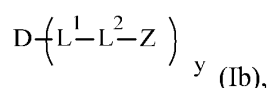
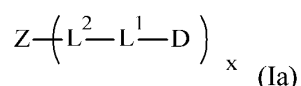


Claims

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, 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 claim 1, 4 or 5, wherein the starting dose 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 imperfect, 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. The PTH conjugate of any one of claims 1 to 8, wherein the starting dose is administered to a patient as one subcutaneous injection.
10. The PTH conjugate of any one of claims 1 to 9, wherein the PTH conjugate is of formula (Ia) or (Ib)



wherein

-D is a PTH moiety;

-L¹- is a linker moiety covalently and reversibly attached to -D;

-L²- is a chemical bond or is a spacer moiety;

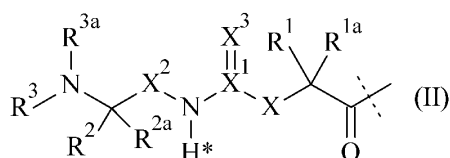
-Z is a polymeric moiety or a substituted fatty acid moiety;

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 or 16; and

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

- 20 11. The PTH conjugate of claim 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. The PTH conjugate of claims 10 or 11, wherein the moiety -L¹- is of formula (II):



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

-X- is -C(R⁴R^{4a})-; -N(R⁴)-; -O-; -C(R⁴R^{4a})-C(R⁵R^{5a})-; -C(R⁵R^{5a})-C(R⁴R^{4a})-; -C(R⁴R^{4a})-N(R⁶)-; -N(R⁶)-C(R⁴R^{4a})-; -C(R⁴R^{4a})-O-; -O-C(R⁴R^{4a})-; or -C(R⁷R^{7a})-;

X¹ is C; or S(O);

-X²- is -C(R⁸R^{8a})-; or -C(R⁸R^{8a})-C(R⁹R^{9a})-;

=X³ is =O; =S; or =N-CN;

-R¹, -R^{1a}, -R², -R^{2a}, -R⁴, -R^{4a}, -R⁵, -R^{5a}, -R⁶, -R⁸, -R^{8a}, -R⁹, -R^{9a} are independently selected from the group consisting of -H; and C₁₋₆ alkyl;

-R³, -R^{3a} are independently selected from the group consisting of -H; and C₁₋₆ alkyl, provided that in case one of -R³, -R^{3a} or both are other than -H they are connected to N to which they are attached through an SP³-hybridized carbon atom;

-R⁷ is -N(R¹⁰R^{10a}); or -NR¹⁰-(C=O)-R¹¹;

-R^{7a}, -R¹⁰, -R^{10a}, -R¹¹ are independently of each other -H; or C₁₋₆ 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 -R¹/-R^{1a}, -R²/-R^{2a}, -R⁴/-R^{4a}, -R⁵/-R^{5a}, -R⁸/-R^{8a}, -R⁹/-R^{9a} are joined together with the atom to which they are attached to form a C₃₋₁₀ cycloalkyl; or 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs -R¹/-R⁴, -R¹/-R⁵, -R¹/-R⁶, -R¹/-R^{7a}, -R⁴/-R⁵, -R⁴/-R⁶, -R⁸/-R⁹, -R²/-R³ are joined together with the atoms to which they are attached to form a ring A;

optionally, R³/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; C₃₋₁₀ cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein -L¹- is substituted with -L²-Z and wherein -L¹- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (II) is not replaced by -L²-Z or a substituent;

wherein

- L²- is a single chemical bond or a spacer;
 -Z is a polymeric moiety or a fatty acid-based moiety.

13. The PTH conjugate of any one of claims 10 to 12, wherein -Z is a polymeric moiety.
- 5
14. The PTH conjugate of any one of claims 10 to 13, 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),
 10 poly(butylene 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),
 20 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
 25 polymers, xylans, and copolymers thereof.
15. The PTH conjugate of any one of claims 10 to 14, wherein -Z is a PEG-based polymer.
- 30
16. The PTH conjugate of any one of claims 10 to 15, wherein -Z is a branched PEG-based polymer.

17. A method of treating, controlling, delaying or preventing in a patient suffering from a disease which can be treated, controlled, delayed or prevented with PTH, comprising administering an effective amount 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 acceptable salt thereof to the patient in a starting dose ranging from 0.8 to 4.9 nmol/day.