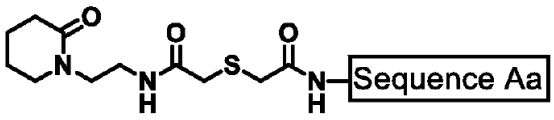
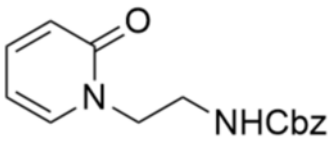
CLAIMS

1. A method of synthesizing an N-terminal conjugated peptidyl compound of formula (I):



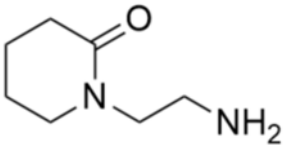
(I),

wherein Sequence Aa is a peptide, the method comprising the step of reducing benzyl 2-(2-oxopyridin-1(2H)-yl)ethylcarbamate (XIX):



(XIX)

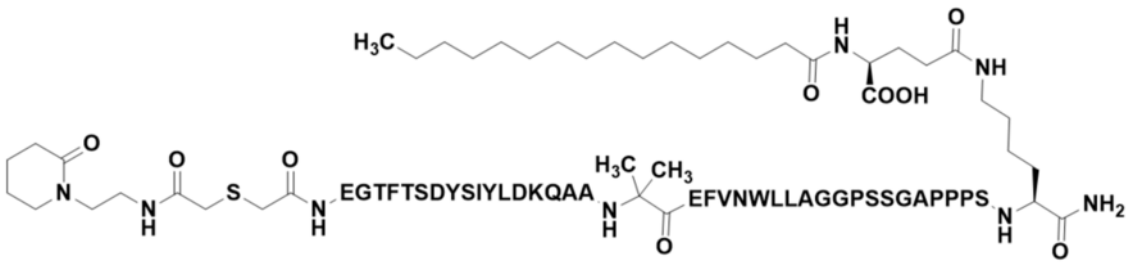
to 1-(2-aminoethyl)piperidin-2-one (XX):



(XX)

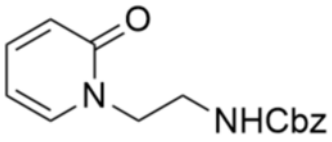
with a catalyst in the presence of H_2.

2. A method of synthesizing a compound of formula (XVI):



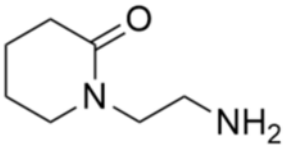
(XVI; SEQ ID NO: 16),

the method comprising the step of reducing benzyl 2-(2-oxopyridin-1(2H)-yl)ethylcarbamate (XIX):



(XIX)

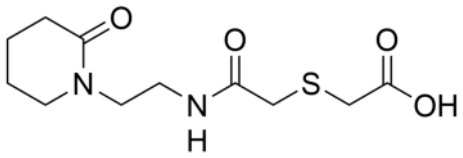
to 1-(2-aminoethyl)piperidin-2-one (XX):



(XX)

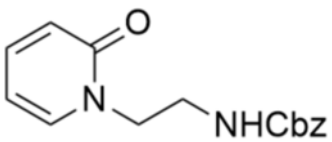
with a catalyst in the presence of H_2.

3. A method of synthesizing 2-((2-oxo-2-((2-(2-oxopiperidin-1-yl)ethyl)amino)ethyl)thio)acetic acid (XVII):



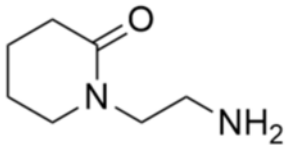
(XVII),

the method comprising the step of reducing benzyl 2-(2-oxopyridin-1(2H)-yl)ethylcarbamate (XIX):



(XIX)

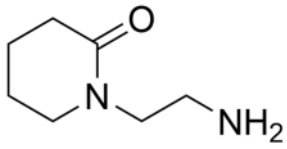
to 1-(2-aminoethyl)piperidin-2-one (XX):



(XX)

with a catalyst in the presence of H_2, optionally wherein the catalyst for reduction is palladium on carbon or palladium hydroxide on carbon.

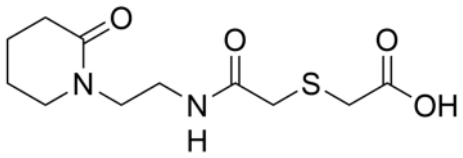
4. The method of any one of claims 1-3, wherein the method further comprises the step of reacting 1-(2-aminoethyl)piperidin-2-one (XX):



(XX)

or a salt thereof, optionally the hydrobromide salt thereof, with 1,4-oxathiane-2,6-dione to produce

2-((2-oxo-2-((2-(2-oxopiperidin-1-yl)ethyl)amino)ethyl)thio)acetic acid (XVII):



(XVII).

5. The method of claim 1 or 4, wherein Sequence Aa comprises the formula W-R^5, wherein W is a peptide sequence and R^5 is conjugated to the C-terminus of W, wherein W comprises the following sequence:

EGT(Xaa4)(Xaa5)SD(Xaa8)S(Xaa10)(Xaa11)(Xaa12)(Xaa13)(Xaa14)(Xaa15)(Xaa16)(Xaa17)(Xaa18)(Xaa19)(Xaa20)(Xaa21)(Xaa22)WL(Xaa25)(Xaa26)(Xaa27)GPSSGAPPP(Xaa37) (SEQ ID NO:1);

wherein:

Xaa4 is F;

Xaa5 is T or I;

Xaa8 is Y, V, L, or K*;

Xaa10 is I or S;

Xaa11 is Y, Y*, Q, A, or (Aib);

Xaa12 is L, M, or L*;

Xaa13 is D or E;

Xaa14 is K, G, R, or E;

Xaa15 is Q or I;

Xaa16 is A, H, or R;

Xaa17 is A, Q, or V;

Xaa18 is A, (Aib), K*, K, or Q;

Xaa19 is A, D, E, (Aib), or L;

Xaa20 is F or A;

Xaa21 is V or I;

Xaa22 is N, A, Q, K*, or E;

Xaa25 is I, L or V;

Xaa26 is A, K, or I;

Xaa27 is Q-R, G-R-G-K*, Q, or G; and

Xaa37 is S or absent; wherein

K* is a lysine residue substituted with a modifying group;

L* is 2-amino-2-methylpentanoic acid, optionally (S)-2-amino-2-methylpentanoic acid; and

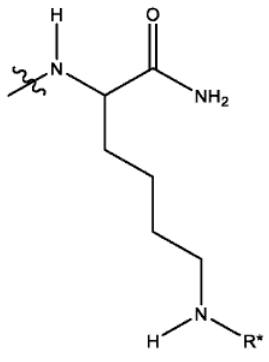
Y* is 2-amino-3-(4-hydroxyphenyl)-2-methylpropanoic acid, optionally (S)-2-amino-3-(4-hydroxyphenyl)-2-methylpropanoic acid; and

R^5 is a C-terminal amino acid amide or a C-terminal amino acid that is optionally substituted with 1 or 2 modifying groups selected from an acyl group and a PEG group.

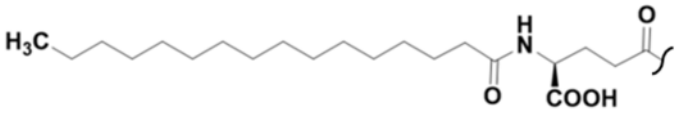
6. The method of claim 5, wherein W comprises the following sequence: EGTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPS (SEQ ID NO:4).

7. The method of claim 5 or 6, wherein R^5 is a C-terminal lysyl amide residue that is optionally substituted with 1 or 2 modifying groups selected from an acyl group and a PEG group.

8. The method of any one of claims 5-7, wherein R^5 comprises formula (II):

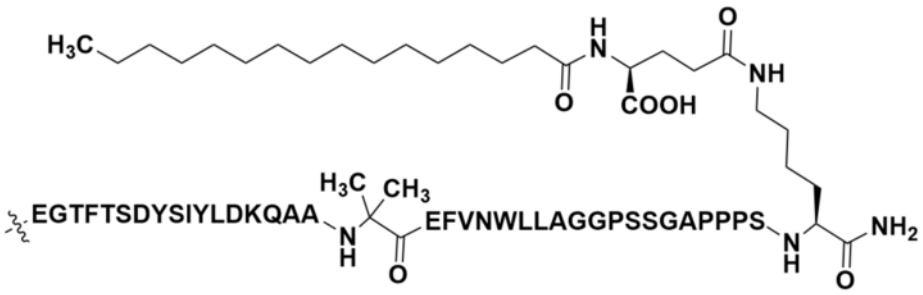


(II), and wherein R* comprises the structure (IV):



(IV).

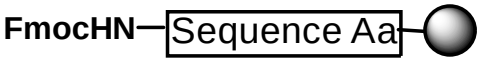
9. The method of any one of claims 5-8, wherein W-R^5 comprises the structure (V):



(V; SEQ ID NO: 5).

10. The method of any one of claims 1 and 4-9, further comprising the steps of

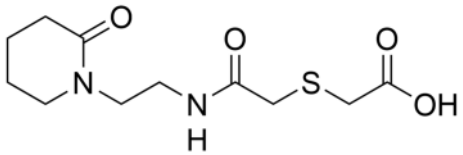
(i) treating the resin-bound peptide of formula (XXIII):



(XXIII)

with 20% piperidine in DMF, and

(ii) reacting the product of step (i) with 2-((2-oxo-2-((2-(2-oxopiperidin-1-yl)ethyl)amino)ethyl)thio)acetic acid (XVII):

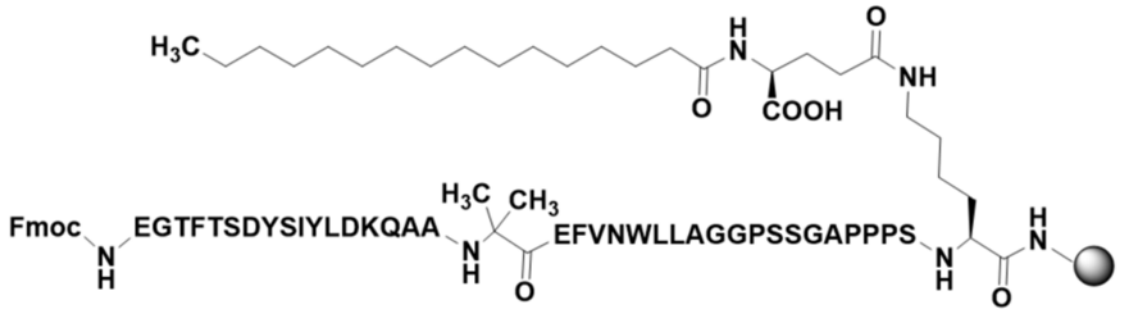


(XVII)

under amide bond-forming conditions.

11. The method of any one of claims 2 and 5-10, further comprising the steps of

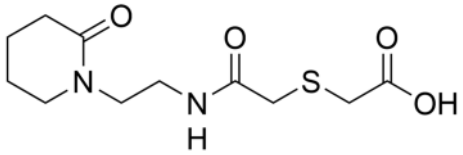
(i) treating the resin-bound peptide of formula (XXII):



(XXII; SEQ ID NO: 17)

with 20% piperidine in DMF, and

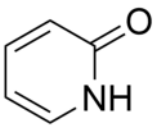
(ii) reacting the product of step (i) with 2-((2-oxo-2-((2-(2-oxopiperidin-1-yl)ethyl)amino)ethyl)thio)acetic acid (XVII):



(XVII)

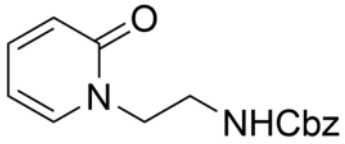
under amide bond-forming conditions, optionally wherein the amide bond-forming conditions comprise use of a coupling reagent, further optionally wherein the coupling reagent is hexafluorophosphate azabenzotriazole tetramethyl uronium.

12. The method of any one of claims 1-11, wherein the method further comprises the step of reacting pyridin-2(*1H*)-one (XVIII):



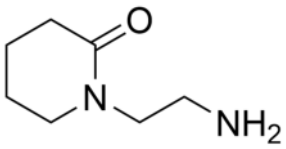
(XVIII)

with benzyl (2-bromoethyl)carbamate in the presence of a non-nucleophilic base to produce benzyl 2-(2-oxopyridin-1(2H)-yl)ethylcarbamate (XIX):



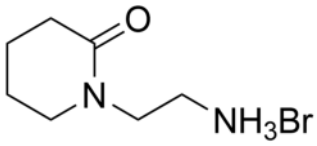
(XIX), optionally wherein the non-nucleophilic base is sodium hydride.

13. The method of any one of claims 1-12, wherein the method further comprises the step of reacting 1-(2-aminoethyl)piperidin-2-one (XX):



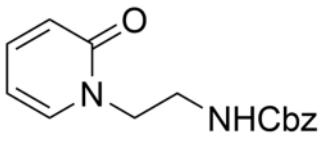
(XX)

with hydrobromic acid to produce 1-(2-aminoethyl)piperidin-2-one hydrobromide (XXI):



(XXI).

14. A compound which is benzyl 2-(2-oxopyridin-1(2H)-yl)ethylcarbamate (XIX):



(XIX).