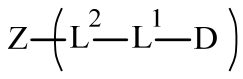
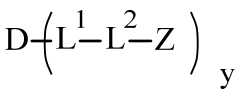
Claims

1. A PTH prodrug or a pharmaceutically acceptable salt thereof, wherein the prodrug is of formula (Ia) or (Ib)


(Ia),


(Ib),

wherein

-D is a PTH moiety;

-L^1- is a reversible prodrug linker moiety conjugated to the N-terminal amine functional group of -D, wherein the linkage between -L^1- and -D is cleavable in the absence of enzymes under physiological conditions with a half-life ranging from one hour to two months;

-L^2- is a single chemical bond or a spacer moiety;

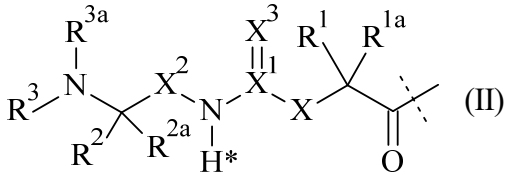
-Z is a branched PEG-based polymer;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16; and

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5.

2. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 1, wherein -D has the sequence of SEQ ID NO:51.

3. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 1 or 2, wherein the moiety -L^1- is of formula (II):


(II),

wherein the dashed line indicates the attachment to the N-terminal amine functional group -D;

-X- is -C(R^4R^{4a})-; -N(R^4)-; -O-; -C(R^4R^{4a})-C(R^5R^{5a})-; -C(R^5R^{5a})-C(R^4R^{4a})-; -C(R^4R^{4a})-N(R^6)-; -N(R^6)-C(R^4R^{4a})-; -C(R^4R^{4a})-O-; -O-C(R^4R^{4a})-; or -C(R^7R^{7a})-;

X^1 is C; or S(O);

$-X^2-$ is $-C(R^8R^{8a})-$; or $-C(R^8R^{8a})-C(R^9R^{9a})-$;

$=X^3$ is =O; =S; or =N-CN;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$, $-R^{9a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl;

$-R^3$, $-R^{3a}$ are independently selected from the group consisting of -H; and C_{1-6} alkyl, provided that in case one of $-R^3$, $-R^{3a}$ or both are other than -H they are connected to the N to which they are attached through an sp^3-hybridized carbon atom;

$-R^7$ is $-N(R^{10}R^{10a})$; or $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$, $-R^{11}$ are independently of each other -H; or C_{1-6} alkyl;

optionally, one or more of the pairs $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$, $-R^{8a}/-R^{9a}$ form a chemical bond;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$, $-R^9/-R^{9a}$ are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, $-R^2/-R^3$ are joined together with the atoms to which they are attached to form a ring A;

optionally, $-R^3/-R^{3a}$ are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

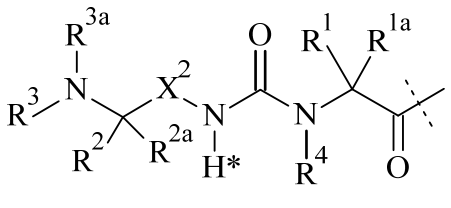
wherein $-L^1-$ is substituted with $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by $-L^2-Z$ or a substituent;

wherein

$-L^2-$ is a single chemical bond or a spacer; and

-Z is a PEG-based carrier.

4. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein the moiety $-L^1-$ is of formula (IIb-i):



(IIb-i),

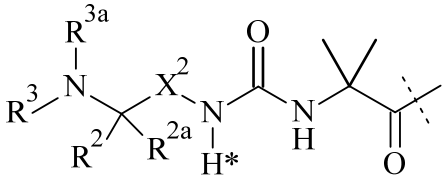
wherein

the dashed line indicates the attachment to the N-terminal amine functional group of -D by forming an amide bond;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$, $-R^4$ and $-X^2-$ are used as defined in claim 3; and

wherein $-L^1-$ is substituted with $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-i) is not replaced by $-L^2-Z$ or a substituent.

5. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein the moiety $-L^1-$ is of formula (IIb-ii):



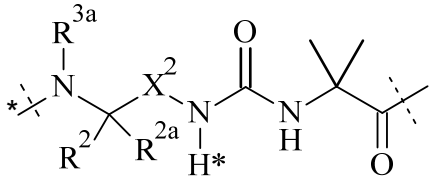
(IIb-ii),

wherein the dashed line indicates the attachment to the N-terminal amine functional group of -D by forming an amide bond;

$-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-X^2-$ are used as defined in claim 3; and

wherein $-L^1-$ is substituted with $-L^2-Z$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-ii) is not replaced by $-L^2-Z$ or a substituent.

6. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 5, wherein the moiety $-L^1-$ is of formula (IIb-ii'):



(IIb-ii'),

wherein

the dashed line indicates the attachment to the N-terminal amine functional group of -D by forming an amide bond;

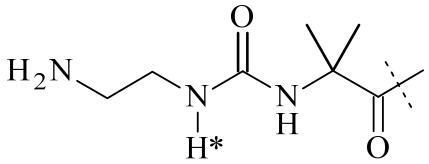
the dashed line marked with the asterisk indicates attachment to -L^2-;

-R^2, -R^{2a}, -R^{3a} and -X^2- are used as defined in claim 3; and

wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-ii') is not replaced by a substituent.

7. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 6, wherein -X^2- is -$C(R^8R^{8a})$-.

8. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 5 or 7, wherein the moiety -L^1- is of formula (IIb-iii):



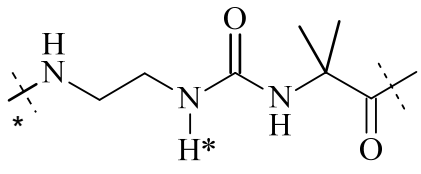
(IIb-iii),

wherein

the dashed line indicates the attachment to the N-terminal amine functional group of -D by forming an amide bond;

wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii) is not replaced by -L^2-Z or a substituent.

9. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 8, wherein the moiety -L^1- is of formula (IIb-iii'):



(IIb-iii'),

wherein

the dashed line indicates the attachment to the N-terminal functional group of -D by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to -L^2-;

wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii') is not replaced by a substituent.

10. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 9, wherein -L^2- is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)$_2$N(R^{y1})-, -S(O)N(R^{y1})-, -S(O)$_2$-, -S(O)-, -N(R^{y1})S(O)$_2$N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-, -OC(O)N(R^{y1})-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, 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-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})-, and -OC(O)N(R^{y3})-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, 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-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

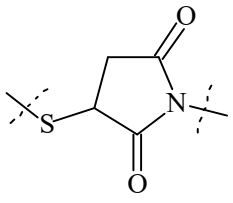
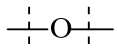
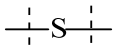
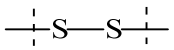
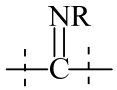
each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more -R^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -NO$_2$, -OC(O)R^{y5}, -N(R^{y5})C(O)R^{y5a}, -N(R^{y5})S(O)$_2R^{y5a}$, -N(R^{y5})S(O)R^{y5a}, -N(R^{y5})C(O)OR^{y5a}, -N(R^{y5})C(O)N($R^{y5a}R^{y5b}$), -OC(O)N($R^{y5}R^{y5a}$), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

each $-R^{y3}$, $-R^{y3a}$, $-R^{y4}$, $-R^{y4a}$, $-R^{y5}$, $-R^{y5a}$ and $-R^{y5b}$ is 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.

11. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, wherein $-L^2-$ has a molecular weight in the range of from 14 g/mol to 750 g/mol.

12. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 11, wherein $-L^2-$ comprises a moiety selected from


, 
, 
, 
, 
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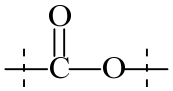
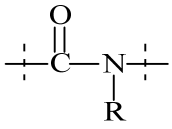
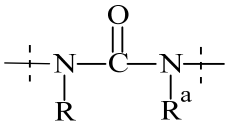
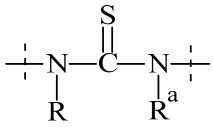

, 
, 
, 
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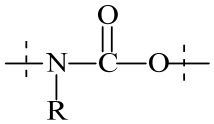
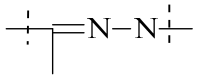
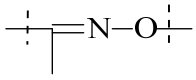
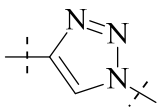

, 
, 
, 
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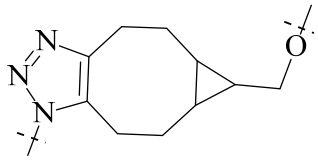
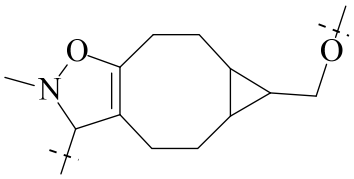
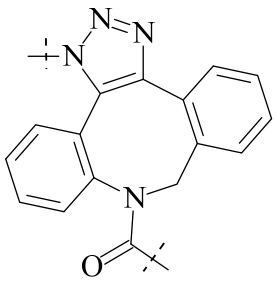

, 
, 
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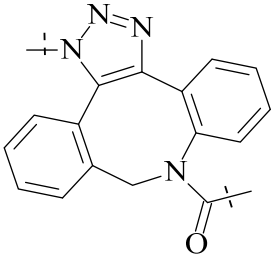
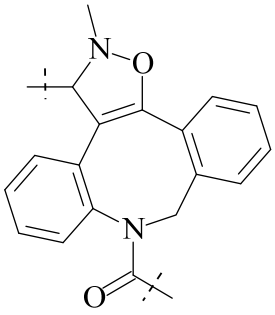
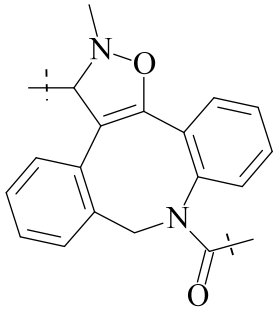

, 
, 
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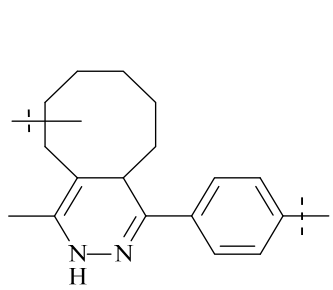
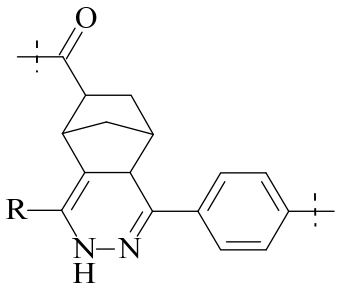
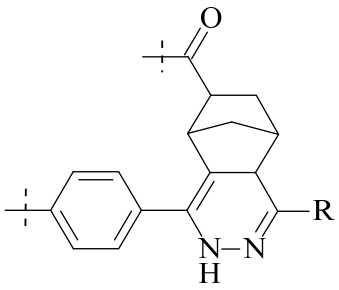
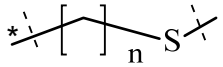

, 
, and 
;

wherein

dashed lines indicate attachment to the rest of -L^2-, -L^1- and/or -Z, respectively; and -R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

13. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 12, wherein -L^2- has a chain length of 1 to 20 atoms.

14. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 13, wherein -L^2- is of formula (i):


(i),

wherein

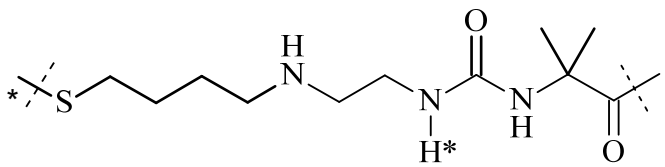
the dashed line marked with the asterisk indicates attachment to -L^1-;

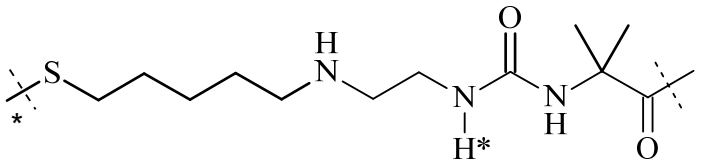
the unmarked dashed line indicates attachment to -Z;

n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and wherein the moiety of formula (i) is optionally further substituted.

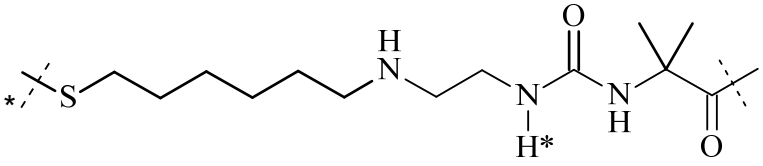
15. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 14, wherein n is 6.

16. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 15, wherein the moiety -L^1-L^2- is selected from the group consisting of


(IIcb-i),



(IIcb-ii) and



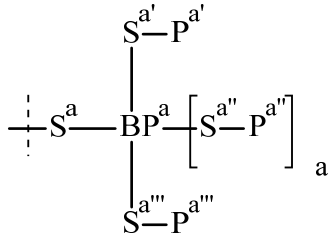
(IIcb-iii);

wherein

the unmarked dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to -Z.

17. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 16, wherein -Z comprises a moiety of formula (a)



(a),

wherein

the dashed line indicates attachment to -L^2- or to the remainder of -Z;

BP^a is a branching point selected from the group consisting of -N<, -CR< and >C<;

-R is selected from the group consisting of -H and C_{1-6} alkyl;

a is 0 if BP^a is -N< or -CR< and a is 1 if BP^a is >C<;

-S^a-, -$S^{a'}$-, -$S^{a''}$- and -$S^{a'''}$- are independently of each other a chemical bond or are selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R′^{1}, 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′-, -C(O)O-, -O-, -C(O)-, -C(O)N(R′^{2})-, -S(O)$_2$N(R′^{2})-, -S(O)N(R′^{2})-, -S(O)$_2$-, -S(O)-, -N(R′^{2})S(O)$_2$N(R′^{2a})-, -S-, -N(R′^{2})-, -OC(OR′^{2})(R′^{2a})-, -N(R′^{2})C(O)N(R′^{2a})-, and -OC(O)N(R′^{2})-;

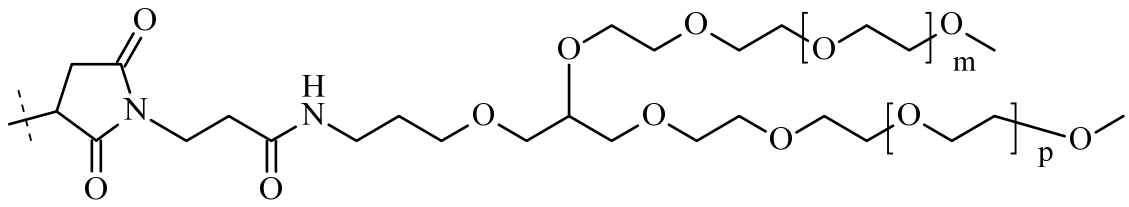
each -T′- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T′- is independently optionally substituted with one or more -R′^{1}, which are the same or different;

each -R′^{1} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR′^{3}, -OR′^{3}, -C(O)R′^{3}, -C(O)N(R′^{3}R′^{3a}), -S(O)$_2$N(R′^{3}R′^{3a}), -S(O)N(R′^{3}R′^{3a}), -S(O)$_2$R′^{3}, -S(O)R′^{3}, -N(R′^{3})S(O)$_2$N(R′^{3a}R′^{3b}), -SR′^{3}, -N(R′^{3}R′^{3a}), -NO$_2$, -OC(O)R′^{3}, -N(R′^{3})C(O)R′^{3a}, -N(R′^{3})S(O)$_2$R′^{3a}, -N(R′^{3})S(O)R′^{3a}, -N(R′^{3})C(O)OR′^{3a}, -N(R′^{3})C(O)N(R′^{3a}R′^{3b}), -OC(O)N(R′^{3}R′^{3a}), and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

each -R′^{2}, -R′^{2a}, -R′^{3}, -R′^{3a} and -R′^{3b} is 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; and

-P$^{a'}$, -P$^{a''}$ and -P$^{a'''}$ are independently a polymeric moiety.

18. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 17, wherein -Z comprises a moiety of formula (b):



(b),

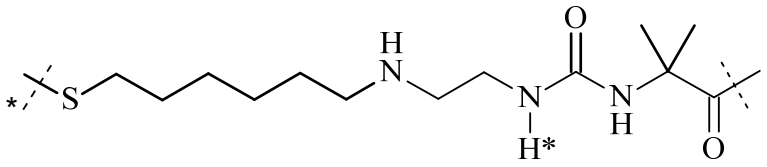
wherein

the dashed line indicates attachment to -L^{2}- or to the remainder of -Z; and

m and p are independently of each other an integer ranging from and including 150 to 1000.

19. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 18, wherein m and p are independently of each other an integer ranging from and including 400 to 500.

20. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 19, wherein the moiety -L^{1}-L^{2}- is of formula (IIf-i):

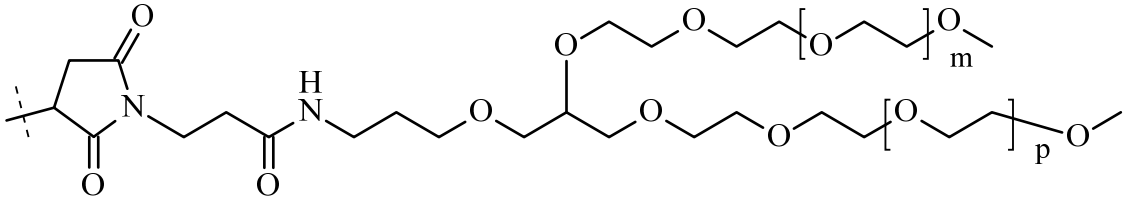


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to the N-terminal amine functional group of -D by forming an amide bond; and

the dashed line marked with the asterisk indicates attachment to a moiety



wherein

m and p are independently an integer ranging from and including 400 to 500.

21. A pharmaceutical composition comprising at least one PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 20 and at least one excipient.

22. The pharmaceutical composition of claim 21, wherein the pharmaceutical composition has a pH ranging from and including pH 4 to pH 6.

23. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 20 or the pharmaceutical composition of claim 21 or 22 for use as a medicament.

24. Use of the PTH prodrug or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20 or the pharmaceutical composition of claim 21 or 22 for the manufacture of a medicament for the treatment of a disease selected from the group consisting of hypoparathyroidism, hyperphosphatemia, osteoporosis, fracture repair, osteomalacia, osteomalacia and osteoporosis in patients with hypophosphatasia, steroid-induced osteoporosis, male osteoporosis, arthritis, osteoarthritis, osteogenesis imperfecta, fibrous dysplasia, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with

malignancy, osteopenia, periodontal disease, bone fracture, alopecia, chemotherapy-induced alopecia, and thrombocytopenia.

25. The use of claim 24, wherein the disease is hypoparathyroidism.