BRIEF SUMMARY

[0013a] In one aspect, there is provided a compound, comprising a peptide and a conjugating group, wherein the peptide comprises an amino acid sequence having the formula:

X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7

wherein

X_1 is D-cysteine;

X_2 is an amino acid sequence selected from the group consisting of D-arginine and a non-cationic amino acid;

X_3 is D-arginine;

X_4 is an amino acid selected from the group consisting of D-arginine and a non-cationic amino acid;

X_5 is D-arginine;

X_6 is a non-cationic amino acid;

X_7 is D-arginine; and

wherein the peptide is linked to the conjugating group by a disulfide bond.

[0014] ~~In one aspect,~~ Also disclosed is a compound, comprising the formula

X_1 - X_2 - X_3 – X_4 – X_5 – X_6 – X_7

~~is provided,~~ wherein X_1 is a subunit comprising a thiol-containing group; X_5 is a cationic subunit; X_6 is a non-cationic subunit; X_7 is a cationic subunit; and at least one, preferably two, of X_2, X_3 and X_4 is/are independently a cationic subunit; and wherein the compound has activity to decrease parathyroid hormone concentration. In one embodiment, the decrease in parathyroid hormone concentration is a decrease in blood or plasma parathyroid hormone concentration in a subject treated with the compound relative to the blood or plasma parathyroid hormone concentration in the subject prior to treatment. In another embodiment, the decrease in parathyroid hormone concentration is achieved in the absence of a histamine response.

[0015] In another embodiment X_3 and X_4 are non-cationic while X_1, X_5 , X_6 and X_7 are cationic.

[0016] In one embodiment, the X_1 subunit is a thiol-containing amino acid residue. In another embodiment, the thiol group of the X_1 subunit is an organic thiol-containing moiety.

[0017] In another embodiment, when the X_1 subunit is a thiol-containing amino acid residue, it is selected from the group consisting of L-cysteine, D-cysteine, glutathione, n-acetylated cysteine, homocysteine and pegylated cysteine.

[0018] In yet another embodiment, the organic thiol-containing moiety is selected from thiol-alkyl, or thioacyl moieties such as 3-mercaptopropyl or 3-mercaptopropionyl, mercaptopropionic acid, mercaptoacetic acid, thiobenzyl, or thiopropyl. In still another embodiment, the organic-thiol-containing moiety is mercaptopropionic acid.

[0019] In still another embodiment, the X_1 subunit is modified chemically to comprise an acetyl group, a benzoyl group, a butyl group, or another amino acid such as acetylated-beta-alanine.

[0020] In yet another embodiment, when the X_1 subunit comprises a thiol moiety, the X_1 subunit is joined by a covalent linkage to a second thiol moiety.

[0021] In another embodiment, the formula X_1 - X_2 - X_3 – X_4 – X_5 – X_6 – X_7 is comprised of a contiguous sequence of amino acid residues (designated herein as (X_{aa1})-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) SEQ ID NO:1) or a sequence of organic compound subunits (non-amino acid residues).

[0022] In another embodiment, the contiguous sequence of amino acid residues is a contiguous sequence of L-amino acid residues, a contiguous sequence of D-amino acid residues, a contiguous sequence of a mixture of L-amino acid residues and D-amino acid residues, or a mixture of amino acid residues and non-natural amino acid residues.

[0023] In another embodiment, the contiguous sequence of amino acid residues is linked to a compound to facilitate transport across a cell membrane. In another embodiment, the contiguous sequence of amino acid residues is linked to a compound that enhances delivery of the sequence into or across one or more layers of tissue.

[0024] In another embodiment, the contiguous sequence of amino acid residues is contained within a sequence of amino acid residues from 8-50 amino acid residues, 8-40 amino acid residues, 8-30 amino acid residues or 8-20 amino acid residues in length. In yet another embodiment, the contiguous sequence of amino acid residues is contained within a sequence of amino acid residues from 8-19 amino acid residues, 8-18 amino acid residues, 8-17 amino acid residues, 8-16 amino acid residues, 8-15 amino acid residues, 8-14 amino acid residues, 8-13 amino acid residues, 8-12 amino acid residues, 8-11 amino acid residues, 8-10 amino acid residues, or 8-9 amino acid residues in length.

[0025] In another embodiment, the X_3 subunit is a cationic amino acid residue.

[0026] In another embodiment, the X_2 subunit is a non-cationic amino acid residue, and in another embodiment, the X_4 subunit is a non-cationic amino acid residue. In one embodiment, the non-cationic amino acid residue is a D-amino acid.

[0027] In another embodiment, X_3 and X_4 are cationic D-amino acid residues.

[0028] In another embodiment, the X_5 subunit is a D-amino acid residue.

[0029] In another ~~aspect~~embodiment, the contiguous sequence in any of the described compounds is covalently attached via the thiol-containing group in the X_1 subunit to a second contiguous sequence. For example, the second contiguous sequence can be identical to the contiguous sequence (to form a dimer), or can be non-identical, as would be the case when attached to a moiety that facilitates transfer of the contiguous sequence across a cell membrane.

[0030] In another ~~aspect~~embodiment, a conjugate comprised of the peptide carrrar (SEQ ID NO:2) is provided, where the peptide is conjugated at its N-terminal residue to a Cys residue.

[0031] In one embodiment, the peptide is chemically modified at the N-terminus, the C-terminus, or both.

[0032] In another embodiment, the N-terminus of the peptide is chemically modified by acetylation and the C-terminus is chemically modified by amidation.

[0033] In another embodiment, the conjugate is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

[0033a] In one aspect, there is provided a compound comprising Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

[0033b] In one aspect, there is provided a compound comprising Ac-c(C)arrrar-NH_2 (SEQ ID NO:3), wherein the conjugating group is acetylated.

[0033c] In one aspect, there is provided a compound comprising Ac-c(c)arrrar-NH_2 (SEQ ID NO:142).

[0033d] In one aspect, there is provided a compound comprising Ac-c(C)rrarar-NH_2 (SEQ ID NO:28).

[0033e] In one aspect, there is provided a compound comprising Ac-c(C)rrarar-NH_2 (SEQ ID NO:28), wherein the conjugating group is acetylated.

[0033f] In one aspect, there is provided a compound comprising:

Ac-crrarar-NH_2 (SEQ ID NO:25)

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Ac-crrarar-NH_2 (SEQ ID NO:25)

[0033g] In one aspect, there is provided a compound comprising:

Ac-carrrar-NH_2 (SEQ ID NO:26)

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Ac-carrrar-NH_2 (SEQ ID NO:26)

[0033h] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable excipient or carrier for use in treating secondary hyperparathyroidism (SHPT) in a subject.

[0033i] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable excipient or carrier for use in decreasing parathyroid hormone levels in a subject.

[0033j] In one aspect, there is provided use of a composition comprising a compound as defined above for manufacture of a medicament for treating secondary hyperparathyroidism (SHPT) in a subject.

[0033k] In one aspect, there is provided use of a composition comprising a compound as defined above for manufacture of a medicament for decreasing parathyroid hormone levels in a subject.

[0034] In another ~~aspect~~embodiment, a method of treating secondary hyperparathyroidism (SHPT) in a subject is contemplated, wherein a compound as described herein is provided to the subject. In various embodiments, the subject can be suffering from chronic kidney disease or other condition.

[0035] In another ~~aspect~~embodiment, a method of decreasing parathyroid hormone in a subject is contemplated, wherein a compound as described herein is provided to the subject.

[0036] In another ~~aspect~~embodiment, a treatment regimen is provided, the regimen comprising providing a compound according to any of those described herein, in combination with a second agent.

[0037] In one embodiment, the second therapeutic agent is vitamin D, a vitamin D analog or cinacalcet hydrochloride.

[0038] In any of the aspects or embodiments described herein, any one or more of the sequences is contemplated to be individually excepted or removed from the scope of the claims. In certain embodiments, the peptides identified by any one or more of SEQ ID NOs: 162-182, individually or in any combination, are excluded from the claimed compounds, compositions and methods.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] FIG. 1 is a graph of parathyroid hormone level, as percent of the baseline pre-dose value, as a function of time, in hours, in rats with acute renal insufficiency (1K1C model), where the rats were dosed with Ac-crrrr-NH_2 (SEQ ID NO:4, diamonds), Ac-crrrrr-NH_2 (SEQ ID NO:5, closed squares), Ac-crrrrrr-NH_2 (SEQ ID NO:6, triangles), Ac-crrrrrrr-NH_2 (SEQ ID NO:7, open squares), or saline control (x symbols);

[0040] FIG. 2A is a graph of IP_1 concentration, in nM, as a function of compound concentration of Ac-carrrar-NH_2 (SEQ ID NO:26, squares) and Ac-arrrar- NH_2 (SEQ ID NO:29, triangles), as a measure of the compound's ability to activate the human CaSR in an *in vitro* cell assay when the human CaSR is expressed as a stable transfected HEK-293 cell line;

[0041] FIG. 2B shows the reduction in PTH concentration upon *in vivo* administration of peptides identified as SEQ ID NO:26 (Ac-carrrar-NH_2) (squares) and as SEQ ID NO:29 (Ac-arrrar-NH_2) (diamonds), where the peptides were administered as an IV bolus to

Claims

We claim:

1. A compound, comprising the formula:

$$X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7$$

wherein

X_1 is a subunit comprising a thiol-containing group;

X_5 is a cationic subunit;

X_6 is a non-cationic subunit;

X_7 is a cationic a subunit; and

at least two of X_2, X_3 and X_4 are independently a cationic subunit; and

wherein said compound has activity to decrease parathyroid hormone level in a subject.

2. The compound of claim 1, wherein the thiol group on the X_1 subunit is selected from the group consisting of thiol-containing amino acid residues and organic thiol-containing moieties.

3. The compound of claim 2, wherein the thiol-containing amino acid residue is selected from the group consisting of cysteine, glutathione, n-acetylated cysteine and PEGylated cysteine.

4. The compound of claim 2, wherein the organic thiol-containing moiety is selected from mercaptopropionic acid, mercaptoacetic acid, thiobenzyl, and thiopropyl.

5. The compound of claim 1, wherein the X_1 subunit is modified chemically to comprise an acetyl group, a benzoyl group, a butyl group, an acetylated-beta-alanine or is joined by a covalent linkage to another thiol moiety.

6. The compound of claim 1, wherein the formula $X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7$ is comprised of a contiguous sequence of amino acid residues, a contiguous sequence of organic compounds, or a mixture thereof.

7. The compound of claim 6, wherein the contiguous sequence of amino acid residues is a contiguous sequence of L-amino acid residues, a contiguous sequence of D-amino acid residues, a contiguous sequence of a mixture of L-amino acid residues

and D-amino acid residues, or a mixture of amino acid residues and non-natural amino acid residues.

8. The compound of claim 1, wherein the formula X_1 - X_2 - X_3 – X_4 – X_5 – X_6 – X_7 is a contiguous sequence of amino acid residues.

9. The compound of claim 8, wherein the contiguous sequence of amino acid residues is conjugated to a compound to facilitate transport across a cell membrane.

10. The compound of claim 8, wherein the contiguous sequence of amino acid residues is contained within a sequence of amino acid residues between 8-50 amino acid residues in length.

11. The compound of claim 6, wherein the X_3 subunit is a cationic amino acid residue.

12. The compound of claim 11, wherein the X_2 subunit is a non-cationic amino acid residue.

13. The compound of claim 11, wherein X_4 is a non-cationic amino acid residue.

14. The compound of claim 12 or claim 13, wherein the non-cationic amino acid residue is a D-amino acid.

15. The compound of claim 6, wherein X_3 and X_4 are cationic D-amino acid residues.

16. The compound of claim 15, wherein X_5 is a D-amino acid residue.

17. A compound according to any one of claims 1-16, wherein the formula is covalently attached via the thiol-containing group in the X_1 subunit to a second contiguous sequence.

18. The compound of claim 17, wherein the second contiguous sequence is identical to the formula.

19. The compound of claim 17, wherein the second contiguous sequence is a peptide that facilitates transfer of the compound across a cell membrane.

20. A conjugate comprised of a peptide comprising the sequence carrrar (SEQ ID NO:2) and a conjugating group, said peptide linked by a disulfide bond at its N-terminal residue to the conjugating group.

21. The conjugate of claim 20, wherein the peptide is chemically modified at the N-terminus, the C-terminus, or both.

22. The conjugate of claim 20, wherein the N-terminus is chemically modified by acetylation and the C-terminus is chemically modified by amidation.

23. The conjugate of claim 20, wherein the conjugate is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

24. A composition for use in treating secondary hyperparathyroidism (SHPT) in a subject, comprising providing a compound according to any one of claims 1-19 or a conjugate according to any one of claims 20-23.

25. A composition for use in SHPT in a subject suffering from chronic kidney disease, comprising providing a compound according to any one of claims 1-19 or a conjugate according to any one of claims 20-23.

26. A composition for use in decreasing parathyroid hormone levels in a subject, comprising providing a compound according to any one of claims 1-19 or a conjugate according to any one of claims 20-23.

27. The composition according to any one of claims 24, 25 or 26, wherein said composition is provided transdermally.

28. A treatment regimen, comprising a compound according to any one of claims 1-16 or a conjugate according to any one of claims 20-23 and a second therapeutic agent.

29. The regimen of claim 28, wherein the second therapeutic agent is vitamin D, a vitamin D analog or cinacalcet hydrochloride.

Claims

We claim:

1. A compound, comprising a peptide and a conjugating group, wherein the peptide comprises an amino acid sequence having the formula:

$$X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7$$

wherein

X_1 is D-cysteine;

X_2 is an amino acid sequence selected from the group consisting of D-arginine and a non-cationic amino acid;

X_3 is D-arginine;

X_4 is an amino acid selected from the group consisting of D-arginine and a non-cationic amino acid;

X_5 is D-arginine;

X_6 is a non-cationic amino acid;

X_7 is D-arginine; and

wherein the peptide is linked to the conjugating group by a disulfide bond.

2. The compound of claim 1, wherein the N-terminus of the peptide is acetylated.

3. The compound of claim 1, wherein the C-terminus is amidated.

4. The compound of claim 2, wherein the C-terminus is aminated.

5. The compound of claim 1, wherein the conjugating group is selected from the group consisting of cysteine, homocysteine, glutathione, pegylated cysteine and a thiol-containing polypeptide.

6. The compound of claim 5, wherein the conjugating group is acetylated.

7. The compound of claim 1, wherein the conjugating group is cysteine.

8. The compound of claim 7, wherein the conjugating group is acetylated.

9. The compound of claim 1, wherein the compound is a homodimer.

10. The compound of claim 1, wherein X_2 is D-arginine.

11. The compound of claim 10, wherein the N-terminus of the peptide is acetylated.

12. The compound of claim 11, wherein the C-terminus of the peptide is amidated.

13. The compound of claim 10, wherein the compound is a homodimer.

14. The compound of claim 5, wherein X_4 is D-arginine.

15. The compound of claim 14, wherein the conjugating group is cysteine.

16. The compound of claim 15, wherein the conjugating group is acetylated.

17. The compound of claim 14, wherein the N-terminus of the peptide is acylated.

18. The compound of claim 17, wherein the C-terminus of the peptide is amidated.

19. The compound of claim 5, wherein the conjugating group is cysteine.

20. The compound of claim 19, wherein the conjugating group is acetylated.

21. The compound of claim 10, wherein X_4 is D-alanine.

22. The compound of claim 21, wherein the conjugating group is L-cysteine.

23. The compound of claim 21, wherein the conjugating group is D-cysteine.

24. The compound of claim 22, wherein the conjugating group is acetylated.

25. The compound of claim 23, wherein the conjugating group is acetylated.

26. The compound of claim 21, wherein the compound is a homodimer.

27. The compound of claim 21, wherein the N-terminus of the peptide is acetylated.

28. The compound of claim 27, wherein the C-terminus of the peptide is amidated.

29. The compound of claim 14, wherein the compound is a homodimer.

30. The compound of claim 14, wherein X_2 is D-alanine.

31. The compound of claim 30, wherein the conjugating group is L-cysteine.

32. The compound of claim 30, wherein the conjugating group is D-cysteine.

33. The compound of claim 31, wherein the conjugating group is acetylated.

34. The compound of claim 32, wherein the conjugating group is acetylated.

35. The compound of claim 30, wherein the compound is a homodimer.

36. The compound of claim 30, wherein the N-terminus of the peptide is acetylated.

37. The compound of claim 36, wherein the C-terminus of the peptide is amidated.

38. The compound of claim 1, wherein the peptide is 8 to 15 amino acid residues in length.

39. The compound of claim 38, wherein the peptide is 8 to 11 amino acid residues in length.

40. The compound of claim 39, wherein the peptide is 8 to 9 amino acid residues in length.

41. The compound of claim 1, wherein the peptide consists of the amino acid sequence having the formula:

$$X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7$$

42. A compound comprising Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

43. A compound comprising Ac-c(C)arrrar-NH_2 (SEQ ID NO:3), wherein the conjugating group is acetylated.

44. A compound comprising Ac-c(c)arrrar-NH_2 (SEQ ID NO:142).

45. A compound comprising Ac-c(C)rrarar-NH_2 (SEQ ID NO:28).

46. A compound comprising Ac-c(C)rrarar-NH_2 (SEQ ID NO:28), wherein the conjugating group is acetylated.

47. A compound comprising:

Ac-crrarar-NH_2 (SEQ ID NO:25)

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Ac-crrarar-NH_2 (SEQ ID NO:25)

48. A compound comprising:

Ac-carrrar-NH_2 (SEQ ID NO:26)

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Ac-carrrar-NH_2 (SEQ ID NO:26)

49. A pharmaceutical composition comprising a compound according to any one of claims 1-48 and a pharmaceutically acceptable excipient or carrier for use in treating secondary hyperparathyroidism (SHPT) in a subject.

50. A pharmaceutical composition comprising a compound according to any one of claims 1-48 and a pharmaceutically acceptable excipient or carrier for use in decreasing parathyroid hormone levels in a subject.

51. The pharmaceutical composition according to claim 49, wherein the composition is provided intravenously.

52. The pharmaceutical composition according to claim 49, wherein said composition is provided transdermally.

53. The pharmaceutical composition according to claim 50, wherein the composition is provided transdermally.

54. The pharmaceutical composition according to claim 50, wherein the composition is provided intravenously.

55. Use of a composition comprising a compound according to any one of claims 1-48 for manufacture of a medicament for treating secondary hyperparathyroidism (SHPT) in a subject.

56. Use of a composition comprising a compound according to any one of claims 1-48 for manufacture of a medicament for decreasing parathyroid hormone levels in a subject.

57. The use according to claim 55, further comprising a second therapeutic agent.

58. The use according to claim 57, wherein the second therapeutic agent is vitamin D, a vitamin D analog or cinacalcet hydrochloride.

59. The use according to claim 56, further comprising a second therapeutic agent.

60. The use according to claim 59, wherein the second therapeutic agent is vitamin D, a vitamin D analog or cinacalcet hydrochloride.