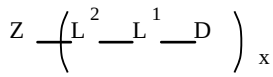
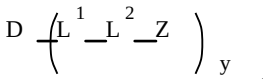
Claims

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 connected to the PTH moiety -D through a functional group of PTH;

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

-Z is a water-soluble carrier moiety;

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. A PTH prodrug or a pharmaceutically acceptable salt thereof comprising a conjugate D-L, wherein

-D is a PTH moiety; and

-L comprises a reversible prodrug linker moiety -L^1-, which moiety -L^1- is connected to the PTH moiety -D through a functional group of PTH;

wherein -L^1- is substituted with -L^2-Z' and is optionally further substituted; wherein

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

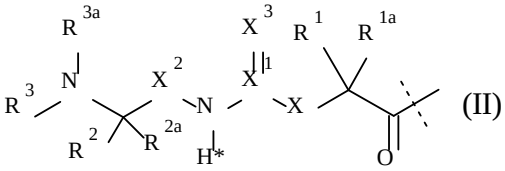
-Z' is a water-insoluble carrier moiety.

3. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 1 or 2, wherein the moiety -L^1- is either conjugated to a functional group of the side chain of an amino acid residue of -D, to the N-terminal amine functional group or to the C-terminal carboxyl functional group of -D or to a nitrogen atom in the backbone polypeptide chain of -D.

4. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein -L^1- is conjugated to the N-terminal amine functional group of -D.

5. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein -D has the sequence of SEQ ID NO:51.

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 (II):



(II)

,

wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of -D which is a PTH moiety;

-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 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 $-L^2-Z$ or $-L^2-Z'$ 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 $-L^2-Z'$ or a substituent;

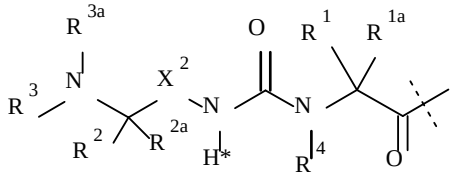
wherein

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

$-Z$ is a water-soluble carrier; and

$-Z'$ is a water-insoluble carrier.

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



(IIb-i),

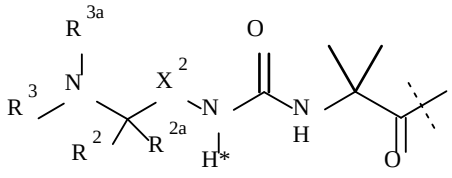
wherein

the dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety 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 6; and

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ 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 $-L^2-Z'$ or a substituent.

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



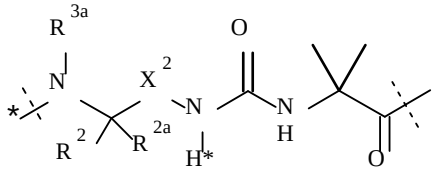
(IIb-ii),

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

$-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-X^2-$ are used as defined in claim 6; and

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ 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 $-L^2-Z'$ 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-ii'):



(IIb-ii'),

wherein

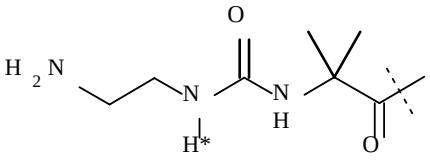
the dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety by forming an amide bond;

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 6; 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.

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



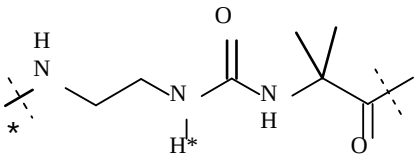
(IIb-iii),

wherein

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

wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ 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 $-L^2-Z'$ or a substituent.

11. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, wherein the moiety -L^1- is of formula (IIb-iii'):



(IIb-iii'),

wherein

the 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 -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.

12. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 11, 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})-;

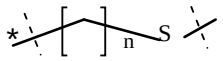
-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, 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), $-COOR^{y5}$, $-OR^{y5}$, $-C(O)R^{y5}$, $-C(O)N(R^{y5}R^{y5a})$, $-S(O)_2N(R^{y5}R^{y5a})$, $-S(O)N(R^{y5}R^{y5a})$, $-S(O)_2R^{y5}$, $-S(O)R^{y5}$, $-N(R^{y5})S(O)_2N(R^{y5a}R^{y5b})$, $-SR^{y5}$, $-N(R^{y5}R^{y5a})$, $-NO_2$, $-OC(O)R^{y5}$, $-N(R^{y5})C(O)R^{y5a}$, $-N(R^{y5})S(O)_2R^{y5a}$, $-N(R^{y5})S(O)R^{y5a}$, $-N(R^{y5})C(O)OR^{y5a}$, $-N(R^{y5})C(O)N(R^{y5a}R^{y5b})$, $-OC(O)N(R^{y5}R^{y5a})$, 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.

13. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 12, wherein $-L^2-$ is of formula (i):



(i),

wherein

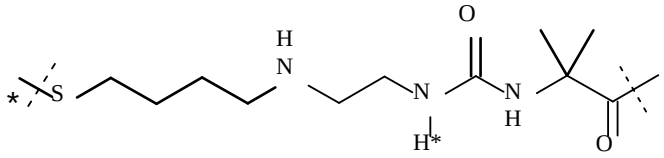
the dashed line marked with the asterisk indicates attachment to $-L^1-$;

the unmarked dashed line indicates attachment to -Z or -Z';

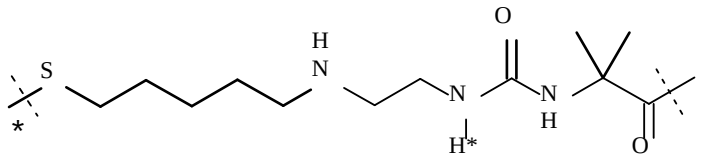
n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and wherein the moiety of formula (i) is optionally further substituted.

14. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 13, wherein n is 6.

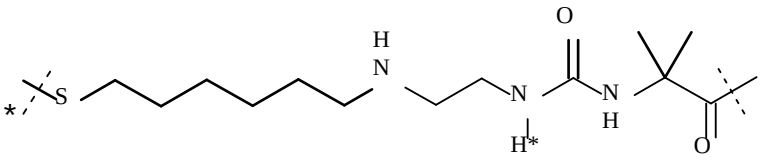
15. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 13, wherein the moiety $-L^1-L^2-$ is selected from the group consisting of



(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 or -Z'.

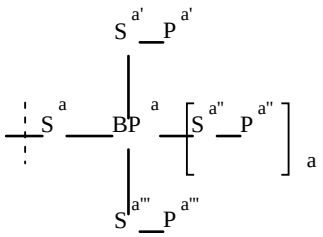
16. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 15, wherein -Z comprises a C_{8-24} alkyl or a polymer.

17. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 16, wherein -Z comprises a polymer, preferably a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids),

poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

18. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 17, wherein -Z is a branched polymer.

19. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 18, 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 n 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)-;

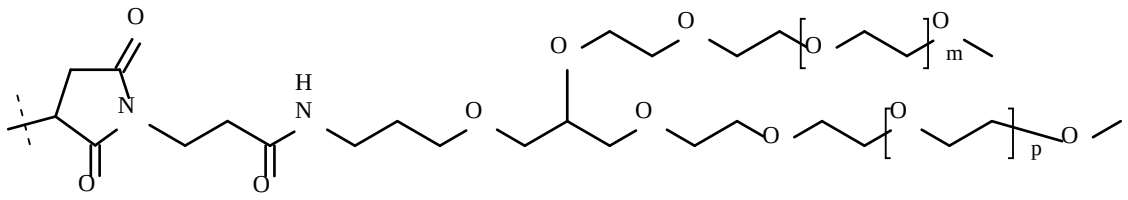
each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently 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), $-COOR^3$, $-OR^3$, $-C(O)R^3$, $-C(O)N(R^3R^{3a})$, $-S(O)_2N(R^3R^{3a})$, $-S(O)N(R^3R^{3a})$, $-S(O)_2R^3$, $-S(O)R^3$, $-N(R^3)S(O)_2N(R^{3a}R^{3b})$, $-SR^3$, $-N(R^3R^{3a})$, $-NO_2$, $-OC(O)R^3$, $-N(R^3)C(O)R^{3a}$, $-N(R^3)S(O)_2R^{3a}$, $-N(R^3)S(O)R^{3a}$, $-N(R^3)C(O)OR^{3a}$, $-N(R^3)C(O)N(R^{3a}R^{3b})$, $-OC(O)N(R^3R^{3a})$, 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.

20. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 19, wherein Z comprises a moiety of formula (b):



(b),

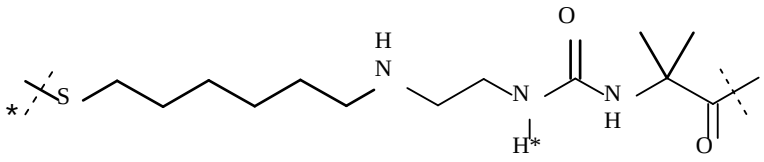
wherein

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.

21. The PTH prodrug or a pharmaceutically acceptable salt thereof of claim 20, wherein m and p are independently of each other an integer ranging from and including 400 to 500.

22. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 or 3 to 21, wherein the PTH prodrug is of formula (IIf-i):

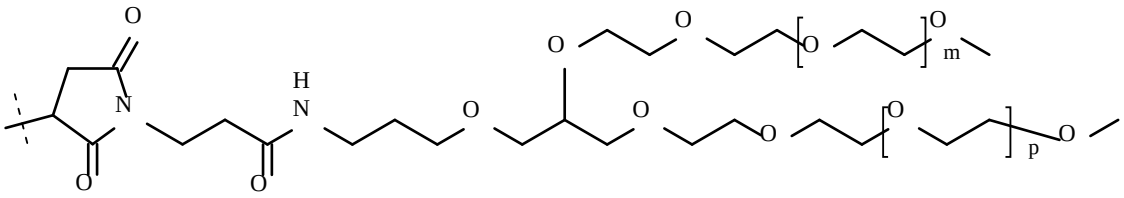


(IIf-i),

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 a moiety



wherein

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

23. A pharmaceutical composition comprising at least one PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 22 and at least one excipient.

24. The pharmaceutical composition of claim 23, wherein the pharmaceutical composition has a pH ranging from and including pH 4 to pH 6.

25. The PTH prodrug or a pharmaceutically acceptable salt thereof of any one of claims 1 to 22 or the pharmaceutical composition of claim 23 or 24 for use as a medicament.

26. Use of the PTH prodrug or the pharmaceutically acceptable salt thereof of any one of claims 1 to 22 or the pharmaceutical composition of claim 23 or 24 for the manufacture of a medicament for the treatment of a disease which can be treated with PTH.

27. The use of claim 26, wherein the disease is 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 imperfect, fibrous dysplasia, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy, osteopenia, periodontal disease, bone fracture, alopecia, chemotherapy-induced alopecia, and thrombocytopenia.

28. The use of claim 26 or 27, wherein the disease is hypoparathyroidism.