CLAIMS

~~**What is claimed is:**~~

~~1. A composition consisting of an oxyntomodulin, a polyethylene glycol polymer (PEG polymer) and 9-fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS).~~

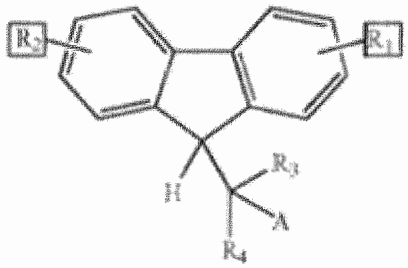
~~2. The composition of claim 1, wherein said PEG polymer is attached to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~3. The composition of claim 1, wherein said oxyntomodulin consists of the amino acid sequence set forth in SEQ ID NO: 1.~~

~~4. The composition of claim 1, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~5. The composition of claim 1, wherein said PEG polymer is PEG30, PEG_{40} or PEG_{60}.~~

~~6~~1. A pharmaceutical composition comprising ~~the composition of claim 1~~ an oxyntomodulin reverse PEGylated conjugate of the formula (X)n-Y, wherein Y is an oxyntomodulin peptide, wherein X is a radical of formula (i)



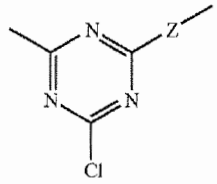
(i)

wherein R_1 is a radical containing a polymer polyethylene glycol (PEG) moiety; wherein R_2 is selected from the group consisting of hydrogen and $-SO_3H$; wherein R_3 and R_4 are each hydrogen; wherein A is a covalent bond when the radical is linked to a carboxyl, phosphate or mercapto group of the drug Y, or A is (OCO) when the radical is linked to an amino or hydroxyl group of the drug Y; and wherein n is an integer of at least one; and a pharmaceutical acceptable carrier.

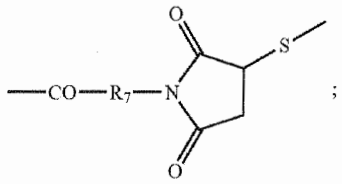
2. The pharmaceutical composition according to claim 1, wherein X is a radical of formula (i), R_2, R_3 and R_4 are each hydrogen and A is (OCO) or X is a radical of formula (i) wherein R_2 is $-SO_3H$ at position 2 of the ring, R_3 and R_4 are each hydrogen, and A is (OCO).

3. The pharmaceutical composition according to claim 1, wherein R_1 is a radical of the formula $-R_5-R_6$-PEG, wherein R_5 is selected from the group consisting of –NH-, -S-, -CO-, -COO-, $-CH_2-$, $-SO_2-$, $-SO_3-$, $-PO_2-$, and $-PO_3-$; and R_6 is a bond or a radical by which the PEG moiety is covalently attached to R_5.

4. The pharmaceutical composition according to claim 3, wherein R_5 is –NH- and R_6 is selected from the group consisting of –CO-, -COO-, $-CH_2-$, $-CH(CH_3)-$, CO-NH-, -CS-NH, $-CO-CH_2-NH-CO-$, $-CO-CH(CH_3)-NH-CO-$, $CO-CH_2-NH-CO-NH$,



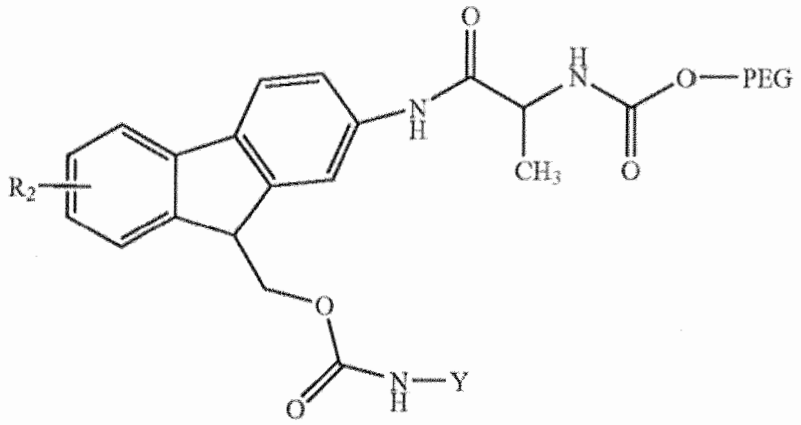
, and



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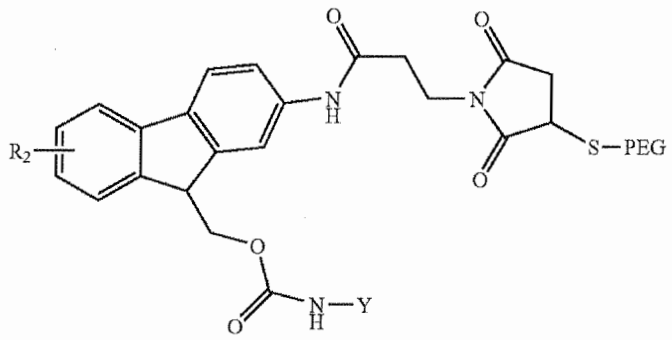
wherein Z is O, S, or NH; and wherein R_7 is selected from the group consisting of C_1-C_{18} straight or branched alkylene, phenylene, an oxyalkylene radical having 3-18 carbon atoms in the backbone, a residue of a peptide containing 2-10 amino acid residues, and a residue of a saccharide containing 1-10 monosaccharide residues.

5. The pharmaceutical composition according to claim 1, wherein said oxyntomodulin reverse PEGylated conjugate of formula (X)n-Y is



wherein R_2 is H or $-SO_3H$ at position 2 of the ring, and NH-Y is oxyntomodulin and, when R_2 is H said compound is a PEG-Fmoc-Y conjugate; or, when R_2 is $-SO_3H$ at position 2 of the ring, said compound is a PEG-FMS-Y conjugate.

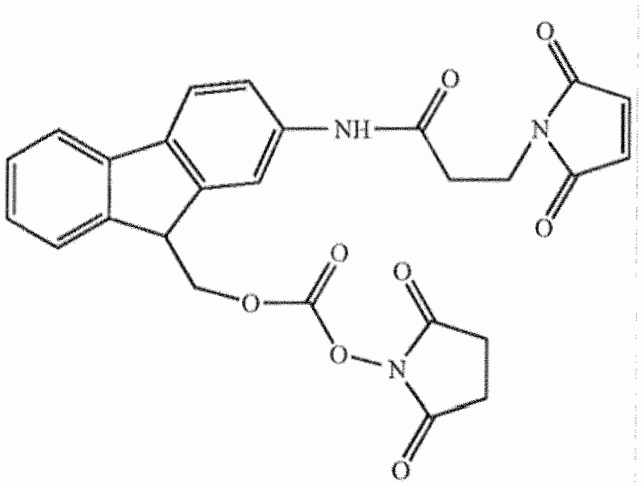
6. The pharmaceutical composition according to claim 1, wherein said oxyntomodulin reverse PEGylated conjugate of formula (X)n-Y is a PEG-Fmoc-Y conjugate or PEG-FMS-Y conjugate:



wherein, for PEG-Fmoc-Y, R_2 is H, and for PEG-FMS-Y, R_2 is $-SO_3H$.

7. The pharmaceutical composition according to claim 1, wherein the PEG moiety is a 40 kDa branched PEG and n is 1 to 3.

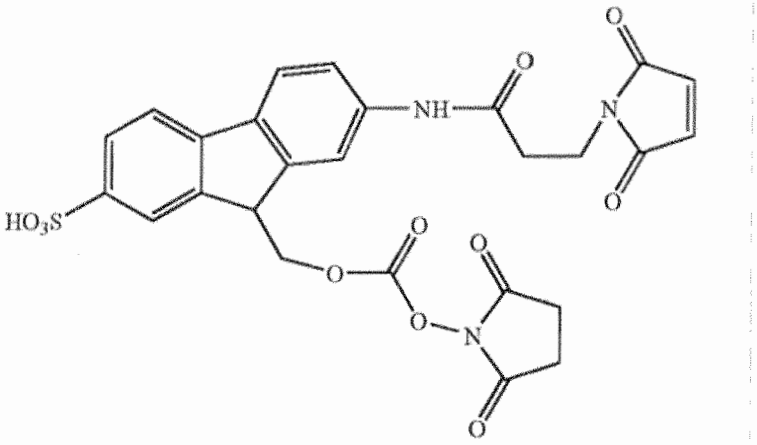
8. The pharmaceutical composition according to claim 1, wherein said oxyntomodulin reverse PEGylated conjugate is prepared from a MAL-Fmoc-NHS having the formula:



Precursor 7

and wherein said conjugate is designated as (PEG-Fmoc-)n-Y.

9. The pharmaceutical composition according to claim 1, wherein said oxyntomodulin reverse PEGylated conjugate is prepared from a MAL-FMS-NHS having the formula:



Precursor 8

and wherein said conjugate is designated as (PEG-FMS-)n-Y.

10. The pharmaceutical composition according to claim 8, wherein Y is linked to the Fmoc radical through an amino group.

11. The pharmaceutical composition according to claim 9, wherein Y is linked to the FMS radical through an amino group.

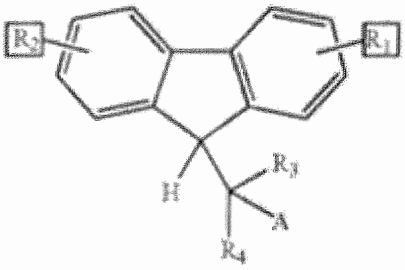
12. The pharmaceutical composition according to any one of claims 10 or 11, wherein

said amino group consists of the amino terminus of said oxyntomodulin.

13. The pharmaceutical composition according to any one of claims 8 or 9, wherein the PEG is linked to the FMS or Fmoc radical through a sulfhydryl group.

14. The pharmaceutical composition according to claim 1, wherein said oxyntomodulin consists of the amino acid sequence set forth in SEQ ID NO: 1.

15. An oxyntomodulin reverse PEGylated conjugate of the formula (X)n-Y, wherein Y is an oxyntomodulin peptide, wherein X is a radical of formula (i)



(i)

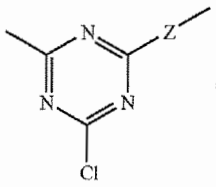
wherein R_1 is a radical containing a polymer polyethylene glycol (PEG) moiety; wherein R_2 is selected from the group consisting of hydrogen and $-SO_3H$; wherein R_3 and R_4 are each hydrogen; wherein A is a covalent bond when the radical is linked to a carboxyl, phosphate or mercapto group of the drug Y, or A is (OCO) when the radical is linked to an amino or hydroxyl group of the drug Y; and wherein n is an integer of at least one.

16. The conjugate according to claim 15, wherein X is a radical of formula (i), R_2, R_3 and R_4 are each hydrogen and A is (OCO) or X is a radical of formula (i) wherein R_2 is $-SO_3H$ at position 2 of the ring, R_3 and R_4 are each hydrogen, and A is (OCO).

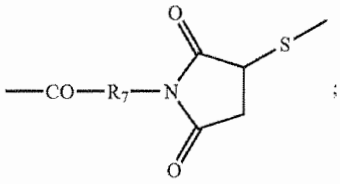
17. The conjugate according to claim 15, wherein R_1 is a radical of the formula $-R_5$-R_6-PEG, wherein R_5 is selected from the group consisting of –NH-, -S-, -CO-, -COO-, $-CH_2$-, $-SO_2$-, $-SO_3$-, $-PO_2$-, and $-PO_3$-; and R_6 is a bond or a radical by which the PEG moiety is covalently attached to R_5.

18. The conjugate according to claim 17, wherein R_5 is –NH- and R_6 is selected from

the group consisting of –CO-, -COO-, -CH_2-, -$CH(CH_3)$-, CO-NH-, -CS-NH, -CO-CH_2-NH-CO-, -CO-$CH(CH_3)$-NH-CO-, CO-CH_2-NH-CO-NH,



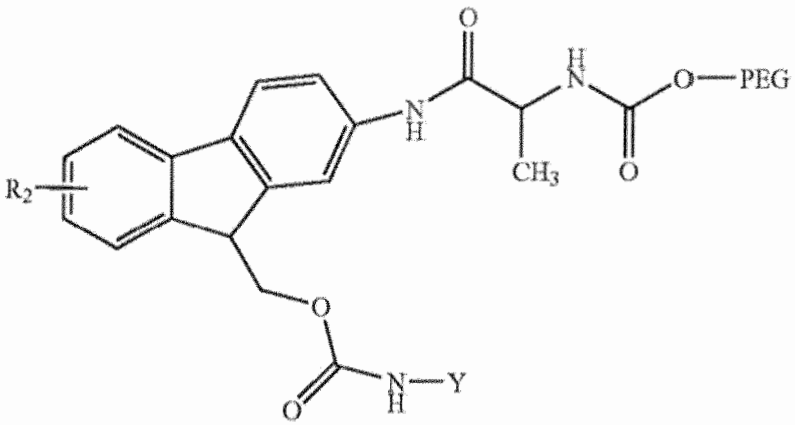
, and



;

wherein Z is O, S, or NH; and wherein R_7 is selected from the group consisting of C1-C18 straight or branched alkylene, phenylene, an oxyalkylene radical having 3-18 carbon atoms in the backbone, a residue of a peptide containing 2-10 amino acid residues, and a residue of a saccharide containing 1-10 monosaccharide residues.

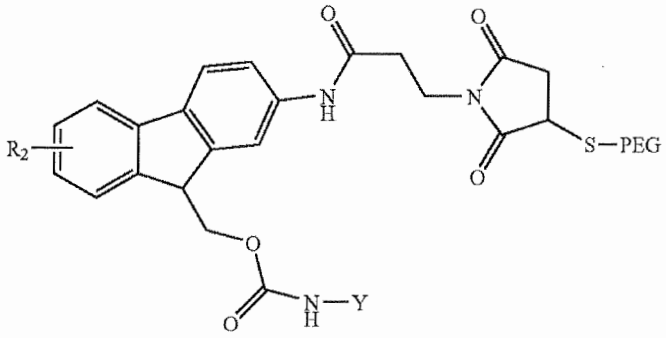
19. The conjugate according to claim 15, wherein said conjugate of formula (X)n-Y is



,

wherein R_2 is H or –SO_3H at position 2 of the ring, and NH-Y is oxyntomodulin and, when R_2 is H said conjugate is a PEG-Fmoc-Y conjugate; or, when R_2 is –SO_3H at position 2 of the ring, said conjugate is a PEG-FMS-Y conjugate.

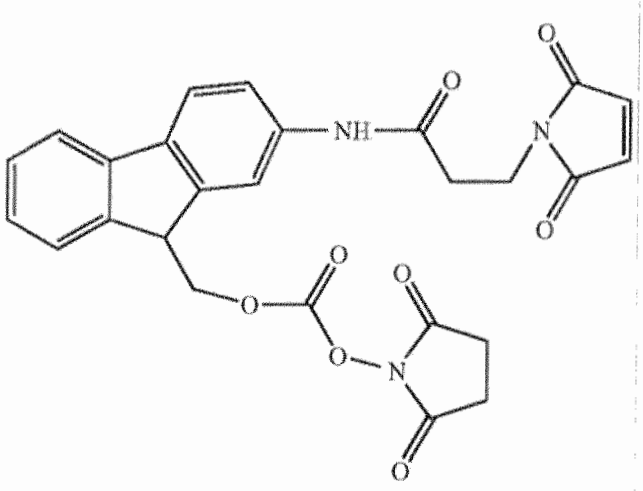
20. The conjugate according to claim 15, wherein said conjugate of formula (X)n-Y is a PEG-Fmoc-Y conjugate or PEG-FMS-Y conjugate



wherein, NH-Y is oxyntomodulin and for PEG-Fmoc-Y, R_2 is H, and for PEG-FMS-Y, R_2 is $-SO_3H$.

21. The conjugate according to claim 15, wherein the PEG moiety is a 40 kDa branched PEG and n is 1 to 3.

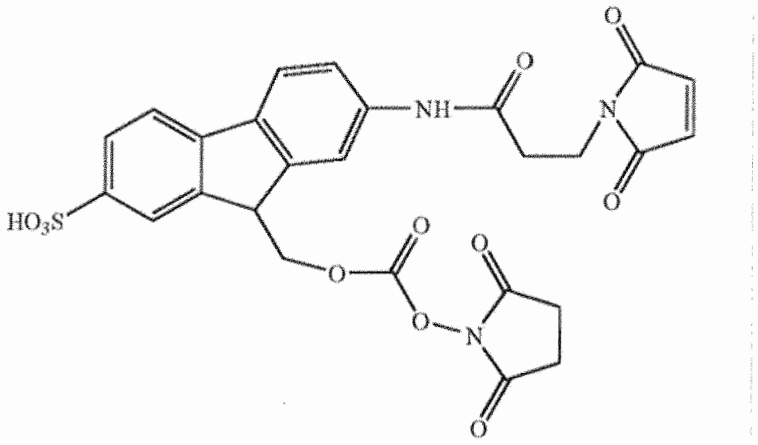
22. The conjugate according to claim 15, wherein said conjugate is prepared from a MAL-Fmoc-NHS having the formula:



Precursor 7

and wherein said compound is designated as (PEG-Fmoc-)n-Y.

23. The conjugate according to claim 15, wherein said conjugate is prepared from a MAL-FMS-NHS having the formula:



Precursor 8

and wherein said conjugate is designated as (PEG-FMS-)n-Y.

24. The conjugate according to claim 22, wherein Y is linked to the Fmoc radical through an amino group.

25. The conjugate according to claim 23, wherein Y is linked to the FMS radical through an amino group.

26. The conjugate according to any one of claims 24 or 25, wherein said amino group consists of the amino terminus of said oxyntomodulin.

27. The conjugate according to any one of claims 22 or 23, wherein the PEG is linked to the FMS or Fmoc radical through a sulfhydryl group.

28. The conjugate according to claim 15, wherein said oxyntomodulin consists of the amino acid sequence set forth in SEQ ID NO: 1.

~~7~~29. A method for extending the biological half-life of oxyntomodulin, said method consisting of the step of conjugating oxyntomodulin, a polyethylene glycol polymer (PEG polymer) and 9-fiuorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS) in a molar ratio of about 1:1:0.5 to about 1:1:3.5, wherein an oxyntomodulin reverse PEGylated conjugate is formed and said conjugate has extended biological half-life.

~~8. The method of claim 7, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.~~

~~9. The method of claim 7, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~10. The method of claim 7, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~11. The method of claim 7, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~12~~30. ~~A method of inducing glucose tolerance, glycemic control, or both in a subject in need thereof, comprising the step of administering to said subject~~ Use of an effective amount of the pharmaceutical composition of claim 1, for the preparation of a medicament for inducing glucose tolerance in a subject ~~and a pharmaceutical acceptable carrier~~.

~~13. The method of claim 12, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.~~

~~14. The method of claim 12, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~15. The method of claim 12, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~16. The method of claim 12, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~17~~31. A method of improving the area under the curve (AUC) of oxyntomodulin, said method consisting of the step of conjugating a polyethylene glycol polymer (PEG polymer) to the amino terminus of said oxyntomodulin via 9-fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS), wherein an oxyntomodulin reverse PEGylated conjugate is formed and said conjugate has improved AUC compared with oxyntomodulin.

~~18. The method of claim 17, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.~~

~~19. The method of claim 17, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~20. The method of claim 17, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~21. The method of claim 17, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~22~~32. A method of reducing the dosing frequency of oxyntomodulin, said method consisting of the step of conjugating a polyethylene glycol polymer (PEG polymer) to the amino terminus of said oxyntomodulin via 9-fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS), wherein an oxyntomodulin reverse PEGylated conjugate is formed and said conjugate has enhanced potency.

~~23. The method of claim 22, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.~~

~~24. The method of claim 22, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~25. The method of claim 22, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~26. The method of claim 22, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~27~~33. Use of an effective amount of the pharmaceutical composition of claim 1, for the preparation of a medicament~~A method~~ for reducing food intake, reducing body weight, or both in a subject~~, comprising the step of administering oxyntomodulin conjugated to polyethylene glycol polymer (PEG polymer) via a flexible linker to said subject, wherein said flexible linker is 9-fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS)~~.

~~28. The method of claim 27, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.~~

~~29. The method of claim 27, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.~~

~~30. The method of claim 27, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.~~

~~31. The method of claim 27, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~32~~34. Use of an effective amount of the pharmaceutical composition of claim 1, for the preparation of a medicament ~~A method~~ for increasing insulin sensitivity in a subject~~, comprising the step of administering to the subject an effective amount of a composition comprising oxyntomodulin conjugated to polyethylene glycol polymer (PEG polymer)~~.

~~33. The method of claim 32, wherein said PEG polymer is PEG_{30}, PEG_{40} or PEG_{60}.~~

~~34. The method of claim 32, wherein said oxyntomodulin is conjugated to said polyethylene glycol polymer (PEG polymer) via a linker.~~

~~35. The method of claim 33, wherein said linker is a cleavable flexible linker.~~

~~36. The method of claim 33, wherein the linker is a non-cleavable linker.~~

~~37. The method of claim 35, wherein said flexible linker is 9-fluorenylmethoxycarbonyl (Fmoc) or 2-sulfo-9-fluorenylmethoxycarbonyl (FMS).~~

~~38. The method of claim 36, wherein said linker is *N*-(ε-Maleimidocaproyloxu) succinimide ester (EMCS).~~

~~39. The method of claim 32, wherein administering said composition results in an acute increase in insulin sensitivity in said subject.~~

35. Use of a pharmaceutical composition according to claim 1, or a conjugate according to claim 15, in the manufacture of a medicament for treating obesity.

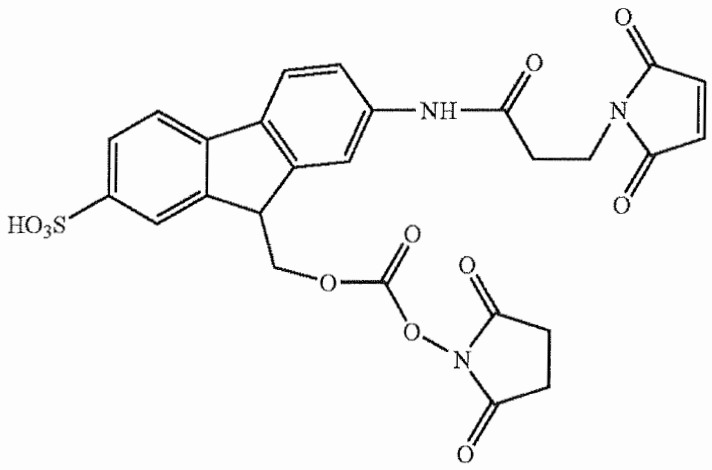
36. The method of any one of claims 29, 31, and 32, or the use of any one of claims 30 and 33-35, wherein said oxyntomodulin consists of an amino acid sequence of SEQ ID NO: 1.

37. The method of any one of claims 29, 31, and 32, or the use of any one of claims 30 and 33-35, wherein said PEG polymer is conjugated to the amino terminus or lysine residue of said oxyntomodulin via Fmoc or FMS.

38. The method of any one of claims 29, 31, and 32, or the use of any one of claims 30 and 33-35, wherein said PEG polymer is a PEG polymer with a sulfhydryl moiety.

39. The method of any one of claims 29, 31, and 32, or the use of any one of claims 30 and 33-35, wherein said PEG polymer is PEG_{30} or PEG_{40}.

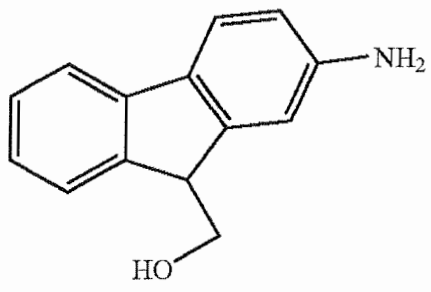
40. A process for producing a conjugate of claim 15, said process comprising the step of reacting a compound of formula:



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with a PEG-SH, and oxyntomodulin to form PEG-FMS-OXM.

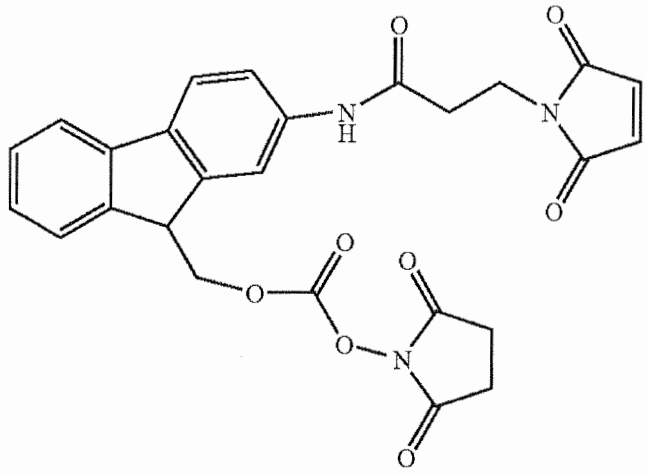
41. A process for producing a conjugate of claim 15 comprising the step of reacting a compound of formula:



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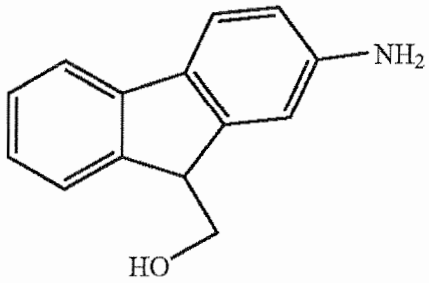
with 3-maleimideopropionic acid and N-hydroxysuccinimide to form an intermediate

compound of formula:

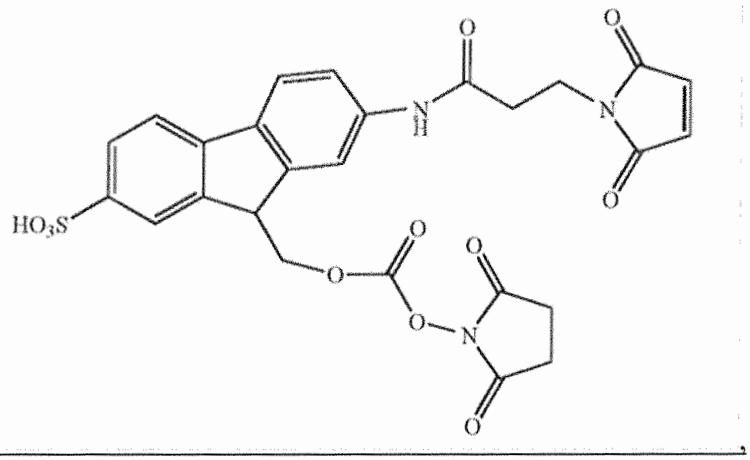


wherein said intermediate is reacted with oxyntomodulin and PEG-SH to form PEG-Fmoc-OXM.

42. A process for producing a conjugate of claim 15,, said process comprising the step of: reacting a compound of formula:



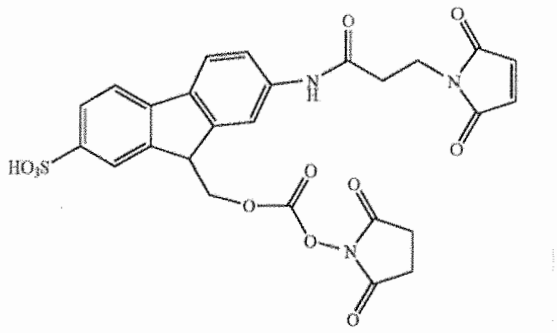
with 3-maleimideopropionic acid and N-hydroxysuccinimide to form an intermediate, wherein said intermediate is reacted with a sulfating agent to form an intermediate compound of formula:



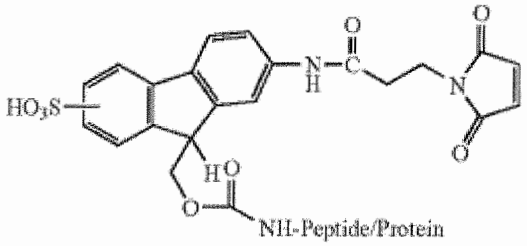
wherein said compound is reacted with oxyntomodulin and PEG-SH to form PEG-FMS-OXM.

43. A process for preparing a conjugate of claim 15, said process comprising the steps of:

(a) reacting MAL-FMS-NHS

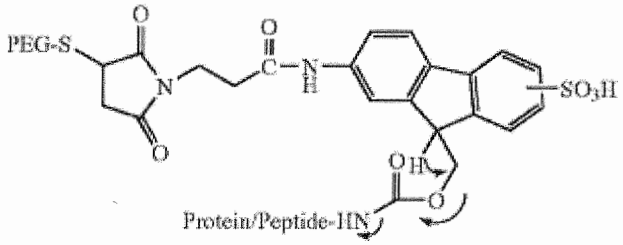


with an amino group of a Peptide/Protein to form



; and

(b) reacting the resultant conjugate with PEG-SH to form the PEG-S-MAL-FMS-NH-Peptide/Protein conjugate

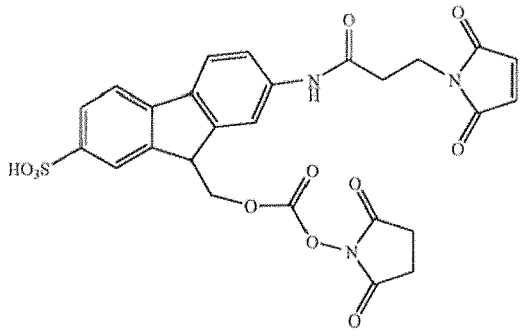


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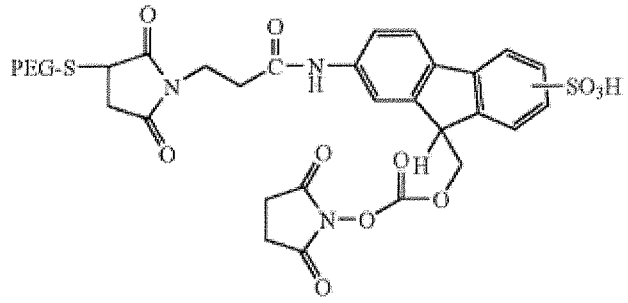
wherein the NH-Peptide/Protein is oxyntomodulin.

44. A process for preparing a compound of claim 15, said process comprising the steps of:

(a) reacting MAL-FMS-NHS

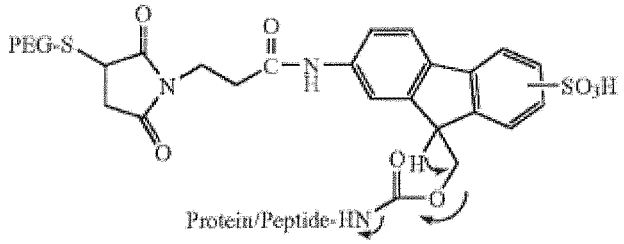


with PEG-SH to form



; and

(b) reacting the resultant conjugate with an amino group of a Peptide/Protein to form the PEG-S-MAL-FMS-NH-Peptide/Protein conjugate



;

wherein the NH-Peptide/Protein is oxyntomodulin.

45. The process according to any one of claims 43-44, wherein the process occurs in two steps, step (a) and then step (b).

46. The process according to any one of claims 43-44, wherein reacting MAL-FMS-NHS, oxyntomodulin and PEG-SH occurs in one-step.

47. The process according to any one of claims 43-44, wherein oxyntomodulin reacts via a terminal amino group.