Claims

1. A PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof for use in the treatment of hypoparathyroidism, ~~control, delay or prevention of a disease that can be treated, controlled, delayed or prevented with PTH,~~ wherein the starting dose ranges from 0.8 to 4.9 nmol/day.

2. The PTH conjugate of claim 1, wherein the starting dose ranges from 2.9 to 4.5 nmol/day.

3. The PTH conjugate of claim 1, wherein the starting dose ranges from 3.6 to 4.4 nmol/day.

4. The PTH conjugate of claim 1, wherein the starting dose ranges from 0.8 to 3.9 nmol/day.

5. The PTH conjugate of claim 1 or 4, wherein the starting dose ranges from 1.5 to 3.4 nmol/day.

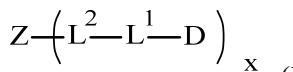
6. The PTH conjugate of any one of claims 1, 4 or 5, wherein the starting dose is 2.9 ± 0.3 nmol/day.

~~7. The PTH conjugate of any one of claims 1 to 6, wherein the disease that can be treated, controlled, delayed or prevented with PTH 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 imperfecta, fibrous dysplasia, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy, osteopenia, periodontal disease, bone fracture, alopecia, chemotherapy-induced alopecia, and thrombocytopenia.~~

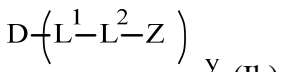
~~8. The PTH conjugate of any one of claims 1 to 7, wherein the disease that can be treated, controlled, delayed or prevented with PTH is hypoparathyroidism.~~

~~9~~7. The PTH conjugate of any one of claims 1 to ~~6~~8, wherein the starting dose is to be administered to a patient as one subcutaneous injection.

~~10~~8. The PTH conjugate of any one of claims 1 to ~~7~~9, wherein the PTH conjugate is of formula (Ia) or (Ib)



(Ia),



(Ib),

wherein

-D is a PTH moiety;

-L^1- is a linker moiety covalently and reversibly attached to -D;

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

-Z is a polymeric moiety or a fatty acid-based moiety;

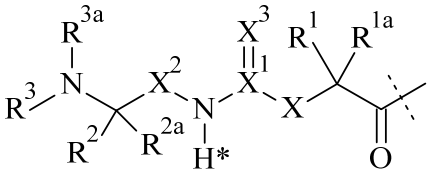
x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16; and

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

~~11~~9. The PTH conjugate of claim ~~8~~10, wherein -D has the sequence of SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114 or SEQ ID NO:115.

~~12~~10. The PTH conjugate of claim ~~8~~10 or ~~9~~11, wherein -D has the sequence of SEQ ID NO:51.

~~13~~11. The PTH conjugate of any one of claims ~~8~~10 to 10~~12~~, wherein the moiety -L^1- is of formula (II):



(II)

,

wherein the dashed line indicates the attachment to an amine, hydroxyl or thiol of -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

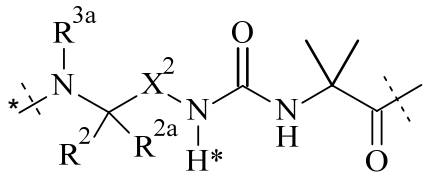
wherein -L^1- is substituted with -L^2-Z and wherein -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by -L^2-Z or a substituent;

wherein

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

-Z is a polymeric moiety or a fatty acid-based moiety.

~~14~~12. The PTH conjugate of any one of claims ~~8~~10 to 11~~13~~, wherein the moiety -L^1- is of formula (IIb-ii′):



(IIb-ii’),

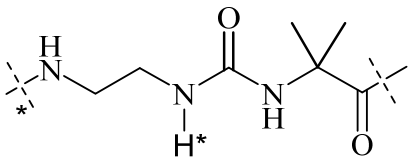
wherein

the unmarked dashed line indicates the attachment to an amine of -D by forming an amide bond and 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 11~~13~~;

-L^1- is substituted with one moiety -L^2-Z and -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-ii’) is not replaced by a substituent; and wherein -L^2- and -Z are used as defined in claim ~~8~~10.

~~15~~13. The PTH conjugate of any one of claims ~~8~~10 to 12~~14~~, wherein the moiety -L^1- is of formula (IIb-iii’):



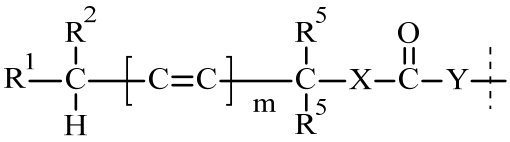
(IIb-iii’),

wherein

the dashed line indicates the attachment to an amine of -D by forming an amide bond and the dashed line marked with the asterisk indicates attachment to -L^2-;

-L^1- is substituted with -L^2-Z and -L^1- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii') is not replaced by a substituent; and wherein -L^2- and -Z are used as defined in claim ~~8~~10.

~~16~~14. The PTH conjugate of any one of claims ~~8~~10 to 10~~12~~, wherein the moiety -L^1- is of formula (IV):



(IV),

wherein

the dashed line indicates attachment to -D and attachment is through a functional group of -D selected from the group consisting of -OH, -SH and -NH_2;

m is 0 or 1;

at least one or both of -R^1 and -R^2 is/are independently of each other selected from the group consisting of -CN, -NO_2, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted alkynyl, -$C(O)R^3$, -$S(O)R^3$, -$S(O)_2R^3$, and -SR^4,

one and only one of -R^1 and -R^2 is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted arylalkyl, and optionally substituted heteroarylalkyl;

-R^3 is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR^9 and -$N(R^9)_2$;

-R^4 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each -R^5 is independently selected from the group consisting of -H, optionally substituted alkyl, optionally substituted alkenylalkyl, optionally substituted alkynylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

$-R^9$ is selected from the group consisting of -H and optionally substituted alkyl;

-Y- is absent and -X- is -O- or -S-; or

-Y- is $-N(Q)CH_2-$ and -X- is -O-;

Q is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

optionally, $-R^1$ and $-R^2$ may be joined to form a 3 to 8-membered ring; and

optionally, both $-R^9$ together with the nitrogen to which they are attached form a heterocyclic ring;

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

wherein

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

-Z is a polymeric moiety or fatty acid-based moiety.

15~~17~~. The PTH conjugate of any one of claims 1 to 14~~16~~, wherein the PTH conjugate releases PTH under physiological conditions with a half-life ranging from 6 hours to one week.

~~18~~16. The PTH conjugate of any one of claims 8~~10~~ to 15~~17~~, wherein $-L^2-$ is a spacer moiety.

~~19~~17. The PTH conjugate of any one of claims 8~~10~~ to 16~~18~~, wherein $-L^2-$ is selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{y1})-$, $-S(O)_2N(R^{y1})-$, $-S(O)N(R^{y1})$, $-S(O)_2-$, -S(O)-, $-N(R^{y1})S(O)_2N(R^{y1a})-$, -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)-, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, -S(O)-, $-N(R^{y3})S(O)_2N(R^{y3a})-$, -S-, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$, and $-OC(O)N(R^{y3})-$;

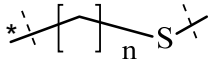
-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, 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.

~~20~~18. The PTH conjugate of any one of claims ~~8~~10 to 17~~19~~, 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.

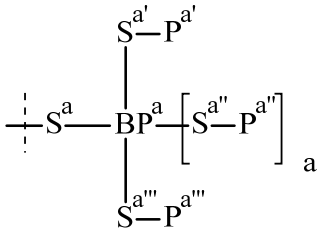
~~21~~19. The PTH conjugate of any one of claims 8~~10~~ to 18~~20~~, wherein -Z is a polymeric moiety.

~~22~~20. The PTH conjugate of any one of claims 8~~10~~ to 19~~21~~, wherein -Z is a polymeric moiety comprising 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.

~~23~~21. The PTH conjugate of any one of claims 8~~10~~ to 20~~22~~, wherein -Z is a PEG-based polymer.

~~24~~22. The PTH conjugate of any one of claims 8~~10~~ to 21~~23~~, wherein -Z is a branched PEG-based polymer.

~~25~~23. The PTH conjugate of any one of claims ~~8~~10 to ~~22~~24, 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)-;

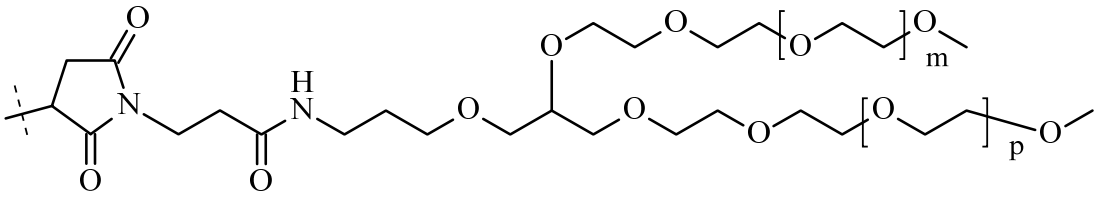
each -T- is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each -T- is independently 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^3R^{3a}), -S(O)$_2$N(R^3R^{3a}), -S(O)N(R^3R^{3a}), -S(O)$_2R^3$, -S(O)R^3, -N(R^3)S(O)$_2$N($R^{3a}R^{3b}$), -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.

~~26~~24. The PTH conjugate of any one of claims 8~~10~~ to 23~~25~~, wherein -Z comprises a moiety of formula (b):



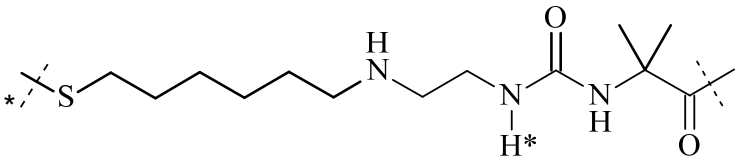
(b),

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; preferably an integer ranging from and including 150 to 500; more preferably an integer ranging from and including 200 to 500; and most preferably an integer ranging from and including 400 to 500.

~~27~~25. The PTH conjugate of any one of claims 1 to 13~~15~~ and 15~~17~~ to 24~~26~~, wherein the PTH conjugate is of formula (IIf-i):

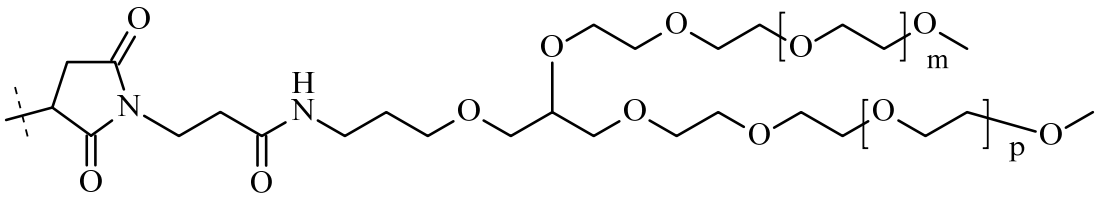


(IIf-i),

wherein

the unmarked dashed line indicates the attachment to a nitrogen 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.

~~28~~26. The PTH conjugate of claim 25~~27~~, wherein -D is attached to the PTH conjugate of formula (IIf-i) through the N-terminal amine functional group of -D.

~~29~~27. Use of the PTH conjugate or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 26~~28~~ 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~~.

28. Use of a PTH conjugate, in which a PTH moiety is reversibly conjugated to a polymeric moiety or fatty acid-based moiety, or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising said PTH conjugate or pharmaceutically acceptably salt thereof in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the medicament is to be administered at a starting dose that ranges from 0.8 to 4.9 nmol/day.