
PTH compounds with low peak-to-trough ratios

The present invention relates to a pharmaceutical composition comprising a PTH compound,
5 wherein after subcutaneous administration the pharmacokinetic profile of the PTH compound exhibits a peak to trough ratio of less than 4 within one injection interval.

Hypoparathyroidism is a rare endocrine disorder of calcium and phosphate metabolism that most often arises as a result of parathyroid gland damage or removal during surgery of the
10 thyroid gland. Hypoparathyroidism is unusual among endocrine disorders in that it has not been treated, until recently, by replacement with the missing hormone, parathyroid hormone, or PTH. Conventional therapy for hypoparathyroidism involves large doses of vitamin D and oral calcium supplementation, which, although often effective, is associated with marked swings in blood Ca^{2+} resulting in hypercalcemia and hypocalcemia, excess urinary calcium
15 excretion, and nephrocalcinosis.

Calcium is the most abundant mineral in the human body, and its tight regulation is required for many critical biological functions, such as bone mineralization, muscle contraction, nerve conduction, hormone release, and blood coagulation. It is particularly important to maintain
20 calcium concentration as stable as possible, because of the high sensitivity of a variety of cell systems or organs, including the central nervous system, muscle, and exo/endocrine glands, to small variations in Ca^{2+} . PTH is a major regulator of calcium homeostasis.

The inappropriately low PTH level in relation to serum Ca^{2+} concentration, characteristic of
25 hypoparathyroidism, leads to decreased renal tubular reabsorption of Ca^{2+} and simultaneously, to increased renal tubular reabsorption of phosphate. Thus, the main biochemical abnormalities of hypoparathyroidism are hypocalcemia and hyperphosphatemia. Clinical features of the disease include symptoms of hypocalcemia, such as perioral numbness, paresthesias, and carpal/pedal muscle spasms. Laryngeal spasm, tetany, and
30 seizures are serious and potentially life-threatening complications. Hyperphosphatemia and an elevated calcium x phosphate product contributes to ectopic deposition of insoluble calcium phosphate complexes in soft tissues, including vasculature, brain, kidneys, and other organs.

Standard therapy of hypoparathyroidism is oral calcium and vitamin D supplementation. The
35 goals of therapy are to a) ameliorate symptoms of hypocalcemia; b) maintain fasting serum

calcium within or slightly below to the low-normal range; c) maintain fasting serum phosphorus within the high normal range or only slightly elevated; d) avoid or minimize hypercalciuria; e) maintain a calcium-phosphate product at levels well below the upper limit of normal and f) avoid ectopic calcification of the kidney (stones and nephrocalcinosis) and other soft tissues.

Several concerns arise with prolonged use of calcium and active vitamin D in large doses, particularly with regard to hypercalciuria, kidney stones, nephrocalcinosis and ectopic soft tissue calcification. In addition, conventional therapy with calcium and active vitamin D does not alleviate quality of life complaints nor does it reverse abnormalities in bone remodeling characteristic of the disease. In short, there is a high need for improved therapies for hypoparathyroidism.

In 2015, Natpara, PTH(1-84), was approved for once-daily subcutaneous injection as an adjunct to vitamin D and calcium in patients with hypoparathyroidism. Natpara, PTH(1-84), was approved to control hypocalcemia based on a pivotal trial demonstrating that 42 percent of PTH(1-84) treated participants achieved normal blood calcium levels on reduced doses of calcium supplements and active forms of vitamin D, compared to 3 percent of placebo-treated participants. Following a time course in which serum calcium was monitored after injection, 71 percent of patients treated with PTH(1-84) developed hypercalcemia at one or more measurements during a 24-hour period. PTH(1-84) reduced urinary calcium excretion 2-8 hours after injection but over the 24-hour period, urinary calcium excretion did not change. Similarly, urinary phosphate excretion increased only during the first 8 hours after PTH(1-84) injection.

While this represents an important advance in the treatment of the disease, Natpara has not demonstrated an ability to reduce incidences of hypercalcemia (elevated serum calcium levels), hypocalcemia (low serum calcium), or hypercalciuria (elevated urinary calcium) relative to conventional therapy in treated patients.

As such, there is a high need for improved PTH based therapies for hypoparathyroidism.

PTH(1-34), or teriparatide, was approved by the FDA in 2002 for the treatment of osteoporosis. Despite not being approved for this indication, PTH(1-34) has historically been

used for treatment of hypoparathyroidism with patients receiving twice- or thrice-daily injections. To facilitate more physiological PTH levels, clinical studies have been conducted with PTH(1–34) administered by pump delivery in comparison with twice-daily injections. Over 6-months, pump delivery produced normal, steady state calcium levels with minimal fluctuation and avoided the rise in serum and urine calcium levels that are evident soon after PTH injection. The marked reduction in urinary calcium excretion when PTH(1–34) is administered by pump may indicate that PTH must be continuously exposed to the renal tubule for the renal calcium-conserving effects to be realized. Pump delivery of PTH(1–34) achieved simultaneous normalization of markers of bone turnover, serum calcium, and urine calcium excretion. These results were achieved with a lower daily PTH(1–34) dose and a reduced need for magnesium supplementation compared with the twice daily PTH(1–34) injection regimen.

However, continuous pump therapy is inconvenient and challenging for patients, and it is an object of the current invention to provide for a more convenient therapeutic option of providing continuous exposure to PTH.

Long-term bolus administration of PTH is associated with a progressive cortical bone loss due to increased bone metabolism. In a 6-year follow-up of patients treated with PTH(1–84) (Rubin, JCEM 2016) bone turnover markers remained greater than pretreatment values, peaking at the early years after PTH(1–84) initiation and declining thereafter but remaining significantly higher than baseline values by year 6. Bone mineral density (BMD) by dual X-ray absorptometry (DXA) was consistent with known site-specific effects of PTH, namely increases in lumbar spine and declines in the distal 1/3 radius (i/3 radius). The decrease observed at the i/3 radius is consistent with the known effects of intermittent PTH to increase cortical porosity and endosteal resorption.

It is an object of this invention to provide for a method of intermittently administering PTH, with lower elevation of bone turnover markers than currently applied PTH therapies. Preferably intermittent means with daily intervals, or alternatively or more preferably with weekly intervals.

In the preclinical development program of both Forteo, PTH(1–34) and Natpara, PTH(1–84) a dose dependent increase in osteosarcoma rate was observed in rats treated with daily

injections of the PTH compound. In the Natpara study, dosing of the high dose rats were discontinued due to excessive deaths in this group, primarily from metastatic osteosarcoma.

As such it is an object of this invention to provide for an intermittent PTH replacement
5 therapy that provides for symptom control with a lower administered dose. Preferably intermittent means with daily intervals, or alternatively or more preferably with weekly intervals.

In summary, there is a need for a more convenient and safer treatment of hypoparathyroidism
10 with reduced side-effects.

It is therefore an object of the present invention to at least partially overcome the shortcomings described above.

15 This object is achieved with a pharmaceutical composition comprising a PTH compound, wherein after administration, preferably subcutaneous administration, the pharmacokinetic profile of the PTH compound exhibits a peak to trough ratio of less than 4 within one injection interval.

20 It was surprisingly found that such PTH compound is capable of achieving a stable plasma profile of PTH which ensures physiological serum and urinary calcium levels or even reduced urinary calcium levels comparable to those measured in healthy subjects.

Within the present invention the terms are used having the meaning as follows.

25

As used herein the term “injection interval” refers to the time between two consecutive administrations of the pharmaceutical composition of the present invention.

As used herein the term “steady-state” refers to a state achieved after a multitude of constant
30 doses, such as after 3, 4, 5, 6, 7 or more constant doses, of a medicament have been administered to a patient with constant time intervals between two consecutive administration, which state is characterized in that the plasma levels of the PTH compound, if the PTH compound does not release PTH, i.e. is a stable PTH compound, or of released PTH, if the PTH compound is a controlled-release PTH compound, at the beginning and at the end of an

interval vary by no more than 10%, preferably by no more than 7.5%, even more preferably by no more than 5%, even more preferably by no more than 4% and most preferably by no more than 3%. The term “beginning of an interval” refers to the time point at which a dose is administered and the term “end of an interval” refers to the time point at which the next dose is administered.

As used herein the term “peak to trough ratio” refers to the ratio between the highest plasma concentration and the lowest plasma concentration of the PTH compound at steady state. If the PTH compound does not release PTH, i.e. is a stable PTH compound, or of released PTH, if the PTH compound is a controlled-release PTH compound, within the time period between two consecutive administrations to a non-human primate, preferably to a cynomolgus monkey. However, as there is a good correlation between free PTH and total PTH (i.e. the sum of PTH still comprised in the PTH compound and released PTH), so total PTH provides a sufficiently good approximation. The time period between two consecutive administrations is also referred to as “injection interval”, “administration interval” or “interval”.

As used herein the term “controlled-release PTH compound” refers to any compound, conjugate, crystal or admixture that comprises at least one PTH molecule or PTH moiety and from which the at least one PTH molecule or PTH moiety is released with a release half-life of at least 12 hours.

As used herein the terms “release half-life” and “half-life” refer to the time required under physiological conditions (i.e. aqueous buffer, pH 7.4, 37°C) until half of all PTH or PTH moieties, respectively, comprised in a controlled-release PTH compound are released from said controlled-release PTH compound.

As used herein the term “stable PTH compound” refers to any covalent conjugate of at least one PTH moiety to another moiety, wherein the at least one PTH moiety is connected to said other moiety through a stable linkage.

As used herein the term “PTH” refers all PTH polypeptides, preferably from mammalian species, more preferably from human and mammalian species, more preferably from human and murine species, as well as their variants, analogs, orthologs, homologs, and derivatives and fragments thereof, that are characterized by raising serum calcium and renal phosphorus

excretion, and lowering serum phosphorus and renal calcium excretion. The term “PTH” also refers to all PTH-related polypeptides (PTHrP), such as the polypeptide of SEQ ID NO:121, that bind to and activate the common PTH/PTHrP1 receptor. Preferably, the term “PTH” refers to the PTH polypeptide of SEQ ID NO:51 as well as its variants, homologs and
5 derivatives exhibiting essentially the same biological activity, i.e. raising serum calcium and renal phosphorus excretion, and lowering serum phosphorus and renal calcium excretion.

Preferably, the term “PTH” refers to the following polypeptide sequences:

10 SEQ ID NO:1 (PTH 1-84)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNVLTAKSQ

SEQ ID NO:2 (PTH 1-83)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
15 NVLVESHEKSLGEADKADVNVLTAKS

SEQ ID NO:3 (PTH 1-82)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNVLTAK

SEQ ID NO:4 (PTH 1-81)

20 SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNVLTAK

SEQ ID NO:5 (PTH 1-80)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNVLT

25 SEQ ID NO:6 (PTH 1-79)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNVLT

SEQ ID NO:7 (PTH 1-78)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
30 NVLVESHEKSLGEADKADVNVL

SEQ ID NO:8 (PTH 1-77)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADVNV

SEQ ID NO:9 (PTH 1-76)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV

SEQ ID NO:10 (PTH 1-75)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

5 NVLVESHEKSLGEADKADV

SEQ ID NO:11 (PTH 1-74)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADKAD

SEQ ID NO:12 (PTH 1-73)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADKA

SEQ ID NO:13 (PTH 1-72)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADK

15 SEQ ID NO:14 (PTH 1-71)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEAD

SEQ ID NO:15 (PTH 1-70)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

20 NVLVESHEKSLGEA

SEQ ID NO:16 (PTH 1-69)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGE

SEQ ID NO:17 (PTH 1-68)

25 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLG

SEQ ID NO:18 (PTH 1-67)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSL

30 SEQ ID NO:19 (PTH 1-66)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKS

SEQ ID NO:20 (PTH 1-65)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEK

SEQ ID NO:21 (PTH 1-64)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

5 NVLVESHE

SEQ ID NO:22 (PTH 1-63)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESH

SEQ ID NO:23 (PTH 1-62)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVES

SEQ ID NO:24 (PTH 1-61)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVE

15 SEQ ID NO:25 (PTH 1-60)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLV

SEQ ID NO:26 (PTH 1-59)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

20 NVL

SEQ ID NO:27 (PTH 1-58)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NV

SEQ ID NO:28 (PTH 1-57)

25 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

N

SEQ ID NO:29 (PTH 1-56)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

SEQ ID NO:30 (PTH 1-55)

30 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

SEQ ID NO:31 (PTH 1-54)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKK

SEQ ID NO:32 (PTH 1-53)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRK

SEQ ID NO:33 (PTH 1-52)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPR

SEQ ID NO:34 (PTH 1-51)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR

5 SEQ ID NO:35 (PTH 1-50)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR

SEQ ID NO:36 (PTH 1-49)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQ

SEQ ID NO:37 (PTH 1-48)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGS

SEQ ID NO:38 (PTH 1-47)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAG

SEQ ID NO:39 (PTH 1-46)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDA

15 SEQ ID NO:40 (PTH 1-45)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRD

SEQ ID NO:41 (PTH 1-44)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPR

SEQ ID NO:42 (PTH 1-43)

20 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAP

SEQ ID NO:43 (PTH 1-42)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLA

SEQ ID NO:44 (PTH 1-41)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPL

25 SEQ ID NO:45 (PTH 1-40)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAP

SEQ ID NO:46 (PTH 1-39)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGA

SEQ ID NO:47 (PTH 1-38)

30 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALG

SEQ ID NO:48 (PTH 1-37)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVAL

SEQ ID NO:49 (PTH 1-36)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVA

SEQ ID NO:50 (PTH 1-35)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFV

SEQ ID NO:51 (PTH 1-34)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF

5 SEQ ID NO:52 (PTH 1-33)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHN

SEQ ID NO:53 (PTH 1-32)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH

SEQ ID NO:54 (PTH 1-31)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDV

SEQ ID NO:55 (PTH 1-30)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQD

SEQ ID NO:56 (PTH 1-29)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQ

15 SEQ ID NO:57 (PTH 1-28)

SVSEIQLMHNLGKHLNSMERVEWLRKKL

SEQ ID NO:58 (PTH 1-27)

SVSEIQLMHNLGKHLNSMERVEWLRKK

SEQ ID NO:59 (PTH 1-26)

20 SVSEIQLMHNLGKHLNSMERVEWLRK

SEQ ID NO:60 (PTH 1-25)

SVSEIQLMHNLGKHLNSMERVEWLR

SEQ ID NO:61 (amidated PTH 1-84)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

25 NVLVESHEKSLGEADKADVNVLTAKSQ; wherein the C-terminus is amidated

SEQ ID NO:62 (amidated PTH 1-83)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADKADVNVLTAKS; wherein the C-terminus is amidated

SEQ ID NO:63 (amidated PTH 1-82)

30 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADKADVNVLTAK; wherein the C-terminus is amidated

SEQ ID NO:64 (amidated PTH 1-81)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSLGEADKADVNVLTAK; wherein the C-terminus is amidated

SEQ ID NO:65 (amidated PTH 1-80)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV NVLTK; wherein the C-terminus is amidated

SEQ ID NO:66 (amidated PTH 1-79)

- 5 SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV NVLT; wherein the C-terminus is amidated

SEQ ID NO:67 (amidated PTH 1-78)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV NVL; wherein the C-terminus is amidated

- 10 SEQ ID NO:68 (amidated PTH 1-77)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV NV; wherein the C-terminus is amidated

SEQ ID NO:69 (amidated PTH 1-76)

- 15 SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV N; wherein the C-terminus is amidated

SEQ ID NO:70 (amidated PTH 1-75)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKADV; wherein the C-terminus is amidated

SEQ ID NO:71 (amidated PTH 1-74)

- 20 SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKAD; wherein the C-terminus is amidated

SEQ ID NO:72 (amidated PTH 1-73)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADKA; wherein the C-terminus is amidated

- 25 SEQ ID NO:73 (amidated PTH 1-72)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEADK; wherein the C-terminus is amidated

SEQ ID NO:74 (amidated PTH 1-71)

- 30 SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEAD; wherein the C-terminus is amidated

SEQ ID NO:75 (amidated PTH 1-70)

SVSEIQLMHN LGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLGEA; wherein the C-terminus is amidated

SEQ ID NO:76 (amidated PTH 1-69)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NVLVESHEKSLG; wherein the C-terminus is amidated

SEQ ID NO:77 (amidated PTH 1-68)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

5 NVLVESHEKSLG; wherein the C-terminus is amidated

SEQ ID NO:78 (amidated PTH 1-67)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKSL; wherein the C-terminus is amidated

SEQ ID NO:79 (amidated PTH 1-66)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEKS; wherein the C-terminus is amidated

SEQ ID NO:80 (amidated PTH 1-65)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHEK; wherein the C-terminus is amidated

15 SEQ ID NO:81 (amidated PTH 1-64)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVESHE; wherein the C-terminus is amidated

SEQ ID NO:82 (amidated PTH 1-63)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

20 NVLVESH; wherein the C-terminus is amidated

SEQ ID NO:83 (amidated PTH 1-62)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVES; wherein the C-terminus is amidated

SEQ ID NO:84 (amidated PTH 1-61)

25 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLVE; wherein the C-terminus is amidated

SEQ ID NO:85 (amidated PTH 1-60)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVLV; wherein the C-terminus is amidated

30 SEQ ID NO:86 (amidated PTH 1-59)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

NVL; wherein the C-terminus is amidated

SEQ ID NO:87 (amidated PTH 1-58)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED
NV; wherein the C-terminus is amidated

SEQ ID NO:88 (amidated PTH 1-57)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

5 N; wherein the C-terminus is amidated

SEQ ID NO:89 (amidated PTH 1-56)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKED

; wherein the C-terminus is amidated

SEQ ID NO:90 (amidated PTH 1-55)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE;
wherein the C-terminus is amidated

SEQ ID NO:91 (amidated PTH 1-54)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKK;

wherein the C-terminus is amidated

15 SEQ ID NO:92 (amidated PTH 1-53)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRK;

wherein the C-terminus is amidated

SEQ ID NO:93 (amidated PTH 1-52)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPR;

20 wherein the C-terminus is amidated

SEQ ID NO:94 (amidated PTH 1-51)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRP;

wherein the C-terminus is amidated

SEQ ID NO:95 (amidated PTH 1-50)

25 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR; wherein
the C-terminus is amidated

SEQ ID NO:96 (amidated PTH 1-49)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQ; wherein
the C-terminus is amidated

30 SEQ ID NO:97 (amidated PTH 1-48)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGS; wherein the
C-terminus is amidated

SEQ ID NO:98 (amidated PTH 1-47)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAG; wherein the C-terminus is amidated

SEQ ID NO:99 (amidated PTH 1-46)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDA; wherein the C-terminus is amidated

SEQ ID NO:100 (amidated PTH 1-45)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRD; wherein the C-terminus is amidated

SEQ ID NO:101 (amidated PTH 1-44)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPR; wherein the C-terminus is amidated

SEQ ID NO:102 (amidated PTH 1-43)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAP; wherein the C-terminus is amidated

SEQ ID NO:103 (amidated PTH 1-42)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLA; wherein the C-terminus is amidated

SEQ ID NO:104 (amidated PTH 1-41)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPL; wherein the C-terminus is amidated

SEQ ID NO:105 (amidated PTH 1-40)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAP; wherein the C-terminus is amidated

SEQ ID NO:106 (amidated PTH 1-39)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGA; wherein the C-terminus is amidated

SEQ ID NO:107 (amidated PTH 1-38)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALG; wherein the C-terminus is amidated

SEQ ID NO:108 (amidated PTH 1-37)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVAL; wherein the C-terminus is amidated

SEQ ID NO:109 (amidated PTH 1-36)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVA; wherein the C-terminus is amidated

SEQ ID NO:110 (amidated PTH 1-35)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFV; wherein the C-terminus is
5 amidated

SEQ ID NO:111 (amidated PTH 1-34)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF; wherein the C-terminus is amidated

SEQ ID NO:112 (amidated PTH 1-33)

10 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHN; wherein the C-terminus is amidated

SEQ ID NO:113 (amidated PTH 1-32)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH; wherein the C-terminus is amidated

SEQ ID NO:114 (amidated PTH 1-31)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDV; wherein the C-terminus is amidated

15 SEQ ID NO:115 (amidated PTH 1-30)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQD; wherein the C-terminus is amidated

SEQ ID NO:116 (amidated PTH 1-29)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQ; wherein the C-terminus is amidated

SEQ ID NO:117 (amidated PTH 1-28)

20 SVSEIQLMHNLGKHLNSMERVEWLRKKL; wherein the C-terminus is amidated

SEQ ID NO:118 (amidated PTH 1-27)

SVSEIQLMHNLGKHLNSMERVEWLRKK; wherein the C-terminus is amidated

SEQ ID NO:119 (amidated PTH 1-26)

SVSEIQLMHNLGKHLNSMERVEWLRK; wherein the C-terminus is amidated

25 SEQ ID NO:120 (amidated PTH 1-25)

SVSEIQLMHNLGKHLNSMERVEWLR; wherein the C-terminus is amidated

SEQ ID NO:121 (PTHrP)

AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEIHAEIRATSEVSPNSKPSPNTKNHPVRF

GSDDEGRYLTQETNKVETYKEQPLKTPGKKKKKGKPGKRKEQEKKKRRTRSAWLDS

30 GVTGSGLEGDHLSDTSTTSLELDSRRH

More preferably, the term “PTH” refers to the sequence of SEQ ID: NOs 47, 48, 49, 50, 51, 52, 53, 54, 55, 107, 108, 109, 110, 111, 112, 113, 114 and 115. Even more preferably, the

term “PTH” refers to the sequence of SEQ ID:NOs 50, 51, 52, 110, 111 and 112. In a particularly preferred embodiment the term “PTH” refers to the sequence of SEQ ID NO:51.

As used herein, the term “PTH polypeptide variant” refers to a polypeptide from the same species that differs from a reference PTH or PTHrP polypeptide. Preferably, such reference is a PTH polypeptide sequence and has the sequence of SEQ ID NO:51. Generally, differences are limited so that the amino acid sequence of the reference and the variant are closely similar overall and, in many regions, identical. Preferably, PTH polypeptide variants are at least 70%, 80%, 90%, or 95% identical to a reference PTH or PTHrP polypeptide, preferably to the PTH polypeptide of SEQ ID NO:51. By a polypeptide having an amino acid sequence at least, for example, 95% “identical” to a query amino acid sequence, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. These alterations of the reference sequence may occur at the amino (N-terminal) or carboxy terminal (C-terminal) positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence. The query sequence may be an entire amino acid sequence of the reference sequence or any fragment specified as described herein. Preferably, the query sequence is the sequence of SEQ ID NO:51.

Such PTH polypeptide variants may be naturally occurring variants, such as naturally occurring allelic variants encoded by one of several alternate forms of a PTH or PTHrP occupying a given locus on a chromosome or an organism, or isoforms encoded by naturally occurring splice variants originating from a single primary transcript. Alternatively, a PTH polypeptide variant may be a variant that is not known to occur naturally and that can be made by mutagenesis techniques known in the art.

It is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus of a bioactive polypeptide without substantial loss of biological function. Such N- and/or C-terminal deletions are also encompassed by the term PTH polypeptide variant.

It is also recognized by one of ordinary skill in the art that some amino acid sequences of PTH or PTHrP polypeptides can be varied without significant effect of the structure or function of

the polypeptide. Such mutants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al. (1990), Science 247:1306-1310, which is hereby
5 incorporated by reference in its entirety, wherein the authors indicate that there are two main approaches for studying the tolerance of the amino acid sequence to change.

The term PTH polypeptide also encompasses all PTH and PTHrP polypeptides encoded by PTH and PTHrP analogs, orthologs, and/or species homologs. It is also recognized by one of
10 ordinary skill in the art that PTHrP and PTHrP analogs bind to activate the common PTH/PTHrP1 receptor, so the term PTH polypeptide also encompasses all PTHrP analogs. As used herein, the term "PTH analog" refers to PTH and PTHrP of different and unrelated organisms which perform the same functions in each organism but which did not originate from an ancestral structure that the organisms' ancestors had in common. Instead, analogous
15 PTH and PTHrP arose separately and then later evolved to perform the same or similar functions. In other words, analogous PTH and PTHrP polypeptides are polypeptides with quite different amino acid sequences but that perform the same biological activity, namely raising serum calcium and renal phosphorus excretion, and lowering serum phosphorus and renal calcium excretion.

20 As used herein the term "PTH ortholog" refers to PTH and PTHrP within two different species which sequences are related to each other via a common homologous PTH or PTHrP in an ancestral species, but which have evolved to become different from each other.

25 As used herein, the term "PTH homolog" refers to PTH and PTHrP of different organisms which perform the same functions in each organism and which originate from an ancestral structure that the organisms' ancestors had in common. In other words, homologous PTH polypeptides are polypeptides with quite similar amino acid sequences that perform the same biological activity, namely raising serum calcium and renal phosphorus excretion, and
30 lowering serum phosphorus and renal calcium excretion. Preferably, PTH polypeptide homologs may be defined as polypeptides exhibiting at least 40%, 50%, 60%, 70%, 80%, 90% or 95% identity to a reference PTH or PTHrP polypeptide, preferably the PTH polypeptide of SEQ ID NO:51.

Thus, a PTH polypeptide according to the invention may be, for example: (i) one in which at least one of the amino acids residues is substituted with a conserved or non-conserved amino acid residue, preferably a conserved amino acid residue, and such substituted amino acid residue may or may not be one encoded by the genetic code; and/or (ii) one in which at least one of the amino acid residues includes a substituent group; and/or (iii) one in which the PTH polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol); and/or (iv) one in which additional amino acids are fused to the PTH polypeptide, such as an IgG Fc fusion region polypeptide or leader or secretory sequence or a sequence which is employed for purification of the above form of the polypeptide or a pre-protein sequence.

As used herein, the term “PTH polypeptide fragment” refers to any polypeptide comprising a contiguous span of a part of the amino acid sequence of a PTH or PTHrP polypeptide, preferably the polypeptide of SEQ ID NO:51.

More specifically, a PTH polypeptide fragment comprises at least 6, such as at least 8, at least 10 or at least 17 consecutive amino acids of a PTH or PTHrP polypeptide, more preferably of the polypeptide of SEQ ID NO:51. A PTH polypeptide fragment may additionally be described as sub-genuses of PTH or PTHrP polypeptides comprising at least 6 amino acids, wherein “at least 6” is defined as any integer between 6 and the integer representing the C-terminal amino acid of a PTH or PTHrP polypeptide, preferably of the polypeptide of SEQ ID No:51. Further included are species of PTH or PTHrP polypeptide fragments at least 6 amino acids in length, as described above, that are further specified in terms of their N-terminal and C-terminal positions. Also encompassed by the term “PTH polypeptide fragment” as individual species are all PTH or PTHrP polypeptide fragments, at least 6 amino acids in length, as described above, that may be particularly specified by a N-terminal and C-terminal position. That is, every combination of a N-terminal and C-terminal position that a fragment at least 6 contiguous amino acid residues in length could occupy, on any given amino acid sequence of a PTH or PTHrP polypeptide, preferably the PTH polypeptide of SEQ ID:NO51, is included in the present invention.

The term “PTH” also includes poly(amino acid) conjugates which have a sequence as described above, but having a backbone that comprises both amide and non-amide linkages, such as ester linkages, like for example depsipeptides. Depsipeptides are chains of amino acid

residues in which the backbone comprises both amide (peptide) and ester bonds. Accordingly, the term “side chain” as used herein refers either to the moiety attached to the alpha-carbon of an amino acid moiety, if the amino acid moiety is connected through amine bonds such as in polypeptides, or to any carbon atom-comprising moiety attached to the backbone of a poly(amino acid) conjugate, such as for example in the case of depsipeptides. Preferably, the term “PTH” refers to polypeptides having a backbone formed through amide (peptide) bonds.

As the term PTH includes the above-described variants, analogs, orthologs, homologs, derivatives and fragments of PTH and PTHrP, all references to specific positions within a reference sequence also include the equivalent positions in variants, analogs, orthologs, homologs, derivatives and fragments of a PTH or PTHrP moiety, even if not specifically mentioned.

As used herein the term “micelle” means an aggregate of amphiphilic molecules dispersed in a liquid colloid. In aqueous solution a typical micelle forms an aggregate with the hydrophilic moiety of the surfactant molecules facing the surrounding solvent and the hydrophobic moiety of the surfactant molecule facing inwards, also called “normal-phase micelle”. “Invers micelles” have the hydrophilic moiety facing inwards and the hydrophobic moiety facing the surrounding solvent.

As used herein the term “liposome” refers to a vesicle, preferably a spherical vesicle, having at least one lipid bilayer. Preferably, liposomes comprise phospholipids, even more preferably phosphatidylcholine. The term “liposome” refers to various structures and sizes, such as, for example, to multilamellar liposome vesicles (MLV) having more than one concentric lipid bilayer with an average diameter of 100 to 1000 nm, small unilamellar liposome vesicles (SUV) having one lipid bilayer and an average diameter of 25 to 100 nm, large unilamellar liposome vesicles (LUV) having one lipid bilayer and an average diameter of about 1000 nm and giant unilamellar vesicles (GUV) having one lipid bilayer and an average diameter of 1 to 100 μm. The term “liposome” also includes elastic vesicles such as transferosomes and ethosomes, for example.

As used herein the term “aquasome” refers to spherical nanoparticles having a diameter of 60 to 300 nm that comprise at least three layers of self-assembled structure, namely a solid phase

nanocrystalline core coated with an oligomeric film to which drug molecules are adsorbed with or without modification of the drug.

As used herein the term “ethosome” refers to lipid vesicles comprising phospholipids and ethanol and/or isopropanol in relatively high concentration and water, having a size ranging from tens of nanometers to micrometers.

As used herein the term “LeciPlex” refers to positively charged phospholipid-based vesicular system which comprises soy PC, a cationic agent, and a bio-compatible solvent like PEG 300, PEG 400, diethylene glycol monoethyl ether, tetrahydrofurfuryl alcohol polyethylene glycol ether or 2-pyrrolidone or *N*-methyl-2-pyrrolidone.

As used herein the term “niosome” refers to unilamellar or multilamellar vesicles comprising non-ionic surfactants.

As used herein the term “pharmacosome” refers to ultrafine vesicular, micellar or hexagonal aggregates from lipids covalently bound to biologically active moieties.

As used herein the term “proniosome” refers to dry formulations of surfactant-coated carrier which on rehydration and mild agitation gives niosomes.

As used herein the term “polymersome” refers to an artificial spherical vesicle comprising a membrane formed from amphiphilic synthetic block copolymers and may optionally comprise an aqueous solution in its core. A polymersome has a diameter ranging from 50 nm to 5 μ m and larger. The term also includes syntosomes, which are polymersomes engineered to comprise channels that allow certain chemicals to pass through the membrane into or out of the vesicle.

As used herein the term “sphingosome” refers to a concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid.

As used herein the term “transferosome” refers to ultraflexible lipid vesicles comprising an aqueous core that are formed from a mixture of common polar and suitable edge-activated

lipids which facilitate the formation of highly curved bilayers which render the transferosome highly deformable.

As used herein the term “ufasome” refers to a vesicle comprising unsaturated fatty acids.

5

As used herein the term “polypeptide” refers to a peptide comprising up to and including 50 amino acid monomers.

As used herein the term “protein” refers to a peptide of more than 50 amino acid residues.

10 Preferably a protein comprises at most 20000 amino acid residues, such as at most 15000 amino acid residues, such as at most 10000 amino acid residues, such as at most 5000 amino acid residues, such as at most 4000 amino acid residues, such as at most 3000 amino acid residues, such as at most 2000 amino acid residues, such as at most 1000 amino acid residues.

15 As used herein the term “physiological conditions” refers to an aqueous buffer at pH 7.4, 37°C.

As used herein the term “pharmaceutical composition” refers to a composition containing one or more active ingredients, such as for example at least one controlled-release PTH
20 compounds, and one or more excipients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients of the composition, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by
25 admixing one or more controlled-release PTH compound and a pharmaceutically acceptable excipient.

As used herein the term “liquid composition” refers to a mixture comprising water-soluble PTH compound, preferably water-soluble controlled-release PTH compound, and one or more
30 solvents, such as water.

The term “suspension composition” relates to a mixture comprising water-insoluble PTH compound, preferably water-insoluble controlled-release PTH compound, and one or more solvents, such as water.

As used herein, the term “dry composition” means that a pharmaceutical composition is provided in a dry form. Suitable methods for drying are spray-drying and lyophilization, i.e. freeze-drying. Such dry composition of prodrug has a residual water content of a maximum of 10 %, preferably less than 5% and more preferably less than 2%, determined according to Karl Fischer. Preferably, the pharmaceutical composition of the present invention is dried by lyophilization.

The term “drug” as used herein refers to a substance, such as PTH, used in the treatment, cure, prevention, or diagnosis of a disease or used to otherwise enhance physical or mental well-being. If a drug is conjugated to another moiety, the moiety of the resulting product that originated from the drug is referred to as “biologically active moiety”.

As used herein the term “prodrug” refers to a conjugate in which a biologically active moiety is reversibly and covalently connected to a specialized protective group through a reversible linker moiety, also referred to as “reversible prodrug linker moiety”, which comprises a reversible linkage with the biologically active moiety and wherein the specialized protective group alters or eliminates undesirable properties in the parent molecule. This also includes the enhancement of desirable properties in the drug and the suppression of undesirable properties. The specialized non-toxic protective group is referred to as “carrier”. A prodrug releases the reversibly and covalently bound biologically active moiety in the form of its corresponding drug. In other words, a prodrug is a conjugate comprising a biologically active moiety which is covalently and reversibly conjugated to a carrier moiety via a reversible prodrug linker moiety, which covalent and reversible conjugation of the carrier to the reversible prodrug linker moiety is either directly or through a spacer. Such conjugate releases the formerly conjugated biologically active moiety in the form of a free drug.

As used herein the term “reversible prodrug linker moiety” is a spacer moiety that connects a biologically active moiety, such as a PTH moiety, to a carrier moiety, either directly or through a further spacer moiety and wherein the linkage between the reversible prodrug linker moiety and the biologically active moiety is reversible. Preferably, the linkage between the carrier moiety and the reversible prodrug linker moiety is a stable.

A “biodegradable linkage” or a “reversible linkage” is a linkage that is hydrolytically degradable, i.e. cleavable, in the absence of enzymes under physiological conditions (aqueous

buffer at pH 7.4, 37°C) with a half-life ranging from one hour to three months, preferably from one hour to two months, even more preferably from one hour to one month, even more preferably from one hour to three weeks, most preferably from one hour to two weeks. Accordingly, a “stable linkage” is a linkage having a half-life under physiological conditions
5 (aqueous buffer at pH 7.4, 37°C) of more than three months.

As used herein, the term “traceless prodrug linker” means a reversible prodrug linker, i.e. a linker moiety reversibly and covalently connecting the biologically active moiety with the carrier, which upon cleavage releases the drug in its free form. As used herein, the term “free
10 form” of a drug means the drug in its unmodified, pharmacologically active form.

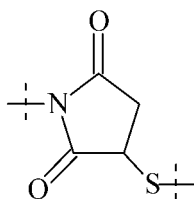
As used herein, the term “excipient” refers to a diluent, adjuvant, or vehicle with which the therapeutic, such as a drug or prodrug, is administered. Such pharmaceutical excipient can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or
15 synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred excipient when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred excipients when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid excipients for injectable
20 solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, mannitol, trehalose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The pharmaceutical composition, if desired, can also contain minor amounts of wetting or emulsifying agents, pH buffering agents, like, for example, acetate,
25 succinate, tris, carbonate, phosphate, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), MES (2-(*N*-morpholino)ethanesulfonic acid), or can contain detergents, like Tween, poloxamers, poloxamines, CHAPS, Igepal, or amino acids like, for example, glycine, lysine, or histidine. These pharmaceutical compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The
30 pharmaceutical composition can be formulated as a suppository, with traditional binders and excipients such as triglycerides. Oral formulation can include standard excipients such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such compositions will contain a therapeutically effective amount of the drug or biologically active moiety, together with a suitable amount of

excipient so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

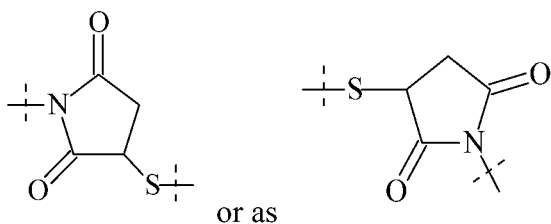
As used herein, the term “reagent” means a chemical compound which comprises at least one functional group for reaction with the functional group of another chemical compound or drug. It is understood that a drug comprising a functional group (such as a primary or secondary amine or hydroxyl functional group) is also a reagent.

As used herein, the term “moiety” means a part of a molecule, which lacks one or more atom(s) compared to the corresponding reagent. If, for example, a reagent of the formula “H-X-H” reacts with another reagent and becomes part of the reaction product, the corresponding moiety of the reaction product has the structure “H-X-” or “-X-”, whereas each “-” indicates attachment to another moiety. Accordingly, a biologically active moiety is released from a prodrug as a drug.

It is understood that if the sequence or chemical structure of a group of atoms is provided which group of atoms is attached to two moieties or is interrupting a moiety, said sequence or chemical structure can be attached to the two moieties in either orientation, unless explicitly stated otherwise. For example, a moiety “-C(O)N(R¹)-” can be attached to two moieties or interrupting a moiety either as “-C(O)N(R¹)-” or as “-N(R¹)C(O)-”. Similarly, a moiety



can be attached to two moieties or can interrupt a moiety either as



As used herein, the term “functional group” means a group of atoms which can react with other groups of atoms. Functional groups include but are not limited to the following groups: carboxylic acid (-(C=O)OH), primary or secondary amine (-NH₂, -NH-), maleimide, thiol

(-SH), sulfonic acid ($-(O=S=O)OH$), carbonate, carbamate ($-O(C=O)N<$), hydroxyl ($-OH$), aldehyde ($-(C=O)H$), ketone ($-(C=O)-$), hydrazine ($>N-N<$), isocyanate, isothiocyanate, phosphoric acid ($-O(P=O)OHOH$), phosphonic acid ($-O(P=O)OHH$), haloacetyl, alkyl halide, acryloyl, aryl fluoride, hydroxylamine, disulfide, sulfonamides, sulfuric acid, vinyl sulfone, vinyl ketone, diazoalkane, oxirane, and aziridine.

In case the PTH compound, preferably controlled-release PTH compound, of the present invention comprise one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the PTH compound, preferably the controlled-release PTH compound, of the present invention comprising acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. PTH compound, preferably controlled-release PTH compound, of the present invention comprising one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. For the person skilled in the art further methods are known for converting the basic group into a cation like the alkylation of an amine group resulting in a positively-charge ammonium group and an appropriate counterion of the salt. If the PTH compound, preferably the controlled-release PTH compound, of the present invention simultaneously comprise acidic and basic groups, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these compounds with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly

suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

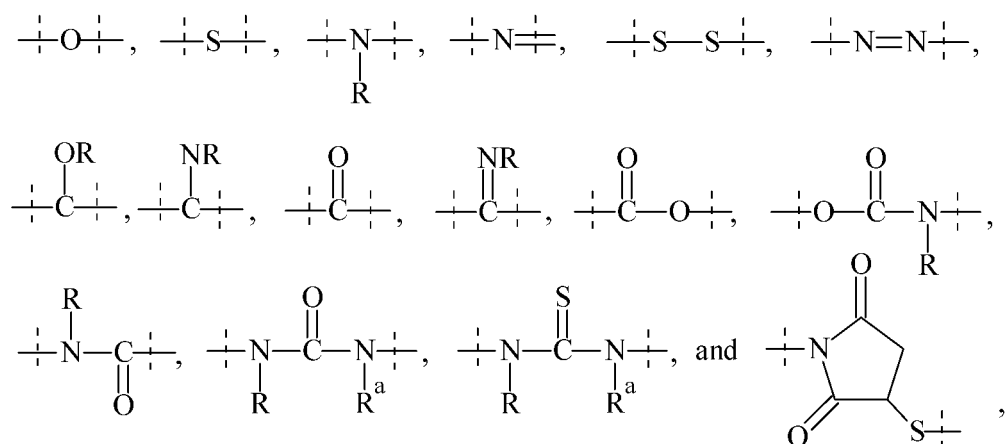
The term "pharmaceutically acceptable" means a substance that does cause harm when administered to a patient and preferably means approved by a regulatory agency, such as the EMA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, preferably for use in humans.

As used herein the term "about" in combination with a numerical value is used to indicate a range ranging from and including the numerical value plus and minus no more than 10% of said numerical value, more preferably no more than 8% of said numerical value, even more preferably no more than 5% of said numerical value and most preferably no more than 2% of said numerical value. For example, the phrase "about 200" is used to mean a range ranging from and including 200 +/- 10%, i.e. ranging from and including 180 to 220; preferably 200 +/- 8%, i.e. ranging from and including 184 to 216; even more preferably ranging from and including 200 +/-5%, i.e. ranging from and including 190 to 210; and most preferably 200 +/- 2%, i.e. ranging from and including 196 to 204. It is understood that a percentage given as "about 20%" does not mean "20% +/- 10%", i.e. ranging from and including 10 to 30%, but "about 20%" means ranging from and including 18 to 22%, i.e. plus and minus 10% of the numerical value which is 20.

As used herein, the term "polymer" means a molecule comprising repeating structural units, i.e. the monomers, connected by chemical bonds in a linear, circular, branched, crosslinked or dendrimeric way or a combination thereof, which may be of synthetic or biological origin or a combination of both. It is understood that a polymer may also comprise one or more other chemical groups and/or moieties, such as, for example, one or more functional groups. Preferably, a soluble polymer has a molecular weight of at least 0.5 kDa, e.g. a molecular weight of at least 1 kDa, a molecular weight of at least 2 kDa, a molecular weight of at least 3 kDa or a molecular weight of at least 5 kDa. If the polymer is soluble, it preferable has a molecular weight of at most 1000 kDa, such as at most 750 kDa, such as at most 500 kDa, such as at most 300 kDa, such as at most 200 kDa, such as at most 100 kDa. It is understood that for insoluble polymers, such as hydrogels, no meaningful molecular weight ranges can be provided. It is understood that also a protein is a polymer in which the amino acids are the repeating structural units, even though the side chains of each amino acid may be different.

As used herein, the term “polymeric” means a reagent or a moiety comprising one or more polymers or polymer moieties. A polymeric reagent or moiety may optionally also comprise one or more other moiety/moieties, which are preferably selected from the group consisting of:

- 5 • C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and
- linkages selected from the group comprising



10 wherein

dashed lines indicate attachment to the remainder of the moiety or reagent, and -R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

15 The person skilled in the art understands that the polymerization products obtained from a polymerization reaction do not all have the same molecular weight, but rather exhibit a molecular weight distribution. Consequently, the molecular weight ranges, molecular weights, ranges of numbers of monomers in a polymer and numbers of monomers in a polymer as used herein, refer to the number average molecular weight and number average of monomers, i.e.

20 to the arithmetic mean of the molecular weight of the polymer or polymeric moiety and the arithmetic mean of the number of monomers of the polymer or polymeric moiety.

Accordingly, in a polymeric moiety comprising “x” monomer units any integer given for “x” therefore corresponds to the arithmetic mean number of monomers. Any range of integers
25 given for “x” provides the range of integers in which the arithmetic mean numbers of monomers lies. An integer for “x” given as “about x” means that the arithmetic mean numbers

of monomers lies in a range of integers of $x \pm 10\%$, preferably $x \pm 8\%$, more preferably $x \pm 5\%$ and most preferably $x \pm 2\%$.

As used herein, the term “number average molecular weight” means the ordinary arithmetic
5 mean of the molecular weights of the individual polymers.

As used herein the term “water-soluble” with reference to a carrier means that when such carrier is part of PTH compound, preferably the controlled-release PTH compound, of the present invention at least 1 g of the PTH compound, preferably controlled-release PTH
10 compound, comprising such water-soluble carrier can be dissolved in one liter of water at 20°C to form a homogeneous solution. Accordingly, the term “water-insoluble” with reference to a carrier means that when such carrier is part of a PTH compound, preferably controlled-release PTH compound, of the present invention less than 1 g of the PTH compound, preferably controlled-release PTH compound, comprising such water-insoluble
15 carrier can be dissolved in one liter of water at 20°C to form a homogeneous solution.

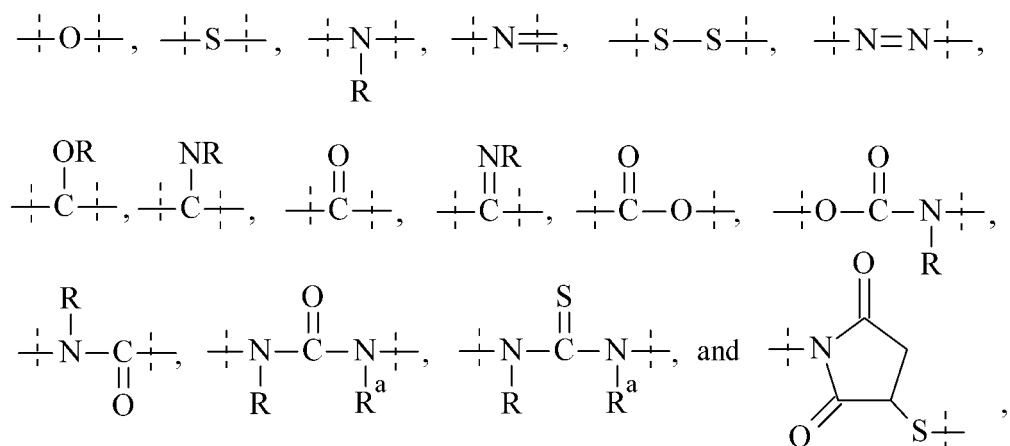
As used herein the term “water-soluble” with reference to the PTH compound means that at least 1 g of the PTH compound can be dissolved in one liter of water at 20°C to form a homogeneous solution. Accordingly, the term “water-insoluble” with reference to the PTH
20 compound means that less than 1 g of the PTH compound can be dissolved in one liter of water at 20°C to form a homogeneous solution.

As used herein, the term “hydrogel” means a hydrophilic or amphiphilic polymeric network composed of homopolymers or copolymers, which is insoluble due to the presence of
25 covalent chemical crosslinks. The crosslinks provide the network structure and physical integrity.

As used herein the term “thermogelling” means a compound that is a liquid or a low viscosity solution having a viscosity of less than 500 cps at 25°C at a shear rate of about 0.1 /second at
30 a low temperature, which low temperature ranges between about 0°C to about 10°C, but which is a higher viscosity compound of less than 10000 cps at 25°C at a shear rate of about 0.1/second at a higher temperature, which higher temperature ranges between about 30°C to about 40°C, such as at about 37°C.

As used herein, the term “PEG-based” in relation to a moiety or reagent means that said moiety or reagent comprises PEG. Preferably, a PEG-based moiety or reagent comprises at least 10% (w/w) PEG, such as at least 20% (w/w) PEG, such as at least 30% (w/w) PEG, such as at least 40% (w/w) PEG, such as at least 50% (w/w), such as at least 60 (w/w) PEG, such as at least 70% (w/w) PEG, such as at least 80% (w/w) PEG, such as at least 90% (w/w) PEG, such as at least 95%. The remaining weight percentage of the PEG-based moiety or reagent are other moieties preferably selected from the following moieties and linkages:

- C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclcyl, 8- to 11-membered heterobicyclcyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and
- linkages selected from the group comprising



wherein

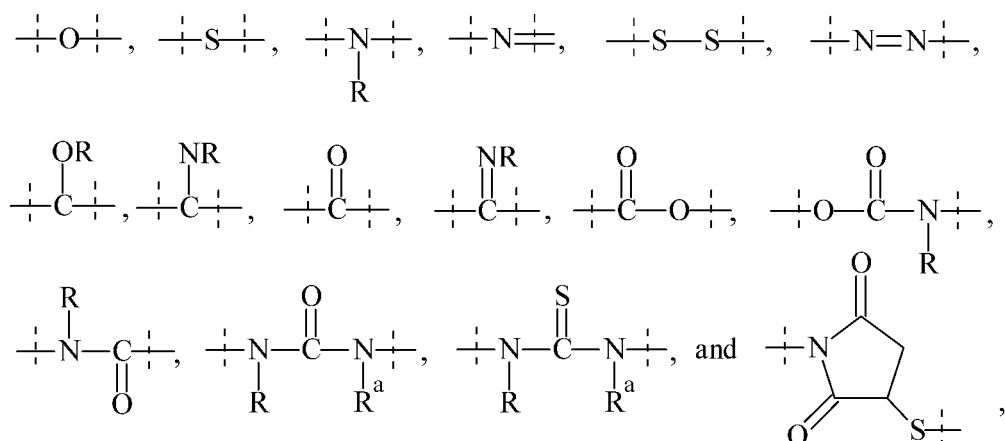
dashed lines indicate attachment to the remainder of the moiety or reagent, and

-R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

As used herein, the term “PEG-based comprising at least X% PEG” in relation to a moiety or reagent means that said moiety or reagent comprises at least X% (w/w) ethylene glycol units (-CH₂CH₂O-), wherein the ethylene glycol units may be arranged blockwise, alternating or may be randomly distributed within the moiety or reagent and preferably all ethylene glycol units of said moiety or reagent are present in one block; the remaining weight percentage of the PEG-based moiety or reagent are other moieties preferably selected from the following moieties and linkages:

- C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, C₂₋₅₀ alkynyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclcyl, 8- to 11-membered heterobicyclcyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl; and

- linkages selected from the group comprising



wherein

dashed lines indicate attachment to the remainder of the moiety or reagent, and

- 5 -R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

The term “hyaluronic acid-based comprising at least X% hyaluronic acid” is used accordingly.

10

The term “spacer moiety” as used here in means any moiety that connects two other moieties. Preferably, a spacer moiety is selected from the group consisting of -T-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ 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})-;

15

- 20 each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 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;

- 25 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}), -NO₂, -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

- 5 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.

10 The term “substituted” as used herein means that one or more $-H$ atom(s) of a molecule or moiety are replaced by a different atom or a group of atoms, which are referred to as “substituent”.

Preferably, the one or more further optional substituents are independently of each other selected from the group consisting of halogen, $-CN$, $-COOR^{x1}$, $-OR^{x1}$, $-C(O)R^{x1}$,
 15 $-C(O)N(R^{x1}R^{x1a})$, $-S(O)_2N(R^{x1}R^{x1a})$, $-S(O)N(R^{x1}R^{x1a})$, $-S(O)_2R^{x1}$, $-S(O)R^{x1}$,
 $-N(R^{x1})S(O)_2N(R^{x1a}R^{x1b})$, $-SR^{x1}$, $-N(R^{x1}R^{x1a})$, $-NO_2$, $-OC(O)R^{x1}$, $-N(R^{x1})C(O)R^{x1a}$,
 $-N(R^{x1})S(O)_2R^{x1a}$, $-N(R^{x1})S(O)R^{x1a}$, $-N(R^{x1})C(O)OR^{x1a}$, $-N(R^{x1})C(O)N(R^{x1a}R^{x1b})$,
 $-OC(O)N(R^{x1}R^{x1a})$, $-T^0$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T^0$, C_{1-50} alkyl,
 20 C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{x2}$, 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 $-T^0$ -, $-C(O)O$ -, $-O$ -,
 $-C(O)$ -, $-C(O)N(R^{x3})$ -, $-S(O)_2N(R^{x3})$ -, $-S(O)N(R^{x3})$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^{x3})S(O)_2N(R^{x3a})$ -,
 $-S$ -, $-N(R^{x3})$ -, $-OC(OR^{x3})(R^{x3a})$ -, $-N(R^{x3})C(O)N(R^{x3a})$ -, and $-OC(O)N(R^{x3})$ -;

25 $-R^{x1}$, $-R^{x1a}$, $-R^{x1b}$ are independently of each other selected from the group consisting of $-H$, $-T^0$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-T^0$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-R^{x2}$, 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 $-T^0$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -,
 30 $-C(O)N(R^{x3})$ -, $-S(O)_2N(R^{x3})$ -, $-S(O)N(R^{x3})$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^{x3})S(O)_2N(R^{x3a})$ -, $-S$ -,
 $-N(R^{x3})$ -, $-OC(OR^{x3})(R^{x3a})$ -, $-N(R^{x3})C(O)N(R^{x3a})$ -, and $-OC(O)N(R^{x3})$ -;

each T^0 is independently 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

heterobicycyl; wherein each T^0 is independently optionally substituted with one or more $-R^{x2}$, which are the same or different;

each $-R^{x2}$ is independently selected from the group consisting of halogen, $-CN$, oxo
 5 $(=O)$, $-COOR^{x4}$, $-OR^{x4}$, $-C(O)R^{x4}$, $-C(O)N(R^{x4}R^{x4a})$, $-S(O)_2N(R^{x4}R^{x4a})$, $-S(O)N(R^{x4}R^{x4a})$,
 $-S(O)_2R^{x4}$, $-S(O)R^{x4}$, $-N(R^{x4})S(O)_2N(R^{x4a}R^{x4b})$, $-SR^{x4}$, $-N(R^{x4}R^{x4a})$, $-NO_2$, $-OC(O)R^{x4}$,
 $-N(R^{x4})C(O)R^{x4a}$, $-N(R^{x4})S(O)_2R^{x4a}$, $-N(R^{x4})S(O)R^{x4a}$, $-N(R^{x4})C(O)OR^{x4a}$,
 $-N(R^{x4})C(O)N(R^{x4a}R^{x4b})$, $-OC(O)N(R^{x4}R^{x4a})$, 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 $-R^{x3}$, $-R^{x3a}$, $-R^{x4}$, $-R^{x4a}$, $-R^{x4b}$ 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.

More preferably, the one or more further optional substituents are independently of each other
 selected from the group consisting of halogen, $-CN$, $-COOR^{x1}$, $-OR^{x1}$, $-C(O)R^{x1}$,
 $-C(O)N(R^{x1}R^{x1a})$, $-S(O)_2N(R^{x1}R^{x1a})$, $-S(O)N(R^{x1}R^{x1a})$, $-S(O)_2R^{x1}$, $-S(O)R^{x1}$,
 $-N(R^{x1})S(O)_2N(R^{x1a}R^{x1b})$, $-SR^{x1}$, $-N(R^{x1}R^{x1a})$, $-NO_2$, $-OC(O)R^{x1}$, $-N(R^{x1})C(O)R^{x1a}$,
 $-N(R^{x1})S(O)_2R^{x1a}$, $-N(R^{x1})S(O)R^{x1a}$, $-N(R^{x1})C(O)OR^{x1a}$, $-N(R^{x1})C(O)N(R^{x1a}R^{x1b})$,
 20 $-OC(O)N(R^{x1}R^{x1a})$, $-T^0$, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl; wherein $-T^0$, C_{1-10} alkyl,
 C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally substituted with one or more $-R^{x2}$, which are the
 same or different and wherein C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl are optionally
 interrupted by one or more groups selected from the group consisting of $-T^0$ -, $-C(O)O$ -,
 $-O$ -, $-C(O)$ -, $-C(O)N(R^{x3})$ -, $-S(O)_2N(R^{x3})$ -, $-S(O)N(R^{x3})$ -, $-S(O)_2$ -, $-S(O)$ -,
 25 $-N(R^{x3})S(O)_2N(R^{x3a})$ -, $-S$ -, $-N(R^{x3})$ -, $-OC(OR^{x3})(R^{x3a})$ -, $-N(R^{x3})C(O)N(R^{x3a})$ -,
 and $-OC(O)N(R^{x3})$ -;

each $-R^{x1}$, $-R^{x1a}$, $-R^{x1b}$, $-R^{x3}$, $-R^{x3a}$ is independently selected from the group consisting of $-H$,
 halogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

each T^0 is independently 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
 heterobicycyl; wherein each T^0 is independently optionally substituted with one or more $-R^{x2}$,
 which are the same or different;

each $-R^{x2}$ is independently selected from the group consisting of halogen, $-CN$, oxo ($=O$), $-COOR^{x4}$, $-OR^{x4}$, $-C(O)R^{x4}$, $-C(O)N(R^{x4}R^{x4a})$, $-S(O)_2N(R^{x4}R^{x4a})$, $-S(O)N(R^{x4}R^{x4a})$, $-S(O)_2R^{x4}$, $-S(O)R^{x4}$, $-N(R^{x4})S(O)_2N(R^{x4a}R^{x4b})$, $-SR^{x4}$, $-N(R^{x4}R^{x4a})$, $-NO_2$, $-OC(O)R^{x4}$, $-N(R^{x4})C(O)R^{x4a}$, $-N(R^{x4})S(O)_2R^{x4a}$, $-N(R^{x4})S(O)R^{x4a}$, $-N(R^{x4})C(O)OR^{x4a}$, $-N(R^{x4})C(O)N(R^{x4a}R^{x4b})$, $-OC(O)N(R^{x4}R^{x4a})$, 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 $-R^{x4}$, $-R^{x4a}$, $-R^{x4b}$ is independently selected from the group consisting of $-H$, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

10

Even more preferably, the one or more further optional substituents are independently of each other selected from the group consisting of halogen, $-CN$, $-COOR^{x1}$, $-OR^{x1}$, $-C(O)R^{x1}$, $-C(O)N(R^{x1}R^{x1a})$, $-S(O)_2N(R^{x1}R^{x1a})$, $-S(O)N(R^{x1}R^{x1a})$, $-S(O)_2R^{x1}$, $-S(O)R^{x1}$, $-N(R^{x1})S(O)_2N(R^{x1a}R^{x1b})$, $-SR^{x1}$, $-N(R^{x1}R^{x1a})$, $-NO_2$, $-OC(O)R^{x1}$, $-N(R^{x1})C(O)R^{x1a}$, $-N(R^{x1})S(O)_2R^{x1a}$, $-N(R^{x1})S(O)R^{x1a}$, $-N(R^{x1})C(O)OR^{x1a}$, $-N(R^{x1})C(O)N(R^{x1a}R^{x1b})$, $-OC(O)N(R^{x1}R^{x1a})$, $-T^0$, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein $-T^0$, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more $-R^{x2}$, which are the same or different and wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T^0$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^{x3})$ -, $-S(O)_2N(R^{x3})$ -, $-S(O)N(R^{x3})$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^{x3})S(O)_2N(R^{x3a})$ -, $-S$ -, $-N(R^{x3})$ -, $-OC(OR^{x3})(R^{x3a})$ -, $-N(R^{x3})C(O)N(R^{x3a})$ -, and $-OC(O)N(R^{x3})$ -;

20

each $-R^{x1}$, $-R^{x1a}$, $-R^{x1b}$, $-R^{x2}$, $-R^{x3}$, $-R^{x3a}$ is independently selected from the group consisting of $-H$, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

25

each T^0 is independently 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; wherein each T^0 is independently optionally substituted with one or more $-R^{x2}$, which are the same or different.

30

Preferably, a maximum of 6 $-H$ atoms of an optionally substituted molecule are independently replaced by a substituent, e.g. 5 $-H$ atoms are independently replaced by a substituent, 4 $-H$ atoms are independently replaced by a substituent, 3 $-H$ atoms are independently replaced by

a substituent, 2 -H atoms are independently replaced by a substituent, or 1 -H atom is replaced by a substituent.

The term “interrupted” means that a moiety is inserted between two carbon atoms or – if the insertion is at one of the moiety’s ends – between a carbon or heteroatom and a hydrogen atom, preferably between a carbon and a hydrogen atom.

As used herein, the term “C₁₋₄ alkyl” alone or in combination means a straight-chain or branched alkyl moiety having 1 to 4 carbon atoms. If present at the end of a molecule, examples of straight-chain or branched C₁₋₄ alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. When two moieties of a molecule are linked by the C₁₋₄ alkyl, then examples for such C₁₋₄ alkyl groups are -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)-, -C(CH₃)₂-. Each hydrogen of a C₁₋₄ alkyl carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₄ alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₁₋₆ alkyl” alone or in combination means a straight-chain or branched alkyl moiety having 1 to 6 carbon atoms. If present at the end of a molecule, examples of straight-chain and branched C₁₋₆ alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl. When two moieties of a molecule are linked by the C₁₋₆ alkyl group, then examples for such C₁₋₆ alkyl groups are -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -CH(C₂H₅)- and -C(CH₃)₂-. Each hydrogen atom of a C₁₋₆ carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₆ alkyl may be interrupted by one or more moieties as defined below.

Accordingly, “C₁₋₁₀ alkyl”, “C₁₋₂₀ alkyl” or “C₁₋₅₀ alkyl” means an alkyl chain having 1 to 10, 1 to 20 or 1 to 50 carbon atoms, respectively, wherein each hydrogen atom of the C₁₋₁₀, C₁₋₂₀ or C₁₋₅₀ carbon may optionally be replaced by a substituent as defined above. Optionally, a C₁₋₁₀ or C₁₋₅₀ alkyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₂₋₆ alkenyl” alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to

6 carbon atoms. If present at the end of a molecule, examples are $-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CHCH}_2-\text{CH}_3$ and $-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$. When two moieties of a molecule are linked by the C_{2-6} alkenyl group, then an example for such C_{2-6} alkenyl is $-\text{CH}=\text{CH}-$. Each hydrogen atom of a C_{2-6} alkenyl moiety may optionally be replaced by a substituent as defined above. Optionally, a C_{2-6} alkenyl may be interrupted by one or more moieties as defined below.

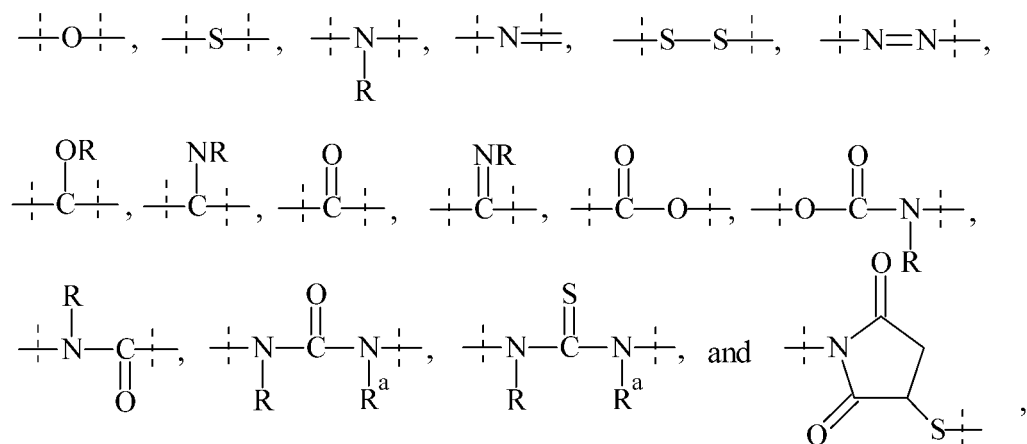
Accordingly, the term " C_{2-10} alkenyl", " C_{2-20} alkenyl" or " C_{2-50} alkenyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms. Each hydrogen atom of a C_{2-10} alkenyl, C_{2-20} alkenyl or C_{2-50} alkenyl group may optionally be replaced by a substituent as defined above. Optionally, a C_{2-10} alkenyl, C_{2-20} alkenyl or C_{2-50} alkenyl may be interrupted by one or more moieties as defined below.

As used herein, the term " C_{2-6} alkynyl" alone or in combination means straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are $-\text{C}\equiv\text{CH}$, $-\text{CH}_2-\text{C}\equiv\text{CH}$, $\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$ and $\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_3$. When two moieties of a molecule are linked by the alkynyl group, then an example is $-\text{C}\equiv\text{C}-$. Each hydrogen atom of a C_{2-6} alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C_{2-6} alkynyl may be interrupted by one or more moieties as defined below.

Accordingly, as used herein, the term " C_{2-10} alkynyl", " C_{2-20} alkynyl" and " C_{2-50} alkynyl" alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon triple bond having 2 to 10, 2 to 20 or 2 to 50 carbon atoms, respectively. Each hydrogen atom of a C_{2-10} alkynyl, C_{2-20} alkynyl or C_{2-50} alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C_{2-10} alkynyl, C_{2-20} alkynyl or C_{2-50} alkynyl may be interrupted by one or more moieties as defined below.

As mentioned above, a C_{1-4} alkyl, C_{1-6} alkyl, C_{1-10} alkyl, C_{1-20} alkyl, C_{1-50} alkyl, C_{2-6} alkenyl, C_{2-10} alkenyl, C_{2-20} alkenyl, C_{2-50} alkenyl, C_{2-6} alkynyl, C_{2-10} alkynyl, C_{2-20} alkenyl or C_{2-50}

alkynyl may optionally be interrupted by one or more moieties which are preferably selected from the group consisting of



wherein

- 5 dashed lines indicate attachment to the remainder of the moiety or reagent; and
 -R and -R^a are independently of each other selected from the group consisting of -H, methyl, ethyl, propyl, butyl, pentyl and hexyl.

As used herein, the term "C₃₋₁₀ cycloalkyl" means a cyclic alkyl chain having 3 to 10 carbon
 10 atoms, which may be saturated or unsaturated, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl. Each hydrogen atom of a C₃₋₁₀ cycloalkyl carbon may be replaced by a substituent as defined above. The term "C₃₋₁₀ cycloalkyl" also includes bridged bicycles like norbornane or norbornene.

- 15 The term "8- to 30-membered carbopolycyclyl" or "8- to 30-membered carbopolycycle" means a cyclic moiety of two or more rings with 8 to 30 ring atoms, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated). Preferably a 8- to 30-membered carbopolycyclyl means a cyclic moiety of two, three, four or five rings,
 20 preferably of two, three or four rings.

As used herein, the term "3- to 10-membered heterocyclyl" or "3- to 10-membered heterocycle" means a ring with 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or
 25 un-saturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or

nitrogen atom. Examples for 3- to 10-membered heterocycles include but are not limited to aziridine, oxirane, thiirane, azirine, oxirene, thiirene, azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine and homopiperazine. Each hydrogen atom of a 3- to 10-membered heterocyclyl or 3- to 10-membered heterocyclic group may be replaced by a substituent as defined below.

As used herein, the term "8- to 11-membered heterobicycyl" or "8- to 11-membered heterobicycle" means a heterocyclic moiety of two rings with 8 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one ring atom up to 6 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for an 8- to 11-membered heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, quinoline, dihydroquinoline, tetrahydroquinoline, decahydroquinoline, isoquinoline, decahydroisoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine and pteridine. The term 8- to 11-membered heterobicycle also includes spiro structures of two rings like 1,4-dioxo-8-azaspiro[4.5]decane or bridged heterocycles like 8-aza-bicyclo[3.2.1]octane. Each hydrogen atom of an 8- to 11-membered heterobicycyl or 8- to 11-membered heterobicycle carbon may be replaced by a substituent as defined below.

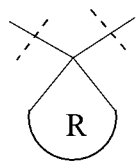
Similarly, the term "8- to 30-membered heteropolycyclyl" or "8- to 30-membered heteropolycycle" means a heterocyclic moiety of more than two rings with 8 to 30 ring atoms, preferably of three, four or five rings, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or unsaturated), wherein at least one ring atom up to 10 ring atoms are replaced by a heteroatom selected from the group of sulfur (including -S(O)-,

-S(O)₂-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of a molecule via a carbon or nitrogen atom.

It is understood that the phrase “the pair R^x/R^y is joined together with the atom to which they are attached to form a C₃₋₁₀ cycloalkyl or a 3- to 10-membered heterocyclyl” in relation with a moiety of the structure

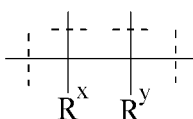


means that R^x and R^y form the following structure:

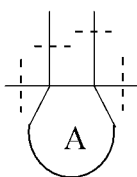


wherein R is C₃₋₁₀ cycloalkyl or 3- to 10-membered heterocyclyl.

It is also understood that the phrase “the pair R^x/R^y is joint together with the atoms to which they are attached to form a ring A” in relation with a moiety of the structure



means that R^x and R^y form the following structure:



As used herein, "halogen" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

In general, the term “comprise” or “comprising” also encompasses “consist of” or “consisting of”.

Preferably, the PTH compound comprises a PTH molecule or PTH moiety having 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. More preferably the PTH molecule or PTH moiety has the sequence of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:110, SEQ ID NO:111 or SEQ ID NO:112.

5

In one embodiment the PTH molecule or PTH moiety has the sequence of SEQ ID NO:50.

In another embodiment the PTH molecule or PTH moiety has the sequence of SEQ ID NO:52.

10

In another embodiment the PTH molecule or PTH moiety has the sequence of SEQ ID NO:110.

15

In another embodiment the PTH molecule or PTH moiety has the sequence of SEQ ID NO:111.

In another embodiment the PTH molecule or PTH moiety has the sequence of SEQ ID NO:112.

20

Most preferably the PTH molecule or PTH moiety has the sequence of SEQ ID NO:51.

25

Administration of the PTH compound is preferably via subcutaneous administration. In another embodiment administration of the PTH compound is via intravenous administration. In a further embodiment administration of the PTH compound is via intramuscular administration.

30

The time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, i.e. the administration interval, is preferably at least 24 hours, such as 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, every 84 hours, 96 hours, 108 hours, 120 hours, 132 hours, 144 hours, 156 hours, one week, two weeks, three weeks or four weeks.

In one embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is 24 hours.

In another embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is 48 hours.

In another embodiment the time period between two consecutive administrations, preferably
5 between two consecutive subcutaneous administrations, is 72 hours.

In another embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is 96 hours.

10 In another embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is 120 hours.

In another embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is 144 hours.

15 In another embodiment the time period between two consecutive administrations, preferably between two consecutive subcutaneous administrations, is one week.

The peak to trough ratio measured in each administration interval is less than 4, preferably
20 less than 3.8, more preferably less than 3.6, even more preferably less than 3.4, even more preferably less than 3.2, even more preferably less than 3, even more preferably less than 2.8, even more preferably less than 2.6, even more preferably less than 2.4, even more preferably less than 2.2 and most preferably less than 2.

25 Preferably the subcutaneous administration is via subcutaneous injection. Preferably, said subcutaneous injection occurs with a pen device.

In one embodiment the PTH compound is a stable PTH compound.

30 In one embodiment the PTH compound is a stable PTH compound in which at least one PTH moiety is covalently conjugated through a stable linkage to a polymeric moiety, either directly or through a spacer moiety.

Preferably, in such stable PTH compounds the PTH moiety is covalently conjugated through a stable linkage to a water-soluble polymeric moiety, either directly or through a spacer moiety.

Preferably, such polymeric moiety is selected from the group consisting of 2-methacryloyl-
5 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),
10 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),
15 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, dextrans, gelatins,
hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins,
20 rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other
carbohydrate-based polymers, xylans, and copolymers thereof.

Even more preferably, the polymeric moiety is a PEG-based moiety.

25 In another embodiment the at least one PTH moiety is covalently conjugated through a stable
linkage to an albumin-binding moiety. Preferably, said albumin-binding moiety is a C₈₋₂₄
alkyl moiety or fatty acid derivative. Preferred fatty acid derivatives are those disclosed in
WO 2005/027978 A2 and WO 2014/060512 A1, which are herewith incorporated by
reference.

30

In another embodiment the stable PTH compound is a fusion protein, i.e. a PTH moiety stably
and covalently bound to another peptide or protein moiety via a peptide bond.

In a preferred embodiment the PTH compound is a controlled-release PTH compound.

In one embodiment the controlled-release PTH compound is water-insoluble.

Preferably, a water-insoluble controlled-release PTH compound is selected from the group consisting of crystals, nanoparticles, microparticles, nanospheres and microspheres.

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In one embodiment the water-insoluble controlled-release PTH compound is a crystal comprising at least one PTH molecule or PTH moiety.

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In another embodiment the water-insoluble controlled-release PTH compound is a nanoparticle comprising at least one PTH molecule or PTH moiety.

In another embodiment the water-insoluble controlled-release PTH compound is a microparticle comprising at least one PTH molecule or PTH moiety.

15

In another embodiment the water-insoluble controlled-release PTH compound is a nanosphere comprising at least one PTH molecule or PTH moiety.

In another embodiment the water-insoluble controlled-release PTH compound is a microsphere comprising at least one PTH molecule or PTH moiety.

20

In one embodiment the water-insoluble controlled-release PTH compound is a vesicle comprising at least one PTH molecule or PTH moiety. Preferably, such vesicle comprising at least one PTH molecule or PTH moiety is a micelle, liposome or polymersome.

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In one embodiment the water-insoluble controlled-release PTH compound is a micelle comprising at least one PTH molecule or PTH moiety.

30

In another embodiment the water-insoluble controlled-release PTH compound is a liposome comprising at least one PTH molecule or PTH moiety. Preferably, such liposome is selected from the group consisting of aquasomes; non-ionic surfactant vesicles, such as niosomes and proniosomes; cationic liposomes, such as LeciPlex; transfersomes; ethosomes; ufasomes; sphingosomes; and pharmacosomes.

In another embodiment the water-insoluble controlled-release PTH compound is a polymersome comprising at least one PTH molecule or PTH moiety.

In another embodiment the water-insoluble controlled-release PTH compound comprises at least one PTH molecule non-covalently embedded in a water-insoluble polymer. Preferably, such water-insoluble polymer comprises 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), 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), 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, dextrans, 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.

In a preferred embodiment the water-insoluble controlled-release PTH compound comprises at least one PTH molecule non-covalently embedded in poly(lactic-co-glycolic acid) (PLGA).

In another embodiment the water-insoluble controlled-release PTH compound comprises at least one PTH moiety covalently and reversibly conjugated to a water-insoluble polymer. Preferably such water-insoluble polymer comprises 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), 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),
 5 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
 10 celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrans, 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.

15 In one embodiment such water-insoluble controlled-release PTH compound is a compound 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
 20 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.

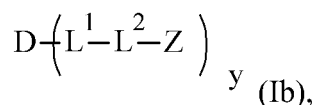
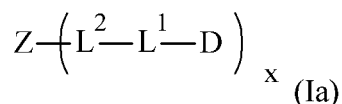
25 It is understood that a multitude of moieties $-L^2-L^1-D$ is connected to a water-insoluble carrier $-Z'$ and that such controlled-release PTH compounds are PTH prodrugs, more specifically carrier-linked PTH prodrugs.

Preferred embodiments for -D, $-L^1-$, $-L^2-$ and $-Z'$ are as described below.

30

In a preferred embodiment the controlled-release PTH compound is water-soluble.

In a preferred embodiment such water-soluble controlled-release PTH compound is a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt thereof



wherein

-D is a PTH moiety;

5 -L¹- is a reversible prodrug linker moiety connected to the PTH moiety -D through a functional group of PTH;

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

-Z is a water-soluble carrier moiety;

10 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 1, 2, 3, 4 and 5.

It is understood that the compounds of formula (Ia) and (Ib) are PTH prodrugs, more specifically water-soluble PTH prodrugs.

15

Preferably, -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. More preferably -D has
20 the sequence of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:110, SEQ ID NO:111 or SEQ ID NO:112.

In one embodiment -D has the sequence of SEQ ID NO:50.

25 In another embodiment -D has the sequence of SEQ ID NO:52.

In another embodiment -D has the sequence of SEQ ID NO:110.

In another embodiment -D has the sequence of SEQ ID NO:111.

30

In another embodiment -D has the sequence of SEQ ID NO:112.

Most preferably -D has the sequence of SEQ ID NO:51.

The moiety -L¹- 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. Attachment to either the N-terminus or C-terminus can either be directly through the corresponding amine or carboxyl functional group, respectively, or indirectly wherein a spacer moiety is first conjugated to the amine or carboxyl functional group to which spacer moiety -L¹- is conjugated.

Preferably, the amino acid residue of PTH to which -L¹- is conjugated comprises a functional group selected from the group consisting carboxylic acid, primary and secondary amine, maleimide, thiol, sulfonic acid, carbonate, carbamate, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid, phosphonic acid, haloacetyl, alkyl halide, acryloyl, aryl fluoride, hydroxylamine, sulfate, disulfide, vinyl sulfone, vinyl ketone, diazoalkane, oxirane, guanidine and aziridine. Even more preferably the amino acid residue of PTH to which -L¹- is conjugated comprises a functional group selected from the group consisting hydroxyl, primary and secondary amine and guanidine. Even more preferably the amino acid residue of PTH to which -L¹- is conjugated comprises a primary or secondary amine functional group. Most preferably the amino acid residue of PTH to which -L¹- is conjugated comprises a primary amine functional group.

If the moiety -L¹- is conjugated to a functional group of the side chain of an amino acid residue of PTH said amino acid residue is selected from the group consisting of proteinogenic amino acid residues and non-proteinogenic amino acid residues.

In one embodiment -L¹- is conjugated to a functional group of the side chain of a non-proteinogenic amino acid residue of PTH. It is understood that such non-proteinogenic amino acid is not found in the sequence of native PTH or fragments thereof and that it may only be present in variants and derivatives of PTH.

In another embodiment -L¹- is conjugated to a functional group of the side chain of a proteinogenic amino acid residue of PTH. Preferably said amino acid is selected from the group consisting of histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid,

glutamic acid and arginine. Even more preferably said amino acid is selected from the group consisting of lysine, aspartic acid, arginine and serine. Even more preferably said amino acid is selected from the group consisting of lysine, arginine and serine.

- 5 In one embodiment $-L^1$ - is conjugated to a functional group of the side chain of a histidine of PTH.

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a lysine of PTH.

10

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a tryptophan of PTH.

15

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a serine of PTH.

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In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a threonine of PTH.

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a tyrosine of PTH.

25

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of an aspartic acid of PTH.

In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of a glutamic acid of PTH.

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In another embodiment $-L^1$ - is conjugated to a functional group of the side chain of an arginine of PTH.

It is understood that not every PTH moiety may comprise all of these amino acid residues.

In a preferred embodiment $-L^1-$ is conjugated to the N-terminal amine functional group of PTH, either directly through the corresponding amine functional group or indirectly wherein a spacer moiety is first conjugated to the amine functional group to which spacer moiety $-L^1-$ is conjugated. Even more preferably, $-L^1-$ is directly conjugated to the N-terminal amine functional group of PTH.

In an equally preferred embodiment $-L^1-$ is conjugated to the C-terminal functional group of PTH, either directly through the corresponding carboxyl functional group or indirectly wherein a spacer moiety is first conjugated to the carboxyl functional group to which spacer moiety $-L^1-$ is conjugated.

Most preferably L^1- is directly conjugated to the N-terminal amine functional group of PTH.

The moiety $-L^1-$ can be connected to $-D$ through any type of linkage, provided that it is reversible. Preferably, $-L^1-$ is connected to $-D$ through a linkage selected from the group consisting of amide, ester, carbamate, acetal, aminal, imine, oxime, hydrazone, disulfide and acylguanidine. Even more preferably $-L^1-$ is connected to $-D$ through a linkage selected from the group consisting of amide, ester, carbamate and acylguanidin. It is understood that some of these linkages are not reversible *per se*, but that in the present invention neighboring groups comprised in $-L^1-$ render these linkage reversible.

In one embodiment $-L^1-$ is connected to $-D$ through an ester linkage.

In another embodiment $-L^1-$ is connected to $-D$ through a carbamate linkage.

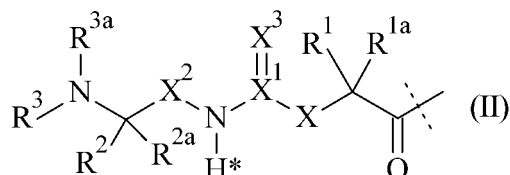
In another embodiment $-L^1-$ is connected to $-D$ through an acylguanidine.

In a preferred embodiment $-L^1-$ is connected to $-D$ through an amide linkage.

The moiety $-L^1-$ is a reversible prodrug linker from which the drug, i.e. PTH, is released in its free form, i.e. it is a traceless prodrug linker. Suitable prodrug linkers are known in the art, such as for example the reversible prodrug linker moieties disclosed in WO 2005/099768 A2, WO 2006/136586 A2, WO 2011/089216 A1 and WO 2013/024053 A1, which are incorporated by reference herewith.

In another embodiment -L¹- is a reversible prodrug linker as described in WO 2011/012722 A1, WO 2011/089214 A1, WO 2011/089215 A1, WO 2013/024052 A1 and WO 2013/160340 A1 which are incorporated by reference herewith.

- 5 A particularly preferred moiety -L¹- is disclosed in WO 2009/095479 A2. Accordingly, in a preferred embodiment the moiety -L¹- is of formula (II):



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

- 10 -X- is selected from the group consisting of -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})-; and -C(R⁷R^{7a})-;
- X¹ is selected from the group consisting of C; and S(O);
- X²- is selected from the group consisting of -C(R⁸R^{8a})-; and -C(R⁸R^{8a})-C(R⁹R^{9a})-;
- 15 =X³ is selected from the group consisting of =O; =S; and =N-CN;
- R¹, -R^{1a}, -R², -R^{2a}, -R⁴, -R^{4a}, -R⁵, -R^{5a}, -R⁶, -R⁸, -R^{8a}, -R⁹, and -R^{9a} are independently selected from the group consisting of -H; and C₁₋₆ alkyl;
- R³, and -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
- 20 connected to N to which they are attached through an sp³-hybridized carbon atom;
- R⁷ is selected from the group consisting of -N(R¹⁰R^{10a}); and -NR¹⁰-(C=O)-R¹¹;
- R^{7a}, -R¹⁰, -R^{10a}, and -R¹¹ are independently of each other selected from the group consisting of -H; and C₁₋₆ alkyl;
- 25 optionally, one or more of the pairs -R^{1a}/R^{4a}, -R^{1a}/R^{5a}, -R^{1a}/R^{7a}, -R^{4a}/R^{5a}, and -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}, and -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 $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, and $-R^2/-R^3$ 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;

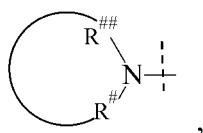
$-Z$ is a water-soluble carrier; and

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

Preferably $-L^1-$ of formula (II) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In one embodiment $-L^1-$ of formula (II) is not further substituted.

It is understood that if $-R^3/-R^{3a}$ of formula (II) are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle, only such 3- to 10-membered heterocycles may be formed in which the atoms directly attached to the nitrogen are sp^3 -hybridized carbon atoms. In other words, such 3- to 10-membered heterocycle formed by $-R^3/-R^{3a}$ together with the nitrogen atom to which they are attached has the following structure:



wherein

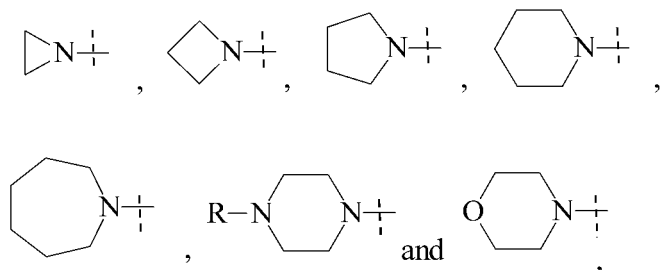
the dashed line indicates attachment to the rest of $-L^1-$;

the ring comprises 3 to 10 atoms comprising at least one nitrogen; and

$R^{\#}$ and $R^{##}$ represent an sp^3 -hybridized carbon atom.

It is also understood that the 3- to 10-membered heterocycle may be further substituted.

Exemplary embodiments of suitable 3- to 10-membered heterocycles formed by $-R^3/-R^{3a}$ of formula (II) together with the nitrogen atom to which they are attached are the following:

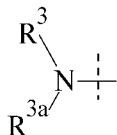


wherein

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

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

- 10 $-L^1$ of formula (II) may optionally be further substituted. In general, any substituent may be used as far as the cleavage principle is not affected, i.e. the hydrogen marked with the asterisk in formula (II) is not replaced and the nitrogen of the moiety



- 15 of formula (II) remains part of a primary, secondary or tertiary amine, i.e. $-R^3$ and $-R^{3a}$ are independently of each other $-H$ or are connected to $-N<$ through an sp^3 -hybridized carbon atom.

- In one embodiment $-R^1$ or $-R^{1a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^2$ or $-R^{2a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another
 20 embodiment $-R^3$ or $-R^{3a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^4$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^5$ or $-R^{5a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^6$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another
 25 embodiment $-R^7$ or $-R^{7a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^8$ or $-R^{8a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^9$ or $-R^{9a}$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^{10}$ is substituted with $-L^2-Z$ or $-L^2-Z'$. In another embodiment $-R^{11}$ is

substituted with $-L^2-Z$ or $-L^2-Z'$. Preferably, $-R^3$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$.

Preferably, $-X-$ of formula (II) is selected from the group consisting
5 of $-C(R^4R^{4a})-$, $-N(R^4)-$ and $-C(R^7R^{7a})-$.

In one embodiment $-X-$ of formula (II) is $-C(R^4R^{4a})-$.

In one preferred embodiment $-X-$ of formula (II) is $-C(R^7R^{7a})-$.

10

Preferably, $-R^7$ of formula (II) is $-NR^{10}-(C=O)-R^{11}$.

Preferably, $-R^{7a}$ of formula (II) is selected from $-H$, methyl and ethyl. Most preferably $-R^{7a}$ of
formula (II) is $-H$.

15

Preferably, $-R^{10}$ is selected from $-H$, methyl and ethyl. Most preferably $-R^{10}$ is methyl.

Preferably, $-R^{11}$ is selected from $-H$, methyl and ethyl. Most preferably $-R^{11}$ is $-H$.

20 Preferably, $-R^{11}$ is substituted with $-L^2-Z$ or $-L^2-Z'$.

In another preferred embodiment $-X-$ of formula (II) is $-N(R^4)-$.

Preferably, $-R^4$ is selected from the group consisting of $-H$, methyl and ethyl. Preferably, $-R^4$
25 is $-H$.

Preferably, X^1 of formula (II) is C .

Preferably, $=X^3$ of formula (II) is $=O$.

30

Preferably, $-X^2-$ of formula (II) is $-C(R^8R^{8a})-$.

Preferably $-R^8$ and $-R^{8a}$ of formula (II) are independently selected from the group consisting of -H, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula (II) is -H. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (II) are -H.

- 5 Preferably, $-R^1$ and $-R^{1a}$ of formula (II) are independently selected from the group consisting of -H, methyl and ethyl.

In one preferred embodiment at least one of $-R^1$ and $-R^{1a}$ of formula (II) is -H, more preferably both $-R^1$ and $-R^{1a}$ of formula (II) are -H.

10

In another preferred embodiment at least one of $-R^1$ and $-R^{1a}$ of formula (II) is methyl, more preferably both $-R^1$ and $-R^{1a}$ of formula (II) are methyl.

- 15 Preferably, $-R^2$ and $-R^{2a}$ of formula (II) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of $-R^2$ and $-R^{2a}$ of formula (II) is -H. Even more preferably both $-R^2$ and $-R^{2a}$ of formula (II) are H.

Preferably, $-R^3$ and $-R^{3a}$ of formula (II) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl.

20

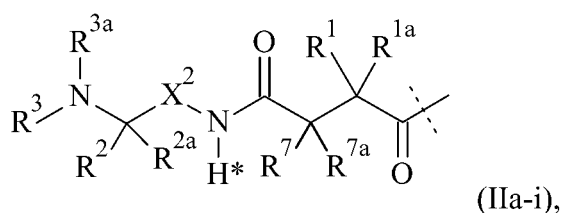
In one preferred embodiment at least one of $-R^3$ and $-R^{3a}$ of formula (II) is methyl, more preferably $-R^3$ of formula (II) is methyl and $-R^{3a}$ of formula (II) is -H.

In another preferred embodiment $-R^3$ and $-R^{3a}$ of formula (II) are both -H.

25

Preferably, -D is connected to $-L^1$ - through a nitrogen by forming an amide bond.

In one preferred embodiment the moiety $-L^1$ - is of formula (IIa-i):



30

wherein

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

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$, $-R^7$, $-R^{7a}$ and $-X^2$ - are used as defined in formula (II); and

- 5 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 (IIa-i) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

- 10 It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIa-i) or both are other than -H they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

Preferably $-L^1$ - of formula (IIa-i) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

- 15 Preferably the moiety $-L^1$ - of formula (IIa-i) is not further substituted.

Preferably, $-R^1$ and $-R^{1a}$ of formula (IIa-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of $-R^1$ and $-R^{1a}$ of formula (IIa-i) is -H. Even more preferably both $-R^1$ and $-R^{1a}$ of formula (IIa-i) are -H.

- 20 Preferably, $-R^7$ of formula (IIa-i) is $-NR^{10}-(C=O)-R^{11}$.

Preferably, $-R^{7a}$ of formula (II-i) is selected from -H, methyl and ethyl. Most preferably $-R^{7a}$ of formula (II-i) is -H.

- 25 Preferably, $-R^{10}$ of formula (IIa-i) is selected from -H, methyl and ethyl. Most preferably $-R^{10}$ of formula (IIa-i) is methyl.

Preferably, $-R^{11}$ of formula (IIa-i) is selected from -H, methyl and ethyl. Most preferably $-R^{11}$ of formula (IIa-i) is -H.

30

Preferably, $-R^{11}$ of formula (IIa-i) is substituted with $-L^2-Z$ or $-L^2-Z'$.

Preferably, $-X^2$ - of formula (IIa-i) is $-C(R^8R^{8a})$ -.

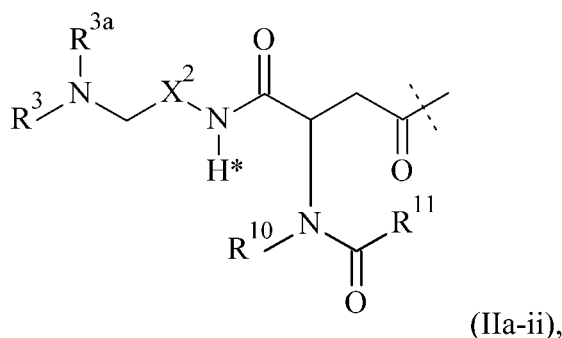
Preferably $-R^8$ and $-R^{8a}$ of formula (IIa-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula (IIa-i) is -H. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (IIa-i) are -H.

- 5 Preferably, $-R^2$ and $-R^{2a}$ of formula (IIa-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of $-R^2$ and $-R^{2a}$ of formula (IIa-i) is -H. Even more preferably both $-R^2$ and $-R^{2a}$ of formula (IIa-i) are H.

- 10 Preferably, $-R^3$ and $-R^{3a}$ of formula (IIa-i) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Even more preferably at least one of $-R^3$ and $-R^{3a}$ of formula (IIa-i) is methyl.

Preferably, $-R^3$ of formula (IIa-i) is -H and $-R^{3a}$ of formula (IIa-i) is methyl.

- 15 More preferably the moiety $-L^1-$ is of formula (IIa-ii):



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

$-R^2$, $-R^{2a}$, $-R^{10}$, $-R^{11}$ and $-X^2$ are used as defined in formula (II); and

- 20 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 (IIa-ii) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

- 25 It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIa-ii) or both are other than -H they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

Preferably $-L^1-$ of formula (IIa-ii) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

Preferably the moiety $-L^1-$ of formula (IIa-ii) is not further substituted.

Preferably, -X²- of formula (IIa-ii) is -C(R⁸R^{8a})-.

Preferably $-R^8$ and $-R^{8a}$ of formula (IIa-ii) are independently selected from the group consisting of $-H$, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula 5 (IIa-ii) is $-H$. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (IIa-ii) are $-H$.

Preferably, $-R^3$ and $-R^{3a}$ of formula (IIa-ii) are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. Even more preferably at least one of $-R^3$ and $-R^{3a}$ of formula (IIa-ii) is methyl.

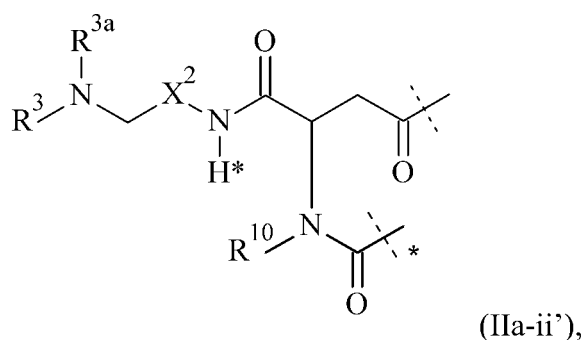
Preferably, -R³ of formula (IIa-ii) is -H and -R^{3a} of formula (IIa-ii) is methyl.

Preferably, -R¹⁰ of formula (IIa-ii) is selected from -H, methyl and ethyl. Most preferably -R¹⁰ of formula (IIa-ii) is methyl.

Preferably, -R¹¹ of formula (IIa-ii) is selected from -H, methyl and ethyl. Most preferably -R¹¹ of formula (IIa-ii) is -H.

Preferably, -R¹¹ of formula (IIa-ii) is substituted with -L²-Z or -L²-Z'.

In an even more preferred embodiment the moiety -L¹- is of formula (IIa-ii'):



wherein

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 $-L^2$;

$-\text{R}^3$, $-\text{R}^{3a}$, $-\text{R}^{10}$ and $-\text{X}^2-$ are used as defined in formula (II); and

wherein -L¹- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIa-ii') is not replaced by a substituent.

It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIa-ii') or both are other than $-H$ they are connected to N to which they are attached through a sp^3 -hybridized carbon atom.

Preferably the moiety $-L^1$ - of formula (IIa-ii') is not further substituted.

5

Preferably, $-X^2$ - of formula (IIa-ii') is $-C(R^8R^{8a})-$.

Preferably $-R^8$ and $-R^{8a}$ of formula (IIa-ii') are independently selected from the group consisting of $-H$, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula (IIa-ii') is $-H$. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (IIa-ii') are $-H$.

10

Preferably, $-R^3$ and $-R^{3a}$ of formula (IIa-ii') are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. Even more preferably at least one of $-R^3$ and $-R^{3a}$ of formula (IIa-ii') is methyl.

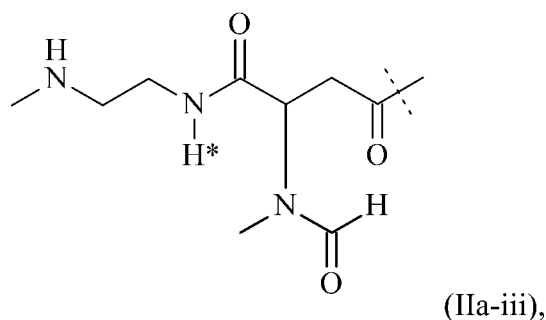
15

Preferably, $-R^3$ of formula (IIa-ii') is $-H$ and $-R^{3a}$ of formula (IIa-ii') is methyl.

Preferably, $-R^{10}$ of formula (IIa-ii') is selected from $-H$, methyl and ethyl. Most preferably $-R^{10}$ of formula (IIa-ii') is methyl.

20

Even more preferably the moiety $-L^1$ - is of formula (IIa-iii):



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

25

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 (IIa-iii) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

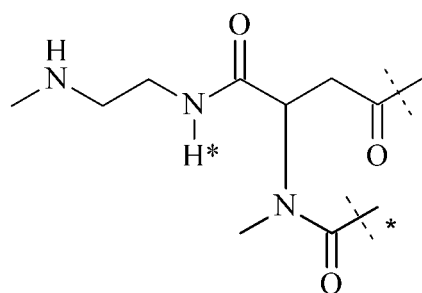
It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIa-iii) or both are other than $-H$ they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

Preferably $-L^1$ - of formula (IIa-iii) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

5

Preferably the moiety $-L^1$ - of formula (IIa-iii) is not further substituted.

Most preferably the moiety $-L^1$ - is of formula (IIa-iii'):



(IIa-iii'),

10

wherein

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 $-L^2$ -;

$-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$ and $-X^2$ - are used as defined in formula (II); and

15

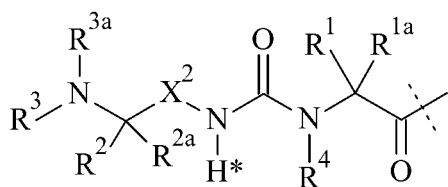
wherein $-L^1$ - is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIa-iii') is not replaced by a substituent.

It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIa-iii') or both are other than $-H$ they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

20

Preferably the moiety $-L^1$ - of formula (IIa-iii') is not further substituted.

In another preferred embodiment the moiety $-L^1$ - is of formula (IIb-i)



(IIb-i),

25

wherein

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

-R¹, -R^{1a}, -R², -R^{2a}, -R³, -R^{3a}, -R⁴ and -X²- are used as defined in formula (II); and wherein -L¹- is substituted with -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-i) is not replaced by -L²-Z or -L²-Z' or a substituent.

It is understood that in case one of -R³, -R^{3a} of formula (IIb-i) or both are other than -H they are connected to N to which they are attached through an sp³-hybridized carbon atom.

Preferably -L¹- of formula (IIb-i) is substituted with one moiety -L²-Z or -L²-Z'.

Preferably the moiety -L¹- of formula (IIb-i) is not further substituted.

Preferably, -R¹ and -R^{1a} of formula (IIb-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of -R¹ and -R^{1a} of formula (IIb-i) is methyl. Even more preferably both -R¹ and -R^{1a} of formula (IIb-i) are methyl.

Preferably, -R⁴ of formula (IIb-i) is selected from the group consisting of -H, methyl and ethyl. More preferably, -R⁴ of formula (IIb-i) is -H.

Preferably, -X²- of formula (IIb-i) is -C(R⁸R^{8a})-.

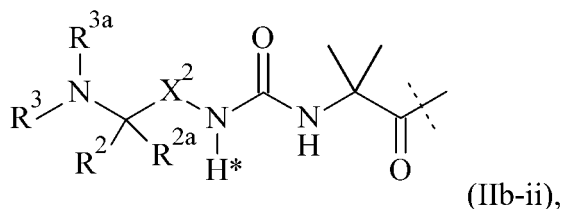
Preferably -R⁸ and -R^{8a} of formula (IIb-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably at least one of -R⁸ and -R^{8a} of formula (IIb-i) is -H. Even more preferably both -R⁸ and -R^{8a} of formula (IIb-i) are -H.

Preferably, -R² and -R^{2a} of formula (IIb-i) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of -R² and -R^{2a} of formula (IIb-i) is -H. Even more preferably both -R² and -R^{2a} of formula (IIb-i) are H.

Preferably, -R³ and -R^{3a} of formula (IIb-i) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Even more preferably at least one of -R³

and $-R^{3a}$ of formula (IIb-i) is -H. Even more preferably both $-R^3$ and $-R^{3a}$ of formula (IIb-i) are -H.

More preferably the moiety $-L^1$ is of formula (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 formula (II); 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.

It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIb-ii) or both are other than -H they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

Preferably $-L^1$ of formula (IIb-ii) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

Preferably the moiety $-L^1$ of formula (IIb-ii) is not further substituted.

Preferably, $-X^2$ of formula (IIb-ii) is $-C(R^8R^{8a})$.

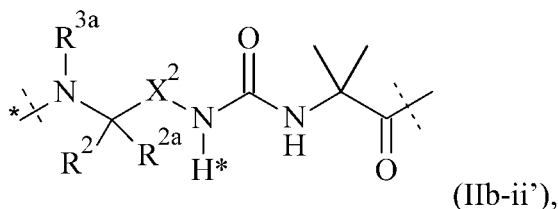
Preferably $-R^8$ and $-R^{8a}$ of formula (IIb-ii) are independently selected from the group consisting of -H, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula (IIb-ii) is -H. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (IIb-ii) are -H.

Preferably, $-R^2$ and $-R^{2a}$ of formula (IIb-ii) are independently selected from the group consisting of -H, methyl and ethyl. More preferably, at least one of $-R^2$ and $-R^{2a}$ of formula (IIb-ii) is -H. Even more preferably both $-R^2$ and $-R^{2a}$ of formula (IIb-ii) are H.

Preferably, $-R^3$ and $-R^{3a}$ of formula (IIb-ii) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Even more preferably at least one of $-R^3$

and $-R^{3a}$ of formula (IIb-ii) is $-H$. Even more preferably both $-R^3$ and $-R^{3a}$ of formula (IIb-ii) are $-H$.

Even more preferably the moiety $-L^1-$ is of formula (IIb-ii'):



wherein

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

$-R^2$, $-R^{2a}$, $-R^{3a}$ and $-X^2-$ are used as defined in formula (II); 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.

It is understood that in case $-R^{3a}$ of formula (IIb-ii') is other than $-H$ it are connected to N to which it is attached through an sp^3 -hybridized carbon atom.

Preferably the moiety $-L^1-$ of formula (IIb-ii') is not further substituted.

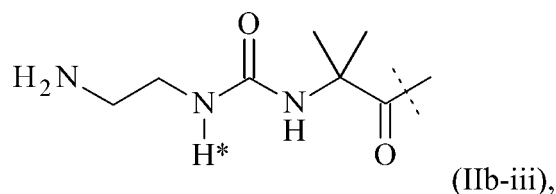
Preferably, $-X^2-$ of formula (IIb-ii') is $-C(R^8R^{8a})-$.

Preferably $-R^8$ and $-R^{8a}$ of formula (IIb-ii') are independently selected from the group consisting of $-H$, methyl and ethyl. More preferably at least one of $-R^8$ and $-R^{8a}$ of formula (IIb-ii') is $-H$. Even more preferably both $-R^8$ and $-R^{8a}$ of formula (IIb-ii') are $-H$.

Preferably, $-R^2$ and $-R^{2a}$ of formula (IIb-ii') are independently selected from the group consisting of $-H$, methyl and ethyl. More preferably, at least one of $-R^2$ and $-R^{2a}$ of formula (IIb-ii') is $-H$. Even more preferably both $-R^2$ and $-R^{2a}$ of formula (IIb-ii') are H .

Preferably, $-R^{3a}$ of formula (IIb-ii') is selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. In one embodiment $-R^{3a}$ of formula (IIb-ii') is $-H$.

Even more preferably the moiety $-L^1-$ is of formula (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

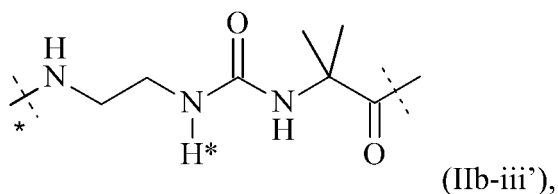
wherein $-L^1-$ is substituted with $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

- 10 It is understood that in case one of $-R^3$, $-R^{3a}$ of formula (IIb-iii) or both are other than -H they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

Preferably $-L^1-$ of formula (IIb-iii) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

- 15 Preferably the moiety $-L^1-$ of formula (IIb-iii) is not further substituted.

Most preferably the moiety $-L^1-$ is of formula (IIb-iii'):



wherein

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

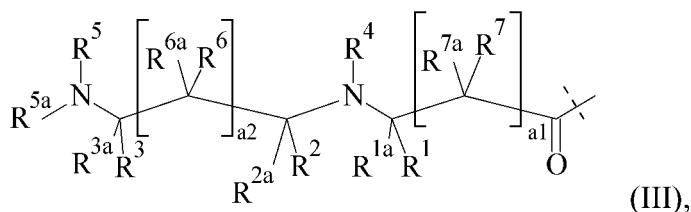
the dashed line marked with the asterisk indicates attachment of $-L^2-Z$ or $-L^2-Z'$; and

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

It is understood that the nitrogen adjacent to the dashed line marked with the asterisk in formula (IIb-iii') is attached to $-L^2-$ through an sp^3 -hybridized carbon atom.

Preferably the moiety $-L^1-$ of formula (IIb-iii') is not further substituted.

Another preferred moiety $-L^1-$ is disclosed in WO2016/020373A1. Accordingly, in another preferred embodiment the moiety $-L^1-$ is of formula (III):



wherein

the dashed line indicates attachment to a primary or secondary amine or hydroxyl of $-D$ which is a PTH moiety by forming an amide or ester linkage, respectively;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$ and $-R^{3a}$ are independently of each other selected from the group consisting of $-H$, $-C(R^8R^{8a}R^{8b})$, $-C(=O)R^8$, $-C\equiv N$, $-C(=NR^8)R^{8a}$, $-CR^8(=CR^{8a}R^{8b})$, $-C\equiv CR^8$ and $-T$;

$-R^4$, $-R^5$ and $-R^{5a}$ are independently of each other selected from the group consisting of $-H$, $-C(R^9R^{9a}R^{9b})$ and $-T$;

$a1$ and $a2$ are independently of each other 0 or 1;

each $-R^6$, $-R^{6a}$, $-R^7$, $-R^{7a}$, $-R^8$, $-R^{8a}$, $-R^{8b}$, $-R^9$, $-R^{9a}$, and $-R^{9b}$ are independently of each other selected from the group consisting of $-H$, halogen, $-CN$, $-COOR^{10}$, $-OR^{10}$, $-C(O)R^{10}$, $-C(O)N(R^{10}R^{10a})$, $-S(O)_2N(R^{10}R^{10a})$, $-S(O)N(R^{10}R^{10a})$, $-S(O)_2R^{10}$, $-S(O)R^{10}$, $-N(R^{10})S(O)_2N(R^{10a}R^{10b})$, $-SR^{10}$, $-N(R^{10}R^{10a})$, $-NO_2$, $-OC(O)R^{10}$, $-N(R^{10})C(O)R^{10a}$, $-N(R^{10})S(O)_2R^{10a}$, $-N(R^{10})S(O)R^{10a}$, $-N(R^{10})C(O)OR^{10a}$, $-N(R^{10})C(O)N(R^{10a}R^{10b})$, $-OC(O)N(R^{10}R^{10a})$, $-T$, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl; wherein $-T$, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more $-R^{11}$, which are the same or different and wherein C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally interrupted by one or more groups selected from the group consisting of $-T$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^{12})$ -, $-S(O)_2N(R^{12})$ -, $-S(O)N(R^{12})$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^{12})S(O)_2N(R^{12a})$ -, $-S$ -, $-N(R^{12})$ -, $-OC(OR^{12})(R^{12a})$ -, $-N(R^{12})C(O)N(R^{12a})$ -, and $-OC(O)N(R^{12})$;

each $-R^{10}$, $-R^{10a}$, and $-R^{10b}$ is independently selected from the group consisting of $-H$, $-T$, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl; wherein $-T$, C_{1-20} alkyl, C_{2-20} alkenyl, and C_{2-20} alkynyl are optionally substituted with one or more $-R^{11}$, which are the same or different and wherein C_{1-20} alkyl, C_{2-20}

alkenyl, and C₂₋₂₀ 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(R¹²)-, -S(O)₂N(R¹²)-, -S(O)N(R¹²)-, -S(O)₂-, -S(O)-, -N(R¹²)S(O)₂N(R^{12a})-, -S-, -N(R¹²)-, -OC(OR¹²)(R^{12a})-, -N(R¹²)C(O)N(R^{12a})-, and -OC(O)N(R¹²)-;

each T is independently of each other selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicycyl; wherein each T is independently optionally substituted with one or more -R¹¹, which are the same or different;

each -R¹¹ is independently of each other selected from halogen, -CN, oxo (=O), -COOR¹³, -OR¹³, -C(O)R¹³, -C(O)N(R¹³R^{13a}), -S(O)₂N(R¹³R^{13a}), -S(O)N(R¹³R^{13a}), -S(O)₂R¹³, -S(O)R¹³, -N(R¹³)S(O)₂N(R^{13a}R^{13b}), -SR¹³, -N(R¹³R^{13a}), -NO₂, -OC(O)R¹³, -N(R¹³)C(O)R^{13a}, -N(R¹³)S(O)₂R^{13a}, -N(R¹³)S(O)R^{13a}, -N(R¹³)C(O)OR^{13a}, -N(R¹³)C(O)N(R^{13a}R^{13b}), -OC(O)N(R¹³R^{13a}), and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

each -R¹², -R^{12a}, -R¹³, -R^{13a}, and -R^{13b} is independently selected from the group consisting of -H, and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

optionally, one or more of the pairs -R¹/-R^{1a}, -R²/-R^{2a}, -R³/-R^{3a}, -R⁶/-R^{6a}, and -R⁷/-R^{7a} are joined together with the atom to which they are attached to form a C₃₋₁₀ cycloalkyl or a 3- to 10-membered heterocyclyl;

optionally, one or more of the pairs -R¹/-R², -R¹/-R³, -R¹/-R⁴, -R¹/-R⁵, -R¹/-R⁶, -R¹/-R⁷, -R²/-R³, -R²/-R⁴, -R²/-R⁵, -R²/-R⁶, -R²/-R⁷, -R³/-R⁴, -R³/-R⁵, -R³/-R⁶, -R³/-R⁷, -R⁴/-R⁵, -R⁴/-R⁶, -R⁴/-R⁷, -R⁵/-R⁶, -R⁵/-R⁷, and -R⁶/-R⁷ are joint together with the atoms to which they are attached to form a ring A;

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 heterobicycyl;

wherein -L¹- is substituted with -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted;

wherein

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

-Z is a water-soluble carrier; and
 -Z' is a water-insoluble carrier.

The optional further substituents of -L¹- of formula (III) are preferably as described above.

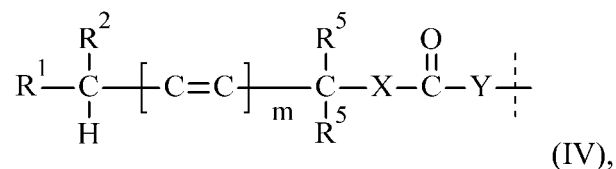
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Preferably -L¹- of formula (III) is substituted with one moiety -L²-Z or -L²-Z'.

In one embodiment -L¹- of formula (III) is not further substituted.

10 Additional preferred embodiments for -L¹- are disclosed in EP1536334B1, WO2009/009712A1, WO2008/034122A1, WO2009/143412A2, WO2011/082368A2, and US8618124B2, which are herewith incorporated by reference in their entirety.

Additional preferred embodiments for -L¹- are disclosed in US8946405B2 and
 15 US8754190B2, which are herewith incorporated by reference in their entirety. Accordingly, a preferred moiety -L¹- is of formula (IV):



wherein

the dashed line indicates attachment to -D which is a PTH moiety and wherein
 20 attachment is through a functional group of -D selected from the group consisting of -OH, -SH and -NH₂;

m is 0 or 1;

at least one or both of -R¹ and -R² is/are independently of each other selected from the
 group consisting of -CN, -NO₂, optionally substituted aryl, optionally
 25 substituted heteroaryl, optionally substituted alkenyl, optionally substituted
 alkynyl, -C(O)R³, -S(O)R³, -S(O)₂R³, and -SR⁴,

one and only one of -R¹ and -R² is selected from the group consisting of -H, optionally
 substituted alkyl, optionally substituted arylalkyl, and optionally substituted
 heteroarylalkyl;

30 -R³ 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 $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted;

wherein

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

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

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

Only in the context of formula (IV) the terms used have the following meaning:

The term “alkyl” as used herein includes linear, branched or cyclic saturated hydrocarbon groups of 1 to 8 carbons, or in some embodiments 1 to 6 or 1 to 4 carbon atoms.

The term “alkoxy” includes alkyl groups bonded to oxygen, including methoxy, ethoxy, isopropoxy, cyclopropoxy, cyclobutoxy, and similar.

The term “alkenyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon double bonds.

5 The term “alkynyl” includes non-aromatic unsaturated hydrocarbons with carbon-carbon triple bonds.

10 The term “aryl” includes aromatic hydrocarbon groups of 6 to 18 carbons, preferably 6 to 10 carbons, including groups such as phenyl, naphthyl, and anthracenyl. The term “heteroaryl” includes aromatic rings comprising 3 to 15 carbons containing at least one N, O or S atom, preferably 3 to 7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.

15 In some instance, alkenyl, alkynyl, aryl or heteroaryl moieties may be coupled to the remainder of the molecule through an alkylene linkage. Under those circumstances, the substituent will be referred to as alkenylalkyl, alkynylalkyl, arylalkyl or heteroarylalkyl, indicating that an alkylene moiety is between the alkenyl, alkynyl, aryl or heteroaryl moiety and the molecule to which the alkenyl, alkynyl, aryl or heteroaryl is coupled.

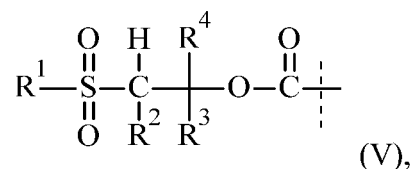
20 The term “halogen” includes bromo, fluoro, chloro and iodo.

The term “heterocyclic ring” refers to a 4 to 8 membered aromatic or non-aromatic ring comprising 3 to 7 carbon atoms and at least one N, O, or S atom. Examples are piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidine, and tetrahydrofuranyl, as well as the exemplary
25 groups provided for the term “heteroaryl” above.

When a ring system is optionally substituted, suitable substituents are selected from the group consisting of alkyl, alkenyl, alkynyl, or an additional ring, each optionally further substituted. Optional substituents on any group, including the above, include halo, nitro,
30 cyano, -OR, -SR, -NR₂, -OCOR, -NRCOR, -COOR, -CONR₂, -SOR, -SO₂R, -SONR₂, -SO₂N R₂, wherein each R is independently alkyl, alkenyl, alkynyl, aryl or heteroaryl, or two R groups taken together with the atoms to which they are attached form a ring.

Preferably -L¹- of formula (IV) is substituted with one moiety -L²-Z or -L²-Z'.

An additional preferred embodiment for $-L^1-$ is disclosed in WO2013/036857A1, which is herewith incorporated by reference in its entirety. Accordingly, a preferred moiety $-L^1-$ is of formula (V):



5 wherein

the dashed line indicates attachment to $-D$ which is a PTH moiety and wherein attachment is through an amine functional group of $-D$;

$-R^1$ is selected from the group consisting of optionally substituted C_1 - C_6 linear, branched, or cyclic alkyl; optionally substituted aryl; optionally substituted heteroaryl; alkoxy; and $-NR^5_2$;

$-R^2$ is selected from the group consisting of $-H$; optionally substituted C_1 - C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

$-R^3$ is selected from the group consisting of $-H$; optionally substituted C_1 - C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

$-R^4$ is selected from the group consisting of $-H$; optionally substituted C_1 - C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl;

each $-R^5$ is independently of each other selected from the group consisting of $-H$; optionally substituted C_1 - C_6 alkyl; optionally substituted aryl; and optionally substituted heteroaryl; or when taken together two $-R^5$ can be cycloalkyl or cycloheteroalkyl;

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

wherein

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

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

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

Only in the context of formula (V) the terms used have the following meaning:

“Alkyl”, “alkenyl”, and “alkynyl” include linear, branched or cyclic hydrocarbon groups of 1-8 carbons or 1-6 carbons or 1-4 carbons wherein alkyl is a saturated hydrocarbon, alkenyl

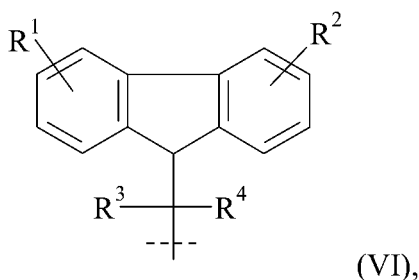
includes one or more carbon-carbon double bonds and alkynyl includes one or more carbon-carbon triple bonds. Unless otherwise specified these contain 1-6 C.

“Aryl” includes aromatic hydrocarbon groups of 6-18 carbons, preferably 6-10 carbons, including groups such as phenyl, naphthyl, and anthracene “Heteroaryl” includes aromatic rings comprising 3-15 carbons containing at least one N, O or S atom, preferably 3-7 carbons containing at least one N, O or S atom, including groups such as pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, indenyl, and similar.

The term “substituted” means an alkyl, alkenyl, alkynyl, aryl, or heteroaryl group comprising one or more substituent groups in place of one or more hydrogen atoms. Substituents may generally be selected from halogen including F, Cl, Br, and I; lower alkyl including linear, branched, and cyclic; lower haloalkyl including fluoroalkyl, chloroalkyl, bromoalkyl, and iodoalkyl; OH; lower alkoxy including linear, branched, and cyclic; SH; lower alkylthio including linear, branched and cyclic; amino, alkylamino, dialkylamino, silyl including alkylsilyl, alkoxy-silyl, and arylsilyl; nitro; cyano; carbonyl; carboxylic acid, carboxylic ester, carboxylic amide, aminocarbonyl; aminoacyl; carbamate; urea; thiocarbamate; thiourea; ketone; sulfone; sulfonamide; aryl including phenyl, naphthyl, and anthracenyl; heteroaryl including 5-member heteroaryls including as pyrrole, imidazole, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, thiadiazole, triazole, oxadiazole, and tetrazole, 6-member heteroaryls including pyridine, pyrimidine, pyrazine, and fused heteroaryls including benzofuran, benzothiophene, benzoxazole, benzimidazole, indole, benzothiazole, benzisoxazole, and benzisothiazole.

Preferably -L¹- of formula (V) is substituted with one moiety -L²-Z or -L²-Z’.

A further preferred embodiment for -L¹- is disclosed in US7585837B2, which is herewith incorporated by reference in its entirety. Accordingly, a preferred moiety -L¹- is of formula (VI):



wherein

the dashed line indicates attachment to -D which is a PTH moiety and wherein attachment is through an amine functional group of -D;

5 R¹ and R² are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, aryl, alkaryl, aralkyl, halogen, nitro, -SO₃H, -SO₂NHR⁵, amino, ammonium, carboxyl, PO₃H₂, and OPO₃H₂;

R³, R⁴, and R⁵ are independently selected from the group consisting of hydrogen, alkyl, and aryl;

10 wherein -L¹- is substituted with -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted;

wherein

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

-Z is a water-soluble carrier; and

15 -Z' is a water-insoluble carrier.

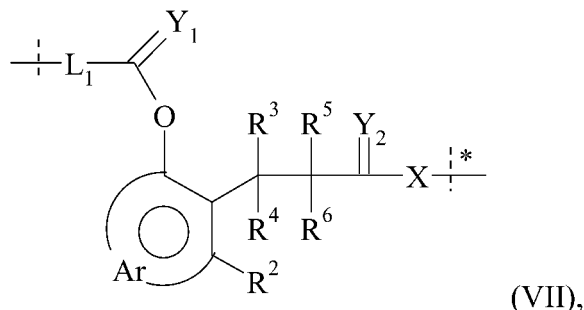
Suitable substituents for formulas (VI) are alkyl (such as C₁₋₆ alkyl), alkenyl (such as C₂₋₆ alkenyl), alkynyl (such as C₂₋₆ alkynyl), aryl (such as phenyl), heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl (such as aromatic 4 to 7 membered heterocycle) or halogen
20 moieties.

Only in the context of formula (VI) the terms used have the following meaning:

The terms “alkyl”, “alkoxy”, “alkoxyalkyl”, “aryl”, “alkaryl” and “aralkyl” mean alkyl
25 radicals of 1-8, preferably 1-4 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl and butyl, and aryl radicals of 6-10 carbon atoms, e.g. phenyl and naphthyl. The term “halogen” includes bromo, fluoro, chloro and iodo.

Preferably -L¹- of formula (VI) is substituted with one moiety -L²-Z or -L²-Z'.

A further preferred embodiment for $-L^1-$ is disclosed in WO2002/089789A1, which is herewith incorporated by reference in its entirety. Accordingly, a preferred moiety $-L^1-$ is of formula (VII):



wherein

the dashed line indicates attachment to $-D$ which is a PTH moiety and wherein attachment is through an amine functional group of $-D$;

L_1 is a bifunctional linking group,

Y_1 and Y_2 are independently O, S or NR^7 ;

R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, and C_{1-6} heteroalkoxy;

Ar is a moiety which when included in formula (VII) forms a multisubstituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

X is a chemical bond or a moiety that is actively transported into a target cell, a hydrophobic moiety, or a combination thereof,

y is 0 or 1;

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

wherein

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

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

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

Only in the context of formula (VII) the terms used have the following meaning:

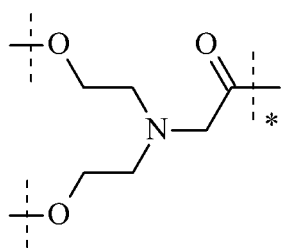
The term "alkyl" shall be understood to include, e.g. straight, branched, substituted C_{1-12} alkyls, including alkoxy, C_{3-8} cycloalkyls or substituted cycloalkyls, etc.

The term “substituted” shall be understood to include adding or replacing one or more atoms contained within a functional group or compounds with one or more different atoms.

Substituted alkyls include carboxyalkyls, aminoalkyls, dialkylaminos, hydroxyalkyls and mercaptoalkyls; substituted cycloalkyls include moieties such as 4-chlorocyclohexyl; aryls include moieties such as naphthyl; substituted aryls include moieties such as 3-bromo-phenyl; aralkyls include moieties such as toluylyl; heteroalkyls include moieties such as ethylthiophene; substituted heteroalkyls include moieties such as 3-methoxythiophene; alkoxy includes moieties such as methoxy; and phenoxy includes moieties such as 3-nitrophenoxy. Halogens shall be understood to include fluoro, chloro, iodo and bromo.

Preferably $-L^1-$ of formula (VII) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In another preferred embodiment $-L^1-$ comprises a substructure of formula (VIII)



(VIII),

wherein

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

the unmarked dashed lines indicate attachment to the remainder of $-L^1-$; and

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

wherein

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

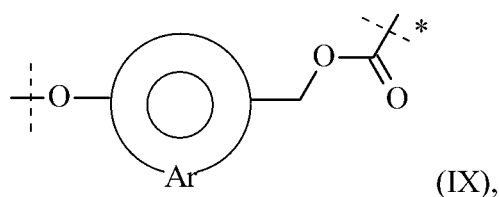
$-Z$ is a water-soluble carrier; and

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

Preferably $-L^1-$ of formula (VIII) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In one embodiment $-L^1-$ of formula (VIII) is not further substituted.

In another preferred embodiment $-L^1-$ comprises a substructure of formula (IX)



wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D which is a PTH moiety by forming a carbamate bond;

5 the unmarked dashed lines indicate attachment to the remainder of -L¹-; and wherein -L¹- is substituted with -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted;

wherein

-L²- is a single chemical bond or a spacer;
 10 -Z is a water-soluble carrier; and
 -Z' is a water-insoluble carrier.

Preferably -L¹- of formula (IX) is substituted with one moiety -L²-Z or -L²-Z'.

15 In one embodiment -L¹- of formula (IX) is not further substituted.

In the prodrugs of the present invention -L²- is a chemical bond or a spacer moiety.

In one embodiment -L²- is a chemical bond.

20

In another embodiment -L²- is a spacer moiety.

When -L²- is other than a single chemical bond, -L²- is preferably 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-,
 25 -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})-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally interrupted by one or more groups selected from the group consisting
 30 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,
 5 C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ 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)₂N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)₂-, -S(O)-, -N(R^{y4})S(O)₂N(R^{y4a})-, -S-,
 10 -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, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;
 15 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}),
 20 -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}), -NO₂, -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 C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different; and

25 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 C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different.

When -L²- is other than a single chemical bond, -L²- is even more preferably selected
 30 from -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})-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T-, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, and C₂₋₂₀ 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})-;

- 5 -R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -T, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl; wherein -T, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ 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)₂N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)₂-, -S(O)-, -N(R^{y4})S(O)₂N(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})-;
- 10

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 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;

15

-R^{y2} is 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}), -NO₂, -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 C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different; and

20

each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently of each other selected from the group consisting of -H, and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different.

25

30 When -L²- is other than a single chemical bond, -L²- is even more preferably 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})-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ 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 $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^{y3})-$, $-S(O)_2N(R^{y3})-$, $-S(O)N(R^{y3})-$, $-S(O)_2-$, $-S(O)-$, $-N(R^{y3})S(O)_2N(R^{y3a})-$, $-S-$, $-N(R^{y3})-$, $-OC(OR^{y3})(R^{y3a})-$, $-N(R^{y3})C(O)N(R^{y3a})-$,
 5 and $-OC(O)N(R^{y3})-$;

$-R^{y1}$ and $-R^{y1a}$ are independently selected from the group consisting of $-H$, $-T$, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl;

10 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;

each $-R^{y2}$ is independently selected from the group consisting of halogen, and C_{1-6} alkyl; and

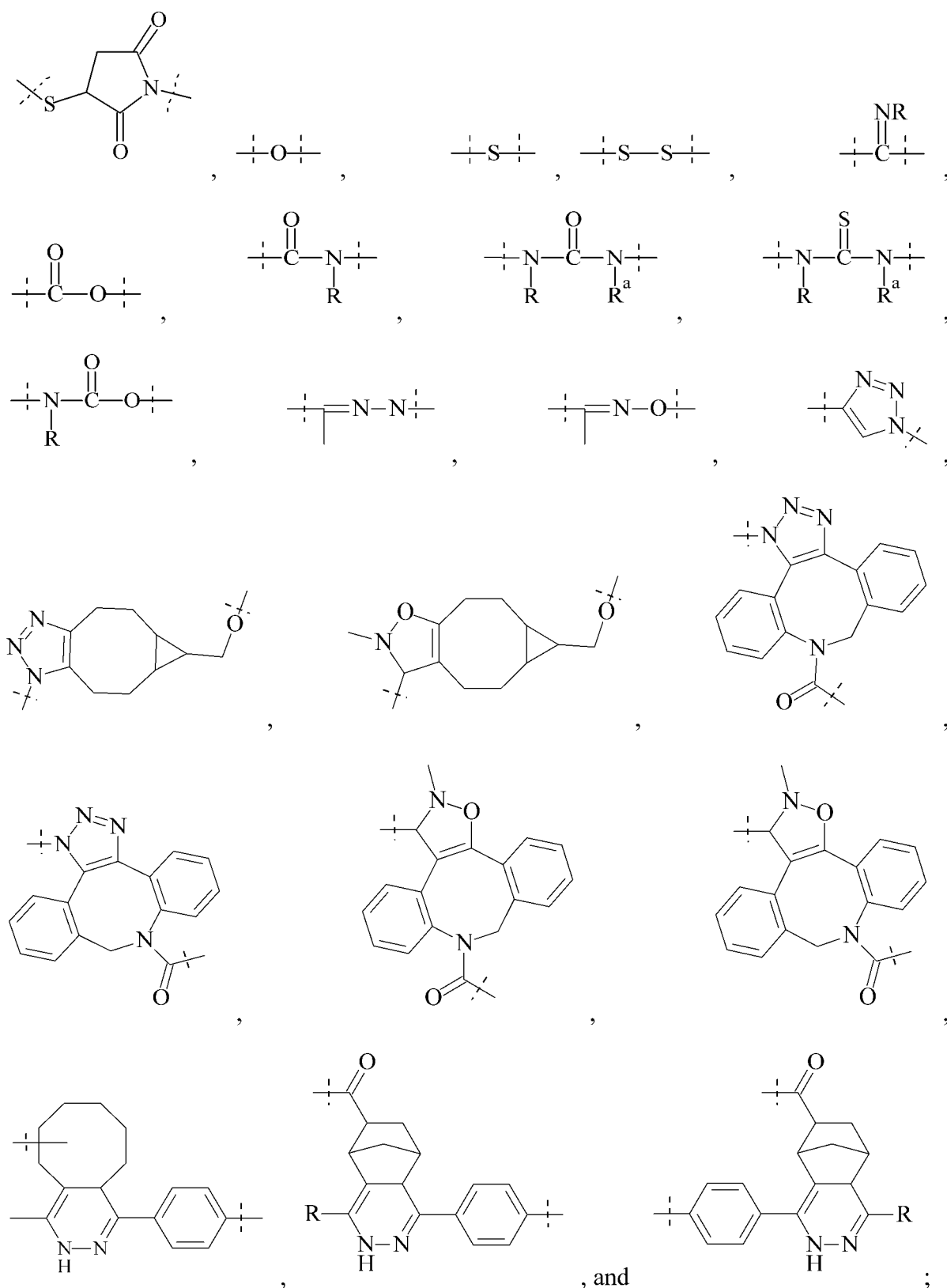
15 each $-R^{y3}$, $-R^{y3a}$, $-R^{y4}$, $-R^{y4a}$, $-R^{y5}$, $-R^{y5a}$ and $-R^{y5b}$ is independently of each other selected from the group consisting of $-H$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

20 Even more preferably, $-L^2-$ is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from $-O-$, $-T-$ and $-C(O)N(R^{y1})-$; and which C_{1-20} alkyl chain is optionally substituted with one or more groups independently selected from $-OH$, $-T$ and $-C(O)N(R^{y6}R^{y6a})$; wherein $-R^{y1}$, $-R^{y6}$, $-R^{y6a}$ are independently selected from the group consisting of H and C_{1-4} alkyl and wherein T is selected from the group consisting of phenyl,
 25 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.

Preferably, $-L^2-$ has a molecular weight in the range of from 14 g/mol to 750 g/mol.

30

Preferably, $-L^2-$ comprises a moiety selected from



wherein

dashed lines indicate attachment to the rest of $-L^2$ -, $-L^1$ -, $-Z$ and/or $-Z'$, respectively; and

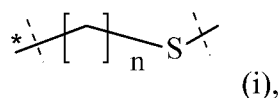
$-R$ and $-R^a$ are independently of each other selected from the group consisting of $-H$, methyl, ethyl, propyl, butyl, pentyl and hexyl.

In one preferred embodiment $-L^2-$ has a chain lengths of 1 to 20 atoms.

As used herein the term “chain length” with regard to the moiety $-L^2-$ refers to the number of atoms of $-L^2-$ present in the shortest connection between $-L^1-$ and $-Z$.

5

Preferably, $-L^2-$ is of formula (i)



wherein

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

10

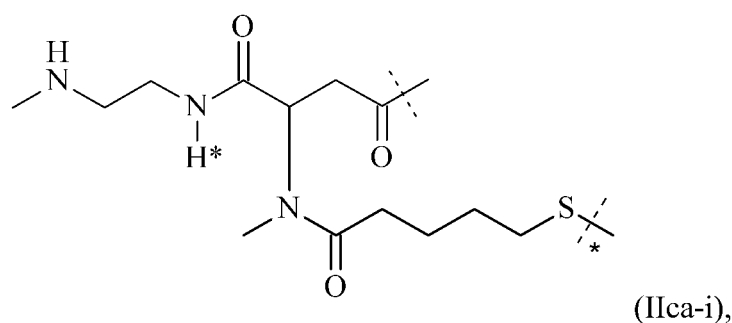
the unmarked dashed line indicates attachment to $-Z$ or $-Z'$;

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

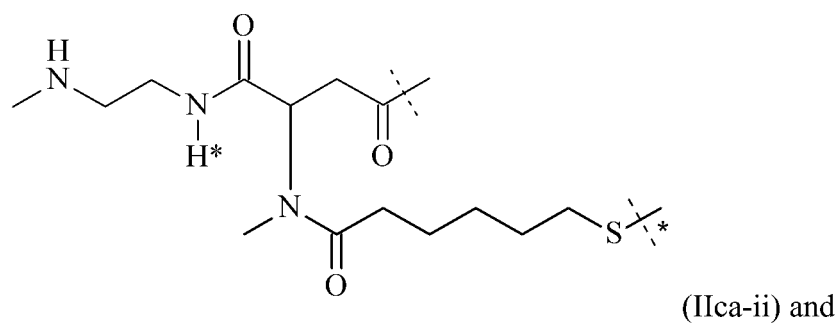
wherein the moiety of formula (i) is optionally further substituted.

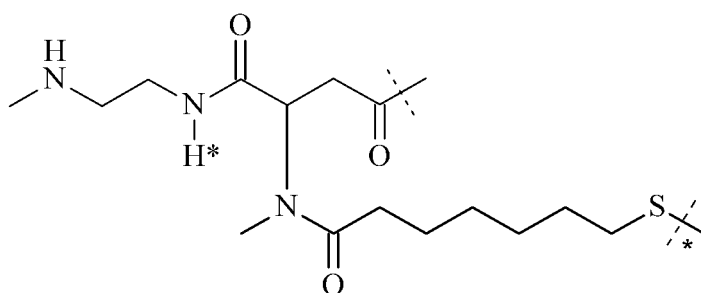
- 15 Preferably, n of formula (i) is selected from the group consisting of 3, 4, 5, 6, 7, 8, and 9. Even more preferably n of formula (i) is 4, 5, 6, or 7. In one embodiment n of formula (i) is 4. In another embodiment n of formula (i) is 5. In another embodiment n of formula (i) is 6.

In one preferred embodiment the moiety $-L^1-L^2-$ is selected from the group consisting of



20





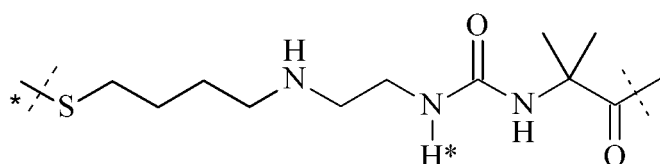
(IIca-iii);

wherein

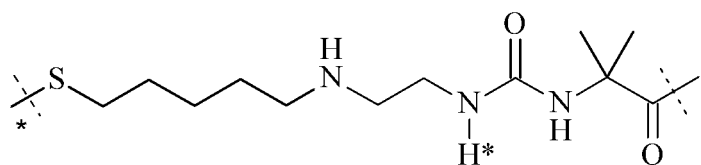
the unmarked dashed line indicates the attachment to a nitrogen of -D which is a PTH moiety by forming an amide bond; and

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

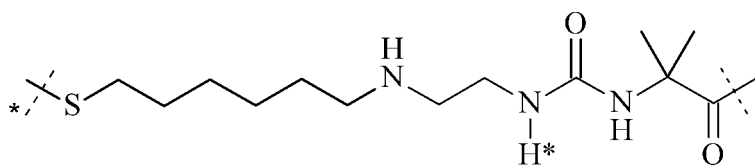
In another preferred embodiment the moiety $-L^1-L^2-$ is selected from the group consisting of



(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

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

In a preferred embodiment the moiety $-L^1-L^2-$ is of formula (IIca-ii).

In another preferred embodiment the moiety $-L^1-L^2-$ is of formula (IIcb-iii).

Preferably, the controlled-release PTH compound of the present invention is of formula (Ia) with $x = 1$.

The carrier -Z comprises a C₈₋₂₄ alkyl or a polymer. Preferably, -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), 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), 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.

Preferably, -Z has a molecular weight ranging from 5 to 200 kDa. Even more preferably, -Z has a molecular weight ranging from 8 to 100 kDa, even more preferably ranging from 10 to 80 kDa, even more preferably from 12 to 60, even more preferably from 15 to 40 and most preferably -Z has a molecular weight of about 20 kDa. In another equally preferred embodiment -Z has a molecular weight of about 40 kDa.

In one embodiment such water-soluble carrier -Z comprises a protein. Preferred proteins are selected from the group consisting of carboxyl-terminal polypeptide of the chorionic gonadotropin as described in US 2012/0035101 A1 which are herewith incorporated by reference; albumin; XTEN sequences as described in WO 2011123813 A2 which are herewith incorporated by reference; proline/alanine random coil sequences as described in

WO 2011/144756 A1 which are herewith incorporated by reference; proline/alanine/serine random coil sequences as described in WO 2008/155134 A1 and WO 2013/024049 A1 which are herewith incorporated by reference; and Fc fusion proteins.

5 In one embodiment -Z is a polysarcosine.

In another preferred embodiment -Z comprises a poly(N-methylglycine).

In a particularly preferred embodiment -Z comprises a random coil protein moiety.

10

In one preferred embodiment -Z comprises one random coil protein moiety.

In another preferred embodiment -Z comprises two random coil proteins moieties.

15 In another preferred embodiment -Z comprises three random coil proteins moieties.

In another preferred embodiment -Z comprises four random coil proteins moieties.

In another preferred embodiment -Z comprises five random coil proteins moieties.

20

In another preferred embodiment -Z comprises six random coil proteins moieties.

In another preferred embodiment -Z comprises seven random coil proteins moieties.

25 In another preferred embodiment -Z comprises eight random coil proteins moieties.

Preferably such random coil protein moiety comprises at least 25 amino acid residues and at most 2000 amino acids. Even more preferably such random coil protein moiety comprises at least 30 amino acid residues and at most 1500 amino acid residues. Even more preferably
30 such random coil protein moiety comprises at least 50 amino acid residues and at most 500 amino acid residues.

In a preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least

95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine and proline. Even more preferably, at least 10%, but less than 75%, preferably less than 65%, of the total number of amino acid residues of such random coil protein moiety are proline residues.

5 Preferably, such random coil protein moiety is as described in WO 2011/144756 A1 which is hereby incorporated by reference in its entirety. Even more preferably -Z comprises at least one moiety selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14,
10 SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:51 and SEQ ID NO:61 as disclosed in WO2011/144756 which are hereby incorporated by reference. A moiety comprising such random coil protein comprising alanine and proline will be referred to as "PA" or "PA moiety".

15 Accordingly, -Z comprises a PA moiety.

In an equally preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total
20 number of amino acids forming said random coil protein moiety are selected from alanine, serine and proline. Even more preferably, at least 4%, but less than 40% of the total number of amino acid residues of such random coil protein moiety are proline residues. Preferably, such random coil protein moiety is as described in WO 2008/155134 A1 which is hereby incorporated by reference in its entirety. Even more preferably -Z comprises at least one
25 moiety selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54 and
30 SEQ ID NO:56 as disclosed in WO 2008/155134 A1, which are hereby incorporated by reference. A moiety comprising such random coil protein moiety comprising alanine, serine and proline will be referred to as "PAS" or "PAS moiety".

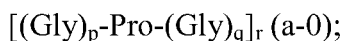
Accordingly, -Z comprises a PAS moiety.

In an equally preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine, glycine and proline. A moiety comprising such random coil protein moiety comprising
 5 alanine, glycine and proline will be referred to as "PAG" or "PAG moiety".

Accordingly, -Z comprises a PAG moiety.

10 In an equally preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from proline and glycine. A moiety comprising such random coil protein moiety comprising proline and
 15 glycine will be referred to as "PG" or "PG moiety".

Preferably, such PG moiety comprises a moiety of formula (a-0)



wherein

20 p is selected from the group consisting of 0, 1, 2, 3, 4 and 5;

q is selected from the group consisting of 0, 1, 2, 3, 4 and 5;

r is an integer ranging from and including 10 to 1000;

provided that at least one of p and q is at least 1;

25 Preferably, p of formula (a-0) is selected from the group consisting of 1, 2 and 3.

Preferably, q of formula (a-0) is selected from 0, 1 and 2.

Even more preferably the PG moiety comprises the sequence of SEQ ID NO:122:

30 GGPGGPGPGGGPGGGPGGGPG

Even more preferably, the PG moiety comprises the sequence of formula (a-0-a)



wherein

v is an integer ranging from and including 1 to 50.

It is understood that the sequence of formula (a-0-a) comprises v replicates of the sequence of SEQ ID NO:122.

5

Accordingly, -Z comprises a PG moiety.

In an equally preferred embodiment, -Z comprises a random coil protein moiety of which at least 80%, preferably at least 85%, even more preferably at least 90%, even more preferably at least 95%, even more preferably at least 98% and most preferably at least 99% of the total number of amino acids forming said random coil protein moiety are selected from alanine, glycine, serine, threonine, glutamate and proline. Preferably, such random coil protein moiety is as described in WO 2010/091122 A1 which is hereby incorporated by reference. Even more preferably -Z comprises at least one moiety selected from the group consisting of SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184; SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:759, SEQ ID NO:760, SEQ ID NO:761, SEQ ID NO:762, SEQ ID NO:763, SEQ ID NO:764, SEQ ID NO:765, SEQ ID NO:766, SEQ ID NO:767, SEQ ID NO:768, SEQ ID NO:769, SEQ ID NO:770, SEQ ID NO:771, SEQ ID NO:772, SEQ ID NO:773, SEQ ID NO:774, SEQ ID NO:775, SEQ ID NO:776, SEQ ID NO:777, SEQ ID NO:778, SEQ ID NO:779, SEQ ID NO:1715, SEQ ID NO:1716, SEQ ID NO:1718, SEQ ID NO:1719, SEQ ID NO:1720, SEQ ID NO:1721 and SEQ ID NO:1722 as disclosed in WO2010/091122A1, which are hereby incorporated by reference. A moiety comprising such random coil protein moiety comprising alanine, glycine, serine, threonine, glutamate and proline will be referred to as "XTEN" or "XTEN moiety" in line with its designation in WO 2010/091122 A1.

Accordingly, -Z comprises an XTEN moiety.

In another preferred embodiment, -Z comprises a fatty acid derivate. Preferred fatty acid derivatives are those disclosed in WO 2005/027978 A2 and WO 2014/060512 A1 which are herewith incorporated by reference.

- 5 In another preferred embodiment -Z is a hyaluronic acid-based polymer.

In one embodiment -Z is a carrier as disclosed in WO 2012/02047 A1 which is herewith incorporated by reference.

- 10 In another embodiment -Z is a carrier as disclosed in WO 2013/024048 A1 which is herewith incorporated by reference.

In another preferred embodiment -Z is a PEG-based polymer, such as a linear, branched or multi-arm PEG-based polymer.

15

In one embodiment -Z is a linear PEG-based polymer.

In another embodiment -Z is a multi-arm PEG-based polymer. Preferably, -Z is a multi-arm PEG-based polymer having at least 4 PEG-based arms.

20

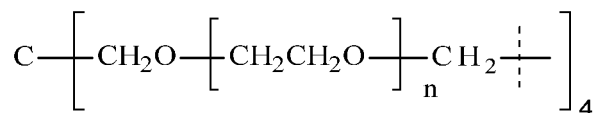
- Preferably, such multi-arm PEG-based polymer -Z is connected to a multitude of moieties $-L^2-L^1-D$, wherein each moiety $-L^2-L^1-D$ is preferably connected to the end of an arm, preferably to the end of an arm. Preferably such multi-arm PEG-based polymer -Z is connected to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 moieties $-L^2-L^1-D$. Even more preferably such multi-arm PEG-based polymer -Z is connected to 2, 3, 4, 6 or 8 moieties $-L^2-L^1-D$. Even more preferably such multi-arm PEG-based polymer -Z is connected to 2, 4 or 6 moieties $-L^2-L^1-D$, even more preferably such multi-arm PEG-based polymer -Z is connected to 4 or 6 moieties $-L^2-L^1-D$, and most preferably such multi-arm PEG-based polymer -Z is connected to 4 moieties $-L^2-L^1-D$.

30

Preferably, such multi-arm PEG-based polymer -Z is a multi-arm PEG derivative as, for instance, detailed in the products list of JenKem Technology, USA (accessed by download from <http://www.jenkemusa.com/Pages/PEGProducts.aspx> on Dec 18, 2014), such as a 4-arm-PEG derivative, in particular a 4-arm-PEG comprising a pentaerythritol core, an 8-arm-

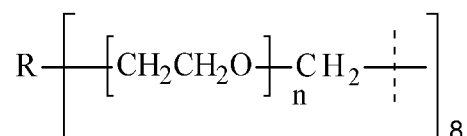
PEG derivative comprising a hexaglycerin core, and an 8-arm-PEG derivative comprising a tripentaerythritol core. More preferably, the water-soluble PEG-based carrier -Z comprises a moiety selected from:

- 5 a 4-arm PEG Amine comprising a pentaerythritol core:



with n ranging from 20 to 500;

an 8-arm PEG Amine comprising a hexaglycerin core:

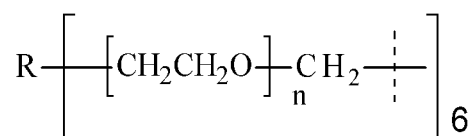


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with n ranging from 20 to 500; and

R = hexaglycerin or tripentaerythritol core structure; and

a 6-arm PEG Amine comprising a sorbitol or dipentaerythritol core:



15

with n ranging from 20 to 500; and

R = comprising a sorbitol or dipentaerythritol core;

and wherein dashed lines indicate attachment to the rest of the PTH prodrug.

20

In a preferred embodiment -Z is a branched PEG-based polymer. In one embodiment -Z is a branched PEG-based polymer having one, two, three, four, five or six branching points. Preferably, -Z is a branched PEG-based polymer having one, two or three branching points. In one embodiment -Z is a branched PEG-based polymer having one branching point. In another
 25 embodiment -Z is a branched PEG-based polymer having two branching points. In another embodiment -Z is a branched PEG-based polymer having three branching points.

A branching point is preferably selected from the group consisting of $-N<$, $-CH<$ and $>C<$.

Preferably, such branched PEG-based moiety $-Z$ has a molecular weight of at least 10 kDa.

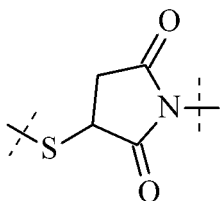
- 5 In one embodiment such branched moiety $-Z$ has a molecular weight ranging from and including 10 kDa to 500 kDa, more preferably ranging from and including 10 kDa to 250 Da, even more preferably ranging from and including 10 kDa to 150 kDa, even more preferably ranging from and including 12 kDa to 100 kDa and most preferably ranging from and including 15 kDa to 80 kDa.

10

Preferably, such branched moiety $-Z$ has a molecular weight ranging from and including 10 kDa to 80 kDa. In one embodiment the molecular weight is about 10 kDa. In another embodiment the molecular weight of such branched moiety $-Z$ is about 20 kDa. In another embodiment the molecular weight of such branched moiety $-Z$ is about 30 kDa. In another embodiment the molecular weight of such a branched moiety $-Z$ is about 40 kDa. In another embodiment the molecular weight of such a branched moiety $-Z$ is about 50 kDa. In another embodiment the molecular weight of such a branched moiety $-Z$ is about 60 kDa. In another embodiment the molecular weight of such a branched moiety $-Z$ is about 70 kDa. In another embodiment the molecular weight of such a branched moiety $-Z$ is about 80 kDa. Most preferably, such branched moiety $-Z$ has a molecular weight of about 40 kDa.

20

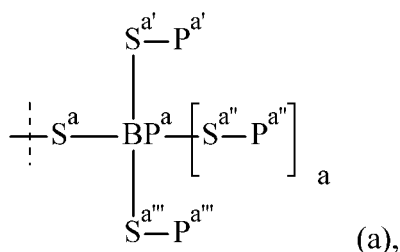
Preferably, $-Z$ or $-Z'$ comprises a moiety



In an equally preferred embodiment $-Z$ comprises an amide bond.

25

Preferably $-Z$ comprises a moiety of formula (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;

5 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 $-T-$, $-C(O)O-$, $-O-$, $-C(O)-$, $-C(O)N(R^2)-$, $-S(O)_2N(R^2)-$, $-S(O)N(R^2)-$, $-S(O)_2-$, $-S(O)-$, $-N(R^2)S(O)_2N(R^{2a})-$, $-S-$, $-N(R^2)-$, $-OC(OR^2)(R^{2a})-$, $-N(R^2)C(O)N(R^{2a})-$, and $-OC(O)N(R^2)-$;

10 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;

20 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;

25 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.

30 In one embodiment BP^a of formula (a) is $-N<$.

In another embodiment BP^a of formula (a) is $>C<$.

In a preferred embodiment BP^a of formula (a) is -CR<. Preferably, -R is -H. Accordingly, a of formula (a) is 0.

In one embodiment -S^a- of formula (a) is a chemical bond.

5

In another embodiment -S^a- of formula (a) is selected from the group consisting of C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl, which C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R⁴)-, -S(O)₂N(R⁴)-, -S(O)N(R⁴)-, -S(O)₂-, -S(O)-, -N(R⁴)S(O)₂N(R^{4a})-, -S-, -N(R⁴)-, -OC(OR⁴)(R^{4a})-, -N(R⁴)C(O)N(R^{4a})-, and -OC(O)N(R⁴)-; 10 wherein -T- is a 3- to 10-membered heterocyclyl; and -R⁴ and -R^{4a} are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl.

Preferably -S^a- of formula (a) is selected from the group consisting of C₁₋₁₀ alkyl which is interrupted by one or more chemical groups selected from the group consisting 15 of -T-, -C(O)N(R⁴)- and -O-.

In one embodiment -S^{a'}- of formula (a) is a chemical bond.

20 In another embodiment -S^{a'}- of formula (a) is selected from the group consisting of C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl, which C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of -C(O)O-, -O-, -C(O)-, -C(O)N(R⁴)-, -S(O)₂N(R⁴)-, -S(O)N(R⁴)-, -S(O)₂-, -S(O)-, -N(R⁴)S(O)₂N(R^{4a})-, -S-, -N(R⁴)-, -OC(OR⁴)(R^{4a})-, -N(R⁴)C(O)N(R^{4a})-, and -OC(O)N(R⁴)-; 25 wherein -R⁴ and -R^{4a} are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Preferably -S^{a'}- of formula (a) is selected from the group consisting of methyl, ethyl, propyl, butyl, which are optionally interrupted by one or more chemical groups selected from the group consisting of -O-, -C(O)- and -C(O)N(R⁴)-.

30 In one embodiment -S^{a''}- of formula (a) is a chemical bond.

In another embodiment -S^{a''}- of formula (a) is selected from the group consisting of C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl, which C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of

-C(O)O-, -O-, -C(O)-, -C(O)N(R⁴)-, -S(O)₂N(R⁴)-, -S(O)N(R⁴)-, -S(O)₂-, -S(O)-, -N(R⁴)S(O)₂N(R^{4a})-, -S-, -N(R⁴)-, -OC(OR⁴)(R^{4a})-, -N(R⁴)C(O)N(R^{4a})-, and -OC(O)N(R⁴)-; wherein -R⁴ and -R^{4a} are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Preferably -S^{a'''} - of formula (a) is selected from the group consisting of methyl, ethyl, propyl, butyl, which are optionally interrupted by one or more chemical groups selected from the group consisting of -O-, -C(O)- and -C(O)N(R⁴)-.

In one embodiment -S^{a'''} - of formula (a) is a chemical bond.

10 In another embodiment -S^{a'''} - of formula (a) is selected from the group consisting of C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl, which C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl and C₂₋₁₀ alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of -C(O)O-, -O-, -C(O)-, -C(O)N(R⁴)-, -S(O)₂N(R⁴)-, -S(O)N(R⁴)-, -S(O)₂-, -S(O)-, -N(R⁴)S(O)₂N(R^{4a})-, -S-, -N(R⁴)-, -OC(OR⁴)(R^{4a})-, -N(R⁴)C(O)N(R^{4a})-, and -OC(O)N(R⁴)-; wherein -R⁴ and -R^{4a} are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. Preferably -S^{a'''} - of formula (a) is selected from the group consisting of methyl, ethyl, propyl, butyl, which are optionally interrupted by one or more chemical groups selected from the group consisting of -O-, -C(O)- and -C(O)N(R⁴)-.

20 Preferably, -P^{a'}, -P^{a''} and -P^{a'''} of formula (a) independently comprise 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), 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), 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.

- 5 More preferably, $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently comprise a PEG-based moiety. Even more preferably, $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently comprise a PEG-based moiety comprising at least 20% PEG, even more preferably at least 30%, even more preferably at least 40% PEG, even more preferably at least 50% PEG, even more preferably at least 60% PEG, even more preferably at least 70% PEG, even more preferably at
10 least 80% PEG and most preferably at least 90% PEG.

- Preferably, $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently have a molecular weight ranging from and including 5 kDa to 50 kDa, more preferably have a molecular weight ranging from and including 5 kDa to 40 kDa, even more preferably ranging from and including 7.5 kDa to
15 35 kDa, even more preferably ranging from and 7.5 to 30 kDa, even more preferably ranging from and including 10 to 30 kDa.

In one embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 5 kDa.

- 20 In another embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 7.5 kDa.

In another embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 10 kDa.

- 25 In another embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 12.5 kDa.

- In another embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 15
30 kDa.

In another embodiment $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 20 kDa.

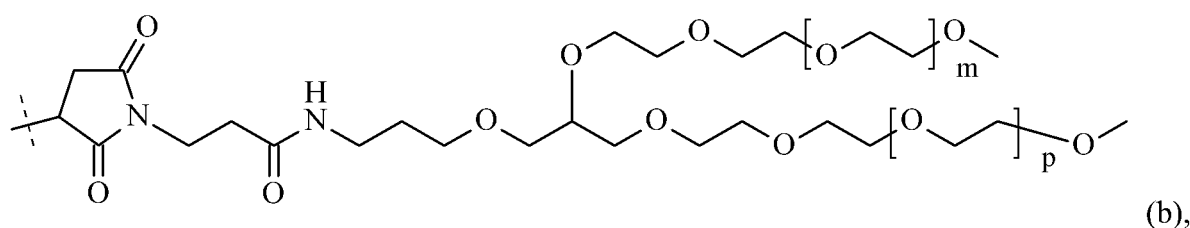
In one embodiment -Z comprises one moiety of formula (a).

In another embodiment -Z comprises two moieties of formula (a).

5 In another embodiment -Z comprises three moieties of formula (a).

Preferably, -Z is a moiety of formula (a).

More preferably, -Z comprises a moiety of formula (b)



wherein

the dashed line indicates attachment to -L²- 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.

Preferably, m and p of formula (b) are the same integer.

20 Most preferably m and p of formula (b) are about 450.

Preferably, -Z is a moiety of formula (b).

The carrier -Z' is a water-insoluble polymer, even more preferably a hydrogel. Preferably, such hydrogel comprises 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),
5 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,
10 rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

If the carrier -Z' is a hydrogel, it is preferably a hydrogel comprising PEG or hyaluronic acid. Most preferably such hydrogel comprises PEG.

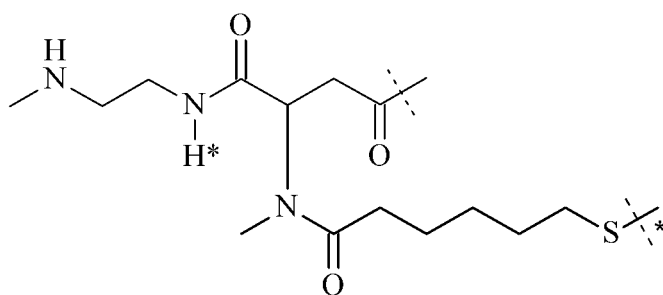
15

Even more preferably, the carrier -Z' is a hydrogel as described in WO 2006/003014 A2, WO 2011/012715 A1 or WO 2014/056926 A1, which are herewith incorporated by reference in their entirety.

20 In another embodiment -Z' is a polymer network formed through the physical aggregation of polymer chains, which physical aggregation is preferably caused by hydrogen bonds, crystallization, helix formation or complexation. In one embodiment such polymer network is a thermogelling polymer.

25 If the controlled-release PTH compound of the present invention is a prodrug, its total mass is preferably at least 10 kDa, such as at least 12 kDa, such as at least 15 kDa, such as at least 20 kDa or such as at least 30 kDa. If the controlled-release PTH compound is a water-soluble prodrug, its total mass preferably is at most 250 kDa, such as at most 200 kDa, 180 kDa, 150 kDa or 100 kDa. It is understood that no meaningful upper molecular weight limit can be
30 provided in case the controlled-release PTH compound is water-insoluble.

In one preferred embodiment the controlled-release PTH compound is of formula (IIe-i):

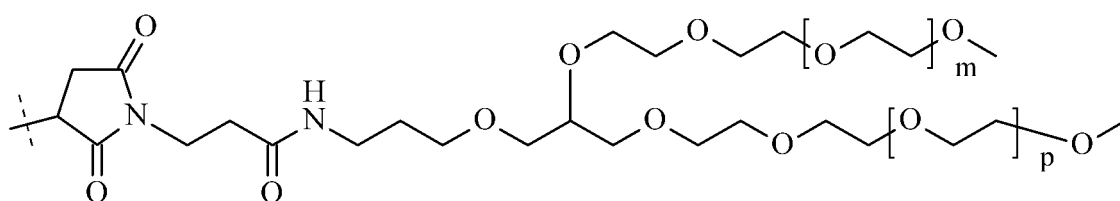


(Ile-i),

wherein

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

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



wherein

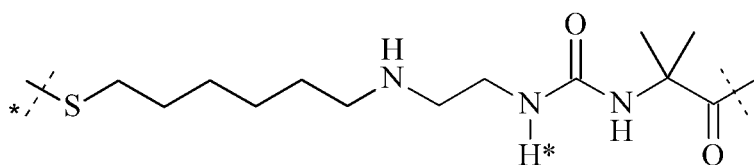
m and p are independently an integer ranging from and including 400 to 500.

10

Preferably, -D is attached to the PTH prodrug of formula (Ile-i) through the N-terminal amine functional group of the PTH moiety.

In another preferred embodiment the PTH prodrug of the present invention is of formula (IIf-

15 i):

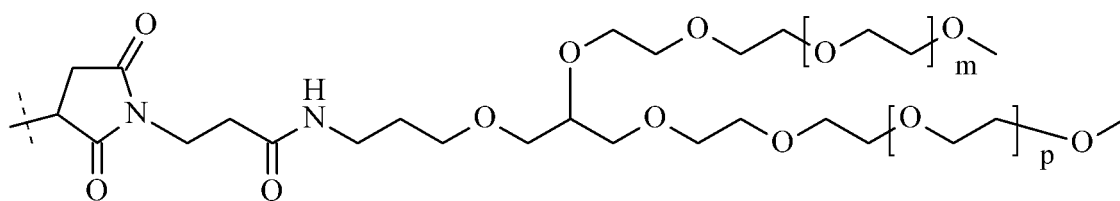


(IIf-i),

wherein

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

20 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.

5

Preferably, -D is attached to the PTH prodrug of formula (IIf-i) through the N-terminal amine functional group of the PTH moiety.

10

In a preferred embodiment the residual activity of the controlled-release PTH in the form of a PTH prodrug is less than 10%, more preferably less than 1%, even more preferably less than 0.1%, even more preferably less than 0.01%, even more preferably less than 0.001% and most preferably less than 0.0001%.

15

As used herein the term “residual activity” refers to the activity exhibited by the PTH prodrug with the PTH moiety bound to a carrier in relation to the activity exhibited by the corresponding free PTH. In this context the term “activity” refers to binding to an activation domain of the PTH/PTHrP1 receptor resulting in activation of adenylate cyclase to generate cAMP, phospholipase C to generate intracellular calcium, or osteoblastic expression of RANKL (which binds to RANK (Receptor Activator of Nuclear Factor kB) on osteoclasts. It is understood that measuring the residual activity of the PTH prodrug of the present invention takes time during which a certain amount of PTH may be released from the PTH prodrug of the present invention and that such released PTH will distort the results measured for the PTH prodrug. It is thus accepted practice to test the residual activity of a prodrug with a conjugate in which the drug moiety, in this case PTH, is non-reversibly, i.e. stably, bound to a carrier, which as closely as possible resembles the structure of the PTH prodrug for which residual activity is to be measured.

25

30

Preferably, the pharmaceutical composition of the present invention has a pH ranging from and including pH 3 to pH 8. More preferably, the pharmaceutical composition has a pH ranging from and including pH 4 to pH 6. Most preferably, the pharmaceutical composition has a pH ranging from and including pH 4 to pH 5.

In one embodiment the pharmaceutical composition of the present invention is a liquid or suspension formulation. It is understood that the pharmaceutical composition is a suspension formulation if the controlled-release PTH compound of the present invention is water-insoluble.

5

In another embodiment the pharmaceutical composition of the present invention is a dry formulation which is reconstituted before administration to a patient.

10

Such liquid, suspension, dry or reconstituted pharmaceutical composition comprises at least one excipient. Excipients used in parenteral formulations may be categorized as, for example, buffering agents, isotonicity modifiers, preservatives, stabilizers, anti-adsorption agents, oxidation protection agents, viscosifiers/viscosity enhancing agents, or other auxiliary agents. However, in some cases, one excipient may have dual or triple functions. Preferably, the at least one excipient comprised in the pharmaceutical composition of the present invention is selected from the group consisting of

15

20

(i) Buffering agents: physiologically tolerated buffers to maintain pH in a desired range, such as sodium phosphate, bicarbonate, succinate, histidine, citrate and acetate, sulphate, nitrate, chloride, pyruvate; antacids such as $\text{Mg}(\text{OH})_2$ or ZnCO_3 may be also used;

25

(ii) Isotonicity modifiers: to minimize pain that can result from cell damage due to osmotic pressure differences at the injection depot; glycerin and sodium chloride are examples; effective concentrations can be determined by osmometry using an assumed osmolality of 285-315 mOsmol/kg for serum;

30

(iii) Preservatives and/or antimicrobials: multidose parenteral formulations require the addition of preservatives at a sufficient concentration to minimize risk of patients becoming infected upon injection and corresponding regulatory requirements have been established; typical preservatives include m-cresol, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosal, sorbic acid, potassium sorbate, benzoic acid, chlorocresol, and benzalkonium chloride;

- (iv) Stabilizers: Stabilisation is achieved by strengthening of the protein-stabilising forces, by destabilisation of the denatured state, or by direct binding of excipients to the protein; stabilizers may be amino acids such as alanine, arginine, aspartic acid, glycine, histidine, lysine, proline, sugars such as glucose, sucrose, trehalose, polyols such as glycerol, mannitol, sorbitol, salts such as potassium phosphate, sodium sulphate, chelating agents such as EDTA, hexaphosphate, ligands such as divalent metal ions (zinc, calcium, etc.), other salts or organic molecules such as phenolic derivatives; in addition, oligomers or polymers such as cyclodextrins, dextran, dendrimers, PEG or PVP or protamine or HSA may be used;
- (v) Anti-adsorption agents: Mainly ionic or non-ionic surfactants or other proteins or soluble polymers are used to coat or adsorb competitively to the inner surface of the formulation's container; e.g., poloxamer (Pluronic F-68), PEG dodecyl ether (Brij 35), polysorbate 20 and 80, dextran, polyethylene glycol, PEG-polyhistidine, BSA and HSA and gelatins; chosen concentration and type of excipient depends on the effect to be avoided but typically a monolayer of surfactant is formed at the interface just above the CMC value;
- (vi) Oxidation protection agents: antioxidants such as ascorbic acid, ectoine, methionine, glutathione, monothioglycerol, morin, polyethylenimine (PEI), propyl gallate, and vitamin E; chelating agents such as citric acid, EDTA, hexaphosphate, and thioglycolic acid may also be used;
- (vii) Viscosifiers or viscosity enhancers: in case of a suspension retard settling of the particles in the vial and syringe and are used in order to facilitate mixing and resuspension of the particles and to make the suspension easier to inject (i.e., low force on the syringe plunger); suitable viscosifiers or viscosity enhancers are, for example, carbomer viscosifiers like Carbopol 940, Carbopol Ultrez 10, cellulose derivatives like hydroxypropylmethylcellulose (hypromellose, HPMC) or diethylaminoethyl cellulose (DEAE or DEAE-C), colloidal magnesium silicate (Veegum) or sodium silicate, hydroxyapatite gel, tricalcium phosphate gel, xanthans, carrageenans like Satia gum UTC 30, aliphatic poly(hydroxy acids), such as poly(D,L- or L-lactic acid) (PLA) and poly(glycolic acid) (PGA) and their copolymers (PLGA), terpolymers of D,L-lactide, glycolide and caprolactone, poloxamers, hydrophilic poly(oxyethylene) blocks and

hydrophobic poly(oxypropylene) blocks to make up a triblock of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (e.g. Pluronic®), polyetherester copolymer, such as a polyethylene glycol terephthalate/polybutylene terephthalate copolymer, sucrose acetate isobutyrate (SAIB), dextran or derivatives thereof, combinations of
5 dextrans and PEG, polydimethylsiloxane, collagen, chitosan, polyvinyl alcohol (PVA) and derivatives, polyalkylimides, poly (acrylamide-co-diallyldimethyl ammonium (DADMA)), polyvinylpyrrolidone (PVP), glycosaminoglycans (GAGs) such as dermatan sulfate, chondroitin sulfate, keratan sulfate, heparin, heparan sulfate, hyaluronan, ABA triblock or AB block copolymers composed of hydrophobic A-
10 blocks, such as polylactide (PLA) or poly(lactide-co-glycolide) (PLGA), and hydrophilic B-blocks, such as polyethylene glycol (PEG) or polyvinyl pyrrolidone; such block copolymers as well as the abovementioned poloxamers may exhibit reverse thermal gelation behavior (fluid state at room temperature to facilitate administration and gel state above sol-gel transition temperature at body temperature after injection);

15
(viii) Spreading or diffusing agent: modifies the permeability of connective tissue through the hydrolysis of components of the extracellular matrix in the intrastitial space such as but not limited to hyaluronic acid, a polysaccharide found in the intercellular space of connective tissue; a spreading agent such as but not limited to hyaluronidase
20 temporarily decreases the viscosity of the extracellular matrix and promotes diffusion of injected drugs; and

(ix) Other auxiliary agents: such as wetting agents, viscosity modifiers, antibiotics, hyaluronidase; acids and bases such as hydrochloric acid and sodium hydroxide are
25 auxiliary agents necessary for pH adjustment during manufacture.

A further aspect of the present invention is a method of treating, controlling, delaying or preventing in a mammalian patient, preferably a human patient, one or more conditions which can be treated, controlled, delayed or prevented with PTH, comprising the step of
30 administering a pharmaceutical composition comprising at least one controlled-release PTH compound once every 24 hours in a dosage of no more than 70% of the molar equivalent dosage of PTH 1-84 required to maintain serum calcium above 8.5 mg/dL over a 24 hour period.

Preferred embodiments of the controlled-release PTH compound are as described above.

Preferably, the condition 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. More preferably, the condition that can be treated, controlled, delayed or prevented with PTH is selected from the group consisting of hypoparathyroidism, hyperphosphatemia, fracture repair, arthritis, osteoarthritis, rheumatoid arthritis, osteopenia, periodontal disease, bone fracture, alopecia, chemotherapy-induced alopecia, and thrombocytopenia.

Most preferably said condition is hypoparathyroidism.

Preferably, the patient undergoing the method of treatment of the present invention is a mammalian patient, preferably a human patient.

Examples

Materials and Methods

Side chain protected PTH(1-34) (SEQ ID NO:51) on TCP resin having Boc protected N-terminus and ivDde protected side chain of Lys26 (synthesized by Fmoc-strategy) was obtained from custom peptide synthesis providers.

Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus (synthesized by Fmoc-strategy) was obtained from custom peptide synthesis providers.

PEG 2x20 kDa maleimide, Sunbright GL2-400MA was purchased from NOF Europe N.V., Grobbendonk, Belgium. S-Trityl-6-mercaptohexanoic acid was purchased from Polypeptide, Strasbourg, France. HATU was obtained from Merck Biosciences GmbH, Schwalbach/Ts, Germany. Fmoc-N-Me-Asp(OBn)-OH was obtained from Peptide International Inc.,

Louisville, KY, USA. Fmoc-Aib-OH was purchased from Iris Biotech GmbH, Marktredwitz, Germany. All other chemicals and reagents were purchased from Sigma Aldrich GmbH, Taufkirchen, Germany, unless a different supplier is mentioned.

- 5 Compound **11a** (examples 11-15) was synthesized following the procedure described in patent WO29095479A2, example 1.

Syringes equipped with polyethylenene frits (MultiSynTech GmbH, Witten, Germany) were used as reaction vessels or for washing steps of peptide resins.

10

General procedure for the removal of ivDde protecting group from side chain protected PTH on resin: The resin was pre-swollen in DMF for 30 min and the solvent was discarded. The ivDde group was removed by incubating the resin with DMF/hydrazine hydrate 4/1 (v/v, 2.5 mL/g resin) for 8 x 15 min. For each step fresh DMF/hydrazine hydrate solution was used.

- 15 Finally, the resin was washed with DMF (10 x), DCM (10 x) and dried *in vacuo*.

General procedure for the removal of Fmoc protecting group from protected PTH on resin: The resin was pre-swollen in DMF for 30 min and the solvent was discarded. The Fmoc group was removed by incubating the resin with DMF/piperidine/DBU 96/2/2 (v/v/v, 2.5 mL/g resin) for 3 x 10 min. For each step fresh DMF/piperidine/DBU solution was used. Finally, the resin was washed with DMF (10 x), DCM (10 x) and dried *in vacuo*.

20

RP-HPLC purification:

For preparative RP-HPLC a Waters 600 controller and a 2487 Dual Absorbance Detector was used, equipped with the following columns: Waters XBridgeTM BEH300 Prep C18 5 μ m, 150 x 10 mm, flow rate 6 mL/min, or Waters XBridgeTM BEH300 Prep C18 10 μ m, 150 x 30 mm, flow rate 40 mL/min. Linear gradients of solvent system A (water containing 0.1 % TFA v/v) and solvent system B (acetonitrile containing 0.1 % TFA v/v) were used. HPLC fractions containing product were pooled and lyophilized if not stated otherwise.

25

30

Flash Chromatography:

Flash chromatography purifications were performed on an Isolera One system from Biotage AB, Sweden, using Biotage KP-Sil silica cartridges and n-heptane and ethyl acetate as eluents. Products were detected at 254 nm.

Ion exchange chromatography:

Ion exchange chromatography (IEX) was performed using an Amersham Bioscience AEKTAbasic system equipped with a MacroCap SP cation exchanger column (Amersham Bioscience/GE Healthcare). 17 mM acetic acid pH 4.5 (solvent A) and 17 mM acetic acid, 1 M NaCl, pH 4.5 (solvent B) were used as mobile phases.

Size exclusion chromatography:

Size exclusion chromatography (SEC) was performed using an Amersham Bioscience AEKTAbasic system equipped with HiPrep 26/10 desalting columns (Amersham Bioscience/GE Healthcare). 0.1 % (v/v) acetic acid was used as mobile phase.

Analytical methods

Analytical ultra-performance LC (UPLC)-MS was performed on a Waters Acquity system equipped with a Waters BEH300 C18 column (2.1 x 50 mm, 1.7 μ m particle size, flow: 0.25 mL/min; solvent A: water containing 0.04% TFA (v/v), solvent B: acetonitrile containing 0.05% TFA (v/v)) coupled to a LTQ Orbitrap Discovery mass spectrometer from Thermo Scientific or coupled to a Waters Micromass ZQ.

Quantification of plasma total PTH(1-34) concentrations:

Plasma total PTH(1-34) concentrations were determined by quantification of a signature peptide close to the N-terminus (sequence: IQLMHNLGK) and a C-terminal signature peptide (sequence: LQDVHNF) after plasma protein precipitation, followed by sequential digestion with Endoproteinase Lys-C (origin: Lysobacter enzymogenes) and Endoproteinase Glu-C (origin: Staphylococcus aureus V8) of the supernatant. Subsequently, analysis by reversed phase liquid chromatography and detection by mass spectrometry (RP-HPLC-MS) was performed.

Calibration standards of PTH(1-34) conjugate in blank heparin or EDTA plasma were prepared in concentration ranges from 1 to 1000 ng/mL PTH(1-34) eq (dilution with rat plasma) and 1 to 1000 ng/mL PTH(1-34) eq (dilution with monkey plasma).

These solutions were used for the generation of a calibration curve. For quality control, three samples independent from the calibration standard solutions were prepared accordingly.

Concentrations at the lower end (3-5 fold concentration of the respective LLOQ), the middle range (0.05 – 0.1 fold concentration of the respective ULOQ) and the upper end (0.5-0.8 fold concentration of the respective ULOQ).

- 5 Sample preparation volumes can be altered depending on the targeted signal response after sample preparation. Processing procedure of the protein precipitation is described here for the analysis of plasma samples originated in rat species. Protein precipitation was carried out first by addition of 100 µL of internal standard solution (625 ng/mL of deuterated conjugate) and then by addition of 400 µL of acetonitrile to 50 µL of the plasma sample. 2 times 150 µL of
10 the supernatant were transferred into a new well-plate and evaporated to dryness (under a gentle nitrogen stream at 50 °C). 50 µL of reconstitution solvent (50 mM Tris 0.5 mM CaCl₂ buffer, adjusted to pH 8.0) were used to dissolve the residue. Proteolytic digestion was performed as follows:
- 15 20 µg of Lys-C (order number 125-05061, Wako Chemicals GmbH, Neuss, Germany) were dissolved in 80 µL of 10 mM acetic acid. 3 µL of the Lys-C solution were added to each cavity and samples incubated for 15 hours at 37°C. Afterwards 10 µg of Glu-C (order number V1651, Promega GmbH, Mannheim, Germany) were dissolved in 25 µL water, and 1.5 µL of the Glu-C solution added to each cavity and incubation continued for 1.5 hours at 37°C. After
20 incubation samples were acidified with 2 µL water/formic acid 4:6 (v/v) and 10 µL were injected into the UPLC-MS system.

Chromatography was performed on a Waters Acquity BEH300 C18 analytical column (1.7 µm particle size; column dimensions 50 x 2.1 mm). Water (UPLC grade) containing 0.1 %
25 formic acid (v/v) was used as mobile phase A and acetonitrile (UPLC grade) with 0.1 % formic acid as mobile phase B.

Mass analysis was performed on an AB Sciex 6500⁺ QTrap in multiple reaction monitoring (MRM) mode, monitoring the transition m/z 352.0 to 462.1 (signature peptide
30 IQLMHNLGK), 355.4 to 467.1 (signature peptide IQLMHNLGK, internal standard), 436.9 to 631.4 (signature peptide LQDVHNF), and 441.9 to 631.4 (signature peptide LQDVHNF, internal standard).

Quantification of plasma PEG concentrations:

Plasma total PEG concentrations were determined by quantification of the polymeric part of PTH(1-34) conjugates after plasma protein precipitation and enzymatic digestion of the supernatant. Analysis by size exclusion chromatography and detection by mass spectrometry (SEC-MS) followed.

5

Calibration standards of PTH(1-34) conjugate in blank heparinized monkey plasma were prepared in concentration ranges from 50 to 4500 ng/mL PEG equivalents.

10

These solutions were used for the generation of a quadratic calibration curve. Calibration curves were weighted $1/x$. For quality control, three samples independent from the calibration standard solutions were prepared accordingly. Concentrations at the lower end (2-4 fold concentration of the LLOQ), the middle range (0.1 - 0.2 fold concentration of the ULOQ) and the upper end (0.8 fold concentration of the ULOQ). Protein precipitation was carried out by addition of 200 μ L of precooled (5-10 °C) methanol to 100 μ L of the plasma sample. 180 μ L of the supernatant were transferred into a new well-plate and evaporated to dryness (under a gentle nitrogen stream at 45 °C). 50 μ L of reconstitution solvent (50 mM Tris 0.5 mM CaCl_2 buffer, adjusted to pH 8.0) were used to dissolve the residue. Proteolytic digestion was performed as follows: 20 μ g of Lys-C (order number 125-05061, Wako Chemicals GmbH, Neuss, Germany) were dissolved in 80 μ L of 10 mM acetic acid. 3 μ L of the Lys-C solution were added to each cavity and samples incubated for 15 hours at 37°C. Afterwards 10 μ g of Glu-C (order number V1651, Promega GmbH, Mannheim, Germany) were dissolved in 25 μ L water, and 1.5 μ L of the Glu-C solution added to each cavity and incubation continued for 1.5 hours at 37°C. After incubation samples were acidified with 2 μ L water/formic acid 4:6 (v/v) and 5 μ L were injected into the SEC-MS system.

25

30

SEC-MS analysis was carried out by using an Agilent 1290 UPLC coupled to an Agilent 6460 TripleQuad mass spectrometer via an ESI probe. Acquisition of a distinct precursor ion of the polymer was achieved by applying high voltage in-source fragmentation (200-300V) at the MS interface. Chromatography was performed on a TOSOH TSK Gel SuperAW3000 analytical column (4.0 μ m particle size; column dimensions 150 x 6.0 mm) at a flow rate of 0.50 mL/min ($T = 65$ °C). Water (UPLC grade) containing 0.1 % formic acid (v/v) was used as mobile phase A and acetonitrile (UPLC grade) with 0.1 % formic acid as mobile phase B. The chromatographic setup for sample analysis comprises an isocratic elution of 50% B over 8 minutes.

Mass analysis was performed in single reaction monitoring (SRM) mode, monitoring the transition m/z 133.1 to 45.1.

Quantification of plasma Free PTH concentrations:

- 5 Free PTH concentrations in acidified plasma were determined as the sum of peptide PTH(1-34) and peptide PTH(1-33) after plasma protein precipitation, followed by solid phase extraction. Subsequently, analysis using liquid chromatography separation and detection by mass spectrometry (LC-MS) was performed.
- 10 Calibration standards of PTH(1-34) and PTH(1-33) in blank acidified EDTA rat plasma were prepared in concentrations ranging from 5.00 to 500 pg/mL in acidified plasma for each analyte. The corresponding concentration range is 7.00 to 700 pg/mL for both analytes in neat plasma, as plasma is acidified as volume ratio plasma : 0.5 M citrate buffer pH 4 = 1 : 0.4 v/v.
- 15 Standard solutions were used for the generation of a calibration curve. For quality control, three samples were prepared independent of the calibration standard solutions at 15.0, 150 and 400 pg/mL in acidified plasma.

Protein precipitation was carried out by addition of 150 μ L of cold acetonitrile to 150 μ L of the plasma sample after addition of 50.0 μ L of cold internal standard solution, followed by centrifugation. The supernatant was decanted into a new polypropylene tube and 900 μ L of cold water was added. After another centrifugation step, the tubes were kept in ice-water until loading on the SPE column.

- 25 Solid phase extraction: the HLB μ elution columns were conditioned with 200 μ L methanol followed by 200 μ L water. The columns were loaded 3 times with 420 μ L of the diluted samples by applying positive pressure. The SPE-columns were washed with 200 μ L of methanol:water 5:95 v/v. The samples were eluted with 40.0 μ L SPE elution solvent (Acetonitrile:water:Trifluoroacetic acid 60:40:1 v/v/v), followed by 40.0 μ L of water. The elution solvent was left standing on the columns for 2 minutes, after which very gentle pressure was applied for elution.
- 30

Separation between metabolites and interfering endogenous compounds was achieved by LC-MS using an Xselect CSH C18 column (2.1x100mm, 2.5 μ m) at 50°C and using 0.2% Formic

acid and 0.5% dimethyl sulfoxide in water as mobile phase A, 0.5% dimethyl sulfoxide in acetonitrile:methanol (75:25, v/v) as mobile phase B, and operating at a gradient with a flow rate of 0.500 mL/min.

- 5 A triple 6500 quadrupole mass spectrometer equipped with a turbo ion spray source was used for detection in positive ion mode. For PTH(1-34), PTH(1-33) and PTH(1-33) (Leu-d₁₀)₃, quantification was done by counting 5 times the same SRM transition.

Quantification is based on multiple reaction monitoring (MRM) of the transitions of m/z:

- 687.3-787.3 for PTH(1-34)
10 662.8-757.9 for PTH(1-33)
692.3-793.3 for PTH(1-34) (Leu-d₁₀)₃
667.8-763.9 for PTH(1-33) (Leu-d₁₀)₃

A linear calibration curve with a $1/x^2$ weighing factor was used for both analytes.

15

Concentrations of free PTH were determined in acidified plasma, as a means to stabilize the analytes. Acidified plasma was prepared by diluting rat EDTA plasma 1.4 times (in case of blank, zero, calibration and QC samples) or rat whole blood (in case of study samples) 1.2 times. Assuming approximately 50% (v/v) of whole blood being plasma, the neat plasma concentrations are approximately 1.4 times higher than the reported concentrations in acidified plasma. Free PTH concentrations are calculated as sum of Free PTH (1-34) and Free PTH (1-33) in PTH(1-34) equivalents).

20

- Due to the reversible nature of the attachment of -L¹- to -D, measurements for PTH receptor activity were made using stable analogs of the PTH prodrugs of the present invention, i.e. they were made using similar structures to those of the PTH prodrugs of the present invention which instead of a reversible attachment of -Z to -D have a stable attachment.

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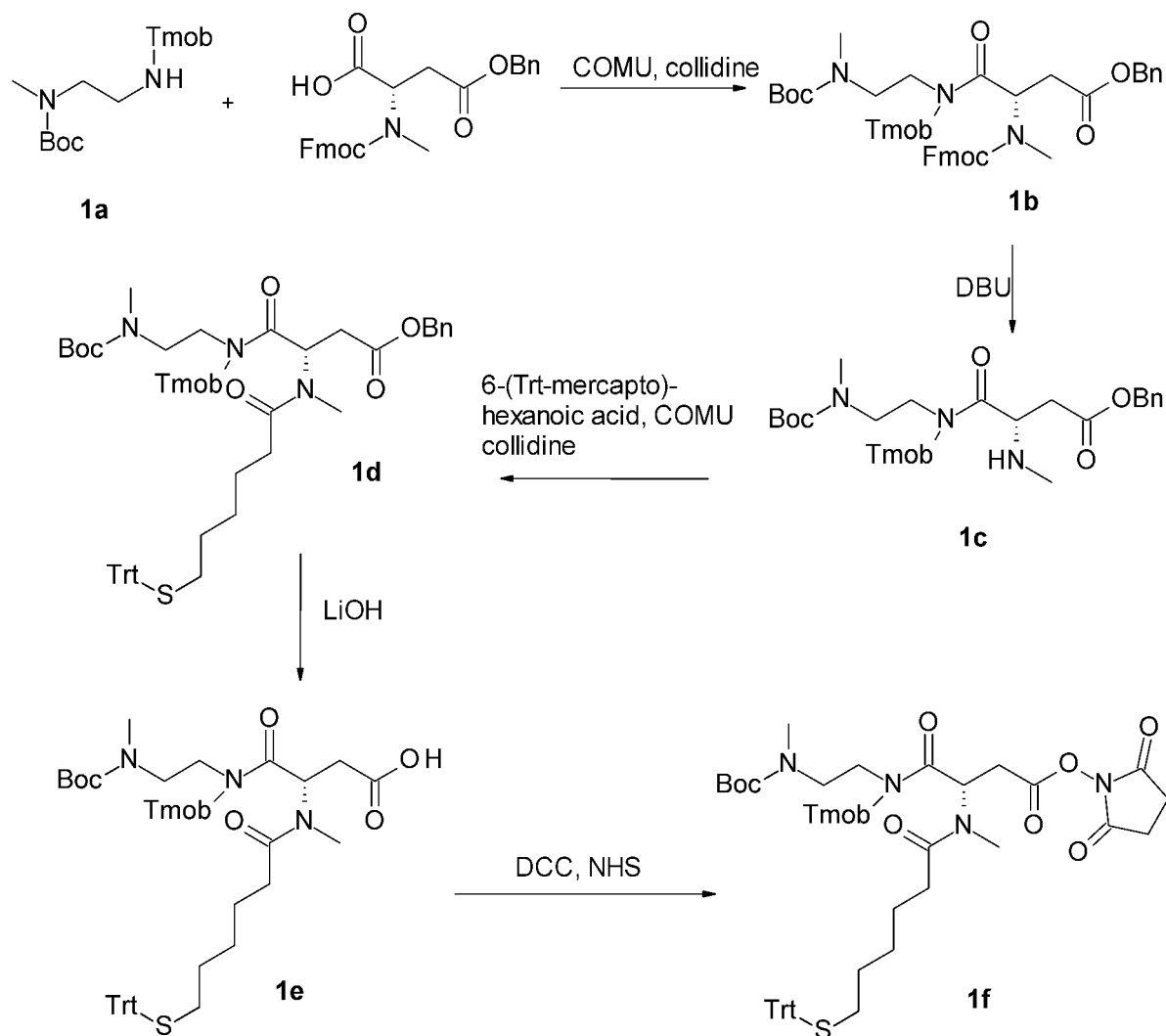
- This was necessary, because the PTH prodrugs of the present invention would release PTH in the course of the experiment and said released PTH would have influenced the result.

30

Example 1

Synthesis of linker reagent 1f

Linker reagent 1f was synthesized according to the following scheme:



- 5 To a solution of N-methyl-N-Boc-ethylenediamine (2 g, 11.48 mmol) and NaCNBH₃ (819 mg, 12.63 mmol) in MeOH (20 mL) was added 2,4,6-trimethoxybenzaldehyde (2.08 g, 10.61 mmol) portion wise. The mixture was stirred at rt for 90 min, acidified with 3 M HCl (4 mL) and stirred further 15 min. The reaction mixture was added to saturated NaHCO₃ solution (200 mL) and extracted 5 x with DCM. The combined organic phases were dried over Na₂SO₄
- 10 and the solvents were evaporated *in vacuo*. The resulting N-methyl-N-Boc-N'-Tmob-ethylenediamine **1a** was dried in high vacuum and used in the next reaction step without further purification.

Yield: 3.76 g (11.48 mmol, 89 % purity, **1a**: double Tmob protected product = 8 :1)

MS: m/z 355.22 = [M+H]⁺, (calculated monoisotopic mass = 354.21).

15

To a solution of **1a** (2 g, 5.65 mmol) in DCM (24 mL) COMU (4.84 g, 11.3 mmol), N-Fmoc-N-Me-Asp(OBn)-OH (2.08 g, 4.52 mmol) and 2,4,6-collidine (2.65 mL, 20.34 mmol) were added. The reaction mixture was stirred for 3 h at rt, diluted with DCM (250 mL) and washed

3 x with 0.1 M H₂SO₄ (100 mL) and 3 x with brine (100 mL). The aqueous phases were re-extracted with DCM (100 mL). The combined organic phases were dried over Na₂SO₄, filtrated and the residue concentrated to a volume of 24 mL. **1b** was purified using flash chromatography.

5 Yield: 5.31 g (148 %, 6.66 mmol)

MS: m/z 796.38 = [M+H]⁺, (calculated monoisotopic mass = 795.37).

To a solution of **1b** (5.31 g, max. 4.52 mmol ref. to N-Fmoc-N-Me-Asp(OBn)-OH) in THF (60 mL) DBU (1.8 mL, 3 % v/v) was added. The solution was stirred for 12 min at rt, diluted
10 with DCM (400 mL) and washed 3 x with 0.1 M H₂SO₄ (150 mL) and 3 x with brine (150 mL). The aqueous phases were re-extracted with DCM (100 mL). The combined organic phases were dried over Na₂SO₄ and filtrated. **1c** was isolated upon evaporation of the solvent and used in the next reaction without further purification.

MS: m/z 574.31 = [M+H]⁺, (calculated monoisotopic mass = 573.30).

15

1c (5.31 g, 4.52 mmol, crude) was dissolved in acetonitrile (26 mL) and COMU (3.87 g, 9.04 mmol), 6-tritylmercaptohexanoic acid (2.12 g, 5.42 mmol) and 2,4,6-collidine (2.35 mL, 18.08 mmol) were added. The reaction mixture was stirred for 4 h at rt, diluted with DCM (400 mL) and washed 3 x with 0.1 M H₂SO₄ (100 mL) and 3 x with brine (100 mL). The
20 aqueous phases were re-extracted with DCM (100 mL). The combined organic phases were dried over Na₂SO₄, filtered and **1d** was isolated upon evaporation of the solvent. Product **1d** was purified using flash chromatography.

Yield: 2.63 g (62 %, 94 % purity)

MS: m/z 856.41 = [M+H]⁺, (calculated monoisotopic mass = 855.41).

25

To a solution of **1d** (2.63 g, 2.78 mmol) in i-PrOH (33 mL) and H₂O (11 mL) was added LiOH (267 mg, 11.12 mmol) and the reaction mixture was stirred for 70 min at rt. The mixture was diluted with DCM (200 mL) and washed 3 x with 0.1 M H₂SO₄ (50 mL) and 3 x with brine (50 mL). The aqueous phases were re-extracted with DCM (100 mL). The
30 combined organic phases were dried over Na₂SO₄, filtered and **1e** was isolated upon evaporation of the solvent. **1e** was purified using flash chromatography.

Yield: 2.1 g (88 %)

MS: m/z 878.4 = [M+Na]⁺, (calculated monoisotopic mass = 837.40).

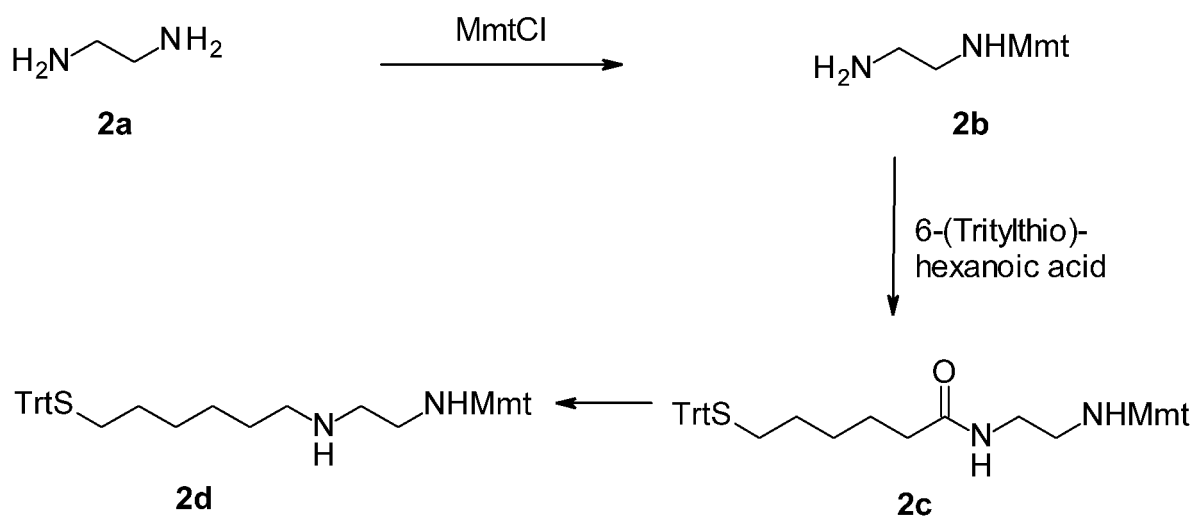
To a solution of **1e** (170 mg, 0.198 mmol) in anhydrous DCM (4 mL) were added DCC (123 mg, 0.59 mmol), and a catalytic amount of DMAP. After 5 min, N-hydroxy-succinimide (114 mg, 0.99 mmol) was added and the reaction mixture was stirred at rt for 1 h. The reaction mixture was filtered, the solvent was removed *in vacuo* and the residue was taken up in 90 % acetonitrile plus 0.1 % TFA (3.4 mL). The crude mixture was purified by RP-HPLC. Product fractions were neutralized with 0.5 M pH 7.4 phosphate buffer and concentrated. The remaining aqueous phase was extracted with DCM and **1f** was isolated upon evaporation of the solvent.

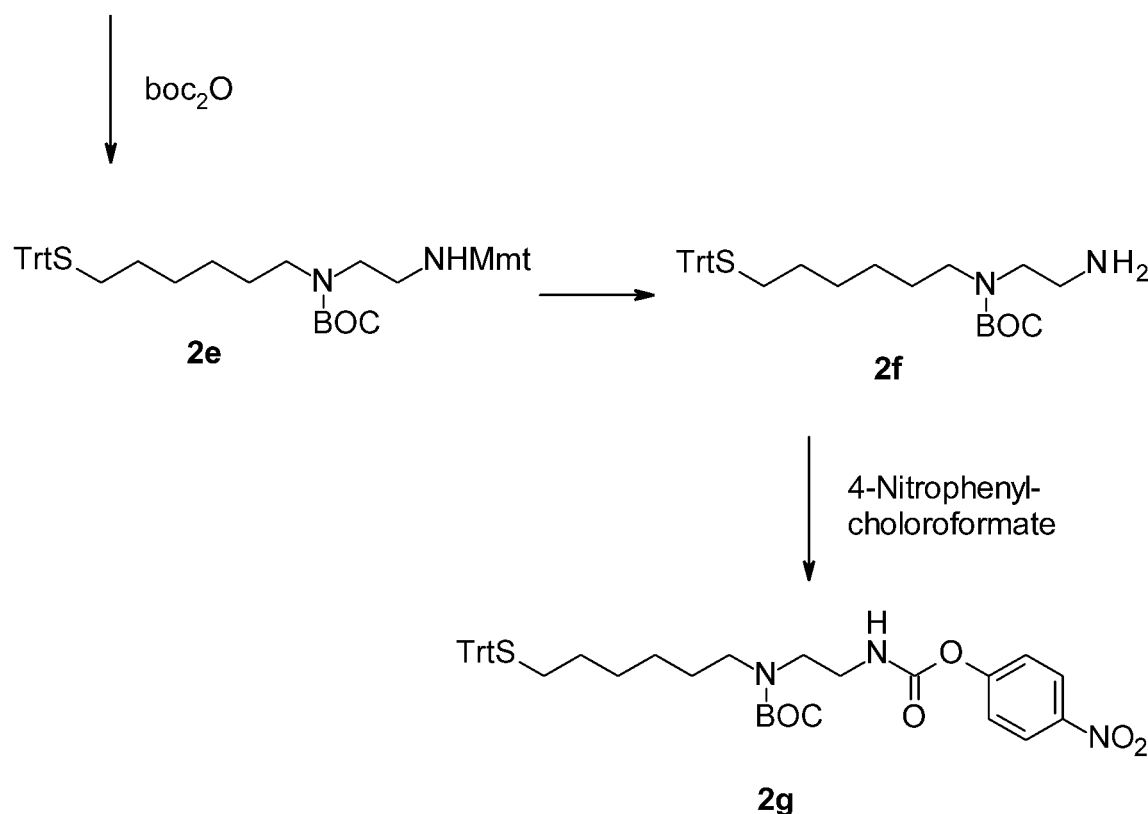
Yield: 154 mg (81%)

MS: m/z 953.4 = $[M+H]^+$, (calculated monoisotopic mass = 952.43).

Example 2

Synthesis of linker reagent **2g**





4-Methoxytriphenylmethyl chloride (3.00 g, 9.71 mmol) was dissolved in DCM (20 mL) and added dropwise under stirring to a solution of ethylenediamine **2a** (6.5 mL, 97.3 mmol) in DCM (20 mL). The reaction mixture was stirred for 2 h at rt after which it was diluted with diethyl ether (300 mL), washed 3 x with brine/0.1 M NaOH 30/1 (v/v) and once with brine. The organic phase was dried over Na₂SO₄ and **2b** was isolated upon evaporation of the solvent.

Yield: 3.18 g (98%)

Mmt protected intermediate **2b** (3.18 g, 9.56 mmol) was dissolved in DCM (30 mL). 6-(Tritylthio)-hexanoic acid (4.48 g, 11.5 mmol), PyBOP (5.67 g, 10.9 mmol) and DIPEA (5.0 mL, 28.6 mmol) were added and the mixture was stirred for 30 min at rt. The solution was diluted with diethyl ether (250 mL), washed 3 x with brine/0.1 M NaOH 30/1 (v/v) and once with brine. The organic phase was dried over Na₂SO₄ and the solvent was removed in vacuo. **2c** was purified using flash chromatography.

Yield: 5.69 g (85 %)

MS: m/z 705.4 = [M+H]⁺, (calculated monoisotopic mass = 704.34).

Compound **2c** (3.19 g, 4.53 mmol) was dissolved in anhydrous THF (50 mL), 1 M BH₃·THF solution in THF (8.5 mL, 8.5 mmol) was added and the mixture was stirred for 16 h at rt.

More 1 M $\text{BH}_3 \cdot \text{THF}$ solution in THF (14 mL, 14.0 mmol) was added and the mixture was stirred for further 16 h at rt. Methanol (8.5 mL) and $\text{N,N}'$ -dimethyl-ethylendiamine (3.00 mL, 27.9 mmol) were added and the mixture was heated under reflux for 3 h. The mixture was allowed to cool down and ethyl acetate (300 mL) was added. The solution was washed 2 x
5 with aqueous Na_2CO_3 and 2 x with aqueous NaHCO_3 . The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to obtain **2d**.

Yield: 3.22 g (103 %)

MS: m/z 691.4 = $[\text{M}+\text{H}]^+$, (calculated monoisotopic mass = 690.36).

10 Di-tert-butyl dicarbonate (2.32 g, 10.6 mmol) and DIPEA (3.09 mL, 17.7 mmol) were dissolved in DCM (5 mL) and added to a solution of **2d** (2.45 g, 3.55 mmol) in DCM (5 mL). The mixture was stirred for 30 min at rt. The solution was concentrated in vacuo and purified by flash chromatography to obtain product **2e**.

Yield: 2.09 g (74 %)

15 MS: m/z 791.4 = $[\text{M}+\text{H}]^+$, (calculated monoisotopic mass = 790.42).

Compound **2e** (5.01 g, 6.34 mmol) was dissolved in acetonitrile (80 mL). 0.4 M aqueous HCl (80 mL) followed by acetonitrile (20 mL) was added and the mixture was stirred for 1 h at rt. The pH was adjusted to pH 5.5 by addition of aqueous 5 M NaOH. The organic solvent was
20 removed in vacuo and the remaining aqueous solution was extracted 4 x with DCM. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo to obtain product **2f**.

Yield: 4.77 g (95 %)

MS: m/z 519.3 = $[\text{M}+\text{H}]^+$, (calculated monoisotopic mass = 518.30).

25

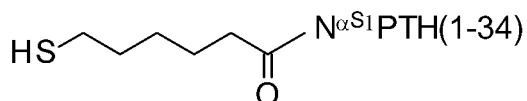
Compound **2f** (5.27 g, 6.65 mmol) was dissolved in DCM (30 mL) and added to a solution of p-nitrophenyl chloroformate (2.01 g, 9.98 mmol) in DCM (25 mL). 2,4,6-trimethylpyridine (4.38 mL, 33.3 mmol) was added and the solution was stirred for 45 min at rt. The solution was concentrated *in vacuo* and purified by flash chromatography to obtain product **2g**.

30 Yield: 4.04 g (89 %)

MS: m/z 706.32 = $[\text{M}+\text{Na}]^+$, (calculated monoisotopic mass = 683.30).

Example 3

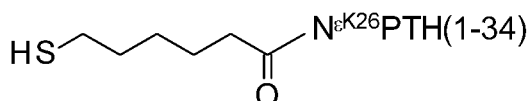
Synthesis of permanent S1 PTH(1-34) conjugate 3

**3**

Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of 6-tritylmercaptohexanoic acid (62.5 mg, 160 μ mol), PyBOP (80.1 mg, 154 μ mol) and DIPEA (53 μ L, 306 μ mol) in DMF (2 mL) was added to 0.21 g (51 μ mol) of the resin. The suspension was agitated for 80 min at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 10 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **3** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 36 mg (14 %), **3***8 TFA

MS: m/z 1062.31 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1062.30).

Example 4**Synthesis of permanent K26 PTH(1-34) conjugate 4****4**

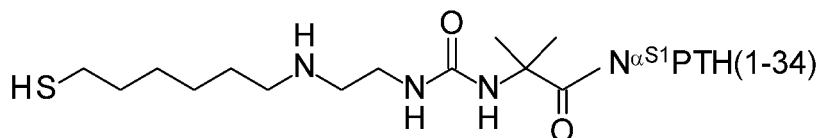
Side chain protected PTH(1-34) on TCP resin having Boc protected N-terminus and ivDde protected side chain of Lys26 was ivDde deprotected according to the procedure given in Materials and Methods. A solution of 6-tritylmercaptohexanoic acid (107 mg, 273 μ mol), PyBOP (141 mg, 273 μ mol) and DIPEA (95 μ L, 545 μ mol) in DMF (3 mL) was added to 0.80 g (90.9 μ mol) of the resin. The suspension was agitated for 1 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 6 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **4** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 40 mg (8 %), **4***8 TFA

MS: m/z 1062.30 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1062.30).

Example 5

5 Synthesis of transient S1 PTH(1-34) conjugate



5

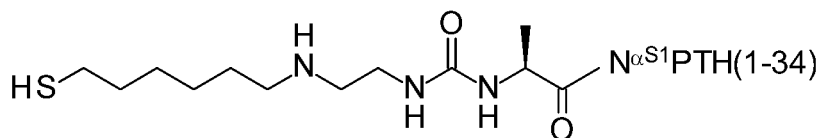
Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of Fmoc-Aib-OH (79 mg, 244 μ mol), PyBOP (127 mg, 244 μ mol) and DIPEA (64 μ L, 365 μ mol) in DMF (1.5 mL) was added to 0.60 g (61 μ mol) of the resin. The suspension was agitated for 16 h at rt. The resin was washed 10 x with DMF and Fmoc-deprotected as described above. A solution of **2g** (167 mg, 244 μ mol) and DIPEA (64 μ L, 365 μ mol) in DMF (1.5 mL) was added to the resin. The suspension was agitated for 24 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 7 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **5** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 78 mg (24 %), **5***9 TFA

MS: m/z 1101.59 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1101.57).

Example 6

Synthesis of transient S1 PTH(1-34) conjugate 6



6

Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of Fmoc-Ala-OH (32 mg, 102 μ mol), PyBOP (53 mg, 102 μ mol) and DIPEA (27 μ L, 152 μ mol) in DMF (3 mL) was added to 0.25 g (25 μ mol) of the resin. The suspension was shaken for 1 h

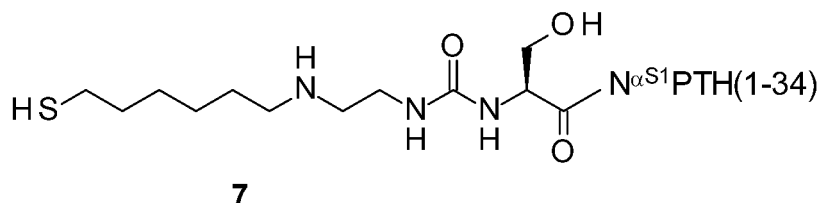
at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried under vacuum. Fmoc-deprotection was performed as described above. A solution of **2g** (69 mg, 102 μ mol) and DIPEA (27 μ L, 152 μ mol) in DMF (3 mL) was added to the resin. The suspension was agitated for 1.5 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 3 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **6** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 25 mg (18 %), **6***9 TFA

MS: m/z 1098.75 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1098.07).

Example 7

Synthesis of transient S1 PTH(1-34) conjugate **7**



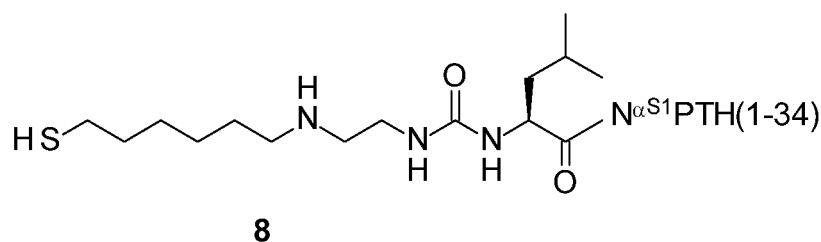
Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of Fmoc-Ser(Trt)-OH (117 mg, 205 μ mol), PyBOP (108 mg, 207 μ mol) and DIPEA (53 μ L, 305 μ mol) in DMF (2 mL) was added to 0.50 g (51 μ mol) of the resin. The suspension was agitated for 1 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried under vacuum. Fmoc-deprotection was performed as described above. A solution of **2g** (144 mg, 211 μ mol) and DIPEA (53 μ L, 305 μ mol) in DMF (1.8 mL) was added to the resin. The suspension was shaken for 7 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 6 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **7** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 54 mg (20 %), **7***9 TFA

MS: m/z 1102.08 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1102.07).

Example 8

5 Synthesis of transient S1 PTH(1-34) conjugate 8



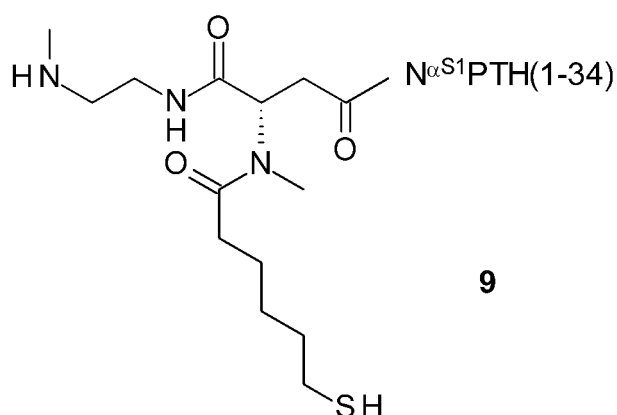
Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of Fmoc-Leu-OH (36 mg, 102 μ mol), PyBOP (53 mg, 102 μ mol) and DIPEA (27 μ L, 152 μ mol) in DMF (3 mL) was added to 0.25 g (25 μ mol) of the resin. The suspension was agitated for 1 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried under vacuum. Fmoc-deprotection was performed as described above. A solution of **2g** (69 mg, 102 μ mol) and DIPEA (27 μ L, 152 μ mol) in DMF (3 mL) was added to the resin. The suspension was agitated for 1.5 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried *in vacuo*. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 3 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **8** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

20 Yield: 31 mg (22 %), **8***9 TFA

MS: m/z 1109.32 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1108.58).

Example 9

25 Synthesis of transient S1 PTH(1-34) conjugate 9



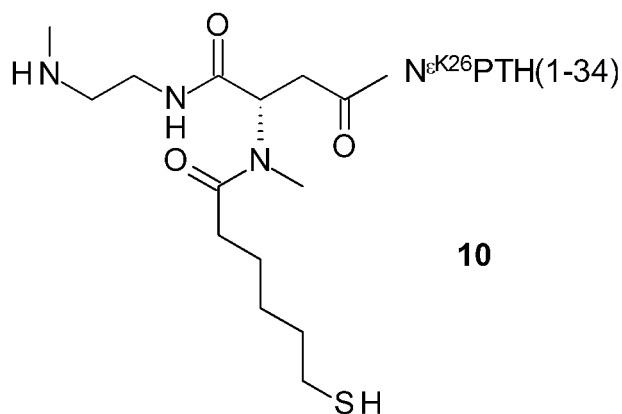
Side chain protected PTH(1-34) on TCP resin having Fmoc protected N-terminus was Fmoc deprotected according to the procedure given in Materials and Methods. A solution of **1e** (182 mg, 213 μmol), PyBOP (111 mg, 213 μmol) and DIPEA (93 μL , 532 μmol) in DMF (5 mL) was added to 2.00 g (107 μmol) of the resin. The suspension was agitated for 16 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried under vacuum. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 20 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and agitating the suspension for 1 h at rt. Crude **9** was precipitated in pre-cooled diethyl ether (-18 $^{\circ}\text{C}$). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 47 mg (8 %), 9*9 TFA

MS: m/z 1108.58 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1108.57).

Example 10

Synthesis of transient K26 PTH(1-34) conjugate 10



Side chain protected PTH(1-34) on TCP resin having Boc protected N-terminus and ivDde protected side chain of Lys26 was ivDde deprotected according to the procedure given in

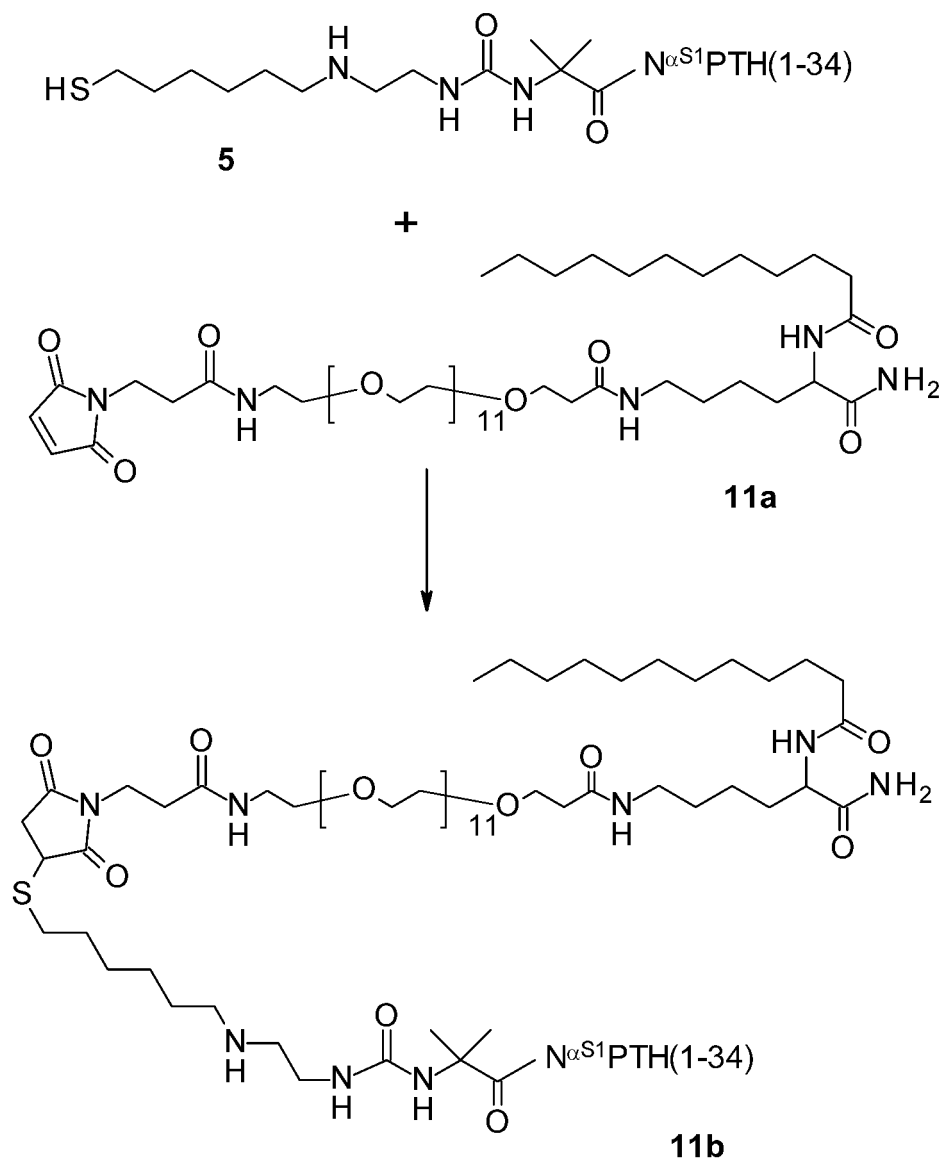
Materials and Methods. A solution of **1f** (867 mg, 910 μ mol) and DIPEA (0.24 mL, 1.36 mmol) in DMF (5 mL) was added to 1.91 g (227 μ mol) of the resin. The suspension was agitated for 1 h at rt. The resin was washed 10 x with DMF, 10 x with DCM and dried under vacuum. Cleavage of the peptide from the resin and removal of protecting groups was achieved by adding 20 mL cleavage cocktail 100/3/3/2/1 (v/w/v/v/v) TFA/DTT/TES/water/thioanisole and shaking the suspension for 1 h at rt. Crude **10** was precipitated in pre-cooled diethyl ether (-18 °C). The precipitate was dissolved in ACN/water and purified by RP-HPLC. The product fractions were freeze-dried.

Yield: 92 mg (7 %), **10***9 TFA

MS: m/z 1108.58 = $[M+4H]^{4+}$, (calculated monoisotopic mass for $[M+4H]^{4+}$ = 1108.57).

Example 11

Synthesis of low molecular weight transient S1 PEG conjugate **11b**



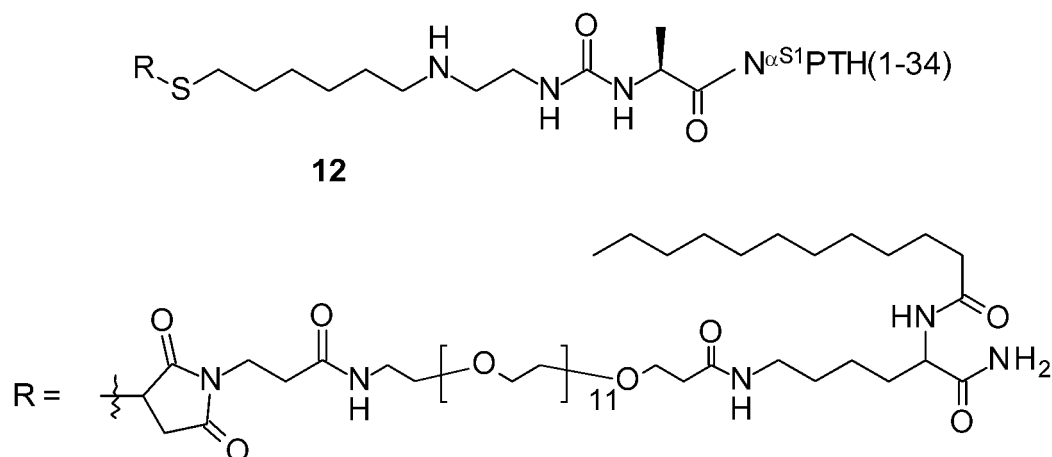
0.15 mL of a 0.5 M NaH₂PO₄ buffer (pH 7.4) was added to 0.5 mL of a 20 mg/mL solution of thiol **5** (10 mg, 1.84 μmol) in 1/1 (v/v) acetonitrile/water containing 0.1 % TFA (v/v). The solution was incubated at rt for 10 min after which 238 μL of a 10 mg/mL solution of maleimide **11a** (2.4 mg, 2.21 μmol) in 1/1 (v/v) acetonitrile/water containing 0.1 % TFA (v/v) were added. The solution was incubated for 20 min at rt. 10 μL TFA was added and the mixture was purified by RP-HPLC. The product fractions were freeze-dried to obtain **11b**.

Yield: 3.1 mg (26 %), **11b***9 TFA

MS: m/z 1097.00 = [M+4H]⁴⁺, (calculated monoisotopic mass for [M+5H]⁵⁺ = 1096.99).

Example 12

Synthesis of low molecular weight transient S1 PEG conjugate **12**



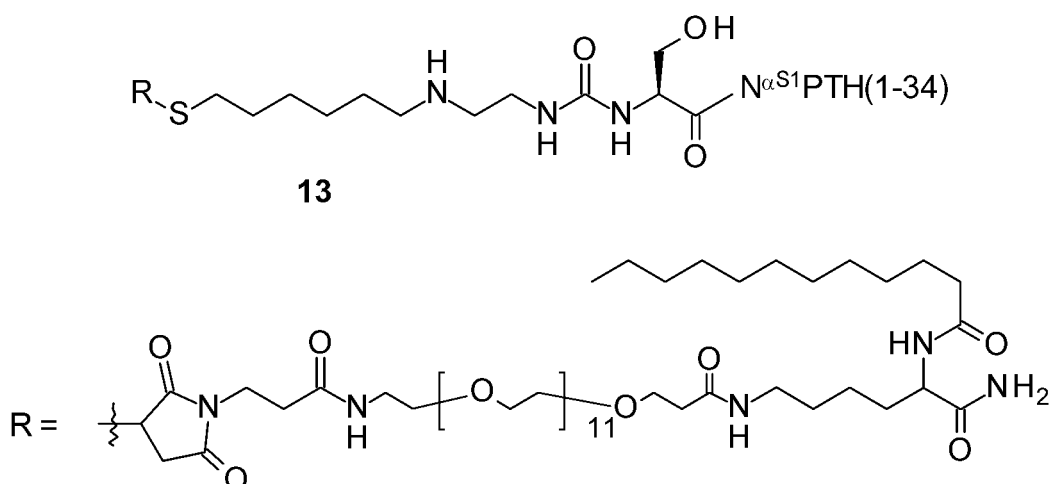
Conjugate **12** was synthesized as described for **11b** by using thiol **6** (10 mg, 1.85 μmol) and maleimide **11a** (2.4 mg, 2.21 μmol).

Yield: 10 mg (83 %), **12***9 TFA

MS: m/z 1094.20 = [M+4H]⁴⁺, (calculated monoisotopic mass for [M+4H]⁴⁺ = 1094.19).

Example 13

Synthesis of low molecular weight transient S1 PEG conjugate **13**



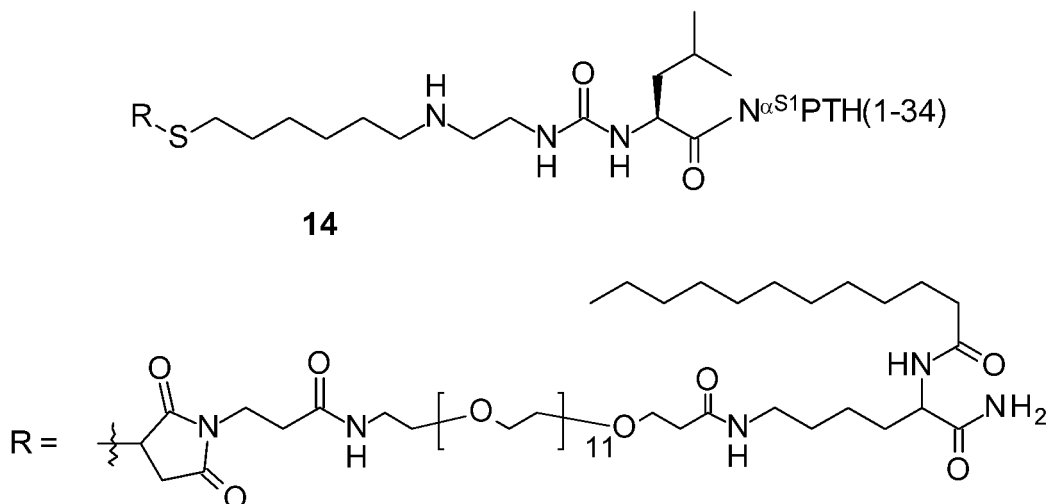
Conjugate **13** was synthesized as described for **11b** by using thiol **7** (10 mg, 1.84 μmol) and maleimide **11a** (2.4 mg, 2.21 μmol).

5 Yield: 8 mg (67 %), **13***9 TFA

MS: m/z 1097.40 = $[\text{M}+5\text{H}]^{5+}$, (calculated monoisotopic mass for $[\text{M}+5\text{H}]^{5+}$ = 1097.39).

Example 14

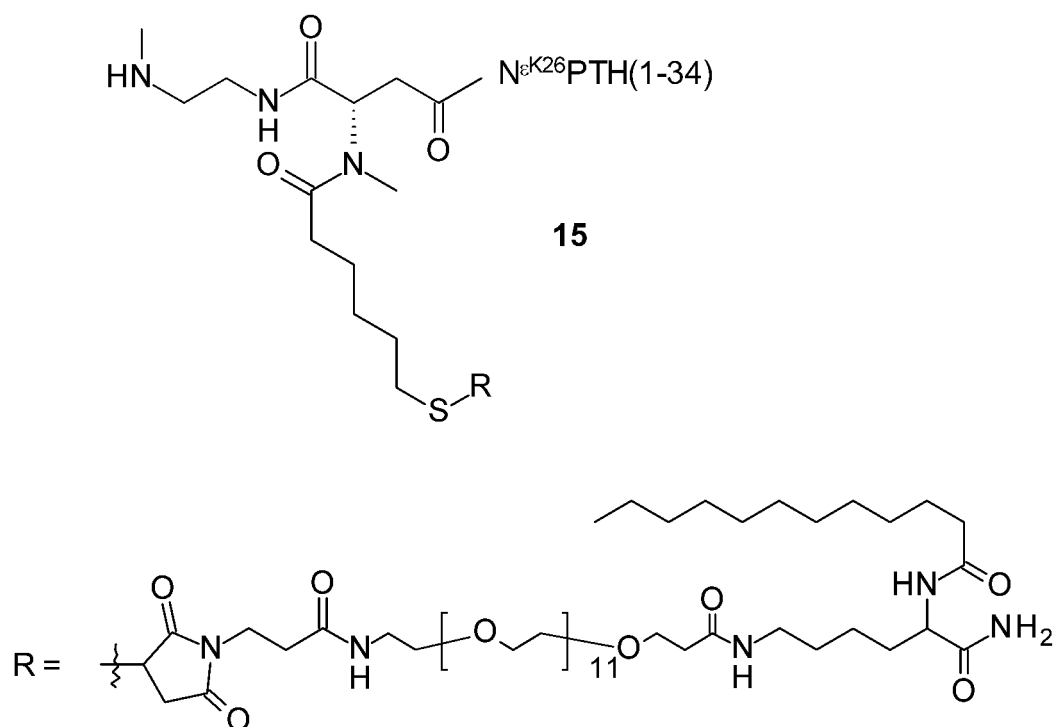
10 Synthesis of low molecular weight transient S1 PEG conjugate **14**



Conjugate **14** was synthesized as described for **11b** by using thiol **8** (10 mg, 1.83 μmol) and maleimide **11a** (2.4 mg, 2.21 μmol).

15 Yield: 4 mg (33 %), **14***9 TFA

MS: m/z 1378.01 = $[\text{M}+4\text{H}]^{4+}$, (calculated monoisotopic mass for $[\text{M}+4\text{H}]^{4+}$ = 1378.00).

Example 15**Synthesis of low molecular weight transient K26 PEG conjugate 15**

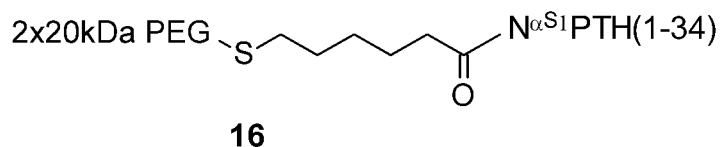
5

Conjugate **15** was synthesized as described for **11b** by using thiol **10** (5.2 mg, 0.95 μmol) and maleimide **11a** (1.23 mg, 1.14 μmol).

Yield: 2.1 mg (33 %), **15***9 TFA

MS: m/z 1102.60 = $[M+5H]^{5+}$, (calculated monoisotopic mass for $[M+5H]^{5+}$ = 1102.59).

10

Example 16**Synthesis of permanent 2x20 kDa S1 PEG conjugate 16**

15

772 μL of a solution containing thiol **3** (19.4 mg/mL, 15 mg, 3.54 μmol) and 2.5 mg/mL Boc-L-Met in 1/1 (v/v) acetonitrile/water containing 0.1 % TFA (v/v) were added to 1.87 mL of a solution containing PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 187 mg, 4.32 μmol) and 2.5 mg/mL Boc-L-Met in water containing 0.1 % TFA (v/v). 0.5 M NaH_2PO_4 buffer (0.66 mL, pH 7.0) was added and the mixture was stirred for 30 min at rt. 10 μL of a 270 mg/mL

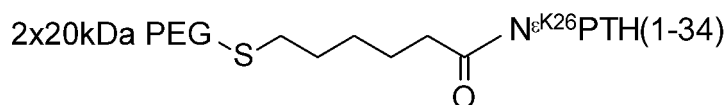
20

solution of 2-mercaptoethanol in water was added. The mixture was stirred for 5 min at rt and 0.33 mL 1 M HCl were added. Conjugate **16** was purified by IEX followed by RP-HPLC using a linear gradient of solvent system A (water containing 0.1 % AcOH v/v) and solvent system B (acetonitrile containing 0.1 % AcOH v/v). The product containing fractions were freeze-dried.

Yield: 97 mg (2.01 μ mol, 57 %) conjugate **16***8 AcOH

Example 17

Synthesis of permanent 2x20 kDa K26 PEG conjugate **17**



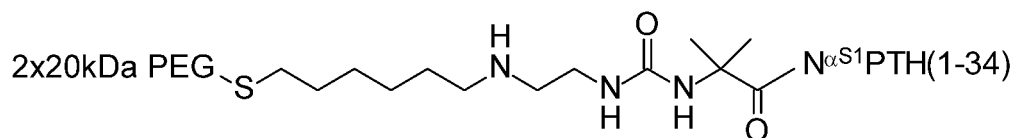
17

Conjugate **17** was prepared as described for **16** by reaction of thiol **4** (15 mg, 3.53 μ mol) and PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 187 mg, 4.32 μ mol).

Yield: 80 mg (1.79 μ mol, 51 %) conjugate **17***8 AcOH

Example 18

Synthesis of transient 2x20 kDa S1 PEG conjugate **18**



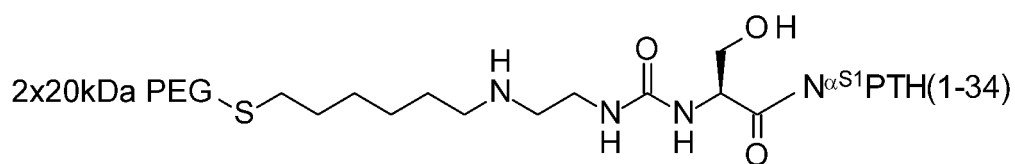
18

Conjugate **18** was prepared as described for **16** by reaction of thiol **5** (37 mg, 8.40 μ mol) and PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 445 mg, 9.24 μ mol). The reaction was quenched by addition of 50 μ L TFA without prior addition of 2-mercaptoethanol. Conjugate **18** was purified by IEX followed by SEC for desalting. The product containing fractions were freeze-dried.

Yield: 161 mg (3.33 μ mol, 40 %) conjugate **18***9 AcOH

Example 19

Synthesis of transient 2x20 kDa S1 PEG conjugate **19**

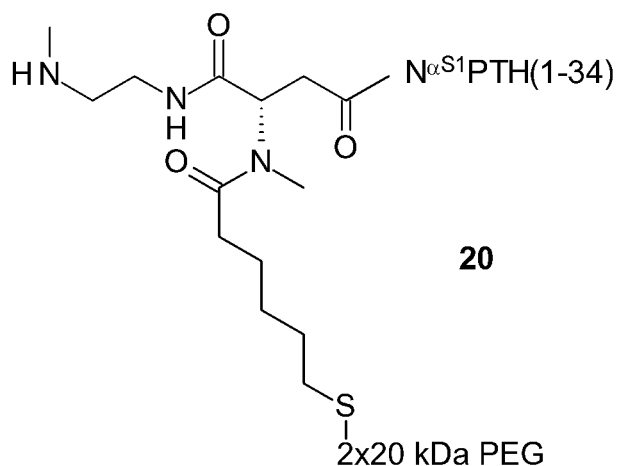
**19**

Conjugate **19** was prepared as described for **16** by reaction of thiol **7** (27 mg, 6.14 μmol) and PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 325 mg, 7.50 μmol).

5 Yield: 249 mg (5.16 μmol , 84 %) conjugate **19***9 AcOH

Example 20

Synthesis of transient 2x20 kDa S1 PEG conjugate **20**

**20**

10

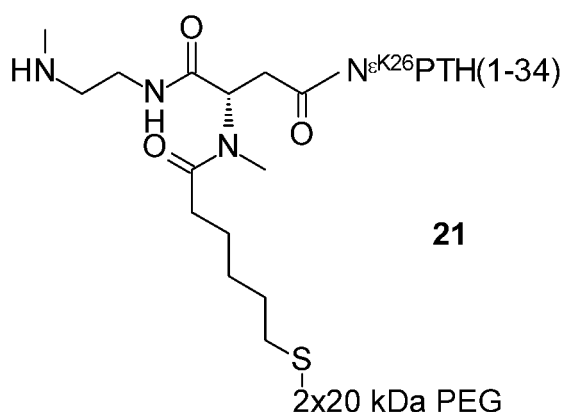
Conjugate **20** was prepared as described for **16** by reaction of thiol **9** (38 mg, 8.59 μmol) and PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 455 mg, 9.45 μmol). The reaction was quenched by addition of 50 μL TFA without prior addition of 2-mercaptoethanol. Conjugate **20** was purified by IEX followed by SEC for desalting. The product containing fractions were freeze-dried.

15

Yield: 194 mg (4.01 μmol , 47 %) conjugate **20***9 AcOH

Example 21

Synthesis of transient 2x20 kDa K26 PEG conjugate **21**



Conjugate **21** was prepared as described for **16** by reaction of thiol **10** (34 mg, 7.58 μ mol) and PEG 2x20 kDa maleimide (Sunbright GL2-400MA, 401 mg, 9.26 μ mol).

5 Yield: 256 mg (5.30 μ mol, 70 %) conjugate **21***9 AcOH

Example 22

In vitro release kinetics of transient low molecular weight PEG conjugates

Conjugates **11b**, **12**, **13**, **14**, and **15** were dissolved in pH 7.4 phosphate buffer (60 mM NaH₂PO₄, 3 mM EDTA, 0.01 % Tween-20, adjusted to pH 7.4 by NaOH) containing 0.05 mg/mL pentafluorophenol as internal standard at a concentration of approximately 1 mg conjugate/mL. The solutions were filtered sterile and incubated at 37°C. At time points, aliquots were withdrawn and analysed by RP-HPLC and ESI-MS. The fraction of released PTH at a particular time point was calculated from the ratio of UV peak areas of liberated PTH and PEG conjugate. The % released PTH was plotted against incubation time. Curve-fitting software was applied to calculate the corresponding half times of release.

Results:

For conjugate **11b** a release half life time of 3.2 d was obtained.

20 For conjugate **12** a release half life time of 8.7 d was obtained.

For conjugate **13** a release half life time of 10.8 d was obtained.

For conjugate **14** a release half life time of 25.3 d was obtained.

For conjugate **15** a release half life time of 6.9 d was obtained.

25 Example 23

In vitro release kinetics of transient 2x20 kDa PEG conjugates

Conjugates **18**, **19**, **20**, and **21** were dissolved in pH 7.4 phosphate buffer (60 mM NaH₂PO₄, 3 mM EDTA, 0.01 % Tween-20, adjusted to pH 7.4 by NaOH) containing 0.08 mg/mL

pentafluorophenol as internal standard at a concentration of approximately 5 mg conjugate/mL. The solutions were filtered sterile and incubated at 37°C. At time points, aliquots were withdrawn and analysed by RP-HPLC. The fraction of released PTH at a particular time point was calculated from the ratio of UV peak areas of liberated PTH and PEG conjugate. The % released PTH was plotted against incubation time. Curve-fitting software was applied to calculate the corresponding half times of release.

Results:

For conjugate **18** a release half life time of 2.8 d was obtained.

For conjugate **19** a release half life time of 13.4 d was obtained.

For conjugate **20** a release half life time of 1.3 d was obtained

For conjugate **21** a release half life time of 7.1 d was obtained

Example 24

PTH receptor activity of permanent 2x20 kDa PEG conjugates 16 and 17 in cell based assay

The residual PTH activity of permanently PEGylated conjugates **16** and **17** was quantified by measuring cAMP production from HEK293 cells over-expressing the PTH/PTHrP1 receptor (Hohenstein A, Hebell M, Zikry H, El Ghazaly M, Mueller F, Rohde, J. Development and validation of a novel cell-based assay for potency determination of human parathyroid hormone (PTH), Journal of Pharmaceutical and Biomedical Analysis September 2014, 98: 345–350). PTH(1-34) from NIBSC (National Institute for Biological Standards and Control, UK) was used as reference standard.

Results:

For conjugate **16** a receptor activity of 0.12 % was found relative to PTH(1-34) reference

For conjugate **17** a receptor activity of 0.11 % was found relative to PTH(1-34) reference

The results indicate an effective lowering of receptor activity in the permanent 2x20 kDa PEG conjugates **16** and **17**. It can be concluded that similar conjugates with transiently Ser1 or Lys26 linked PTH (like e.g. **18** and **21**) are suitable PTH prodrugs providing low residual receptor activity. Direct analysis of transient conjugates in the cell assay is not possible due to linker cleavage under the assay conditions. The released PTH would influence the assay result.

Example 25**Pharmacokinetic study of permanent 2x20 kDa PEG conjugates 16 and 17 in rats**

Male Wistar rats (6 weeks, 230-260 g) received either a single intravenous (2 groups, n = 3 animals each) or a single subcutaneous (2 groups, n = 3 animals each) administration of **16** or **17** at doses of 29 µg/rat PTH_{eq} and 31 µg/rat PTH_{eq} respectively. Blood samples were collected up to 168 h post dose, and plasma was generated. Plasma PTH(1-34) concentrations were determined by quantification of the N-terminal signature peptide (sequence: IQLMHNLGK) and the C-terminal signature peptide (sequence: LQDVHNF) after LysC and GluC digestion as described in Materials and Methods.

Results: Dose administrations were well tolerated with no visible signs of discomfort during administration and following administration. No dose site reactions were observed any time throughout the study. After intravenous injection of **16** and **17** the total PTH(1-34) t_{max} was observed at 15 min (earliest time point analyzed), followed by a slow decay in total PTH(1-34) content with a half life time of approx. 13 h and 11 h respectively. After subcutaneous injection the total PTH(1-34) concentration peaked at a t_{max} of 24 h for both **16** and **17**, followed by a slow decay in total PTH(1-34) content with half life times of approx. 1.5 days for both conjugates. The bioavailability was approx. 40 % and 60 % respectively. Similar PK curves were obtained for the N- and the C-terminal signature peptide up to 168 h post dose, indicating the presence of intact PTH(1-34) in the conjugate.

The favourable long lasting PK and the stability of PTH in the conjugates indicate the suitability of the permanent 2x20 kDa PEG model compounds as slow releasing PTH prodrugs after subcutaneous injection. It can be concluded that similar conjugates with transiently Ser1 (like e.g. **18**) or Lys26 linked PTH are suitable PTH prodrugs providing long lasting levels of released bioactive PTH.

Example 26**Pharmacokinetic study of transient 2x20 kDa S1 PEG conjugate 19 in cynomolgus monkeys**

Male non naïve cynomolgus monkeys (2-4years, 3.7-5.4 kg) received a single subcutaneous (n = 3 animals) administration of **19** at a dose of 70 µg/kg PTH_{eq}. Blood samples were collected up to 504 h post dose, and plasma was generated. Total plasma PTH(1-34) concentrations were determined by quantification of the N-terminal signature peptide

(sequence: IQLMHNLGK) and the C-terminal signature peptide (sequence: LQDVHNF) after LysC and GluC digestion as described in Materials and Methods. The PEG concentrations were determined using the method described in Materials and Methods.

- 5 Results: Dose administrations were well tolerated with no visible signs of discomfort during administration. One animal showed visible signs of discomfort 72 h post dose, but recovered the days after. No dose site reactions were observed any time throughout the study. The total PTH(1-34) concentration peaked at a $t_{\max}$ of 24 h, followed by a slow decay in total PTH(1-34) content with a half life time of approx. 2.5 d for the N-terminal signature peptide
10 and 0.9 d for the C-terminal signature peptide. The PEG concentration peaked at $t_{\max}$ of 24 h, followed by a slow decay in PEG concentration with a half life time of 3.5 d.

It can be concluded that conjugate **19** is a suitable prodrug for sustained delivery of PTH.

15 **Example 27**

Pharmacokinetic study of transient 2x20 kDa S1 PEG conjugate 18 in cynomolgus monkeys

- Non naïve cynomolgus monkeys (2-3 years, 2.5-4 kg) received daily subcutaneous (n = 2 animals – 1 male / 1 female) administration of **18** at dose levels of 0.2, 0.5, and 1 $\mu\text{g/kg PTH}_{\text{eq}}$
20 for 28 days. Blood samples were collected up to 28 days (at days 1, 13, and, 27 samples were collected at pre-dose, 2 h, 4 h, 8 h, 12 h, and 24 h post-dose) and plasma was generated. Plasma PTH(1-34) concentrations were determined by quantification of the N-terminal signature peptide (sequence: IQLMHNLGK) and the C-terminal signature peptide (sequence: LQDVHNF) after LysC and GluC digestion as described in Materials and Methods.

- 25 Results: All dose administrations were performed without incident. No dose site reactions were observed any time throughout the study. Dose linearity was observed in the three groups. Dose stacking was observed from day 1 compared with day 13 and day 27. Total PTH(1-34) concentrations were quantified via the N-terminal signature peptide (sequence:
30 IQLMHNLGK) at steady state (during day 27).

A low peak-to-trough ratio of total PTH(1-34) for all dose groups of below 3 was observed after daily subcutaneous application at steady state in cynomolgus monkeys. As free peptide

concentrations at steady state are correlated to total PTH(1-34) concentration, the peak-to-trough ratio for the free peptide is below 4 in cynomolgus monkeys.

Example 28

5 **Pharmacokinetic study of transient 2x20 kDa S1 PEG conjugate 18 in cynomolgus monkeys**

Naïve cynomolgus monkeys (2-3.5 years, 2-5 kg) (3-5 males / 3-5 females) received daily subcutaneous administrations of **18** at dose levels of 0.2, 0.5 and 1.5 µg PTH/kg. Blood samples were collected at; Day 1: pre-dose, 4 h, 8 h, 12 h, 18 h, and 24 h post-dose, at Day 8: 10 pre-dose, at Day 14: predose, 8h, and 12 h and at Day 28: 3 h, 6 h, 8 h, 12 h, 18 h, 24 h, 72 h, 168 h, and 336 h) and plasma was generated. Total PTH plasma concentrations were determined by quantification of the N-terminal signature peptide (sequence: IQLMHNLGK) after LysC and GluC digestion as presented earlier in Materials and Methods.

15 Results: Systemic exposure expressed as C_{max} and AUC increased in an approximately dose proportional manner. Systemic exposure of Total PTH expressed as AUC accumulated approximately 3-fold from Day 1 to Day 28.

A low mean peak-to-trough ratio of Total PTH for all dose groups of 1.5 was observed after 20 daily subcutaneous administration in cynomolgus monkeys at Day 28 (steady state observed from Day 8). This low mean peak-to-trough ratio of Total PTH can also be translated to Free PTH.

Example 29

25 **Pharmacokinetic study of transient 2x20 kDa S1 PEG conjugate 18 in Sprague-Dawley rats**

Sprague-Dawley Crl:CD(SD) rats (initiation of dosing at 8 weeks of age) received daily subcutaneous administrations of **18** at dose levels of 10, 30 and 60 µg PTH/kg for 28 days. A TK group containing of 9 males and 9 females per dose group was divided into 3 subgroup 30 with 3 rats per subgroup. Blood samples were collected up to 28 days with 3 rats per sex, per sampling time point. Samples were collected at Day 1: pre-dose, 4 h, 8 h, 12 h, 18 h, and 24 h post-dose, and at Day 28: 3 h, 6 h, 8 h, 12 h, 18 h, 24 h, and 336 h and plasma was generated. The total PTH plasma concentrations were determined by quantification of the N-terminal signature peptide (sequence: IQLMHNLGK) after LysC and GluC digestion as presented 35 earlier in Materials and Methods.

The free PTH plasma concentrations were determined by quantification as the sum of PTH(1-34) and PTH(1-33) by LC-MS/MS as presented earlier in Materials and Methods.

Results: Systemic exposure of total PTH and free PTH expressed as mean C_{max} and AUC increased in an approximately dose proportional manner. Systemic exposure of total PTH expressed as mean AUC accumulated 3-6 fold from day 1 to day 28 and free PTH expressed as mean AUC accumulated 2-3 fold from day 1 to day 28. Systemic exposure of total PTH in the female rat was approximately 2-fold higher than in males. Systemic exposure of free PTH was slightly higher in the female rat than in males.

A low mean peak-to-trough ratio of total PTH for all dose groups of 1.2 was observed after daily subcutaneous administration in Sprague-Dawley rats at day 28 (steady state observed from Day 8). A low mean peak-to-trough ratio of free PTH in the range 1.5 - 2.4 was observed after daily subcutaneous administration in Sprague-Dawley rats at day 28.

Abbreviations:

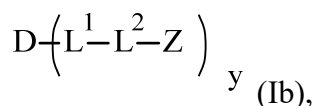
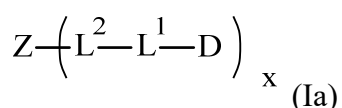
ACN	acetonitrile
AcOH	acetic acid
Aib	2-aminoisobutyric acid
BMD	bone mineral density
Bn	benzyl
Boc	tert-butyloxycarbonyl
COMU	(1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
cAMP	cyclic adenosine monophosphate
d	day
DBU	1,3-diazabicyclo[5.4.0]undecene
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMAP	dimethylamino-pyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DTT	dithiothreitol

	EDTA	ethylenediaminetetraacetic acid
	eq	stoichiometric equivalent
	ESI-MS	electrospray ionization mass spectrometry
	Et	ethyl
5	Fmoc	9-fluorenylmethyloxycarbonyl
	Glu-C	endoproteinase Glu-C
	h	hour
	HATU	O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
10	HPLC	high performance liquid chromatography
	ivDde	4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl
	LC	liquid chromatography
	LTQ	linear trap quadrupole
	Lys-C	endoproteinase Lys-C
15	LLOQ	lower limit of quantification
	Mal	3-maleimido propyl
	Me	methyl
	MeOH	methanol
	min	minutes
20	Mmt	monomethoxytrityl
	MS	mass spectrum / mass spectrometry
	m/z	mass-to-charge ratio
	OtBu	tert-butyloxy
	PEG	poly(ethylene glycol)
25	pH	<i>potentia Hydrogenii</i>
	PK	pharmacokinetics
	Pr	propyl
	PTH	parathyroid hormone
	PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
30	Q-TOF	quadrupole time-of-flight
	RP-HPLC	reversed-phase high performance liquid chromatography
	rt	room temperature
	SIM	single ion monitoring
	SEC	size exclusion chromatography

	sc	subcutaneous
	t _{1/2}	half life
	TCP	tritylchloride polystyrol
	TES	triethylsilane
5	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	Tmob	2,4,6-trimethoxybenzyl
	Trt	triphenylmethyl, trityl
	ULOQ	upper limit of quantification
10	UPLC	ultra performance liquid chromatography
	UV	ultraviolet
	ZQ	single quadrupole

Claims

1. The use of a pharmaceutical composition comprising a water-soluble controlled-release PTH compound in the manufacture of a medicament for the treatment of hypoparathyroidism, wherein the water-soluble controlled-release PTH compound has a total mass of at least 20 kDa and from the water-soluble controlled-release PTH compound at least one PTH molecule is released with a release half-life of at least 12 hours, wherein the PTH compound is to be administered to a non-human primate via subcutaneous administration and a time period between two consecutive subcutaneous administrations is at least 24 hours, wherein after subcutaneous administration the pharmacokinetic profile of the PTH compound exhibits a peak to trough ratio of less than 4 within one injection interval of at least 24 hours, wherein the peak to trough ratio is the ratio of the highest plasma concentration to the lowest plasma concentration of released PTH within the time period between the two consecutive administrations to the non-human primate at steady state and wherein the water-soluble controlled-release PTH compound is a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt thereof



wherein

- D is a PTH moiety and has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, 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:56, SEQ ID

NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, 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, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120 and SEQ ID NO:121;

-L¹- is a reversible prodrug linker moiety connected to the PTH moiety -D through a functional group of PTH;

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

-Z is a PEG-based polymer having a molecular weight of about 40 kDa;

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

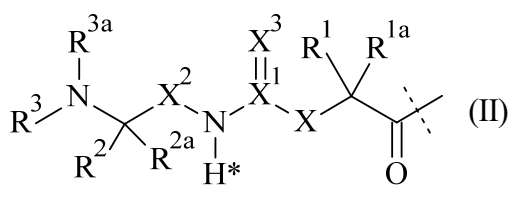
y is an integer selected from the group consisting of 1, 2, 3, 4 and 5.

2. The use of claim 1, wherein the at least one PTH molecule has a sequence selected from the group consisting 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 and SEQ ID NO:115.

3. The use of claim 1 or 2, wherein the at least one PTH molecule has the sequence of SEQ ID NO:51.

4. The use of any one of claims 1 to 3, wherein the time period between the two consecutive subcutaneous administrations is 24 hours.

5. The use of any one of claims 1 to 3, wherein the time period between the two consecutive subcutaneous administrations is one week.
6. The use of any one of claims 1 to 5, wherein the subcutaneous administration is via subcutaneous injection.
7. The use of any one of claims 1 to 6, wherein the subcutaneous administration occurs with a pen device.
8. The use of any one of claims 1 to 7, wherein the peak to trough ratio is less than 3.
9. The use of any one of claims 1 to 8, wherein the peak to trough ratio is less than 2.6.
10. The use of any one of claims 1 to 9, wherein the non-human primate is a cynomolgus monkey.
11. The use of any one of claims 1 to 10, wherein $-L^1-$ is of formula (II):



- wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of $-D$;
- $-X-$ is selected from the group consisting of $-C(R^4R^{4a})-$; $-N(R^4)-$; $-O-$; $-C(R^4R^{4a})-C(R^5R^{5a})-$; $-C(R^5R^{5a})-C(R^4R^{4a})-$; $-C(R^4R^{4a})-N(R^6)-$; $-N(R^6)-C(R^4R^{4a})-$; $-C(R^4R^{4a})-O-$; $-O-C(R^4R^{4a})-$; and $-C(R^7R^{7a})-$;
- X^1 is selected from the group consisting of C; and S(O);
- $-X^2-$ is selected from the group consisting of $-C(R^8R^{8a})-$; and $-C(R^8R^{8a})-C(R^9R^{9a})-$;
- $=X^3$ is selected from the group consisting of $=O$; $=S$; and $=N-CN$;
- $-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^8$, $-R^{8a}$, $-R^9$, and $-R^{9a}$ are independently selected from the group consisting of $-H$; and C_{1-6} alkyl;
- $-R^3$, and $-R^{3a}$ 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 selected from the group consisting of $-N(R^{10}R^{10a})$; and $-NR^{10}-(C=O)-R^{11}$;

$-R^{7a}$, $-R^{10}$, $-R^{10a}$, and $-R^{11}$ are independently of each other selected from the group consisting of $-H$; and C_{1-6} alkyl;

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

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, $-R^4/-R^{4a}$, $-R^5/-R^{5a}$, $-R^8/-R^{8a}$,
and $-R^9/-R^{9a}$ 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 $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$,
10 $-R^4/-R^6$, $-R^8/-R^9$, and $-R^2/-R^3$ 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;
15 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.

20 12. The use of any one of claims 1 to 11, wherein $-L^2$ - is selected from the group
consisting of $-T$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^{y1})$ -, $-S(O)_2N(R^{y1})$ -, $-S(O)N(R^{y1})$ -,
 $-S(O)_2$ -, $-S(O)$ -, $-N(R^{y1})S(O)_2N(R^{y1a})$ -, $-S$ -, $-N(R^{y1})$ -, $-OC(OR^{y1})(R^{y1a})$ -, $-N(R^{y1})C(O)N(R^{y1a})$ -,
 $-OC(O)N(R^{y1})$ -, 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
25 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
30 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 $-T$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^{y4})$ -,
, $-S(O)_2N(R^{y4})$ -, $-S(O)N(R^{y4})$ -, $-S(O)_2$ -, $-S(O)$ -,

$-\text{N}(\text{R}^{y4})\text{S}(\text{O})_2\text{N}(\text{R}^{y4a})-$, $-\text{S}-$, $-\text{N}(\text{R}^{y4})-$, $-\text{OC}(\text{OR}^{y4})(\text{R}^{y4a})-$, $-\text{N}(\text{R}^{y4})\text{C}(\text{O})\text{N}(\text{R}^{y4a})-$,
and $-\text{OC}(\text{O})\text{N}(\text{R}^{y4})-$;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered
5 heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;
wherein each T is independently optionally substituted with one or more $-\text{R}^{y2}$, which are the same or different;

each $-\text{R}^{y2}$ is independently selected from the group consisting of halogen, $-\text{CN}$, oxo
(=O), $-\text{COOR}^{y5}$, $-\text{OR}^{y5}$, $-\text{C}(\text{O})\text{R}^{y5}$, $-\text{C}(\text{O})\text{N}(\text{R}^{y5}\text{R}^{y5a})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{y5}\text{R}^{y5a})$,
10 $-\text{S}(\text{O})\text{N}(\text{R}^{y5}\text{R}^{y5a})$, $-\text{S}(\text{O})_2\text{R}^{y5}$, $-\text{S}(\text{O})\text{R}^{y5}$, $-\text{N}(\text{R}^{y5})\text{S}(\text{O})_2\text{N}(\text{R}^{y5a}\text{R}^{y5b})$, $-\text{SR}^{y5}$, $-\text{N}(\text{R}^{y5}\text{R}^{y5a})$,
 $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{y5}$, $-\text{N}(\text{R}^{y5})\text{C}(\text{O})\text{R}^{y5a}$, $-\text{N}(\text{R}^{y5})\text{S}(\text{O})_2\text{R}^{y5a}$, $-\text{N}(\text{R}^{y5})\text{S}(\text{O})\text{R}^{y5a}$,
 $-\text{N}(\text{R}^{y5})\text{C}(\text{O})\text{OR}^{y5a}$, $-\text{N}(\text{R}^{y5})\text{C}(\text{O})\text{N}(\text{R}^{y5a}\text{R}^{y5b})$, $-\text{OC}(\text{O})\text{N}(\text{R}^{y5}\text{R}^{y5a})$, and C₁₋₆ alkyl; wherein C₁₋₆
alkyl is optionally substituted with one or more halogen, which are the same or different; and
each $-\text{R}^{y3}$, $-\text{R}^{y3a}$, $-\text{R}^{y4}$, $-\text{R}^{y4a}$, $-\text{R}^{y5}$, $-\text{R}^{y5a}$ and $-\text{R}^{y5b}$ is independently selected from the
15 group consisting of $-\text{H}$, and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or
more halogen, which are the same or different.

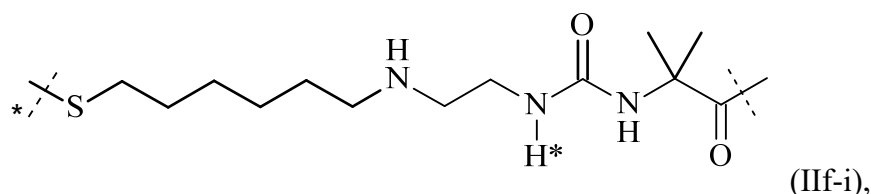
13. The use of any one of claims 1 to 12, wherein $-\text{Z}$ is a branched PEG-based polymer.

20 14. The use of any one of claims 1 to 13, wherein the pharmaceutical composition has a pH
ranging from and including pH 3 to pH 8.

15. The use of any one of claims 1 to 14, wherein the pharmaceutical composition has a pH
ranging from and including pH 4 to pH 5.

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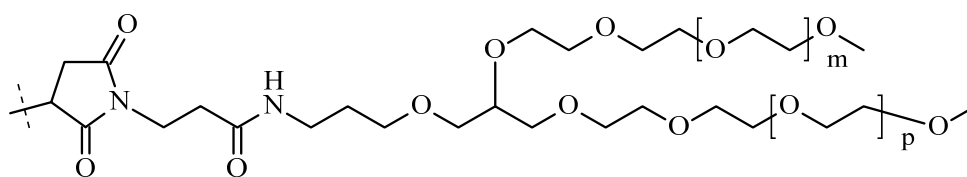
16. The use of any one of claims 1 to 15, wherein the PTH compound is of formula (IIIf-i):



wherein

the unmarked dashed line indicates the attachment to a nitrogen of $-\text{D}$ by
30 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.

5

17. The use of claim 16, wherein m and p are about 450.