

PTH Treatment of Chronic Kidney Disease

The present invention relates to a PTH compound for use in the prevention of chronic kidney disease (CKD) in a subject at risk of developing CKD or in the treatment of a subject having CKD, and to related aspects.

Chronic hypoparathyroidism is a rare endocrine disorder characterized by hypocalcemia, hyperphosphatemia, and absent or insufficient parathyroid hormone (PTH) production. In the absence of PTH, the mechanisms regulating calcium transport and phosphate reabsorption in the PTH receptor-rich renal tubule are deregulated, resulting in disruption to the major role of the kidney in controlling calcium and phosphate homeostasis. There is an increased risk of renal complications in patients with chronic hypoparathyroidism managed with conventional therapy consisting of oral calcium and active vitamin D. It has been shown that patients with chronic hypoparathyroidism are at greater risk of incident chronic kidney disease (CKD), CKD stage progression, progression to End Stage Kidney Disease (ESKD), and faster decline in estimated glomerular filtration rate (eGFR) compared with patients without hypoparathyroidism. Therefore, patients with hypoparathyroidism treated with conventional therapy require close monitoring of symptoms of hypoparathyroidism and comorbidities, including development of chronic kidney disease, risk of renal stones, and renal calcifications.

Although a growing body of research supports an increased risk of renal complications in patients with chronic hypoparathyroidism, the underlying mechanism of this risk in the pathophysiology of hypoparathyroidism remains unknown. Chronic hypoparathyroidism is commonly managed with conventional therapy, which is aimed at maintaining a serum calcium concentration in the lower part of the normal range (i.e., 8.0–8.5 mg/dl; Adv Ther (2021) 38:1876–1888 1885).

Chen et al. (J Clin Endocrinol Metab. 2020; 105: e3557–65) recently reported that in a study of patients with chronic hypoparathyroidism, eGFR declined by 8.0 ml/min/1.73 m² in patients not treated with recombinant human PTH 1–84 (Natpara®) over a 5-year follow-up period. In contrast, eGFR remained stable among patients treated with rhPTH 1–84 or showed only minimal improvement, suggesting that hormone replacement therapy may ameliorate eGFR decline.

Compared with patients who do not have hypoparathyroidism, patients with chronic hypoparathyroidism have a significantly increased risk of developing incident CKD stage 3 and higher. Patients with chronic hypoparathyroidism also have a significantly increased risk of progression to a higher CKD stage and progression to ESKD compared with patients without hypoparathyroidism (Adv Ther (2021) 38:1876–1888 1885).

Thus, there is a need for a more efficacious treatment of chronic kidney disease, in particular in patients with hypoparathyroidism.

It is an objective of this application to at least partially overcome these objections.

This objective is achieved with PTH compound for use in the prevention of chronic kidney disease (CKD) in a subject at risk of developing CKD or in the treatment of a subject having CKD.

It was surprisingly found that administration of a PTH compound, such as a PTH compound that results in an at least 10 times longer receptor signaling compared to PTH 1-84, to a subject having CKD, in particular to a subject having hypoparathyroidism and CKD with an eGFR of less than 60 ml/min/1.73 m², led to a sustained improvement in eGFR, while similar subjects on conventional therapy experienced a decline in eGFR.

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

As used herein the terms “within normal level” and “within normal range” with regards to serum calcium (sCa) refer to the calcium level ordinarily found in a subject of a given species, sex and age. In humans, a normal serum calcium level usually corresponds to a serum calcium level ranging from 8.3 mg/dL (albumin-adjusted) to 10.6 mg/dL (albumin-adjusted). The term “albumin-adjusted” with regards to serum calcium levels means that the measured serum calcium level is corrected for calcium bound to albumin according to the following formula:

$$\text{albumin-adjusted serum calcium (mg/dL)} = \text{measured total Ca (mg/dL)} + 0.8 (4.0 - \text{serum albumin [g/dL]}).$$

Serum calcium levels within the normal range are also referred to as “normocalcemia”.

As used herein the term “starting dose” refers to the dose of the PTH compound that is administered to a subject when first initiating the treatment with the PTH compound, i.e., such subject has not previously received a dose of the PTH compound. It is understood that the subject may continue on such starting dose for some time, such as for several days, weeks or months or for the full length of the treatment or may titrate the dose up or down in response to certain events, such as the occurrence of hypo- or hypercalcemia.

As used herein the term “average” refers to the simple (equally weighted) arithmetic mean, which can be obtained by summing up all the variables in the data set and dividing the result by the number of variables.

A subject is referred to as having “chronic hypoparathyroidism” if the hypoparathyroidism has persisted for at least six months. The terms “subject” and “patient” are used synonymously herein.

As used herein the term “mean improvement” with regards to eGFR refers to the mean improvement in eGFR measured in a population of subjects.

As used herein the term “PTH” refers to all PTH polypeptides, such as from mammalian species, in particular from human and mammalian species, more particularly 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 PTHrP polypeptides, such as the polypeptide of SEQ ID NO:121, that bind to and activate the common PTH/PTHrP1 receptor. In certain embodiments the term “PTH” refers to the PTH polypeptide of SEQ ID NO:51 as well as its variants, homologs and derivatives exhibiting essentially the same biological activity, i.e., raising serum calcium and renal phosphorus excretion, and lowering serum phosphorus and renal calcium excretion. In certain embodiments the term “PTH” refers to the PTH polypeptide of SEQ ID NO:51.

In certain embodiments the term “PTH” refers to one of the following polypeptide sequences:

SEQ ID NO:1 (PTH 1-84)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTAKSQ

SEQ ID NO:2 (PTH 1-83)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTAKS

SEQ ID NO:3 (PTH 1-82)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTAK

SEQ ID NO:4 (PTH 1-81)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTAKA

SEQ ID NO:5 (PTH 1-80)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTAK

SEQ ID NO:6 (PTH 1-79)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLT

SEQ ID NO:7 (PTH 1-78)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLT

SEQ ID NO:8 (PTH 1-77)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNV

SEQ ID NO:9 (PTH 1-76)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNV

SEQ ID NO:10 (PTH 1-75)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADV

SEQ ID NO:11 (PTH 1-74)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKAD

SEQ ID NO:12 (PTH 1-73)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKA

SEQ ID NO:13 (PTH 1-72)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADK

SEQ ID NO:14 (PTH 1-71)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEAD

SEQ ID NO:15 (PTH 1-70)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEA

SEQ ID NO:16 (PTH 1-69)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGE

SEQ ID NO:17 (PTH 1-68)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLG

SEQ ID NO:18 (PTH 1-67)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSL

SEQ ID NO:19 (PTH 1-66)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKS

SEQ ID NO:20 (PTH 1-65)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEK

SEQ ID NO:21 (PTH 1-64)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHE

SEQ ID NO:22 (PTH 1-63)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL VESH

SEQ ID NO:23 (PTH 1-62)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL VES

SEQ ID NO:24 (PTH 1-61)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL VE

SEQ ID NO:25 (PTH 1-60)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL V

SEQ ID NO:26 (PTH 1-59)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL

SEQ ID NO:27 (PTH 1-58)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNV

SEQ ID NO:28 (PTH 1-57)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DN

SEQ ID NO:29 (PTH 1-56)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
D

SEQ ID NO:30 (PTH 1-55)

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)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRP

SEQ ID NO:35 (PTH 1-50)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR

SEQ ID NO:36 (PTH 1-49)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQ

SEQ ID NO:37 (PTH 1-48)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGS

SEQ ID NO:38 (PTH 1-47)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAG

SEQ ID NO:39 (PTH 1-46)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDA

SEQ ID NO:40 (PTH 1-45)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRD

SEQ ID NO:41 (PTH 1-44)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPR

SEQ ID NO:42 (PTH 1-43)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAP

SEQ ID NO:43 (PTH 1-42)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLA

SEQ ID NO:44 (PTH 1-41)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPL

SEQ ID NO:45 (PTH 1-40)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAP

SEQ ID NO:46 (PTH 1-39)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGA

SEQ ID NO:47 (PTH 1-38)

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

SEQ ID NO:52 (PTH 1-33)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHN

SEQ ID NO:53 (PTH 1-32)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH

SEQ ID NO:54 (PTH 1-31)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDV

SEQ ID NO:55 (PTH 1-30)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQD

SEQ ID NO:56 (PTH 1-29)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQ

SEQ ID NO:57 (PTH 1-28)

SVSEIQLMHNLGKHLNSMERVEWLRKKL

SEQ ID NO:58 (PTH 1-27)

SVSEIQLMHNLGKHLNSMERVEWLRKK

SEQ ID NO:59 (PTH 1-26)

SVSEIQLMHNLGKHLNSMERVEWLRK

SEQ ID NO:60 (PTH 1-25)

SVSEIQLMHNLGKHLNSMERVEWLR

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DNVLVESHEKSLGEADKADVNVLTAKSQ; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DNVLVESHEKSLGEADKADVNVLTAKS; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DNVLVESHEKSLGEADKADVNVLTAK; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DNVLVESHEKSLGEADKADVNVLTAKA; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVLTK; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVL; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVNVL; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADNVN; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADVN; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKADV; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKAD; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADKA; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEADK; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEAD; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGEA; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLGE; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSLG; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKSL; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEKS; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHEK; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESHE; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVESH; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVES; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLVE; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVLV; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE
DNVL; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DNV; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

DN; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE

D; wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKKE;

wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRKK;

wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRK;

wherein the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPR;

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)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR; wherein

the C-terminus is amidated

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

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQ; wherein

the C-terminus is amidated

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 amidated

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

jSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF; wherein the C-terminus is amidated

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

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

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)

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

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

SVSEIQLMHNLGKHLNSMERVEWLR; wherein the C-terminus is amidated

SEQ ID NO:121 (PTHrP)

AVSEHQLLDKKGKSIQDLRRRFFLHHLIAEIHTAEIRATSEVSPNSKPSNTKNHPVRF
GSDDEGRYLTQETNKVETYKEQPLKTPGKKKKKGKPGKRKEQEKKKRRTRSAWLDS
GVTGSGLEGDHLSDTSTTSLELDSRRH

and sequences having at least 90%, such as at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% homology thereto.

The terms “PTH molecule” and “PTH moiety” also include 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 proteins and peptides, 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. In certain embodiments the term “PTH” refers to sequences having a backbone formed through amide (peptide) bonds.

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 molecules or PTH moieties, respectively, of a sustained-release PTH compound or of a PTH prodrug are released.

The term “peptide” as used herein refers to a chain of at least 2 and up to and including 50 amino acid monomer moieties, which may also be referred to as “amino acid residues”, linked by peptide (amide) linkages. The amino acid monomers may be selected from the group consisting of proteinogenic amino acids and non-proteinogenic amino acids and may be D- or L-amino acids. The term “peptide” also includes peptidomimetics, such as peptoids, beta-peptides, cyclic peptides and depsipeptides and covers such peptidomimetic chains with up to and including 50 monomer moieties. As used herein, the term “protein” refers to a chain of more than 50 amino acid monomer moieties, which may also be referred to as “amino acid residues”, linked by peptide linkages, in which preferably no more than 12000 amino acid monomers are linked by peptide linkages, such as no more than 10000 amino acid monomer moieties, no more than 8000 amino acid monomer moieties, no more than 5000 amino acid monomer moieties or no more than 2000 amino acid monomer moieties. For simplification, PTH moieties and PTH molecules are generally referred to herein as “protein”.

As used herein the term “physiological conditions” refers to 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 PTH compound, 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, a pharmaceutical composition for use of the present invention encompasses any composition made by admixing one or more PTH compound and a pharmaceutically acceptable excipient.

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 may be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is an example for an excipient when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are examples of excipients when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are in certain embodiments employed as liquid excipients for injectable 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, 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, or sustained-release formulations. The pharmaceutical composition may 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 subject. The formulation should suit the mode of administration.

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

The term “suspension composition” relates to a mixture comprising at least one water-insoluble 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 has a residual water content of a maximum of 10%, such as less than 5% or less than 2%, determined according to Karl Fischer. In certain embodiments such dry pharmaceutical composition 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 “drug moiety”.

As used herein the term “prodrug” refers to a covalent conjugate in which a drug moiety is reversibly and covalently connected to a specialized protective group through a reversible linker moiety, also referred to as “reversible prodrug linker moiety” or “reversible linker moiety”, which is conjugated through a reversible linkage to 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 drug moiety in the form of its corresponding drug. In other words, a prodrug is a conjugate comprising a drug moiety which is covalently and reversibly conjugated to a carrier moiety via a reversible linker moiety, which covalent and reversible conjugation of the carrier to the reversible linker moiety is either directly or through a spacer. Such conjugate releases the formerly conjugated drug moiety in the form of a free unmodified drug.

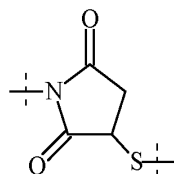
A “reversible linkage” is a linkage that is degradable, i.e. cleavable, in the absence of enzymes under physiological conditions (aqueous buffer at pH 7.4, 37°C) with a half-life ranging from one hour to three months, in certain embodiments from one hour to two months, in certain embodiments from one hour to one month, in certain embodiments from one hour to three weeks, in certain embodiments from one hour to two weeks, in certain embodiments from 12 hours to two weeks, in certain embodiments from 12 hours to one week. Accordingly, a stable linkage is a linkage having a half-life under physiological conditions (aqueous buffer at pH 7.4, 37°C) in the absence of enzymes of more than three months.

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

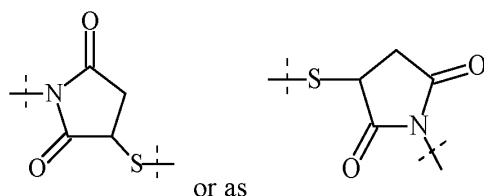
As used herein, the term “reagent” means a chemical compound which comprises at least one functional group for reaction with the functional group of another chemical compound or drug. It is understood that a drug comprising a functional group, such as a primary or secondary amine or hydroxyl functional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

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



may 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, primary or 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, disulfide, sulfonamides, sulfuric acid, vinyl sulfone, vinyl ketone, diazoalkane, oxirane, and aziridine.

In case a PTH compound comprises 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 comprising acidic groups may 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. A PTH compound comprising one or more basic groups, i.e. groups which can be protonated, may be present and may 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 simultaneously comprises acidic and basic groups, the invention also includes, in addition to the salt forms mentioned above, inner salts or betaines (zwitterions). The respective salts may 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 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.

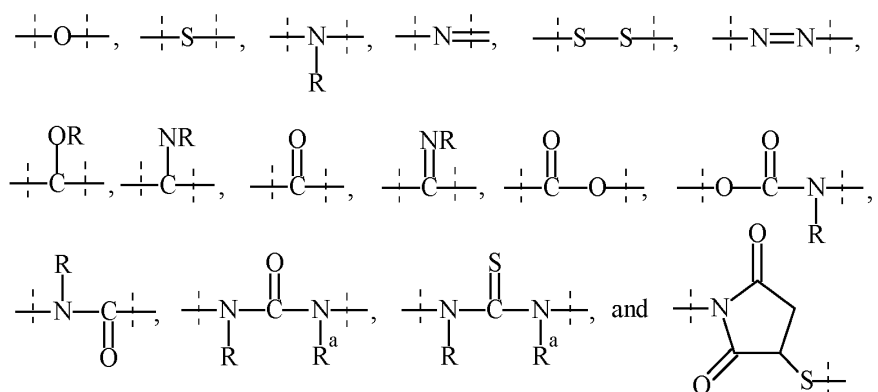
The term "pharmaceutically acceptable" means a substance that does not cause harm when administered to a subject and in certain embodiments means approved by a regulatory agency, such as the EMA (Europe) and/or the FDA (US) and/or any other national regulatory agency for use in animals, in particular for use in humans.

As used herein the terms "about" or "approx." 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, in certain embodiments no more than 8% of said numerical value, in certain embodiments no more than 5% of said numerical value and in certain embodiments no more than 2% of said numerical value. For example, the phrases "about 200" or "approx. 200" is used to mean a range ranging from and including $200 \pm 10\%$, i.e. ranging from and including 180 to 220; in certain embodiments $200 \pm 8\%$, i.e. ranging from and including 184 to 216; in certain embodiments ranging from and including $200 \pm 5\%$, i.e. ranging from and including 190 to 210; and in certain embodiments $200 \pm 2\%$, i.e. ranging from and including 196 to 204. It is understood that a percentage given as "about 20%" or "approx. 20%" does not mean " $20\% \pm 10\%$ ", i.e. ranging from and including 10 to 30%, but "about 20%" or "approx. 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. In certain embodiments 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 in certain embodiments 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, or such as at most 100 kDa. It is understood that for water-insoluble polymers, such as hydrogels, no meaningful molecular weight ranges can be provided. It is understood that also a peptide or 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 in certain embodiments selected from the group consisting of:

- 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



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, 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.

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., 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 given for “x” provides the range of integers in which the arithmetic mean numbers of monomers lie. An integer for “x” given as “about x” means that the arithmetic mean numbers of monomers lie in a range of integers of $x \pm 10\%$, in certain embodiments $x \pm 8\%$, in certain embodiments $x \pm 5\%$ and in certain embodiments $x \pm 2\%$.

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

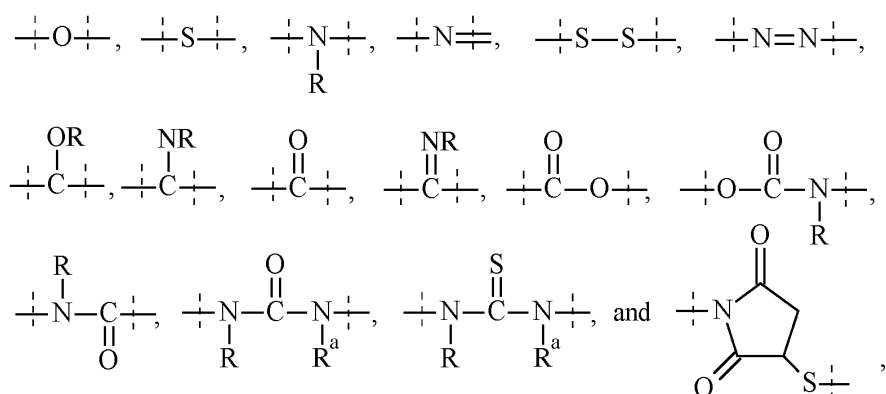
As used herein the term “water-soluble” with reference to the PTH compound means that at least 1 g of the PTH compound may be dissolved in one liter of water at 20°C to form a homogeneous solution. Accordingly, the term “water-insoluble” with reference to PTH compound means that less than 1 g of the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

As used herein, the term “PEG-based” in relation to a moiety or reagent means that said moiety or reagent comprises PEG. In certain embodiments 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 that in certain embodiments are selected from the following moieties and linkages:

- 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



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, 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.

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”.

In certain embodiments 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}), -NO₂, -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}), -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T⁰, C₁₋₅₀ alkyl,

C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{x2}, 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 -T⁰-, -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})-;

-R^{x1}, -R^{x1a}, -R^{x1b} are independently of each other selected from the group consisting of -H, -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T⁰, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{x2}, 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 -T⁰-, -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})-;

each T⁰ is independently 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 T⁰ 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})-, -NO₂, -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 C₁₋₆ alkyl; wherein C₁₋₆ 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 C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments 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}), -NO₂, -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}), -T⁰, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl; wherein -T⁰, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl are optionally substituted with one or more -R^{x2}, 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 -T⁰-, -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})-

each -R^{x1}, -R^{x1a}, -R^{x1b}, -R^{x3}, -R^{x3a} is independently selected from the group consisting of -H, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

each T⁰ is independently 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 T⁰ 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}), -NO₂, -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 C₁₋₆ alkyl; wherein C₁₋₆ 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, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

In certain embodiments 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}), -NO₂, -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}),

$-\text{OC}(\text{O})\text{N}(\text{R}^{\text{x1}}\text{R}^{\text{x1a}})$, $-\text{T}^0$, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein $-\text{T}^0$, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more $-\text{R}^{\text{x2}}$, 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 $-\text{T}^0$ -, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{x3}})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{\text{x3}})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{\text{x3}})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{N}(\text{R}^{\text{x3}})\text{S}(\text{O})_2\text{N}(\text{R}^{\text{x3a}})-$, $-\text{S}-$, $-\text{N}(\text{R}^{\text{x3}})-$, $-\text{OC}(\text{OR}^{\text{x3}})(\text{R}^{\text{x3a}})-$, $-\text{N}(\text{R}^{\text{x3}})\text{C}(\text{O})\text{N}(\text{R}^{\text{x3a}})-$, and $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{x3}})-$;

each $-\text{R}^{\text{x1}}$, $-\text{R}^{\text{x1a}}$, $-\text{R}^{\text{x1b}}$, $-\text{R}^{\text{x2}}$, $-\text{R}^{\text{x3}}$, $-\text{R}^{\text{x3a}}$ is independently selected from the group consisting of $-\text{H}$, 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 $-\text{R}^{\text{x2}}$, which are the same or different.

In certain embodiments a maximum of 6 $-\text{H}$ atoms of an optionally substituted molecule are independently replaced by a substituent, e.g. 5 $-\text{H}$ atoms are independently replaced by a substituent, 4 $-\text{H}$ atoms are independently replaced by a substituent, 3 $-\text{H}$ atoms are independently replaced by a substituent, 2 $-\text{H}$ atoms are independently replaced by a substituent, or 1 $-\text{H}$ 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, in certain embodiments between a carbon and a hydrogen atom.

As used herein, the term “ C_{1-4} 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 C_{1-4} 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 C_{1-4} alkyl, then examples for such C_{1-4} alkyl groups are $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{C}_2\text{H}_5)-$, $-\text{C}(\text{CH}_3)_2-$. Each hydrogen of a C_{1-4} alkyl carbon may optionally be replaced by a substituent as defined above. Optionally, a C_{1-4} 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.

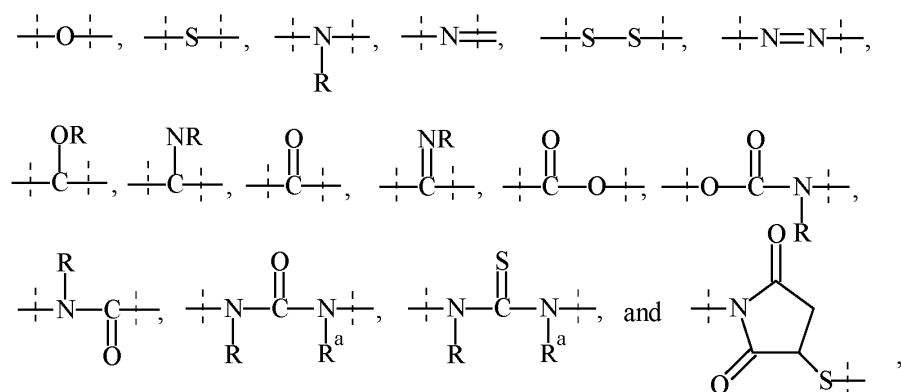
As used herein, the term “C₂₋₆ alkenyl” alone or in combination means a straight-chain or branched hydrocarbon moiety comprising at least one carbon-carbon double bond having 2 to 6 carbon atoms. If present at the end of a molecule, examples are -CH=CH₂, -CH=CH-CH₃, -CH₂-CH=CH₂, -CH=CHCH₂-CH₃ and -CH=CH-CH=CH₂. When two moieties of a molecule are linked by the C₂₋₆ alkenyl group, then an example for such C₂₋₆ alkenyl is -CH=CH-. Each hydrogen atom of a C₂₋₆ alkenyl moiety may optionally be replaced by a substituent as defined above. Optionally, a C₂₋₆ alkenyl may be interrupted by one or more moieties as defined below.

Accordingly, the term “C₂₋₁₀ alkenyl”, “C₂₋₂₀ alkenyl” or “C₂₋₅₀ 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 C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl or C₂₋₅₀ alkenyl group may optionally be replaced by a substituent as defined above. Optionally, a C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl or C₂₋₅₀ alkenyl may be interrupted by one or more moieties as defined below.

As used herein, the term “C₂₋₆ 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 -C≡CH, -CH₂-C≡CH, CH₂-CH₂-C≡CH and CH₂-C≡C-CH₃. When two moieties of a molecule are linked by the alkynyl group, then an example is -C≡C-. Each hydrogen atom of a C₂₋₆ alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C₂₋₆ alkynyl may be interrupted by one or more moieties as defined below.

Accordingly, as used herein, the term “C₂₋₁₀ alkynyl”, “C₂₋₂₀ alkynyl” and “C₂₋₅₀ 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 C₂₋₁₀ alkynyl, C₂₋₂₀ alkynyl or C₂₋₅₀ alkynyl group may optionally be replaced by a substituent as defined above. Optionally, one or more double bond(s) may occur. Optionally, a C₂₋₁₀ alkynyl, C₂₋₂₀ alkynyl or C₂₋₅₀ alkynyl may be interrupted by one or more moieties as defined below.

As mentioned above, a C₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₁₀ alkyl, C₁₋₂₀ alkyl, C₁₋₅₀ alkyl, C₂₋₆ alkenyl, C₂₋₁₀ alkenyl, C₂₋₂₀ alkenyl, C₂₋₅₀ alkenyl, C₂₋₆ alkynyl, C₂₋₁₀ alkynyl, C₂₋₂₀ alkynyl or C₂₋₅₀ alkynyl may optionally be interrupted by one or more moieties which in certain embodiments are selected from the group consisting of



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, 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.

As used herein, the term "C₃₋₁₀ cycloalkyl" means a cyclic alkyl chain having 3 to 10 carbon 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.

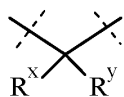
The term "8- to 30-membered carbopolycyclyl" or "8- to 30-membered carbopolycycle" means a cyclic moiety of two or more rings with 8 to 30 ring atoms, where two neighboring rings share at least one ring atom and that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring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

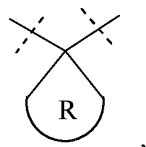
As used herein, the term "8- to 11-membered heterobicycyl" or "8- to 11-membered heterobicycle" means a heterocyclic moiety of two rings with 8 to 11 ring atoms, where at least one ring atom is shared by both rings and that may contain up to the maximum number of double bonds (aromatic or non-aromatic 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 heteropolycycyl" or "8- to 30-membered heteropolycycle" means a heterocyclic moiety of more than two rings with 8 to 30 ring atoms, in certain embodiments 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)- and -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 heterocycyl" in relation with a moiety of the structure

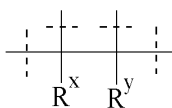


means that R^x and R^y form the following structure:

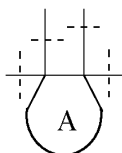


wherein R is C₃₋₁₀ cycloalkyl or 3- to 10-membered heterocyclyl.

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. In certain embodiments halogen is fluoro or chloro.

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

In certain embodiments the PTH compound is used in the treatment of a subject having CKD.

In certain embodiments the PTH compound is used in the prevention of CKD in a subject at risk of developing CKD.

In certain embodiments the subject at risk of developing CKD or having CKD is a mammalian subject, such as a human subject, such as an adult or pediatric subject. In certain embodiments the subject is a male human subject. In certain embodiments the subject is a female human subject. In certain embodiments the subject having CKD has hypoparathyroidism, such as chronic hypoparathyroidism. Chronic hypoparathyroidism may be due to surgery, a genetic cause, immune system-related damage of the parathyroid glands or the hypoparathyroidism

may be idiopathic. In certain embodiments the subject has chronic hypoparathyroidism due to surgery. In certain embodiments the subject has chronic hypoparathyroidism due to thyroid surgery. In certain embodiments the subject has chronic hypoparathyroidism due to parathyroid gland surgery. In certain embodiments the subject has chronic hypoparathyroidism due to a genetic cause. In certain embodiments the subject has chronic hypoparathyroidism due to autosomal dominant hypocalcemia type I. In certain embodiments the subject has chronic hypoparathyroidism due to immune-related damage of the parathyroid glands. In certain embodiments the subject has idiopathic chronic hypoparathyroidism.

In certain embodiments the subject is controlled on conventional therapy, i.e., active vitamin D and calcium supplement, prior to initiating treatment with the PTH compound. Such conventional therapy is typically administered orally.

In certain embodiments the kidney function of a subject at risk of developing CKD or having CKD is assessed by blood and/or urine test at least once prior to administration of a pharmaceutically effective dose of the PTH compound.

In certain embodiments the kidney function of the subject at risk of CKD or having CKD is assessed at least twice, once as a baseline before the first administration of the PTH compound and once after administration of one or more doses of the PTH compound. Suitably, the second assessment is done after a plurality of doses, such as after at least two weeks, at least four weeks or at least two months of treatment. The second assessment may be after two weeks of treatment, after four weeks of treatment, after six weeks of treatment, after eight weeks of treatment, after three months of treatment, after four months of treatment, after five months of treatment, after six months of treatment, after seven months of treatment, after eight months of treatment, after nine months of treatment, after ten months of treatment, after eleven months of treatment or after one year of treatment.

Suitable blood and urine tests are known in the art. An exemplary blood test to assess CKD is a serum creatinine blood test measuring the amount of creatinine in blood. A suitable urine test to assess chronic kidney disease is for example the urine albumin-to-creatinine ratio (UACR).

Blood and/or urine tests may also be used to determine the estimated glomerular filtration rate (eGFR). Suitable methods to determine the eGFR are known in the art, such as for example the Modification of Diet in Renal Disease (MDRD) formula, either in the form of the 4-variable MDRD formula based on serum creatinine, age, ethnicity and gender or in the form of the original MDRD formula, which in addition includes blood urea nitrogen and albumin levels. Depending on the degree of renal impairment the subject may be classified in any of stage 1 (normal), stage 2 (mild), stage 3 (moderate), stage 4 (severe) or stage 5 (end stage renal disease) according to the following classification based on eGFR:

CKD Stage	Description	eGFR (ml/min/1.73 m ²)
1	Normal GFR	≥ 90
2	Mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	End stage renal disease (ESRD)	< 15

The blood and/or urine test may comprise (i) determining a specific parameter in a sample of the subject's blood and/or urine, respectively, such as determining the creatinine in blood or determining the albumin-to-creatinine ratio in urine, and (ii) comparing this parameter with a reference. If the reference indicates that the person is at risk of developing CKD or has CKD, treatment with the PTH compound may be initiated.

In certain embodiments the eGFR is indicative of CKD.

In certain embodiments the subject has an eGFR indicative of stage 3 or worse, i.e., has an eGFR of less than 60 ml/min/1.73 m².

In certain embodiments the subject at risk of developing CKD has an eGFR indicative of stage 1 or stage 2 at the initiation of the treatment with the PTH compound, i.e., has a normal eGFR or an eGFR that is mildly decreased, and does not progress to stage 3 for at least 1 year while treated with the PTH compound, for at least 2 years while treated with the PTH compound, for at least 3 years while treated with the PTH compound, for at least 4 years while treated with the PTH compound, for at least 5 years while treated with the PTH compound, for at least 10 years while treated with the PTH compound, for at least 15 years while treated with the PTH compound or at least until the end of the treatment with the PTH compound.

In certain embodiments the subject having CKD has an eGFR indicative of stage 3 at the initiation of the treatment with the PTH compound, i.e., has a moderate decrease in eGFR, and does not progress to stage 4 for at least 1 year while treated with the PTH compound, for at least 2 years while treated with the PTH compound, for at least 3 years while treated with the PTH compound, for at least 4 years while treated with the PTH compound, for at least 5 years while treated with the PTH compound, for at least 10 years while treated with the PTH compound, for at least 15 years while treated with the PTH compound or at least until the end of the treatment with the PTH compound.

In certain embodiments the subject having CKD has an eGFR indicative of stage 4 at the initiation of the treatment with the PTH compound, i.e., has a severe decrease in eGFR, and does not progress to stage 5 for at least 1 year while treated with the PTH compound, for at least 2 years while treated with the PTH compound, for at least 3 years while treated with the PTH compound, for at least 4 years while treated with the PTH compound, for at least 5 years while treated with the PTH compound, for at least 10 years while treated with the PTH compound, for at least 15 years while treated with the PTH compound or at least until the end of the treatment with the PTH compound.

In certain embodiments the treatment with the PTH compound prevents progression to the next higher CKD Stage in a patient having CKD, i.e., progression from stage 3 to stage 4 or progression from stage 4 to stage 5, for at least 2 years, for at least 3 years, for at least 4 years, for at least 5 years, for at least 10 years, for at least 15 years or at least until the end of the treatment with the PTH compound.

In certain embodiments the subject has hypoparathyroidism, such as chronic hypoparathyroidism.

In certain embodiments treatment with the PTH compound slows CKD stage progression compared to treatment with the standard of care, i.e., oral calcium and activated vitamin D, or treatment with PTH 1-84, for example by a factor of 2, by factor of 3, by a factor of 4, by a factor of 6, by a factor of 7, by a factor of 8, by a factor of 9 or by a factor of 10, in particular in subjects having hypoparathyroidism, such as chronic hypoparathyroidism. In certain

embodiments treatment with the PTH compound prevents progression to end stage kidney disease, in particular in subjects having hypoparathyroidism, such as chronic hypoparathyroidism.

Treatment with the PTH compound improves a subject's eGFR. In certain embodiments treatment with the PTH compound results in a mean improvement of the eGFR of at least 5 ml/min/1.73 m², of at least 6 ml/min/1.73 m², of at least 7 ml/min/1.73 m², of at least 8 ml/min/1.73 m², of at least 9 ml/min/1.73 m², of at least 10 ml/min/1.73 m² or of at least 11 ml/min/1.73 m². In certain embodiments such mean improvement of the eGFR is achieved within 26 weeks of treatment with the PTH compound. In certain embodiments the mean improvement is achieved with 52 weeks of treatment. In certain embodiments the mean improvement can be measured after at least 110 weeks of treatment with the PTH compound. In certain embodiments the increase in mean eGFR is sustained, meaning lasts for an extended period of time, such as for six months, one year, two years, three years, five years, ten years, for as long as the treatment with the PTH compound lasts or until the end of the subject's life.

In certain embodiments the increase in mean eGFR is numerically higher in subjects with a baseline eGFR <60 mL/min/1.73 m² than in subjects with a baseline eGFR of ≥60 mL/min/1.73 m². Accordingly, in certain embodiments the subject having CKD is a subject having an eGFR of <60 mL/min/1.73 m², i.e. the subject to be treated with the PTH compound has an eGFR indicative of stage 3, 4 or 5.

It was surprisingly found that especially subjects with an eGFR of less than 60 ml/min/1.73 m² benefitted from the treatment with the PTH compound by showing a particularly high increase in eGFR.

In certain embodiments treatment with the PTH compound reduces or eliminates the occurrence of nephrolithiasis. In certain embodiments treatment with the PTH compound reduces or eliminates the occurrence of renal calcification.

In certain embodiments a patient treated with the PTH compound does not require administration of active vitamin D. In certain embodiments a patient treated with the PTH compound is independent from conventional therapy, which is active vitamin D and ≤600

mg/day of calcium). In certain embodiments a patient treated with the PTH compound maintains normocalcemia. In certain embodiments a patient treated with the PTH compound regains normocalcemia.

In certain embodiments the PTH compound is administered multiple times. Treatment may start upon diagnosis of CKD, or in the case of a subject with hypoparathyroidism upon diagnosis of hypoparathyroidism. Administration of the PTH compound may for example be daily or weekly. Treatment may proceed for six months, one year, two years, three years, five years, ten years, until medically indicated or until the end of the subject's life.

The PTH compound may be administered to the subject daily. The PTH compound may be administered to the subject weekly.

In certain embodiments a single dose of the PTH compound results in an at least 10 times longer receptor signaling compared to a single equimolar dose of PTH 1-84, an at least 15 times longer receptor signaling compared to a single equimolar dose of PTH 1-84 or an at least 20 times longer receptor signaling compared to a single equimolar dose of PTH 1-84. Such PTH compound may or may not have an extended circulation half-life in blood. An extended circulation half-life would be a circulation half-life in blood that is at least 10 times longer than the circulation half-life of PTH 1-84 in blood, in each case measured after a single administration, in which the dose of the PTH compound and of PTH 1-84 are equimolar (with regards to the PTH).

In certain embodiments the PTH compound is a peptide. In certain embodiments the PTH compound is a peptide of SEQ ID NO:122, which is also known as AZP-3601 or eneboparatide: AVAEIQLMHQRAKWIQDARRRAFLHKLIAEIHTAEI

In certain embodiments PTH compound is a water-insoluble compound, which in certain embodiments is selected from the group of crystals, nanoparticles, microparticles, nanospheres and microspheres. One or more PTH drugs may be non-covalently embedded in such crystals, nanoparticles, microparticles, nanospheres and microspheres or may be covalently conjugated to such crystals, nanoparticles, microparticles, nanospheres and microspheres. Covalent conjugation may either be a stable conjugation, i.e., may be a conjugation via a stable bond, or

may be a reversible conjugation, i.e., may be a conjugation via a reversible bond to such crystals, nanoparticles, microparticles, nanospheres and microspheres.

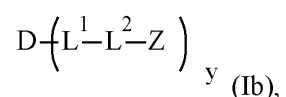
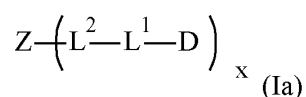
In certain embodiments the PTH compound is a crystal comprising at least one PTH molecule. In certain embodiments the PTH compound is a nanoparticle comprising at least one PTH molecule. In certain embodiments the PTH compound is a microparticle comprising at least one PTH molecule. In certain embodiments the PTH compound is a nanosphere comprising at least one PTH compound. In certain embodiments PTH compound is a microsphere comprising at least one PTH compound. In certain embodiments the compound is a vesicle comprising at least one PTH compound, such as a micelle, liposome or polymersome.

In certain embodiments the PTH compound is a water-insoluble PTH compound comprising at least one PTH molecule non-covalently embedded in a water-insoluble polymer. In certain embodiments 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 certain embodiments the water-insoluble polymer is poly(lactic-co-glycolic acid) (PLGA).

In certain embodiments the PTH compound is a conjugate or its pharmaceutically acceptable salt comprising a carrier moiety Z' to which one or more moieties $-L^2-L^1-D$ are conjugated, wherein each $-L^2-$ is independently either absent or a spacer moiety; each $-L^1-$ is independently a linker moiety to which $-D$ is reversibly and covalently conjugated; each $-D$ is independently a PTH moiety; and Z' is a hydrogel. Such long-acting PTH compound is a sustained-release PTH compound. Specific embodiments for $-D$, $-L^1-$, $-L^2-$ and Z' are as described elsewhere herein.

In certain embodiments the PTH compound is water-soluble.

In certain embodiments the PTH compound is of formula (Ia) or (Ib)



wherein

each $-D$ is individually a PTH moiety;

each $-L^1-$ is individually a linker moiety covalently and reversibly connected to $-D$;

each $-L^2-$ is individually absent or a spacer moiety;

each $-Z$ is individually a carrier moiety, such as a fatty acid derivate or a polymer;

x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25; and

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

In certain embodiments the PTH compound is of formula (Ia). In certain embodiments the PTH compound is of formula (Ia) and x is selected from the group consisting of 1, 2, 3 and 4. In certain embodiments the PTH compound is of formula (Ia) and x is 1.

In certain embodiments the PTH compound is of formula (Ib). In certain embodiments the PTH compound is of formula (Ib) and y is selected from the group consisting of 2, 3 and 4.

Embodiments for $-D$, $-L^1-$, $-L^2-$ and $-Z$ are as described elsewhere herein.

In certain embodiments -D is a PTH moiety comprising a sequence with at least 90% homology, such as with at least 91% homology, at least 92% homology, at least 93% homology, at least 94% homology, at least 95% homology, at least 96% homology, at least 97% homology, at least 98% homology or at least 99% homology, to 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, SEQ ID NO:121 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at least 95% homology to 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, SEQ ID NO:121 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising 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, SEQ ID NO:121 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at least 90% homology, such as with at least 91% homology, at least 92% homology, at least 93% homology, at least 94% homology, at least 95% homology, at least 96% homology, at least 97% homology, at least 98% homology or at least 99% homology, to a sequence selected from the group consisting of 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: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:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at 95% homology to a sequence selected from the group consisting of 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: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:122.

In certain embodiments -D is selected from the group consisting of 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: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:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at least 90% homology, such as with at least 91% homology, at least 92% homology, at least 93% homology, at least 94% homology, at least 95% homology, at least 96% homology, at least 97% homology, at least 98% homology or at least 99% homology, to 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, SEQ ID NO:115 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at 95% homology to a sequence selected from the group consisting 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, SEQ ID NO:115 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising 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, SEQ ID NO:115 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at least 90% homology, such as with at least 91% homology, at least 92% homology, at least 93% homology, at least 94% homology, at least 95% homology, at least 96% homology, at least 97% homology, at least 98% homology or at least 99% homology, to a sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112 and SEQ ID NO:122.

In certain embodiments -D is a PTH moiety comprising a sequence with at 95% homology to a sequence selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112 and SEQ ID NO:122.

In certain embodiments -D is selected from the group consisting of SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112 and SEQ ID NO:122.

In certain embodiments -D is of SEQ ID NO:50. In certain embodiments -D is of SEQ ID NO:52. In certain embodiments -D is of SEQ ID NO:110. In certain embodiments -D is of SEQ ID NO:111. In certain embodiments -D is of SEQ ID NO:112. In certain embodiments -D is of SEQ ID NO:111. In certain embodiments -D is of SEQ ID NO:122.

In certain embodiments -D is of SEQ ID NO:51.

In certain embodiments -D is of SEQ ID NO:122:

AVAEIQLMHQRAKWIQDARR RAFLHKLIAEIHTAEI

A 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, 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.

In certain embodiments -L¹- is conjugated to -D via a functional group selected from the group consisting of carboxylic acid, primary amine, 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. In certain embodiments -L¹- is conjugated to -D via a functional group selected from the group consisting of hydroxyl, primary amine, secondary amine and guanidine. In certain embodiments -L¹- is conjugated to -D via a primary or secondary amine functional group. In certain embodiments -L¹- is conjugated to -D via a primary amine functional group. It is understood that not every functional group may be present in proteinogenic amino acids and that it may only be introduced via one or more post-translational modifications or may originate from a non-proteinogenic amino acid.

In certain embodiments -L¹- is conjugated to a functional group of the side chain of a proteinogenic amino acid residue of -D. In certain embodiments said proteinogenic amino acid is selected from the group consisting of histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid, glutamic acid and arginine. In certain embodiments said proteinogenic amino acid is selected from the group consisting of lysine, aspartic acid, arginine and serine. In certain embodiments said proteinogenic amino acid is selected from the group consisting of lysine, arginine and serine. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a histidine of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a lysine of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a tryptophan of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a serine of -D. In certain embodiments -L¹- is conjugated

to a functional group of the side chain of a threonine of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a tyrosine of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of an aspartic acid of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of a glutamic acid of -D. In certain embodiments -L¹- is conjugated to a functional group of the side chain of an arginine of -D. It is understood that not every moiety -D may comprise all of these amino acid residues.

In certain embodiments -L¹- is conjugated to the N-terminal amine functional group of -D, 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 -L¹- is conjugated. In certain embodiments -L¹- is directly conjugated to the N-terminal amine functional group of -D. In certain embodiments -L¹- is conjugated to the C-terminal functional group of -D, 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 -L¹- is conjugated. In certain embodiments -L¹- is directly conjugated to the N-terminal amine functional group of -D.

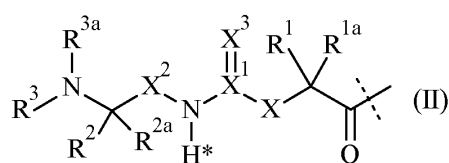
The moiety -L¹- can be connected to -D through any type of linkage, provided that it is reversible. In certain embodiments -L¹- is connected to -D through a linkage selected from the group consisting of amide, ester, carbamate, acetal, aminal, imine, oxime, hydrazone, disulfide and acylguanidine. In certain embodiments -L¹- is connected to -D through a linkage selected from the group consisting of amide, ester, carbamate and acylguanidine. It is understood that some of these linkages are not reversible *per se*, but that in the present invention neighboring groups comprised in -L¹- render these linkages reversible. In certain embodiments -L¹- is connected to -D through an ester linkage. In certain embodiments -L¹- is connected to -D through a carbamate linkage. In certain embodiments -L¹- is connected to -D through an acylguanidine. In certain embodiments -L¹- is connected to -D through an amide linkage.

The moiety -L¹- 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 in their entirety herewith.

In certain embodiments $-L^1-$ 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 in their entirety herewith.

In certain embodiments $-L^1-$ is disclosed in WO 2009/095479 A2. Accordingly, in certain embodiments the moiety $-L^1-$ is of formula (II):



wherein the dashed line indicates 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 $-R^{1a}/-R^{4a}$, $-R^{1a}/-R^{5a}$, $-R^{1a}/-R^{7a}$, $-R^{4a}/-R^{5a}$, 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 $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^{7a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^8/-R^9$, 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;

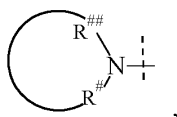
A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicycyl; and

wherein $-L^1-$ is substituted with at least one $-L^2-Z$ 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.

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

In certain embodiments $-L^1-$ 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

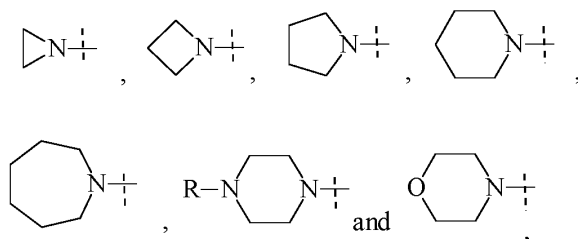
the dashed line indicates attachment to the rest of $-L^1-$;

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:

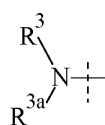


wherein

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.

$-L^1$ 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



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 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 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 $-L^2-Z'$. In certain embodiments $-R^3$ of formula (II) is substituted with $-L^2-Z$ or $-L^2-Z'$.

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

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

In certain embodiments $-R^{7a}$ of formula (II) is selected from -H, methyl and ethyl. In certain embodiments $-R^{7a}$ of formula (II) is -H.

In certain embodiments $-R^{10}$ is selected from -H, methyl and ethyl. In certain embodiments $-R^{10}$ is methyl.

In certain embodiments $-R^{11}$ is selected from -H, methyl and ethyl. In certain embodiments $-R^{11}$ is -H. In certain embodiments $-R^{11}$ is substituted with $-L^2-Z$ or $-L^2-Z'$.

In certain embodiments -X- of formula (II) is $-N(R^4)-$.

In certain embodiments $-R^4$ is selected from the group consisting of -H, methyl and ethyl. In certain embodiments $-R^4$ is -H.

In certain embodiments X^1 of formula (II) is C.

In certain embodiments $=X^3$ of formula (II) is =O.

In certain embodiments $-X^2-$ of formula (II) is $-C(R^8R^{8a})-$.

In certain embodiments $-R^8$ and $-R^{8a}$ of formula (II) are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of $-R^8$ and $-R^{8a}$ of formula (II) is -H. In certain embodiments both $-R^8$ and $-R^{8a}$ of formula (II) are -H.

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

In certain embodiments at least one of $-R^1$ and $-R^{1a}$ of formula (II) is $-H$. In certain embodiments $-R^1$ and $-R^{1a}$ of formula (II) are $-H$.

In certain embodiments at least one of $-R^1$ and $-R^{1a}$ of formula (II) is methyl. In certain embodiments both $-R^1$ and $-R^{1a}$ of formula (II) are methyl.

In certain embodiments $-R^2$ and $-R^{2a}$ of formula (II) are independently selected from the group consisting of $-H$, methyl and ethyl. In certain embodiments at least one of $-R^2$ and $-R^{2a}$ of formula (II) is $-H$. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (II) are H .

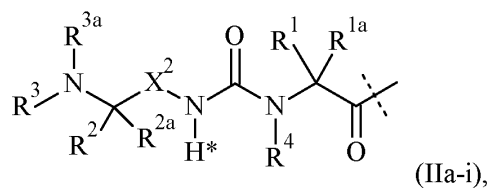
In certain embodiments $-R^3$ and $-R^{3a}$ of formula (II) are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl.

In certain embodiments at least one of $-R^3$ and $-R^{3a}$ of formula (II) is methyl. In certain embodiments $-R^3$ of formula (II) is methyl and $-R^{3a}$ of formula (II) is $-H$.

In certain embodiments $-R^3$ and $-R^{3a}$ of formula (II) are both $-H$.

In certain embodiments $-D$ is connected to $-L^1$ of formula (II) through a nitrogen by forming an amide bond.

In certain embodiments the moiety $-L^1$ is of formula (IIa-i)



wherein

the dashed line indicates attachment to a nitrogen of $-D$ through an amide bond;

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

wherein $-L^1$ is substituted with at least one $-L^2-Z$ 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.

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.

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

In certain embodiments the moiety $-L^1$ - of formula (IIa-i) is not further substituted.

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

In certain embodiments $-R^4$ of formula (IIa-i) is selected from the group consisting of $-H$, methyl and ethyl. In certain embodiments $-R^4$ of formula (IIa-i) is $-H$.

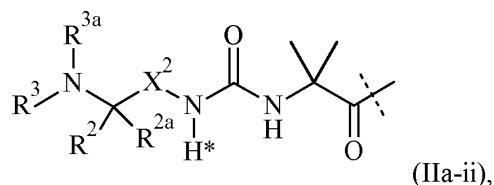
In certain embodiments $-X^2$ - of formula (IIa-i) is $-C(R^8R^{8a})$ -.

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

In certain embodiments $-R^2$ and $-R^{2a}$ of formula (IIa-i) are independently selected from the group consisting of $-H$, methyl and ethyl. In certain embodiments at least one of $-R^2$ and $-R^{2a}$ of formula (IIa-i) is $-H$. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (IIa-i) are H .

In certain embodiments $-R^3$ and $-R^{3a}$ of formula (IIa-i) are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. In certain embodiments at least one of $-R^3$ and $-R^{3a}$ of formula (IIa-i) is $-H$. In certain embodiments both $-R^3$ and $-R^{3a}$ of formula (IIa-i) are $-H$.

In certain embodiments the moiety $-L^1$ - is of formula (IIa-ii):



wherein the dashed line indicates attachment to a nitrogen of -D through an amide bond; -R², -R^{2a}, -R³, -R^{3a} and -X²- are used as defined in formula (II); and wherein -L¹- is substituted with at least one -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIa-ii) 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 (IIa-ii) or both are other than -H they are connected to N to which they are attached through an sp³-hybridized carbon atom.

In certain embodiments -L¹- of formula (IIa-ii) is substituted with one moiety -L²-Z or -L²-Z'.

In certain embodiments the moiety -L¹- of formula (IIa-ii) is not further substituted.

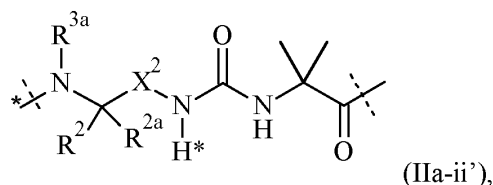
In certain embodiments -X²- of formula (IIa-ii) is -C(R⁸R^{8a})-.

In certain embodiments -R⁸ and -R^{8a} of formula (IIa-ii) are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R⁸ and -R^{8a} of formula (IIa-ii) is -H. In certain embodiments both -R⁸ and -R^{8a} of formula (IIa-ii) are -H.

In certain embodiments -R² and -R^{2a} of formula (IIa-ii) are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R² and -R^{2a} of formula (IIa-ii) is -H. In certain embodiments both -R² and -R^{2a} of formula (IIa-ii) are H.

In certain embodiments -R³ and -R^{3a} of formula (IIa-ii) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. In certain embodiments at least one of -R³ and -R^{3a} of formula (IIa-ii) is -H. In certain embodiments both -R³ and -R^{3a} of formula (IIa-ii) are -H.

In certain embodiments the moiety -L¹- is of formula (IIa-ii'):



wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond;

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

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

wherein $-L^1$ 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 $-R^{3a}$ of formula (IIa-ii') is other than -H it is connected to N to which it is attached through an sp^3 -hybridized carbon atom.

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

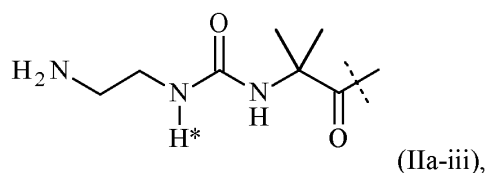
In certain embodiments $-X^2$ of formula (IIa-ii') is $-C(R^8R^{8a})$.

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

In certain embodiments $-R^2$ and $-R^{2a}$ of formula (IIa-ii') are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of $-R^2$ and $-R^{2a}$ of formula (IIa-ii') is -H. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (IIa-ii') are H.

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

In certain embodiments the moiety $-L^1$ is of formula (IIa-iii):



wherein

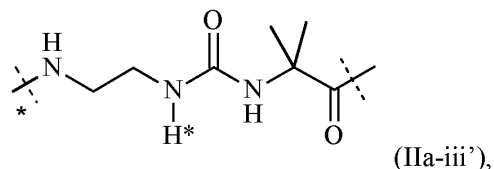
the dashed line indicates attachment to a nitrogen of -D through an amide bond; and wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIa-iii) is not replaced by $-L^2-Z$ 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.

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

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

In certain embodiments the moiety $-L^1-$ is of formula (IIa-iii'):



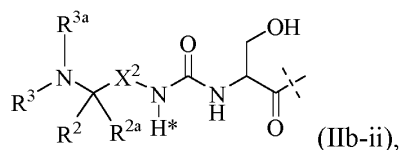
wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond; the dashed line marked with the asterisk indicates attachment to $-L^2-$; and 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 the nitrogen adjacent to the dashed line marked with the asterisk in formula (IIa-iii') is attached to $-L^2-$ through an sp^3 -hybridized carbon atom.

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

In certain embodiments the moiety $-L^1-$ is of formula (IIb-ii):



wherein the dashed line indicates attachment to a nitrogen of $-D$ through 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 at least one $-L^2-Z$ 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.

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

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

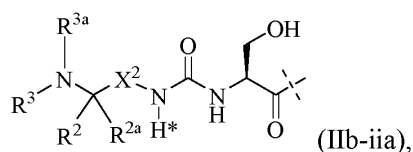
In certain embodiments $-X^2-$ of formula (IIb-ii) is $-C(R^8R^{8a})-$.

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

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

In certain embodiments $-R^3$ and $-R^{3a}$ of formula (IIb-ii) are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. In certain embodiments at least one of $-R^3$ and $-R^{3a}$ of formula (IIb-ii) is $-H$. In certain embodiments both $-R^3$ and $-R^{3a}$ of formula (IIb-ii) are $-H$.

In certain embodiments the moiety $-L^1-$ is of formula (IIb-iii):



wherein the dashed line indicates attachment to a nitrogen of -D through 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 at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIa-iiia) 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-iiia) or both are other than -H they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

In certain embodiments $-L^1$ of formula (IIb-iiia) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In certain embodiments the moiety $-L^1$ of formula (IIb-iiia) is not further substituted.

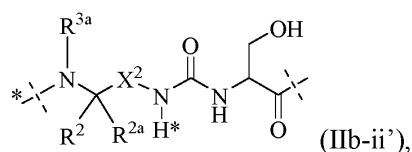
In certain embodiments $-X^2$ of formula (IIb-iiia) is $-C(R^8R^{8a})$.

In certain embodiments $-R^8$ and $-R^{8a}$ of formula (IIb-iiia) are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of $-R^8$ and $-R^{8a}$ of formula (IIb-iiia) is -H. In certain embodiments both $-R^8$ and $-R^{8a}$ of formula (IIb-iiia) are -H.

In certain embodiments $-R^2$ and $-R^{2a}$ of formula (IIb-iiia) are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of $-R^2$ and $-R^{2a}$ of formula (IIb-iiia) is -H. In certain embodiments both $-R^2$ and $-R^{2a}$ of formula (IIb-iiia) are H.

In certain embodiments $-R^3$ and $-R^{3a}$ of formula (IIb-iiia) are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. In certain embodiments at least one of $-R^3$ and $-R^{3a}$ of formula (IIb-iiia) is -H. In certain embodiments both $-R^3$ and $-R^{3a}$ of formula (IIb-iiia) are -H.

In certain embodiments the moiety $-L^1$ is of formula (IIb-ii'):



wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond;

the dashed line marked with the asterisk indicates attachment to -L²-;

-R², -R^{2a}, -R^{3a} and -X²- are used as defined in formula (II); and

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

It is understood that in case -R^{3a} of formula (IIb-ii') is other than -H it is connected to N to which it is attached through an sp³-hybridized carbon atom.

In certain embodiments the moiety -L¹- of formula (IIb-ii') is not further substituted.

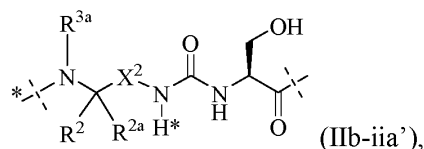
In certain embodiments -X²- of formula (IIb-ii') is -C(R⁸R^{8a})-.

In certain embodiments -R⁸ and -R^{8a} of formula (IIb-ii') are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R⁸ and -R^{8a} of formula (IIb-ii') is -H. In certain embodiments both -R⁸ and -R^{8a} of formula (IIb-ii') are -H.

In certain embodiments -R² and -R^{2a} of formula (IIb-ii') are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R² and -R^{2a} of formula (IIb-ii') is -H. In certain embodiments both -R² and -R^{2a} of formula (IIb-ii') are H.

In certain embodiments -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.

In certain embodiments the moiety -L¹- is of formula (IIb-iii'):



wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond;

the dashed line marked with the asterisk indicates attachment to -L²-;

-R², -R^{2a}, -R^{3a} and -X²- are used as defined in formula (II); and

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

It is understood that in case -R^{3a} of formula (IIb-iiia') is other than -H it is connected to N to which it is attached through an sp³-hybridized carbon atom.

In certain embodiments the moiety -L¹- of formula (IIb-iiia') is not further substituted.

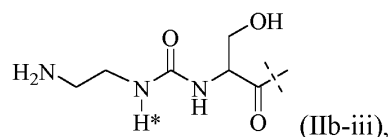
In certain embodiments -X²- of formula (IIb-iiia') is -C(R⁸R^{8a})-.

In certain embodiments -R⁸ and -R^{8a} of formula (IIb-iiia') are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R⁸ and -R^{8a} of formula (IIb-iiia') is -H. In certain embodiments both -R⁸ and -R^{8a} of formula (IIb-iiia') are -H.

In certain embodiments -R² and -R^{2a} of formula (IIb-iiia') are independently selected from the group consisting of -H, methyl and ethyl. In certain embodiments at least one of -R² and -R^{2a} of formula (IIb-iiia') is -H. In certain embodiments both -R² and -R^{2a} of formula (IIb-iiia') are H.

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

In certain embodiments the moiety -L¹- is of formula (IIb-iii):



wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond; and

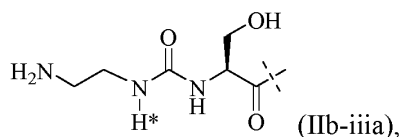
wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iii) is not replaced by $-L^2-Z$ or $-L^2-Z'$ or a substituent.

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.

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

In certain embodiments the moiety $-L^1-$ of formula (IIb-iii) is not further substituted.

In certain embodiments the moiety $-L^1-$ is of formula (IIb-iiiia):



wherein

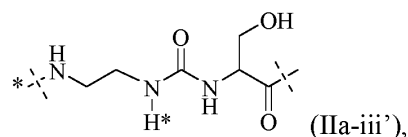
the dashed line indicates attachment to a nitrogen of $-D$ through an amide bond; and wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (IIb-iiiia) is not replaced 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-iiiia) or both are other than $-H$ they are connected to N to which they are attached through an sp^3 -hybridized carbon atom.

In certain embodiments $-L^1-$ of formula (IIb-iiiia) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In certain embodiments the moiety $-L^1-$ of formula (IIb-iiiia) is not further substituted.

In certain embodiments the moiety $-L^1-$ is of formula (IIa-iii'):



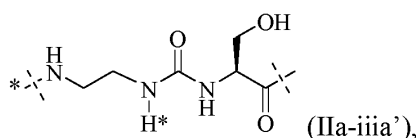
wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond;
 the dashed line marked with the asterisk indicates attachment to -L²-; and
 wherein -L¹- 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 the nitrogen adjacent to the dashed line marked with the asterisk in formula
 (IIa-iii') is attached to -L²- through an sp³-hybridized carbon atom.

In certain embodiments the moiety -L¹- of formula (IIa-iii') is not further substituted.

In certain embodiments the moiety -L¹- is of formula (IIb-iiia'):



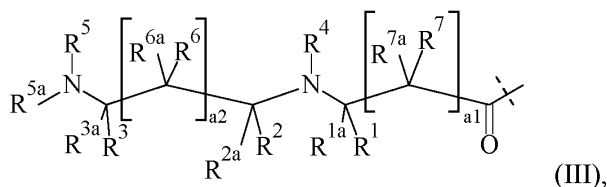
wherein

the dashed line indicates attachment to a nitrogen of -D through an amide bond;
 the dashed line marked with the asterisk indicates attachment to -L²-; and
 wherein -L¹- is optionally further substituted, provided that the hydrogen marked with
 the asterisk in formula (IIa-iiia') is not replaced by a substituent.

It is understood that the nitrogen adjacent to the dashed line marked with the asterisk in formula
 (IIa-iiia') is attached to -L²- through an sp³-hybridized carbon atom.

In certain embodiments the moiety -L¹- of formula (IIa-iiia') is not further substituted.

In certain embodiments -L¹- is disclosed in WO2016/020373A1. Accordingly, in certain
 embodiments the moiety -L¹- is of formula (III):



wherein

the dashed line indicates attachment to a primary or secondary amine or hydroxyl of -D through 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 $-T$;

a_1 and a_2 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 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 T is independently of each other 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 is independently optionally substituted with one or more $-R^{11}$, which are the same or different;

each $-R^{11}$ is independently of each other selected from halogen, $-\text{CN}$, oxo ($=\text{O}$), $-\text{COOR}^{13}$, $-\text{OR}^{13}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{N}(\text{R}^{13}\text{R}^{13a})$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{13}\text{R}^{13a})$, $-\text{S}(\text{O})\text{N}(\text{R}^{13}\text{R}^{13a})$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{N}(\text{R}^{13})\text{S}(\text{O})_2\text{N}(\text{R}^{13a}\text{R}^{13b})$, $-\text{SR}^{13}$, $-\text{N}(\text{R}^{13}\text{R}^{13a})$, $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{13}$, $-\text{N}(\text{R}^{13})\text{C}(\text{O})\text{R}^{13a}$, $-\text{N}(\text{R}^{13})\text{S}(\text{O})_2\text{R}^{13a}$, $-\text{N}(\text{R}^{13})\text{S}(\text{O})\text{R}^{13a}$, $-\text{N}(\text{R}^{13})\text{C}(\text{O})\text{OR}^{13a}$, $-\text{N}(\text{R}^{13})\text{C}(\text{O})\text{N}(\text{R}^{13a}\text{R}^{13b})$, $-\text{OC}(\text{O})\text{N}(\text{R}^{13}\text{R}^{13a})$, 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 $-R^{12}$, $-R^{12a}$, $-R^{13}$, $-R^{13a}$, and $-R^{13b}$ is independently selected from the group consisting of $-\text{H}$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

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

optionally, one or more of the pairs $-R^1/-R^2$, $-R^1/-R^3$, $-R^1/-R^4$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^7$, $-R^2/-R^3$, $-R^2/-R^4$, $-R^2/-R^5$, $-R^2/-R^6$, $-R^2/-R^7$, $-R^3/-R^4$, $-R^3/-R^5$, $-R^3/-R^6$, $-R^3/-R^7$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^4/-R^7$, $-R^5/-R^6$, $-R^5/-R^7$, and $-R^6/-R^7$ 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; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl;

wherein $-L^1-$ is substituted with at least one $-L^2-\text{Z}$ or $-L^2-\text{Z}'$ and wherein $-L^1-$ is optionally further substituted.

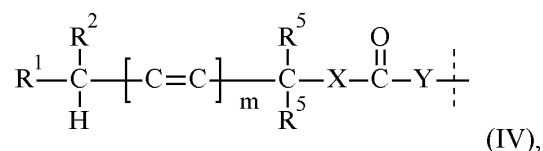
The optional further substituents of $-L^1-$ of formula (III) are in certain embodiments as described above.

In certain embodiments $-L^1-$ of formula (III) is substituted with one moiety $-L^2-\text{Z}$ or $-L^2-\text{Z}'$.

In certain embodiments $-L^1-$ of formula (III) is not further substituted.

In certain embodiments $-L^1-$ is as disclosed in EP1536334B1, WO2009/009712A1, WO2008/034122A1, WO2009/143412A2, WO2011/082368A2, and US8618124B2, which are herewith incorporated by reference in their entirety.

In certain embodiments -L¹- is as disclosed in US8946405B2 and US8754190B2, which are herewith incorporated by reference in their entirety. Accordingly, in certain embodiments -L¹- is of formula (IV):



wherein

the dashed line indicates attachment to -D and wherein 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 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;

-R³ is selected from the group consisting of -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR⁹ and -N(R⁹)₂;

-R⁴ is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each -R⁵ 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;

-R⁹ 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)CH₂- 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, -R¹ and -R² may be joined to form a 3 to 8-membered ring; and
optionally, both -R⁹ together with the nitrogen to which they are attached form a heterocyclic ring;
wherein -L¹- is substituted with at least one -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted.

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 certain 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.

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

The term “aryl” includes aromatic hydrocarbon groups of 6 to 18 carbons, such as 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, such as 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.

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.

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

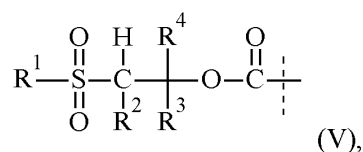
The term “heterocyclic ring” refers to a 4 to 8 membered aromatic or non-aromatic ring comprising 3 to 7 carbon atoms and at least one N, O, or S atom. Examples are piperidiny, piperaziny, tetrahydropyrany, pyrrolidine, and tetrahydrofurany, as well as the exemplary groups provided for the term “heteroaryl” 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, cyano, -OR, -SR, -NR₂, -OCOR, -NRCOR, -COOR, -CONR₂, -SOR, -SO₂R, -SONR₂, -SO₂NR₂, 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.

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

In certain embodiments -L¹- of formula (IV) is not further substituted.

In certain embodiments -L¹- is as disclosed in WO2013/036857A1, which is herewith incorporated by reference in its entirety. Accordingly, in certain embodiments -L¹- is of formula (V):



wherein

the dashed line indicates attachment to -D through an amine functional group of -D;

-R¹ is selected from the group consisting of optionally substituted C₁-C₆ linear, branched, or cyclic alkyl; optionally substituted aryl; optionally substituted heteroaryl; alkoxy; and -NR⁵₂;

-R² is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
-R³ is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
-R⁴ is selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl;
each -R⁵ is independently of each other selected from the group consisting of -H; optionally substituted C₁-C₆ alkyl; optionally substituted aryl; and optionally substituted heteroaryl; or when taken together two -R⁵ can be cycloalkyl or cycloheteroalkyl;
wherein -L¹- is substituted with at least one -L²-Z or -L²-Z' and wherein -L¹- is optionally further substituted.

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, such as 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, such as 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.

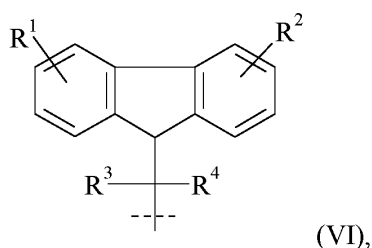
The term “substituted” means an alkyl, alkenyl, alkynyl, aryl, or heteroaryl group comprising one or more substituent groups in place of one or more hydrogen atoms. Substituents may generally be selected from halogen including F, Cl, Br, and I; lower alkyl including linear, branched, and cyclic; lower 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.

In certain embodiments $-L^1-$ of formula (V) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In certain embodiments $-L^1-$ of formula (V) is not further substituted.

In certain embodiments $-L^1-$ is as disclosed in US7585837B2, which is herewith incorporated by reference in its entirety. Accordingly, in certain embodiments $-L^1-$ is of formula (VI):



wherein

the dashed line indicates attachment to $-D$ through an amine functional group of $-D$;

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkoxyalkyl, aryl, alkaryl, aralkyl, halogen, nitro, $-SO_3H$, $-SO_2NHR^5$, amino, ammonium, carboxyl, PO_3H_2 , and OPO_3H_2 ;

R^3 , R^4 , and R^5 are independently selected from the group consisting of hydrogen, alkyl, and aryl;

wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted.

Suitable substituents for formulas (VI) are alkyl (such as C_{1-6} alkyl), alkenyl (such as C_{2-6} alkenyl), alkynyl (such as C_{2-6} alkynyl), aryl (such as phenyl), heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl (such as aromatic 4 to 7 membered heterocycle) or halogen moieties.

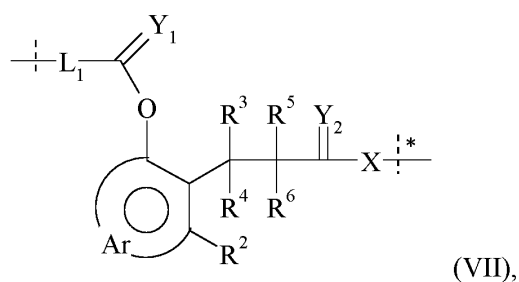
Only in the context of formula (VI) the terms used have the following meaning:

The terms “alkyl”, “alkoxy”, “alkoxyalkyl”, “aryl”, “alkaryl” and “aralkyl” mean alkyl radicals of 1-8, such as 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.

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

In certain embodiments -L¹- of formula (VI) is not further substituted.

A further preferred embodiment for -L¹- is disclosed in WO2002/089789A1, which is herewith incorporated by reference in its entirety. Accordingly, a preferred moiety -L¹- is of formula (VII):



wherein

the dashed line indicates attachment to -D through an amine functional group of -D;

L_1 is a bifunctional linking group,

Y_1 and Y_2 are independently O, S or NR⁷;

R², R³, R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of hydrogen, C₁₋₆ alkyls, C₃₋₁₂ branched alkyls, C₃₋₈ cycloalkyls, C₁₋₆ substituted alkyls, C₃₋₈ substituted cycloalkyls, aryls, substituted aryls, aralkyls, C₁₋₆ heteroalkyls, substituted C₁₋₆ heteroalkyls, C₁₋₆ alkoxy, phenoxy, and C₁₋₆ 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 at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted.

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.

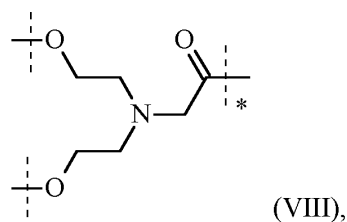
The term “substituted” shall be understood to include adding or replacing one or more atoms contained within a functional group or compounds with one or more different atoms.

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 toluyl; 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. Halo- shall be understood to include fluoro, chloro, iodo and bromo.

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

In certain embodiments $-L^1-$ of formula (VII) is not further substituted.

In certain embodiments $-L^1-$ comprises a substructure of formula (VIII)



wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D through an amide bond;

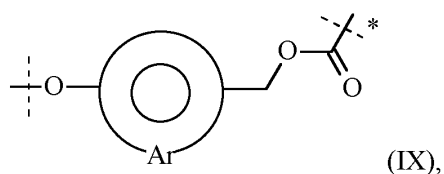
the unmarked dashed lines indicate attachment to the remainder of $-L^1-$; and

wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted.

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

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

In certain embodiments $-L^1-$ comprises a substructure of formula (IX)



wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of $-D$ through a carbamate bond;

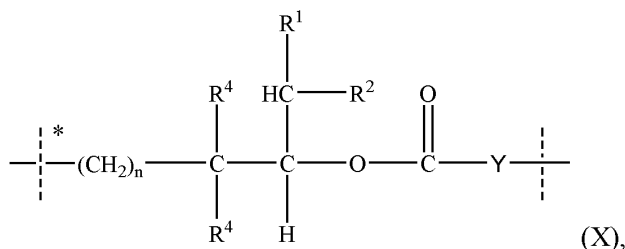
the unmarked dashed lines indicate attachment to the remainder of $-L^1-$; and

wherein $-L^1-$ is substituted with at least one $-L^2-Z$ or $-L^2-Z'$ and wherein $-L^1-$ is optionally further substituted.

In certain embodiments $-L^1-$ of formula (IX) is substituted with one moiety $-L^2-Z$ or $-L^2-Z'$.

In certain embodiments $-L^1-$ of formula (IX) is not further substituted.

In certain embodiments $-L^1-$ has a structure as disclosed in WO2020/206358 A1. Accordingly, in certain embodiments the moiety $-L^1-$ is of formula (X):



wherein

the unmarked dashed line indicates attachment to $-D$;

the dashed line marked with the asterisk indicates attachment to $-L^2-Z$ or $-L^2-Z'$;
n is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;
 $-R^1$ and $-R^2$ are independently an electron-withdrawing group, alkyl, or -H, and wherein at least one of $-R^1$ or $-R^2$ is an electron-withdrawing group;
each $-R^4$ is independently C_1-C_3 alkyl or the two $-R^4$ are taken together with the carbon atom to which they are attached to form a 3- to 6-membered ring; and
 $-Y-$ is absent when $-D$ is a drug moiety connected through an amine, or $-Y-$ is $-N(R^6)CH_2-$ when $-D$ is a drug moiety connected through a phenol, alcohol, thiol, thiophenol, imidazole, or non-basic amine; wherein $-R^6$ is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

In certain embodiments n of formula (X) is an integer selected from 1, 2, 3, 4, 5 and 6. In certain embodiments n of formula (X) is an integer selected from 1, 2 and 3. In certain embodiments n of formula (X) is an integer from 0, 1, 2 and 3. In certain embodiments n of formula (X) is 1. In certain embodiments n of formula (X) is 2. In certain embodiments n of formula (X) is 3.

In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is selected from the group consisting of -CN; $-NO_2$; optionally substituted aryl; optionally substituted heteroaryl; optionally substituted alkenyl; optionally substituted alkynyl; $-COR^3$, $-SOR^3$, or $-SO_2R^3$, wherein $-R^3$ is -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$ or $-NR^8_2$, wherein each $-R^8$ is independently -H or optionally substituted alkyl, or both $-R^8$ groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or $-SR^9$, wherein $-R^9$ is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is -CN. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is $-NO_2$. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is optionally substituted aryl comprising 6 to 10 carbons. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is optionally substituted phenyl, naphthyl, or anthracenyl. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula

(X) is optionally substituted heteroaryl comprising 3 to 7 carbons and comprising at least one N, O, or S atom. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is optionally substituted pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, or indenyl. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is optionally substituted alkenyl containing 2 to 20 carbon atoms. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is optionally substituted alkynyl comprising 2 to 20 carbon atoms. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is $-COR^3$, $-SOR^3$, or $-SO_2R^3$, wherein $-R^3$ is -H, optionally substituted alkyl comprising 1 to 20 carbon atoms, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$ or $-NR^8_2$, wherein each $-R^8$ is independently -H or optionally substituted alkyl comprising 1 to 20 carbon atoms, or both $-R^8$ groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring. In certain embodiments the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (X) is $-SR^9$, wherein $-R^9$ is optionally substituted alkyl comprising 1 to 20 carbon atoms, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

In certain embodiments at least one of $-R^1$ or $-R^2$ of formula (X) is -CN, $-SOR^3$ or $-SO_2R^3$. In certain embodiments at least one of $-R^1$ and $-R^2$ of formula (X) is -CN or $-SO_2R^3$. In certain embodiments at least one of $-R^1$ and $-R^2$ of formula (X) is -CN or $-SO_2R^3$, wherein $-R^3$ is optionally substituted alkyl, optionally substituted aryl, or $-NR^8_2$. In certain embodiments at least one of $-R^1$ and $-R^2$ of formula (X) is -CN, $-SO_2N(CH_3)_2$, $-SO_2CH_3$, phenyl substituted with $-SO_2$, phenyl substituted with $-SO_2$ and -Cl, $-SO_2N(CH_2CH_2)_2O$, $-SO_2CH(CH_3)_2$, $-SO_2N(CH_3)(CH_2CH_3)$, or $-SO_2N(CH_2CH_2OCH_3)_2$.

In certain embodiments each $-R^4$ of formula (X) is independently C_1 - C_3 alkyl. In certain embodiments both $-R^4$ are methyl.

In certain embodiments -Y- of formula (X) is absent. In certain embodiments -Y- of formula (X) is $-N(R^6)CH_2-$.

In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-CN$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2N(CH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is SO_2CH_3 , $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2N(CH_2CH_2)_2CHCH_3$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is phenyl substituted with $-SO_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is phenyl substituted with $-SO_2$ and $-Cl$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2N(CH_2CH_2)_2O$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2CH(CH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2N(CH_3)(CH_2CH_3)$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is $-SO_2N(CH_2CH_2OCH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 1, $-R^1$ is phenyl substituted with $-SO_2$ and $-CH_3$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$.

In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-CN$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2N(CH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is SO_2CH_3 , $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2N(CH_2CH_2)_2CHCH_3$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is phenyl substituted with $-SO_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is phenyl substituted with $-SO_2$ and $-Cl$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2N(CH_2CH_2)_2O$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2CH(CH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2N(CH_3)(CH_2CH_3)$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is $-SO_2N(CH_2CH_2OCH_3)_2$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 2, $-R^1$ is phenyl substituted with $-SO_2$ and $-CH_3$, $-R^2$ is $-H$, and $-R^4$ is $-CH_3$.

In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{CN}$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is SO_2CH_3 , $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{CHCH}_3$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is phenyl substituted with $-\text{SO}_2$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is phenyl substituted with $-\text{SO}_2$ and $-\text{Cl}$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is $-\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$. In certain embodiments $-L^1-$ is of formula (X), wherein n is 3, $-R^1$ is phenyl substituted with $-\text{SO}_2$ and $-\text{CH}_3$, $-R^2$ is $-\text{H}$, and $-R^4$ is $-\text{CH}_3$.

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

The term "alkyl" refers to linear, branched, or cyclic saturated hydrocarbon groups of 1 to 20, 1 to 12, 1 to 8, 1 to 6, or 1 to 4 carbon atoms. In certain embodiments an alkyl is linear or branched. Examples of linear or branched alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl. In certain embodiments an alkyl is cyclic. Examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentadienyl, and cyclohexyl.

The term "alkoxy" refers to alkyl groups bonded to oxygen, including methoxy, ethoxy, isopropoxy, cyclopropoxy, and cyclobutoxy.

The term "alkenyl" refers to non-aromatic unsaturated hydrocarbons with carbon-carbon double bonds and 2 to 20, 2 to 12, 2 to 8, 2 to 6, or 2 to 4 carbon atoms.

The term "alkynyl" refers to non-aromatic unsaturated hydrocarbons with carbon-carbon triple bonds and 2 to 20, 2 to 12, 2 to 8, 2 to 6, or 2 to 4 carbon atoms.

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

In certain embodiments alkenyl, alkynyl, aryl or heteroaryl moieties may be coupled to the remainder of the molecule through an alkyl 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.

The term "halogen" or "halo" refers to bromo, fluoro, chloro and iodo.

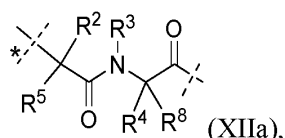
The term "heterocyclic ring" or "heterocyclyl" refers to a 3- to 15-membered aromatic or non-aromatic ring comprising at least one N, O, or S atom. Examples include piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidine, and tetrahydrofuranlyl, as well as the exemplary groups provided for the term "heteroaryl" above. In certain embodiments a heterocyclic ring or heterocyclyl is non-aromatic. In certain embodiments a heterocyclic ring or heterocyclyl is aromatic.

The term "optionally substituted" refers to a group may be unsubstituted or substituted by one or more (e.g., 1, 2, 3, 4 or 5) of the substituents which may be the same or different. Examples of substituents include alkyl, alkenyl, alkynyl, halogen, -CN, -OR^{aa}, -SR^{aa}, -NR^{aa}R^{bb}, -NO₂, -C=NH(OR^{aa}), -C(O)R^{aa}, -OC(O)R^{aa}, -C(O)OR^{aa}, -C(O)NR^{aa}R^{bb}, -OC(O)NR^{aa}R^{bb}, -NR^{aa}C(O)R^{bb}, -NR^{aa}C(O)OR^{bb}, -S(O)R^{aa}, -S(O)₂R^{aa}, -NR^{aa}S(O)R^{bb}, -C(O)NR^{aa}S(O)R^{bb}, -NR^{aa}S(O)₂R^{bb}, -C(O)NR^{aa}S(O)₂R^{bb}, -S(O)NR^{aa}R^{bb}, -S(O)₂NR^{aa}R^{bb}, -P(O)(OR^{aa})(OR^{bb}), heterocyclyl, heteroaryl, or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl, and aryl are each independently optionally substituted by -R^{cc}, wherein -R^{aa} and -R^{bb} are each independently -H, alkyl, alkenyl, alkynyl, heterocyclyl, heteroaryl, or aryl, or -R^{aa} and -R^{bb} are taken together with the nitrogen atom to which they

attach to form a heterocyclyl, which is optionally substituted by alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, or -CN, and wherein: each -R^{cc} is independently alkyl, alkenyl, alkynyl, halogen, heterocyclyl, heteroaryl, aryl, -CN, or -NO₂.

In certain embodiments -L¹- has a structure as disclosed in formula I of WO2021/242756 A1.

Accordingly, in certain embodiments the moiety -L¹- is of formula (XIIa):



wherein

the unmarked dashed line indicates attachment to -D-;

the dashed line marked with the asterisk indicates attachment to -L²-;

-R², -R⁴ and -R⁸ are independently selected from the group consisting of -H or C₁₋₄ alkyl;

-R³ is C₁₋₄ alkyl or -R³ and -R⁴ together with the atoms to which they are attached form a 5- or 6-membered heterocyclic ring;

-R⁵ is -NH₂;

with the proviso that when -R⁴ and -R³ together with the atoms to which they are attached form a 5- or 6-membered heterocyclic ring -R² is not -H; and

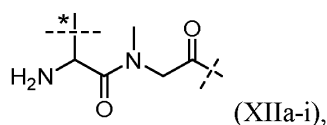
wherein the -L¹- of formula (XIIa) is optionally substituted.

In certain embodiments both -R⁴ and -R⁸ of formula (XIIa) are -H.

In certain embodiments -R³ of formula (XIIa) is methyl. In certain embodiments -R³ of formula (XIIa) is -H.

In certain embodiments -R² of formula (XIIa) is -H.

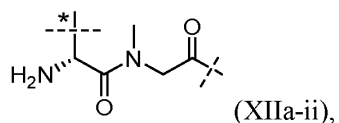
In certain embodiments -L¹- is of formula (XIIa-i)



the unmarked dashed line indicates attachment to -D-; and

the dashed line marked with the asterisk indicates attachment to -L²-.

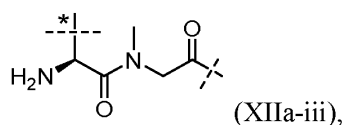
In certain embodiments $-L^1-$ is of formula (XIIa-ii)



the unmarked dashed line indicates attachment to $-D-$; and

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

In certain embodiments $-L^1-$ is of formula (XIIa-iii)

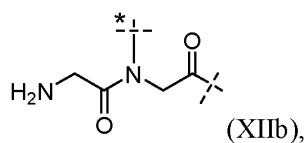


the unmarked dashed line indicates attachment to $-D-$; and

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

In certain embodiments $-L^1-$ has a structure as disclosed in formula II of WO2022/096636 A1.

Accordingly, in certain embodiments the moiety $-L^1-$ is of formula (XIIb):

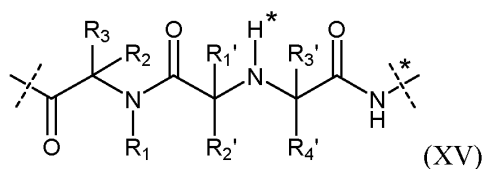


wherein

the unmarked dashed line indicates attachment to $-D-$; and

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

Another embodiment for $-L^1-$ is disclosed in WO2024/100552A1, which is herewith incorporated by reference in its entirety. Accordingly, in certain embodiments $-L^1-$ is of formula (XV):



wherein

the unmarked dashed line indicates attachment to a nitrogen, sulfur or oxygen of -D by forming an amide, a thioester or an ester bond;

the dashed line marked with the asterisk indicates attachment to -L²-;

-R¹ is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group and a substituted carbonyl group;

each of -R₂, -R₃, -R₁', -R₂', -R₃' and -R₄' is independently -H, a substituted C₁-C₅₀ alkyl group, or an unsubstituted C₁-C₅₀ alkyl group;

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

Only in the context of formula (XV) the term "aryl" means aryl radicals of 6-10 carbon atoms, e.g. phenyl, benzyl and naphthyl.

In certain embodiments -L²- is a chemical bond. In certain embodiments -L²- is a spacer moiety, such as a spacer moiety 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 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})-;

-R^{y1} and -R^{y1a} are independently of each other selected from the group consisting of -H, -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^{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})-;

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 heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each T is independently optionally substituted with one or more -R^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N(R^{y5}R^{y5a}), -S(O)₂N(R^{y5}R^{y5a}), -S(O)N(R^{y5}R^{y5a}), -S(O)₂R^{y5}, -S(O)R^{y5}, -N(R^{y5})S(O)₂N(R^{y5a}R^{y5b}), -SR^{y5}, -N(R^{y5}R^{y5a}), -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

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.

In certain embodiments -L²- is selected 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})-;

-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)-,

$-\text{C}(\text{O})\text{N}(\text{R}^{\text{y4}})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y4}})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{\text{y4}})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{N}(\text{R}^{\text{y4}})\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y4a}})-$, $-\text{S}-$, $-\text{N}(\text{R}^{\text{y4}})-$, $-\text{OC}(\text{OR}^{\text{y4}})(\text{R}^{\text{y4a}})-$, $-\text{N}(\text{R}^{\text{y4}})\text{C}(\text{O})\text{N}(\text{R}^{\text{y4a}})-$, and $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{y4}})-$;

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

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

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

In certain embodiments $-\text{L}^2-$ is selected from the group consisting of $-\text{T}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{y1}})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y1}})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{\text{y1}})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{N}(\text{R}^{\text{y1}})\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y1a}})-$, $-\text{S}-$, $-\text{N}(\text{R}^{\text{y1}})-$, $-\text{OC}(\text{OR}^{\text{y1}})(\text{R}^{\text{y1a}})-$, $-\text{N}(\text{R}^{\text{y1}})\text{C}(\text{O})\text{N}(\text{R}^{\text{y1a}})-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{y1}})-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein $-\text{T}-$, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more $-\text{R}^{\text{y2}}$, 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 $-\text{T}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{y3}})-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y3}})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{\text{y3}})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{N}(\text{R}^{\text{y3}})\text{S}(\text{O})_2\text{N}(\text{R}^{\text{y3a}})-$, $-\text{S}-$, $-\text{N}(\text{R}^{\text{y3}})-$, $-\text{OC}(\text{OR}^{\text{y3}})(\text{R}^{\text{y3a}})-$, $-\text{N}(\text{R}^{\text{y3}})\text{C}(\text{O})\text{N}(\text{R}^{\text{y3a}})-$, and $-\text{OC}(\text{O})\text{N}(\text{R}^{\text{y3}})-$;

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

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 heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl;

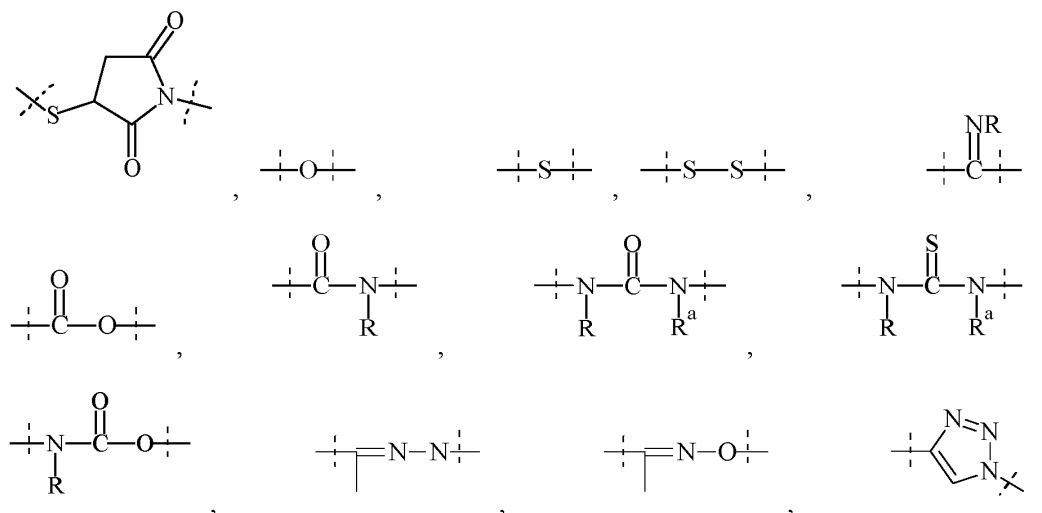
each -R^{y2} is independently selected from the group consisting of halogen, and C₁₋₆ alkyl; and

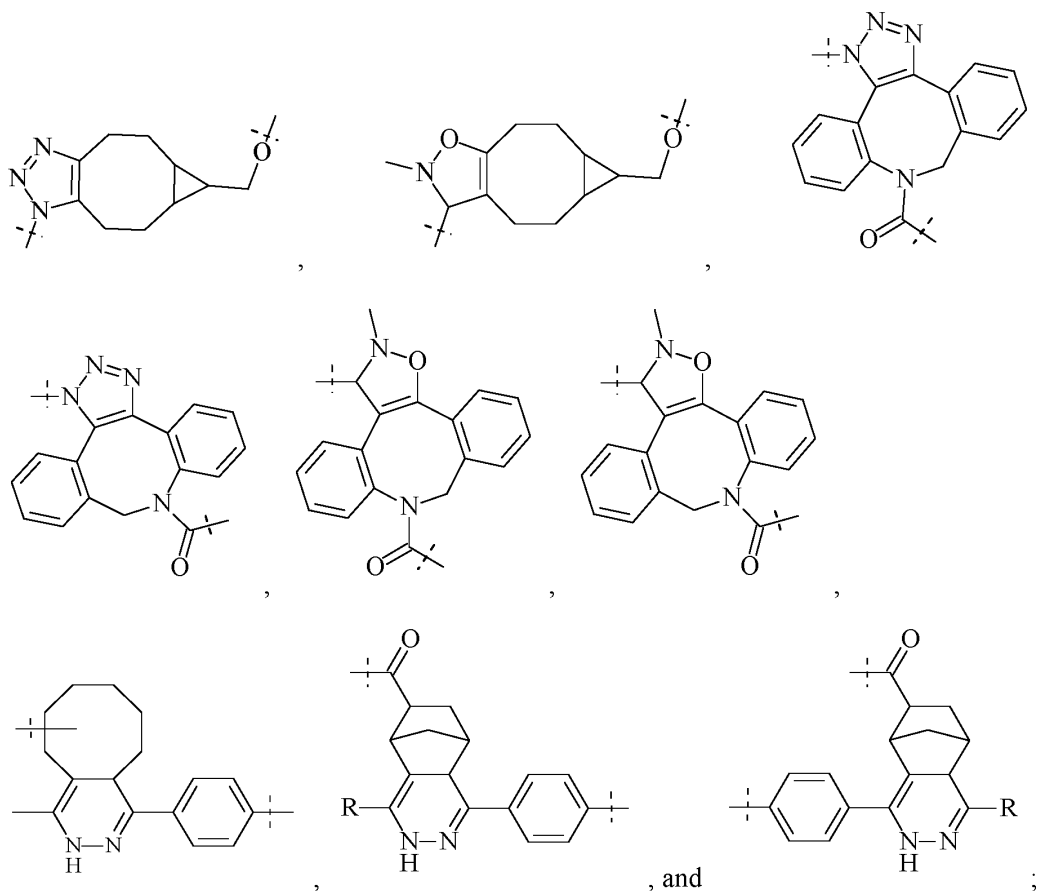
each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently of each other selected from the group consisting of -H, and C₁₋₆ alkyl; wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different.

In certain embodiments -L²- is a C₁₋₂₀ alkyl chain, which is optionally interrupted by one or more groups independently selected from -O-, -T- and -C(O)N(R^{y1})-; and which C₁₋₂₀ 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 C₁₋₄ alkyl and wherein T is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl.

In certain embodiments -L²- has a molecular weight in the range of from 14 g/mol to 750 g/mol.

In certain embodiments -L²- comprises a moiety selected from





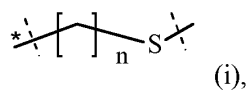
wherein

dashed lines indicate attachment to the remainder 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 certain embodiments $-L^2-$ has a chain length 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 $-Z$.

In certain embodiments $-L^2-$ is of formula (i)



wherein

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

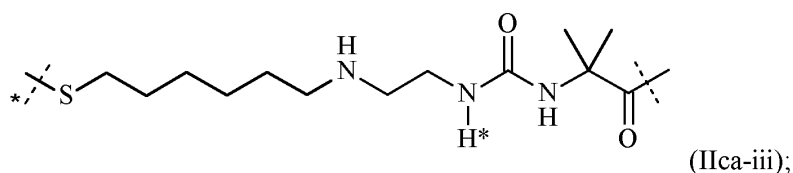
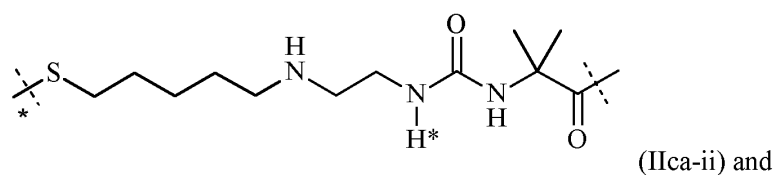
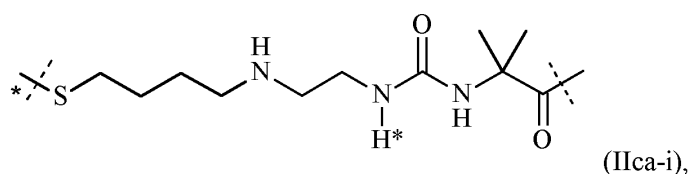
the unmarked dashed line indicates attachment to $-Z$ or $-Z'$;

n is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 18; and

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

In certain embodiments n of formula (i) is selected from the group consisting of 3, 4, 5, 6, 7, 8, and 9. In certain embodiments n of formula (i) is 4, 5, 6, or 7. In certain embodiments n of formula (i) is 4. In certain embodiments n of formula (i) is 5. In certain embodiments n of formula (i) is 6.

In certain embodiments the moiety $-L^1-L^2-$ is selected from the group consisting of



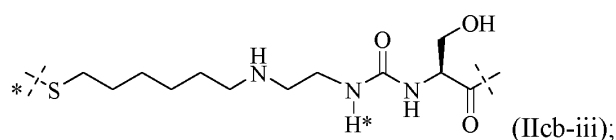
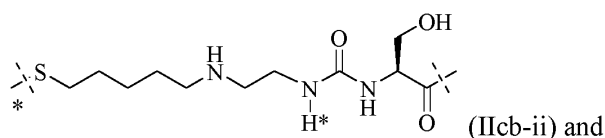
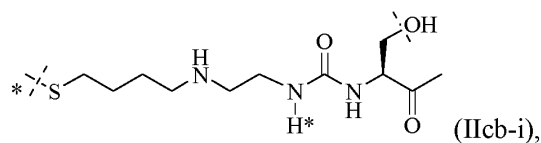
wherein

the unmarked dashed line indicates the attachment to a nitrogen of $-D$ by forming an amide bond; and

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

In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIca-i). In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIca-ii). In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIcb-iii).

In certain embodiments the moiety $-L^1-L^2-$ is selected from the group consisting of



wherein

the unmarked dashed line indicates the attachment to a nitrogen of $-D$ by forming an amide bond; and

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

In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIcb-i). In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIcb-ii). In certain embodiments the moiety $-L^1-L^2-$ is of formula (IIcb-iii).

The moiety $-Z$ comprises a fatty acid derivate or a polymer. In certain embodiments $-Z$ comprises a polymer, such as a polymer selected from the group consisting of 2-methacryloyloxyethyl 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 certain embodiments -Z comprises poly(ethylene glycol) (PEG).

In certain embodiments -Z has a molecular weight ranging from 5 to 200 kDa. In certain embodiments -Z has a molecular weight ranging from 8 to 100 kDa, such as ranging from 10 to 80 kDa, from 12 to 60 kDa, or from 15 to 40 kDa. In certain embodiments -Z has a molecular weight of about 20 kDa. In certain embodiments -Z has a molecular weight of about 40 kDa.

In certain embodiments -Z comprises PEG and has a molecular weight ranging from 5 to 200 kDa. In certain embodiments -Z comprises PEG and has a molecular weight ranging from 8 to 100 kDa, such as ranging from 10 to 80 kDa, from 12 to 60 kDa, or from 15 to 40 kDa. In certain embodiments -Z comprises PEG and has a molecular weight of about 20 kDa. In certain embodiments -Z comprises PEG and has a molecular weight of about 40 kDa.

In certain embodiments -Z comprises a protein, such as a protein 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 2011/23813 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. In certain embodiments -Z is a polysarcosine. In certain embodiments -Z comprises a poly(N-methylglycine). In certain embodiments -Z comprises a random coil protein moiety.

In certain embodiments -Z comprises a fatty acid derivate, such as a derivative as disclosed in WO 2005/027978 A2 and WO 2014/060512 A1, which are herewith incorporated by reference in their entirety. In certain embodiments -Z is a hyaluronic acid-based polymer. In certain embodiments -Z is a carrier as disclosed in WO 2012/02047 A1, which is herewith incorporated by reference in its entirety. In certain embodiments -Z is a carrier as disclosed in WO 2013/024048 A1, which is herewith incorporated by reference in its entirety. In certain embodiments -Z is a PEG-based polymer, such as a linear, branched, cyclic, dendritic or multi-arm PEG-based polymer. In certain embodiments -Z is a linear PEG-based polymer. In certain embodiments -Z is a multi-arm PEG-based polymer. In certain embodiments -Z is a multi-arm PEG-based polymer having at least 4 PEG-based arms.

In certain embodiments 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 in certain embodiments connected to the end of an arm. In certain embodiments 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 $-L^2-L^1-D$. In certain embodiments such multi-arm PEG-based polymer -Z is connected to 2, 3, 4, 6 or 8 moieties $-L^2-L^1-D$. In certain embodiments such multi-arm PEG-based polymer -Z is connected to 2, 4 or 6 moieties $-L^2-L^1-D$. In certain embodiments such multi-arm PEG-based polymer -Z is connected to 4 or 6 moieties $-L^2-L^1-D$. In certain embodiments such multi-arm PEG-based polymer -Z is connected to 4 moieties $-L^2-L^1-D$.

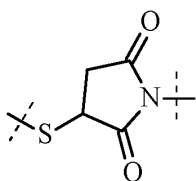
In certain embodiments -Z is a cyclic PEG-based polymer. In certain embodiments -Z is a dendritic PEG-based polymer.

In certain embodiments -Z is a branched PEG-based polymer. In certain embodiments -Z is a branched PEG-based polymer having one, two, three, four, five or six branching points. In certain embodiments -Z is a branched PEG-based polymer having one, two or three branching points. In certain embodiments -Z is a branched PEG-based polymer having one branching point. In certain embodiments -Z is a branched PEG-based polymer having two branching points. In certain embodiments -Z is a branched PEG-based polymer having three branching points. In certain embodiments a branching point may be selected from the group consisting of $-N<$, $-CH<$ and $>C<$.

In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 5 to 200 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 8 to 160 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 10 to 120 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 12 to 100 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 15 to 90 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 20 to 80 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight ranging from 25 to 60 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight of approx. 20 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight of approx. 40 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight of approx. 60 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight of approx. 80 kDa. In certain embodiments -Z is a branched PEG-based polymer with one branching point and a molecular weight of approx. 40 kDa.

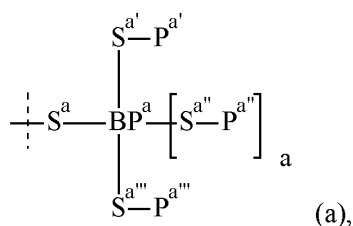
In certain embodiments -Z is a branched PEG-based polymer with one branching point, which branching point is -CH<, and a molecular weight of approx. 40 kDa.

In certain embodiments -Z or Z' comprises a moiety



In certain embodiments -Z or Z' comprises an amide bond.

In certain embodiments -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 $-\text{N}<$, $-\text{CR}<$ and $>\text{C}<$;

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

a is 0 if BP^a is $-\text{N}<$ or $-\text{CR}<$ and n is 1 if BP^a is $>\text{C}<$;

$-\text{S}^a$ -, $-\text{S}^{a'}$ -, $-\text{S}^{a''}$ - and $-\text{S}^{a'''}$ - 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 $-\text{R}^1$, 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 $-\text{T}-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^2)-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^2)-$, $-\text{S}(\text{O})\text{N}(\text{R}^2)-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{N}(\text{R}^2)\text{S}(\text{O})_2\text{N}(\text{R}^{2a})-$, $-\text{S}-$, $-\text{N}(\text{R}^2)-$, $-\text{OC}(\text{OR}^2)(\text{R}^{2a})-$, $-\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^{2a})-$, and $-\text{OC}(\text{O})\text{N}(\text{R}^2)-$;

each $-\text{T}-$ 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 heterobicycyl, 8-to 30-membered carbopolycyclyl, and 8- to 30-membered heteropolycyclyl; wherein each $-\text{T}-$ is independently optionally substituted with one or more $-\text{R}^1$, which are the same or different;

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

each $-\text{R}^2$, $-\text{R}^{2a}$, $-\text{R}^3$, $-\text{R}^{3a}$ and $-\text{R}^{3b}$ is independently selected from the group consisting of $-\text{H}$, 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

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

In certain embodiments BP^a of formula (a) is $-N<$. In certain embodiments BP^a of formula (a) is $>C<$. In certain embodiments BP^a of formula (a) is $-CR<$. In certain embodiments $-R$ is $-H$. Accordingly, a of formula (a) is 0.

In certain embodiments $-S^a$ of formula (a) is a chemical bond. In certain embodiments $-S^a$ of formula (a) is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, which C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of $-T$ -, $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^4)$ -, $-S(O)_2N(R^4)$ -, $-S(O)N(R^4)$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^4)S(O)_2N(R^{4a})$ -, $-S$ -, $-N(R^4)$ -, $-OC(OR^4)(R^{4a})$ -, $-N(R^4)C(O)N(R^{4a})$ -, and $-OC(O)N(R^4)$ -, wherein $-T$ is a 3- to 10-membered heterocyclyl; and $-R^4$ and $-R^{4a}$ are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. In certain embodiments $-S^a$ of formula (a) is selected from the group consisting of C_{1-10} alkyl which is interrupted by one or more chemical groups selected from the group consisting of $-T$ -, $-C(O)N(R^4)$ - and $-O$ -.

In certain embodiments $-S^{a'}$ of formula (a) is a chemical bond. In certain embodiments $-S^{a'}$ of formula (a) is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, which C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^4)$ -, $-S(O)_2N(R^4)$ -, $-S(O)N(R^4)$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^4)S(O)_2N(R^{4a})$ -, $-S$ -, $-N(R^4)$ -, $-OC(OR^4)(R^{4a})$ -, $-N(R^4)C(O)N(R^{4a})$ -, and $-OC(O)N(R^4)$ -, wherein $-R^4$ and $-R^{4a}$ are independently selected from the group consisting of $-H$, methyl, ethyl, propyl and butyl. In certain embodiments $-S^{a'}$ 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 $-C(O)N(R^4)$ -.

In certain embodiments $-S^{a''}$ of formula (a) is a chemical bond. In certain embodiments $-S^{a''}$ of formula (a) is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, which C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl are optionally interrupted by one or more chemical groups selected from the group consisting of $-C(O)O$ -, $-O$ -, $-C(O)$ -, $-C(O)N(R^4)$ -, $-S(O)_2N(R^4)$ -, $-S(O)N(R^4)$ -, $-S(O)_2$ -, $-S(O)$ -, $-N(R^4)S(O)_2N(R^{4a})$ -, $-S$ -, $-N(R^4)$ -, $-OC(OR^4)(R^{4a})$ -, $-N(R^4)C(O)N(R^{4a})$ -, and $-OC(O)N(R^4)$ -,

wherein $-R^4$ and $-R^{4a}$ are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. In certain embodiments $-S^{a''}$ 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(R^4)-.

In certain embodiments $-S^{a'''}$ of formula (a) is a chemical bond. In certain embodiments $-S^{a''''}$ of formula (a) is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} alkynyl, which C_{1-10} alkyl, C_{2-10} alkenyl and C_{2-10} 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(R^4)-, -S(O)₂N(R^4)-, -S(O)N(R^4)-, -S(O)₂-, -S(O)-, -N(R^4)S(O)₂N(R^{4a})-, -S-, -N(R^4)-, -OC(OR⁴)(R^{4a})-, -N(R^4)C(O)N(R^{4a})-, and -OC(O)N(R^4)-; wherein $-R^4$ and $-R^{4a}$ are independently selected from the group consisting of -H, methyl, ethyl, propyl and butyl. In certain embodiments $-S^{a''''}$ 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(R^4)-.

In certain embodiments $-P^{a'}$, $-P^{a''}$ 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, dextrans, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins,

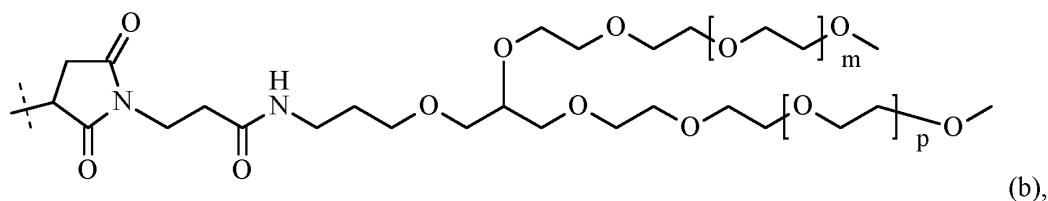
rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently comprise a PEG-based moiety. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently comprise a PEG-based moiety comprising at least 20% PEG, such as at least 30%, such as at least 40% PEG, such as at least 50% PEG, such as at least 60% PEG, such as at least 70% PEG, such as at least 80% PEG or such as at least 90% PEG.

In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) independently have a molecular weight ranging from and including 5 kDa to 50 kDa, such as from and including 5 kDa to 40 kDa, such as from and including 7.5 kDa to 35 kDa, such as from and including 7.5 to 30 kDa or such as from and including 10 to 30 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 5 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 7.5 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 10 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 12.5 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 15 kDa. In certain embodiments $-P^{a'}$, $-P^{a''}$ and $-P^{a'''}$ of formula (a) have a molecular weight of about 20 kDa.

In certain embodiments $-Z$ comprises one moiety of formula (a). In certain embodiments $-Z$ comprises two moieties of formula (a). In certain embodiments $-Z$ comprises three moieties of formula (a). In certain embodiments $-Z$ is a moiety of formula (a).

In certain embodiments $-Z$ comprises a moiety of formula (b)



wherein

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

m and p are independently of each other an integer ranging from and including 150 to 1000; such as an integer ranging from and including 150 to 600; such as an integer ranging from and including 200 to 550; or such as an integer ranging from and including 400 to 500.

In certain embodiments m and p of formula (b) are the same integer. In certain embodiments m and p of formula (b) both range from 400 to 500.

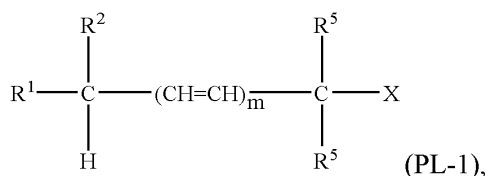
In certain embodiments -Z is a moiety of formula (b) and the dashed line indicates attachment to -L²-.

In certain embodiments, Z' is a hydrogel.

In certain embodiments, Z' is a PEG-based or hyaluronic acid-based hydrogel. In certain embodiments, Z' is a PEG-based hydrogel. In certain embodiments, Z' is a hyaluronic acid-based hydrogel.

In certain embodiments, Z' is a hydrogel as described in WO 2006/003014 A2, WO 2011/012715 A1, WO 2014/056926 A1, WO2020/064846 or WO2020/064847 which are herewith incorporated by reference in their entirety.

In certain embodiments, Z' is a hydrogel as disclosed in WO 2013/036847 A1. In particular, in certain embodiments, Z' is a hydrogel produced by a method comprising the step of reacting at least a first reactive polymer with a cleavable crosslinker compound, wherein said cleavable crosslinker compound comprises a first functional group -Y¹ that reacts with the first reactive polymer and further comprises a moiety that is cleaved by elimination under physiological conditions wherein said moiety comprises a second functional group -Y² that reacts with a second reactive polymer. In certain embodiments, the cleavable crosslinker compound is of formula (PL-1):



wherein

m is 0 or 1;

-X comprises a functional group capable of connecting to a reactive polymer that is amenable to elimination under physiological conditions and said second functional group -Y²;

at least one of -R¹, -R² and -R⁵ comprises said first functional group -Y¹ capable of connecting to a polymer;

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

optionally, -R¹ and -R² may be joined to form a 3- to 8-membered ring;

at least one or both of -R¹ and -R² is independently selected from the group consisting of -CN, -NO₂, aryl, heteroaryl, alkenyl, alkynyl, -COR³, -SOR³, -SO₂R³ and -SR⁴;

-R³ is selected from the group consisting of -H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -OR⁹ and -NR⁹₂;

-R⁴ is selected from the group consisting of alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

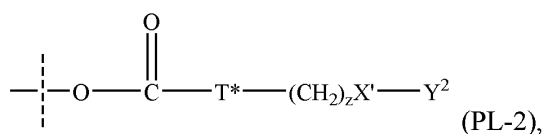
each -R⁵ is independently selected from the group consisting of -H, alkyl, alkenylalkyl, alkynylalkyl, (OCH₂CH₂)_pO-alkyl with p being an integer ranging from 1 to 1000, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

each -R⁹ is independently selected from the group consisting of -H and alkyl or both -R⁹ together with the nitrogen to which they are attached form a heterocyclic ring;

and wherein the moiety of formula (PL-1) is optionally further substituted.

The following paragraphs describe such hydrogel in more detail.

In certain embodiments, -X of formula (PL-1) is selected from the group consisting of succinimidyl carbonate, sulfosuccinimidyl carbonate halides, thioethers, esters, nitrophenyl carbonate, chloroformate, fluoroformate, optionally substituted phenols and formula (PL-2):



wherein

the dashed line indicates attachment to the remainder of formula (PL-1);

-T*- is selected from the group consisting of -O-, -S- and -NR⁶-;

z is an integer selected from the group consisting of 1, 2, 3, 4, 5 and 6;

-X'- is absent or is selected from the group consisting of -OR⁷- and -SR⁷-;

-Y² is a functional group capable of connecting with a reactive polymer;

-R⁶ is selected from the group consisting of -H, alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; and

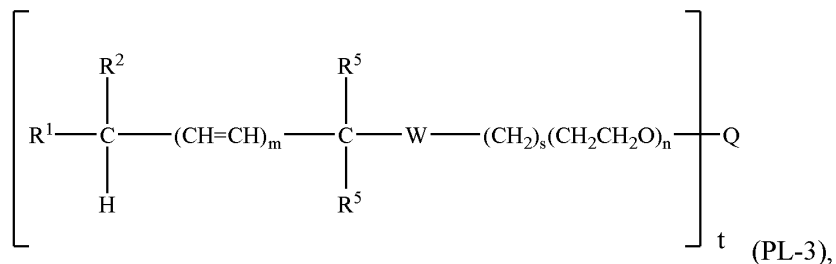
-R⁷ is selected from the group consisting of alkylene, phenylene and (OCH₂CH₂)_p, with p being an integer ranging from 1 to 1000.

In certain embodiments, -X of formula (PL-1) comprises an activated carbonate such as succinimidyl carbonate, sulfosuccinimidyl carbonate, or nitrophenyl carbonate. In certain embodiments, -X of formula (PL-1) comprises a carbonyl halide such as O(C=O)Cl or O(C=O)F. In certain embodiments, -X of formula (PL-1) has the formula (PL-2). In certain embodiments, -X of formula (PL-1) is OR⁷ or SR⁷, wherein R⁷ is optionally substituted alkylene, optionally substituted phenylene or (OCH₂CH₂)_p, wherein p is 1 to 1000.

In certain embodiments, p of formula (PL-2) is an integer ranging from 1 to 100. In certain embodiments, p of formula (PL-2) is an integer ranging from 1 to 10.

In certain embodiments, -Y¹ of formula (PL-1) and -Y² of formula (PL-2) independently comprise N₃, NH₂, NH-CO₂^tBu, SH, S^tBu, maleimide, CO₂H, CO₂^tBu, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate or acrylamide, wherein ^tBu is tert-butyl, and wherein when one of -Y¹ or -Y² comprises N₃ the other does not comprise alkyne or cyclooctyne; when one of -Y¹ or -Y² comprises SH the other does not comprise maleimide, acrylate or acrylamide; when one of -Y¹ or -Y² comprises NH₂ the other does not comprise CO₂H; and when one of -Y¹ or -Y² comprises 1,3-diene or cyclopentadiene the other does not comprise furan.

In certain embodiments, the cleavable crosslinker compound is of formula (PL-3):



wherein

m is 0 or 1;

n is an integer selected from 1 to 1000;

s is 0, 1 or 2;

t is selected from the group consisting of 2, 4, 8, 16 and 32;

-W- is selected from the group consisting of -O(C=O)O-, -O(C=O)NH-, -O(C=O)S-, -O(C=O)NR⁶CH₂O- and -O(C=O)NR⁶S-;

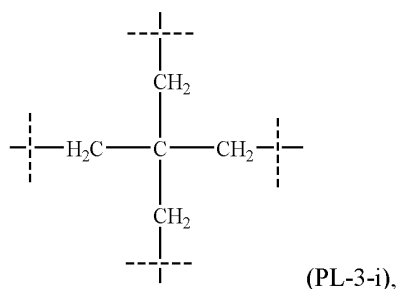
-Q is a core group having a valency=t, which connects the multiple arms of the cleavable crosslinking compound;

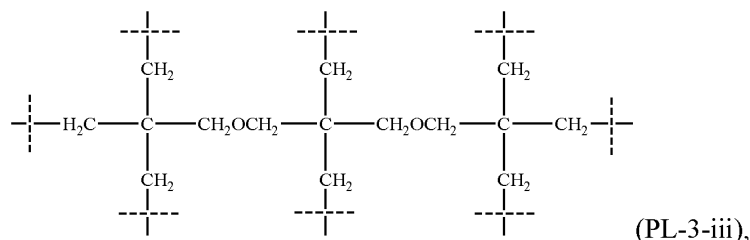
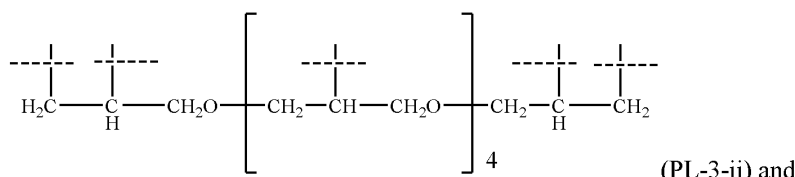
wherein t is an integer selected from 2, 4, 8, 16 and 32; and

wherein -R¹, -R² and -R⁵ are defined as in formula (PL-1).

In certain embodiments, t of formula (PL-3) is 2. In certain embodiments, t of formula (PL-3) is 4. In certain embodiments, t of formula (PL-3) is 8. In certain embodiments, t of formula (PL-3) is 16. In certain embodiments, t of formula (PL-3) is 32.

In certain embodiments, -Q of formula (PL-3) has a structure selected from the group consisting of:





wherein the dashed lines indicate attachment to the remainder of the cleavable crosslinker compound.

In certain embodiments, -Q of formula (PL-3) has the structure of (PL-3-i). In certain embodiments, -Q of formula (PL-3) has the structure of (PL-3-ii). In certain embodiments, -Q of formula (PL-3) has the structure of (PL-3-iii).

In certain embodiments, the cleavable crosslinker compound is of formula (PL-3), wherein m is 0, n is approximately 100, s is 0, t is 4, -W- is -O(C=O)NH-, -Q has the structure of (PL-3i), -R² is H, one -R⁵ is -H and the other -R⁵ is (CH₂)₅N₃, and -R¹ is (4-chlorophenyl)SO₂, phenyl substituted with -SO₂, morpholino-SO₂, or -CN.

In certain embodiments, -Y¹ of formula (PL-3) comprises N₃, NH₂, NH-CO₂^tBu, SH, S^tBu, maleimide, CO₂H, CO₂^tBu, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate or acrylamide, wherein ^tBu is tert-butyl.

In certain embodiments, each -Y¹ of formula (PL-1) or (PL-3) and -Y² of formula (PL-2) independently comprises N₃, NH₂, NH-CO₂^tBu, SH, S^tBu, maleimide, CO₂H, CO₂^tBu, 1,3-diene, cyclopentadiene, furan, alkyne, cyclooctyne, acrylate or acrylamide.

In certain embodiments, one of -Y¹ and -Y² is azide and the other is a reactive functional group selected from the group consisting of acetylene, cyclooctyne, and maleimide. In certain embodiments, one of -Y¹ and -Y² is thiol and the other is a reactive functional group selected from the group consisting of maleimide, acrylate, acrylamide, vinylsulfone, vinylsulfonamide,

and halocarbonyl. In certain embodiments, one of $-Y^1$ and $-Y^2$ is amine and the other is a selective reactive functional group selected from carboxylic acid and activated carboxylic acid. In certain embodiments, one of $-Y^1$ and $-Y^2$ is maleimide and the other is a selective reactive functional group selected from the group consisting of 1,3-diene, cyclopentadiene, and furan.

In certain embodiments, the first and any second polymer is selected from the group consisting of homopolymeric or copolymeric polyethylene glycols, polypropylene glycols, poly(N-vinylpyrrolidone), polymethacrylates, polyphosphazenes, polylactides, polyacrylamides, polyglycolates, polyethylene imines, agaroses, dextrans, gelatins, collagens, polylysines, chitosans, alginates, hyaluronans, pectins and carrageenans that either comprise suitable reactive functionalities or is of formula $[Y^3-(CH_2)_s(CH_2CH_2O)_n]_tQ$, wherein $-Y^3$ is a reactive functional group, s is 0, 1 or 2, n is an integer selected from the group ranging from 10 to 1000, $-Q$ is a core group having valency t , and t is an integer selected from the group consisting of 2, 4, 8, 16 and 32.

In certain embodiments, the first polymer comprises a multi-arm polymer. In certain embodiments, the first polymer comprises at least three arms. In certain embodiments, the first polymer comprises at least four arms. In certain embodiments, the first polymer comprises at least five arms. In certain embodiments, the first polymer comprises at least six arms. In certain embodiments, the first polymer comprises at least seven arms. In certain embodiments, the first polymer comprises at least eight arms.

In certain embodiments, the second polymer comprises a multi-arm polymer. In certain embodiments, the second polymer comprises at least three arms. In certain embodiments, the second polymer comprises at least four arms. In certain embodiments, the second polymer comprises at least five arms. In certain embodiments, the second polymer comprises at least six arms. In certain embodiments, the second polymer comprises at least seven arms. In certain embodiments, the second polymer comprises at least eight arms.

In certain embodiments, the first polymer comprises a 2-arm polyethylene glycol polymer. In certain embodiments, the first polymer comprises a 4-arm polyethylene glycol polymer. In certain embodiments, the first polymer comprises an 8-arm polyethylene glycol polymer. In

certain embodiments, the first polymer comprises a 16-arm polyethylene glycol polymer. In certain embodiments, the first polymer comprises a 32-arm polyethylene glycol polymer.

In certain embodiments, the second polymer comprises a 2-arm polyethylene glycol polymer. In certain embodiments, the second polymer comprises a 4-arm polyethylene glycol polymer. In certain embodiments, the second polymer comprises an 8-arm polyethylene glycol polymer. In certain embodiments, the second polymer comprises a 16-arm polyethylene glycol polymer. In certain embodiments, the second polymer comprises a 32-arm polyethylene glycol polymer.

In certain embodiments, the first and a second reactive polymer are reacted with said cleavable crosslinker compound, either sequentially or simultaneously.

In certain embodiments, the first and second functional groups are the same.

Only in the context of formulas (PL-1), (PL-2) and (PL-3) the terms used have the following meaning:

The term “a moiety capable of being cleaved by elimination under physiological conditions” refers to a structure comprising a group $\text{H-C}-(\text{CH}=\text{CH})_m\text{-C-X'}$ wherein m is 0 or 1 and X' is a leaving group, wherein an elimination reaction as described above to remove the elements of HX' can occur at a rate such that the half-life of the reaction is between 1 and 10,000 hours under physiological conditions of pH and temperature. Preferably, the half-life of the reaction is between 1 and 5,000 hours, and more preferably between 1 and 1,000 hours, under physiological conditions of pH and temperature. By physiological conditions of pH and temperature is meant a pH of between 7 and 8 and a temperature between 30 and 40 degrees centigrade

The term “reactive polymer and reactive oligomer” refers to a polymer or oligomer comprising functional groups that are reactive towards other functional groups, most preferably under mild conditions compatible with the stability requirements of peptides, proteins, and other biomolecules. Suitable functional groups found in reactive polymers include maleimides, thiols or protected thiols, alcohols, acrylates, acrylamides, amines or protected amines, carboxylic acids or protected carboxylic acids, azides, alkynes including cycloalkynes, 1,3-dienes

including cyclopentadienes and furans, alpha-halocarbonyls, and N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, or nitrophenyl esters or carbonates.

The term “functional group capable of connecting to a reactive polymer” refers to a functional group that reacts to a corresponding functional group of a reactive polymer to form a covalent bond to the polymer. Suitable functional groups capable of connecting to a reactive polymer include maleimides, thiols or protected thiols, acrylates, acrylamides, amines or protected amines, carboxylic acids or protected carboxylic acids, azides, alkynes including cycloalkynes, 1,3-dienes including cyclopentadienes and furans, alpha-halocarbonyls, and N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, or nitrophenyl esters or carbonates.

The term “substituted” refers to an alkyl, alkenyl, alkynyl, aryl, or heteroaryl group comprising one or more substituent groups in place of one or more hydrogen atoms. Substituent groups 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, alkoxysilyl, 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.

The properties of R^1 and R^2 may be modulated by the optional addition of electron-donating or electron-withdrawing substituents. The term “electron-donating group” refers to a substituent resulting in a decrease in the acidity of the R^1R^2CH ; electron-donating groups are typically associated with negative Hammett σ or Taft σ^* constants and are well-known in the art of physical organic chemistry (Hammett constants refer to aryl/heteroaryl substituents, Taft constants refer to substituents on non-aromatic moieties). Examples of suitable

electron-donating substituents include lower alkyl, lower alkoxy, lower alkylthio, amino, alkylamino, dialkylamino, and silyl.

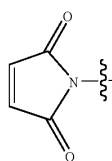
The term “electron-withdrawing group” refers to a substituent resulting in an increase in the acidity of the R^1R^2CH group; electron-withdrawing groups are typically associated with positive Hammett σ or Taft σ^* constants and are well-known in the art of physical organic chemistry. Examples of suitable electron-withdrawing substituents include halogen, difluoromethyl, trifluoromethyl, nitro, cyano, $C(=O)-R^x$, wherein $-R^x$ is H, lower alkyl, lower alkoxy, or amino, or $S(O)_mR^y$, wherein m is 1 or 2 and $-R^y$ is lower alkyl, aryl, or heteroaryl. As is well-known in the art, the electronic influence of a substituent group may depend upon the position of the substituent. For example, an alkoxy substituent on the ortho- or para-position of an aryl ring is electron-donating, and is characterized by a negative Hammett σ constant, while an alkoxy substituent on the meta-position of an aryl ring is electron-withdrawing and is characterized by a positive Hammett σ constant.

The terms “alkyl”, “alkenyl”, and “alkynyl” include linear, branched or cyclic hydrocarbon groups of 1 to 8 carbons or 1 to 6 carbons or 1 to 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 to 6 carbons.

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.

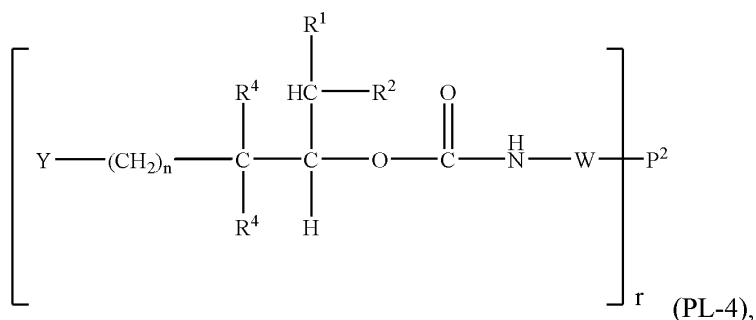
The term “halogen” includes fluoro, chloro, bromo and iodo.

The term “maleimide” is a group of the formula



In certain embodiments, Z' is a hydrogel as disclosed in WO 2020/206358 A1. In particular, in certain embodiments, Z' is a hydrogel produced by a method comprising the steps of

- (a) providing a first prepolymer comprising a multi-arm polymer $-P^2$, wherein said first prepolymer is of formula (PL-4)



wherein

n is an integer selected from 0, 1, 2, 3, 4, 5 and 6;

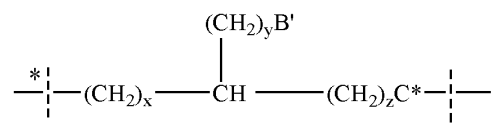
r is an integer higher than 2;

$-\text{Y}$ is a reactive functional group for connecting said first prepolymer to a second prepolymer;

$-\text{R}^1$ and $-\text{R}^2$ are independently an electron-withdrawing group, alkyl, or $-\text{H}$, and wherein at least one of $-\text{R}^1$ and $-\text{R}^2$ is an electron-withdrawing group;

each $-\text{R}^4$ is independently C_1 - C_3 alkyl or the two $-\text{R}^4$ form together with the carbon atom to which they are attached a 3- to 6-membered ring;

$-\text{W}-$ is absent or is



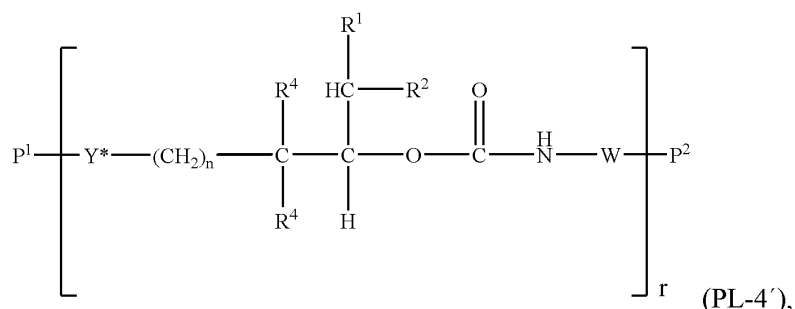
wherein the dashed line marked with the asterisk indicates the attachment to $-\text{NH}-$ and the unmarked dashed line indicates the attachment to $-\text{P}^2$;

each of x , y , and z is independently an integer selected from 0, 1, 2, 3, 4, 5 and 6;

- B' is -NH₂, -ONH₂, ketone, aldehyde, -SH, -OH, -CO₂H, carboxamide group, or a group comprising a cyclooctyne or bicyclononyne; and
- C* is carboxamide, thioether, thiosuccinimidyl, triazole, or oxime;
- (b) providing the second prepolymer comprising a multi-arm polymer -P¹ wherein each arm is terminated by a reactive functional group -Y'' that reacts with -Y of step (a);
- (c) mixing the two prepolymers of steps (a) and (b) under conditions wherein -Y and -Y'' react to form a linkage -Y*-; and optionally
- (d) isolating the resulting hydrogel.

Accordingly, Z' is a hydrogel obtainable from the method described above. In certain embodiments, the hydrogel produced by the preceding method is degradable.

In certain embodiments, -Y and -Y'' react under step (c) to form an insoluble hydrogel matrix comprising crosslinks of formula (PL-4'):



wherein n, r, -P¹, -Y*- , -R⁴, -R¹, -R², -W- and -P² are as defined above.

In certain embodiments, n of formula (PL-4) or (PL-4') is an integer selected from 1, 2, 3, 4, 5 and 6. In certain embodiments, n of formula (PL-4) or (PL-4') is an integer selected from 1, 2 and 3. In certain embodiments, n of formula (PL-4) or (PL-4') is an integer selected from 0, 1, 2 and 3. In certain embodiments, n of formula (PL-4) or (PL-4') is 1. In certain embodiments, n of formula (PL-4) is 2. In certain embodiments, n of formula (PL-4) or (PL-4') is 3.

In certain embodiments, the multi-arm -P² of formula (PL-4) or (PL-4') is an r-armed polymer, wherein r is an integer selected from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12. In certain embodiments, r of formula (PL-4) or (PL-4') is an integer selected from 2, 3, 4, 5, 6, 7 and 8. In certain embodiments, r of formula (PL-4) or (PL-4') is an integer selected from 2, 4, 6 and 8. In certain embodiments, r of formula (PL-4) or (PL-4') is 2. In certain embodiments, r of formula (PL-4)

or (PL-4') is 4. In certain embodiments, r of formula (PL-4) or (PL-4') is 6. In certain embodiments, r of formula (PL-4) or (PL-4') is 8.

In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of at least 1 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 100 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 80 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 60 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 40 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 20 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 10 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of 1 to 5 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of about 20 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of about 40 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of about 60 kDa. In certain embodiments, $-P^2$ of formula (PL-4) or (PL-4') has a molecular weight of about 80 kDa.

In certain embodiments, the multi-arm polymer $-P^1$ of step (b) is an r -armed polymer, wherein r is an integer selected from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is an integer selected from 2, 3, 4, 5, 6, 7 and 8. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is an integer selected from 2, 4, 6 and 8. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is 2. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is 4. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is 6. In certain embodiments, the multi-arm $-P^1$ of step (b) is an r -armed polymer, wherein r is 8.

In certain embodiments, $-P^1$ of step (b) has a molecular weight of at least 1 kDa. In certain embodiments, the multi-arm polymer $-P^1$ of step (b) has a molecular weight of 1 to 100 kDa. In certain embodiments, the multi-arm polymer $-P^1$ of step (b) has a molecular weight of 1 to 80 kDa. In certain embodiments, the multi-arm polymer $-P^1$ of step (b) has a molecular weight of 1 to 60 kDa. In certain embodiments, the multi-arm polymer $-P^1$ of step (b) has a molecular weight of 1 to 40 kDa. In certain embodiments, the multi-arm polymer $-P^1$ of step (b) has a

molecular weight of 1 to 20 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of 1 to 10 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of 1 to 5 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of about 20 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of about 40 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of about 60 kDa. In certain embodiments, the multi-arm polymer -P¹ of step (b) has a molecular weight of about 80 kDa.

In certain embodiments, -P¹ of step (b) and -P² of formula (PL-4) or (PL-4') comprise poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), poly(ethylene imine) (PEI), dextrans, hyaluronic acids, or co-polymers thereof. In certain embodiments, -P¹ of step (b) and P² of formula (PL-4) or (PL-4') are PEG-based polymers. In certain embodiments, -P¹ of step (b) and -P² of formula (PL-4) or (PL-4') are hyaluronic acid-based polymers.

In certain embodiments, -R¹ and -R² of formula (PL-4) or (PL-4') are independently electron-withdrawing groups, alkyl, or -H, and wherein at least one of -R¹ and -R² is an electron-withdrawing group.

In certain embodiments, the electron-withdrawing group of -R¹ and -R² of formula (PL-4) or (PL-4') is -CN, -NO₂, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted alkynyl, -COR³, -SOR³, or -SO₂R³, wherein -R³ is -H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR⁸ or -NR⁸₂, wherein each -R⁸ is independently -H or optionally substituted alkyl, or both -R⁸ groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or -SR⁹, wherein -R⁹ is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

In certain embodiments, the electron-withdrawing group of -R¹ and -R² of formula (PL-4) or (PL-4') is -CN. In certain embodiments, the electron-withdrawing group of -R¹ and -R² of formula (PL-4) or (PL-4') is -NO₂. In certain embodiments, the electron-withdrawing group of -R¹ and -R² of formula (PL-4) or (PL-4') is optionally substituted aryl containing 6 to 10

carbons. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is optionally substituted phenyl, naphthyl, or anthracenyl. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is optionally substituted heteroaryl comprising 3 to 7 carbons and containing at least one N, O, or S atom. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is optionally substituted pyrrolyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, quinolyl, indolyl, or indenyl. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is optionally substituted alkenyl containing 2 to 20 carbon atoms. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is optionally substituted alkynyl containing 2 to 20 carbon atoms. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{COR}^3$, $-\text{SOR}^3$, or $-\text{SO}_2\text{R}^3$, wherein R^3 is $-\text{H}$, optionally substituted alkyl containing 1 to 20 carbon atoms, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-\text{OR}^8$ or $-\text{NR}^8_2$, wherein each $-\text{R}^8$ is independently $-\text{H}$ or optionally substituted alkyl containing 1 to 20 carbon atoms, or both $-\text{R}^8$ groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring. In certain embodiments, the electron-withdrawing group of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{SR}^9$, wherein $-\text{R}^9$ is optionally substituted alkyl containing 1 to 20 carbon atoms, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl. In certain embodiments, at least one of $-R^1$ and $-R^2$ is $-\text{CN}$ or $-\text{SO}_2\text{R}^3$.

In certain embodiments, at least one of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{CN}$, $-\text{SOR}^3$ or $-\text{SO}_2\text{R}^3$. In certain embodiments, at least one of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{CN}$ or $-\text{SO}_2\text{R}^3$. In certain embodiments, at least one of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{CN}$ or $-\text{SO}_2\text{R}^3$, wherein $-\text{R}^3$ is optionally substituted alkyl, optionally substituted aryl, or $-\text{NR}^8_2$. In certain embodiments, at least one of $-R^1$ and $-R^2$ of formula (PL-4) or (PL-4') is $-\text{CN}$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$, $-\text{SO}_2\text{CH}_3$, phenyl substituted with $-\text{SO}_2$, phenyl substituted with $-\text{SO}_2$ and $-\text{Cl}$, $-\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$, $-\text{SO}_2\text{CH}(\text{CH}_3)_2$, $-\text{SO}_2\text{N}(\text{CH}_3)(\text{CH}_2\text{CH}_3)$, or $-\text{SO}_2\text{N}(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$.

In certain embodiments, each $-\text{R}^4$ of formula (PL-4) or (PL-4') is independently C_1 - C_3 alkyl or taken together may form a 3- to 6-membered ring. In certain embodiments, each $-\text{R}^4$ of formula

(PL-4) or (PL-4') is independently C₁-C₃ alkyl. In certain embodiments, both -R⁴ of formula (PL-4) or (PL-4') are methyl.

In certain embodiments, -Y and -Y'' are independently selected from the group consisting of amine, aminooxy, ketone, aldehyde, maleimidyl, thiol, alcohol, azide, 1,2,4,6-tetrazinyl, trans-cyclooctenyl, bicyclononyl, cyclooctynyl, and protected variants thereof.

In certain embodiments, Y and Y'' may react with each other such as in a selective way. For example, when -Y is amine, -Y'' is carboxylic acid, active ester, or active carbonate to yield a residual connecting functional group -Y*- that is amide or carbamate. As another example, when -Y is azide, -Y'' is alkynyl, bicyclononyl, or cyclooctynyl to yield a residual connecting functional group -Y*- that is 1,2,3-triazole. As another example, when -Y is NH₂O, -Y'' is ketone or aldehyde to yield a residual connecting functional group -Y*- that is oxime. As another example, when -Y is SH, -Y'' is maleimide or halocarbonyl to yield a residual connecting functional group -Y*- that is thiosuccinimidyl or thioether. Similarly, these roles of -Y and -Y'' can be reversed to yield -Y*- of opposing orientation.

In certain embodiments, -Y*- comprises an amide, oxime, 1,2,3-triazole, thioether, thiosuccinimide, or ether. In certain embodiments, -Y*- is -L²-.

These conjugation reactions may be performed under conditions known in the art, for example when -Y is azide and -Y'' is cyclooctyne the conjugation occurs in any solvent wherein both components show adequate solubility, although it is known that aqueous solutions show more favorable reaction rates. When mixed in an appropriate solvent, typically an aqueous buffer at a pH of 2 to 7 when -Y and -Y'' are azide/cyclooctyne, or at a pH of 6 to 9 when -Y and -Y'' are an activated ester and an amine, the -Y and -Y'' groups react to form an insoluble hydrogel matrix comprising crosslinks of formula (PL-4'). This process may be carried out in bulk phase, or under conditions of emulsification in a mixed organic/aqueous system so as to form microparticle suspensions such as microspheres that are suitable for injection.

Only in the context of formulas (PL-4) and (PL-4') the terms used have the following meaning:

The term “alkyl” refers to linear, branched, or cyclic saturated hydrocarbon groups of 1 to 20, 1 to 12, 1 to 8, 1 to 6, or 1 to 4 carbon atoms. In certain embodiments an alkyl is linear or branched. Examples of linear or branched alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl. In certain embodiments an alkyl is cyclic. Examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentadienyl, and cyclohexyl.

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

The term “alkenyl” refers to non-aromatic unsaturated hydrocarbons with carbon-carbon double bonds and 2 to 20, 2 to 12, 2 to 8, 2 to 6, or 2 to 4 carbon atoms.

The term “alkynyl” refers to non-aromatic unsaturated hydrocarbons with carbon-carbon triple bonds and 2 to 20, 2 to 12, 2 to 8, 2 to 6, or 2 to 4 carbon atoms.

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

In certain embodiments, alkenyl, alkynyl, aryl or heteroaryl moieties may be coupled to the remainder of the molecule through an alkyl 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.

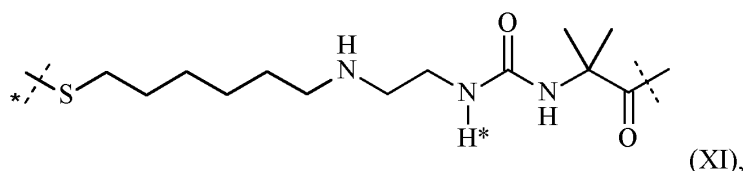
The term “halogen” or “halo” refers to bromo, fluoro, chloro or iodo.

The term “heterocyclic ring” or “heterocyclyl” refers to a 3- to 15-membered aromatic or non-aromatic ring comprising at least one N, O, or S atom. Examples include piperidinyl, piperazinyl, tetrahydropyranyl, pyrrolidine, and tetrahydrofuranyl, as well as the exemplary

groups provided for the term “heteroaryl” above. In certain embodiments, a heterocyclic ring or heterocyclyl is non-aromatic. In certain embodiments, a heterocyclic ring or heterocyclyl is aromatic.

The term “optionally substituted” refers to a group that may be unsubstituted or substituted by one or more (e.g., 1, 2, 3, 4 or 5) of the substituents which may be the same or different. Examples of substituents include alkyl, alkenyl, alkynyl, halogen, -CN, -OR^{aa}, -SR^{aa}, -NR^{aa}R^{bb}, -NO₂, -C=NH(OR^{aa}), -C(O)R^{aa}, -OC(O)R^{aa}, -C(O)OR^{aa}, -C(O)NR^{aa}R^{bb}, -OC(O)NR^{aa}R^{bb}, -NR^{aa}C(O)R^{bb}, -NR^{aa}C(O)OR^{bb}, -S(O)R^{aa}, -S(O)₂R^{aa}, -NR^{aa}S(O)R^{bb}, -C(O)NR^{aa}S(O)R^{bb}, -NR^{aa}S(O)₂R^{bb}, -C(O)NR^{aa}S(O)₂R^{bb}, -S(O)NR^{aa}R^{bb}, -S(O)₂NR^{aa}R^{bb}, -P(O)(OR^{aa})(OR^{bb}), heterocyclyl, heteroaryl, or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl, and aryl are each independently optionally substituted by -R^{cc}, wherein -R^{aa} and -R^{bb} are each independently -H, alkyl, alkenyl, alkynyl, heterocyclyl, heteroaryl, or aryl, or -R^{aa} and -R^{bb} are taken together with the nitrogen atom to which they attach to form a heterocyclyl, which is optionally substituted by alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, or -CN, and wherein: each -R^{cc} is independently alkyl, alkenyl, alkynyl, halogen, heterocyclyl, heteroaryl, aryl, -CN, or -NO₂.

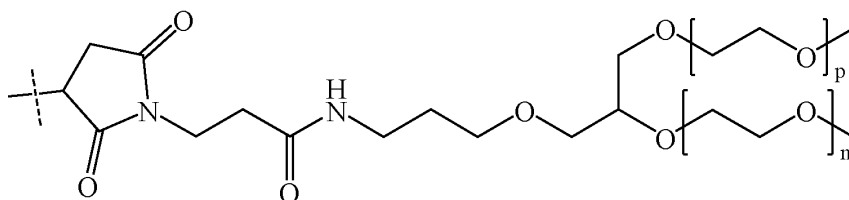
In certain embodiments the PTH compound is a compound of formula (XI)



wherein

the unmarked dashed line indicates the attachment to the nitrogen of the N-terminal amine group of a PTH moiety of SEQ ID NO:51; and

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



wherein

wherein

the dashed line indicates attachment to $-L^2-$ or to the remainder of $-Z$; and
 m and p are independently of each other an integer ranging from and including 150 to 1000; such as an integer ranging from and including 150 to 600; such as an integer ranging from and including 200 to 550; such as an integer ranging from and including 400 to 500 or such as an integer ranging from about 450 to about 500.

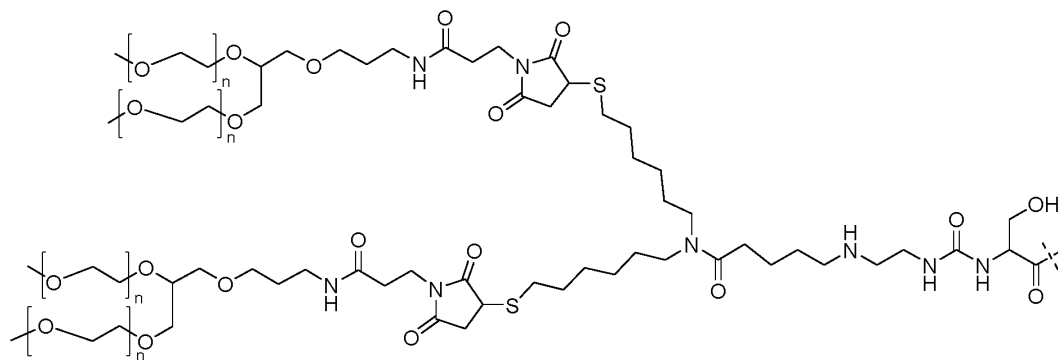
In certain embodiments m and p of formula (XI) are independently an integer ranging from 400 to 500. In certain embodiment m and p of formula (XI) are independently an integer ranging from approx. 450 to 500. In certain embodiment m and p of formula (XI) are independently an integer ranging from 450 to 500.

The compound of formula (XI) is also known as palopegteriparatide, TransCon PTH or ACP-014.

It is understood that the nitrogen of the N-terminal amine group of the PTH moiety of formula (XI) and the carbonyl $-(C=O)-$ group to the left of the unmarked dashed line form an amide bond.

The PTH compound of formula (XI) releases PTH of SEQ ID NO:51, PTH 1-34, meaning that its active PTH is PTH 1-34.

In certain embodiments the PTH compound is a compound of formula (XII)



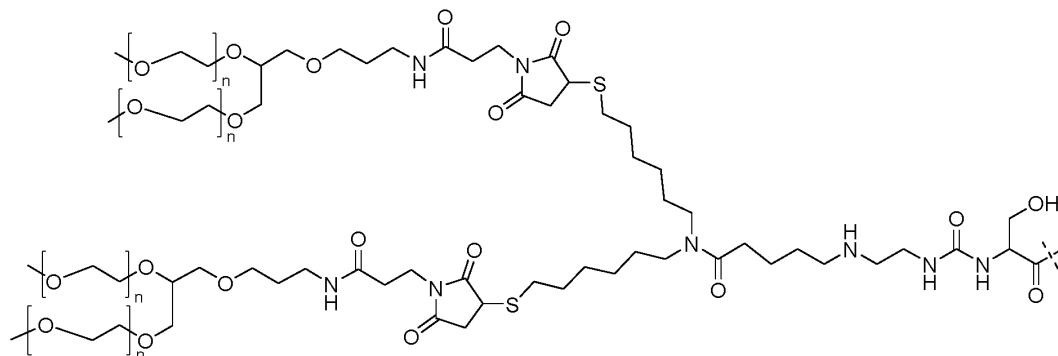
(XII),

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

In certain embodiment the PTH compound is a compound of formula (XII#)



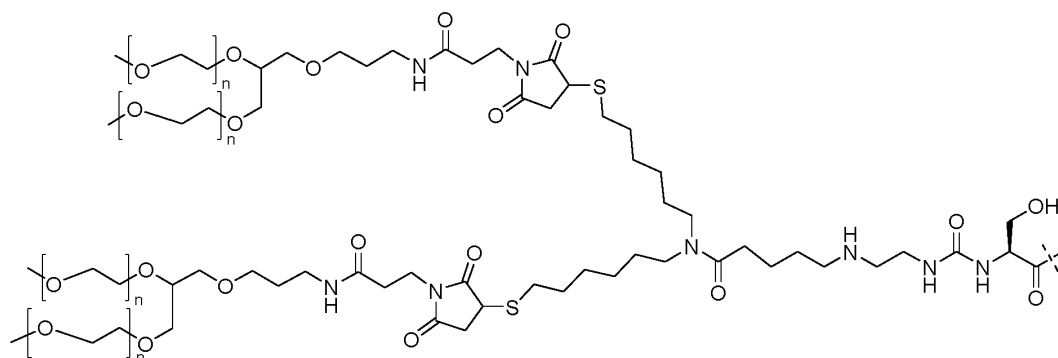
(XII#),

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from and including 150 to 1000; such as an integer ranging from and including 150 to 600; such as an integer ranging from and including 200 to 550; such as an integer ranging from and including 400 to 500 or such as an integer ranging from about 450 to about 500.

In certain embodiments the PTH compound is a compound of formula (XII')



(XII'),

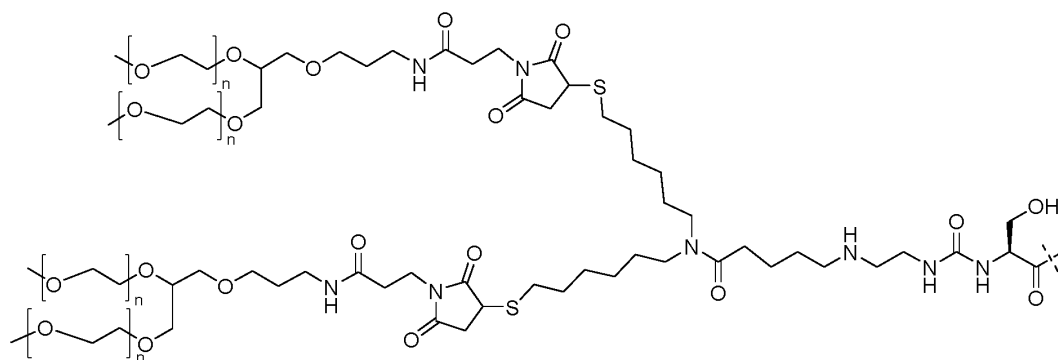
wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

In certain embodiments each n of formula (XII) and (XII') is independently an integer ranging from 200 to 250. In certain embodiments each n of formula (XII) and (XII') is independently an integer ranging from approx. 210 to 240. In certain embodiments each n of formula (XII) and (XII') is independently an integer ranging from 210 to 240. In certain embodiments all n are the same integer.

In certain embodiments the PTH compound is a compound of formula (XII')#

 $(\text{XII}'\#),$

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

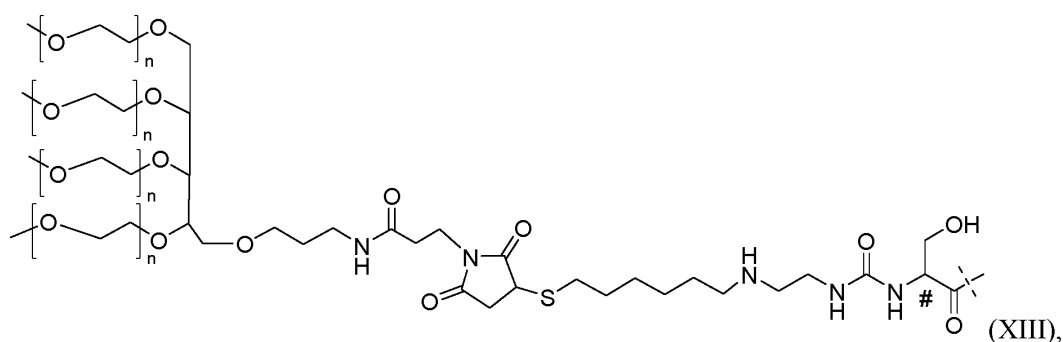
each n is independently an integer ranging from and including 150 to 1000; such as an integer ranging from and including 150 to 600; such as an integer ranging from and including 200 to 550; such as an integer ranging from and including 400 to 500 or such as an integer ranging from about 450 to about 500.

It is understood that the nitrogen of the N-terminal amine group of the PTH moiety and the carbonyl ($-(C=O)-$) group in formula (XII), (XII#), (XII') or (XII'#) to the left of the dashed line form an amide bond.

The PTH compound of formula (XII), (XII#), (XII') or (XII' #) releases PTH of SEQ ID NO:51, PTH 1-34, meaning that the active PTH of the PTH compound of formula (XII), (XII#), (XII') or (XII' #) is PTH 1-34.

In certain embodiments each n of formula (XII) and (XII') is independently an integer ranging from 200 to 250. In certain embodiments each n of formula (XIII) and (XIII') is independently an integer ranging from approx. 210 to 240. In certain embodiments each n of formula (XIII) and (XIII') is independently an integer ranging from 210 to 240. In certain embodiments all n of formula (XII) and (XII') are an integer ranging from 200 to 250. In certain embodiments all n of formula (XIII) and (XIII') are an integer ranging from approx. 210 to 240. In certain embodiments all n of formula (XIII) and (XIII') are an integer ranging from 210 to 240.

In certain embodiments the PTH compound is a compound of formula (XIII)



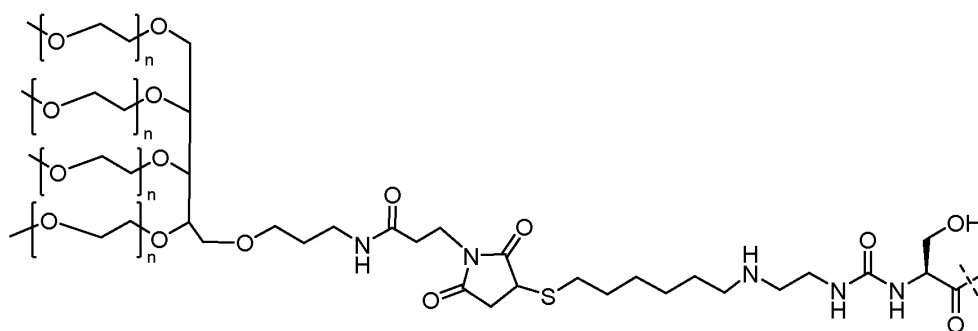
wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

The chiral center marked with “#” in formula (XIII) may be in L- or D-configuration or may be a mixture of both L- and D-configuration. In certain embodiments said chiral center is in L-configuration.

In certain embodiments the second PTH compound is a compound of formula (XIII')



(XIII'),

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

In certain embodiments each n of formula (XIII) and (XIII') is independently an integer ranging from 200 to 250. In certain embodiments each n of formula (XIII) and (XIII') is independently an integer ranging from approx. 210 to 240. In certain embodiments each n of formula (XIII) and (XIII') is independently an integer ranging from 210 to 240. In certain embodiments all n of formula (XIII) and (XIII') are an integer ranging from 200 to 250. In certain embodiments all n of formula (XIII) and (XIII') are an integer ranging from approx. 210 to 240. In certain embodiments all n of formula (XIII) and (XIII') are an integer ranging from 210 to 240.

It is understood that the nitrogen of the N-terminal amine group of the PTH moiety and the carbonyl $-(C=O)-$ group in formula (XIII) and (XIII') to the left of the dashed line form an amide bond.

The PTH compound of formula (XIII) and (XIII') releases PTH of SEQ ID NO:51, PTH 1-34, meaning that the active PTH of the PTH compound of formula (II-b) and (II-b') is PTH 1-34.

In certain embodiments the PTH compound is compound of formula (XIV)

$k(\gamma E-(\text{miniPEG})_2-\gamma E-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})(\text{N-Me})\text{GSVSEIQLMHNLGKHLNSMERVEWLRKK}$
 $\text{LQDVHK}(\gamma E-(\text{miniPEG})_2-\gamma E-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})-\text{OH}$ (XIV),

wherein

k is d-Lys;

γ E is the l-isomer of gamma, glutamic acid;
 miniPEG is $\text{COCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$;
 $\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H}$ is C18 diacid;
 (N-Me)G is sarcosine;
 K is l-isomer of lysine; and
 -OH designates the C-terminal amino acid has a terminal carboxylic acid.

In certain embodiments the second PTH compound is compound of formula (XIV')
 $\text{k}(\gamma\text{E}-(\text{miniPEG})_2-\gamma\text{E}-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})(\text{N-Me})\text{GSVSEIQLMHNLGKHLNSMERVEWLRKK}$
 $\text{LQDVHK}(\gamma\text{E}-(\text{miniPEG})_2-\gamma\text{E}-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})-\text{OH}$ (XIV'),

wherein
 k is d-Lys;
 γ E is the l-isomer of gamma, glutamic acid;
 $(\text{miniPEG})_2$ is $\text{COCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$;
 $\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H}$ is C18 diacid;
 (N-Me)G is sarcosine;
 K is l-isomer of lysine; and
 -OH designates the C-terminal amino acid has a terminal carboxylic acid.

The compound of formula (XIV') corresponds to SEQ ID NO:87 of WO2021/242756 and the sequence "SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHK" corresponds to PTH (1-32) (SEQ ID NO:53) therein + K33.

The compound of formula (XIV) releases a compound of formula (XIV-i)
 $\text{SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHK}(\gamma\text{E}-(\text{miniPEG})_2-\gamma\text{E}-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})-\text{OH}$ (XIV-i),

wherein
 γ E is the l-isomer of gamma, glutamic acid;
 miniPEG is $\text{COCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$;
 $\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H}$ is C18 diacid;
 K is l-isomer of lysine; and
 -OH designates the C-terminal amino acid has a terminal carboxylic acid.

The compound of formula (XIV-i) is the active PTH of the compound of formula (XIV).

The compound of formula (XIV') releases a compound of formula (XIV-i')
 SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHK(γ E-(miniPEG)₂- γ E-
 COC₁₆H₃₂CO₂H)-OH (XIV-i'),

wherein

k is d-Lys;

γ E is the l-isomer of gamma, glutamic acid;

(miniPEG)₂ is COCH₂OCH₂CH₂OCH₂CH₂NH;

COC₁₆H₃₂CO₂H is C18 diacid;

K is l-isomer of lysine; and

-OH designates the C-terminal amino acid has a terminal carboxylic acid.

The compound of formula (XIV-i') is the active PTH of the compound of formula (XIV-i').

In certain embodiments the PTH compound of formula (XIV) or (XIV') is administered in a dose ranging from 300 μ g/week to 500 μ g/week.

The PTH compound may be administered in the form of a pharmaceutical composition. Such pharmaceutical composition comprises at least one PTH compound as described elsewhere herein and at least one excipient.

Such the pharmaceutical composition may have a pH ranging from and including pH 3 to pH 8 or ranging from and including pH 4 to pH 6. In certain embodiments such pharmaceutical composition has a pH ranging from and including pH 4 to pH 5.

In certain embodiments such pharmaceutical composition is a liquid or suspension formulation. It is understood that the pharmaceutical composition is a suspension formulation if the PTH compound is water-insoluble, such as when it comprises a water-insoluble carrier -Z'.

In certain embodiments such pharmaceutical composition is a dry formulation.

Such liquid, suspension or dry pharmaceutical composition comprises at least one excipient. Excipients used in pharmaceutical compositions 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. The at least one excipient comprised in the pharmaceutical composition of the present invention may be selected from the group consisting of

- (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;
- (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;
- (iii) Preservatives and/or antimicrobials: multidose parenteral formulations require the addition of preservatives at a sufficient concentration to minimize risk of subjects 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 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-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);
- (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 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 auxiliary agents necessary for pH adjustment during manufacture.

The PTH compound, its pharmaceutically acceptable salt or the pharmaceutical composition comprising the PTH compound or its pharmaceutically acceptable salt may be administered to a subject by various modes of administration, such as via topical, enteral or parenteral administration and by methods of external application, injection or infusion, including intraarticular, periarticular, intradermal, subcutaneous, intramuscular, intravenous, intraosseous, intraperitoneal, intrathecal, intracapsular, intraorbital, intravitreal, intratympanic, intravesical, intracardiac, transtracheal, subcuticular, subcapsular, subarachnoid, intraspinal, intraventricular, intrasternal injection and infusion, direct delivery to the brain via implanted device allowing delivery of the invention or the like to brain tissue or brain fluids (e.g., Ommaya Reservoir), direct intracerebroventricular injection or infusion, injection or infusion into brain or brain associated regions, injection into the subchoroidal space, retro-orbital injection and ocular instillation. In certain embodiments the PTH compound, its pharmaceutically acceptable salt or the pharmaceutical composition comprising the PTH compound or its pharmaceutically acceptable salt is administered via subcutaneous injection.

Such subcutaneous injection is suitably done with a syringe and needle or with a pen injector. In certain embodiments the PTH compound, its pharmaceutically acceptable salt, the pharmaceutical composition comprising the PTH compound or its pharmaceutically acceptable salt is administered via subcutaneous injection with a pen injection.

The PTH compound, its pharmaceutically acceptable salt, the pharmaceutical composition comprising the PTH compound or its pharmaceutically acceptable salt may be administered as needed by the subject, such as twice a day, once a day, once every two days, once a week, once every two weeks or once a month.

In certain embodiments the PTH compound is the PTH compound of formula (XI), which is administered once a day, for example via subcutaneous injection. A suitable starting dose for treatment with the PTH compound of formula (XI) may be 18 µg/day, wherein the dose is based on the weight of the PTH moiety only and excludes the remainder of the PTH compound.

In certain embodiments the PTH compound is the PTH compound of SEQ ID NO:122, which is administered once a day, for example via subcutaneous injection.

In certain embodiments the PTH compound is the PTH compound of formula (XII) or (XII'), which may be administered once a week, for example via subcutaneous injection.

In certain embodiments the PTH compound is the PTH compound of formula (XIII) or (XIII'), which may be administered once a week, for example via subcutaneous injection.

In certain embodiments the starting dose for the compound of formula (XI) ranges from 12 to 24 µg PTH 1-34 per day. In certain embodiments the starting dose for the compound of formula (XI) ranges from 15 to 21 µg PTH 1-34 per day. In certain embodiments the starting dose for the compound of formula (XI) is 18 ± 3 µg PTH 1-34 per day. In certain embodiments the starting dose for the compound of formula (XI) is 18 µg PTH 1-34 per day.

In certain embodiments the PTH compound is the compound of formula (XI) and is administered to the subject in the form of a pharmaceutical composition. In certain embodiments 1 ml of such pharmaceutical composition comprises 3456 µg of the compound of formula (XI), which corresponds to 300 µg of PTH 1-34, 1.18 mg succinic acid, 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide and water for injection and has a pH of 3.7 to 4.3. In certain embodiments 1 ml of such pharmaceutical composition comprises 3456 µg of the PTH compound of formula (XI), which corresponds to 300 µg of PTH 1-34, 1.18 mg

succinic acid, 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide and water for injection and has a pH of 3.7 to 4.3.

In certain embodiments the number of presentations of such pharmaceutical composition ranges from 2 to 8, each presentation comprising a different dose of the PTH compound of formula (XI). In certain embodiments the number of presentations of the pharmaceutical composition ranges from 2 to 6, each presentation comprising a different dose of the PTH compound of formula (XI). In certain embodiments the number of presentations of the pharmaceutical composition ranges from 2 to 4, each presentation comprising a different dose of the PTH compound of formula (XI). In certain embodiments the pharmaceutical composition is provided in 3 presentations, each presentation comprising a different dose of the PTH compound of formula (XI). In certain embodiments each presentation is a prefilled pen.

In certain embodiments the pharmaceutical composition is provided in 3 presentations, wherein the first presentation is a prefilled pen comprising 168 µg PTH 1-34/0.56 mL, the second presentation is a prefilled pen comprising 294 µg PTH 1-34 /0.98 mL and the third presentation is a prefilled pen comprising 420 µg PTH 1-34/1.4 mL, wherein the PTH 1-34 is provided in the form of the PTH compound of formula (XI).

The first of these three presentations may be used to administer doses of 6, 9 or 12 µg PTH 1-34/day, the second presentation may be used to administer doses of 15, 18 or 21 µg PTH 1-34/day and the third presentation may be used to administer doses of 24, 27 or 30 µg PTH 1-34/day. Doses higher than 30 and up to and including 60 µg PTH 1-34/day may be administered as two sequential administrations. For example, a dose of 33 µg PTH 1-34/day may be administered as a combination of a dose of 15 µg PTH 1-34/day + a dose of 18 µg PTH 1-34/day; a dose of 36 µg PTH 1-34/day may be administered as a combination of a dose of 18 µg PTH 1-34/day + a dose of 18 µg PTH 1-34/day; a dose of 39 µg PTH 1-34/day may be administered as a combination of a dose of 18 µg PTH 1-34/day + a dose of 21 µg PTH 1-34/day; a dose of 42 µg PTH 1-34/day may be administered as a combination of a dose of 21 µg PTH 1-34/day + a dose of 21 µg PTH 1-34/day; a dose of 45 µg PTH 1-34/day may be administered as a combination of a dose of 21 µg PTH 1-34/day + a dose of 24 µg PTH 1-34/day; a dose of 48 µg PTH 1-34/day may be administered as a combination of a dose of 24 µg PTH 1-34/day + a dose of 24 µg PTH 1-34/day; a dose of 51 µg PTH 1-34/day may be

administered as a combination of a dose of 24 µg PTH 1-34/day + a dose of 27 µg PTH 1-34/day; a dose of 54 µg PTH 1-34/day may be administered as a combination of a dose of 27 µg PTH 1-34/day + a dose of 27 µg PTH 1-34/day; a dose of 57 µg PTH 1-34/day may be administered as a combination of a dose of 27 µg PTH 1-34/day + a dose of 30 µg PTH 1-34/day; and a dose of 60 µg PTH 1-34/day may be administered as a combination of a dose of 30 µg PTH 1-34/day + a dose of 30 µg PTH 1-34/day, wherein the PTH 1-34 is provided by the compound of formula (XI).

In a subject having hypoparathyroidism with chronic kidney disease the treatment of step (a) may be initiated by

(i-a) confirming that the serum 25(OH) vitamin D of the subject is within the normal range within two weeks before the first dose of the compound of formula (XI) is administered to the subject and serum calcium is ≥ 7.8 mg/dL at the initiation of treatment;

(i-b) if the subject is taking active vitamin D at the time treatment with the compound of formula (XI) is initiated:

(i-b-i) maintaining the same dose of calcium supplements and discontinue active vitamin D on the same day as the first dose of the compound of formula (XI) is administered, if serum calcium is ≥ 8.3 mg/dL; or

(i-b-ii) reducing the dose of active vitamin D by $\geq 50\%$ on the same day as the first dose of the compound of formula (XI) is administered and maintaining the same dose of calcium supplements, if serum calcium is < 8.3 mg/dL; or

if the subject is not taking active vitamin D at the time treatment with the compound of formula (XI) is initiated:

(i-b-iii) decreasing calcium supplements by at least 1500 mg on the same day as the first dose of the compound of formula (XI) is administered; and

(i-c) optionally continuing dietary calcium supplements at doses of ≤ 600 mg/day as indicated to meet dietary calcium requirements.

In certain embodiments serum 25(OH) vitamin D is within the normal range if its concentration is between 20 and 80 ng/ml.

If the subject is not taking active vitamin D and if calcium supplement doses of ≤ 1500 mg calcium/day are taken, calcium supplement doses are discontinued entirely in step (i-b-iii).

In certain embodiments the treatment of step (a) in a subject having hypoparathyroidism with chronic kidney disease may be initiated by

(i-a) confirming that the serum 25(OH) vitamin D of the subject is within the normal range within two weeks before the first dose of the compound of formula (XI) is administered to the subject and serum calcium is ≥ 7.8 mg/dL at the initiation of treatment;

(i-b) if the subject is taking active vitamin D at the time treatment with the compound of formula (XI) is initiated:

(i-b-i) maintaining the same dose of calcium supplements and reducing active vitamin D dosage by $\geq 50\%$ if serum calcium is ≥ 8.3 mg/dL and current active vitamin D intake is > 1 $\mu\text{g/day}$ on the day of initiating the treatment with the PTH compound; or

(i-b-ii) maintaining the same dose of calcium supplements and discontinuing active vitamin D dosage if serum calcium is ≥ 8.3 mg/dL and current active vitamin D intake is ≤ 1 $\mu\text{g/day}$ on the day of initiating the treatment with the PTH compound; or

(i-b-iii) maintaining the same dose of calcium supplements and reducing active vitamin D dosage by $\geq 50\%$ if serum calcium is ≥ 7.8 to < 8.3 mg/dL at any amount of active vitamin D intake on the day of initiating the treatment with the PTH compound; or

if the subject is not taking active vitamin D at the time treatment with the compound of formula (XI) is initiated:

(i-b-iii) reducing the dose of calcium supplement by at least 1500 mg or discontinuing if current calcium daily dosage is ≤ 1500 mg/day if serum calcium is ≥ 7.8 mg/dL; and

(i-c) optionally continuing dietary calcium supplements at doses of ≤ 600 mg/day as indicated to meet dietary calcium requirements.

In certain embodiments step (a) may in addition to steps (i-a) to (i-c) further comprise the steps of

- (i-d) administering a starting dose of 18 µg PTH 1-34/day in the form of the compound of formula (XI), followed by daily administrations of the same dose;
- (i-e) measuring serum calcium within 7 to 14 days of the first administration of the compound of formula (XI); and
- (i-f) adjusting the dose of the compound of formula (XI), active vitamin D and/or calcium supplement.

In certain embodiments the compound of formula (XI) is administered in step (i-d) as a pharmaceutical composition, of which each ml comprises 3456 µg of the compound of formula (XI), which corresponds to 300 µg of PTH 1-34, 1.18 mg succinic acid, 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide, and water for injection. In certain embodiments the pharmaceutical composition has a pH of 3.7 to 4.3.

Adjusting the dose of the compound of formula (XI), active vitamin D and/or calcium supplement in step (i-f) is performed based on the serum calcium levels from step (i-e).

In certain embodiments adjustments in the dose of the compound of formula (XI), active vitamin D and/or calcium supplement of step (i-f) are performed as follows:

(i-f-i) if serum calcium is <8.3 mg/dL:

- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, the same calcium supplement and active vitamin D doses are continued, and the dose of the compound of formula (XI) is increased by 3 µg; or
- if fewer than 7 days have passed since treatment with the compound of formula (XI) has started or the dose of the compound of formula (XI) was changed, calcium supplements and/or active vitamin D are increased toward prior doses based on physician's clinical judgement and the same dose of the compound of formula (XI) is continued;

(i-f-ii) if serum calcium ranges from 8.3 to 10.6 mg/dL:

- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or since the dose of the compound of formula (XI) was changed and the subject is still taking active vitamin D, active vitamin D is discontinued, and the dose of the compound of formula (XI) is increased by 3 µg;

- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or since the dose of the compound of formula (XI) was changed and the subject is no longer taking active vitamin D, but is taking calcium supplements, wherein the calcium supplement is ≥ 1500 mg/day, the calcium supplement is decreased by ≥ 1500 mg and the dose of the compound of formula (XI) is increased by 3 μg ;
 - if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or since the dose of the compound of formula (XI) was changed and the subject is no longer taking active vitamin D, but is taking calcium supplements, wherein the calcium supplement is less than 1500 mg/day, calcium supplements are discontinued, and the dose of the compound of formula (XI) is increased by 3 μg ;
 - if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or since the dose of the compound of formula (XI) was changed and the subject is no longer taking active vitamin D and is no longer taking calcium supplements, the same dose of the compound of formula (XI) is continued; or
 - if fewer than 7 days have passed since treatment with the compound of formula (XI) was started or since the dose of the compound of formula (XI) was changed, the same dose of the compound of formula (XI), of the calcium supplement and active vitamin D is continued;
- (i-f-iii) if serum calcium ranges from 10.7 to 11.9 mg/dL:
- if the subject is still taking active vitamin D, active vitamin D is discontinued and the same doses of the compound of formula (XI) and calcium supplement are continued;
 - if the subject is not taking active vitamin D but takes calcium supplements at a dose of ≥ 1500 mg/day, calcium supplements are decreased by ≥ 1500 mg and the same dose of the compound of formula (XI) is continued;
 - if the subject is not taking active vitamin D but takes calcium supplements, which calcium supplements are less than 1500 mg per day, calcium supplements are discontinued, and the same dose of the compound of formula (XI) is continued; or

- if the subject is not taking active vitamin D and does not take calcium supplements, the dose of the compound of formula (XI) is decreased by 3 μg ; or
- (i-f-iv) if serum calcium is ≥ 12 mg/dL:
- withhold the compound of formula (XI) for 2 to 3 days, recheck serum calcium and
 - if subsequent serum calcium is <12 mg/dL, resume titration of the compound of formula (XI), active vitamin D and calcium supplements as described in steps (i-f-i) to (i-f-iii) using the most recent serum calcium value obtained; and
 - if serum calcium remains ≥ 12 mg/dL, withhold the compound of formula (XI) for an additional 2 to 3 days, recheck serum calcium and proceed as described in the previous step.

In certain embodiments the dosage range of the compound of formula (XI) administered to the subject ranges from and includes 6 to 60 μg PTH 1-34/day, which doses may be provided in prefilled pens of 168 μg PTH 1-34/0.56 mL (delivering doses of 6, 9 or 12 μg PTH 1-34); 294 μg PTH 1-34/0.98 mL (delivering doses of 15, 18, or 21 μg PTH 1-34); and 420 μg PTH 1-34/1.4 mL (delivering doses of 24, 27, or 30 μg PTH 1-34).

In certain embodiments adjustments in the dose of the compound of formula (XI), active vitamin D and/or calcium supplement of step (i-f) are performed as follows:

if serum calcium is < 8.3 mg/dL:

- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, continuing with the same calcium supplement and active vitamin D doses and increase the dose of the compound of formula (XI) by 3 μg ; or
- if fewer than 7 days have passed since treatment with the compound of formula (XI) has started or the dose of the compound of formula (XI) was changed, increasing calcium supplements and/or active vitamin D toward prior doses based on physician's clinical judgement and continuing the same dose of the compound of formula (XI);

if serum calcium ranges from 8.3 to 10.6 mg/dL:

- if fewer than 7 days have passed since treatment with the compound of formula (XI) has started or the dose of the compound of formula (XI) was changed, continuing with the same dose of the compound of formula (XI), calcium supplements and active vitamin D;
- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, and the subject is still taking active vitamin D, decreasing or discontinuing active vitamin D and increasing the dose of the compound of formula (IX) by 3 μg ;
- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, the subject is no longer taking active vitamin D and is no longer taking calcium supplements, continuing the same dose of the compound of formula (XI);
- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, the subject is no longer taking active vitamin D and is taking calcium supplements with a dose ≥ 1500 mg/day, decreasing calcium supplements by ≥ 1500 mg and increasing the dose of the compound of formula (XI) by 3 μg ;
- if ≥ 7 days have passed since treatment with the compound of formula (XI) was started or the dose of the compound of formula (XI) was changed, the subject is no longer taking active vitamin D and is taking calcium supplements with a dose ≤ 1500 mg/day, discontinue calcium supplements and increasing the dose of the compound of formula (XI) by 3 μg ;

if serum calcium ranges from 10.7 to 11.9 mg/dL:

- if the patient is still taking active vitamin D, decreasing or discontinuing active vitamin D and continuing on the same doses of the compound of formula (XI) and calcium supplements;
- if the patient is no longer taking active vitamin D and is no longer taking calcium supplements, decreasing the dose of the compound of formula (XI) by 3 μg ;
- if the patient is no longer taking active vitamin D and is still taking calcium supplements of ≥ 1500 mg/day, decreasing calcium supplements by ≥ 1500 mg and continuing with the same dose of the compound of formula (XI);

- if the patient is no longer taking active vitamin D and is still taking calcium supplements but with a dose of < 1500 mg/day, discontinuing calcium supplements and continuing with the same dose of the compound of formula (XI);

if serum calcium is 12 mg/dL or more, withholding the compound of formula (XI) for 2 to 3 days and rechecking serum calcium and repeat, if serum calcium remains at 12 mg/dL or more and once serum calcium is < 12 mg/dL, resuming titration of the compound of formula (XI), active vitamin D and calcium supplements as described above.

In certain embodiments the compound of formula (XI) or the pharmaceutical composition comprising the compound of formula (XI) is inspected visually for particulate matter and discoloration prior to administration.

In certain embodiments dose adjustments of the PTH compound of formula (XI), active vitamin D and calcium supplement are made on the same day. After a dose change in the compound of PTH compound of formula (XI), active vitamin D or calcium supplements, serum calcium is in certain embodiments measured within 7 to 14 days and the subject may be monitored for clinical symptoms of hypocalcemia or hypercalcemia and doses of the PTH compound of formula (XI), active vitamin D and/or calcium supplements may be adjusted as described above.

The dose of the PTH compound of formula (XI) may be increased as described above in increments of 3 μg if at least 7 days have elapsed since a prior dose change of the PTH compound of formula (XI). In certain embodiments the dose of the PTH compound of formula (XI) administered to the subject is no more often than every 7 days adjusted. The dose of the PTH compound of formula (XI) may be reduced no more often than every 3 days in 3 μg increments in response to hypercalcemia as described above.

The maintenance dose should be the dose of the PTH compound of formula (XI) that achieves serum calcium within the normal range, without the need for active vitamin D and calcium supplement. Optionally, calcium supplementation sufficient to meet dietary requirements may be continued. Serum calcium may be measured per standard of care once a maintenance dose is achieved.

In certain embodiments step (a) may in addition to steps (i-a) to (i-f) further comprise the steps of

(i-g) administration of a daily maintenance dose; and

(i-h) measuring serum calcium per standard of care.

Optionally, step (i-h) is followed by repeating steps (i-f) to (i-h), if serum calcium levels are not within the normal range, such as within a range from 8.3 to 10.6 mg/dL.

If a dose of the PTH compound of formula (XI) is missed by less than 12 hours, it may be taken as soon as possible. If a dose is missed by more than 12 hours, it may be skipped, and the next dose is then taken as scheduled. If administration of 3 or more consecutive doses is missed, it is recommended to monitor for signs and symptoms of hypocalcemia and to consider measuring serum calcium. If indicated, treatment with active vitamin D and calcium supplement may be resumed. In certain embodiments administration of the PTH compound of formula (XI) is resumed at the prescribed dose as soon as possible after an interruption, which prescribed dose may be the maintenance dose or not. When resuming treatment after an interruption, serum calcium should be measured and doses of the PTH compound of formula (XI), active vitamin D and calcium supplement may be adjusted as described above.

Pharmaceutical compositions and presentations for the PTH compound of formula (XI) as used in steps (i-a) to (i-g) are as described elsewhere herein.

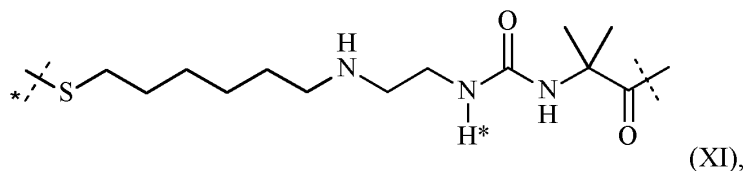
In certain embodiments the PTH compound is the PTH compound of SEQ ID NO:122, which may be administered at a dose ranging from 20 µg to 60 µg per day.

In certain embodiments the PTH is the PTH compound of formula (XII) or (XII') and the initial dose ranges from 100 µg to 250 µg/week, from 101.25 µg to 168.75 µg/week, from 101.25 µg to 168.75 µg/week, from 108 µg to 162 µg/week, from 114.75 µg to 155.25 µg/week, from 121.5 µg to 148.5 or from 128.25 µg to 141.75 µg/week. In certain embodiments the PTH is the PTH compound of formula (XII) or (XII') and the initial dose is about 135 µg/week.

Examples

Synthesis of Compound 1

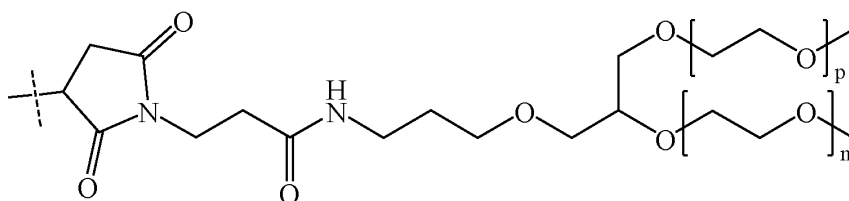
Compound 1 is also known as palopegteriparatide and has the following structure:



wherein

the unmarked dashed line indicates the attachment to the nitrogen of the N-terminal amine group of a PTH moiety of SEQ ID NO:51; and

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



wherein

wherein

the dashed line indicates attachment to -L²- or to the remainder of -Z; and

m and p are an integer ranging from about 450 to about 500.

Compound 1 can be manufactured as described for compound 18 in example 18 of WO2017/148883.

Example 1: TCP-304

In TCP-304 (NCT04701203), a Phase 3, double-blind, placebo-controlled trial, subjects were randomized 3:1 to receive compound 1 or placebo for 26 weeks, followed by an open-label extension period where all subjects received compound 1. In this trial, serum creatinine was measured at routine intervals, and estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [Levey et al., 2006]. The MDRD equation is as follows:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{serum creatinine mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ [if female]} \\ \times 1.212 \text{ [if Black]}$$

Eligibility criteria excluded subjects with an eGFR < 30 mL/min/1.73m². As of 20-JUL-2022, eGFR data for TCP-304 is available from baseline through 52 weeks of follow-up. Mean eGFR at baseline was roughly similar across groups (compound 1: 67.32; Placebo: 72.70) but consistently below the normal level of 90 mL/min/1.73m² (Table 1). The majority of subjects in TCP-304 demonstrated some impairment of renal function at baseline. In total, 28.0% of randomized subjects (compound 1: 31.1%; Placebo: 19.0%) had a baseline eGFR < 60 mL/min/1.73m², defining stage 3a or worse chronic kidney disease (CKD) per the 2012 KDIGO Guidelines for CKD [KDIGO CKD Work Group, 2013; KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.].

Table 1: Baseline Renal Function – TCP-304

Baseline eGFR per MDRD (mL/min/1.73m²)	Compound 1/ Compound 1	Placebo / Compound 1	Total
N	61	21	82
Mean (SD)	67.32 (13.746)	72.20 (14.642)	68.70 (14.088)
Subjects with baseline eGFR (n (%)):			
< 60 mL/min/1.73 m ²	19 (31.1)	4 (19.0)	23 (28.0)
≥ 60 mL/min/1.73 m ²	42 (68.9)	17 (81.0)	59 (72.0)

Abbreviations: eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; N = number of subjects; SD = standard variation

The change from baseline in eGFR over the available 52 weeks of follow up is presented in Table 2. Treatment with compound 1 was associated with a rapid increase (i.e., improvement) in eGFR evident as early as week 4 that was sustained through week 52. Across treatment groups, the slope (95% CI) of the change in eGFR from baseline to week 4 was similar (compound 1/compound 1: 1.25 [0.6, 1.9] mL/min/1.72m²/week [P <.0001]; placebo/compound 1: 1.20 [0.3, 2.1] mL/min/1.72m²/week [P <.01]). After week 4, subjects randomized to compound 1 had stabilization of eGFR, with slope (95% CI) of change in eGFR of 0.20 (-0.2, 0.6) mL/min/1.72m²/week from week 4 to 12 (P ≥.05), 0.07 (-0.1, 0.3) mL/min/1.72m²/week from week 12 to 26 (P ≥.05), and 0.05 (-0.1, 0.2) mL/min/1.72m²/week

from week 26 to 52 ($P \geq .05$). Conversely, subjects randomized to placebo experienced a reversal of eGFR changes back to baseline after week 4, with negative slope (95% CI) of change in eGFR of -0.23 (-0.8, 0.3) mL/min/1.72m²/week from week 4 to 12 ($P \geq .05$) and -0.43 (-0.8, -0.1) mL/min/1.72m²/week from week 12 to 26 ($P < .05$). After starting compound 1 at week 26, the slope (95% CI) of change in eGFR significantly increased to 0.30 (0.1, 0.2) mL/min/1.72m²/week from week 26 to 52 ($P < .01$).

At the end of the blinded treatment period at Week 26, a mean 7.90 mL/min/1.73m² increase in eGFR was observed for subjects randomized to receive compound 1 (95% CI: 5.20, 10.59), compared to a -1.91 mL/min/1.73m² decrease in eGFR for placebo treated subjects (95% CI: -6.05, 2.24) (Table 2). Using a paired t-test, this increase from baseline for subjects receiving compound 1 was found to be significantly greater than 0 ($p < 0.0001$, paired t-test), but not for subjects receiving placebo ($p = 0.3468$). An ANCOVA model with change from baseline in eGFR as a dependent variable, treatment, baseline eGFR group and sex as fixed effects and baseline eGFR and age as covariates was used to determine the treatment difference between compound 1 and placebo at Week 26. Using this model, treatment with compound 1 resulted in a least-squares mean (SE) difference of 8.80 (2.50) mL/min/1.73m² for compound 1 vs. placebo ($p = 0.0007$). In the open-label extension the significant increase in eGFR noted at Week 26 for subjects initially randomized to compound 1 was sustained at Week 52. Specifically, we observed a mean 9.28 mL/min/1.73m² increase from baseline (95% CI: 6.23, 12.33), again significantly greater than 0 by paired t-test ($p < 0.0001$). Subjects initially randomized to placebo experienced a mean 7.55 mL/min/1.73m² increase from baseline in eGFR (95% CI: 3.35, 11.75) after 26 weeks of active compound 1 treatment in the open-label extension. This increase was also significantly greater than 0 by paired t-test ($p = 0.0014$).

Table 2: Change from Baseline in eGFR at Week 26 (End of Blinded Period) and Week 52 (Open-label Extension) – TCP-304

Change from Baseline in eGFR per MDRD (mL/min/1.73m ²)	Compound 1/ Compound 1	Placebo / Compound 1	Total
Week 26	N 60	19	-
Mean (SD)	7.90 (10.421)	-1.91 (8.597)	-
95% CI	5.20, 10.59	-6.05, 2.24	-

p-value		< 0.0001	0.3468	-
Compound 1 vs. Placebo				
LS Mean (SE)†		8.80 (2.50)		
p-value†		0.0007		
Week 52	N	59	19	78
	Mean (SD)	9.28 (11.717)	7.55 (8.718)	8.86 (11.033)
	95% CI	6.23, 12.33	3.35, 11.75	6.37, 11.35
	p-value*	< 0.0001	0.0014	<0.0001

*Derived from paired t-test, testing if change is > 0

†Calculated from ANCOVA model with change from baseline in eGFR as a dependent variable, treatment, baseline eGFR group and sex as fixed effects and baseline eGFR and age as covariates.

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; N = number of subjects; SD = standard variation; SE = standard error

A responder analysis using the intent-to-treat (ITT) population was also conducted to supplement the above analysis, where treatment response was defined as a ≥ 5 mL/min/1.73m² increase in eGFR from baseline (Table 3). For subjects randomized to compound 1, 57.4% and 63.9% of subjects demonstrated an eGFR treatment response at Week 26 and Week 52, respectively. Subjects randomized to placebo had a 23.8% treatment response rate at Week 26, increasing to 52.4% at Week 52 following 26 weeks of treatment with open label active compound 1. An additional responder analysis was conducted, defining treatment response as a ≥ 10 mL/min/1.73m² increase in eGFR from baseline. For subjects randomized to compound 1, 42.6% of subjects experienced ≥ 10 mL/min/1.73m² increase in eGFR from baseline at both Week 26 and Week 52. At Week 26, 9.5% of subjects randomized to placebo had a ≥ 10 mL/min/1.73m² increase in eGFR from baseline, increasing to 28.6% at Week 52 following 26 weeks of treatment with open label active compound 1.

Table 3: Proportion of Patients with ≥ 5 mL/min/1.73m² Increase and ≥ 10 mL/min/1.73m² Increase in eGFR from Baseline (ITT population, All Subjects) – TCP-304

Treatment Response in eGFR per MDRD	Compound 1/ Compound 1	Placebo / Compound 1	Total
N	61	21	82
Treatment Response:			
≥ 5 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	35 (57.4)	5 (23.8)	-
Week 52	39 (63.9)	11 (52.4)	50 (61.0)
≥ 10 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	26 (42.6)	2 (9.5)	-
Week 52	26 (42.6)	6 (28.6)	32 (39.0)

Treatment response either defined as a ≥ 5 mL/min/1.73 m² increase or ≥ 10 mL/min/1.73 m² increase in eGFR from baseline.

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MDRD = Modified Diet in Renal Disease; N = number of subjects in the ITT population; n = number of subjects with treatment response

Results of both the change from baseline and responder analyses demonstrate that treatment with compound 1 in TCP-304 is associated with sustained increases in eGFR > 8 mL/min/1.73m² over 52 weeks of treatment. These changes in eGFR are:

1. substantially higher than the +2.13 to +3.02 mL/min/1.73m² increase estimated for rhPTH(1-84) after 1 year of treatment [Ayodele et al., Adv Ther. 2022 Nov;39(11):5013-5024; Chen et al., J Clin Endocrinol Metab. 2020 Oct 1;105(10):e3557-65]; AND
2. above 5 mL/min/1.73m², a change in eGFR considered clinically significant [Hirst et al., Br J Gen Pract. 2022 Mar 31;72(717):e261-e268, KDIGO CKD Work Group, 2013, Kidney inter., Suppl. 2013; 3: 1-150], for the majority of subjects receiving compound 1 for ≥ 26 weeks.

Analysis in the change from baseline in eGFR over the available 52 weeks of follow up was also done by eGFR subgroup (i.e. < 60 vs. ≥ 60 mL/min/1.73 m²). At baseline, 23 subjects had

an eGFR < 60 mL/min/1.73 m² (Compound 1: n = 19; placebo: n = 4) and 59 subjects had an eGFR ≥ 60 mL/min/1.73 m² (Compound 1: n = 42; placebo: n = 17). Regardless of baseline eGFR subgroup, compound 1 treatment was again associated with a rapid increase in eGFR evident as early as Week 4 and sustained improvement through Week 52. Across treatment groups, the change in eGFR from baseline to Week 4 was similar for both eGFR subgroups. After Week 4, subjects in both eGFR subgroups randomized to compound 1 demonstrated stabilization of eGFR, with the largest numeric mean increases in eGFR observed for subjects with baseline eGFR < 60 mL/min/1.73 m². Conversely, subjects randomized to placebo in both eGFR subgroups experienced a reversal of eGFR changes, with values declining to baseline by Week 26. After starting open label active compound 1 at Week 26, eGFR increased substantially for both eGFR subgroups, with the largest numeric mean increases in eGFR observed for subjects with baseline eGFR < 60 mL/min/1.73 m².

As stated above, 28% of all randomized subjects in TCP-304 had a baseline eGFR < 60 mL/min/1.73m² (Stage 3a CKD or worse). As preservation of remaining kidney function is of critical clinical importance for such patients, a change from baseline analysis for eGFR was performed on this subset through Week 52 (Table 4a). For this eGFR subset, a mean 11.36 mL/min/1.73m² increase in eGFR was observed for subjects receiving compound 1 (95% CI: 6.20, 16.52) at the end of the blinded treatment period at Week 26, compared to a 0.05 mL/min/1.73m² increase in eGFR for placebo treated subjects (95% CI: -9.46, 9.56). By paired t-test, this increase from baseline for subjects receiving compound 1 was significantly greater than 0 (p = 0.0002), but not for subjects receiving placebo (p = 0.9877). Using the ANCOVA model described above, treatment with compound 1 resulted in a least-squares mean (SE) difference of 12.44 (5.86) mL/min/1.73m² for compound 1 vs. placebo (p = 0.0479) for subjects with baseline eGFR < 60 mL/min/1.73m². In the open-label extension, we again observe a sustained increase in eGFR at Week 52 for subjects in this eGFR subset randomized to compound 1. Specifically, we observed a mean 11.46 mL/min/1.73m² increase from baseline (95% CI: 6.03, 16.89), again significantly greater than 0 by paired t-test (p = 0.0003). Further, subjects initially randomized to placebo experienced a mean 11.65 mL/min/1.73m² increase from baseline in eGFR (95% CI: 8.13, 15.17) after 26 weeks of treatment with compound 1 in the open-label extension; this increase was also significantly greater than 0 by paired t-test (p = 0.0018). Importantly, the sustained increases in eGFR observed for subjects in this eGFR subset treated with compound 1 in TCP-

304 are above the clinically significant 5 mL/min/1.73m² change in eGFR [Hirst et al., 2022, KDIGO CKD Work Group, 2013].

Similar results (Table 4b) were observed for subjects with a baseline eGFR $\geq$ 60 mL/min/1.73 m², with a mean 6.29 mL/min/1.73m² increase in eGFR observed for subjects receiving compound 1 (95% CI: 3.13, 9.45) at the end of the blinded treatment period at Week 26, compared to a -2.43 mL/min/1.73m² decrease in eGFR for placebo treated subjects (95% CI: -7.56, 2.71). This increase from baseline for subjects receiving compound 1 was significantly greater than 0 ($p = 0.0002$), but not for subjects receiving placebo ($p = 0.3280$) by paired t-test. Using the ANCOVA model described above, treatment with compound 1 resulted in a least-squares mean (SE) difference of 7.68 (2.68) mL/min/1.73m² for compound 1 vs. placebo ($p = 0.0060$). In the open-label extension, we again observe a sustained, statistically significant 8.25 mL/min/1.73m² increase in eGFR at Week 52 (95% CI: 4.43,12.06, $p < 0.0001$) for subjects in this eGFR subset randomized to compound 1. Further, subjects initially randomized to placebo experienced a mean 6.45 mL/min/1.73m² increase from baseline in eGFR (95% CI: 1.18,11.72) after 26 weeks of treatment with compound 1 in the open-label extension; this increase was also significantly greater than 0 by paired t-test ($p = 0.0199$).

Table 4a: eGFR at Week 26 (End of Blinded Period) and Week 52 (Open-label Extension) for Subjects with Baseline eGFR < 60 mL/min/1.73 m² – TCP-304

Change from Baseline in eGFR per MDRD (mL/min/1.73m ²)	Compound 1/ Compound 1	Placebo / Compound 1	Total
Subjects with baseline eGFR < 60 mL/min/1.73 m ²			
Week 26	N	19	4
Mean (SD)	11.36 (10.71)	0.05 (5.98)	-
95% CI	6.20, 16.52	-9.46, 9.56	-
p-value*	0.0002	0.9877	-
Compound 1 vs. Placebo			
LS Mean (SE)†	12.44 (5.86)		
p-value†	0.0479		

Week 52	N	19	4	23
	Mean (SD)	11.46 (11.26)	11.65 (2.21)	11.49 (10.22)
	95% CI	6.03, 16.89	8.13, 15.17	7.07, 15.91
	p-value*	0.0003	0.0018	< 0.0001

*Derived from paired t-test, testing if change is > 0

†Calculated from ANCOVA model with change from baseline in eGFR as a dependent variable, treatment, baseline eGFR group and sex as fixed effects and baseline eGFR and age as covariates.

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; LS Mean = least-squares mean; N = number of subjects; SD = standard deviation; SE = standard error

Table 4b: eGFR at Week 26 (End of Blinded Period) and Week 52 (Open-label Extension) for Subjects with Baseline eGFR $\geq$ 60 mL/min/1.73 m² – TCP-304

Change from Baseline in eGFR per MDRD (mL/min/1.73m ²)	Compound 1/ Compound 1	Placebo / Compound 1	Total
Subjects with baseline eGFR < 60 mL/min/1.73 m ²			
Week 26	N	41	15
	Mean (SD)	6.29 (10.01)	-2.43 (9.27)
	95% CI	3.13, 9.45	-7.56, 2.71
	p-value*	0.0002	0.3280
Compound 1 vs. Placebo			
	LS Mean (SE)†	7.68 (2.68)	
	p-value†	0.0060	
Week 52	N	40	15
	Mean (SD)	8.25 (11.93)	6.45 (9.52)
	95% CI	4.43,12.06	1.18,11.72
	p-value*	< 0.0001	0.0199

*Derived from paired t-test, testing if change is > 0

†Calculated from ANCOVA model with change from baseline in eGFR as a dependent variable, treatment, baseline eGFR group and sex as fixed effects and baseline eGFR and age as covariates.

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; LS Mean = least-squares mean; N = number of subjects; SD = standard variation; SE = standard error

A responder analysis using the intent-to-treat (ITT) population was also conducted for each eGFR subgroup to supplement the above analysis (Table 5a and Table 5b). For subjects with a baseline eGFR < 60 mL/min/1.73 m² randomized to compound 1, 73.7% and 68.4% of subjects experienced a ≥ 5 mL/min/1.73m² increase in eGFR from baseline at Week 26 and Week 52, respectively. Further, 47.4% and 42.1% of subjects experienced a ≥ 10 mL/min/1.73m² increase in eGFR from baseline at Week 26 and Week 52, respectively. Comparable treatment response rates (regardless of response threshold) were observed at Week 26 and 52 for subjects with baseline eGFR ≥ 60 mL/min/1.73 m² randomized to compound 1.

For subjects a baseline eGFR < 60 mL/min/1.73 m² randomized to placebo, 25% experienced a ≥ 5 mL/min/1.73m² increase in eGFR from baseline at Week 26, increasing to 100% at week 52 following 26 weeks of treatment with open label active compound 1. A 23.5% response rate was observed for subjects with a baseline eGFR ≥ 60 mL/min/1.73 m² at Week 26, with 41.2% of subjects achieving a ≥ 5 mL/min/1.73m² increase in eGFR from baseline at Week 52.

At Week 26, 0% of subjects with a baseline eGFR < 60 mL/min/1.743 m² randomized to placebo had a ≥ 10 mL/min/1.73m² increase in eGFR from baseline, increasing to 75% at Week 52 following 26 weeks of treatment with open label active compound 1. For subjects with baseline eGFR ≥ 60 mL/min/1.743 m² randomized to placebo, 11.8% and 17.6% of subjects experienced a ≥ 10 mL/min/1.73m² increase in eGFR from baseline at Week 26 and Week 52, respectively.

Table 5a: Proportion of Patients with ≥5 mL/min/1.73m² Increase and ≥10 mL/min/1.73m² Increase in eGFR from Baseline for Subjects with Baseline eGFR < 60 (ITT population) – TCP-304

Treatment Response in eGFR per MDRD	Compound 1/ Compound 1	Placebo / Compound 1	Total
N	19	4	23
Treatment Response:			
≥ 5 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	14 (73.7)	1 (25.0)	-
Week 52	13 (68.4)	4 (100.0)	17 (73.9)
≥ 10 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	9 (47.4)	0	-
Week 52	8 (42.1)	3 (75.0)	11 (47.8)

Treatment response defined as a ≥ 5 mL/min/1.73 m² increase or ≥ 10 mL/min/1.73 m² increase in eGFR from baseline.

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MDRD = Modified Diet in Renal Disease; N = number of subjects in the ITT population; n = number of subjects with treatment response

Table 5b: Proportion of Patients with ≥ 5 mL/min/1.73m² Increase and ≥ 10 mL/min/1.73m² Increase in eGFR from Baseline for Subjects with Baseline eGFR ≥ 60 (ITT population) – TCP-304

Treatment Response in eGFR per MDRD	Compound 1/ Compound 1	Placebo / Compound 1	Total
N	42	17	59
Treatment Response:			
≥ 5 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	21 (50.0)	4 (23.5)	-
Week 52	26 (61.9)	7 (41.2)	33 (55.9)
≥ 10 mL/min/1.73m ² increase from baseline (n (%)):			
Week 26	17 (40.5)	2 (11.8)	-
Week 52	18 (42.9)	3 (17.6)	21 (35.6)

Treatment response defined as a ≥ 5 mL/min/1.73 m² increase or ≥ 10 mL/min/1.73 m² increase in eGFR from baseline.

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MDRD = Modified Diet in Renal Disease; N = number of subjects in the ITT population; n = number of subjects with treatment response

The observed improvement from baseline in eGFR was sustained through 104 weeks of follow-up in a subsequent analysis. At week 104, 93% (76/82) of participants remained in the trial. Mean (SD) eGFR was 77.8 (14.8) mL/min/1.73m². Palopegteriparatide treatment resulted in a mean (SD) increase in eGFR of 8.9 (11.0) mL/min/1.73m² ($P < .0001$) from baseline to week 52, which was sustained through week 104 with a mean (SD) change from baseline of 9.0 (10.3) mL/min/1.73m² ($P < .0001$). By week 104, 61% and 44% of participants had an increase in eGFR of ≥ 5 mL/min/1.73m² and ≥ 10 mL/min/1.73m², respectively. Among participants with baseline eGFR < 60 mL/min/1.73m² (n=23), palopegteriparatide treatment resulted in a mean (SD) increase in eGFR of 13.8 (10.0) mL/min/1.73m² from baseline to week 104, and 78% and 57% had an increase in eGFR of ≥ 5 mL/min/1.73m² and ≥ 10 mL/min/1.73m², respectively.

Example 2: TCP-201

In TCP-201 (NCT04009291), a Phase 2, double-blind, placebo-controlled, parallel-group trial, subjects were randomized 1:1:1:1 to receive 4 weeks of treatment with: compound 1, 15 μ g/day; compound 1, 18 μ g/day; compound 1, 21 mcg/day; or corresponding placebo. This 4-week placebo-controlled period was followed by an open-label extension where all subjects received active compound 1. In this trial, eGFR was measured at multiple time points using the MDRD equation [Levey et al., 2006]. Eligibility criteria excluded subjects with an eGFR ≤ 30 mL/min/1.73m². As of 01-JUN-2022, eGFR data for TCP-201 is available from baseline to Week 110 of follow-up. Given the relatively short placebo-controlled period, summary data are provided for all randomized subjects. Mean eGFR at baseline was 69.39 mL/min/1.73m², below the normal level of 90 mL/min/1.73m² (Table 6). In line with TCP-304, the majority of subjects in TCP-201 demonstrated some renal function impairment at baseline. Similar to TCP-304, 30.5% of randomized subjects in TCP-201 (18/59 subjects) had a baseline eGFR < 60 mL/min/1.73m², defining stage 3a or worse CKD per the 2012 KDIGO Guidelines for CKD [KDIGO CKD Work Group, 2013].

Table 6: Baseline Renal Function – TCP-201

Baseline eGFR per MDRD (mL/min/1.73m²)	All Randomized Subjects
N	59
Mean (SD)	69.39 (19.650)
Subjects with baseline eGFR (n (%))	
< 60 mL/min/1.73 m ²	18 (30.5)
≥ 60 mL/min/1.73 m ²	41 (69.5)

Abbreviations: eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; N = number of subjects, SD = standard deviation

Given the sizeable and clinically significant increases in eGFR in TCP-304 for all subjects as well as those with significant baseline renal impairment, we next examined the change from baseline in eGFR over the available 110 weeks in TCP-201 (Table 7). At Week 26, a mean 6.36 mL/min/1.73m² increase in eGFR from baseline was observed for subjects treated with compound 1 (95% CI: 3.55, 9.17) which was significantly greater than 0 ($p < 0.0001$, paired t-test) similar to the early eGFR increase noted in TCP-304. Again in alignment with findings from TCP-304, the increase from baseline in eGFR in TCP-201 further increased at Week 58 (mean increase: 8.54 mL/min/1.73m²; 95% CI: 5.30, 11.78) and was sustained at Week 110 (8.54 mL/min/1.73m²; 95% CI: 5.07, 11.59). The increases from baseline in eGFR were significantly greater than 0 at both Week 58 ($p < 0.0001$) and at Week 110 ($p < 0.0001$).

Table 7: Change from Baseline in eGFR at Week 26, Week 58, and Week 110 for All Subjects (Open-label Extension) – TCP-201

Change from Baseline in eGFR per MDRD (mL/min/1.73m²)	Week 26	Week 58	Week 110
N	55	58	53
Mean (SD)	6.36 (10.392)	8.54 (12.323)	8.33 (11.834)
95% CI	3.55, 9.17	5.30, 11.78	5.07, 11.59
p-value*	< 0.0001	< 0.0001	< 0.0001

*Derived from paired t-test, testing if change is > 0

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; N = number of subjects; SD = standard variation

A responder analysis using the ITT population was also conducted to supplement the above analysis, where treatment response was defined as a ≥ 5 mL/min/1.73m² increase in eGFR from baseline (Table 8). For subjects receiving compound 1, 52.5%, 66.1%, and 55.9% of subjects experienced an eGFR treatment response at Week 26, Week 58, and Week 110, respectively.

Table 8: Proportion of Patients with ≥ 5 mL/min/1.73 m² Increase in eGFR from Baseline (ITT Population) – TCP-201

Treatment Response in eGFR per MDRD	Week 26	Week 58	Week 110
N	59	59	59
Treatment Response (n (%))	31 (52.5)	39 (66.1)	33 (55.9)

Treatment response defined as a ≥ 5 mL/min/1.73 m² increase in eGFR from baseline

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; MDRD = Modified Diet in Renal Disease; N = number of subjects in the ITT population; n = number of subjects with treatment response

These eGFR changes in a similar patient population in TCP-201 complement and corroborate the eGFR findings in TCP-304. Results of both the change from baseline and responder analyses demonstrate that treatment with compound 1 in TCP-201 (in alignment with TCP-304) is associated with sustained increases in eGFR > 8 mL/min/1.73m² through 110 weeks of treatment. These changes in eGFR are:

1. Substantially higher than the +2.13 to +3.02 mL/min/1.73m² increase estimated for rhPTH(1-84) after 1 year of treatment [Ayodele et al., 2022, Chen et al., 2020]; AND
2. Above 5 mL/min/1.73m², a change in eGFR considered clinically significant [Hirst et al., 2022, KDIGO CKD Work Group, 2013], for the majority of subjects receiving compound 1 for ≥ 26 weeks.

As shown above, 30.5% of all randomized subjects in TCP-201 (18/59 subjects) had a baseline eGFR < 60 mL/min/1.73m² (Stage 3a CKD or worse). For this subset of patients

with significant baseline renal impairment, preservation of remaining kidney function is of critical clinical importance. Given the clinically significant increases in eGFR in TCP-304 for all subjects as well as those with significant baseline renal impairment, we next examined the change from baseline in eGFR for subjects with a baseline eGFR < 60 mL/min/1.73m² in TCP-201 (Table 9).

For this subset of subjects in TCP-201 at Week 26, a mean 7.99 mL/min/1.73m² increase in eGFR was observed for subjects receiving compound 1 (95% CI: 3.72, 12.26). Using a paired t-test, this increase from baseline at Week 26 for subjects receiving compound 1 was found to be significantly greater than 0 ($p = 0.0011$). Again, in alignment with findings from TCP-304, the increase from baseline in eGFR for this subset in TCP-201 was sustained at Week 58 (mean increase: 11.79 mL/min/1.73m²; 95% CI: 7.76, 15.83) and at Week 110 (8.49 mL/min/1.73m²; 95% CI: 3.69, 13.28). The increases from baseline in eGFR were significantly greater than 0 at both Week 58 ($p < 0.0001$) and at Week 110 ($p = 0.0018$). These eGFR changes in patients with baseline renal dysfunction in TCP-201 again complement and corroborate the eGFR findings in TCP-304.

Table 9: Change from Baseline in eGFR at Week 26, Week 58, and Week 110 for Subjects with Baseline eGFR < 60 mL/min/1.73 m² (Open-label Extension) – TCP-201

Change from Baseline in eGFR per MDRD (mL/min/1.73m ²)	Week 26	Week 58	Week 110
Subjects with baseline eGFR < 60 mL/min/1.73 m ²			
N	17	18	16
Mean (SD)	7.99 (8.31)	11.79 (8.11)	8.49 (9.00)
95% CI	3.72, 12.26	7.76, 15.83	3.69, 13.28
p-value*	0.0011	< 0.0001	0.0018

* Derived from paired t-test, testing if change is > 0

Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; N = number of subjects

To our knowledge, the data provided in Example 1 (TCP-304) and Example 2 (TCP-201) are the first reports of a long-acting PTH compound causing clinically meaningful and statistically significant increases in eGFR from baseline ($> 8 \text{ mL/min/1.73m}^2$ increase, where $>5 \text{ mL/min/1.73m}^2$ changes are clinically meaningful). Summarizing the data presented in Example 1 (TCP-304) and Example 2 (TCP-201), these observed increases in eGFR:

- 1) manifest at/after 26 weeks of treatment with compound 1 and are significantly elevated compared to placebo;
- 2) are sustained through 104 weeks (TCP-304) and 110 weeks (TCP-201);
- 3) are substantially higher than the $+2.13$ to $+3.02 \text{ mL/min/1.73m}^2$ estimated increase in eGFR after 1 year of treatment with rhPTH(1-84) [Ayodele et al., 2022, Chen et al., 2020];
- 4) are $\geq 5 \text{ mL/min/1.73m}^2$ increased for the majority of subjects treated with compound 1 in TCP-304 and TCP-201 for ≥ 104 weeks; and
- 5) are numerically higher in subjects with significant baseline renal dysfunction (stage 3a CKD or worse).

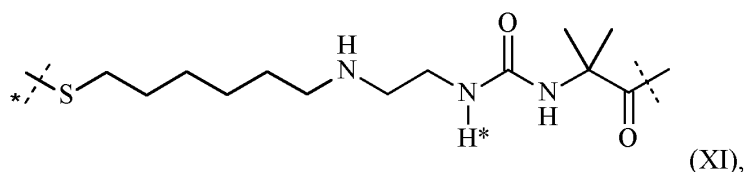
Claims

1. A PTH compound for use in the prevention of chronic kidney disease (CKD) in a subject at risk of developing CKD or in the treatment of a subject having CKD.
2. The PTH compound for use of claim 1, wherein the PTH compound is used in the treatment of a subject having CKD.
3. The PTH compound for use of claim 1, wherein the PTH compound is used for the prevention of CKD in a subject at risk of developing CKD.
4. The PTH compound for use of claim 1 or 3, wherein the kidney function of a subject having CKD is assessed by blood and/or urine test at least once prior to administration of a pharmaceutically effective dose of the PTH compound.
5. The PTH compound for use of any one of claims 1 to 4, wherein the kidney function of a subject being at risk of or having CKD is assessed by blood and/or urine test at least twice, wherein the first assessment is before the first administration of the PTH compound and the second assessment is after administration of one or more doses of the PTH compound.
6. The PTH compound for use of claim 5, wherein the second assessment is done after administration of a plurality of doses.
7. The PTH compound for use of claim 5 or 6, wherein the second assessment is after at least two weeks, after at least four weeks, after at least two months or after at least six months of treatment.
8. The PTH compound for use of any one of claims 4 to 7, wherein the blood test measures the amount of creatinine in blood.
9. The PTH compound for use of any one of claims 4 to 8, wherein the urine test measures the urine albumin-to-creatinine ratio (UCAR).

10. The PTH compound for use of any one of claims 4 to 9, wherein the kidney function is measured in the form of the estimated glomerular filtration rate (eGFR).
11. The PTH compound for use of claim 10, wherein the eGFR is measured at least once prior to administration of a pharmaceutically effective dose of the PTH compound.
12. The PTH compound for use of claim 10 or 11, wherein the eGFR is determined using the Modification of Diet in Renal Disease (MDRD) formula.
13. The PTH compound for use of any one of claims 10 to 12, wherein the eGFR is indicative of CKD.
14. The PTH compound for use of any one of claims 10 to 13, wherein the subject has an eGFR of $< 60 \text{ ml/min/1.73 m}^2$.
15. The PTH compound for use of any one of claims 1 to 14, wherein the subject has hypoparathyroidism.
16. The PTH compound for use of claim 1 to 15, wherein the subject has chronic hypoparathyroidism.
17. The PTH compound for use of any one of claims 1, 2 or 4 to 16, wherein the treatment improves the subject's eGFR.
18. The PTH compound for use of any one of claims 1, 2 or 4 to 17, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least $5 \text{ ml/min/1.73 m}^2$.
19. The PTH compound for use of any one of claims 1, 2 or 4 to 18, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least $6 \text{ ml/min/1.73 m}^2$.

20. The PTH compound for use of any one of claims 1, 2 or 4 to 19, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 7 ml/min/1.73 m².
21. The PTH compound for use of any one of claims 1, 2 or 4 to 20, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 8 ml/min/1.73 m².
22. The PTH compound for use of any one of claims 1, 2 or 4 to 21, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 9 ml/min/1.73 m².
23. The PTH compound for use of any one of claims 17 to 22, wherein the improvement is achieved within 52 weeks of treatment.
24. The PTH compound for use of any one of claims 17 to 23, wherein the mean improvement can be measured after at least 110 weeks of treatment with the PTH compound.
25. The PTH compound for use of any one of claims 1 to 24, wherein the PTH compound is administered multiple times.
26. The PTH compound for use of any one of claims 1, 2 or 4 to 25, wherein treatment starts upon diagnosis of CKD.
27. The PTH compound for use of any one of claims 1, 2 or 4 to 26, wherein treatment proceeds for six months one year, two years, three years, five years, ten years, until medically indicated or until the end of the subject's life.
28. The PTH compound for use of any one of claims 1 to 27, wherein the PTH compound is administered daily.

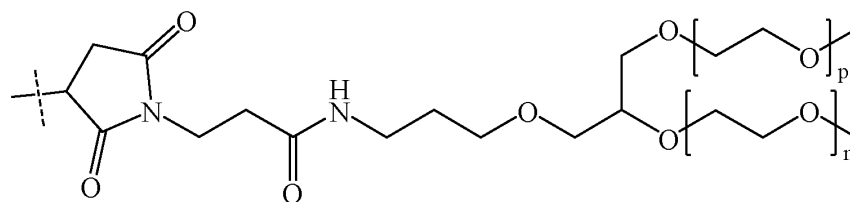
29. The PTH compound for use of any one of claims 1 to 27, wherein the PTH compound is administered weekly.
30. The PTH compound for use of any one of claims 1 to 29, wherein a single dose of the PTH compound results in an at least 10 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
31. The PTH compound for use of any one of claims 1 to 30, wherein a single dose of the PTH compound results in an at least 15 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
32. The PTH compound for use of any one of claims 1 to 31, wherein a single dose of the PTH compound results in an at least 20 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
33. The PTH compound for use of any one of claims 1 to 32, wherein the is a compound of formula (XI)



wherein

the unmarked dashed line indicates the attachment to the nitrogen of the N-terminal amine group of a PTH moiety of SEQ ID NO:51; and

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



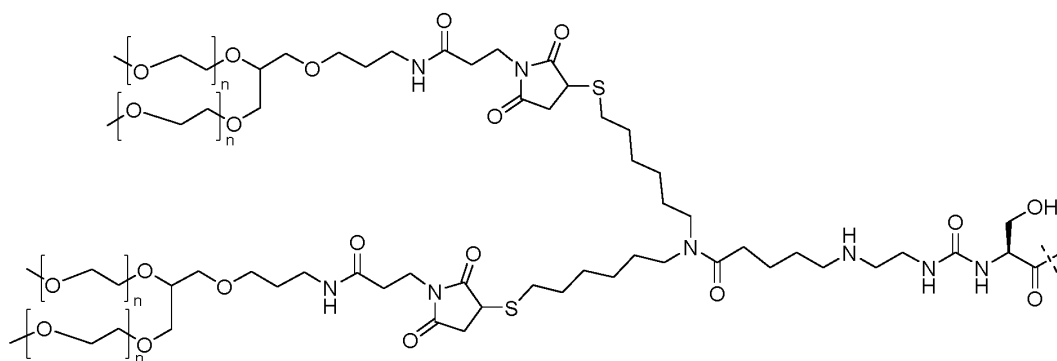
wherein

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; such as an integer ranging from and including 150 to 600; such as an

integer ranging from and including 200 to 550; such as an integer ranging from and including 400 to 500 or such as an integer ranging from about 450 to about 500.

34. The PTH compound for use of any one of claims 1 to 32, wherein the is a compound is a compound of formula (XII')



(XII'),

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

35. The PTH compound for use of any one of claims 1 to 32, wherein the PTH compound has the sequence of SEQ ID NO:122.

36. The PTH compound for use of any one of claims 1 to 32, wherein is compound of formula (XIV)

k(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)(N-Me)GSVSEIQLMHNLGKHLNSMER
VEWLRKKLQDVHK(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)-OH (XIV),

wherein

k is d-Lys;

γ E is the l-isomer of gamma, glutamic acid;

miniPEG is COCH₂OCH₂CH₂OCH₂CH₂NH;

COC₁₆H₃₂CO₂H is C18 diacid;

(N-Me)G is sarcosine;

K is l-isomer of lysine; and

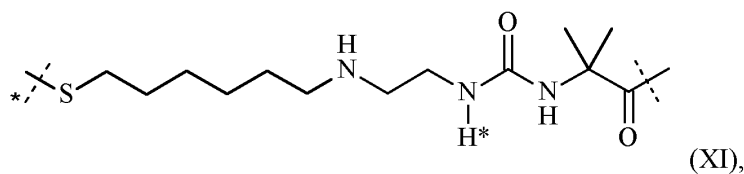
-OH designates the C-terminal amino acid has a terminal carboxylic acid.

37. The PTH compound for use of any one of claims 1 to 32, wherein is compound of formula (XIV')
- $k(\gamma\text{E}-(\text{miniPEG})_2-\gamma\text{E}-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})(\text{N-Me})\text{GSVSEIQLMHNLGKHLNSMER}$
 $\text{VEWLRKKLQDVHK}(\gamma\text{E}-(\text{miniPEG})_2-\gamma\text{E}-\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H})-\text{OH}$ (XIV'),
- wherein
- k is d-Lys;
- γE is the l-isomer of gamma, glutamic acid;
- $(\text{miniPEG})_2$ is $\text{COCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}$;
- $\text{COC}_{16}\text{H}_{32}\text{CO}_2\text{H}$ is C18 diacid;
- (N-Me)G is sarcosine;
- K is l-isomer of lysine; and
- OH designates the C-terminal amino acid has a terminal carboxylic acid.
38. A method of preventing chronic kidney disease (CKD) in a subject at risk of developing CKD or of treating CKD in a subject having CKD, wherein the method comprises administering a pharmaceutically effective dose of a PTH compound to the subject.
39. The method of claim 38, wherein the method is a method of treating CKD in a subject having CKD.
40. The method of claim 38, wherein the method is a method of preventing CKD in a subject at risk of developing CKD.
41. The method of claim 38 or 40, wherein the kidney function of a subject having CKD is assessed by blood and/or urine test at least once prior to administration of a pharmaceutically effective dose of the PTH compound.
42. The method of any one of claims 38 to 41, wherein the kidney function of a subject being at risk of or having CKD is assessed by blood and/or urine test at least twice, wherein the first assessment is before the first administration of the PTH compound and the second assessment is after administration of one or more doses of the PTH compound.

43. The method of claim 42, wherein the second assessment is done after administration of a plurality of doses.
44. The method of claim 42 or 43, wherein the second assessment is after at least two weeks, after at least four weeks, after at least two months or after at least six months of treatment.
45. The method of claims 41 to 44, wherein the blood test measures the amount of creatinine in blood.
46. The method of any one of claims 41 to 45, wherein the urine test measures the urine albumin-to-creatinine ratio (UCAR).
47. The method of any one of claims 41 to 46, wherein the kidney function is measured in the form of the estimated glomerular filtration rate (eGFR).
48. The method of claim 47, wherein the eGFR is measured at least once prior to administration of a pharmaceutically effective dose of the PTH compound.
49. The method of claim 47 or 48, wherein the eGFR is determined using the Modification of Diet in Renal Disease (MDRD) formula.
50. The method of any one of claims 47 to 49, wherein the eGFR is indicative of CKD.
51. The method of any one of claims 47 to 50, wherein the subject has an eGFR of < 60 ml/min/1.73 m².
52. The method of any one of claims 38 to 51, wherein the subject has hypoparathyroidism.
53. The method of claim 38 to 52, wherein the subject has chronic hypoparathyroidism.

54. The method of any one of claims 38, 39 or 41 to 53, wherein the treatment improves the subject's eGFR.
55. The method of any one of claims 38, 39 or 41 to 54, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 5 ml/min/1.73 m².
56. The method of any one of claims 38, 39 or 41 to 55, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 6 ml/min/1.73 m².
57. The method of any one of claims 38, 39 or 41 to 56, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 7 ml/min/1.73 m².
58. The method of any one of claims 38, 39 or 41 to 57, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 8 ml/min/1.73 m².
59. The method of any one of claims 38, 39 or 41 to 58, wherein treatment with the PTH compound results in a mean improvement of the subject's eGFR of at least 9 ml/min/1.73 m².
60. The method of any one of claims 54 to 59, wherein the mean improvement is achieved within 52 weeks of treatment.
61. The method of any one of claims 54 to 60, wherein the mean improvement can be measured after at least 110 weeks of treatment with the PTH compound.
62. The method of any one of claims 1 to 24, wherein the PTH compound is administered multiple times.

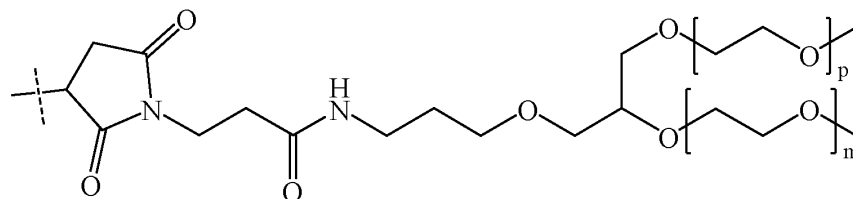
63. The method of any one of claims 38, 39 or 41 to 62, wherein treatment starts upon diagnosis of CKD.
64. The method of any one of claims 38, 39 or 41 to 63, wherein treatment proceeds for six months one year, two years, three years, five years, ten years, until medically indicated or until the end of the subject's life.
65. The method of any one of claims 38 to 64, wherein the PTH compound is administered daily.
66. The method of any one of claims 38 to 64, wherein the PTH compound is administered weekly.
67. The method of any one of claims 38 to 66, wherein a single dose of the PTH compound results in an at least 10 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
68. The method of any one of claims 38 to 67, wherein a single dose of the PTH compound results in an at least 15 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
69. The method of any one of claims 38 to 68, wherein a single dose of the PTH compound results in an at least 20 times longer receptor signaling compared to a single equimolar dose of PTH 1-84.
70. The method of any one of claims 38 to 69, wherein the is a compound of formula (XI)



wherein

the unmarked dashed line indicates the attachment to the nitrogen of the N-terminal amine group of a PTH moiety of SEQ ID NO:51; and

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

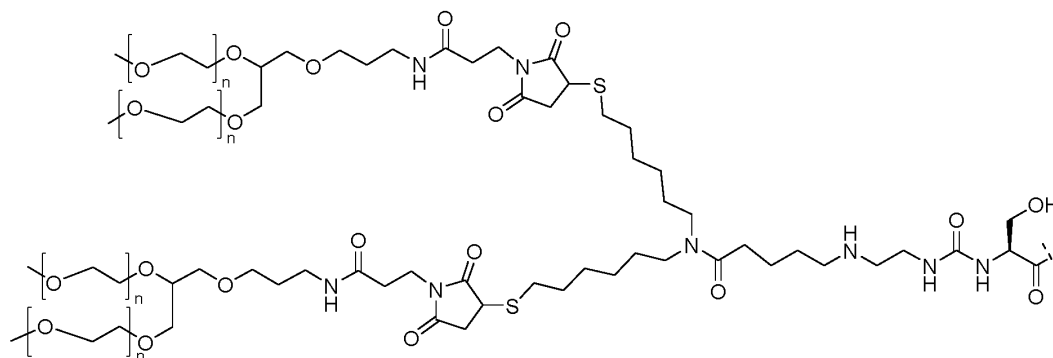


wherein

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

m and p are independently of each other an integer ranging from and including 150 to 1000; such as an integer ranging from and including 150 to 600; such as an integer ranging from and including 200 to 550; such as an integer ranging from and including 400 to 500 or such as an integer ranging from about 450 to about 500.

71. The method of any one of claims 38 to 69, wherein the is a compound is a compound of formula (XII')



(XII'),

wherein

the dashed line indicates attachment to the nitrogen of the N-terminal amine group of a PTH moiety having the sequence of SEQ ID NO:51; and

each n is independently an integer ranging from approx. 200 to 250.

72. The method of any one of claims 38 to 69, wherein the PTH compound has the sequence of SEQ ID NO:122.
73. The method of any one of claims 38 to 69, wherein is compound of formula (XIV)

k(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)(N-Me)GSVSEIQLMHNLGKHLNSMER
VEWLRKKLQDVHK(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)-OH (XIV),

wherein

k is d-Lys;

γ E is the l-isomer of gamma, glutamic acid;

miniPEG is COCH₂OCH₂CH₂OCH₂CH₂NH;

COC₁₆H₃₂CO₂H is C18 diacid;

(N-Me)G is sarcosine;

K is l-isomer of lysine; and

-OH designates the C-terminal amino acid has a terminal carboxylic acid.

74. The method of any one of claims 38 to 69, wherein is compound of formula (XIV')

k(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)(N-Me)GSVSEIQLMHNLGKHLNSMER
VEWLRKKLQDVHK(γ E-(miniPEG)₂- γ E-COC₁₆H₃₂CO₂H)-OH (XIV'),

wherein

k is d-Lys;

γ E is the l-isomer of gamma, glutamic acid;

(miniPEG)₂ is COCH₂OCH₂CH₂OCH₂CH₂NH;

COC₁₆H₃₂CO₂H is C18 diacid;

(N-Me)G is sarcosine;

K is l-isomer of lysine; and

-OH designates the C-terminal amino acid has a terminal carboxylic acid.