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}ERVEWLR$X_{26}X_{27}$LQDX_{31}H-Z, (SEQ ID NO: 133);

SVSEIQLMHX_{10}LX_{12}KHL$X_{56}X_{17}X_{18}$ 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.

~~2. The conjugate of claim 1,~~ 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 $X_{53}FVALGX_{35}$.

~~3~~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}HLNSMERVEWLR$X_{26}X_{27}$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.

~~4~~3. The conjugate of any one of claims 1-~~3~~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

~~5. The conjugate of any one of claims 1-3 wherein~~ 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.

~~6~~

4. The conjugate of any one of claims 1-~~5~~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.

~~7~~5. The conjugate of any one of claims 1-~~6~~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~~.~~

~~8. The conjugate of any one of claims 1-7~~, 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~~.~~

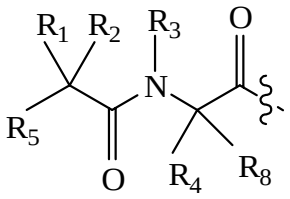
~~9. The conjugate of any one of claims 1-8 wherein~~, or the acylated amino acid of A, X_{33} and X_{35} are each independently selected from lysine or d-lysine wherein the side chain of said lysine or d-lysine is covalently linked to a C16-C22 fatty acid or C16-C22 diacid, optionally through a spacer comprising a gamma glutamic acid linkage.

~~10~~6. The conjugate of ~~claim 9~~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.

~~11~~7. The conjugate of claim ~~9~~5 or ~~10~~6 wherein said ~~spacer~~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.

~~12. The conjugate of claim 11 wherein k is 2 and q is 2 or 4.~~

~~13~~ 8. The conjugate of any one of claims 1-~~5~~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~~.~~

~~14. The conjugate of claim 13~~, 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.

~~15~~9. The conjugate of claim ~~13~~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

~~16. The conjugate of claim 13 wherein~~

ii)

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

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.

~~17~~10. The conjugate of claim ~~16~~9 wherein

i) R_1, is (C_1-C_4 alkyl)NH-[spacer]-$CO(CH_2)_{14-20}COOH$, 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)

~~18. The conjugate of claim 16 wherein~~

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}-$CO(CH_2)_{14-20}COOH$.

~~19. The conjugate of any one of claims 1-18 wherein the first amino acid of the cleavable dipeptide is an amino acid in the D-stereochemical configuration.~~

~~20~~

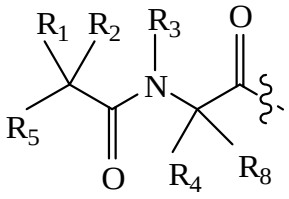
11. A conjugate comprising a PTH peptide, and a self-cleaving dipeptide covalently linked to the N-terminal alpha amine of said PTH peptide via an amide bond, wherein

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

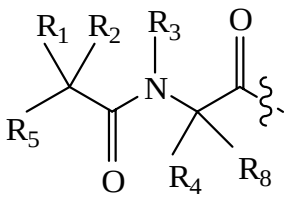
R_5 is NH_2, wherein said spacer of R_1, X_{33} and X_{35} is each independently selected from the group consisting of gamma glutamic acid, gamma glutamic acid-gamma glutamic acid dipeptide, and gamma glutamic acid-[$COCH_2(OCH_2CH_2)_kNH]_q$-gamma glutamic acid wherein k is an integer selected from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

~~21~~12. The conjugate of claim ~~20~~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-[$COCH_2(OCH_2CH_2)_2$NH-$COCH_2(OCH_2CH_2)_2$]NH-gamma glutamic acid}-CO(CH_2)$_{14-20}$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

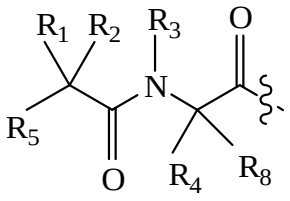
R_5 is NH_2.

~~22~~13. The conjugate of claim ~~19~~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.

~~23. The conjugate of claim 22~~, 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}-$CO(CH_2)_{16}COOH$.

~~24~~14. The conjugate of any one of claims ~~21, 22 or 23~~1-13 wherein the first amino acid of the self-cleaving dipeptide is in the D-stereochemical configuration.

~~25~~15. A pharmaceutical composition comprising the conjugate of any one of claims 1-~~24~~14, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~26~~16. The pharmaceutical composition of claim ~~25~~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.

~~27~~17. The pharmaceutical composition of claim ~~25~~15 or ~~26~~16 further comprising a peptide of SEQ ID NO: 7, SEQ ID NO: 31, or SEQ ID NO: 32 and optionally calcitonin.

18. ~~28. A method of treating hypoparathyroidism, said method comprising administering an effective amount~~Use of the conjugate of any one of claims 1-14 in the manufacture of a ~~pharmaceutical composition of claim 23, 24 or 25 to a patient in need of treatment.~~

~~29. A method of treating~~medicament for the treatment of hypoparathyroidism, osteoporosis or osteopenia~~, said method comprising administering an effective amount of a pharmaceutical composition of claim 22, 23 or 24 to a patient in need of treatment~~.

~~30~~

19. The ~~method~~use of claim ~~28 or 29~~18 wherein the ~~composition~~medicament is to be administered once per week.

~~31~~20. The ~~method~~use of claim ~~28 or 29~~18 wherein the composition is ~~administered daily.~~

~~32. The method of any one of claims 28-31 wherein the composition is~~to be administered orally.

~~33. Use of the composition of any one of claims 25-27, for the treatment of hypoparathyroidism.~~

~~34. Use of the composition of any one of claims 25-27 for the treatment of osteoporosis or osteopenia.~~