79	85	0.04	94.90	—
Example 80	65	0.07	97.18	—
Example 81	74	0.09	97.17	—
Example 82	69	0.06	96.90	—
Example 83	67	0.07	97.73	—
Example 84	67	0.04	96.98	—
Example 85	61	0.05	97.36	—
Example 86	65	0.05	97.48	—
Example 87	72	0.04	97.39	—
Example 88	75	0.04	97.57	—
Example 89	72	0.07	97.56	—

[0694] In vitro LNP studies

[0695] RAW 264.7 cells and HepG2 cells were seeded in the 96-well plates at a density of 50000 cells/well and cultured in 100 μ L DMEM media supplemented with 10% fetal bovine serum for 24 h. 10 μ L LNPs were added and diluted to final mRNA concentration at 1 μ g/mL. LipofectamineTM MessengerMAXTM Reagent (ThermoFisher SCIENTIFIC) was used as control to transfect the same concentration of mRNA. After incubation for 24 h, 100 μ L One-Glo reagent (ONE-GloTM Luciferase Assay System, Promega Corporation) was added and treated for 10 min. The luminescence intensity was measured by a luminescence plate reader (SYNERGY neo2, BioTek). The relative luminescence intensity was obtained by dividing the LNP luminescence value by the Lipofectamine luminescence value and the results were shown in FIG. 4 and Table 2. Luminescence

[0696] Table 2

Lipid	Lipid/MC3 ratio on HepG 2	Lipid/MC3 ratio on CD14+
	cells	monocytes
Example 1	1.0	6.4
Example 2	0.7	6.3
Example 3	1.7	32.3
Example 6	1.7	14.5
Example 15	0.3	16.9
Example 16	0.1	11.8
Example 17	0.7	16.7
Example 18	0.5	2.9
Example 20	0.4	26.7
Example 22	0.5	8.6
Example 23	0.0	2.2
Example 35	0.8	0.8
Example 37	1.1	2.6
Example 39	0.2	0.9
Example 40	1.1	1.8
Example 41	1.1	2.2
Example 42	0.3	1.8
Example 43	1.3	1.9
Example 44	0.1	1.2
Example 45	0.2	2.0
Example 47	0.8	2.0
Example 48	0.5	1.2
Example 49	0.4	3.4
Example 51	0.6	0.8
Example 54	0.1	0.9
Example 56	0.9	0.8
Example 62	0.6	1.9

[0697] In vivo Luc expression

[0698] Luc mRNA LNPs were injected via the tail vein of female C57BL/6 mice (18-22 g) at a dose of 0.3 mg/kg. After 4hours, the mice were injected intraperitoneally with D-Luciferin at a dose of 150 mg/kg. After 15 minutes, mice were sacrificed and the organs were isolated (heart, liver, spleen, lungs, kidneys) and imaged with an IVIS imaging system (Perkin Elmer, Waltham, MA) . Luminescence was quantified using LivingImage software (Perkin Elmer) . Luminescence generated by luciferase expressed in liver and spleen upon administration of formulations including compounds according to Formula (I) relative to formulation including MC3 were shown in Table 3.

[0699] Table 3

Lipid	Lipid/MC3 ratio in liver (Average radiance)	Lipid/MC3 ratio in spleen (Average radiance)
MC3	1	1
Example 3	0.16	1.77
Example 4	0.08	0.88

Example 6	0.23	0.80
Example 17	0.14	1.75
Example 18	0.11	1.02
Example 20	0.24	1.99
Example 22	0.14	1.43
Example 26	0.37	2.53
Example 27	0.15	2.76
Example 31	0.35	1.47
Example 32	0.29	2.56
Example 33	0.29	2.64
Example 34	0.34	2.02
Example 36	0.24	3.10
Example 37	0.61	12.12
Example 39	0.90	6.44
Example 40	1.07	11.63
Example 41	0.79	13.27
Example 42	1.30	10.45
Example 43	1.10	6.09
Example 44	1.43	8.84
Example 45	0.56	11.13
Example 46	1.21	21.13
Example 47	0.77	7.69
Example 48	1.45	10.84
Example 49	0.29	5.42
Example 50	0.36	5.30
Example 51	0.25	6.67
Example 52	0.32	2.66
Example 54	0.32	7.29
Example 55	0.28	10.91
Example 56	0.37	8.15
Example 57	0.48	7.99
Example 58	0.32	11.57
Example 59	0.47	13.25
Example 60	0.29	8.63
Example 61	0.25	4.92
Example 62	0.33	11.59
Example 63	0.32	6.20
Example 64	0.19	3.44
Example 65	0.19	3.54
Example 66	0.19	5.30
Example 67	0.24	7.00

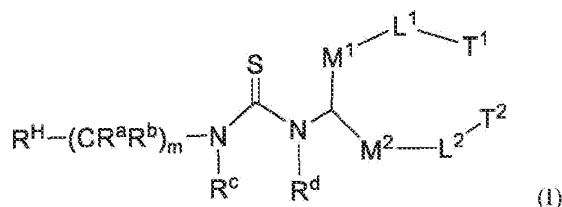
[0700] In vivo T cell response assay

- [0701] Groups of C57BL/6 mice were injected with 15 μ g LNP-loaded OVA mRNA intramuscularly. After 7 days, naive C57BL/6 mice were killed and splenocytes were collected. Grind the spleen on a 70 μ m cell strainer, rinse the strainer with 10-15ml of MACS buffer. After grinding, centrifuge at 300g for 5 minutes and discard the supernatant. Mix the cell pellet evenly, add 5ml of red blood cell lysis buffer, lyse for 5 minutes, then add 10ml of MACS buffer to stop the lysis. Filter the solution through a 40 μ m cell strainer, centrifuge at 300g for 5 minutes, discard the supernatant, and resuspend the cells in 10 mL of RPMI 1640 complete media. ELISPOT plate was prepared by washing 5 times with 200 μ L PBS, then block with 200 μ L of RPMI1640 complete medium for 30 minutes at 37°C. Add 100 μ L OVA peptide (20 μ g/mL) or positive control (2X) into blocked ELISpot plate according to the grouping. Add 100 μ L splenocytes (1×10^6 cells/mL) into the corresponding wells and culture the cells for 18-24h. Then, remove the medium and wash the plate 5 times with PBS (200 μ L/well). Add 100 μ L detection antibody (anti-mouse IFN- γ , 1 μ g/mL in PBS containing 0.5%FBS) to each well and incubate for 2 hours at room temperature. Then, wash plate as above. Add Streptavidin-ALP (1: 1000) in PBS containing 0.5%FBS at 100 μ L/well and incubate for 1 hour at room temperature. Wash the plate as above. Add the ready-to-use substrate solution (BCIP/NBT plus) at 100 μ L/well. Stop color development by washing extensively with water. Leave the plate to dry. Plates were scanned using an ELISpot reader (CTL ImmunoSpot Series S five Versa ELISpot Analyzer (S5Versa-02-9038)). T cell response upon administration of formulations including compounds according to Formula (I) relative to formulation including SM102 were shown in FIG. 5.
- [0702] It is to be understood that, if any prior art publication is referred to herein; such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country.
- [0703] The disclosures of all publications, patents, patent applications and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.
- [0704] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

Claims

[Claim 1]

A compound of Formula (I) :



or a pharmaceutically acceptable salt thereof, or a stereoisomer, a tautomer or a geometric isomer thereof,

R^H is $-N(R^1R^2)$, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein each of said cycloalkyl, aryl, heteroaryl, or heterocyclyl is independently unsubstituted or substituted with one, two or three substituents R^{Ha} ;

R^{Ha} is C_{1-12} alkyl, or $-OH$; wherein said C_{1-12} alkyl is independently unsubstituted or substituted with F , $-OR$, $-CO_2R$, $-SR$, or $-C_{1-6}$ alkyl;

R^1 and R^2 are each independently H or C_{1-12} alkyl or R^1 and R^2 , together with the nitrogen atom to which they attach, form a 4-to 9-membered heterocyclyl comprising 0 or 1 heteroatom selected from oxygen, nitrogen or sulfur, or a 5-to 9-membered heteroaryl comprising 0, 1, or 2 heteroatom selected from oxygen, nitrogen or sulfur; and

each R^a is independently selected from H or C_{1-6} alkyl;

each R^b is independently selected from H or C_{1-6} alkyl;

m is an integer ranging from 1 to 15;

R^c and R^d are each independently selected from H or C_{1-6} alkyl; each of said C_{1-6} alkyl is independently substituted with one, two or three R^M ;

M^1 and M^2 are each independently a single bond, C_{1-18} alkylene or C_{2-18} alkenylene; wherein one or two methylene units of the C_{1-18} alkylene or C_{2-18} alkenylene are optionally and independently replaced by L^{m1} or L^{m2} ; wherein each of said C_{1-18} alkylene or C_{2-18} alkenylene is independently unsubstituted or substituted with one, two or three R^M ;

L^1 and L^2 are independently selected from a single bond, $-C(=O)O-$, $-OC(=O)O-$, $-OC(=O)C(=O)O-$, $-C(=O)S-$, $-C(=S)O-$, $-C(=S)S-$, $-OC(=O)-$, $-OC(=S)-$, $-SC(=O)-$, $-SC(=S)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-S-$, $-NR^L-$, $-C(=O)NR^L-$, $-C(=S)NR^L-$, $-NR^LC(=O)-$, $-NR^LC$

(=S) -, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -OC(=O)NR^L-, -OC(=S)NR^L-, -SC(=S)NR^L-, -SC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=S)O-, -NR^LC(=S)S-, -NR^LC(=O)S-, -CH(OH)-, -CH(SH)-, -P(=O)(OR^L)O-, -S(O)-, -S(O)₂-, -S-S-, a cycloalkylene group, an arylene group, a heteroarylene group and a heterocyclylene group;

R^L is H or C₁₋₁₂alkyl; and

T¹, and T² are each independently C₁₋₂₄alkyl, C₂₋₂₄alkenyl or C₂₋₂₄alkynyl; wherein one or two methylene units of the C₁₋₂₄alkyl, C₂₋₂₄alkenyl or C₂₋₂₄alkynyl are optionally and independently replaced by L^{m1} or L^{m2}; wherein each of said C₁₋₁₂alkylene or C₂₋₁₂alkenylene is independently substituted with one, two or three R^M;

L^{m1} and L^{m2} are independently selected from a single bond, -C(=O)O-, -OC(=O)O-, -OC(=O)C(=O)O-, -C(=O)S-, -C(=S)O-, -C(=S)S-, -OC(=O)-, -OC(=S)-, -SC(=O)-, -SC(=S)-, -C(=O)-, -C(=S)-, -O-, -S-, -NR^{ml}-, -C(=O)NR^{ml}-, -C(=S)NR^L-, -NR^{ml}C(=O)-, -NR^{ml}C(=S)-, -NR^{ml}C(=O)NR^{ml}-, -NR^{ml}C(=S)NR^{ml}-, -OC(=O)NR^{ml}-, -OC(=S)NR^{ml}-, -SC(=S)NR^{ml}-, -SC(=O)NR^{ml}-, -NR^{ml}C(=O)O-, -NR^{ml}C(=S)O-, -NR^{ml}C(=S)S-, -NR^{ml}C(=O)S-, -CH(OH)-, -CH(SH)-, -P(=O)(OR^{ml})O-, -S(O)-, -S(O)₂-, -S-S-, a cycloalkylene group, an arylene group, a heteroarylene group and a heterocyclylene group;

R^{ml} is H or C₁₋₁₂alkyl;

R^M is F, -OR, -CO₂R, -SR, -C₁₋₆alkyl, cycloalkyl, or heterocyclyl;

R is hydrogen, or C₁₋₆alkyl optionally substituted with one, two or three substituents selected from F, cycloalkyl, or heterocyclyl.

[Claim 2]

The compound of claim 1, wherein R^H is -N(R¹R²).

[Claim 3]

The compound of claim 1 or claim 2, wherein

R^H is -N(R¹R²); and R¹ and R² are each independently H or C₁₋₄alkyl;

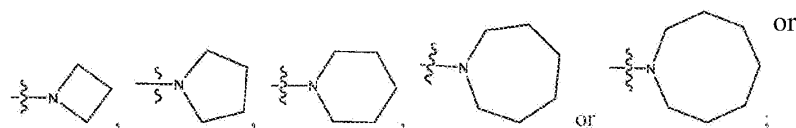
preferably R¹ and R² are each independently methyl, or ethyl;

more preferably R¹ and R² are each independently methyl; or

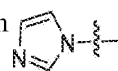
R^H is -N(R¹R²); and R¹ and R², together with the nitrogen atom to which they attach, form a 4-to 8-membered heterocyclyl comprising 0 or 1 heteroatom selected from oxygen, nitrogen or sulfur;

preferably R^H is -N(R¹R²); and R¹ and R², together with the nitrogen atom to which they attach, form a 4-, 5-, 6-, 7- or 8-membered heterocyclyl;

more preferably R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form



R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 5-to 8-membered heteroaryl comprising 0, 1, or 2 heteroatom selected from oxygen, nitrogen or sulfur; preferably R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form a 5-, 6-, 7-or 8-membered heteroaryl; more preferably R^H is $-N(R^1R^2)$; and R^1 and R^2 , together with the nitrogen atom to which they attach, form



- [Claim 4] The compound of any one of claims 1-3, wherein R^a and R^b are each H; or m is 2 or 3 and R^a and R^b are each H.
- [Claim 5] The compound of any one of claims 1-3, wherein the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or C_{1-6} alkyl and R^a and R^b are not both H; or the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or C_{1-6} alkyl; or the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H, methyl or ethyl; or the moiety $-(CR^aR^b)_m-$ is $-(CH_2-CR^aR^b)-$, $-(CR^aR^b-CH_2)-$, $-(CH_2-CH_2-CR^aR^b)-$, $-(CH_2-CR^aR^b-CH_2)-$ or $-(CR^aR^b-CH_2-CH_2)-$, wherein R^a and R^b are H or methyl.
- [Claim 6] The compound of any one of claims 1-5, wherein R^c is H or C_{1-4} alkyl; preferably R^c is H, methyl, or ethyl.
- [Claim 7] The compound of any one of claims 1-6, wherein R^d is H or C_{1-4} alkyl; preferably R^d is H, methyl, or ethyl.
- [Claim 8] The compound of any one of claims 1-7, wherein M^1 and M^2 are each independently C_{4-12} alkylene or C_{4-12} alkenylene;

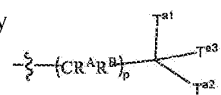
preferably M^1 and M^2 are each independently C_4 alkylene, C_5 alkylene, C_6 alkylene, C_7 alkylene, C_8 alkylene, C_9 alkylene, C_{10} alkylene, C_{11} alkylene, C_{12} alkylene, C_4 alkenylene, C_5 alkenylene, C_6 alkenylene, C_7 alkenylene, C_8 alkenylene, C_9 alkenylene, C_{10} alkenylene, C_{11} alkenylene, C_{12} alkenylene, C_5 alkadienylene, C_6 alkadienylene, C_7 alkadienylene, C_8 alkadienylene, C_9 alkadienylene, C_{10} alkadienylene, C_{11} alkadienylene, or C_{12} alkadienylene.

[Claim 9] The compound of any one of claims 1-8, wherein L^1 and L^2 are independently selected from a single bond, $-C(=O)O-$, $-C(=O)S-$, $-C(=S)O-$, $-C(=S)S-$, $-OC(=O)-$, $-OC(=S)-$, $-SC(=O)-$, $-SC(=S)-$, $-C(=O)-$, $-C(=S)-$, $-O-$, $-S-$, $-OC(=O)O-$, $-OC(=O)C(=O)O-$, $-P(=O)(OR^1)O-$, or $-S-S-$; preferably L^1 and L^2 are independently a single bond.

[Claim 10] The compound of claim 1, wherein L^1 and L^2 are independently $-C(=O)O-$, or $-OC(=O)-$.

[Claim 11] The compound of any one of claims 1-10, wherein T^1 and T^2 are each independently C_{6-12} alkyl or C_{6-12} alkenyl; preferably T^1 and T^2 are each independently C_6 alkyl, C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_6 alkenyl, C_7 alkenyl, C_8 alkenyl, C_9 alkenyl, C_{10} alkenyl, C_{11} alkenyl, C_{12} alkenyl, C_6 alkadienyl, C_7 alkadienyl, C_8 alkadienyl, C_9 alkadienyl, C_{10} alkadienyl, C_{11} alkadienyl, or C_{12} alkadienyl.

[Claim 12] The compound of any one of claims 1 to 10, wherein T^1 and T^2 are each independently



wherein

R^A and R^B are each independently selected from H or C_{1-6} alkyl;

p is an integer ranging from 0 to 12;

T^{a1} is H or C_{1-6} alkyl;

T^{a2} and T^{a3} are each independently C_{1-12} alkyl, C_{2-12} alkenyl or C_{2-12} alkynyl;

provided that the variables R^A , R^B , p , T^{a1} , T^{a2} , and T^{a3} are each selected such that T^1 and T^2 are each independently C_{6-24} alkyl, C_{6-24} alkenyl, or C_{6-24} alkynyl.

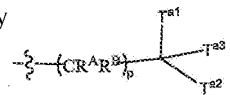
[Claim 13] The compound of claim 12, wherein p is 0.

- [Claim 14] The compound of claim 12, wherein p is 1.
- [Claim 15] The compound of any one of claims 12-14, wherein
 T^{a1} is H and T^{a2} and T^{a3} are each independently C_{4-12} alkyl or C_{4-12} alkenyl; or
 T^{a1} is H and T^{a2} and T^{a3} are each independently C_{4-12} alkyl or C_{4-12} alkadienyl; or
 T^{a1} is H, T^{a2} is C_{3-12} alkyl and T^{a3} is C_{3-12} alkenyl; or
 T^{a1} is H, T^{a2} is C_{3-12} alkyl and T^{a3} is C_{3-12} alkadienyl.
- [Claim 16] The compound of any one of claims 1-15, wherein
 M^1 and M^2 are each independently C_{3-12} alkylene or C_{3-12} alkenylene; L^1 and L^2 are independently a single bond; and T^1 and T^2 are each independently C_{6-12} alkyl or C_{6-12} alkenyl;
preferably M^1 and M^2 are each independently C_4 alkylene, C_5 alkylene, C_6 alkylene, C_7 alkylene, C_8 alkylene, C_9 alkylene, C_{10} alkylene, C_{11} alkylene, C_{12} alkylene, C_4 alkenylene, C_5 alkenylene, C_6 alkenylene, C_7 alkenylene, C_8 alkenylene, C_9 alkenylene, C_{10} alkenylene, C_{11} alkenylene, C_{12} alkenylene, C_5 alkadienylene, C_6 alkadienylene, C_7 alkadienylene, C_8 alkadienylene, C_9 alkadienylene, C_{10} alkadienylene, C_{11} alkadienylene, or C_{12} alkadienylene; and T^1 and T^2 are each independently C_6 alkyl, C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_6 alkenyl, C_7 alkenyl, C_8 alkenyl, C_9 alkenyl, C_{10} alkenyl, C_{11} alkenyl, C_{12} alkenyl, C_6 alkadienyl, C_7 alkadienyl, C_8 alkadienyl, C_9 alkadienyl, C_{10} alkadienyl, C_{11} alkadienyl, or C_{12} alkadienyl.
- [Claim 17] The compound of any one of claims 1-15, wherein
 M^1 and M^2 are each independently C_{3-12} alkylene or C_{3-12} alkenylene; L^1 and L^2 are independently -C(=O)O-, or -OC(=O)-; and T^1 and T^2 are each independently C_{6-12} alkyl or C_{6-12} alkenyl;
preferably M^1 and M^2 are each independently C_4 alkylene, C_5 alkylene, C_6 alkylene, C_7 alkylene, C_8 alkylene, C_9 alkylene, C_{10} alkylene, C_{11} alkylene, C_{12} alkylene, C_4 alkenylene, C_5 alkenylene, C_6 alkenylene, C_7 alkenylene, C_8 alkenylene, C_9 alkenylene, C_{10} alkenylene, C_{11} alkenylene, C_{12} alkenylene, C_5 alkadienylene, C_6 alkadienylene, C_7 alkadienylene, C_8 alkadienylene, C_9 alkadienylene, C_{10} alkadienylene, C_{11} alkadienylene, or C_{12} alkadienylene; and T^1 and T^2 are each independently C_6 alkyl, C_7 alkyl, C_8 alkyl, C_9 alkyl, C_{10} alkyl, C_{11} alkyl, C_{12} alkyl, C_6 alkenyl, C_7 alkenyl, C_8 alkenyl, C_9 alkenyl, C_{10} alkenyl,

C₁₁alkenyl, C₁₂alkenyl, C₆alkadienyl, C₇alkadienyl, C₈alkadienyl, C₉alkadienyl, C₁₀alkadienyl, C₁₁alkadienyl, or C₁₂alkadienyl.

[Claim 18]

The compound of any one of claims 1-15, wherein M¹ and M² are each independently C₄₋₁₂alkylene or C₄₋₁₂alkenylene; L¹ and L² are independently -C(=O)O-, or -OC(=O)-; and T¹ and T² are each independently



[Claim 19]

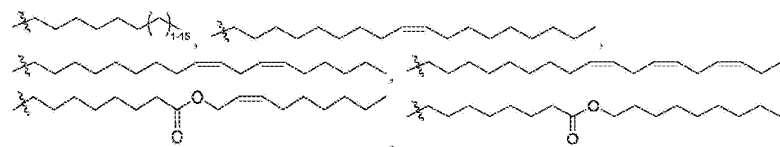
The compound of any one of claims 1-15, wherein the moiety -M²-L²-T², or -M¹-L¹-T¹ is decanyl, undecanyl, dodecanyl, tridecanyl, tetradecanyl, heptadecanyl, octadecanyl, decenyl, decadienyl, undecenyl, undecadienyl, dodecenyl, dodecadienyl, tridecanyl, tridecenyl, tridecedienyl, tetradecenyl, tetradecadienyl, heptadecenyl, heptadecadienyl, octadecaenyl, or octadecadienyl.

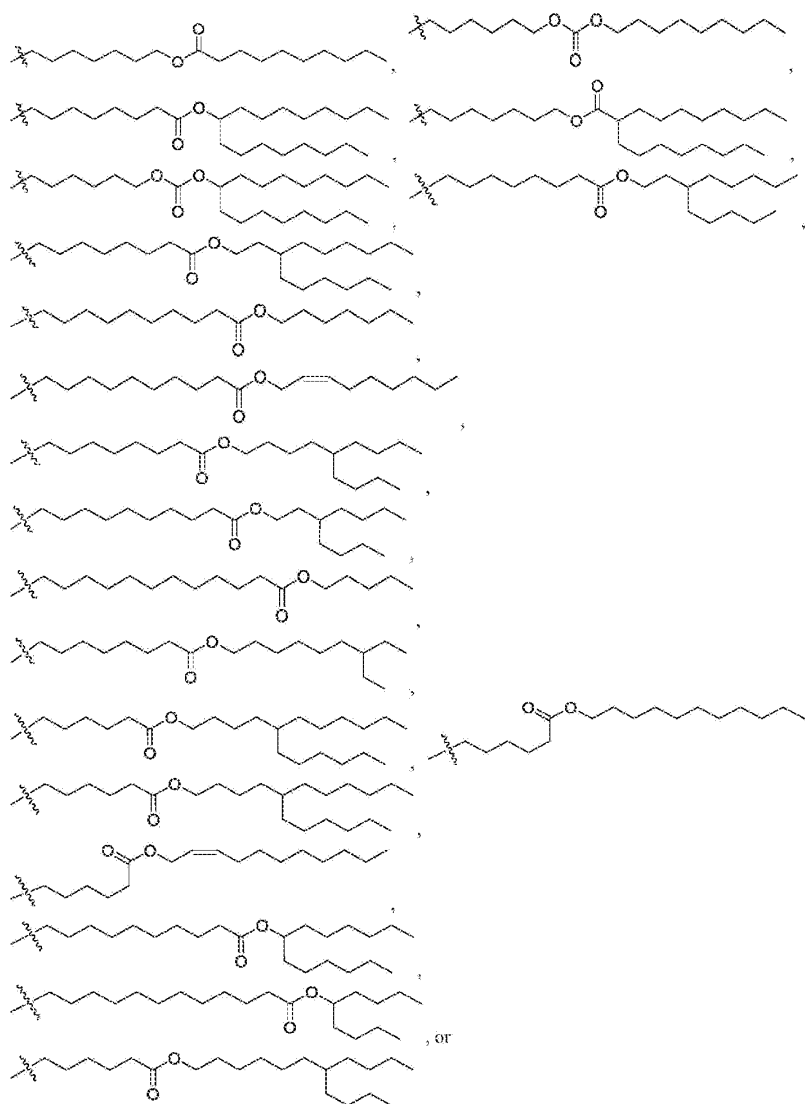
[Claim 20]

The compound of any one of claims 1-15, wherein the moiety -M²-L²-T², or -M¹-L¹-T¹ is decan-2-yl, undecan-3-yl, dodecan-4-yl, tridecan-5-yl, tetradecan-6-yl, 2-methylundecan-3-yl, 2-methyldecan-2-yl, 3-methylundecan-3-yl, 4-methyldodecan-4-yl, or heptadeca-9-yl.

[Claim 21]

The compound of any one of claims 1-15, wherein the moiety -M²-L²-T², or -M¹-L¹-T¹ is

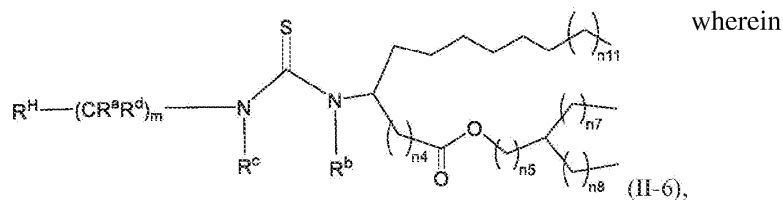
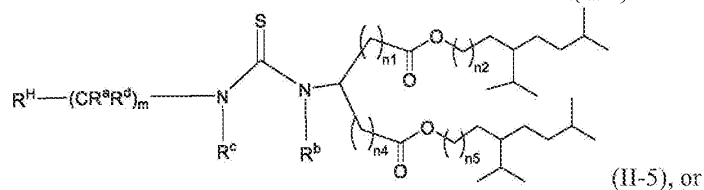
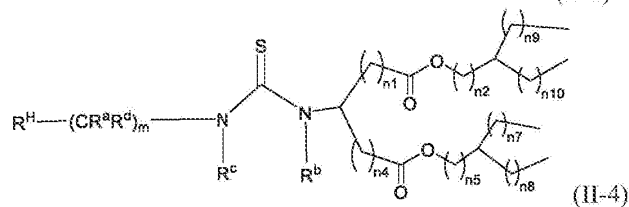
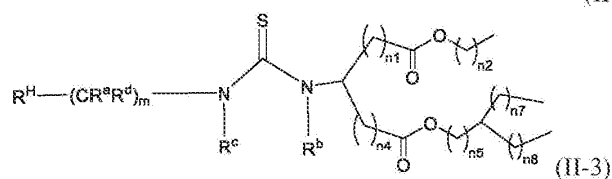
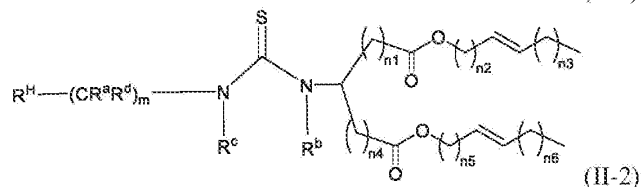
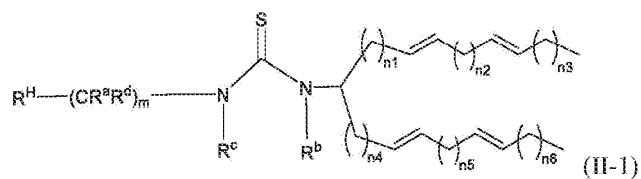




[Claim 22]

The compound of claim 1, wherein a compound of Formula (II-1) - (II-6) :

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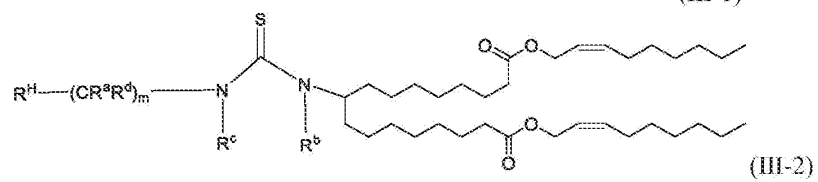
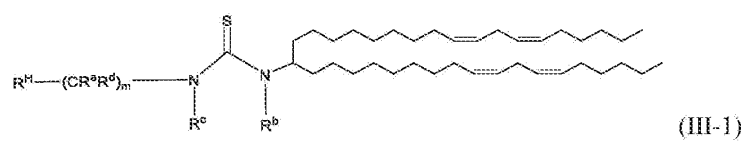
m is an integer ranging from 1 to 15;

$n1, n2, n3, n4, n5, n6, n7, n8, n9, n10,$ and $n11$ are each independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18.

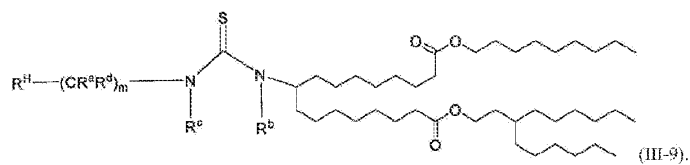
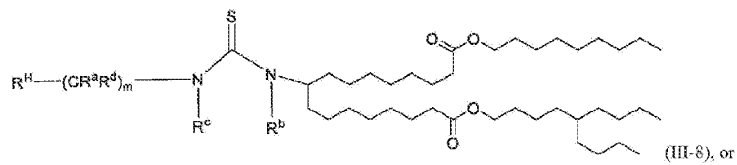
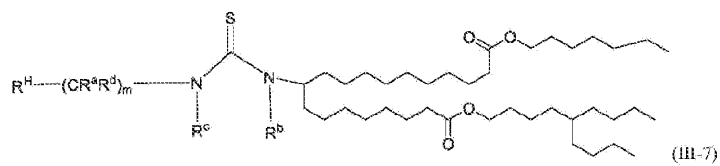
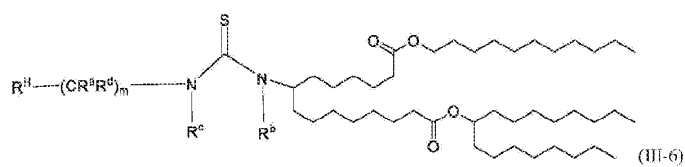
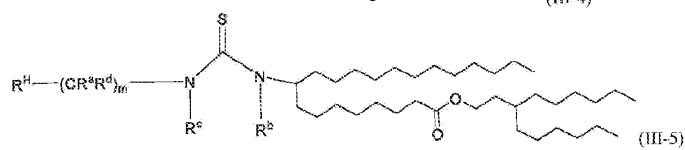
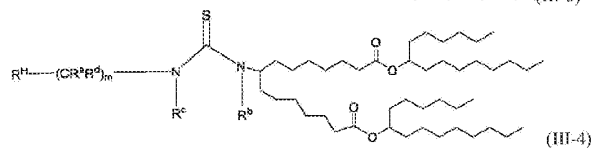
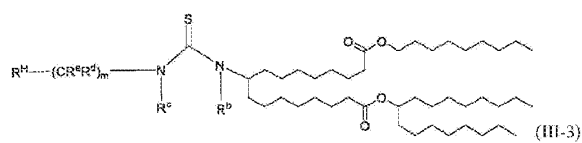
[Claim 23]

The compound of claim 1, selected from Formula (III-1) - (III-9) :

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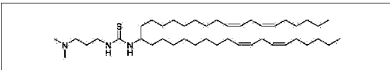
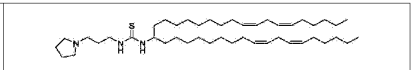
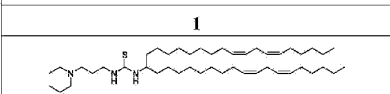
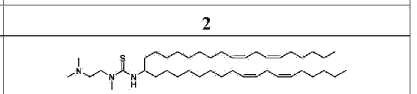
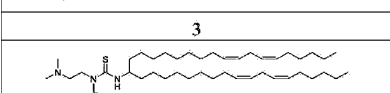
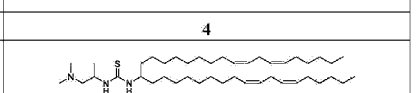
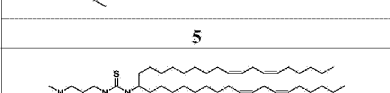
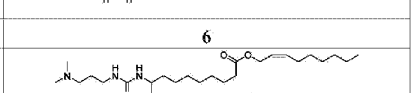
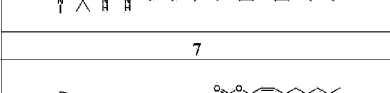
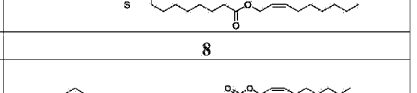
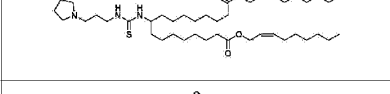
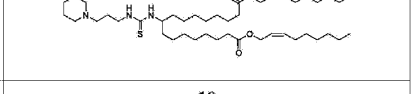
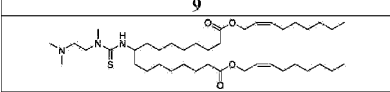
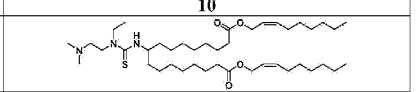
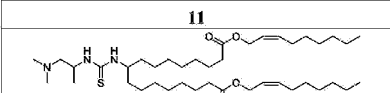
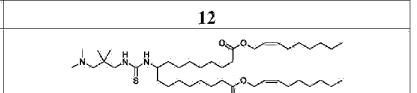
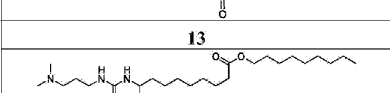
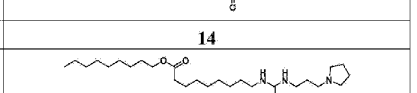
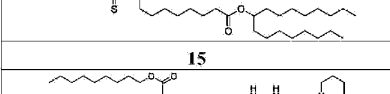
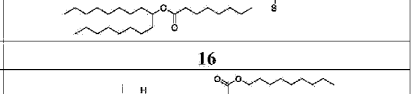
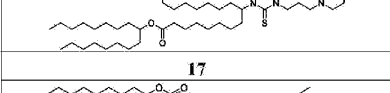
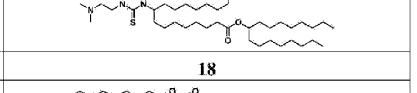
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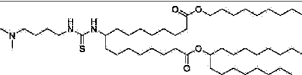
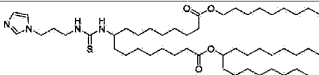
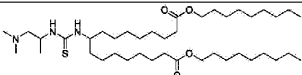
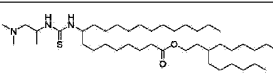
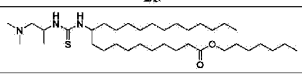
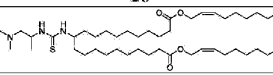
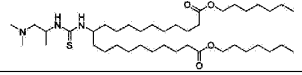
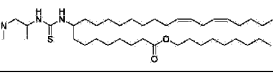
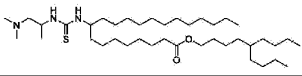
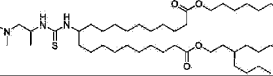
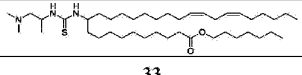
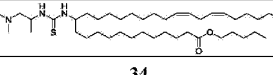
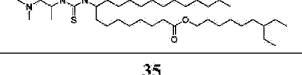
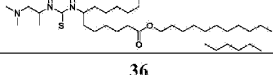
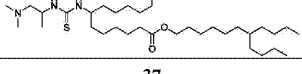
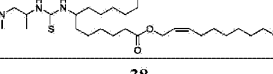
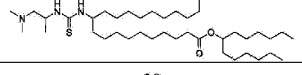
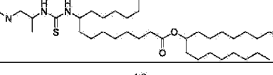
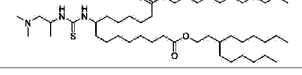
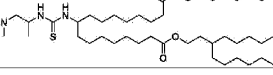
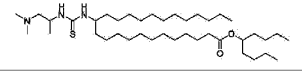
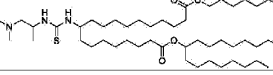
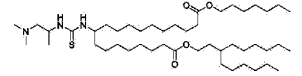
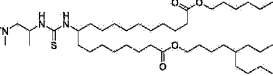


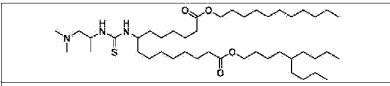
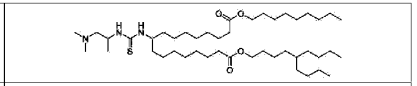
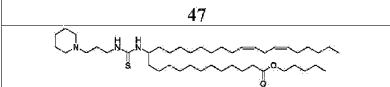
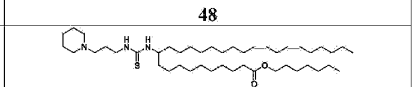
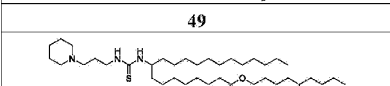
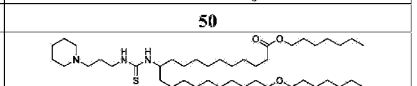
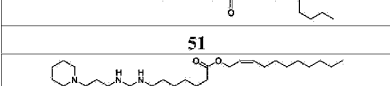
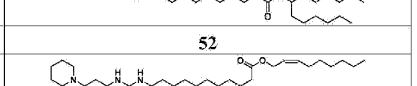
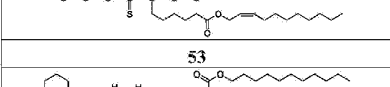
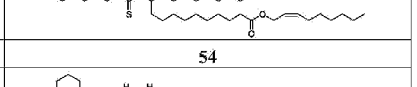
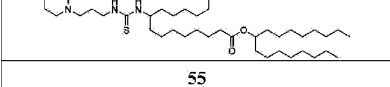
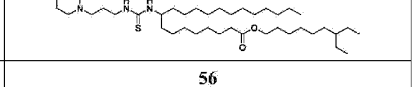
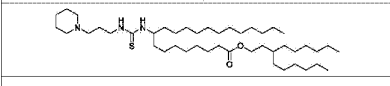
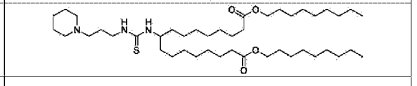
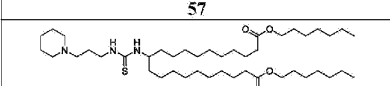
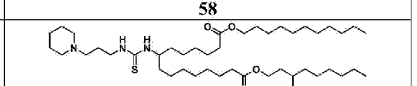
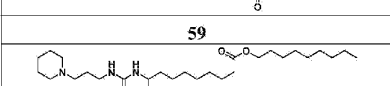
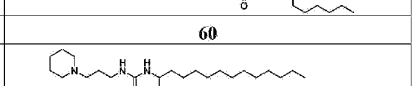
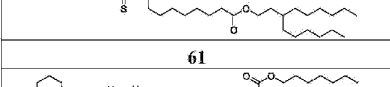
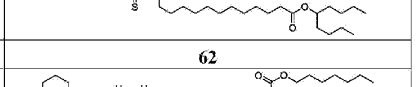
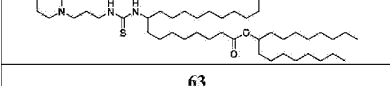
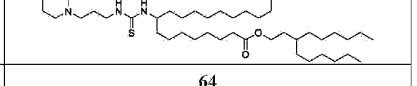
[Claim 24]

A compound selected from the group consisting of:

Rule 26,
27.12.2024

	
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- [Claim 25]

A pharmaceutical composition comprising the compounds of any one of claims 1-24 and a therapeutic and/or prophylactics agent.
- [Claim 26]

The pharmaceutical composition of claim 25, wherein the pharmaceutical compositions further comprise one or more components selected from phospholipids, structural lipids, and polymer conjugated lipids to form lipid nanoparticles (LNP) for the delivery of the therapeutic and/or prophylactics agent.
- [Claim 27]

The pharmaceutical composition of claim 25 or 26, wherein the therapeutic and/or prophylactics agent is a nucleic acid; preferably, the therapeutic and/or prophylactic agent is mRNA vaccine.

- [Claim 28] A method for administering a therapeutic agent to a patient in need thereof, the method comprising preparing a composition of lipid nanoparticles comprising the compound of any one of claims 1 to 24 and a therapeutic and/or prophylactics agent and delivering the composition to the patient.
- [Claim 29] The method of claim 28, wherein the therapeutic agent is a nucleic acid.