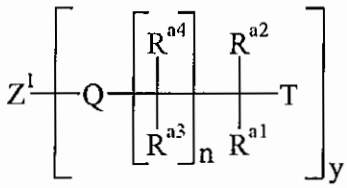
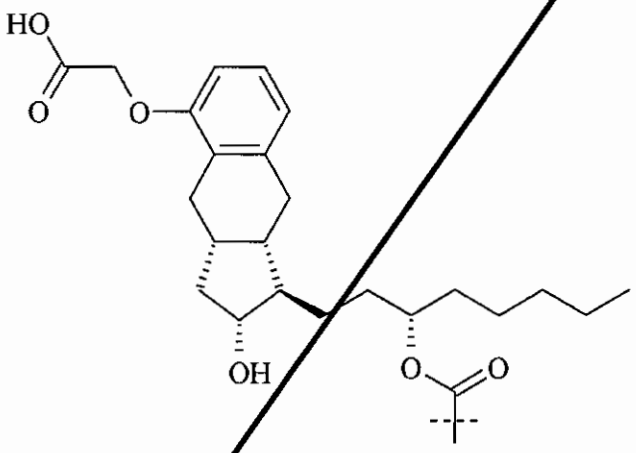
Claims

1. A carrier-linked treprostinil prodrug of formula (II):

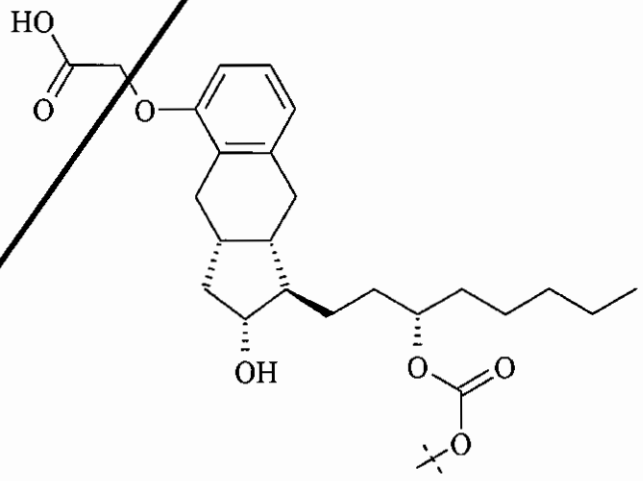


(II),

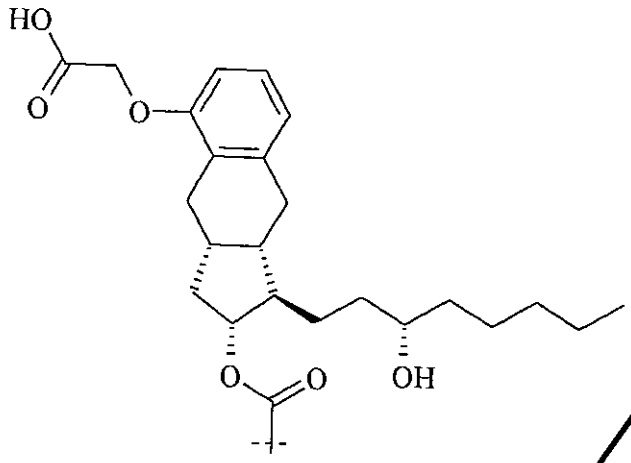
wherein each T is independently selected from structures (i) to (v):



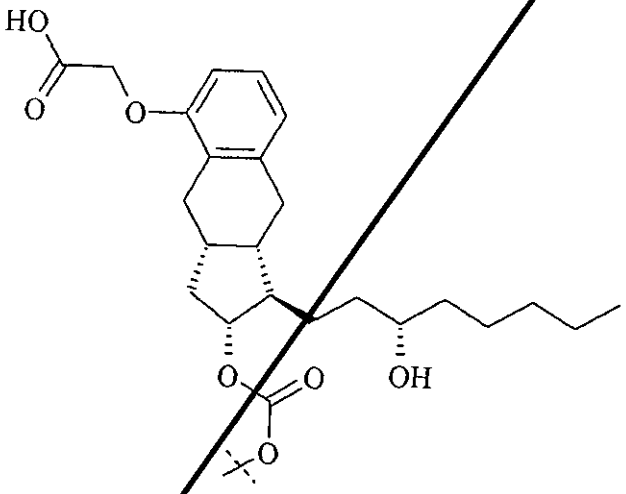
(i),



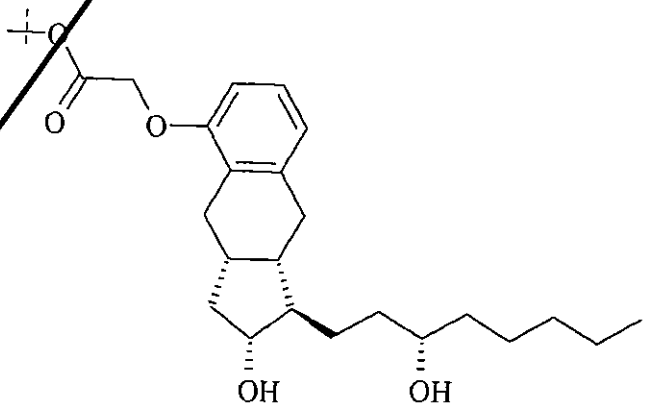
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to the rest of the molecule;

y is an integer ranging of from 1 to 64, preferably ranging from 1 to 16, more preferably y is selected from 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, 12, 13, 14, 15 and 16, even more preferably y is 8,

R^{a1} is selected from the group of unsubstituted alkyl; substituted alkyl; unsubstituted phenyl; substituted phenyl; unsubstituted naphthyl; substituted naphthyl; unsubstituted indenyl; substituted indenyl; unsubstituted indanyl; substituted indanyl; unsubstituted tetralinyl; substituted tetralinyl; unsubstituted C_{3-10} cycloalkyl; substituted C_{3-10} cycloalkyl; unsubstituted 4- to 7-membered heterocyclyl; substituted 4- to 7-membered heterocyclyl; unsubstituted 9- to 11-membered heterobicyclyl; and substituted 9- to 11-membered heterobicyclyl;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

R^{a3} and R^{a4} are independently selected from the group consisting of H, unsubstituted alkyl, and substituted alkyl;

n is 0 or 1;

Q is a spacer moiety;

optionally R^{a1} and R^{a3} are joined together with the atoms to which they are attached to form a ring A;

A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer;

or a pharmaceutical salt thereof.

2. The carrier-linked treprostinil prodrug of claim 1, wherein R^{a2} is H.

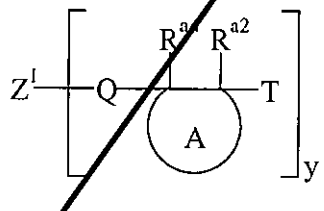
3. The carrier-linked treprostinil prodrug of claim 1 or 2, wherein R^{a4} is selected from H, C_{1-6} alkyl or substituted C_{1-6} alkyl, preferably R^{a4} is H.

4. The carrier-linked treprostinil prodrug of any one of claims 1 to 3, wherein R^{a1} and R^{a3} are joined together with the atoms to which they are attached to form a ring A; wherein A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted; more preferably ring A is selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, and cycloheptane, even more preferably ring A is cyclohexane.

5. The carrier-linked treprostinil prodrug of any one of claims 1 to 4, wherein T is selected from structure (iii).

6. The carrier-linked treprostinil prodrug of any one of claims 1 to 5, wherein y is 4, 6, 8, 10, or 12; preferably, 4, 6, or 8, more preferably y is 4.

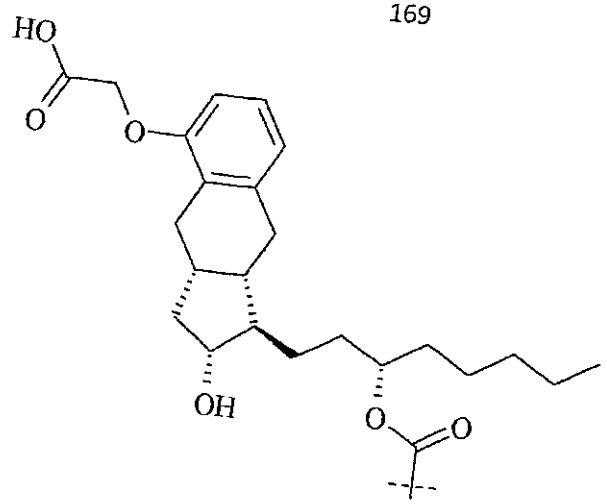
7. The carrier-linked treprostinil prodrug of any one of claims 1 to 6, wherein the carrier-linked treprostinil prodrug has the structure of formula (II-A):



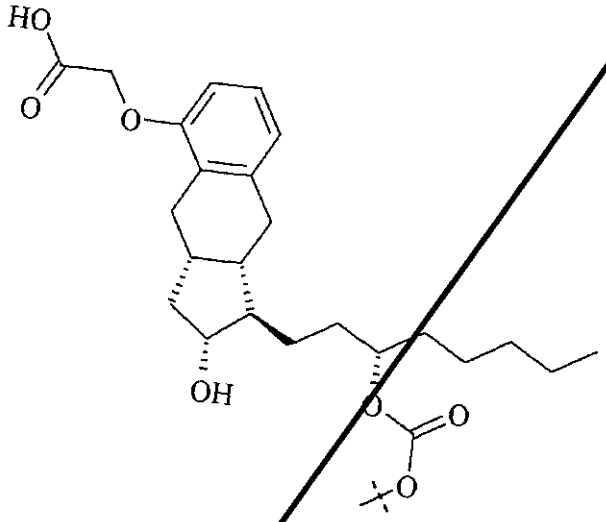
(II-A),

wherein

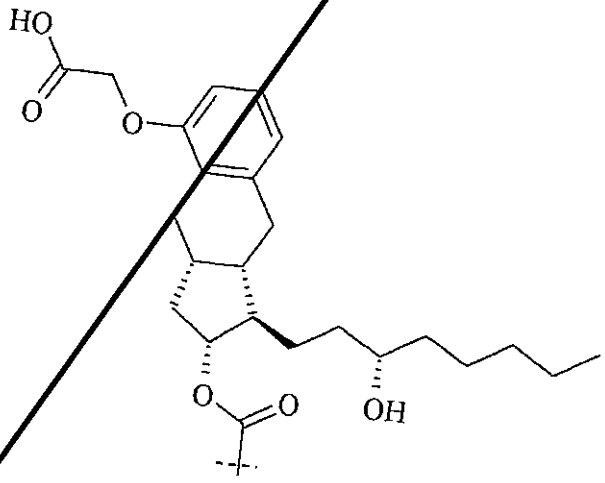
each T is independently selected from structures (i) to (v):



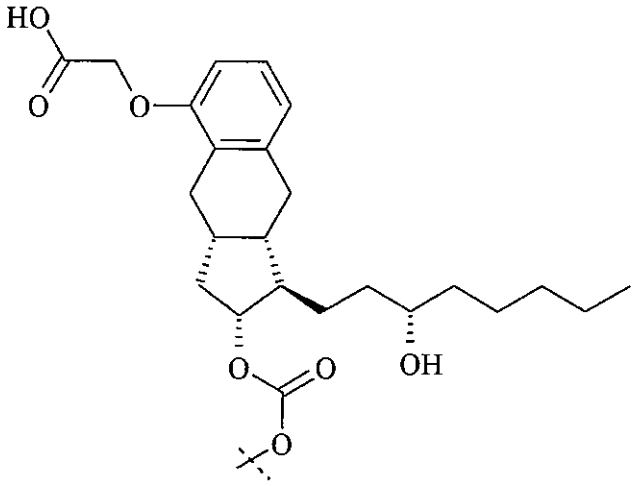
(i),



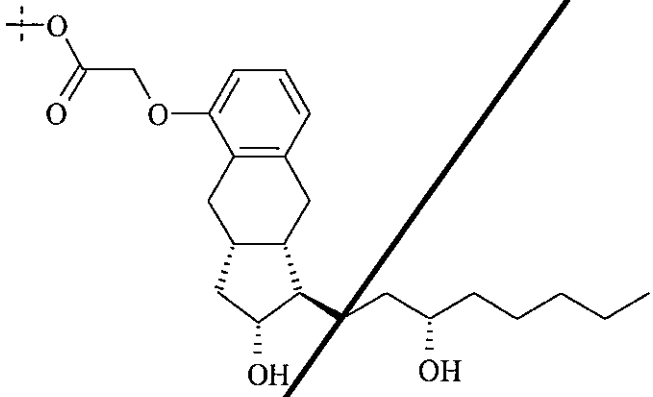
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to the rest of the molecule;

y is an integer ranging of from 1 to 64, preferably ranging from 1 to 16, more preferably y is selected from 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, 12, 13, 14, 15 and 16, even more preferably y is 4, 6, 8, 10 or 12; most preferably 4;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

R^{a4} is selected from the group consisting of H, unsubstituted alkyl, and substituted alkyl;

A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted;

Q is a spacer moiety;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

8. The carrier-linked treprostinil prodrug of any one of claims 1 to 7, wherein Q in formula (II) is selected from $COOR^{a9}$; OR^{a9}; $C(O)R^{a9}$; $C(O)N(R^{a9}R^{a9a})$; $S(O)_2N(R^{a9}R^{a9a})$; $S(O)N(R^{a9}R^{a9a})$; $S(O)_2R^{a9}$; $S(O)R^{a9}$; $N(R^{a9})S(O)_2N(R^{a9a}R^{a9b})$; SR^{a9}; $N(R^{a9}R^{a9a})$; $OC(O)R^{a9}$; $N(R^{a9})C(O)R^{a9a}$; $N(R^{a9})S(O)_2R^{a9a}$; $N(R^{a9})S(O)R^{a9a}$; $N(R^{a9})C(O)OR^{a9a}$; $N(R^{a9})C(O)N(R^{a9a}R^{a9b})$; $OC(O)N(R^{a9}R^{a9a})$; W; C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl, wherein W, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{a10}, which are the same or different, and wherein C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -W-, -C(O)O-; -O-; -C(O)-; -C(O)N(R^{a11})-; -$S(O)_2N(R^{a11})$-; -$S(O)N(R^{a11})$-; -$S(O)_2$-; -S(O)-; -$N(R^{a11})S(O)_2N(R^{a11a})$-; -S-; -$N(R^{a11})$-; -$OC(O)R^{a11}$; -$N(R^{a11})C(O)$-; -$N(R^{a11})S(O)_2$-; -$N(R^{a11})S(O)$-; -$N(R^{a11})C(O)O$-; -$N(R^{a11})C(O)N(R^{a11a})$-; and -$OC(O)N(R^{a11}R^{a11a})$;

R^{a9}, R^{a9a}, R^{a9b} are independently selected from the group consisting of H; W; and C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl, wherein W, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{a10}, which are the same or different, and wherein C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of W, -C(O)O-; -O-; -C(O)-; -C(O)N(R^{a11})-; -$S(O)_2N(R^{a11})$-; -$S(O)N(R^{a11})$-; -$S(O)_2$-; -S(O)-; -$N(R^{a11})S(O)_2N(R^{a11a})$-; -S-; -$N(R^{a11})$-; -$OC(O)R^{a11}$; -$N(R^{a11})C(O)$-; -$N(R^{a11})S(O)_2$-; -$N(R^{a11})S(O)$-; -$N(R^{a11})C(O)O$-; -$N(R^{a11})C(O)N(R^{a11a})$-; and -$OC(O)N(R^{a11}R^{a11a})$;

W is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered heterocyclyl; or 9- to 11-membered

heterobicyclyl, wherein W is optionally substituted with one or more R^{a10}, which are the same or different;

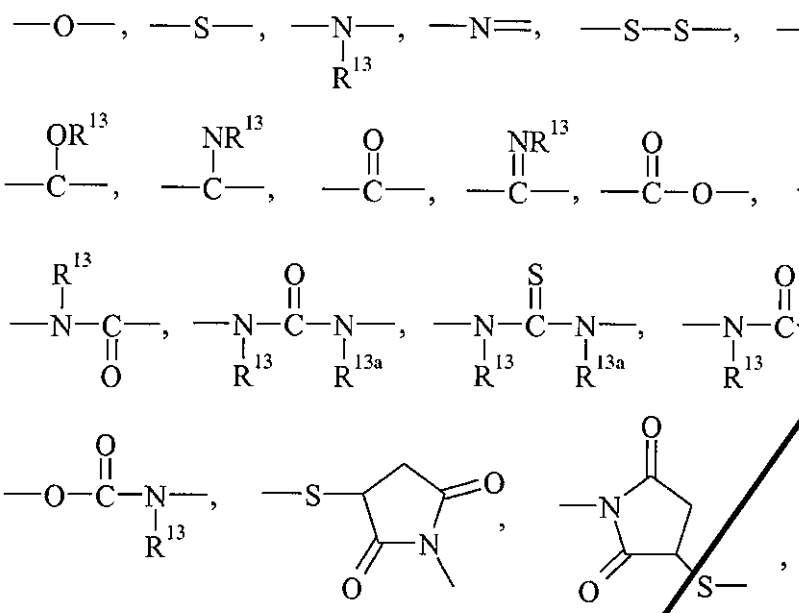
R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a11}, R^{a11a}, R^{a12}, R^{a12a}, R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

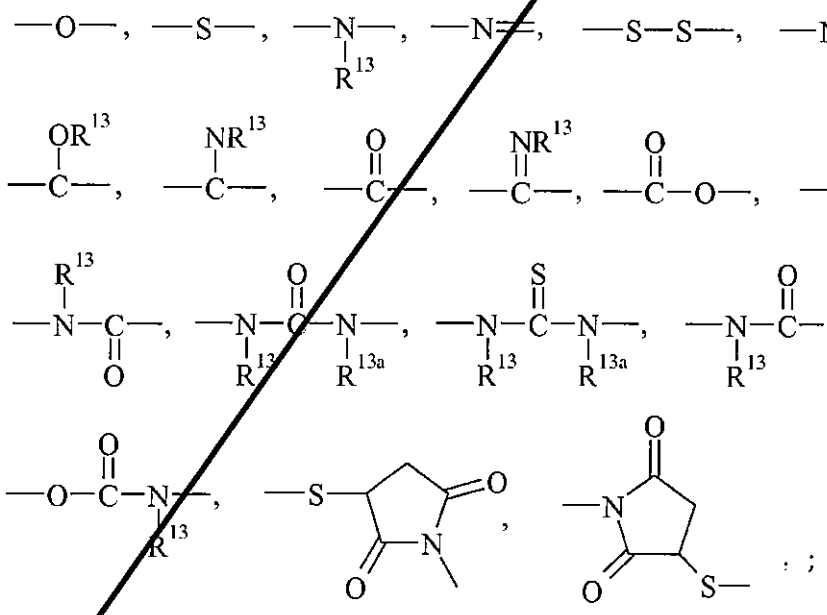
9. The carrier-linked treprostinil prodrug of claim 8, wherein each -Q- is independently -Q^{1a}-Q^1-*, wherein the asterisk indicates the connection to Z^1 and wherein

Q^{1a} is a bond; -C(O)O-; -O-; -C(O)-; $-C(O)N(R^{a9a})$-; $-S(O)_2N(R^{a9a})$-; $-S(O)N(R^{a9a})$-; $-S(O)_2$-; -S(O)-; $-N(R^{a9a})S(O)_2N(R^{a9b})$-; -S-; $-N(R^{a9a})$-; -OC(O)-; $-N(R^{a9a})C(O)$-; $-N(R^{a9a})S(O)_2$-; $-N(R^{a9a})S(O)$-; $-N(R^{a9a})C(O)O$-; $-N(R^{a9a})C(O)N(R^{a9b})$-; $-OC(O)N(R^{a9a})$-; or -W-, preferably $-C(O)N(R^{a9a})$- or $-N(R^{a9a})C(O)$-;

Q^1 is selected from C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl which are optionally substituted with one or more R^{a10}, which are optionally interrupted, provided that Q^1 is at least C_2, by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein each of said group may individually be present one or more times; and which C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl may optionally be terminated at the end connected to Z^1 by a group selected from C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,

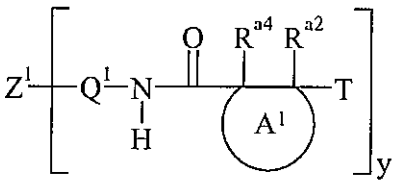


R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a12}, R^{a12a} and R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different,

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; preferably, R^{13} and R^{13a} are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

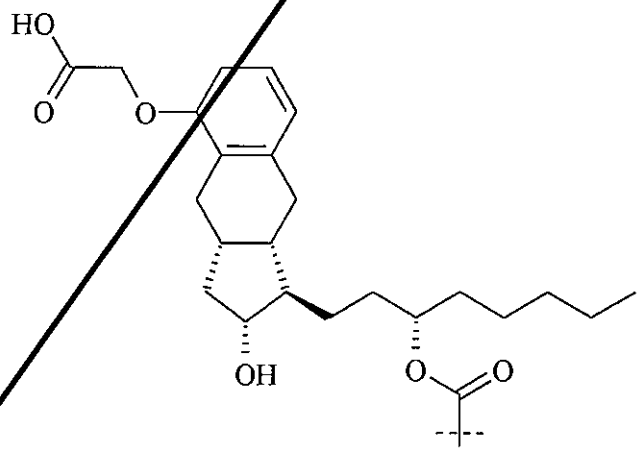
10. The carrier-linked treprostinil prodrug of any one of claims 1 to 9, wherein the carrier-linked treprostinil prodrug is of formula (IIaa):



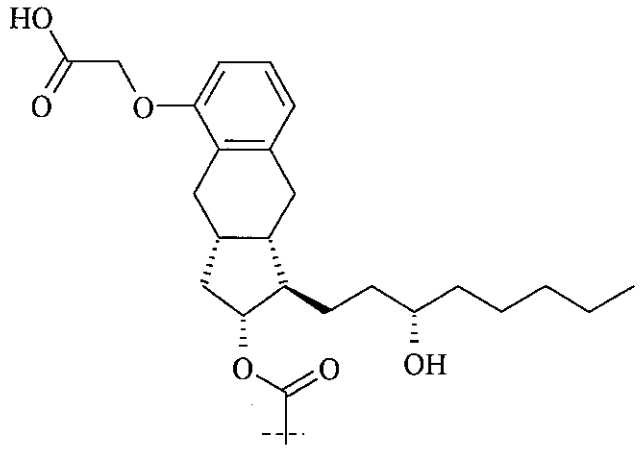
(IIaa),

wherein

each T is independently selected from structures (i) or (iii):



(i),



(iii),

wherein dashed lines indicate attachment to the rest of the molecule;

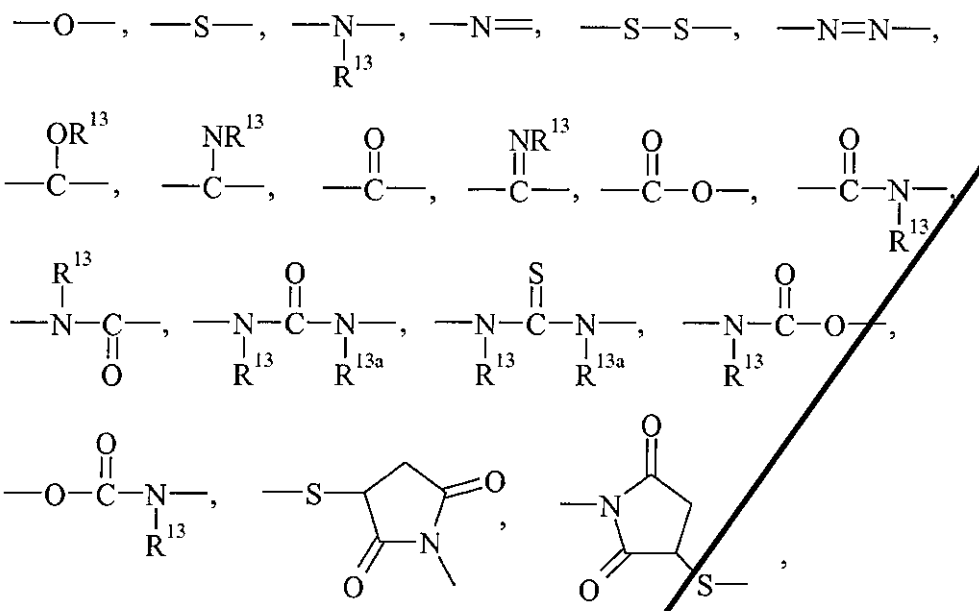
y is an integer ranging of from 1 to 64;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

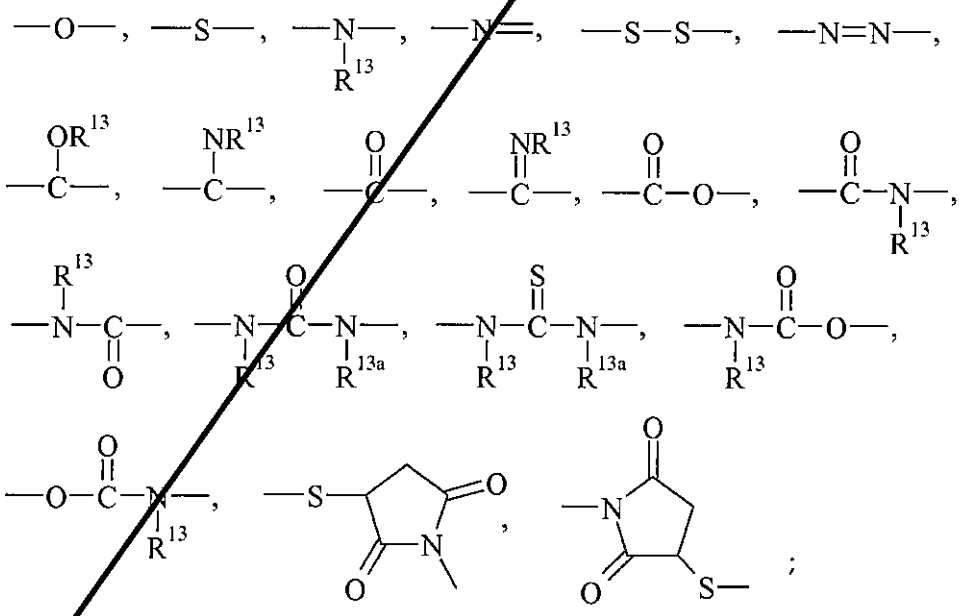
R^{a4} is selected from H, unsubstituted alkyl, and substituted alkyl;

ring A^1 is a C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A^1 is unsubstituted or substituted;

Q^1 is selected from C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl which are optionally substituted with one or more R^{a10}, which are optionally interrupted, provided that Q^1 is at least C_2, by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein each of said group may individually be present one or more times; and which C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl may optionally be terminated at the end connected to Z^1 by a group selected from C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



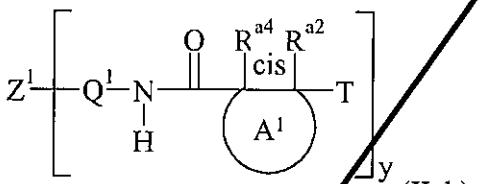
R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a12}, R^{a12a} and R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different,

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; preferably, R^{13} and R^{13a} are independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

11. The carrier-linked treprostinil prodrug of any one of claims 1 to 10, wherein the carrier-linked treprostinil prodrug is of formula (IIab):

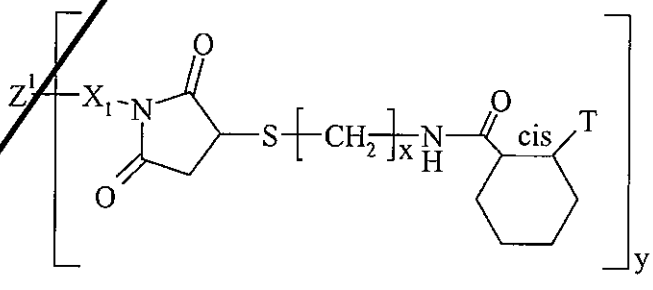


(IIab),

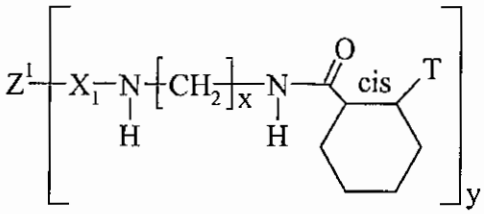
wherein

T, R^{a2}, R^{a4}, A^1, Q^1, Z^1 and y are used as defined in claim 10.

12. The carrier-linked treprostinil prodrug of any one of claims 1 to 11, wherein the carrier-linked treprostinil prodrug is of formula (IIac) or (IIad):



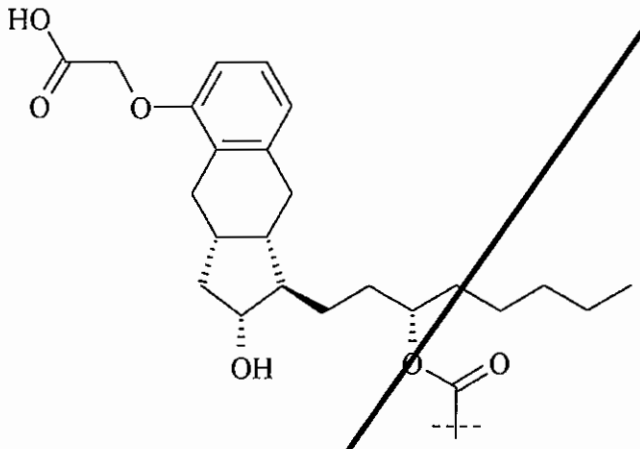
(IIac),



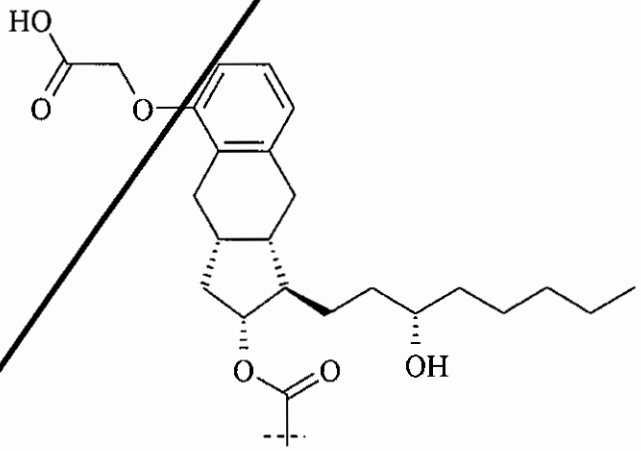
(IIad),

wherein

each T is independently selected from structures (i) or (iii):



(i),



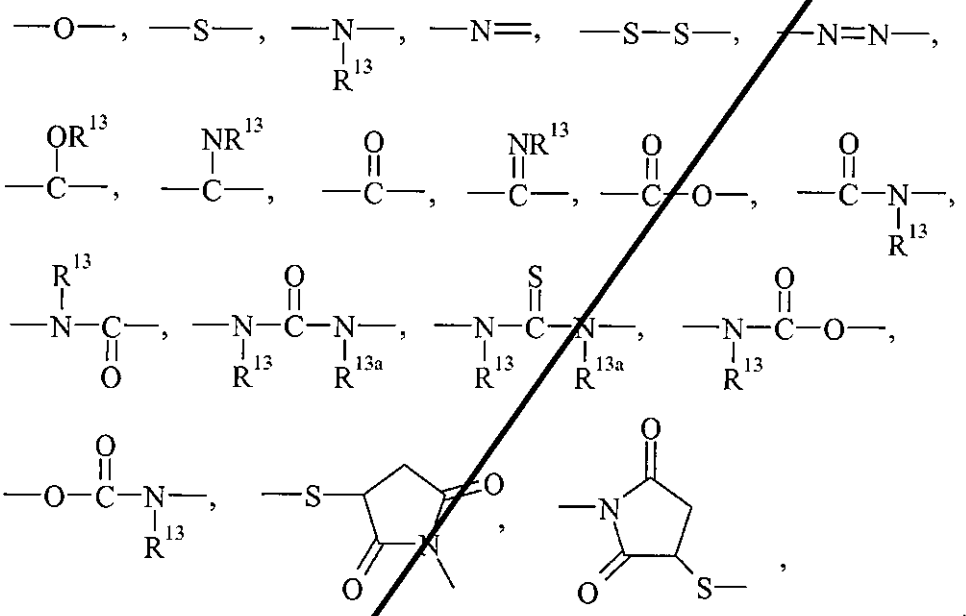
(iii),

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

y is an integer ranging of from 1 to 64

x is selected from 2, 3, 4, 5, 6, 7 or 8,

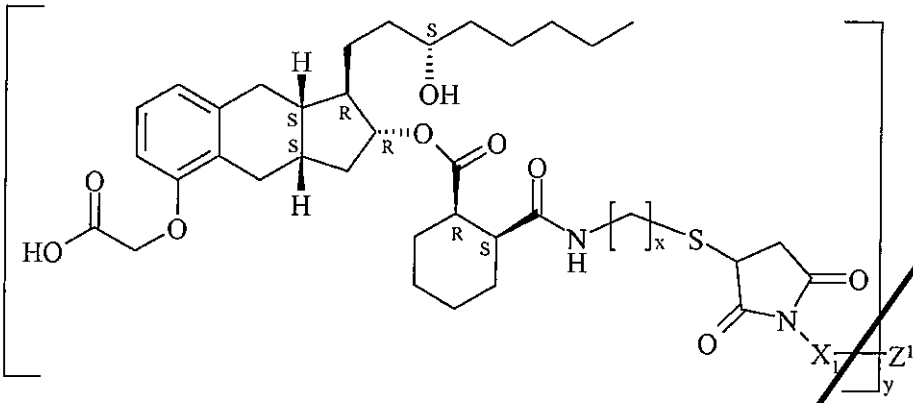
X_1 is selected from C_{1-15} alkyl, C_{2-15} alkenyl and C_{2-15} alkynyl, which are optionally substituted or interrupted by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

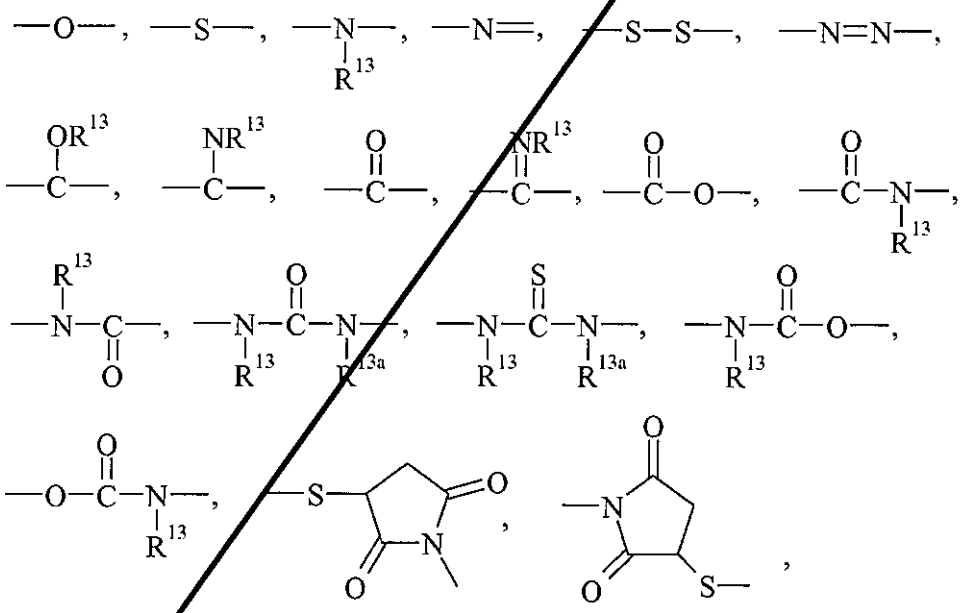
13. The carrier-linked treprostinil prodrug of any one of claims 1 to 12, wherein the carrier-linked treprostinil prodrug is of formula (IIb):



(IIb),

wherein

X_1 is selected from C_{1-15} alkyl, C_{2-15} alkenyl and C_{2-15} alkynyl, which are optionally substituted or interrupted by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

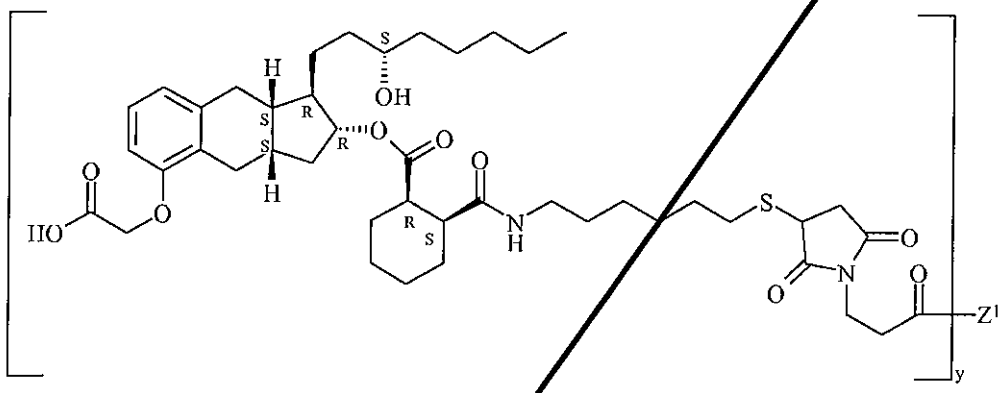
y is an integer ranging of from 1 to 64;

x is selected from 2, 3, 4, 5, 6, 7 or 8;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

14. The carrier-linked treprostinil prodrug of claim 12 or 13, wherein x is 6.

15. The carrier-linked treprostinil prodrug of any one of claims 1 to 14, wherein the carrier-linked treprostinil prodrug has the structure of formula (IIba):



(IIba),

wherein

y is an integer ranging of from 1 to 64; and

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

16. The carrier-linked treprostinil prodrug of any one of claims 1 to 15, wherein the carrier Z^1 has the structure of formula (VII):

$B-(A)_n$ (VII),

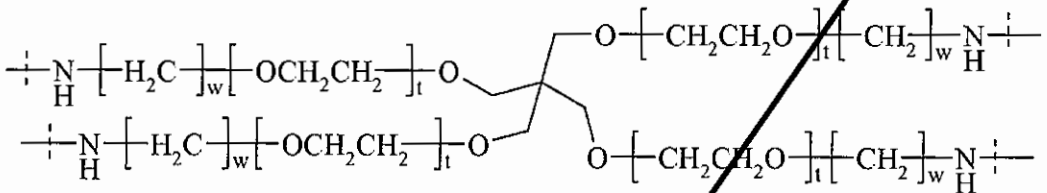
wherein

B is branching core,

A is a poly(ethylene glycol)-based polymeric chain, and

n is an integer of from 3 to 32.

17. The carrier-linked treprostinil prodrug of any one of claims 1 to 16, wherein Z^1 represents a moiety (IIca):



(IIca),

wherein

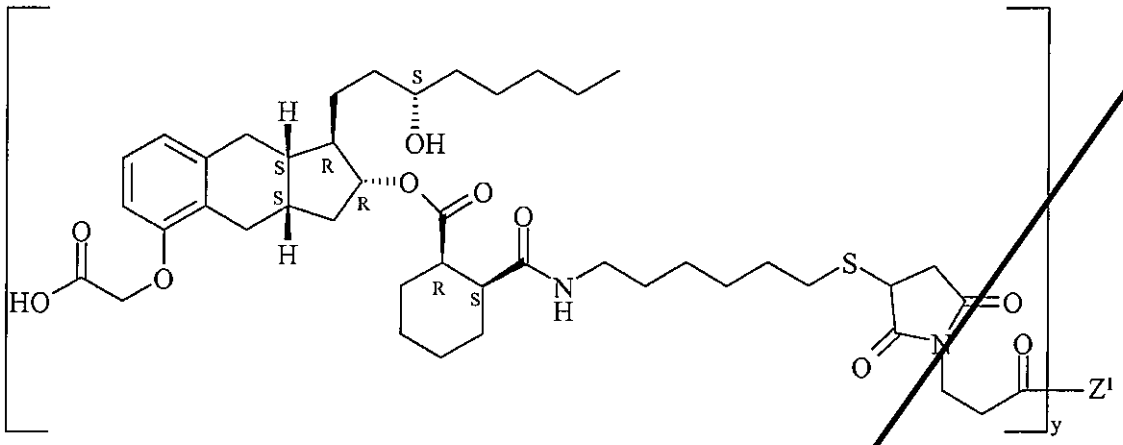
t ranges from 80 to 160;

w ranges from 2 to 6; and

dashed lines indicate attachment to the rest of the carrier-linked treprostinil prodrug.

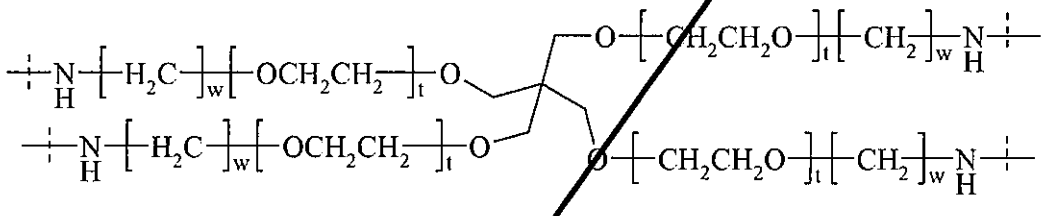
18. The carrier-linked treprostinil prodrug of claim 17, wherein w is 2 or 3.

19. The carrier-linked treprostinil prodrug of any one of claims 1 to 18 of formula (IIc) or a pharmaceutically acceptable salt thereof:



(IIc),

wherein y is 4 and Z^1 represents a moiety (IIca):



(IIca),

wherein dashed lines indicate attachment to the rest of the structure of formula (IIc), t ranges from 80 to 160 and w is 2 or 3.

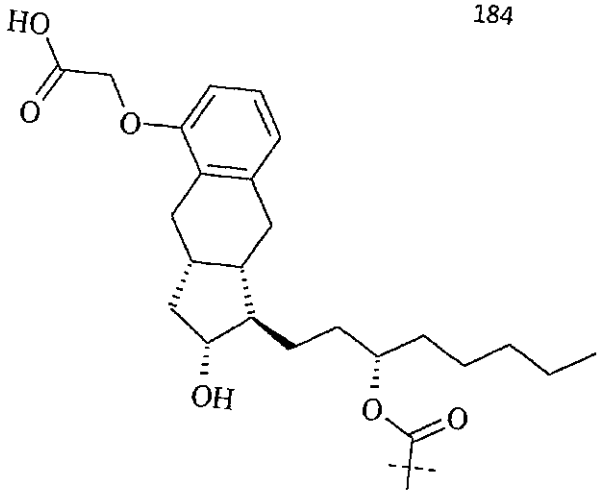
20. The carrier-linked treprostinil prodrug of claim 1, wherein R^{a1} is C_{1-6} alkyl or substituted C_{1-6} alkyl.

21. The carrier-linked treprostinil prodrug of any one of claims 1 to 3, wherein R^{a3} is H, C_{1-6} alkyl or substituted C_{1-6} alkyl.

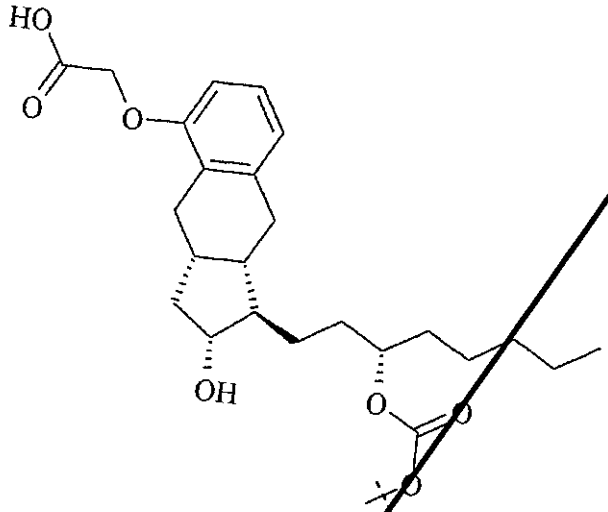
22. A carrier-linked treprostinil prodrug of formula (I):

$$Z^1-(-X^0-T)_y \qquad (I),$$

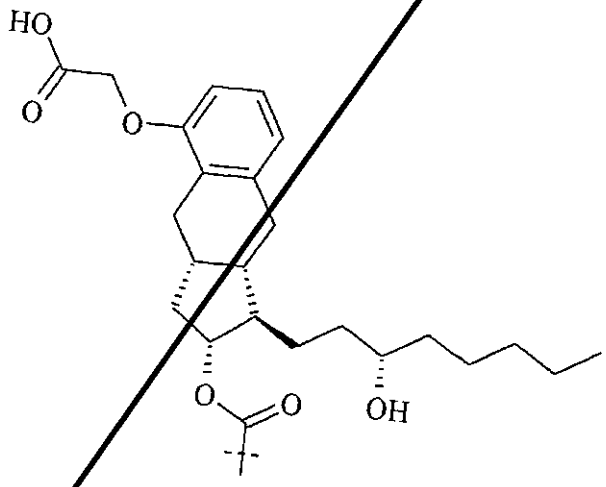
wherein each T is independently selected from structures (i) to (v):



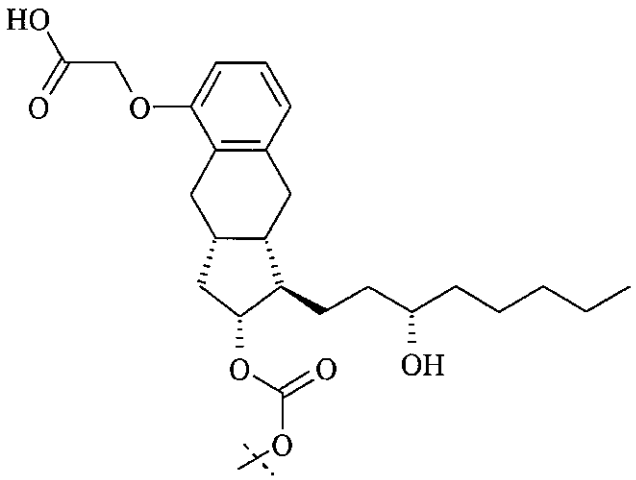
(i),



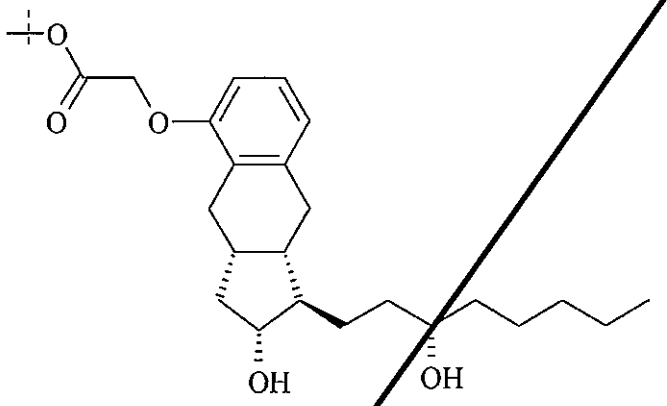
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to X^0;

y is an integer ranging of from 1 to 64, preferably ranging from 1 to 16, more preferably y is selected from 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, 12, 13, 14, 15 and 16, even more preferably y is 8,

each X^0 is independently $(X^{0A})_{m1}$-$(X^{0B})_{m2}$;

m1; m2 are independently 0; or 1;

X^{0A} is T^0;

X^{0B} is a branched or unbranched C_{1-15} alkylene group which is unsubstituted or substituted with one or more R^3, which are the same or different;

R^3 is halogen; C_{1-6} alkyl; CN; $C(O)R^4$; $C(O)OR^4$; OR^4; $C(O)R^4$; $C(O)N(R^4R^{4a})$; $S(O)_2N(R^4R^{4a})$; $S(O)N(R^4R^{4a})$; $S(O)_2R^4$; $S(O)R^4$; $N(R^4)S(O)_2N(R^{4a}R^{4b})$; SR^4; $N(R^4R^{4a})$; NO_2; $OC(O)R^4$; $N(R^4)C(O)R^{4a}$; $N(R^4)SO_2R^{4a}$; $N(R^4)S(O)R^{4a}$; $N(R^4)C(O)N(R^{4a}R^{4b})$; $N(R^4)C(O)OR^{4a}$; $OC(O)N(R^4R^{4a})$; or T^0;

R^4, R^{4a}, R^{4b} are independently selected from the group consisting of H; T^0; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^5, which are the same of different;

R^5 is halogen; CN; $C(O)R^6$; $C(O)OR^6$; OR^6; $C(O)R^6$; $C(O)N(R^6R^{6a})$; $S(O)_2N(R^6R^{6a})$; $S(O)N(R^6R^{6a})$; $S(O)_2R^6$; $S(O)R^6$; $N(R^6)S(O)_2N(R^{6a}R^{6b})$; SR^6; $N(R^6R^{6a})$; NO_2; $OC(O)R^6$; $N(R^6)C(O)R^{6a}$; $N(R^6)SO_2R^{6a}$; $N(R^6)S(O)R^{6a}$; $N(R^6)C(O)N(R^{6a}R^{6b})$; $N(R^6)C(O)OR^{6a}$; $OC(O)N(R^6R^{6a})$;

R^6, R^{6a}, R^{6b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same of different;

T^0 is phenyl; naphthyl; azulenyl; indenyl; indanyl; C_{3-7} cycloalkyl; 3 to 7 membered heterocyclyl; or 8 to 11 membered heterobicyclyl, wherein T^0, is optionally substituted with one or more R^7, which are the same or different;

R^7 is halogen; CN; $COOR^8$; OR^8; $C(O)R^8$; $C(O)N(R^8R^{8a})$; $S(O)_2N(R^8R^{8a})$; $S(O)N(R^8R^{8a})$; $S(O)_2R^8$; $S(O)R^8$; $N(R^8)S(O)_2N(R^{8a}R^{8b})$; SR^8; $N(R^8R^{8a})$; NO_2; $OC(O)R^8$; $N(R^8)C(O)R^{8a}$; $N(R^8)S(O)_2R^{8a}$; $N(R^8)S(O)R^{8a}$; $N(R^8)C(O)OR^{8a}$; $N(R^8)C(O)N(R^{8a}R^{8b})$; $OC(O)N(R^8R^{8a})$; oxo (=O), where the ring is at least partially saturated; C_{1-6} alkyl; C_{2-6} alkenyl; or C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^9, which are the same or different;

R^8, R^{8a}, R^{8b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^{10}, which are the same of different;

R^9, R^{10} are independently selected from the group consisting of halogen; CN; $C(O)R^{11}$; $C(O)OR^{11}$; OR^{11}; $C(O)R^{11}$; $C(O)N(R^{11}R^{11a})$; $S(O)_2N(R^{11}R^{11a})$; $S(O)N(R^{11}R^{11a})$; $S(O)_2R^{11}$; $S(O)R^{11}$; $N(R^{11})S(O)_2N(R^{11a}R^{11b})$; SR^{11}; $N(R^{11}R^{11a})$; NO_2; $OC(O)R^{11}$; $N(R^{11})C(O)R^{11a}$; $N(R^{11})SO_2R^{11a}$; $N(R^{11})S(O)R^{11a}$; $N(R^{11})C(O)N(R^{11a}R^{11b})$; $N(R^{11})C(O)OR^{11a}$; and $OC(O)N(R^{11}R^{11a})$;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same of different;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer,

wherein the carrier is covalently attached to a moiety X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

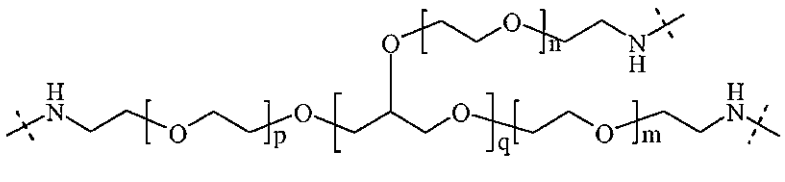
or a pharmaceutically acceptable salt thereof.

23. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 22, wherein Z^1 comprises a PEG-based polymer.

24. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 22 or 23, wherein Z^1 comprises a water-soluble polymer.

25. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 22 to 24, wherein y is an integer of from 4 to 16, preferably y is 8.

26. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 and 20 to 25, wherein Z^1 has the structure of formula (III):



(III),

wherein

dashed lines indicate attachment to X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

each of m, n, and p are independently an integer ranging of from 5 to 500,

and q ranges of from 2 to 32.

27. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 and 20 to 25, wherein Z^1 is of formula (VI):

$B-(A\text{-}Hyp^y)_n$ (VI),

wherein

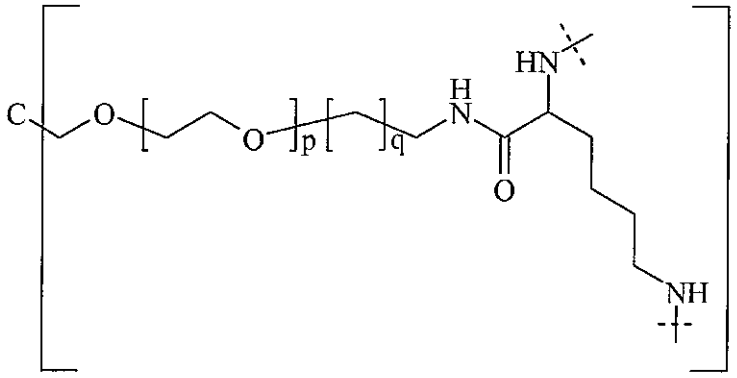
B is a branching core,

each A is independently a poly(ethylene glycol)-based polymeric chain,

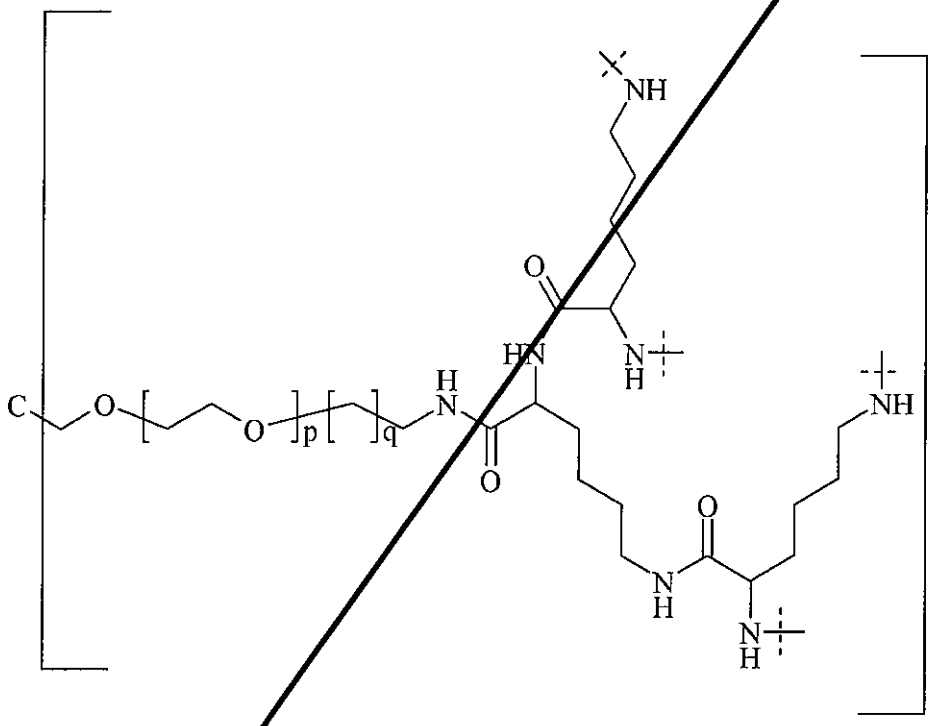
each Hyp^y is independently a branched moiety, and

n is an integer of from 3 to 32.

28. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 27, wherein Z^1 is selected from structures (i-y) to (iii-y):

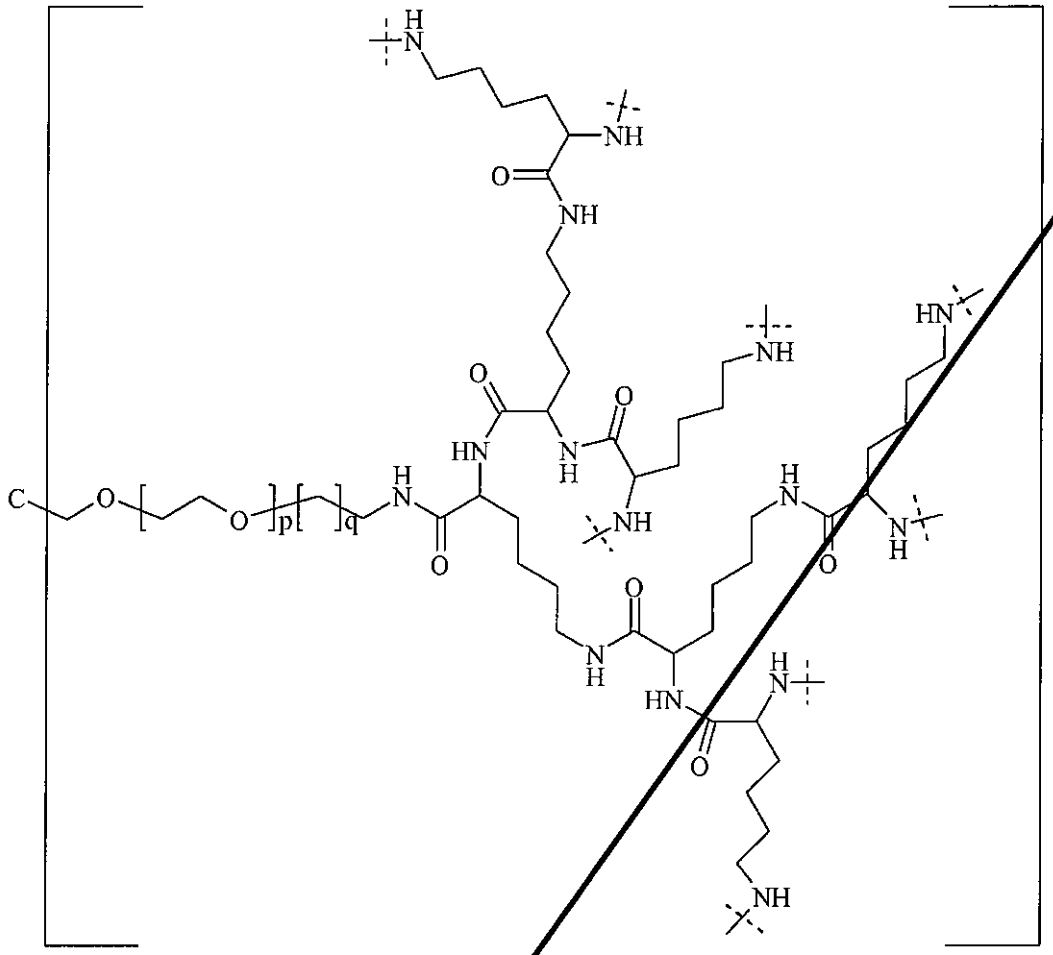


4 (i-y),



4 (ii-y),

5



4

(iii-y);

wherein

dashed lines indicate attachment to X^0 of formula (I) , provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,,

p is an integer of from 5 to 2000, preferably from 10 to 1000, more preferably from 10 to 500, most preferably from 100 to 1000,

q is 1 or 2.

29. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 and 20 to 25, wherein Z^1 has the structure of formula (V)

$$Hyp^1{}_{mx} - POL^x - Hyp^2 \quad (V),$$

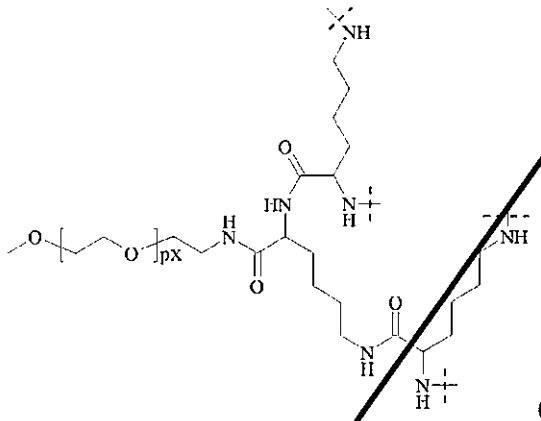
wherein

POL^x is a polymeric moiety having a molecular weight ranging from 0.5 kDa to 160 kDa,

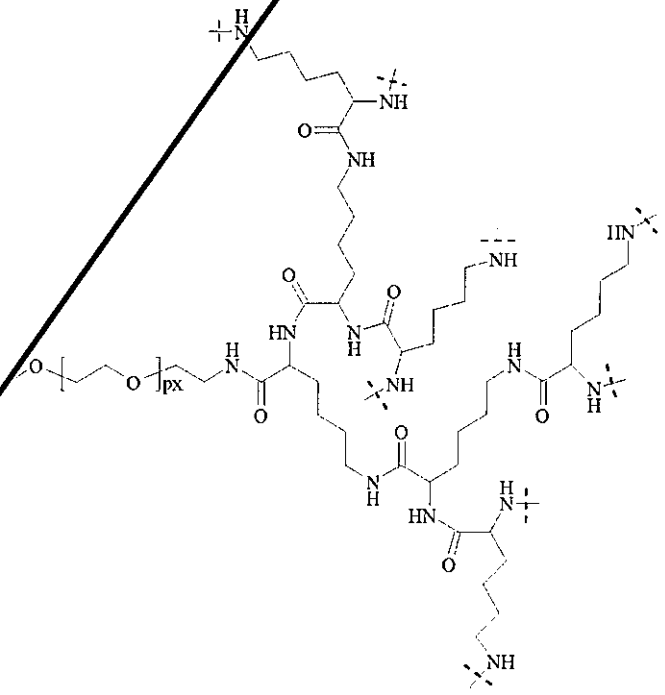
Hyp^1 and Hyp^2 are independently a hyperbranched moiety, and

mx is 0 or 1.

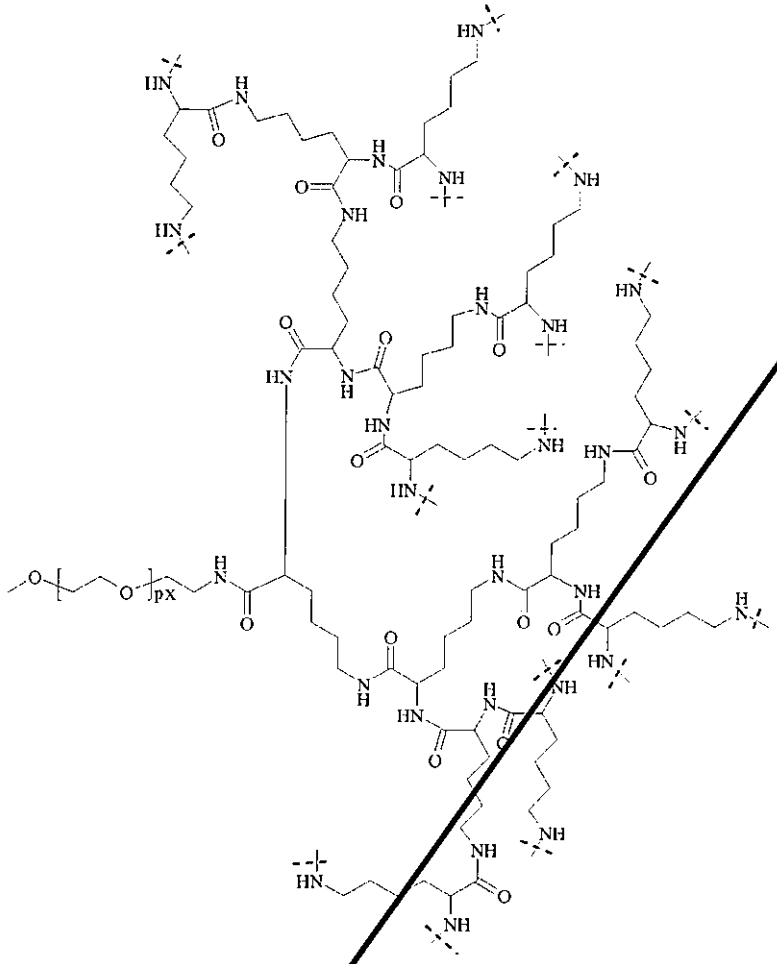
30. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 29, wherein mx is 0 and POL^x – Hyp^2 is selected from the following structures:



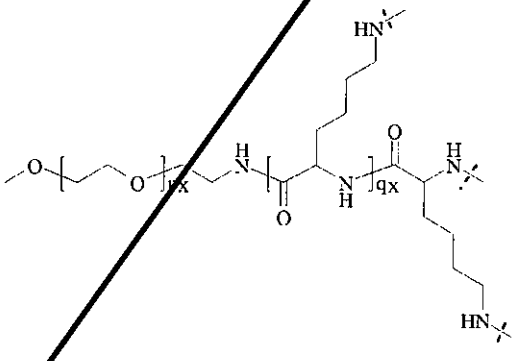
(v-x),



(vi-x),



(vii-x),



(viii-x),

wherein

dashed lines indicate attachment to a moiety X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

px is an integer of from 5 to 2000, preferably 10 to 1000, in particular 100 to 1000, and

qx is an integer of from 0 to 15, preferably 3 to 7, more preferably, qx is 6.

31. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15 and 20 to 25, wherein Z^1 comprises an amino acid sequence of at least 100 amino acid residues, and

wherein the amino acid sequence of at least 100 amino acid residues is in random coil conformation, and,

wherein the amino acid sequence of at least 100 amino acid residues comprises alanine, serine and proline residues.

32. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 22 to 31, wherein each X^0 is unsubstituted.

33. A pharmaceutical composition comprising a carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 32 thereof, optionally together with one or more pharmaceutically acceptable excipients.

34. A pharmaceutical composition according to claim 33,

(i) wherein the carrier-linked treprostinil prodrug is sufficiently dosed in the pharmaceutical composition to provide a therapeutically effective amount of treprostinil for at least 12 hours in one application, and/or

(ii) wherein a single dose of the pharmaceutical composition comprises about 2 to about 6, preferably about 4 mg treprostinil.

35. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 32, or a pharmaceutical composition of claim 33 or 34, for use as a medicament.

36. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 32 or a pharmaceutical composition of claim 33 or 34 for use in a method of treating or preventing a disease or disorder which can be treated and/or prevented by treprostinil.

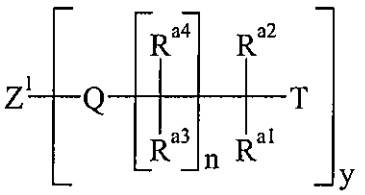
37. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof or the pharmaceutical composition for the use of claim 36, wherein the disease or disorder is pulmonary arterial hypertension.

38. A method of treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more conditions comprising administering to said patient a diagnostically and/or therapeutically effective amount of the carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any of claims 1 to 32 or the pharmaceutical composition of claim 33 or 34.

39. The water-soluble carrier-linked prodrug or a pharmaceutically acceptable salt thereof of any one of claim 1 to 32 or the pharmaceutical composition of claim 33 or 34, for use as medicament for topical, enteral administration, parenteral administration, inhalation, injection, or infusion, intraarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, and intraperitoneal, intrathecal, intracapsular, intraorbital, intracardiac, transtracheal, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intraventricular or intrasternal administration.

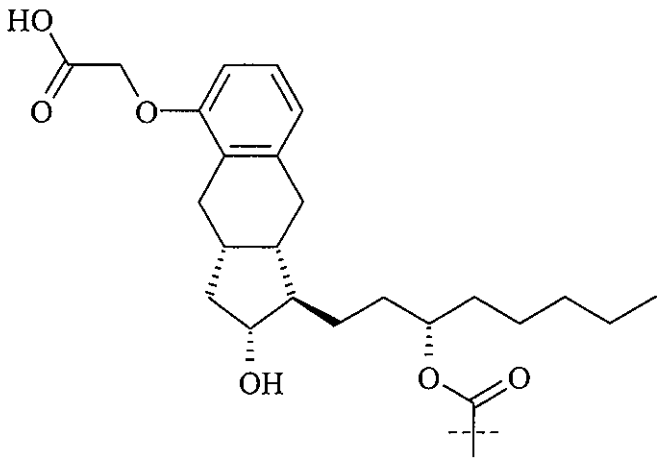
Claims

1. A carrier-linked treprostinil prodrug of formula (II):

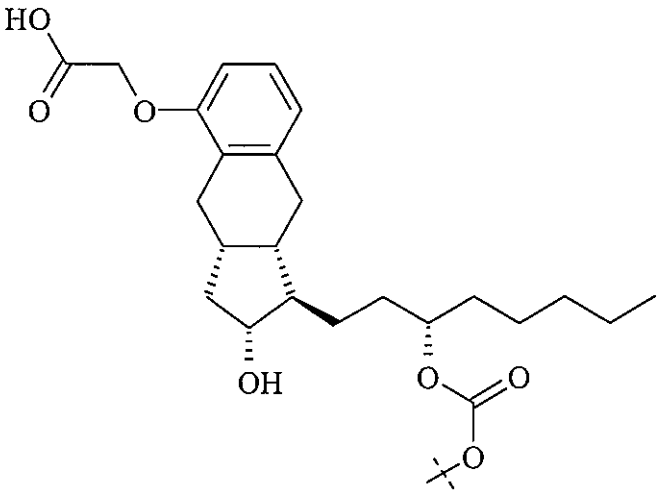


(II),

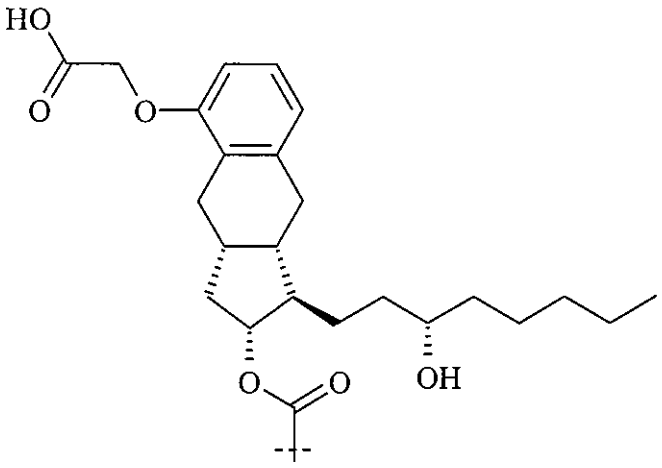
wherein each T is independently selected from structures (i) to (v):



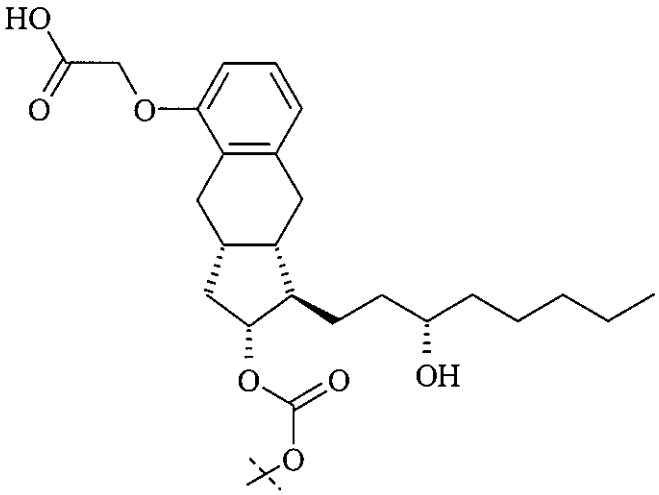
(i),



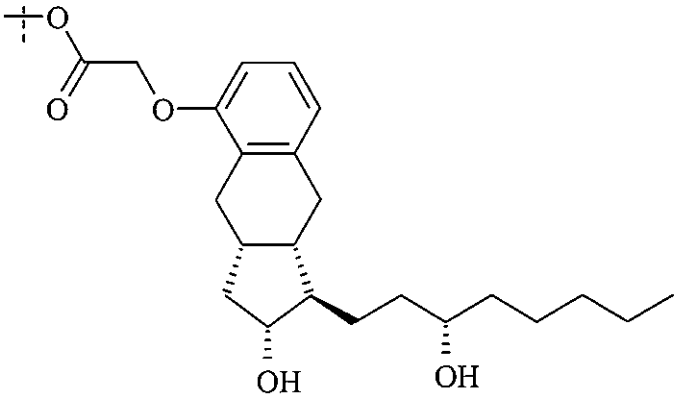
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to the rest of the molecule;

y is an integer ranging of from 1 to 64,

R^{a1} is selected from the group of unsubstituted alkyl; substituted alkyl; unsubstituted phenyl; substituted phenyl; unsubstituted naphthyl; substituted naphthyl; unsubstituted indenyl; substituted indenyl; unsubstituted indanyl; substituted indanyl; unsubstituted tetralinyl; substituted tetralinyl; unsubstituted C_{3-10} cycloalkyl; substituted C_{3-10} cycloalkyl; unsubstituted 4- to 7-membered heterocyclyl; substituted 4- to 7-membered heterocyclyl; unsubstituted 9- to 11-membered heterobicyclyl; and substituted 9- to 11-membered heterobicyclyl;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

R^{a3} and R^{a4} are independently selected from the group consisting of H, unsubstituted alkyl, and substituted alkyl;

n is 0 or 1;

Q is a spacer moiety;

optionally, R^{a1} and R^{a3} are joined together with the atoms to which they are attached to form a ring A;

A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted;

Z^1 is a carrier comprising a covalently bound polymer

or a pharmaceutical salt thereof.

2. The carrier-linked treprostinil prodrug of claim 1, wherein y is an integer ranging of from 1 to 16.

3. The carrier-linked treprostinil prodrug of claim 1 or 2, wherein y is selected from 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, 12, 13, 14, 15 and 16.

4. The carrier-linked treprostinil prodrug of any one of claims 1 to 3, wherein R^{a2} is H.

5. The carrier-linked treprostinil prodrug of any one of claims 1 to 4, wherein R^{a4} is selected from H, C_{1-6} alkyl or substituted C_{1-6} alkyl.

6. The carrier-linked treprostinil prodrug of any one of claims 1 to 5, wherein R^{a4} is H.

7. The carrier-linked treprostinil prodrug of any one of claims 1 to 6, wherein R^{a1} and R^{a3} are joined together with the atoms to which they are attached to form a ring A;

wherein A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted.

8. The carrier-linked treprostinil prodrug of claim 7, wherein ring A is selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, and cycloheptane.

9. The carrier-linked treprostinil prodrug of claim 7 or 8, wherein ring A is cyclohexane.

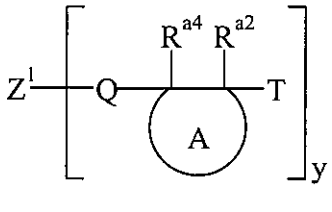
10. The carrier-linked treprostinil prodrug of any one of claims 1 to 9, wherein T is selected from structure (iii).

11. The carrier-linked treprostinil prodrug of any one of claims 1 to 10, wherein y is 4, 6, 8, 10, or 12.

12. The carrier-linked treprostinil prodrug of any one of claims 1 to 11, wherein y is 4, 6, or 8.

13. The carrier-linked treprostinil prodrug of any one of claims 1 to 12, wherein y is 4.

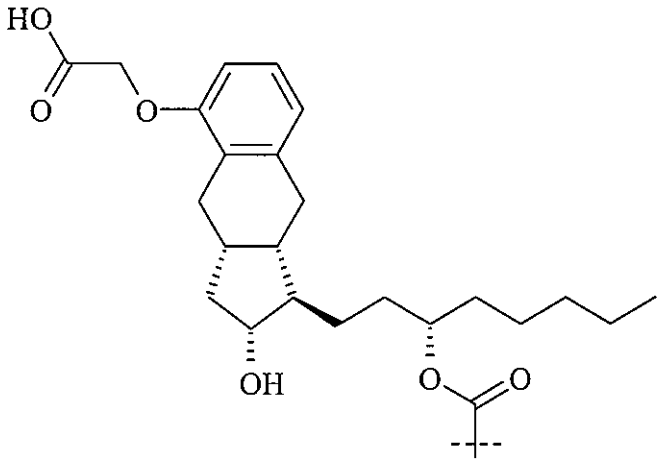
14. The carrier-linked treprostinil prodrug of any one of claims 1 to 13, wherein the carrier-linked treprostinil prodrug has the structure of formula (II-A):



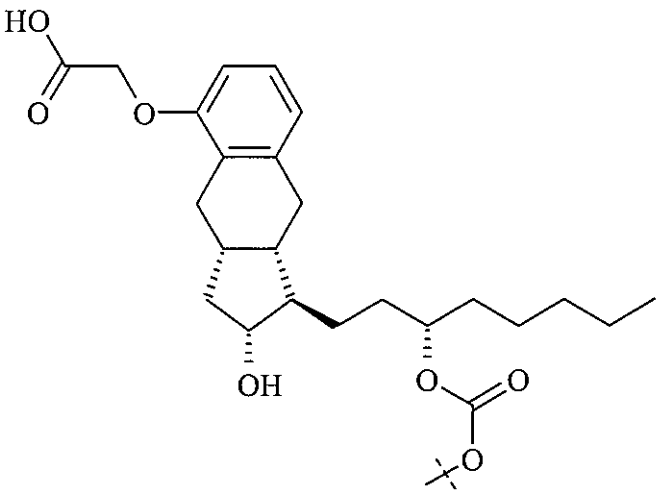
(II-A),

wherein

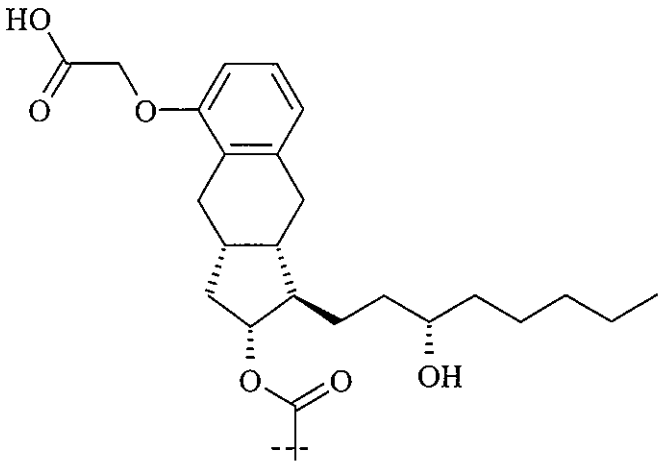
each T is independently selected from structures (i) to (v):



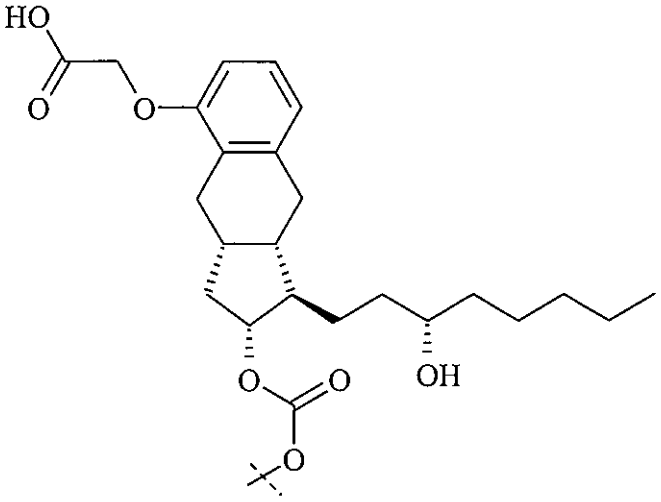
(i),



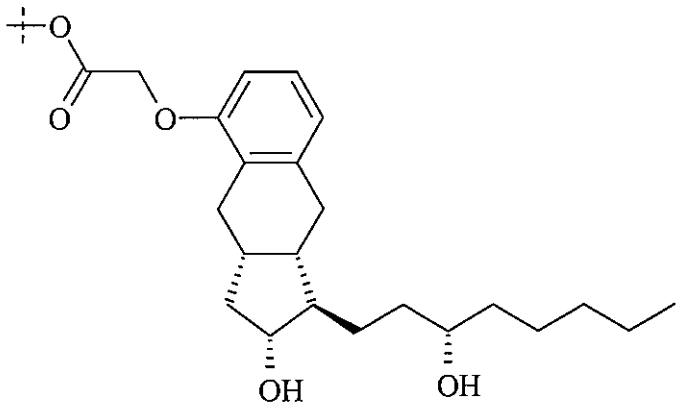
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to the rest of the molecule;

y is an integer ranging of from 1 to 64, preferably ranging from 1 to 16;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

R^{a4} is selected from the group consisting of H, unsubstituted alkyl, and substituted alkyl;

A is selected from phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A is unsubstituted or substituted;

Q is a spacer moiety;

Z^1 is a carrier comprising a covalently bound polymer, preferably a pharmaceutically acceptable polymer.

15. The carrier-linked treprostinil prodrug of claim 14, wherein y is 4.

16. The carrier-linked treprostinil prodrug of any one of claims 1 to 15, wherein Q in formula (II) is selected from $COOR^{a9}$; OR^{a9}; $C(O)R^{a9}$; $C(O)N(R^{a9}R^{a9a})$; $S(O)_2N(R^{a9}R^{a9a})$; $S(O)N(R^{a9}R^{a9a})$; $S(O)_2R^{a9}$; $S(O)R^{a9}$; $N(R^{a9})S(O)_2N(R^{a9a}R^{a9b})$; SR^{a9}; $N(R^{a9}R^{a9a})$; $OC(O)R^{a9}$; $N(R^{a9})C(O)R^{a9a}$; $N(R^{a9})S(O)_2R^{a9a}$; $N(R^{a9})S(O)R^{a9a}$; $N(R^{a9})C(O)OR^{a9a}$; $N(R^{a9})C(O)N(R^{a9a}R^{a9b})$; $OC(O)N(R^{a9}R^{a9a})$; W; C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl, wherein W, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{a10}, which are the same or different, and wherein C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -W-, -C(O)O-; -O-; -C(O)-; $-C(O)N(R^{a11})-$; $-S(O)_2N(R^{a11})-$; $-S(O)N(R^{a11})-$; $-S(O)_2-$; -S(O)-; $-N(R^{a11})S(O)_2N(R^{a11a})-$; -S-; $-N(R^{a11})-$; $-OC(O)R^{a11}$; $-N(R^{a11})C(O)-$; $-N(R^{a11})S(O)_2-$; $-N(R^{a11})S(O)-$; $-N(R^{a11})C(O)O-$; $-N(R^{a11})C(O)N(R^{a11a})-$; and $-OC(O)N(R^{a11}R^{a11a})$;

R^{a9}, R^{a9a}, R^{a9b} are independently selected from the group consisting of H; W; and C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl, wherein W, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{a10}, which are the same or different, and wherein C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of W, -C(O)O-; -O-; -C(O)-; -C(O)N(R^{a11})-; -S(O)$_2$N(R^{a11})-; -S(O)N(R^{a11})-; -S(O)$_2$-; -S(O)-; -N(R^{a11})S(O)$_2$N(R^{a11a})-; -S-; -N(R^{a11})-; -OC(O)R^{a11}; -N(R^{a11})C(O)-; -N(R^{a11})S(O)$_2$-; -N(R^{a11})S(O)-; -N(R^{a11})C(O)O-; -N(R^{a11})C(O)N(R^{a11a})-; and -OC(O)N($R^{a11}R^{a11a}$);

W is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 4- to 7-membered heterocyclyl; or 9- to 11-membered heterobicyclyl, wherein W is optionally substituted with one or more R^{a10}, which are the same or different;

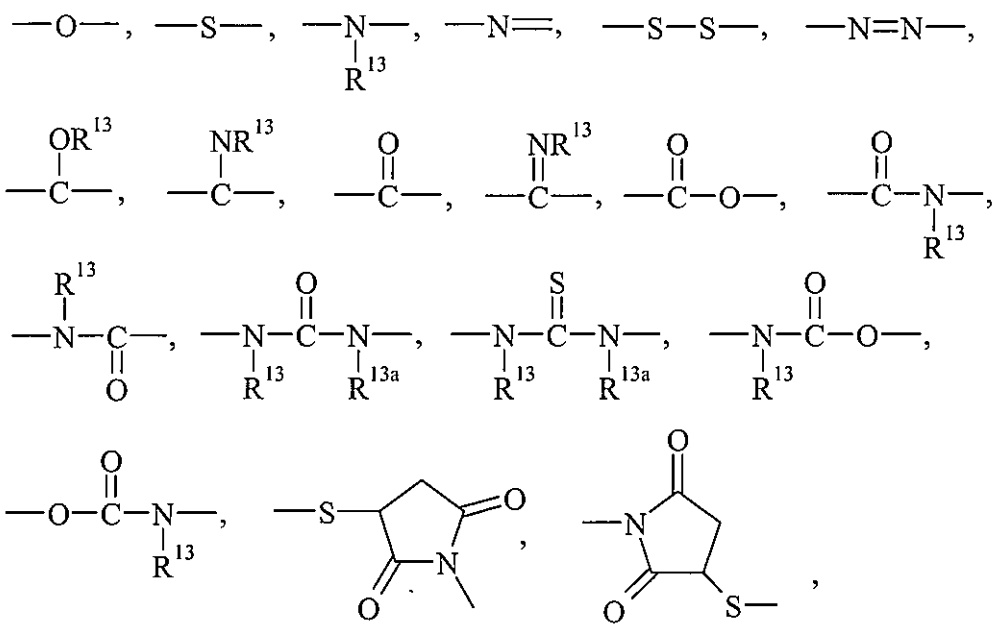
R^{a10} is halogen; CN; oxo (=O); COOR^{a12}; OR^{a12}; C(O)R^{a12}; C(O)N($R^{a12}R^{a12a}$); S(O)$_2$N($R^{a12}R^{a12a}$); S(O)N($R^{a12}R^{a12a}$); S(O)$_2R^{a12}$; S(O)R^{a12}; N(R^{a12})S(O)$_2$N($R^{a12a}R^{a12b}$); SR^{a12}; N($R^{a12}R^{a12a}$); NO_2; OC(O)R^{a12}; N(R^{a12})C(O)R^{a12a}; N(R^{a12})S(O)$_2R^{a12a}$; N(R^{a12})S(O)R^{a12a}; N(R^{a12})C(O)OR^{a12a}; N(R^{a12})C(O)N($R^{a12a}R^{a12b}$); OC(O)N($R^{a12}R^{a12a}$); or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a11}, R^{a11a}, R^{a12}, R^{a12a}, R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

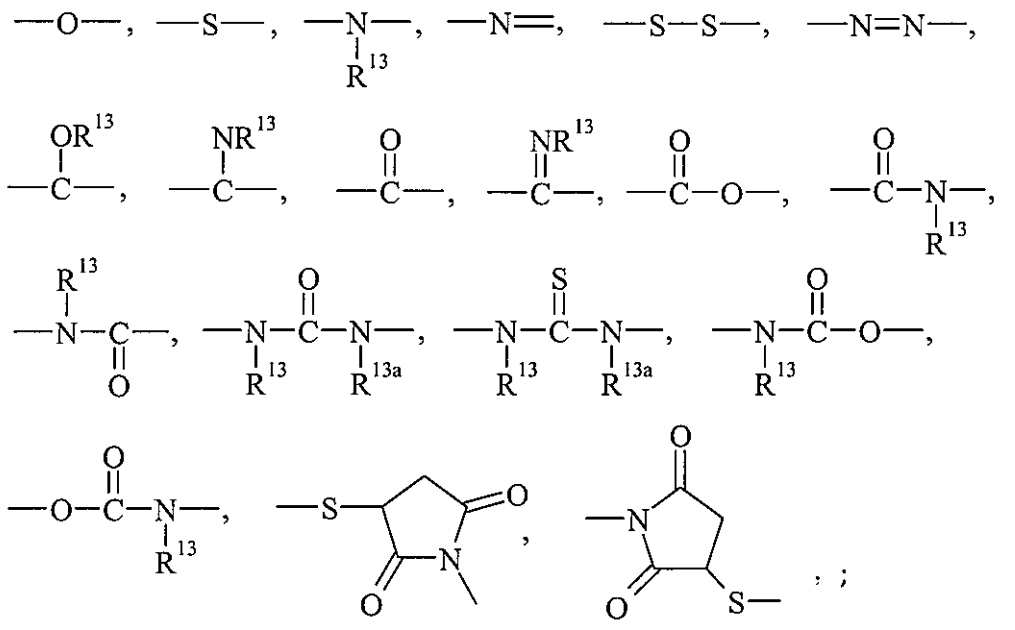
17. The carrier-linked treprostinil prodrug of claim 16, wherein each -Q- is independently -Q^{1a}-Q^{1}-*, wherein the asterisk indicates the connection to Z^1 and wherein

Q^{1a} is a bond; -C(O)O-; -O-; -C(O)-; -C(O)N(R^{a9a})-; -S(O)$_2$N(R^{a9a})-; -S(O)N(R^{a9a})-; -S(O)$_2$-; -S(O)-; -N(R^{a9a})S(O)$_2$N(R^{a9b})-; -S-; -N(R^{a9a})-; -OC(O)-; -N(R^{a9a})C(O)-; -N(R^{a9a})S(O)$_2$-; -N(R^{a9a})S(O)-; -N(R^{a9a})C(O)O-; -N(R^{a9a})C(O)N(R^{a9b})-; -OC(O)N(R^{a9a})-; or -W-;;

Q^1 is selected from C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl which are optionally substituted with one or more R^{a10}, which are optionally interrupted, provided that Q^1 is at least C_2, by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein each of said group may individually be present one or more times; and which C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl may optionally be terminated at the end connected to Z^1 by a group selected from C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,

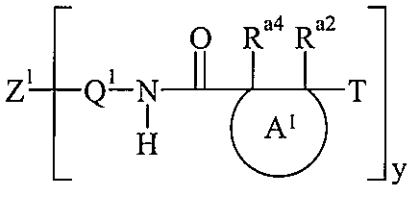


R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a12}, R^{a12a} and R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different,

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

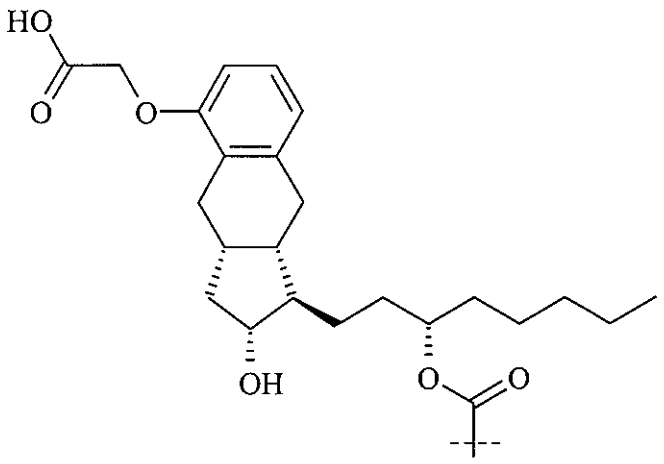
18. The carrier-linked treprostinil prodrug of any one of claims 1 to 17, wherein the carrier-linked treprostinil prodrug is of formula (IIaa):



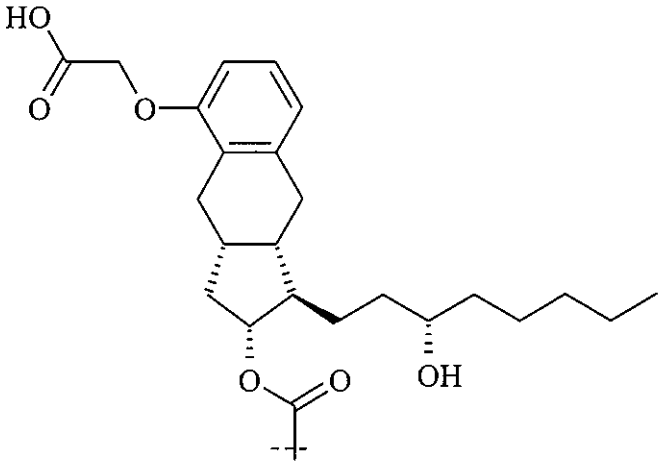
(IIaa),

wherein

each T is independently selected from structures (i) or (iii):



(i),



(iii),

wherein dashed lines indicate attachment to the rest of the molecule;

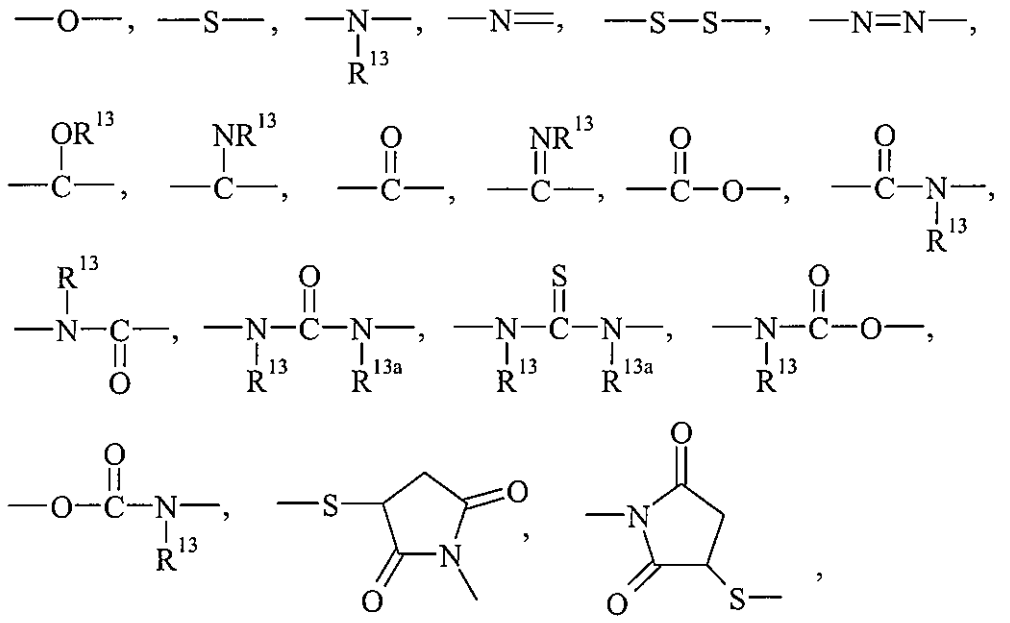
y is an integer ranging of from 1 to 64;

R^{a2} is selected from H, unsubstituted alkyl, and substituted alkyl;

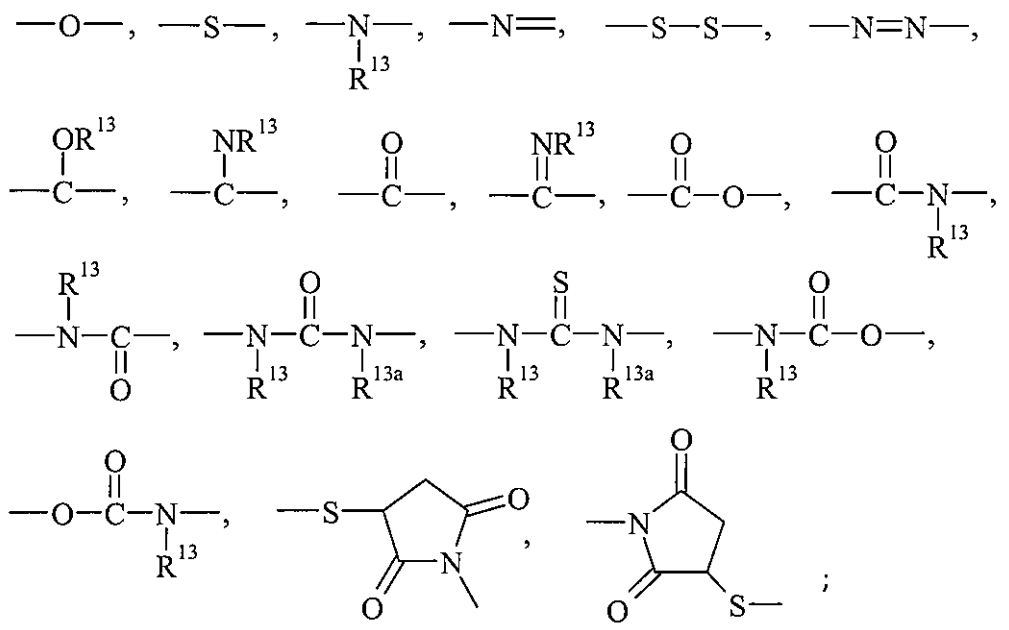
R^{a4} is selected from H, unsubstituted alkyl, and substituted alkyl;

ring A^1 is a C_{3-10} cycloalkyl; 4- to 7-membered aliphatic heterocyclyl; or 9- to 11-membered aliphatic heterobicyclyl, wherein A^1 is unsubstituted or substituted;

Q^1 is selected from C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl which are optionally substituted with one or more R^{a10}, which are optionally interrupted, provided that Q^1 is at least C_2, by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein each of said group may individually be present one or more times; and which C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl may optionally be terminated at the end connected to Z^1 by a group selected from C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



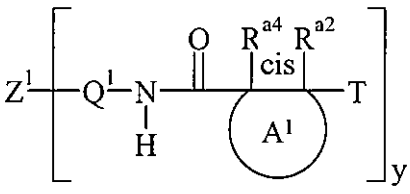
R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^{a12}, R^{a12a} and R^{a12b} are independently selected from the group consisting of H; and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different,

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;;

Z^1 is a carrier comprising a covalently bound polymer.

19. The carrier-linked treprostinil prodrug of any one of claims 1 to 18, wherein the carrier-linked treprostinil prodrug is of formula (IIab):

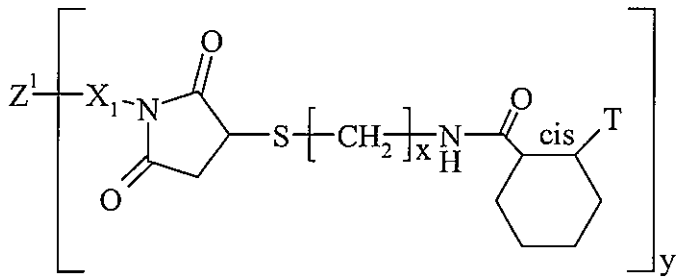


(IIab),

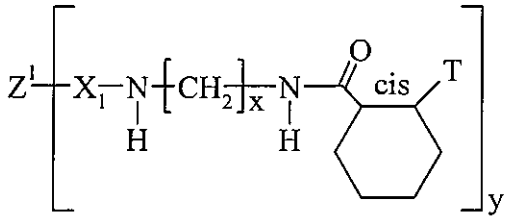
wherein

T, R^{a2}, R^{a4}, A^1, Q^1, Z^1 and y are used as defined in claim 10.

20. The carrier-linked treprostinil prodrug of any one of claims 1 to 19, wherein the carrier-linked treprostinil prodrug is of formula (IIac) or (IIad):



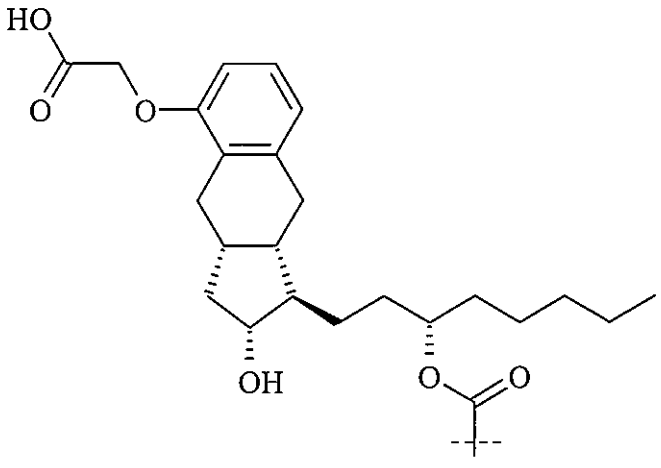
(IIac),



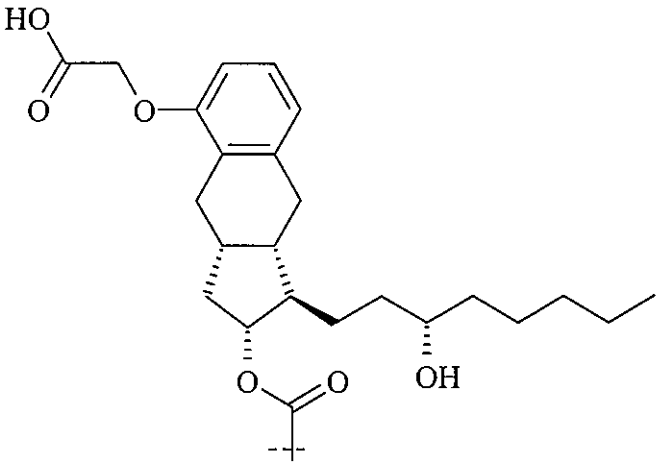
(IIad),

wherein

each T is independently selected from structures (i) or (iii):



(i),



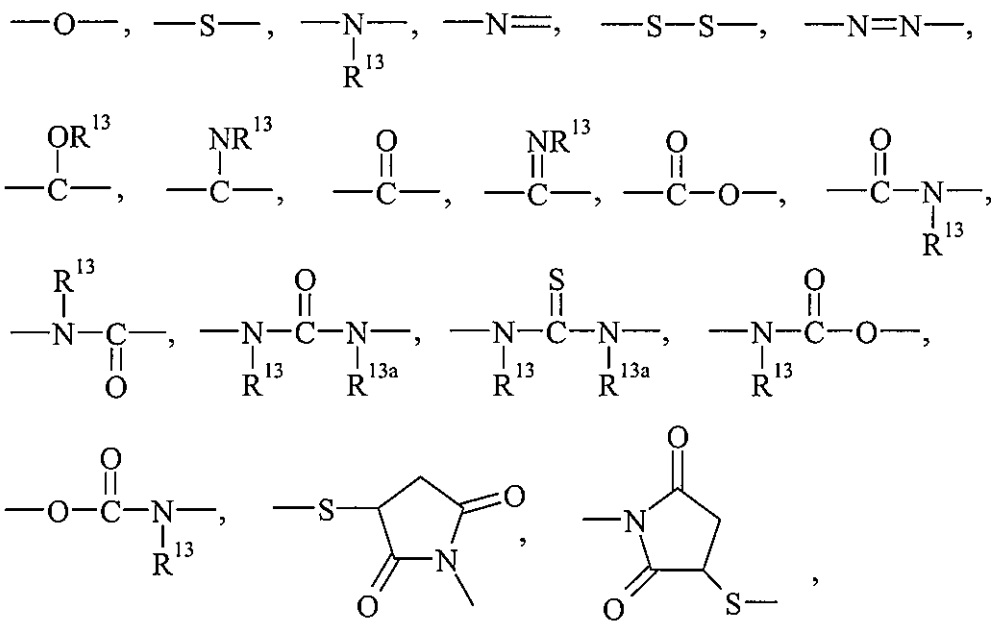
(iii),

Z^1 is a carrier comprising a covalently bound polymer,

y is an integer ranging of from 1 to 64

x is selected from 2, 3, 4, 5, 6, 7 or 8,

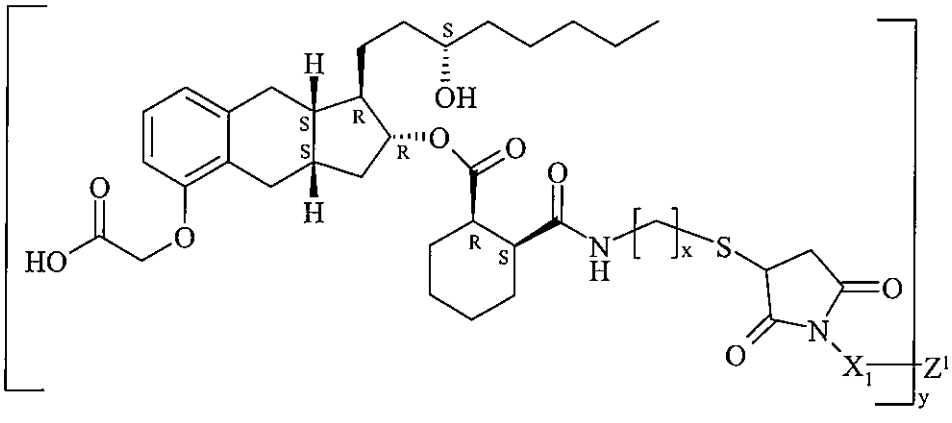
X_1 is selected from C_{1-15} alkyl, C_{2-15} alkenyl and C_{2-15} alkynyl, which are optionally substituted or interrupted by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

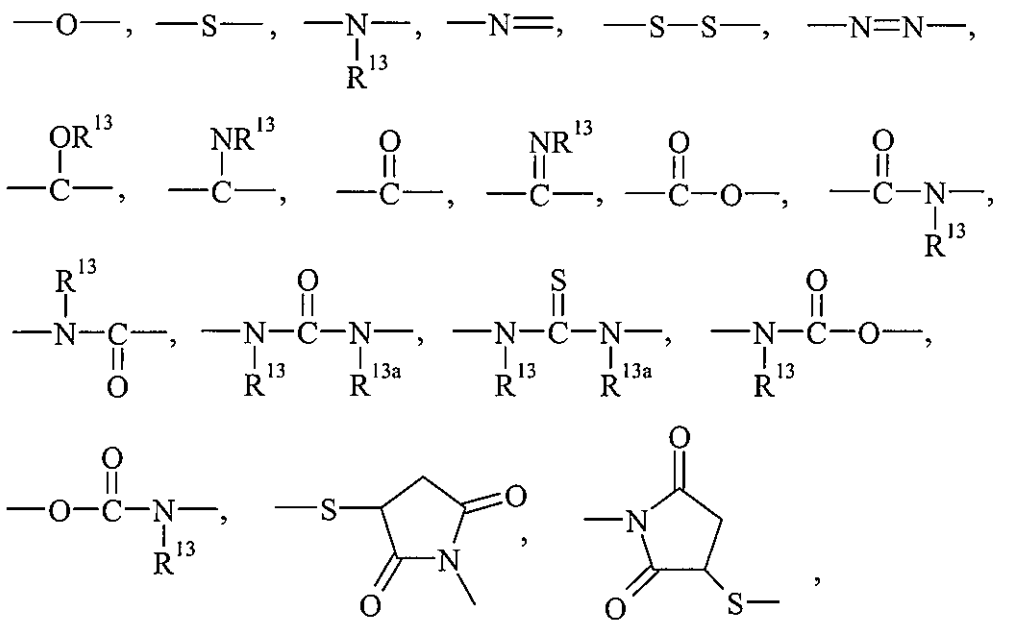
21. The carrier-linked treprostinil prodrug of any one of claims 1 to 20, wherein the carrier-linked treprostinil prodrug is of formula (IIb):



(IIb),

wherein

X_1 is selected from C_{1-15} alkyl, C_{2-15} alkenyl and C_{2-15} alkynyl, which are optionally substituted or interrupted by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein

R^{13} and R^{13a} are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

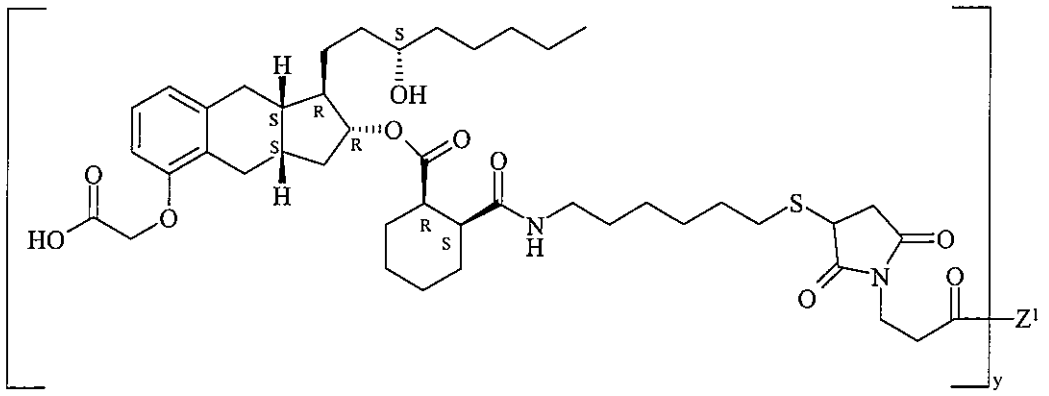
y is an integer ranging of from 1 to 64;

x is selected from 2, 3, 4, 5, 6, 7 or 8;

Z^1 is a carrier comprising a covalently bound polymer.

22. The carrier-linked treprostinil prodrug of claim 20 or 21, wherein x is 6.

23. The carrier-linked treprostinil prodrug of any one of claims 1 to 22, wherein the carrier-linked treprostinil prodrug has the structure of formula (IIba):



(IIba),

wherein

y is an integer ranging of from 1 to 64; and

Z^1 is a carrier comprising a covalently bound polymer.

24. The carrier-linked treprostinil prodrug of any one of claims 1 to 23, wherein the carrier Z^1 has the structure of formula (VII):

$B\text{-}(A)_n$ (VII),

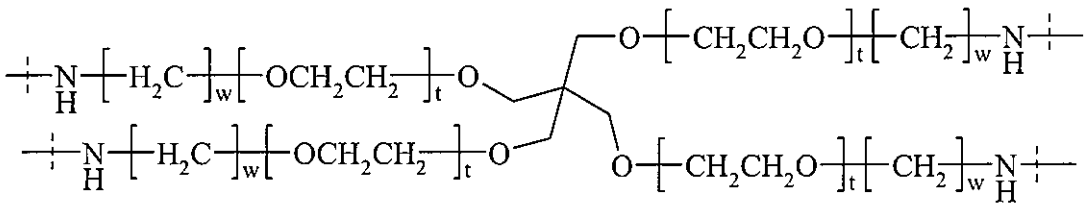
wherein

B is branching core,

A is a poly(ethylene glycol)-based polymeric chain, and

n is an integer of from 3 to 32.

25. The carrier-linked treprostinil prodrug of any one of claims 1 to 24, wherein Z^1 represents a moiety (IIca):



(IIca),

wherein

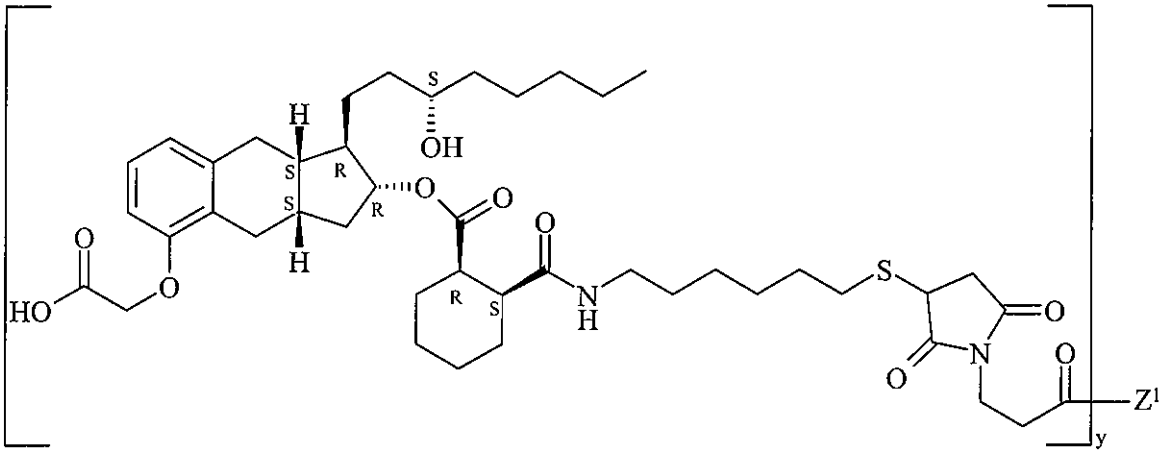
t ranges from 80 to 160;

w ranges from 2 to 6; and

dashed lines indicate attachment to the rest of the carrier-linked treprostinil prodrug.

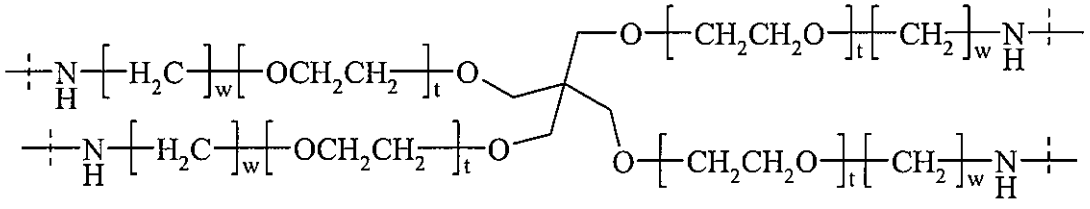
26. The carrier-linked treprostinil prodrug of claim 25, wherein w is 2 or 3.

27. The carrier-linked treprostinil prodrug of any one of claims 1 to 26 of formula (IIc) or a pharmaceutically acceptable salt thereof:



(IIc),

wherein y is 4 and Z^1 represents a moiety (IIca):



(IIca),

wherein dashed lines indicate attachment to the rest of the structure of formula (IIc), t ranges from 80 to 160 and w is 2 or 3.

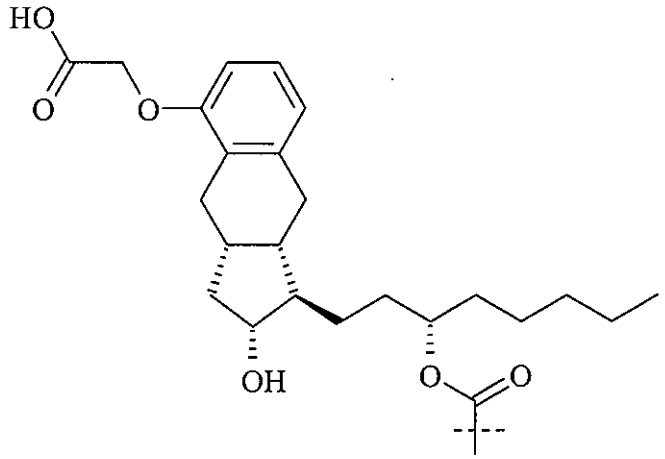
28. The carrier-linked treprostinil prodrug of claim 1, wherein R^{a1} is C_{1-6} alkyl or substituted C_{1-6} alkyl.

29. The carrier-linked treprostinil prodrug of any one of claims 1 to 6, wherein R^{a3} is H, C_{1-6} alkyl or substituted C_{1-6} alkyl.

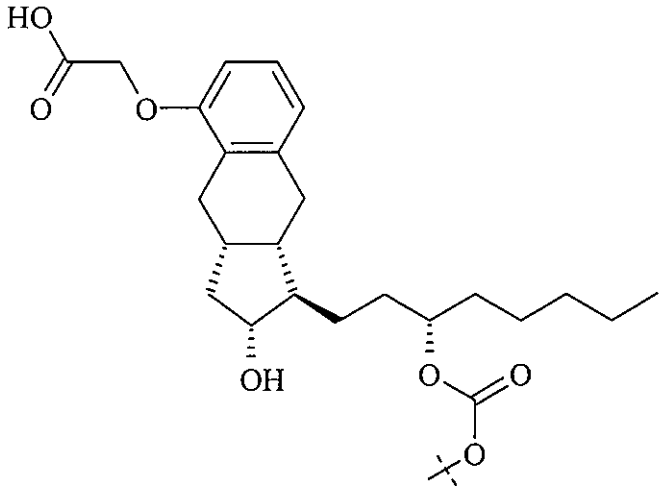
30. A carrier-linked treprostinil prodrug of formula (I):

$$Z^1\text{-}(X^0 - T)_y \qquad (I),$$

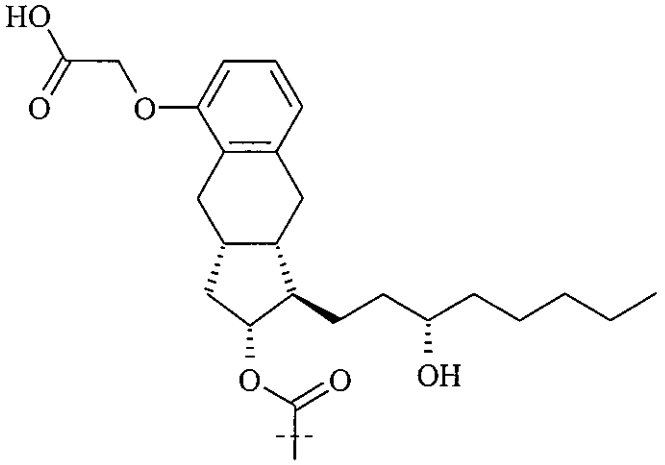
wherein each T is independently selected from structures (i) to (v):



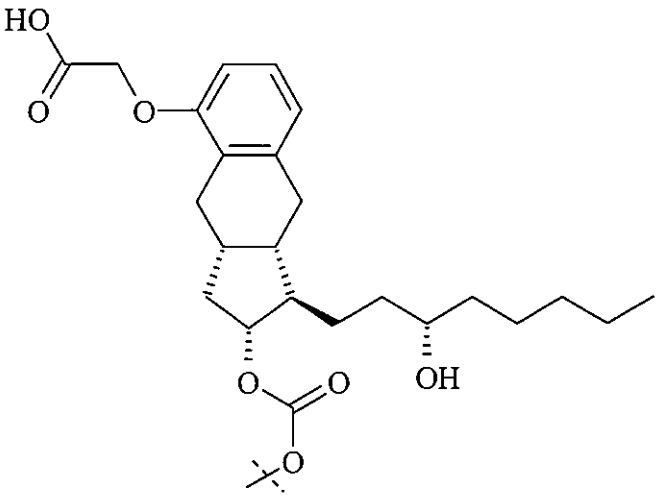
(i),



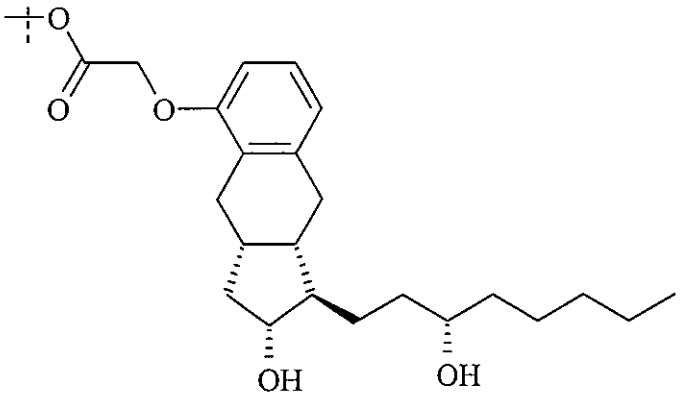
(ii),



(iii),



(iv),



(v),

wherein dashed lines indicating attachment to X^0;

y is an integer ranging of from 1 to 64,

each X^0 is independently $(X^{0A})_{m1}$-$(X^{0B})_{m2}$;

m1; m2 are independently 0; or 1;

X^{0A} is T^0;

X^{0B} is a branched or unbranched C_{1-15} alkylene group which is unsubstituted or substituted with one or more R^3, which are the same or different;

R^3 is halogen; C_{1-6} alkyl; CN; $C(O)R^4$; $C(O)OR^4$; OR^4; $C(O)R^4$; $C(O)N(R^4R^{4a})$; $S(O)_2N(R^4R^{4a})$; $S(O)N(R^4R^{4a})$; $S(O)_2R^4$; $S(O)R^4$; $N(R^4)S(O)_2N(R^{4a}R^{4b})$; SR^4; $N(R^4R^{4a})$; NO_2; $OC(O)R^4$; $N(R^4)C(O)R^{4a}$; $N(R^4)SO_2R^{4a}$; $N(R^4)S(O)R^{4a}$; $N(R^4)C(O)N(R^{4a}R^{4b})$; $N(R^4)C(O)OR^{4a}$; $OC(O)N(R^4R^{4a})$; or T^0;

R^4, R^{4a}, R^{4b} are independently selected from the group consisting of H; T^0; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^5, which are the same of different;

R^5 is halogen; CN; $C(O)R^6$; $C(O)OR^6$; OR^6; $C(O)R^6$; $C(O)N(R^6R^{6a})$; $S(O)_2N(R^6R^{6a})$; $S(O)N(R^6R^{6a})$; $S(O)_2R^6$; $S(O)R^6$; $N(R^6)S(O)_2N(R^{6a}R^{6b})$; SR^6; $N(R^6R^{6a})$; NO_2; $OC(O)R^6$; $N(R^6)C(O)R^{6a}$; $N(R^6)SO_2R^{6a}$; $N(R^6)S(O)R^{6a}$; $N(R^6)C(O)N(R^{6a}R^{6b})$; $N(R^6)C(O)OR^{6a}$; $OC(O)N(R^6R^{6a})$;

R^6, R^{6a}, R^{6b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same of different;

T^0 is phenyl; naphthyl; azulenyl; indenyl; indanyl; C_{3-7} cycloalkyl; 3 to 7 membered heterocyclyl; or 8 to 11 membered heterobicyclyl, wherein T^0, is optionally substituted with one or more R^7, which are the same or different;

R^7 is halogen; CN; $COOR^8$; OR^8; $C(O)R^8$; $C(O)N(R^8R^{8a})$; $S(O)_2N(R^8R^{8a})$; $S(O)N(R^8R^{8a})$; $S(O)_2R^8$; $S(O)R^8$; $N(R^8)S(O)_2N(R^{8a}R^{8b})$; SR^8; $N(R^8R^{8a})$; NO_2; $OC(O)R^8$; $N(R^8)C(O)R^{8a}$; $N(R^8)S(O)_2R^{8a}$; $N(R^8)S(O)R^{8a}$; $N(R^8)C(O)OR^{8a}$; $N(R^8)C(O)N(R^{8a}R^{8b})$; $OC(O)N(R^8R^{8a})$; oxo (=O), where the ring is at least partially saturated; C_{1-6} alkyl; C_{2-6} alkenyl; or C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^9, which are the same or different;

R^8, R^{8a}, R^{8b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more R^{10}, which are the same of different;

R^9, R^{10} are independently selected from the group consisting of halogen; CN; $C(O)R^{11}$; $C(O)OR^{11}$; OR^{11}; $C(O)R^{11}$; $C(O)N(R^{11}R^{11a})$; $S(O)_2N(R^{11}R^{11a})$; $S(O)N(R^{11}R^{11a})$; $S(O)_2R^{11}$; $S(O)R^{11}$; $N(R^{11})S(O)_2N(R^{11a}R^{11b})$; SR^{11}; $N(R^{11}R^{11a})$; NO_2; $OC(O)R^{11}$; $N(R^{11})C(O)R^{11a}$; $N(R^{11})SO_2R^{11a}$; $N(R^{11})S(O)R^{11a}$; $N(R^{11})C(O)N(R^{11a}R^{11b})$; $N(R^{11})C(O)OR^{11a}$; and $OC(O)N(R^{11}R^{11a})$;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same of different;

Z^1 is a carrier comprising a covalently bound polymer,

wherein the carrier is covalently attached to a moiety X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

or a pharmaceutically acceptable salt thereof.

31. The carrier-linked treprostinil prodrug of claim 30, wherein y is an integer ranging of from 1 to 16.

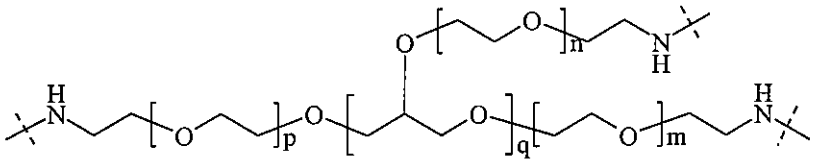
32. The carrier-linked treprostinil prodrug of claim 30, wherein y is selected from 1, 2, 3, 4, 5, 6, 7 8, 9, 10, 11, 12, 13, 14, 15 and 16.

33. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 30 to 32, wherein Z^1 comprises a PEG-based polymer.

34. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 30 to 33, wherein Z^1 comprises a water-soluble polymer.

35. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 30 to 34, wherein y is an integer of from 4 to 16.

36. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 23 and 30 to 35, wherein Z^1 has the structure of formula (III):



(III),

wherein

dashed lines indicate attachment to X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

each of m, n, and p are independently an integer ranging of from 5 to 500,

and q ranges of from 2 to 32.

37. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 23 and 30 to 35, wherein Z^1 is of formula (VI):

$$B\text{-}(\text{-}A\text{-}Hyp^y)_n \quad (VI),$$

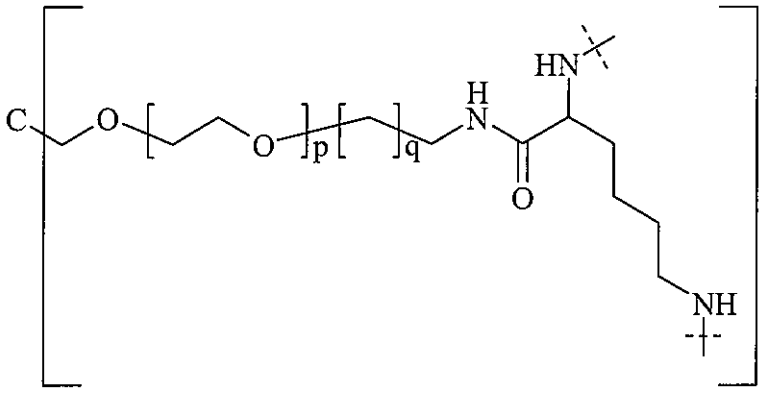
wherein

B is a branching core,
each A is independently a poly(ethylene glycol)-based polymeric chain,

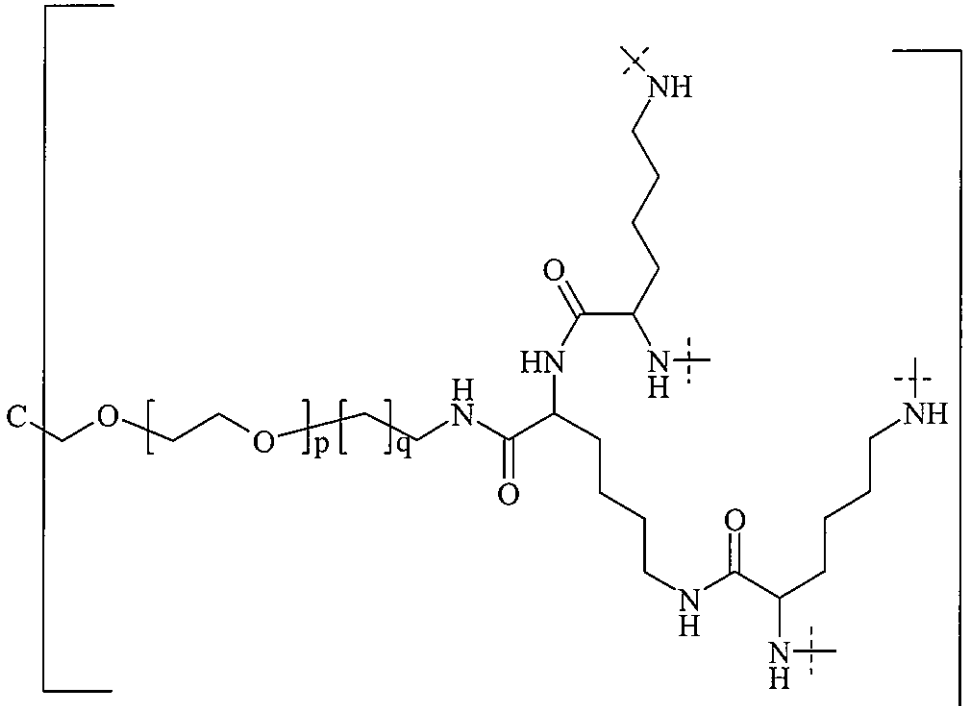
each Hyp^y is independently a branched moiety, and

n is an integer of from 3 to 32.

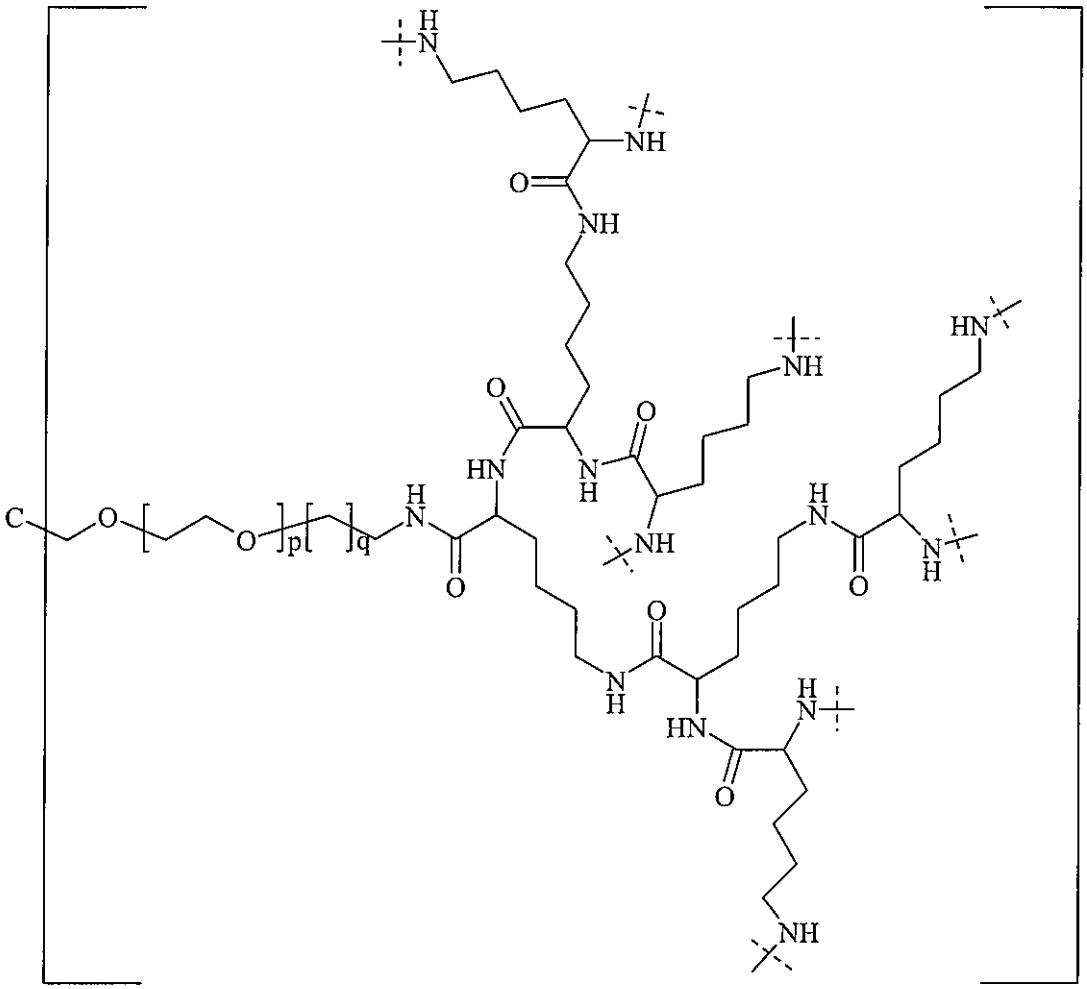
38. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 37, wherein Z^1 is selected from structures (i-y) to (iii-y):



(i-y),



(ii-y),



4

(iii-y);

wherein

dashed lines indicate attachment to X^0 of formula (I) , provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

p is an integer of from 5 to 2000,

q is 1 or 2.

39. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 23 and 30 to 35, wherein Z^1 has the structure of formula (V)

$Hyp^1{}_{mx} - POL^x - Hyp^2$ (V),

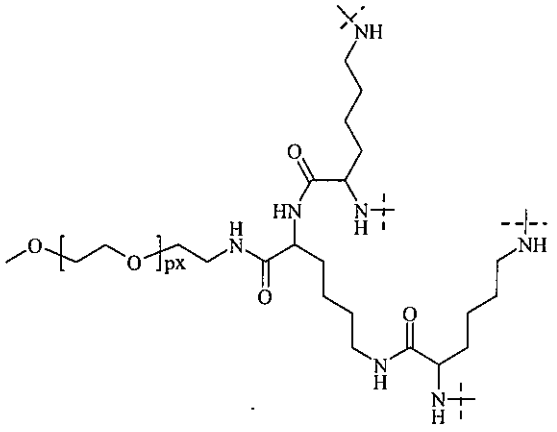
wherein

POL^x is a polymeric moiety having a molecular weight ranging from 0.5 kDa to 160 kDa,

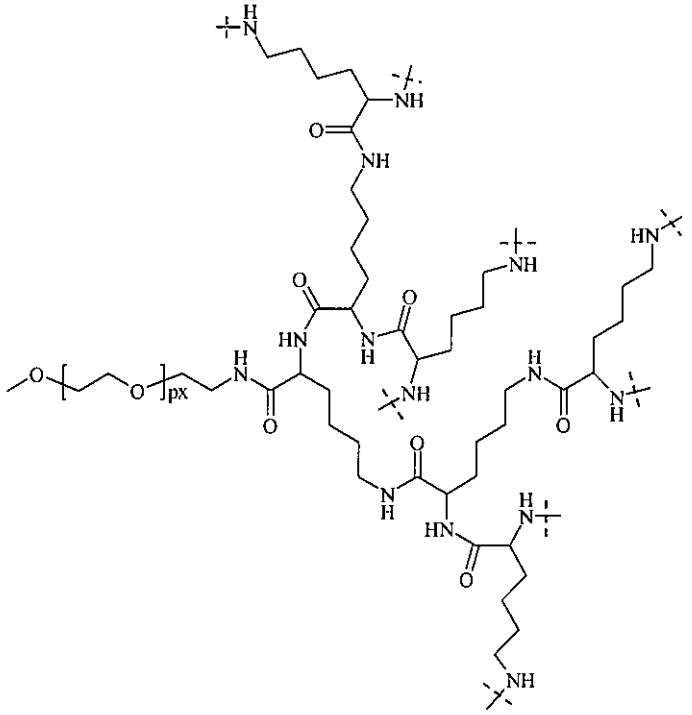
Hyp^1 and Hyp^2 are independently a hyperbranched moiety, and

mx is 0 or 1.

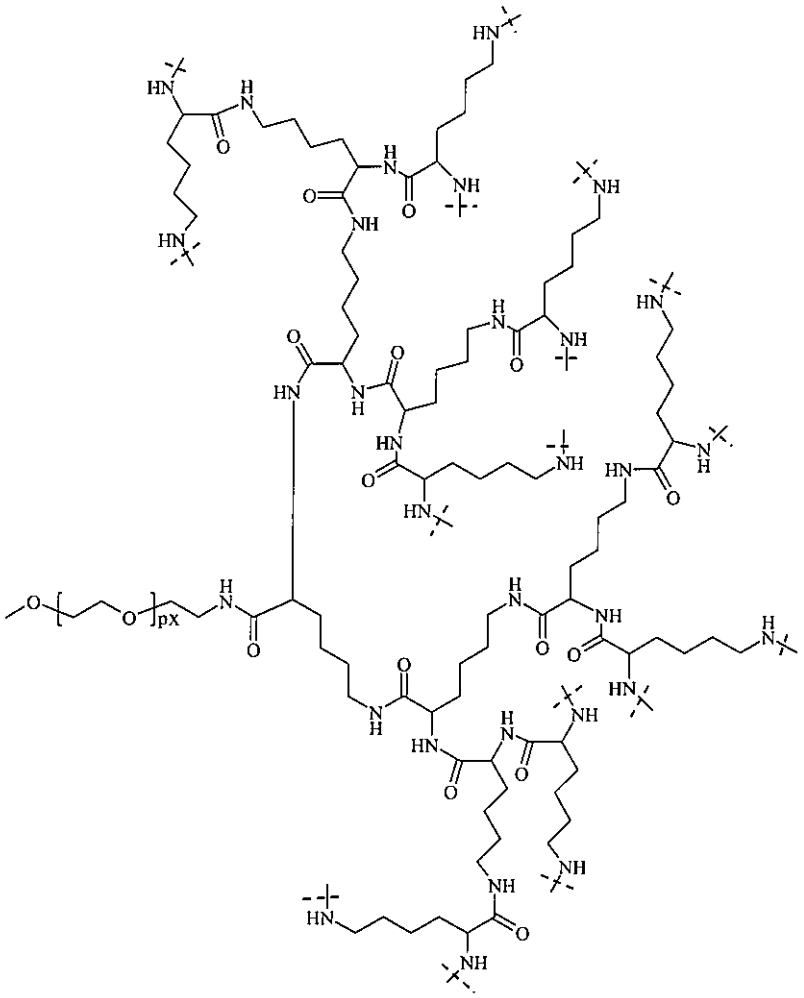
40. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 39, wherein mx is 0 and $POL^x - Hyp^2$ is selected from the following structures:



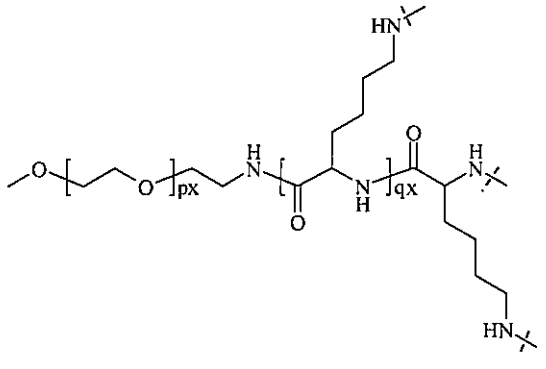
(v-x),



(vi-x),



(vii-x),



(viii-x),

wherein

dashed lines indicate attachment to a moiety X^0, provided that one of m1, m2 is 1 and wherein the carrier is covalently attached to T in case m1, m2 = 0,

px is an integer of from 5 to 2000, and

qx is an integer of from 0 to 15.

41. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 23 and 30 to 35, wherein Z^1 comprises an amino acid sequence of at least 100 amino acid residues, and

wherein the amino acid sequence of at least 100 amino acid residues is in random coil conformation, and,

wherein the amino acid sequence of at least 100 amino acid residues comprises alanine, serine and proline residues.

42. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 30 to 41, wherein each X^0 is unsubstituted.

43. A pharmaceutical composition comprising a carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 42 thereof, optionally together with one or more pharmaceutically acceptable excipients.

44. A pharmaceutical composition according to claim 43,

(i) wherein the carrier-linked treprostinil prodrug is sufficiently dosed in the pharmaceutical composition to provide a therapeutically effective amount of treprostinil for at least 12 hours in one application, and/or

(ii) wherein a single dose of the pharmaceutical composition comprises 2 to 6.

45. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 42, or a pharmaceutical composition of claim 43 or 44, for use as a medicament.

46. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 42 or a pharmaceutical composition of claim 43 or 44 for use in a method of treating or preventing a disease or disorder which can be treated and/or prevented by treprostinil.

47. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof or the pharmaceutical composition for the use of claim 46, wherein the disease or disorder is pulmonary arterial hypertension.

48. The water-soluble carrier-linked prodrug or a pharmaceutically acceptable salt thereof of any one of claim 1 to 42 or the pharmaceutical composition of claim 43 or 44, for use as medicament for topical, enteral administration, parenteral administration, inhalation, injection, or infusion, intraarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, and intraperitoneal, intrathecal, intracapsular, intraorbital, intracardiac, transtracheal, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intraventricular or intrasternal administration.