Claims:

1. A conjugate comprising a PTH peptide, and a self-cleaving dipeptide covalently bound to said PTH peptide via an amide bond,

said PTH peptide comprising an amino acid sequence selected from the group consisting of

SVSEIQLMHX$_{10}$LGX$_{13}$HLX$_{16}$SX$_{18}$ERVEWLRX$_{26}$X$_{27}$LQDX$_{31}$H-Z, (SEQ ID NO: 133);
SVSEIQLMHX$_{10}$LX$_{12}$KHLX$_{56}$X$_{17}$X$_{18}$ ERVEWLRKKLQDVH-Z; (SEQ ID NO: 134);
SVSEIQLMHX$_{10}$LGKHLX$_{16}$SX$_{18}$ERVEWLRKKLQDVH-Z (SEQ ID NO: 135) and
SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH-Z (SEQ ID NO: 7);

wherein Z is X$_{33}$, X$_{33}$F, X$_{33}$FX$_{35}$, X$_{33}$FVX$_{35}$, X$_{33}$FVAX$_{35}$, X$_{33}$FVALX$_{35}$, X$_{33}$FVALGX$_{35}$, X$_{53}$X$_{35}$, X$_{53}$FX$_{35}$, X$_{53}$FVX$_{35}$, X$_{53}$FVAX$_{35}$, X$_{53}$FVALX$_{35}$, or X$_{53}$FVALGX$_{35}$, optionally wherein Z is X$_{33}$, X$_{53}$X$_{35}$, X$_{53}$FX$_{35}$, X$_{53}$FVX$_{35}$, X$_{53}$FVAX$_{35}$, X$_{53}$FVALX$_{35}$, or X$_{53}$FVALGX$_{35}$;

X$_{10}$ and X$_{16}$ are independently Asp, Gln or Asn;

X$_{12}$ is Gly or Aib;

X$_{56}$ is amino isobutyric acid (Aib) or Asn

X$_{17}$ is amino isobutyric acid (Aib) or Ser;

X$_{18}$ is Met, Met(O), Leu, or Nleu;

X$_{13}$, X$_{26}$, and X$_{27}$ are independently selected from the group consisting of Arg, Glu, Asp and Lys;

X$_{31}$ is Gly or Val;

X$_{33}$ and X$_{35}$ each comprise an acylated amino acid comprising a C16-C30 fatty acid or C16-C30 diacid covalently linked to the side chain of the amino acid, optionally via a spacer, optionally wherein the acylated amino acid is selected from the group consisting of Lys, dLys, ornithine, Cys and homocysteine;

X$_{53}$ is Gln or Asn, optionally with the proviso that no more than one of X$_{12}$, X$_{16}$ and X$_{17}$ is Aib, and optionally wherein the C-terminal amino acid is modified to replace the carboxy terminus with an amide;

wherein said self-cleaving dipeptide comprises the structure A-B where A is an amino acid; and

B is an N-alkylated amino acid, optionally wherein Z is X_{33}, $X_{53}X_{35}$, $X_{53}FX_{35}$, $X_{53}FVX_{35}$, $X_{53}FVAX_{35}$, $X_{53}FVALX_{35}$, or $X_{53}FVALGX_{35}$.

2. A conjugate, comprising a PTH peptide and a self-cleaving dipeptide covalently bound to said PTH peptide via an amide bond,

said PTH peptide comprising an amino acid sequence selected from the group consisting of

$SVSEIQLMHNLGX_{13}HLNSMERVEWLRX_{26}X_{27}LQDX_{31}H$-Z, (SEQ ID NO: 5);

$SVSEIQLMHX_{10}LGKHLX_{16}SX_{18}ERVEWLRKKLQDVH$-Z (SEQ ID NO: 135);

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH-Z (SEQ ID NO: 7), and a peptide that differs from the peptide of SEQ ID NO: 7 by 1, 2 or 3 amino acid substitutions;

wherein

Z is $X_{33}F$, $X_{53}X_{35}$, $X_{53}FX_{35}$, or X_{33};

X_{10} and X_{16} are independently Asp, Gln or Asn;

X_{18} is Met, Met(O), Leu, or Nleu;

X_{13}, X_{26}, and X_{27} are independently selected from the group consisting of Arg, Glu, Asp and Lys;

X_{31} is Gly or Val;

X_{33} and X_{35} each comprise an acylated amino acid;

X_{53} is Gln or Asn; and

said self-cleaving dipeptide comprising the general structure

A-B-;

wherein

A is an amino acid or an acylated amino acid;

B is an N-alkylated amino acid;

wherein said acylated amino acid of each of X_{33}, X_{35} and A is independently selected from an amino acid comprising a C16-C30 fatty acid or C16-C30 diacid covalently linked to the amino acid side chain, optionally via a spacer, and said self-cleaving dipeptide is linked to said PTH peptide through formation of an amide bond between B and the N-terminal alpha amine of said PTH peptide, further wherein said optional spacer of each of X_{33}, X_{35} and A comprises one or more

linker moieties independently selected from the group consisting of a gamma glutamic acid, and $COCH_2(OCH_2CH_2)_kNH$, wherein k is an integer selected from the range of 1-8;

with the proviso that when A is a non-acylated amino acid, then A is an amino acid in the D-stereochemical configuration.

3. The conjugate of any one of claims 1-2 wherein

i) said PTH peptide comprises the sequence

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVH-Z (SEQ ID NO: 7),

wherein

Z is $X_{33}F$, $X_{53}X_{35}$, $X_{53}FX_{35}$, or X_{33};

X_{33} and X_{35} are each independently an amino acid comprising a C16-C30 fatty acid or C16-C30 diacid covalently linked to the acid side chain of the amino acid, optionally via a spacer; and

X_{53} is Asn or

ii) said PTH peptide comprises the sequence of

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHX_{33} (SEQ ID NO: 16) or

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFX_{35} (SEQ ID NO: 12)

wherein X_{33} and X_{35} are each independently an amino acid comprising a C16-C22 fatty acid or C16-C22 diacid covalently linked to the side chain of the amino acid, optionally via a spacer.

4. The conjugate of any one of claims 1-3 wherein A is selected from the group consisting of Lys, dLys, acylated-Lys and acylated-dLys wherein said self-cleaving dipeptide is covalently linked to the N-terminal alpha amine of the PTH peptide.

5. The conjugate of any one of claims 1-4 wherein said acylated amino acid of each of X_{33}, X_{35} and A comprises a C16-C30 fatty acid or C16-C30 diacid covalently linked to the amino acid side chain via a spacer, wherein the spacer of each of X_{33}, X_{35} and A is independently selected from a gamma glutamic acid-gamma glutamic acid dipeptide, (Xaa)-

$[COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid and a gamma glutamic acid-$[COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid, wherein

Xaa is selected from Arg, Tyr(OPO_3H_2), and hCys(SO_3H);

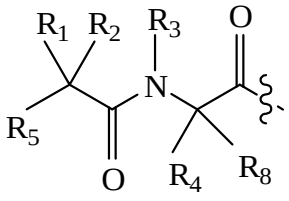
k is an integer selected from the range of 1-8; and

q is an integer selected from the range of 1-8, optionally wherein k is 2 and q is selected from the range of 1-4, optionally wherein the acylated amino acid of A, X_{33} and X_{35} is independently selected from cysteine, homocysteine, ornithine lysine and d-lysine wherein the side chain of said cysteine, homocysteine, ornithine lysine or d-lysine is covalently linked to a C16-C22 fatty acid or C16-C22 diacid, optionally through a spacer, wherein the optional spacer of each of A, X_{33} and X_{35} comprises a gamma glutamic acid linkage, or the acylated amino acid of A, X_{33} and X_{35} are each independently selected from lysine or d-lysine wherein the side chain of said lysine or d-lysine is covalently linked to a C16-C22 fatty acid or C16-C22 diacid, optionally through a spacer comprising a gamma glutamic acid linkage.

6. The conjugate of any one of claims 1-5 wherein the acylated amino acid of A is d-lysine, and X_{33} and X_{35} are each lysine.

7. The conjugate of claim 5 or 6 wherein said spacers of A, X_{33} and X_{35} are each independently selected from compounds comprising the structure: gamma glutamic acid-$[COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid, wherein k is an integer selected from 2, 4 or 8 and q is an integer selected from 1, 2, 4 or 8, optionally wherein k is 2 and q is 2 or 4.

8. The conjugate of any one of claims 1-3 wherein A-B comprises the structure:



I

wherein

R_1, comprises a side chain selected from the group consisting of C_1-C_8 alkyl, (C_1-C_4 alkyl)OH, (C_1-C_4 alkyl)SH, (C_1-C_4 alkyl)COOH, and (C_1-C_4 alkyl)NH_2, optionally wherein a C16-C30 fatty acid or C16-C30 diacid is covalently linked to said side chain, optionally via a spacer

selected from the group consisting of a gamma glutamic acid, a gamma glutamic acid-gamma glutamic acid dipeptide, and a gamma glutamic acid-[$COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid, wherein

k is an integer selected from the range of 1-8; and

q is an integer selected from the range of 1-8, optionally wherein k is 2 and q is selected from the range of 1-8;

R_2, R_4 and R_8 are independently H, or C_1-C_4 alkyl;

R_3 is C_1-C_6 alkyl; and

R_5 is NH_2, optionally wherein the chemical cleavage half-life ($t_{1/2}$) of A-B from said PTH peptide is at least about 48 to 168 hours in standard PBS solution under physiological conditions.

9. The conjugate of claim 8 wherein

i) R_1, is (C_1-C_4 alkyl)NH;

R_2 and R_8 are each H;

R_4 is H, or CH_3;

R_3 is CH_3 and

R_5 is NH_2 or

ii)

R_1, is (C_1-C_4 alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}COOH$, ($C_1$-$C_4$ alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}CH_3$, ($C_1$-$C_4$ alkyl)NH-$CO(CH_2)_{14\text{-}20}COOH$, or ($C_1$-$C_4$ alkyl)NH-$CO(CH_2)_{14\text{-}20}CH_3$;

R_2 and R_8 are each H;

R_4 is H, or CH_3;

R_3 is CH_3 and

R_5 is NH_2, wherein said [spacer] is a linking moiety selected from the group consisting of a gamma glutamic acid, a gamma glutamic acid-gamma glutamic acid dipeptide, and a gamma glutamic acid-[$COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid, wherein k is an integer selected from the range of 2-4 and q is an integer selected from the range of 1-8.

10. The conjugate of claim 9 wherein

i) $R_{1,}$ is (C_1-C_4 alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}COOH$, wherein said [spacer] is a linking moiety comprising the structure gamma glutamic acid-$[COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid, wherein k is 2 or 4 and q is 1, 2 or 4, or

ii)

$R_{1,}$ is (C_4 alkyl)NH-{gamma glutamic acid-$[COCH_2(OCH_2CH_2)_2NH$-$COCH_2(OCH_2CH_2)_2]$NH-gamma glutamic acid}-$CO(CH_2)_{14\text{-}20}COOH$.

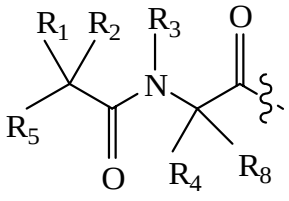
11. A conjugate comprising a PTH peptide, and a self-cleaving dipeptide covalently linked to the N-terminal alpha amine of said PTH peptide via an amide bond, wherein

said PTH peptide comprises the amino acid sequence of

$SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHX_{33}$ (SEQ ID NO: 16), $SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFX_{35}$ (SEQ ID NO: 12), or a peptide that differs from the peptide of SEQ ID NO: 16 or SEQ ID NO: 12 by 1 or 2 amino acid substitutions wherein

X_{33} and X_{35} are each an amino acid comprising a side chain of (C_1-C_4 alkyl)NH-$CO(CH_2)_{14\text{-}20}COOH$, ($C_1$-$C_4$ alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}COOH$, ($C_1$-$C_4$ alkyl)NH-$CO(CH_2)_{14\text{-}20}CH_3$ or (C_1-C_4 alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}CH_3$; and

said self-cleaving dipeptide comprises the general structure:



I

wherein

$R_{1,}$ is (C_1-C_4 alkyl)NH, (C_1-C_4 alkyl)NH-$CO(CH_2)_{14\text{-}20}COOH$, ($C_1$-$C_4$ alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}COOH$, ($C_1$-$C_4$ alkyl)NH-$CO(CH_2)_{14\text{-}20}CH_3$ or (C_1-C_4 alkyl)NH-[spacer]-$CO(CH_2)_{14\text{-}20}CH_3$;

R_2 and R_8 are each H;

R_4 is H, or CH_3;

R_3 is C_1-C_3 alkyl and

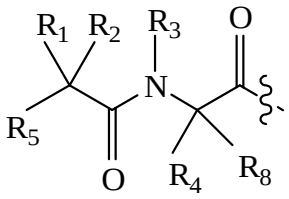
R_5 is NH_2, wherein said spacer of R_1, X_{33} and X_{35} is each independently selected from the group consisting of gamma glutamic acid, gamma glutamic acid-gamma glutamic acid dipeptide, and gamma glutamic acid-$[COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid wherein k is an integer selected from the range of 2-4 and q is an integer selected from the range of 1-4.

12. The conjugate of claim 11 wherein said PTH peptide comprises the amino acid sequence of

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFX_{35} (SEQ ID NO: 12), wherein

X_{35} is an amino acid comprising a side chain of (C_1-C_4 alkyl)NH-{gamma glutamic acid-$[COCH_2(OCH_2CH_2)_2NH$-$COCH_2(OCH_2CH_2)_2]NH$-gamma glutamic acid}-$CO(CH_2)_{14\text{-}20}COOH$; and

said self-cleaving dipeptide comprises the general structure:



I

wherein

R_1, is (C_1-C_4 alkyl)NH-{gamma glutamic acid-$[COCH_2(OCH_2CH_2)_2NH$-$COCH_2(OCH_2CH_2)_2]NH$-gamma glutamic acid}-$CO(CH_2)_{14\text{-}20}COOH$;

R_2, R_4 and R_8 are each H;

R_3 is CH_3; and

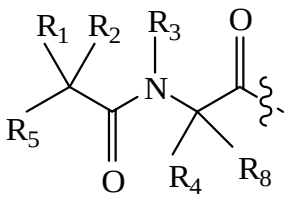
R_5 is NH_2.

13. The conjugate of claim 11 wherein said PTH peptide comprises the amino acid sequence of

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHX_{33} (SEQ ID NO: 16), wherein

X_{33} is an amino acid comprising a side chain of (C_1-C_4 alkyl)NH-{gamma glutamic acid-$[COCH_2(OCH_2CH_2)_k$-$NH]_q$-gamma glutamic acid}-$CO(CH_2)_{14\text{-}20}COOH$; and

said self-cleaving dipeptide comprises the general structure:



I

wherein

$R_{1,}$ is (C_1-C_4 alkyl)NH-{gamma glutamic acid-[$COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid}-$CO(CH_2)_{16\text{-}18}COOH$;

R_2, R_4 and R_8 are each H;

R_3 is CH_3;

R_5 is NH_2;

q is 2 or 4 and

k is 2, optionally wherein

X_{33} is an amino acid comprising a side chain of (C_4 alkyl)NH-{gamma glutamic acid-[$COCH_2(OCH_2CH_2)_2NH$-$COCH_2(OCH_2CH_2)_2$]NH-gamma glutamic acid}-$CO(CH_2)_{16}COOH$; and

$R_{1,}$ is (C_4 alkyl)NH-{gamma glutamic acid-[$COCH_2(OCH_2CH_2)_2NH$-$COCH_2(OCH_2CH_2)_2$]NH-gamma glutamic acid}-$CO(CH_2)_{16}COOH$.

14. The conjugate of any one of claims 1-13 wherein the first amino acid of the self-cleaving dipeptide is in the D-stereochemical configuration.

15. A pharmaceutical composition comprising the conjugate of any one of claims 1-14, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15 formulated for oral delivery wherein said composition further comprises sodium N[8-(2-hydroxybenoyl)aminocaprylate], optionally wherein the composition is formulated in a tablet form.

17. The pharmaceutical composition of claim 15 or 16 further comprising a peptide of SEQ ID NO: 7, SEQ ID NO: 31, or SEQ ID NO: 32 and optionally calcitonin.

18. Use of the conjugate of any one of claims 1-14 in the manufacture of a medicament for the treatment of hypoparathyroidism, osteoporosis or osteopenia.

19. The use of claim 18 wherein the medicament is to be administered once per week.

20. The use of claim 18 wherein the composition is to be administered orally.