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, D-alanine, D-valine, D-leucine, D-phenylalanine, D-serine, D-glutamine, D-norlelucine and D-norvaline ~~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, wherein X_4 is not glycine, proline or an amino acid with an acidic side chain;

X_5 is D-arginine;

X_6 is D-alanine or D-glycine ~~a non-cationic amino acid~~;

X_7 is D-arginine; and

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

wherein the peptide at its N-terminus is linked to the conjugating group by a disulfide bond.

[0014] Also disclosed is 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 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.

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 selected from the group consisting of D-arginine, D-alanine, D-valine, D-leucine, D-phenylalanine, D-serine, D-glutamine, D-norlelucine and D-norvaline;

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, wherein X_4 is not glycine, proline or an amino acid with an acidic side chain;

X_5 is D-arginine;

X_6 is D-alanine or D-glycine;

X_7 is D-arginine; and

wherein at least two of X_2, X_3 and X_4 are independently a cationic subunit; and wherein the peptide at its N-terminus 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 amidated.

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

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)

|

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.

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.

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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.