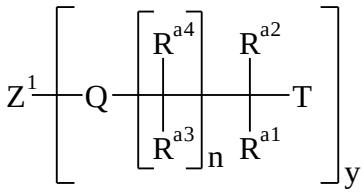
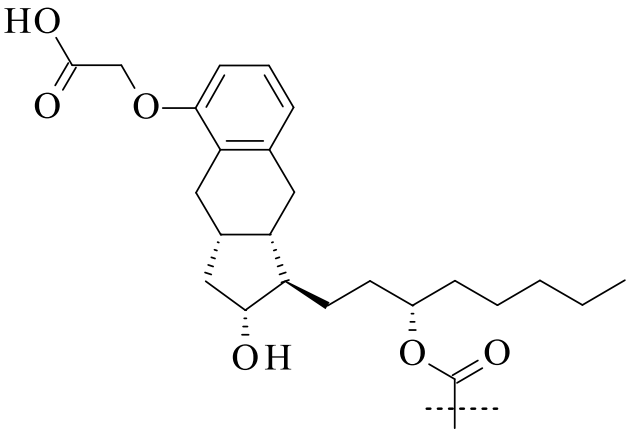
Claims

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

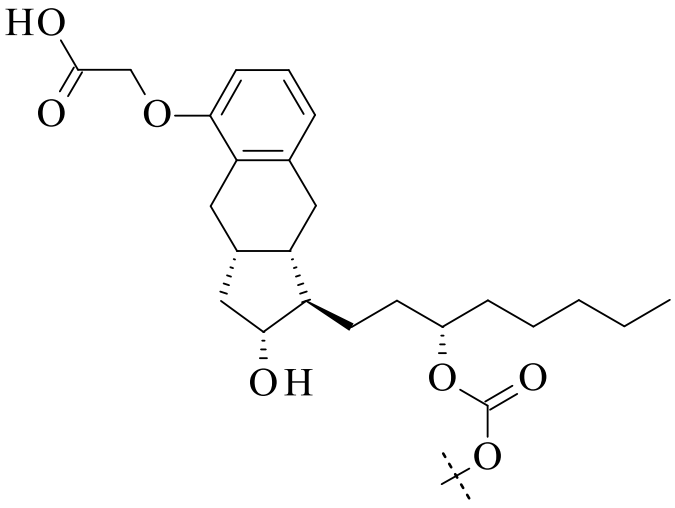


(II),

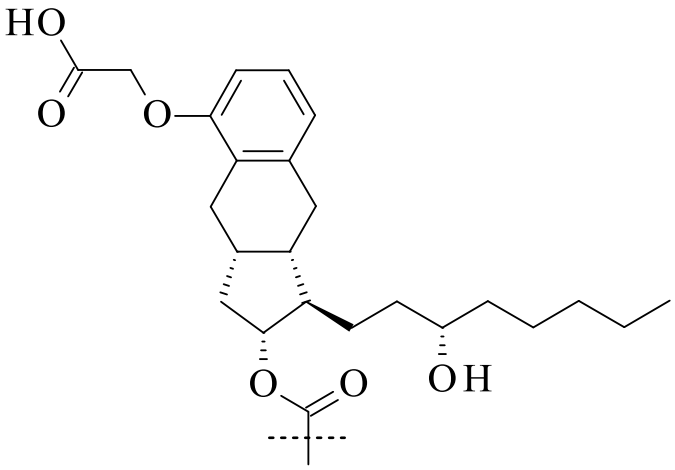
wherein each T is independently selected from structures (i) to (v):



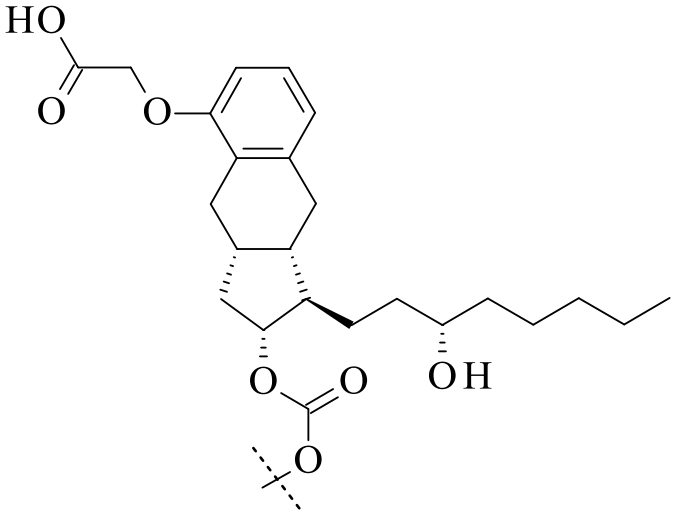
(i),



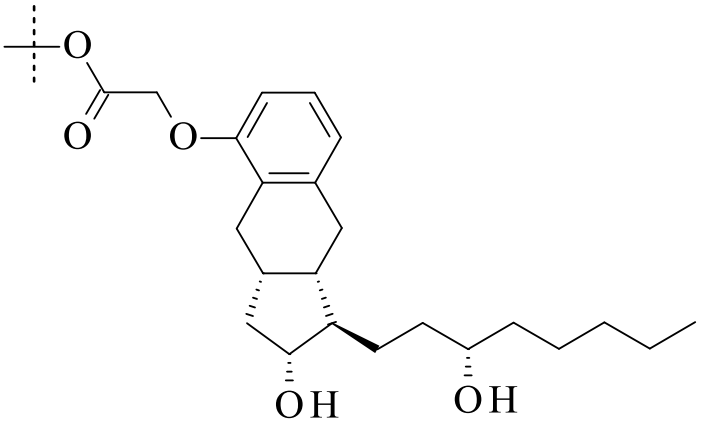
(ii),



(iii),



(iv),



(v),

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

y is an integer ranging from 1 to 64,

R^{a2} is selected from H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} alkyl;

R^{a4} is selected from the group consisting of H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} alkyl;

n is 0 or 1;

Q is a spacer moiety 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;

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,
wherein a substituted moiety is a moiety in which one or more hydrogen atom(s) are replaced by a substituent selected from the group consisting of halogen, CN, $COOR^{b9}$, OR^{b9}, $C(O)R^{b9}$, C(O)N($R^{b9}R^{b9a}$), $S(O)_2$N($R^{b9}R^{b9a}$), S(O)N($R^{b9}R^{b9a}$), $S(O)_2R^{b9}$, $S(O)R^{b9}$, N(R^{b9})$S(O)_2$N($R^{b9a}R^{b9b}$), SR^{b9}, N($R^{b9}R^{b9a}$), NO_2, OC(O)R^{b9}, N(R^{b9})C(O)R^{b9a}, N(R^{b9})$S(O)_2R^{b9a}$, N(R^{b9})S(O)R^{b9a}, N(R^{b9})C(O)OR^{b9a}, N(R^{b9})C(O)N($R^{b9a}R^{b9b}$), OC(O)N($R^{b9}R^{b9a}$), T^b, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl,

wherein T^b, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{b10}, 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 T^b, -C(O)O-; -O-; -C(O)-; -C(O)N(R^{b11})-; -$S(O)_2$N(R^{b11})-; -S(O)N(R^{b11})-; -$S(O)_2$-; -S(O)-; -N(R^{b11})$S(O)_2$N(R^{b11a})-; -S-; -N(R^{b11})-; -OC(O)R^{b11}; -N(R^{b11})C(O)-; -N(R^{b11})$S(O)_2$-; -N(R^{b11})S(O)-; -N(R^{b11})C(O)O-; -N(R^{b11})C(O)N(R^{b11a})-; and -OC(O)N($R^{b11}R^{b11a}$);

R^{b9}, R^{b9a}, R^{b9b} are independently selected from the group consisting of H; T^b; and C_{1-50} alkyl; C_{2-50} alkenyl; and C_{2-50} alkynyl,

wherein T^b, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^{b10}, 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 T^b, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{b11})-, -$S(O)_2$N(R^{b11})-, -S(O)N(R^{b11})-, -$S(O)_2$-, -S(O)-, -N(R^{b11})$S(O)_2$N(R^{b11a})-, -S-, -N(R^{b11})-, -OC(O)R^{b11}, -N(R^{b11})C(O)-, -N(R^{b11})$S(O)_2$-, -N(R^{b11})S(O)-, -N(R^{b11})C(O)O-, -N(R^{b11})C(O)N(R^{b11a})-, and -OC(O)N($R^{b11}R^{b11a}$),

T^b is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 4- to 7-membered heterocyclyl, and 9- to 11-membered heterobicyclyl, wherein T^b is optionally substituted with one or more R^{b10}, which are the same or different,

R^{b10} is halogen, CN, oxo (=O), $COOR^{b12}$, OR^{b12}, $C(O)R^{b12}$, C(O)N($R^{b12}R^{b12a}$), $S(O)_2$N($R^{b12}R^{b12a}$), S(O)N($R^{b12}R^{b12a}$), $S(O)_2R^{b12}$, $S(O)R^{b12}$, N(R^{b12})$S(O)_2$N($R^{b12a}R^{b12b}$), SR^{b12}, N($R^{b12}R^{b12a}$), NO_2, OC(O)R^{b12}, N(R^{b12})C(O)R^{b12a}, N(R^{b12})$S(O)_2R^{b12a}$, N(R^{b12})S(O)R^{b12a}, N(R^{b12})C(O)OR^{b12a}, N(R^{b12})C(O)N($R^{b12a}R^{b12b}$), OC(O)N($R^{b12}R^{b12a}$), 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^{b11}, R^{b11a}, R^{b12}, R^{b12a}, R^{b12b} are independently selected from the group consisting of H; or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different,

Z^1 is a carrier comprising a covalently bound polymer or a pharmaceutical salt thereof, wherein a polymer is a molecule consisting of repeating structural units connected by chemical bonds in a linear, circular, branched, crosslinked or dendrimeric way or a combination thereof, which can be of synthetic or biological origin or a combination of both and which has a molecular weight of at least 500 Da.

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

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

4. The carrier-linked treprostinil prodrug of any one of claims 1 to 3, wherein R^{a4} is H.

5. The carrier-linked treprostinil prodrug of any one of claims 1 to 4, wherein ring A is selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, and cycloheptane.

6. The carrier-linked treprostinil prodrug of any one of claims 1 to 5, wherein ring A is cyclohexane.

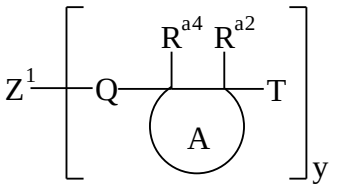
7. The carrier-linked treprostinil prodrug of any one of claims 1 to 6, wherein T is selected from structure (iii).

8. The carrier-linked treprostinil prodrug of any one of claims 1 to 7, wherein y is 4, 6, 8, 10, or 12.

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

10. The carrier-linked treprostinil prodrug of any one of claims 1 to 9, wherein y is 4.

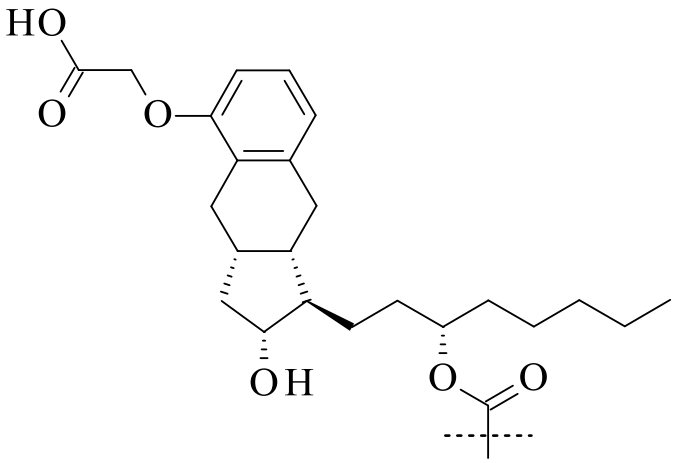
11. The carrier-linked treprostinil prodrug of any one of claims 1 to 10, wherein the carrier-linked treprostinil prodrug has the structure of formula (II-A):



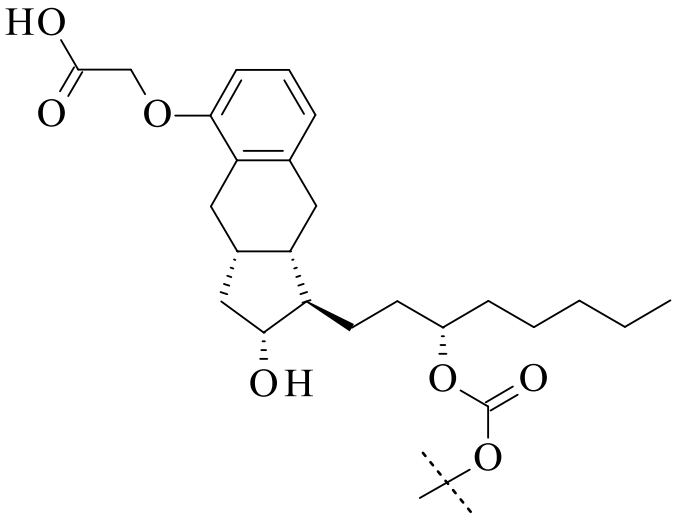
(II-A),

wherein

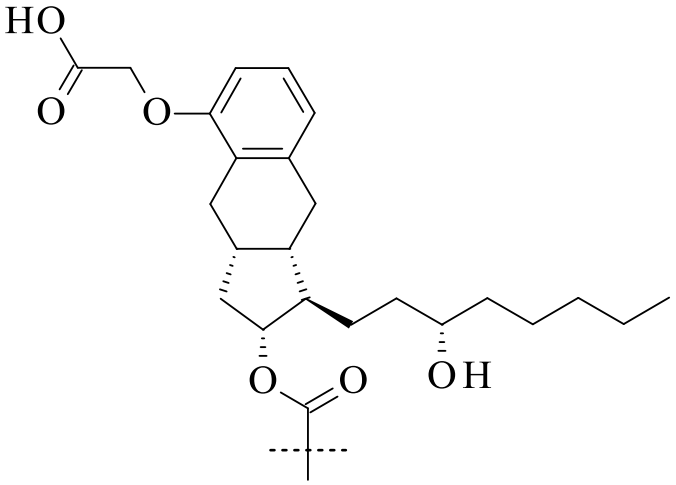
each T is independently selected from structures (i) to (v):



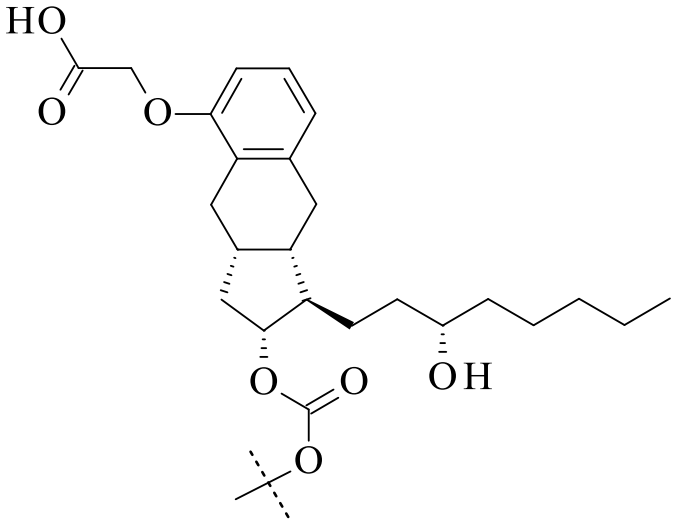
(i),



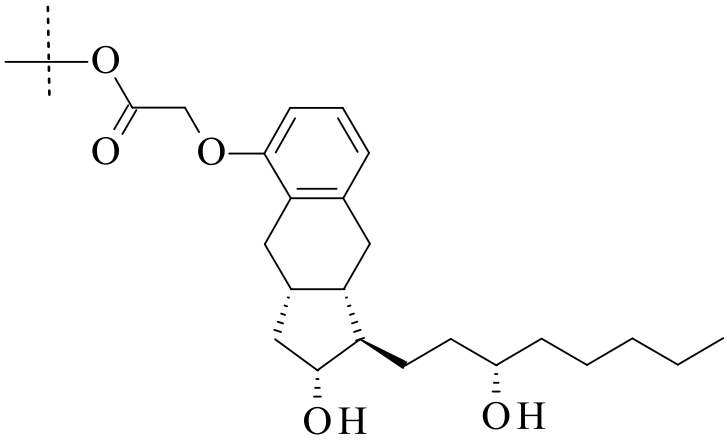
(ii),



(iii),



(iv),



(v),

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

y is an integer ranging from 1 to 64;

R^{a2} is selected from H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} alkyl;

R^{a4} is selected from the group consisting of H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} alkyl;

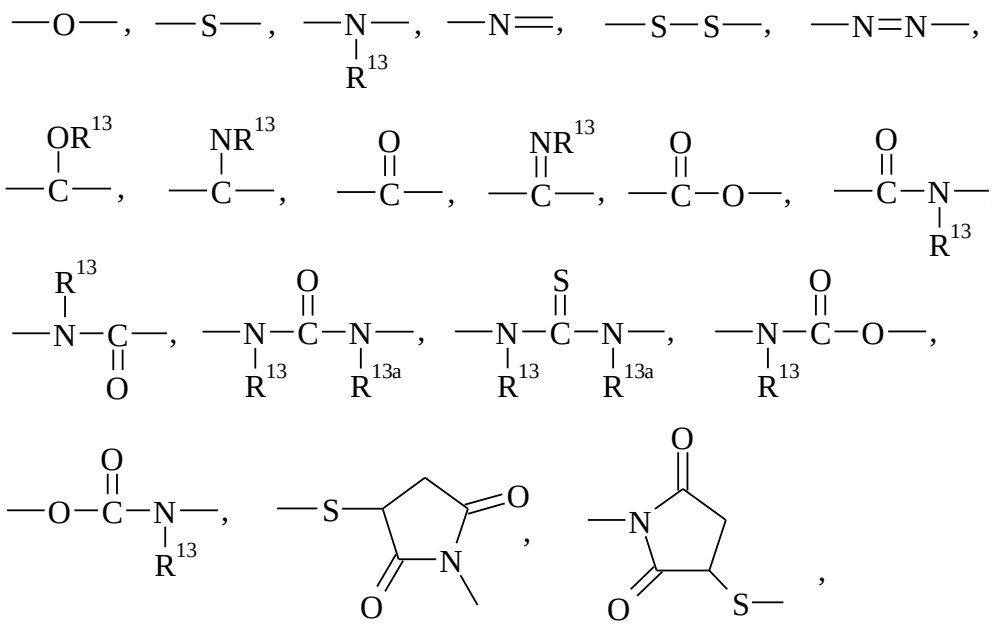
A, Q and Z^1 are used as defined in claim 1.

12. The carrier-linked treprostinil prodrug of claim 11, wherein y is 4.

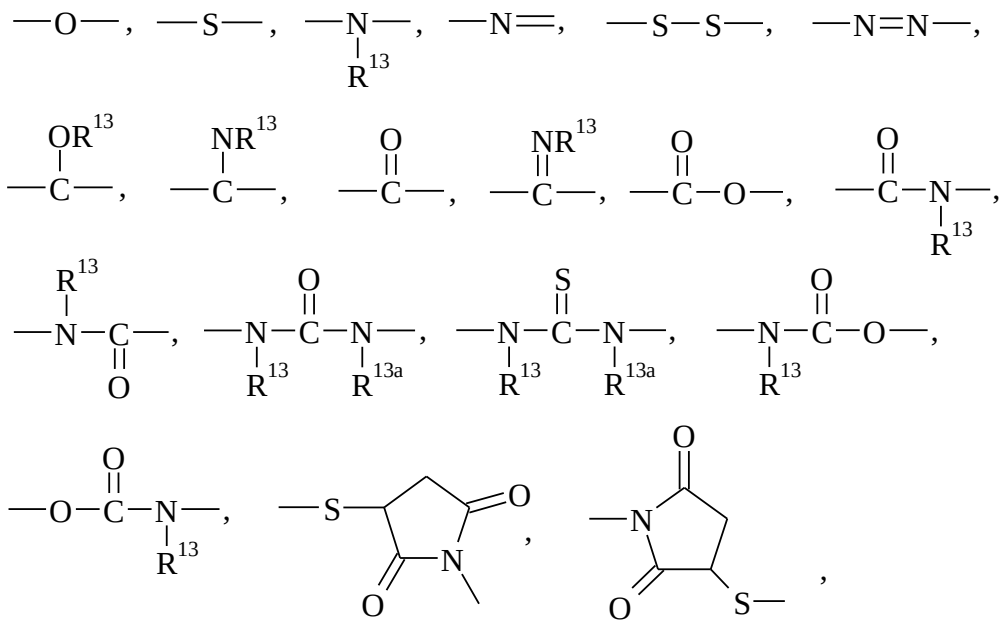
13. The carrier-linked treprostinil prodrug of claim 12, wherein each -Q- is independently $-Q^{1a}-Q^{1}-*$, wherein the asterisk indicates the connection to Z^1 and wherein

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-;

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,

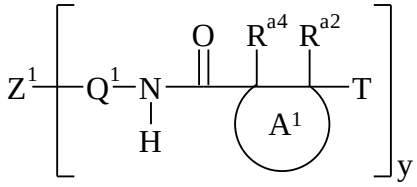


R^{a10} is halogen; CN; oxo (=O); $COOR^{a12}$; OR^{a12}; $C(O)R^{a12}$; $C(O)N(R^{a12}R^{a12a})$; $S(O)_2N(R^{a12}R^{a12a})$; $S(O)N(R^{a12}R^{a12a})$; $S(O)_2R^{a12}$; $S(O)R^{a12}$; $N(R^{a12})S(O)_2N(R^{a12a}R^{a12b})$; SR^{a12}; $N(R^{a12}R^{a12a})$; NO_2; $OC(O)R^{a12}$; $N(R^{a12})C(O)R^{a12a}$; $N(R^{a12})S(O)_2R^{a12a}$; $N(R^{a12})S(O)R^{a12a}$; $N(R^{a12})C(O)OR^{a12a}$; $N(R^{a12})C(O)N(R^{a12a}R^{a12b})$; $OC(O)N(R^{a12}R^{a12a})$; 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.

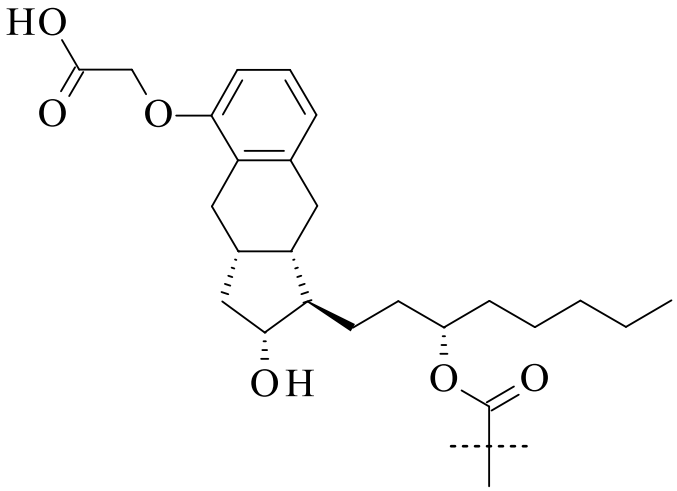
14. The carrier-linked treprostinil prodrug of any one of claims 1 to 13, wherein the carrier-linked treprostinil prodrug is of formula (IIaa):



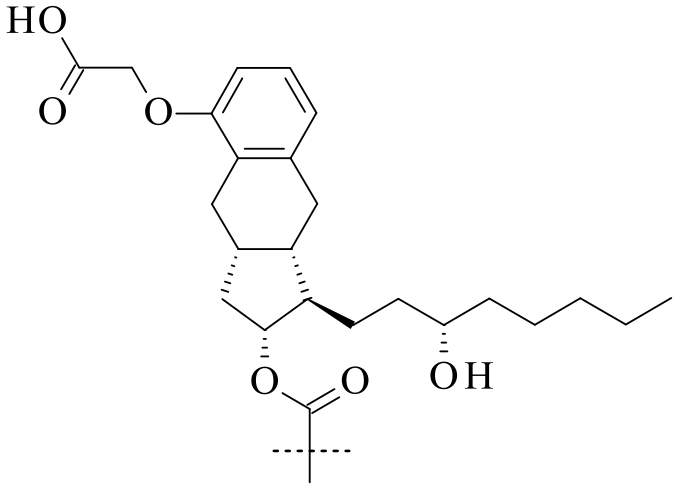
(IIaa),

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 from 1 to 64;

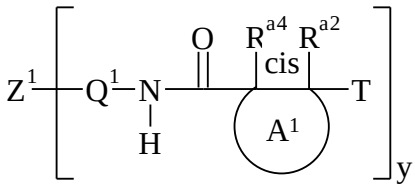
R^{a2} is selected from H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} alkyl;

R^{a4} is selected from H, unsubstituted C_{1-6} alkyl, and substituted C_{1-6} 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, Z^1 are used as defined in claim 13.

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

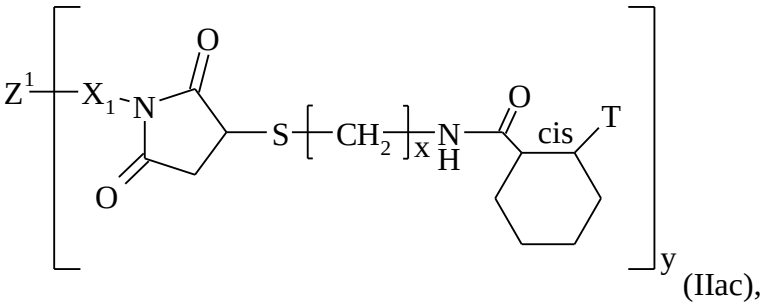


(IIab),

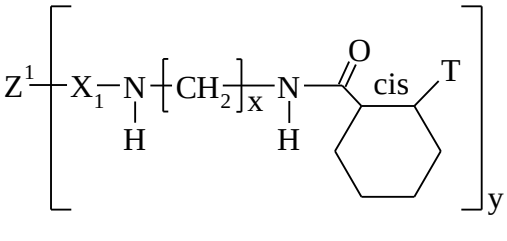
wherein

T, R^{a2}, R^{a4}, A^1, Q^1, Z^1 and y are used as defined in claim 7.

16. The carrier-linked treprostinil prodrug of any one of claims 1 to 15, wherein the carrier-linked treprostinil prodrug is of formula (IIac) or (IIad):



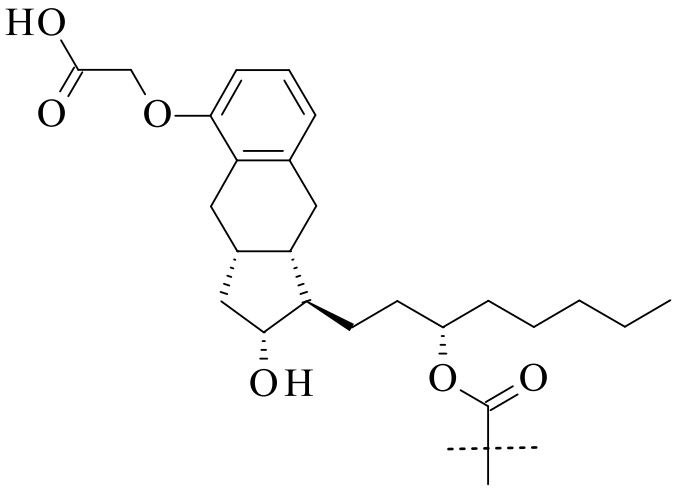
(IIac),



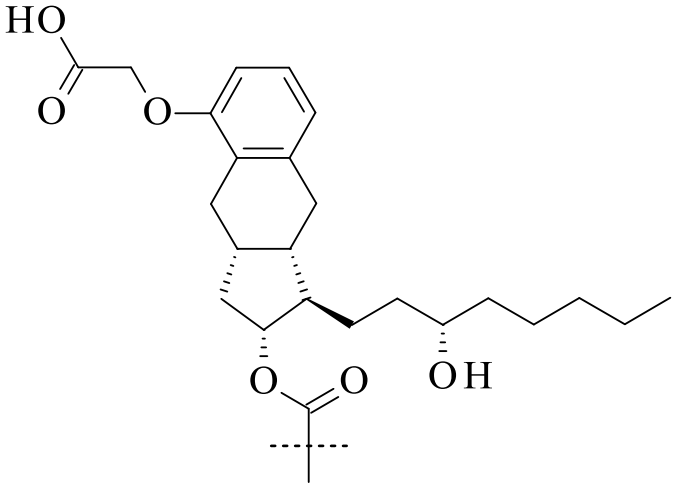
(IIad),

wherein

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



(i),



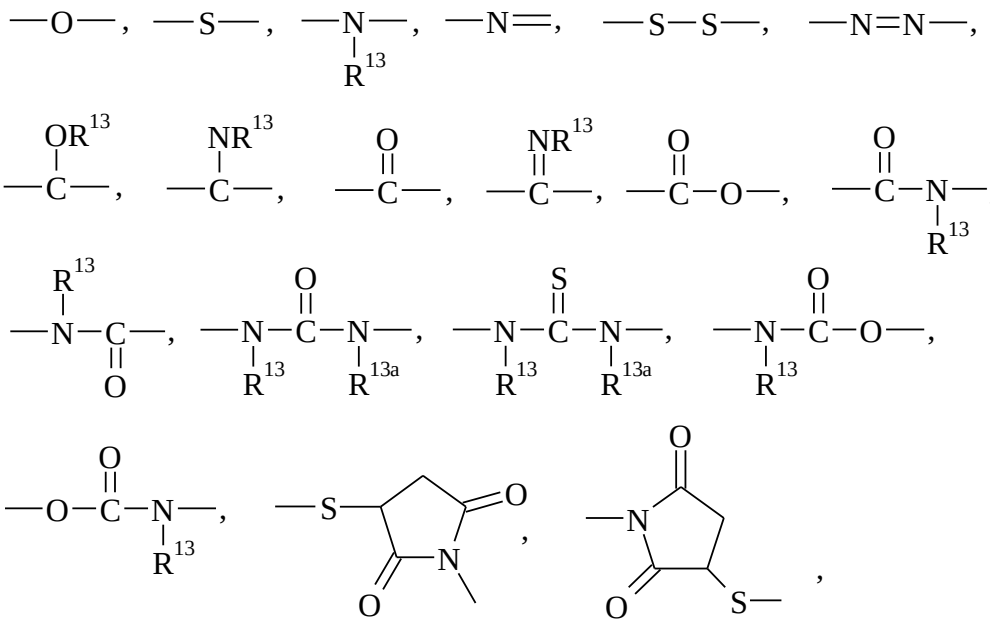
(iii),

Z^1 is used as defined in claim 1;

y is an integer ranging from 1 to 64,

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

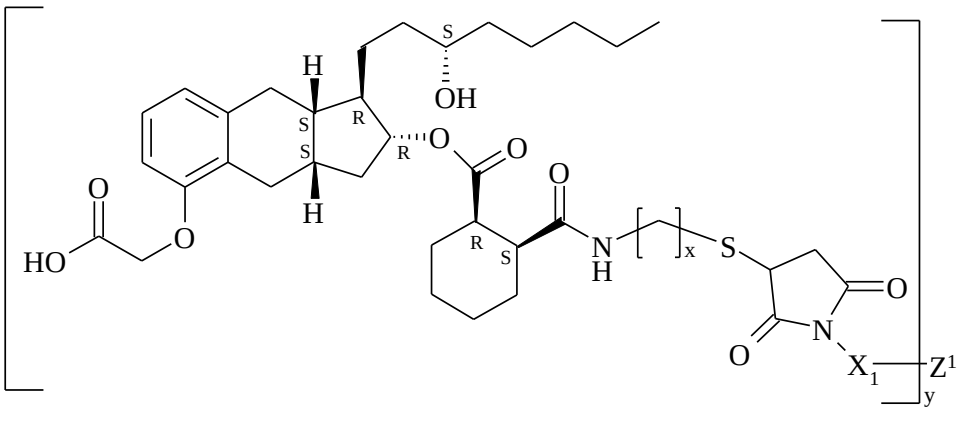
X_1 is selected from C_{1-15} alkyl, C_{2-15} alkenyl and C_{2-15} alkynyl, which are optionally substituted or interrupted by one or more groups selected from the group consisting of C_{3-7} cycloalkyl, 4- to 7-membered heterocyclyl,



wherein

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

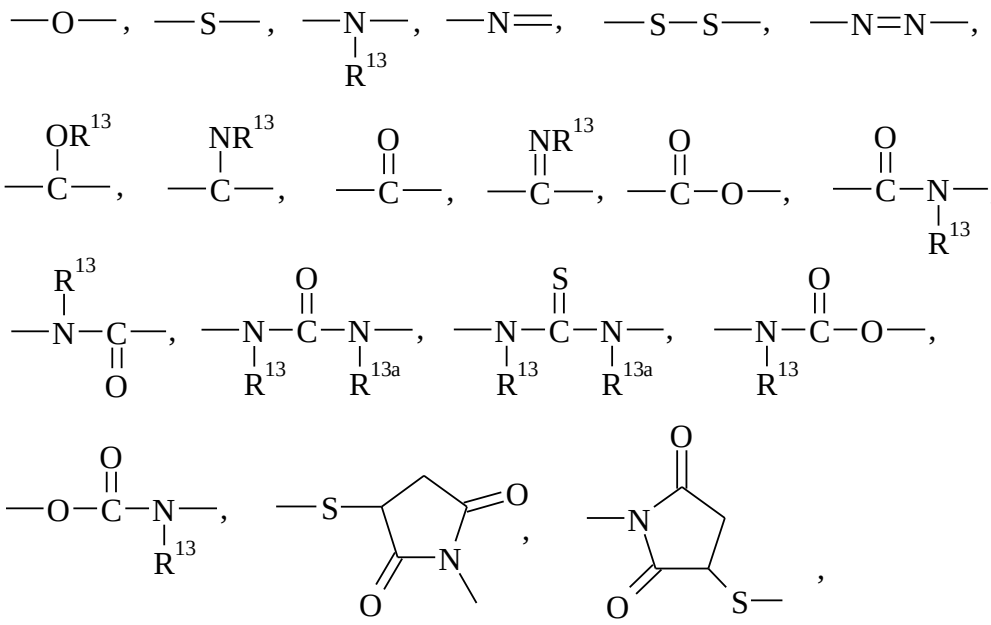
17. The carrier-linked treprostinil prodrug of any one of claims 1 to 16, wherein the carrier-linked treprostinil prodrug is of formula (IIb):



(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.

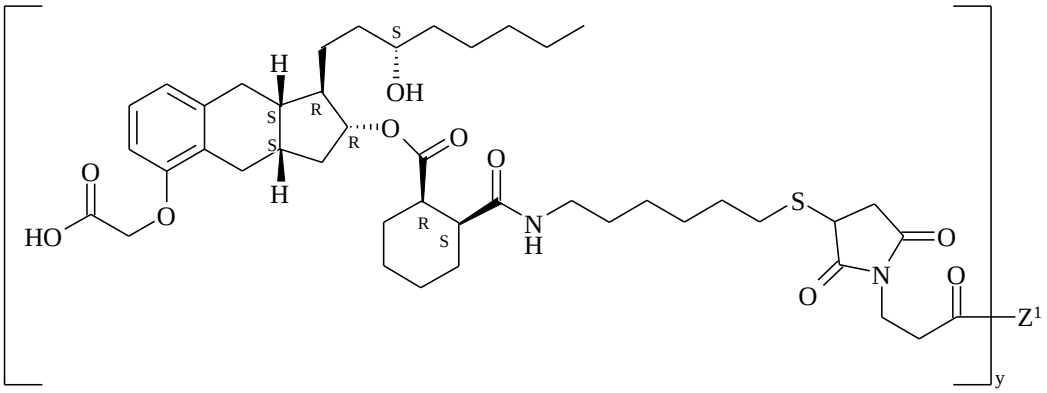
y is an integer ranging from 1 to 64;

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

Z^1 is used as defined in claim 1.

18. The carrier-linked treprostinil prodrug of claim 16 or 17, wherein x is 6.

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



(IIba),

wherein

y is an integer ranging from 1 to 64; and

Z^1 is used as defined in claim 1.

20. The carrier-linked treprostinil prodrug of any one of claims 1 to 19, wherein the carrier Z^1 has the structure of formula (VII):

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

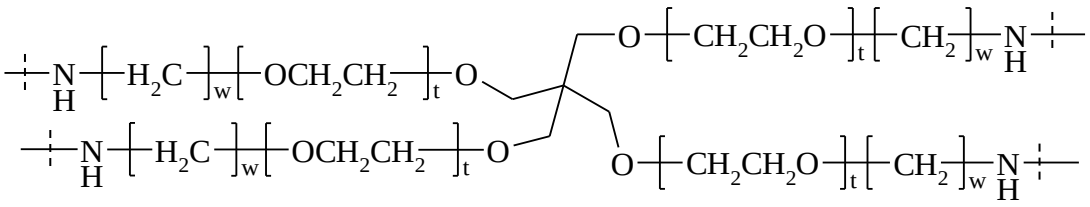
wherein

B is branching core,

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

n is an integer from 3 to 32.

21. The carrier-linked treprostinil prodrug of any one of claims 1 to 20, wherein Z^1 represents a moiety (IIca):



(IIca),

wherein

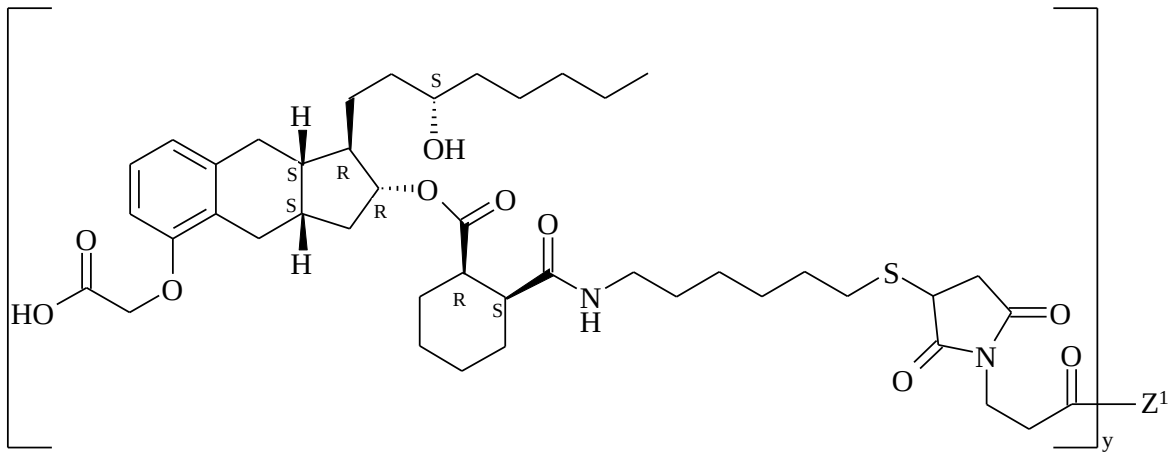
t ranges from 80 to 160;

w ranges from 2 to 6; and

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

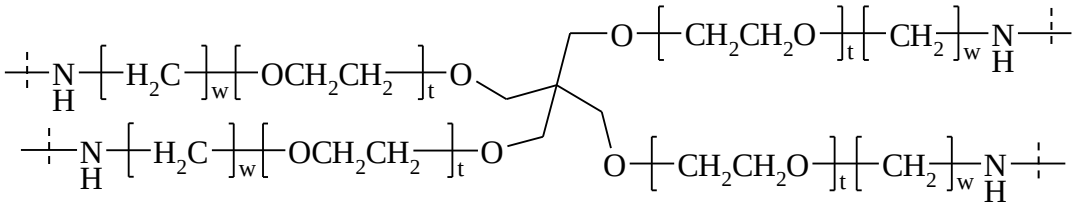
22. The carrier-linked treprostinil prodrug of claim 21, wherein w is 2 or 3.

23. The carrier-linked treprostinil prodrug of any one of claims 1 to 22 of formula (IIc) or a pharmaceutically acceptable salt thereof:



(IIc),

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

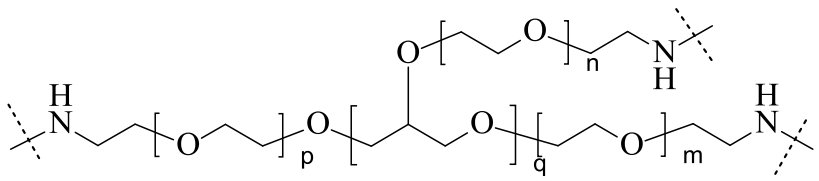


(IIca),

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.

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

25. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19 wherein Z^1 has the structure of formula (III):



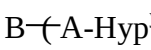
(III),

wherein

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

and q ranges from 2 to 32.

26. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19, wherein Z^1 is of formula (VI):



(VI),

wherein

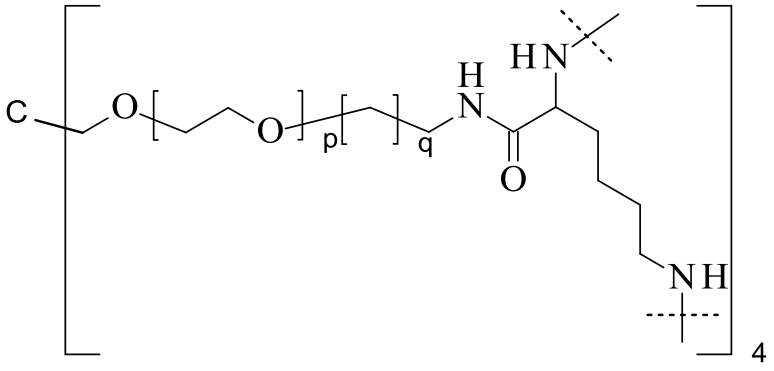
B is a branching core,

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

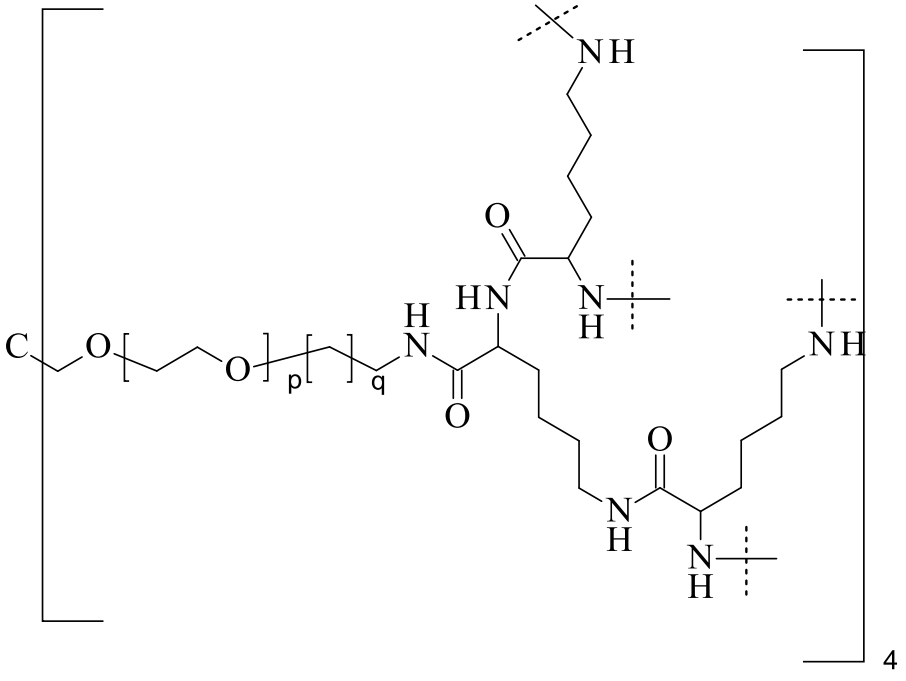
each Hyp^y is independently a branched moiety, and

n is an integer from 3 to 32.

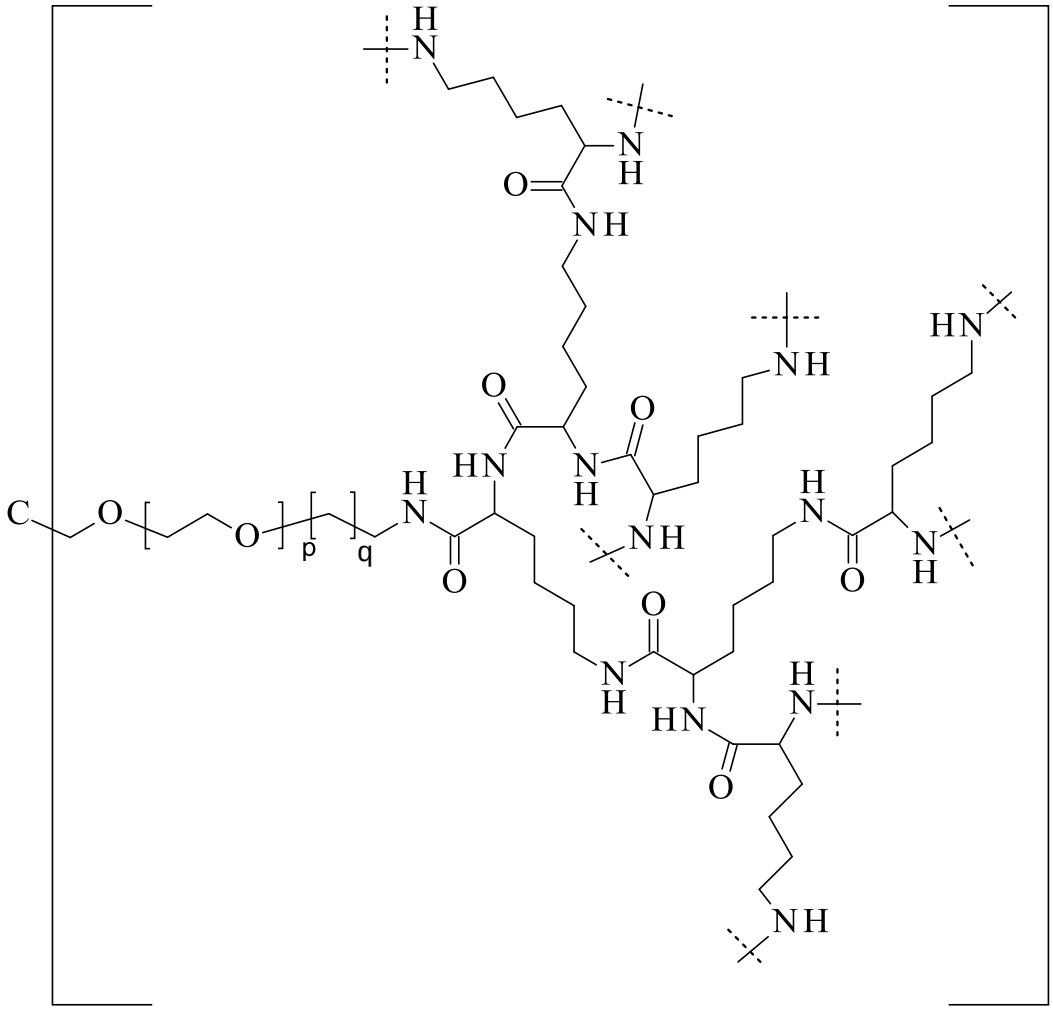
27. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 26, wherein Z^1 is selected from structures (i-y) to (iii-y):



(i-y),



(ii-y),



4

(iii-y);

wherein

p is an integer from 5 to 2000,

q is 1 or 2.

28. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19, wherein Z^1 has the structure of formula (V)

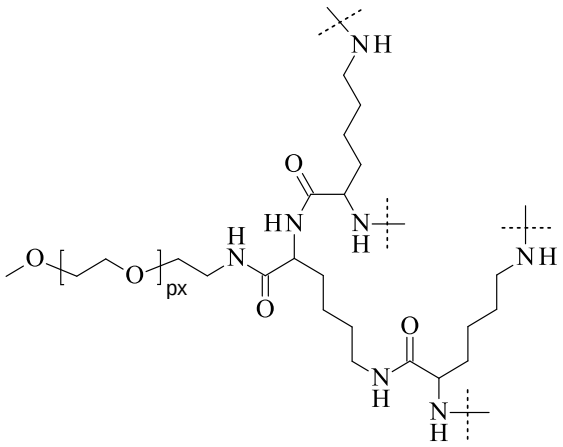
$Hyp^1{}_{mx} – POL^x – Hyp^2$ (V),
wherein

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

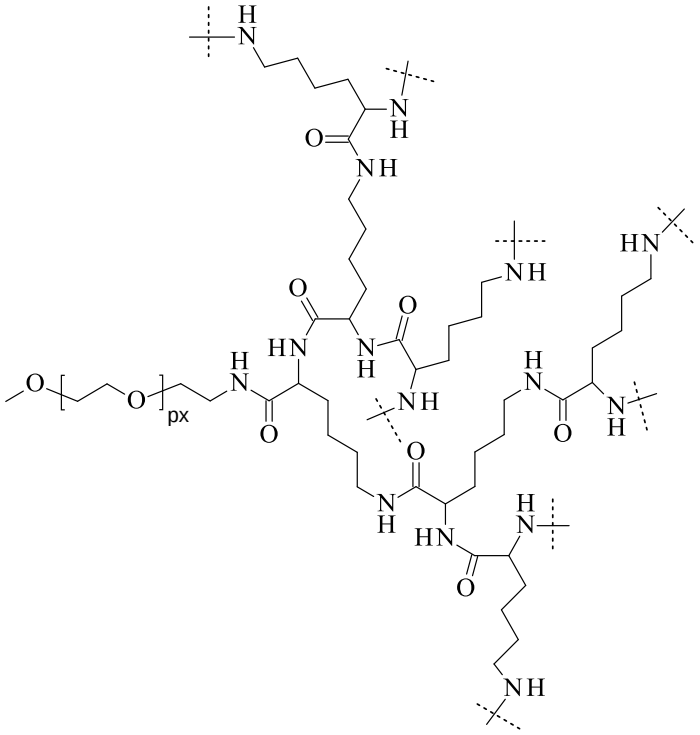
Hyp^1 and Hyp^2 are independently selected from the group consisting of, in bound form, trilysine, tetralysine, pentalysine, hexalysine, heptalysine, octalysine, nonalysine, decalysine, undecalysine, dodecalysine, tridecalysine, tetradecalysine, pentadecalysine, hexadecalysine, and heptadecalysine, and

mx is 0 or 1.

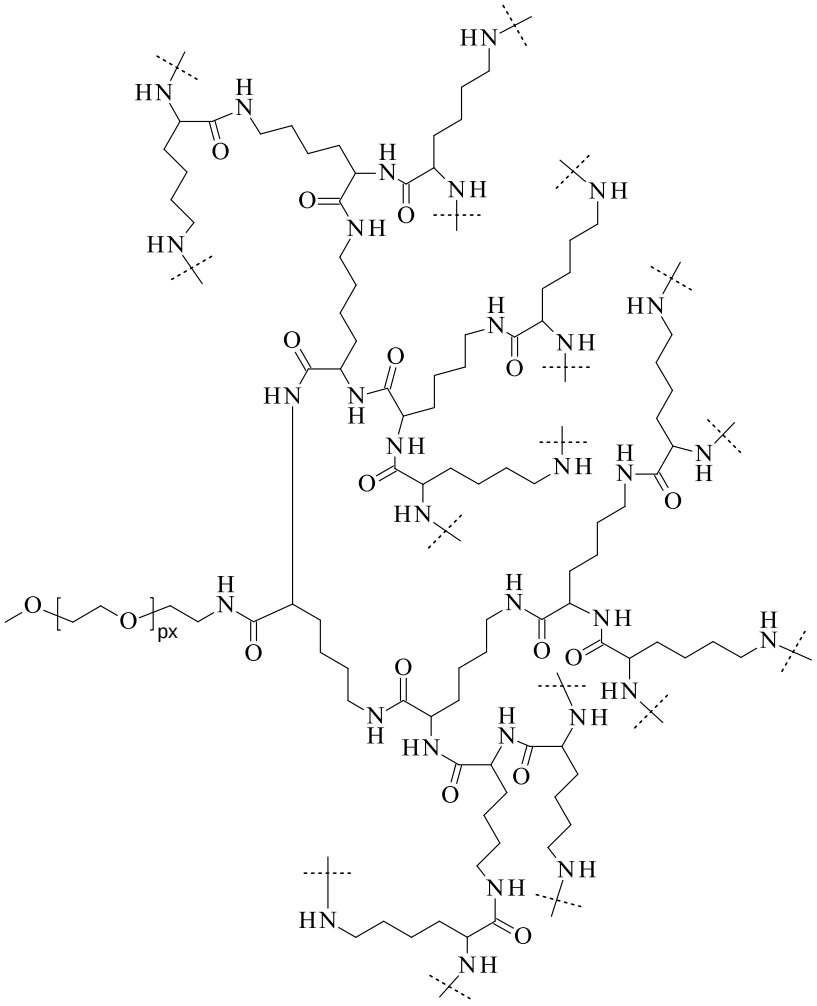
29. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of claim 28, wherein mx is 0 and POL^x – Hyp^2 is selected from the following structures:



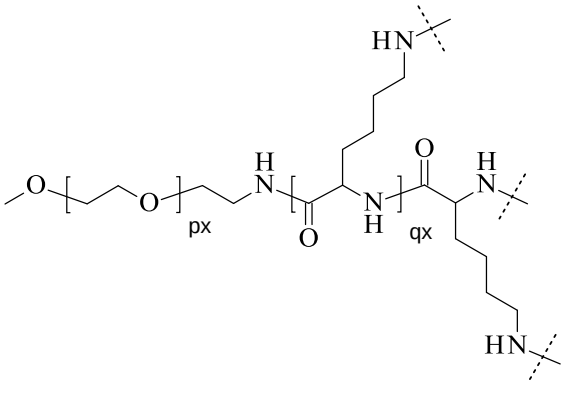
(v-x),



(vi-x),



(vii-x),



(viii-x),

wherein

px is an integer from 5 to 2000, and

qx is an integer from 0 to 15.

30. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19, 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.

31. A pharmaceutical composition comprising a carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 30 thereof, optionally together with one or more pharmaceutically acceptable excipients.

32. A pharmaceutical composition according to claim 31,

(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 mg treprostinil.

33. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 30, or a pharmaceutical composition of claim 31 or 32, for use as a medicament.

34. A carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 30 or a pharmaceutical composition of claim 31 or 32 for use in a method of treating or preventing a disease or disorder which can be treated and/or prevented by treprostinil.

35. The carrier-linked treprostinil prodrug or a pharmaceutically acceptable salt thereof or the pharmaceutical composition for the use of claim 31, wherein the disease or disorder is pulmonary arterial hypertension.

36. The water-soluble carrier-linked prodrug or a pharmaceutically acceptable salt thereof of any one of claim 1 to 30 or the pharmaceutical composition of claim 31 or 32, 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.