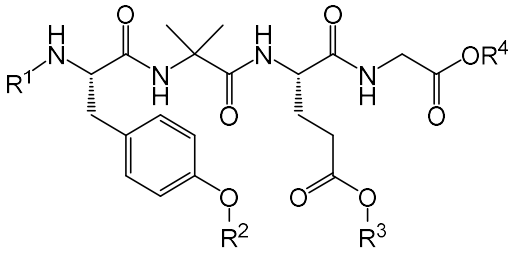


SUMMARY

[0011] The present disclosure describes peptide compounds that are useful for preparing tirzepatide (SEQ ID NO: 1), retatrutide (SEQ ID NO: 12), mazdutide (SEQ ID NO: 16), and other peptides with improved efficiency.

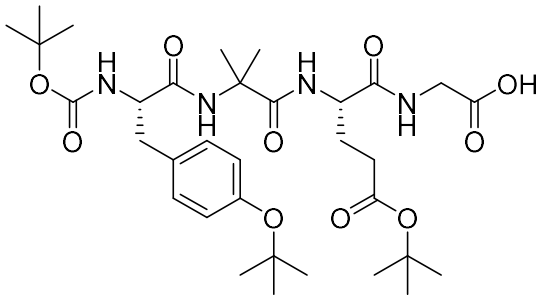
[0012] The present disclosure describes compounds of a Formula (I), or a salt, solvate, or hydrate thereof,



(I)

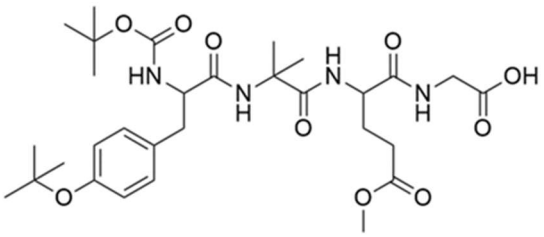
wherein R^1 is H or a protecting group; R^2 is H or a protecting group; R^3 is H or a protecting group; and R^4 is H or a protecting group; and wherein at least one of R^1, R^2, R^3, and R^4 is a protecting group. In some examples, R^1 is H, Fmoc, or Boc. In some examples, R^2 is H or t-butyl. In some examples, R^4 is H or benzyl. In some examples, R^3 is H, t-butyl, benzyl, carboxybenzyl, methyl, allyl, cyclohexyl, or trityl. In some examples, at least two of R^1, R^2, R^3, and R^4 are H. In some examples, at least two of R^1, R^2, R^3, and R^4 are protecting groups.

[0013] In some examples, the compound of Formula (I) is a formula:



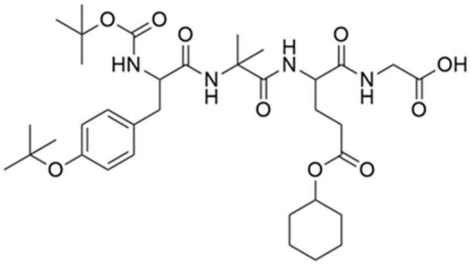
.

[0014] In some examples, the compound of Formula (I) is a formula:



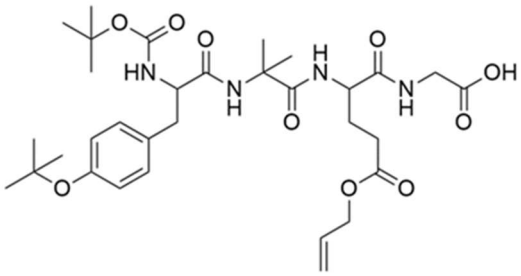
.

[0015] In some examples, the compound of Formula (I) is a formula:



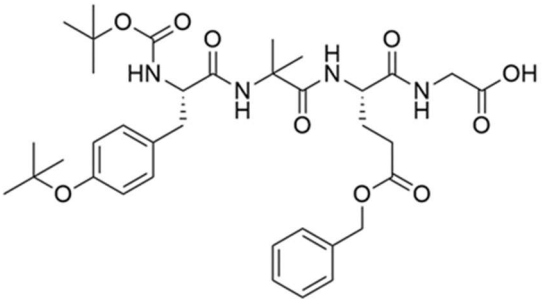
.

[0016] In some examples, the compound of Formula (I) is a formula:



.

[0017] In some examples, the compound of Formula (I) is a formula:



.

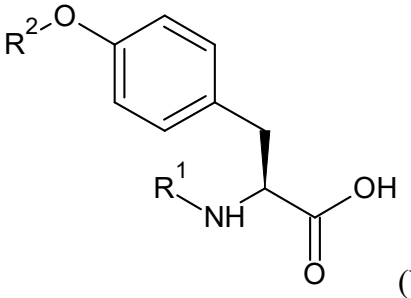
[0018] In some examples, the compound of Formula (I) is a solvate. In some examples, the solvate is produced from methyl t-butyl ether (MTBE) or a mixture comprising MTBE.

[0019] In some examples, the compound of Formula (I) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.2° in

combination of one or more peaks select from 8.4°, 8.8°, 10.4°, 15.5°, 17.1°, and 17.7°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 6.1° in combination of one or more peaks select from 10.3°, 14.9°, 16.8°, 18.1°, and 18.2°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 6.2° in combination of one or more peaks select from 8.9°, 12.3°, 14.9°, 15.4°, and 21.8°.

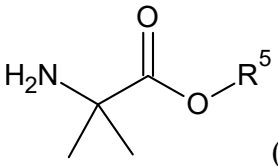
[0020] In some examples, the present disclosure describes a method of synthesizing the compound of Formula (I), the method comprising:

- reacting a compound of formula (Y_{prot})



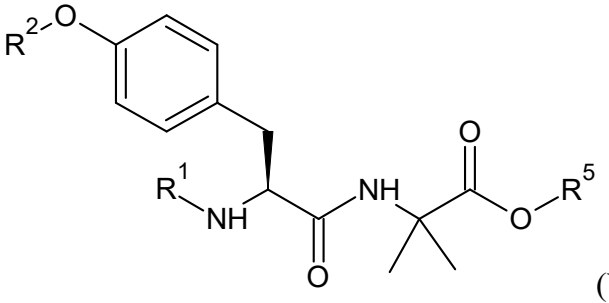
(Y_{prot}),

wherein R^1 and R^2 are protecting groups, and a compound of formula (Aib_{prot})



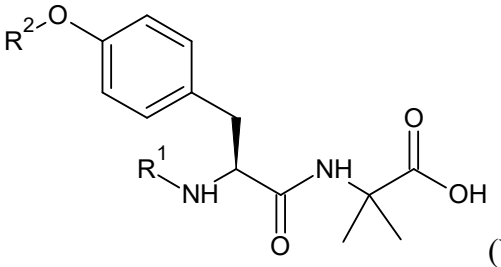
(Aib_{prot}),

wherein R^5 is a protecting group, forming a compound of formula (Y_{prot}-Aib_{prot}),



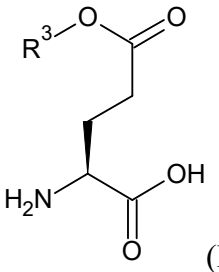
(Y_{prot}-Aib_{prot}),

- removing the protecting group of R^5, and forming a compound of formula (Y_{prot}-Aib)



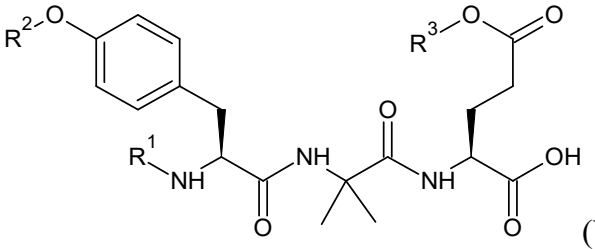
(Y_{prot}-Aib);

- reacting the compound of formula (Y_{prot}-Aib) and a compound of formula (E_{prot})



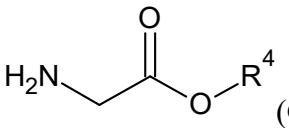
(E_{prot}),

wherein R^3 is a protecting group, forming a compound of a formula (Y_{prot}-Aib-E_{prot})



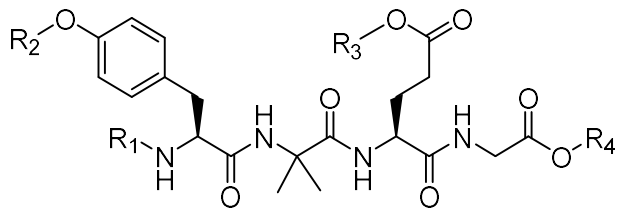
(Y_{prot}-Aib-E_{prot});

- reacting the compound of formula (Y_{prot}-Aib-E_{prot}) and a compound of formula (G_{prot})



(G_{prot}),

wherein R^4 is a protecting group, forming a compound of formula (Y_{prot}-Aib-E_{prot}-G_{prot})



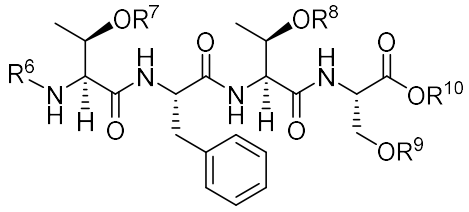
(Y_{prot}-Aib-E_{prot}-G_{prot}); and optionally

- removing one or more of protecting groups R^1, R^2, R^3, and R^4.

[0021] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising conjugating a compound of Formula (I) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 2,

[0022] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 26, the method comprising conjugating a compound of Formula (I) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 27.

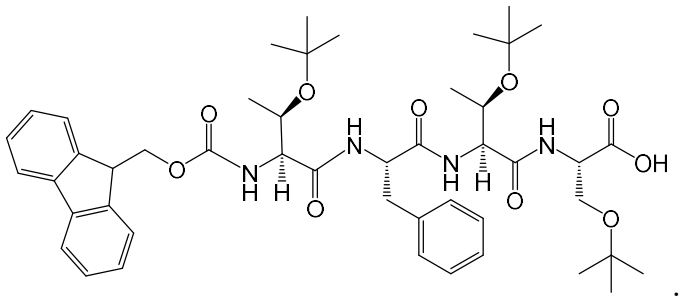
[0023] In some examples, the present disclosure describes compounds of a Formula (II), or a salt, solvate, or hydrate thereof,



(II)

wherein R^6 is H or a protecting group; R^7 is H or a protecting group; R^8 is H or a protecting group; R^9 is H or a protecting group; and R^{10} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, tert-butyl, and trityl groups. In some examples, R^6 is H, Fmoc, or Boc. In some examples, R^7 is H or t-butyl. In some examples, R^8 is H or t-butyl. In some examples, R^9 is H or t-butyl. In some examples, R^{10} is H or benzyl. In some examples, at least one of R^6, R^7, R^8, R^9, and R^{10} is a protecting group. In some examples, R^6, R^7, R^8, R^9, and R^{10} are H.

[0024] In some examples, the compound of Formula (II) is of a formula:



.

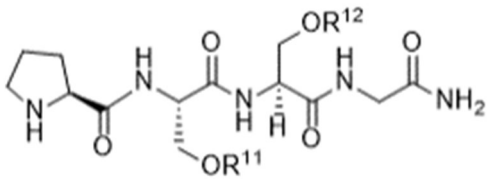
[0025] In some examples, the compound of Formula (I) is a solvate. In some examples, the solvate is produced from a solvent comprising heptane.

[0026] In some examples, the compound of Formula (I) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle $2\theta \pm 0.2$ degrees of 7.7-7.9° in

combination of one or more peaks select from 5.8°, 10.0°, 10.8-10.9°, 11.3-11.4°, 12.0-12.1°, 12.8°, 14.2-14.4°, and 16.8-17.0°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 7.3° in combination of one or more peaks select from 5.1°, 5.7°, 7.6°, 9.5°, and 12.4°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 7.8° in combination of one or more peaks select from 8.5°, 11.5°, 12.0°, 12.8°, 14.3°, 15.5°, 20.2° and 23.3°. In some examples, compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 8.2-8.3° in combination of one or more peaks select from 5.9°, 7.7°, 9.2°, 10.2°, 11.3°, 13.8-13.9°, 15.5-15.7°, 17.1°, and 18.5°.

[0027] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating a compound of Formula (II) via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 3 to form a polypeptide of SEQ ID NO: 4; and (ii) conjugating the polypeptide of SEQ ID NO: 4 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 5.

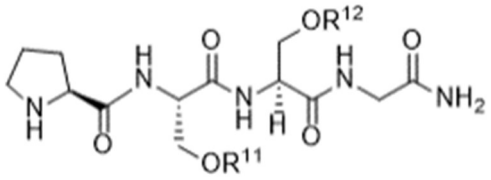
[0028] In some examples, the present disclosure describes compounds of Formula (III), or a salt, solvate, or hydrate thereof,



(III)

wherein R^{11} is H or a protecting group; and R^{12} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{11} is H or t-butyl. In some examples, R^{12} is H or t-butyl. In some examples, at least one of R^{11} and R^{12} is a protecting group. In some examples, R^{11} and R^{12} are H.

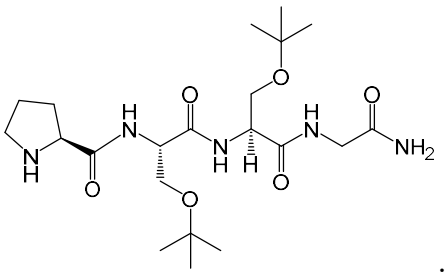
[0028a] In a first aspect, the present disclosure describes a compound of Formula (III), or a salt, solvate, or hydrate thereof,



(III)

wherein R^{11} is H or a protecting group; and R^{12} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0029] In some examples, the compound of Formula (III) is a compound of a formula:



.

[0030] In some examples, the compound of Formula (III) is a solvate.

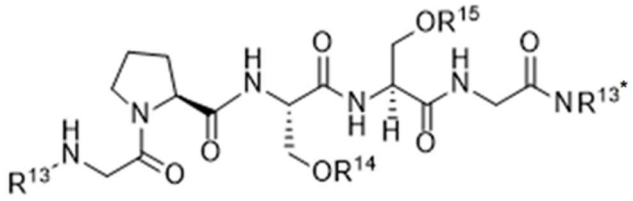
[0031] In some examples, the compound of Formula (III) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 8.0° in combination of one or more peaks select from 7.0°, 10.3°, 14.1°, 15.2°, 16.7°, 18.0°, 19.0°, 19.7°, 20.8°, and 21.9°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 9.0° in combination of one or more peaks select from 5.7°, 9.9°, 16.2°, 17.1°, 17.9°, 18.1°, 18.4°, 18.8°, 19.9°, 20.1°, and 22.5°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.5° in combination of one or more peaks select from 5.6°, 11.9°, 13.3°, 15.4°, 15.6°, 18.1°, 19.9°, and 21.1°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.7° in combination of one or more peaks select from 4.9°, 14.8°, 20.3°, and 21.5°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.5° in combination of one or more peaks select from 5.9°, 10.5°, 10.9°, 12.1°, 13.1°, 15.9°, 17.5°, 20.9°, 21.1°, and 21.9°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 7.8° in combination of one or more peaks select from 11.3°, 11.5°, 15.4°, 15.6°, and 21.5°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.0° in combination of

one or more peaks select from 8.1°, 12.5°, 13.5°, 14.7°, 17.8°, 18.8°, 20.0°, and 22.4°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 21.1° in combination of one or more peaks select from 5.6°, 10.5°, 10.8°, 11.9°, 15.4°, and 23.8°.

[0032] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating a compound of Formula (III) via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 6 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

[0032a] In a second aspect, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating the compound of the first aspect via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 6 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

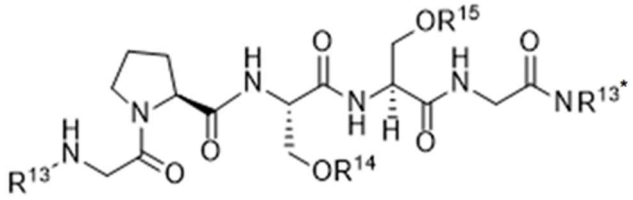
[0033] In some examples, the present disclosure describes compounds of a Formula (IV), or a salt, solvate, or hydrate thereof,



(IV)

wherein R^{13} is H or a protecting group; R^{13*} is H or a protecting group; R^{14} is H or a protecting group; and R^{15} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{13} is H, Fmoc, or Boc. In some examples, R^{13*} is H. In some examples, R^{14} is H or t-butyl. In some examples, R^{15} is H or t-butyl. In some examples, at least one of R^{13}, R^{13*}, R^{14} and R^{15} is a protecting group. In some examples, R^{13}, R^{13*}, R^{14}, and R^{15} are H.

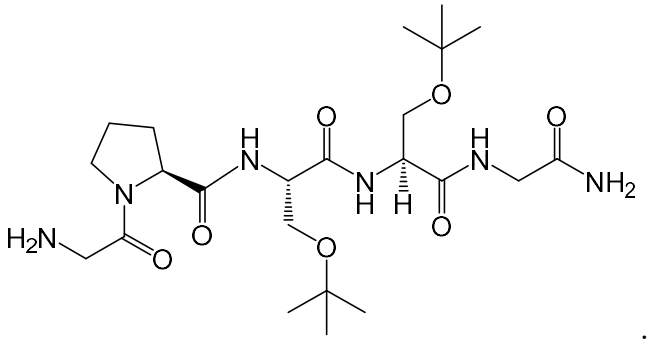
[0033a] In a third aspect, the present disclosure describes a compound of a Formula (IV), or a salt, solvate, or hydrate thereof,



(IV)

wherein R^{13} is H or a protecting group; R^{13*} is H or a protecting group; R^{14} is H or a protecting group; and R^{15} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0034] In some examples, the compound of Formula (IV) is of a formula:



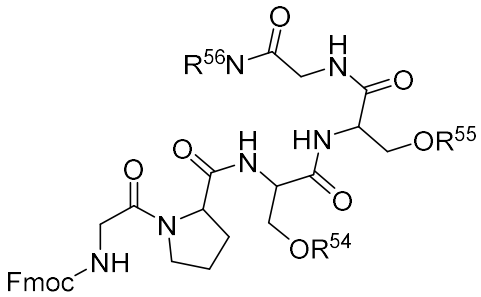
[0035] In some examples, the compound of Formula (IV) is a solvate.

[0036] In some examples, the compound of Formula (IV) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.1° in combination of one or more peaks select from 4.3°, 6.1°, 8.0°, 10.1°, and 18.7°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.2° in combination of one or more peaks select from 6.0°, 6.7°, 10.0°, 10.3°, 16.4°, 17.8°, 18.3°, 19.4°, and 22.4°.

[0037] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating a compound of Formula (IV) via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 9 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

[0037a] In a fourth aspect, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating the compound of the third aspect via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 9 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

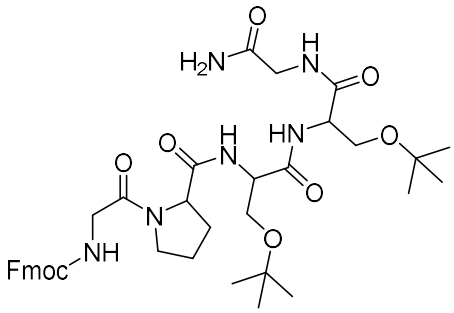
[0038] In some examples, the compound of Formula (IV) is of a formula,



wherein R^{54} is H or a protecting group; R^{55} is H or a protecting group; and R^{56} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{54} is H or *tert*-butyl. In some examples, R^{55} is H or *tert*-butyl. In some

examples, R^{56} is H or Boc. In some examples, at least one of R^{54}, R^{55}, and R^{56} is H. In some examples, at least one of R^{54}, R^{55}, and R^{56} is a protecting group.

[0039] In some examples, the compound of Formula (IV) has a structure of Formula (IV-b):



(IV-b).

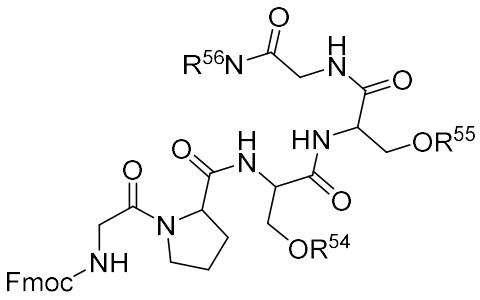
[0040] In some examples, the compound of Formula (IV-b) is a solvate. In some examples, the compound is a solvate produced from acetone. In some examples, the compound is a de-solvate.

[0041] In some examples, the compound of Formula (IV-b) is crystalline. In some examples, the compound is the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.8° and 18.5° in combination of one or more peaks chosen from 8.6°, 9.4°, 12.9°, 13.8°, 17.2°, and 19.4°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.0-7.1° and 7.5-7.7°in combination of one or more peaks chosen from 5.3-5.4°, 9.7-9.9°, and 14.7-14.9. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 8.3° in combination of one or more peaks chosen from 6.3°, 11.4°, 14.3°, and 16.6°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.2° in combination of one or more peaks chosen from 6.8°, 8.6°, 15.8°, and 18.9°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.1° in combination of one or more peaks chosen from 6.3°, 7.8°, 10.0°, and 12.4°.

[0042] In some examples, the present disclosure describes a method of synthesizing the compound of Formula (IV-b), the method comprising:

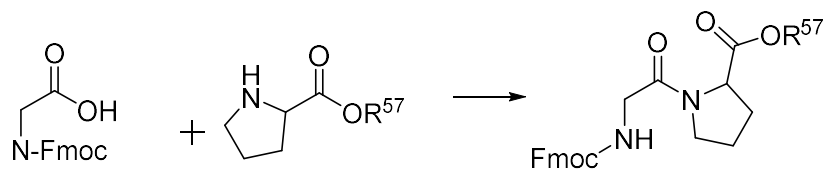
- reacting a compound of formula (Fmoc-G) and a compound of formula (P_{prot}) to form a compound of formula (Fmoc-G-P_{prot})

[0042a] In a fifth aspect, the present disclosure describes a method of synthesizing a compound of formula,



wherein R^{54} is H or a protecting group; R^{55} is H or a protecting group; and R^{56} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups, the method comprising:

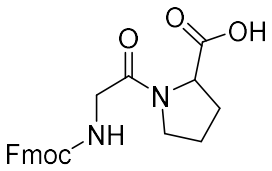
- reacting a compound of formula (Fmoc-G) and a compound of formula (P_{prot}) to form a compound of formula (Fmoc-G-P_{prot})



(Fmoc-G) **(P_{prot})** **((Fmoc-G)-P_{prot})**

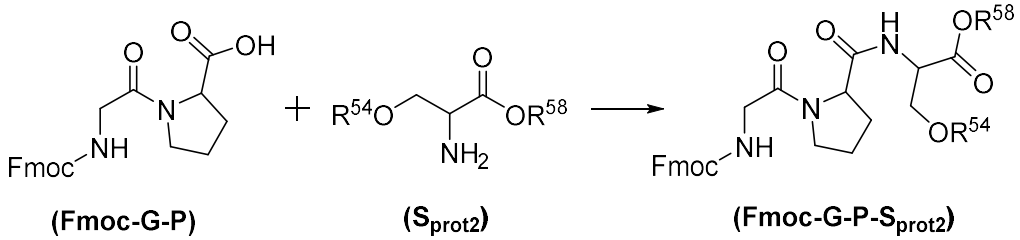
wherein R^{57} is a protecting group;

- removing the protecting group R^{57} to form a compound of (Fmoc-G-P)



(Fmoc-G-P)

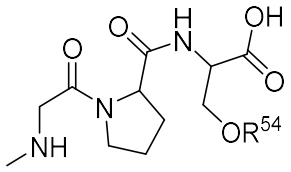
- reacting the compound of formula (Fmoc-G-P) and a compound of formula (S_{prot2}) to form a compound of a formula (Fmoc-G-P-S_{prot2})



(Fmoc-G-P) **(S_{prot2})** **(Fmoc-G-P-S_{prot2})**

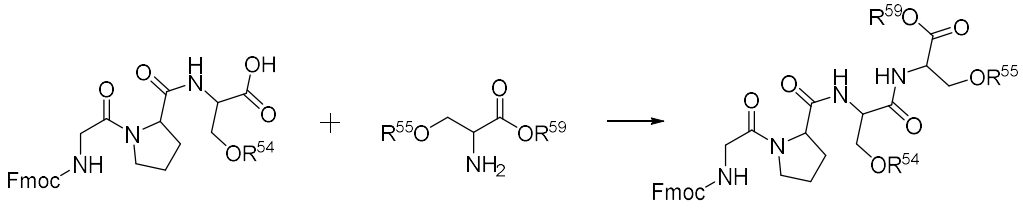
wherein R^{54} and R^{58} are protecting groups;

- removing the protecting group R^{58} to form a compound of (Fmoc-G-P-S_{prot1})



(Fmoc-G-P-S_{prot1}) ;

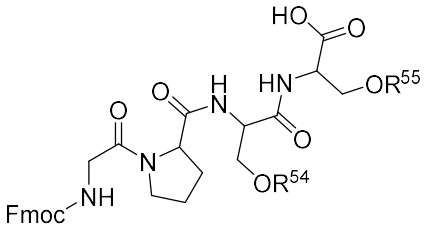
- reacting the compound of formula (Fmoc-G-P-S_{prot1}) and a compound of formula (S_{prot2}) to form a compound of formula (Fmoc-G-P-S_{prot1}-S_{prot2})



(Fmoc-G-P-S_{prot1}) **(S_{prot2})** **(Fmoc-G-P-S_{prot1}-S_{prot2})**

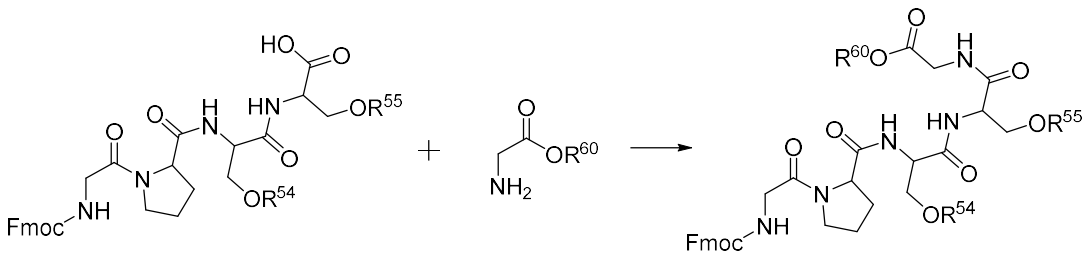
wherein R^{55} and R^{59} are protecting groups; and

- removing the protecting group R^{59} to form a compound of (Fmoc-F-G_{prot1}-S_{prot1}-S_{prot1})



(Fmoc-G-P-S_{prot1}-S_{prot1}) ;

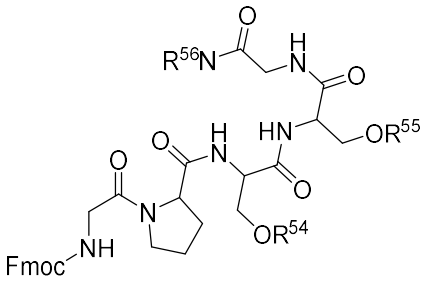
- reacting the compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}) and a compound of formula (G_{prot}) to form a compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot})



(Fmoc-G-P-S_{prot1}-S_{prot1}) **(G_{prot})** **(Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot})**

wherein R^{60} is a protecting group;

- converting the compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot}) to the compound of



; and

- optionally removing one or more protecting groups R^{54}, R^{55}, and R^{56}.

[0043] In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl and trityl groups.

[0044] In some examples, the present disclosure describes a method of synthesizing the polypeptide of SEQ ID NO: 12, the method comprising: (i) conjugating a compound of Formula (IV-b) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22, and (ii) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 23.

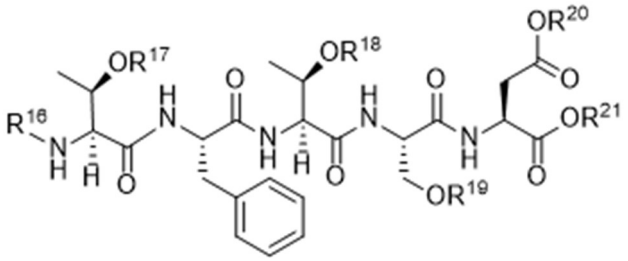
[0045] In some examples, the present disclosure describes a method of synthesizing the polypeptide of SEQ ID NO: 24, the method comprising conjugating a compound of Formula (IV-b) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22.

[0046] In some examples, the present disclosure describes a method of synthesizing the polypeptide of SEQ ID NO: 16, the method comprising conjugating a compound of Formula (IV-b) via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 25.

[0047] In some examples, the present disclosure describes a method of synthesizing the polypeptide of SEQ ID NO: 1, the method comprising: (i) conjugating a compound of Formula (IV-b) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 8, and (ii) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 9.

[0047a] In a sixth aspect, the present disclosure describes a method of synthesizing a polypeptide, wherein: (i) the polypeptide is SEQ ID NO: 12, the method comprising: (i.1) conjugating the compound of paragraph [0038] via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22, and (i.2) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 23; (ii) the polypeptide is SEQ ID NO: 24, the method comprising conjugating the compound of paragraph [0038] via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22; (iii) the polypeptide is SEQ ID NO: 16, the method comprising conjugating the compound of paragraph [0038] via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 25; or (iv) the polypeptide is SEQ ID NO: 1, the method comprising: (iv.1) conjugating the compound of paragraph [0038] via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 8, and (iv.2) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 9.

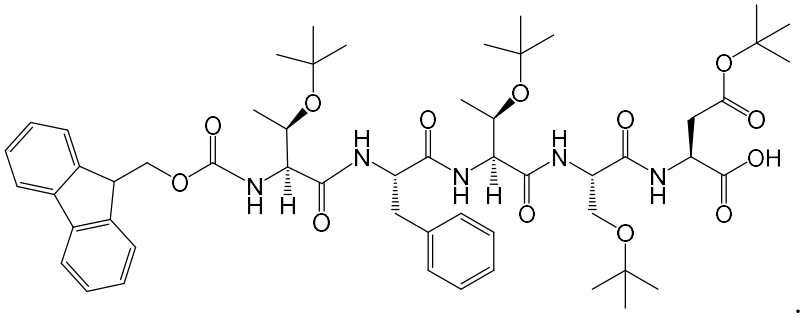
[0048] In some examples, the present disclosure describes a compound of a Formula (V), or a salt, solvate, or hydrate thereof,



(V)

wherein R^{16} is H or a protecting group; R^{17} is H or a protecting group; R^{18} is H or a protecting group; R^{19} is H or a protecting group; R^{20} is H or a protecting group; and R^{21} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{16} is H, Fmoc, or Boc. In some examples, R^{17} is H or t-butyl. In some examples, R^{18} is H or t-butyl. In some examples, R^{19} is H or t-butyl. In some examples, R^{20} is H or t-butyl. In some examples, R^{21} is H or benzyl. In some examples, at least one of R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} is a protecting group. In some examples, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are H.

[0049] In some examples, the compound of Formula (V) is of a formula:

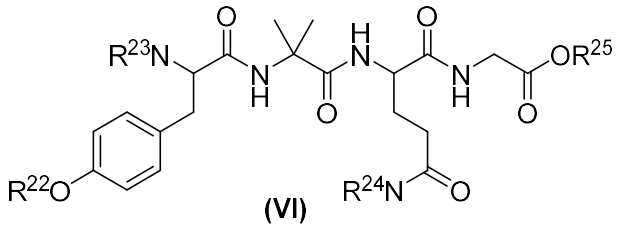


[0050] In some examples, the compound of Formula (V) is a solvate.

[0051] In some examples, the compound of Formula (V) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.8-6.1° in combination of one or more peaks select from 6.7-7.1° and 8.8-9.0°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.0-5.2° in combination of one or more peaks select from 5.3-5.4°, 5.7-6.0°, 6.1-6.2°, 7.6-7.9°, and 8.7-9.1°.

[0052] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating a compound of Formula (V) via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 3 to form a polypeptide of SEQ ID NO: 10; and (ii) conjugating the polypeptide of SEQ ID NO: 10 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 11.

[0053] In some examples, the present disclosure describes a compound of Formula (VI), or a salt, solvate, or hydrate thereof,

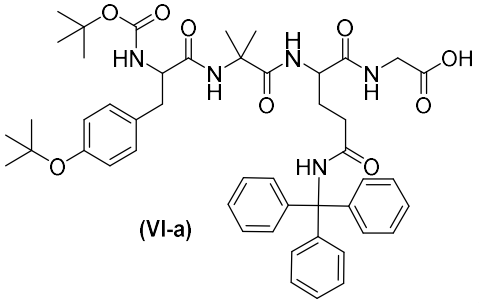


(VI)

wherein R^{22} is H or a protecting group; R^{23} is H or a protecting group; R^{24} is H or a protecting group, and R^{25} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In

some examples, R^{22} is H or Boc. In some examples, R^{23} is H or *tert*-butyl. In some examples, R^{24} is H or trityl. In some examples, R^{25} is H or *tert*-butyl. In some examples, at least one of R^{22}, R^{23}, R^{24}, and R^{25} is H. In some examples, at least one of R^{22}, R^{23}, R^{24}, and R^{25} is a protecting group.

[0054] In some examples, the compound of Formula (VI) is a compound of Formula (VI-a):



(VI-a)

.

[0055] In some examples, the compound of Formula (VI) is a solvate. In some examples, the compound is a solvate produced from pentyl acetate, mixtures comprising pentyl acetate, ethyl acetate, or mixtures comprising 2-methyl tetrahydrofuran and *t*-amyl methyl ether. In some examples, the mixtures comprising pentyl acetate are chosen from mixtures comprising pentyl acetate and *t*-butyl ethyl ether, mixtures comprising pentyl acetate and *t*-amyl methyl ether, or mixtures comprising pentyl acetate and heptane. In some examples, the compound is a de-solvate or a partial de-solvate.

[0056] In some examples, the compound of Formula (VI) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.3-6.4° in combination of one or more peaks chosen from 4.5°, 7.1°, 13.0-13.1°, 15.9-16.0°, and 18.4-18.6°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.0-7.2° in combination of one or more peaks chosen from 5.0-5.4°, 7.6-7.7°, 8.8-8.9°, 9.4-9.5°, and 12.5-12.7°.

[0057] In some examples, the present disclosure describes a method of synthesizing a compound of Formula (VI), the method comprising:

wherein R^{25} is a protecting group; and

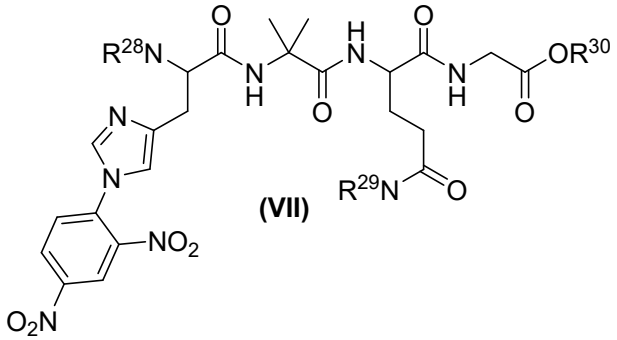
- optionally removing one or more protecting groups R^{22}, R^{23}, R^{24}, and R^{25}.

[0058] In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0059] In some examples, the present disclosure describes a method of synthesizing a polypepetide of SEQ ID NO: 12, the method comprising conjugating a compound of Formula (VI) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 13.

[0060] In some examples, the present disclosure describes a method of synthesizing a polypepetide of SEQ ID NO: 14, the method comprising conjugating a compound of Formula (VI) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 15.

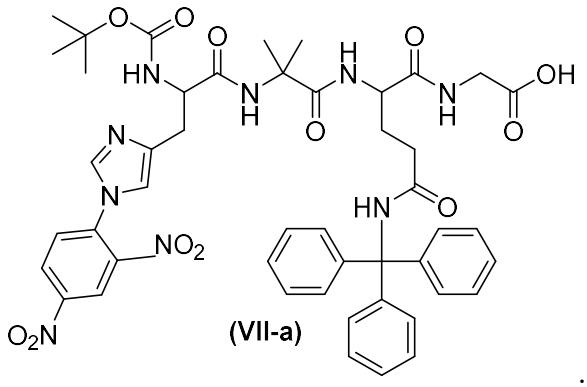
[0061] In some examples, the present disclosure describes a compound of Formula (VII), or a salt, solvate, or hydrate thereof,



(VII)

wherein R^{28} is H or a protecting group; R^{29} is H or a protecting group, and R^{30} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{28} is H or Boc. In some examples, R^{29} is H or trityl. In some examples, R^{30} is H or *tert*-butyl. In some examples, at least one of R^{28}, R^{29}, and R^{30} is H. In some examples, at least one of R^{28}, R^{29}, and R^{30} is a protecting group.

[0062] In some examples, the compound is Formula (VII) is a compound of Formula (VII-a):



(VII-a)

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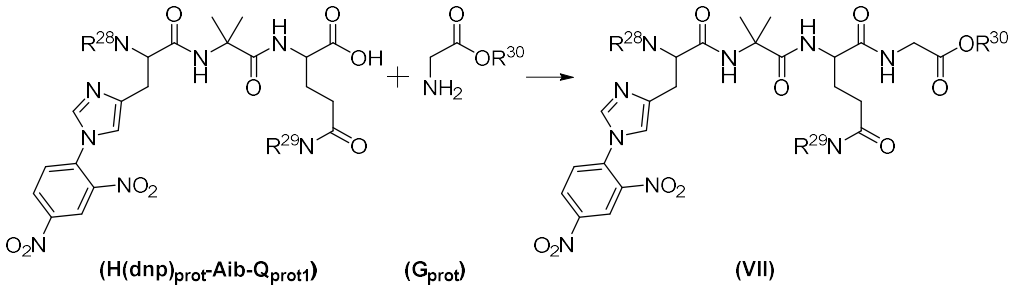
[0063] In some examples, the compound is Formula (VII) is a solvate. In some examples, the compound is a solvate produced from any one of a mixture of acetonitrile and methyl *tert*-butyl ether, a mixture of nitromethane and methyl *tert*-butyl ether, a mixture of tetrahydrofuran and methyl *tert*-butyl ether, methyl acetate, and ethyl acetate.

[0064] In some examples, the compound of Formula (VII) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 4.8° in combination of one or more peaks chosen from 5.6°, 6.2°, 14.8°, and 15.6°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.3° in combination of one or more peaks chosen from 7.7°, 10.5°, 11.3°, 11.6°, and 14.4°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.2° and 6.9°.

[0065] In some examples, the present disclosure describes a method of synthesizing a compound is Formula (VII), the method comprising:

- reacting a compound of formula ($H(dnp)_{prot}$) and a compound of formula (Aib_{prot}) to form a compound of formula ($H(dnp)_{prot}$-Aib_{prot})

- reacting the compound of formula ($H(dnp)_{prot}$-Aib-Q_{prot1}) and a compound of formula (G_{prot}) to form a compound of Formula (VII)



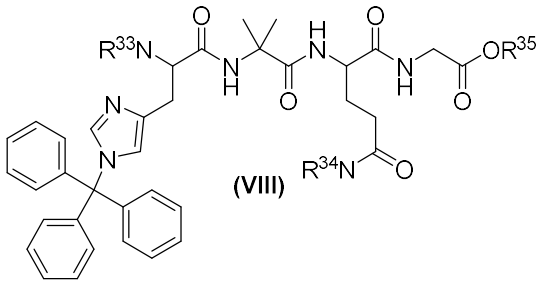
wherein R^{30} is a protecting group; and

- optionally removing one or more protecting groups R^{28}, R^{29}, and R^{30}.

[0066] In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

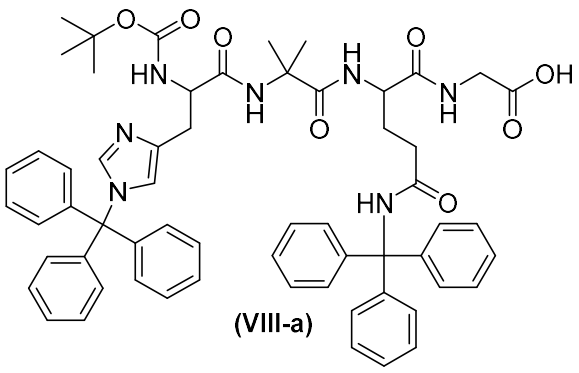
[0067] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 16, the method comprising conjugating a compound of Formula (VII) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 17.

[0068] In some examples, the present disclosure describes a compound of Formula (VIII), or a salt, solvate, or hydrate thereof,



wherein R^{33} is H or a protecting group; R^{34} is H or a protecting group; and R^{35} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{33} is H or Boc. In some examples, R^{34} is H or trityl. In some examples, R^{35} is H or *tert*-butyl. In some examples, at least one of R^{33}, R^{34}, and R^{35} is H. In some examples, at least one of R^{33}, R^{34}, and R^{35} is a protecting group.

[0069] In some examples, the compound of Formula (VIII) is a compound of Formula (VIII-a):



(VIII-a)

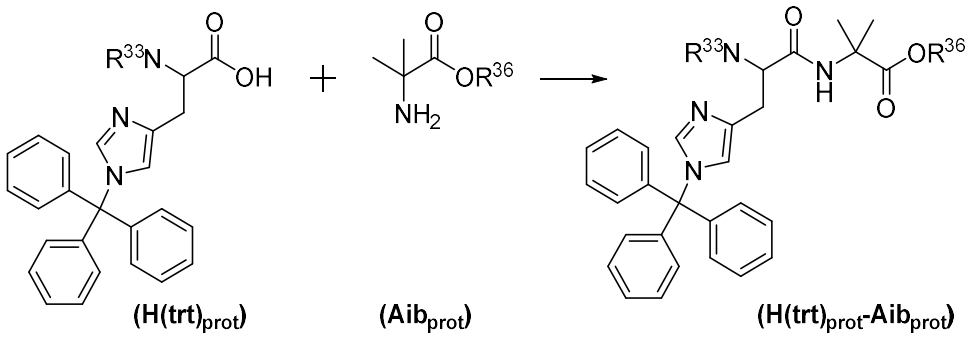
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[0070] In some examples, the compound of Formula (VIII) is a solvate. In some examples, the compound is a solvate produced from any one of a mixture of tetrahydrofuran and methyl *tert*-butyl ether, a mixture of tetrahydrofuran and heptane, a mixture of 1,4-dioxane and water, a mixture of ethyl acetate and methyl *tert*-butyl ether, and a mixture of acetonitrile and methyl *tert*-butyl ether.

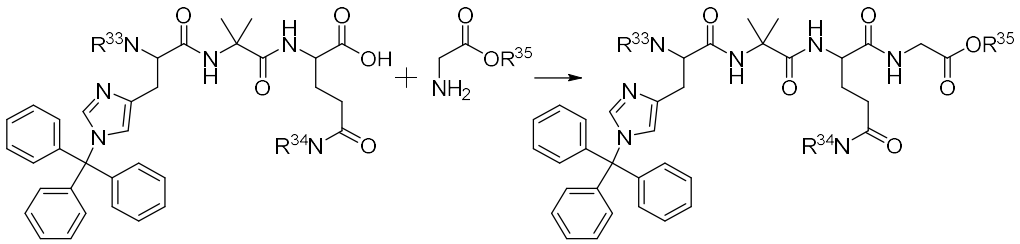
[0071] In some examples, the compound of Formula (VIII) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 4.7° in combination of one or more peaks chosen from 5.5°, 8.2°, 10.1°, 11.8°, 13.3°, 13.6°, and 18.9°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.8° in combination of one or more peaks chosen from 5.3°, 8.9°, 9.2°, 15.2°, 18.6°, and 19.5°.

[0072] In some examples, the present disclosure describes a method of synthesizing a compound of Formula (VIII), the method comprising:

- reacting a compound of formula ($H(trt)_{prot}$) and a compound of formula (Aib_{prot}) to form a compound of formula ($H(trt)_{prot}$-Aib_{prot})



($H(trt)_{prot}$) (Aib_{prot}) ($H(trt)_{prot}$-Aib_{prot})



$(H(trt)_{prot}\text{-}Aib\text{-}Q_{prot1})$ (G_{prot}) (VIII)

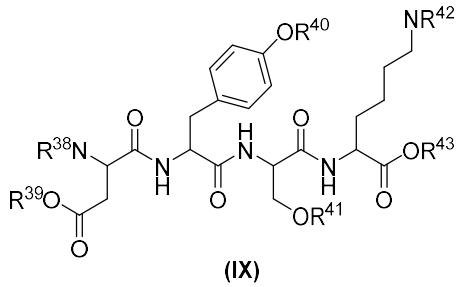
wherein R^{35} is a protecting group; and

- optionally removing one or more protecting groups R^{33}, R^{34}, and R^{35}.

[0073] In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0074] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 16, the method comprising conjugating a compound of Formula (VIII) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 17.

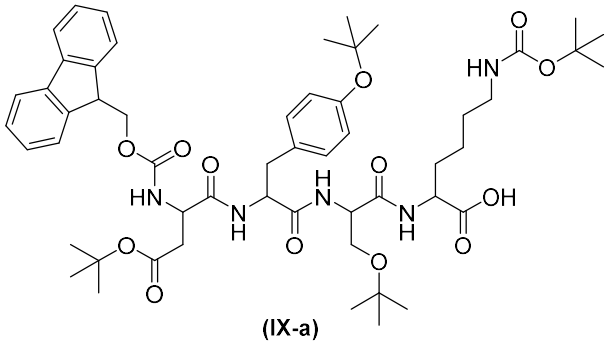
[0075] In some examples, the present disclosure describes a compound of Formula (IX), or a salt, solvate, or hydrate thereof,



(IX)

wherein R^{38} is H or a protecting group; R^{39} is H or a protecting group; R^{40} is H or a protecting group; R^{41} is H or a protecting group; R^{42} is H or a protecting group; and R^{43} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{38} is H or Fmoc. In some examples, R^{39} is H or *tert*-butyl. In some examples, R^{40} is H or *tert*-butyl. In some examples, R^{41} is H or *tert*-butyl. In some examples, R^{42} is H or Boc. In some examples, R^{43} is H or *tert*-butyl. In some examples, at least one of R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, and R^{43} is H. In some examples, at least one of R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, and R^{43} is a protecting group.

[0076] In some examples, the compound is Formula (IX) is a compound of Formula (IX-a):



(IX-a)

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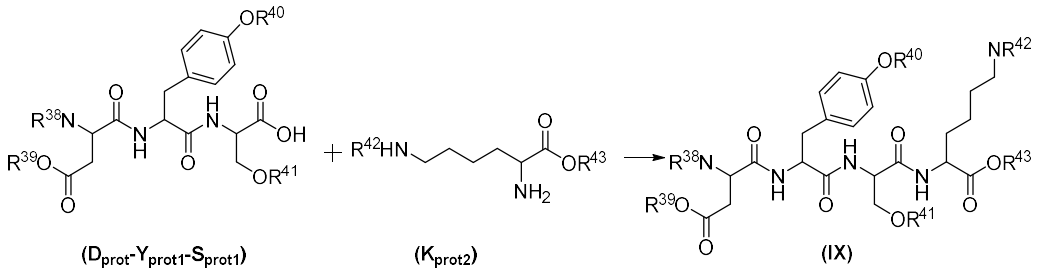
[0077] In some examples, the compound is Formula (IX) is a solvate. In some examples, the compound is a solvate produced from any one of a mixture of methyl acetate and dibutyl ether, a mixture of acetone and dibutyl ether, a mixture of acetonitrile and dibutyl ether, a mixture of ethyl acetate and dibutyl ether, a mixture of methyl acetate and heptane, and a mixture of methyl ethyl ketone and dibutyl ether. In some examples, the compound is a de-solvate or is anhydrous.

[0078] In some examples, the compound is Formula (IX) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.3° in combination of one or more peaks chosen from 6.0°, 6.9°, 7.2°, 8.0°, 12.2°, and 15.6°. In some examples, the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.8° in combination of one or more peaks chosen from 4.4°, 6.6°, 10.1°, 11.4°, 13.4°, and 15.5°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 4.5° and 5.5° in combination of one or more peaks chosen from 6.0° and 7.3°.

[0079] In some examples, the present disclosure describes a method of synthesizing a compound is Formula (IX), the method comprising:

- reacting a compound of formula (D_{prot}) and a compound of formula (Y_{prot2}) to form a compound of formula (D_{prot}-Y_{prot2})

- reacting the compound of formula (D_{prot}-Y_{prot1}-S_{prot1}) and a compound of formula (K_{prot2}) to form a compound of Formula (IX)



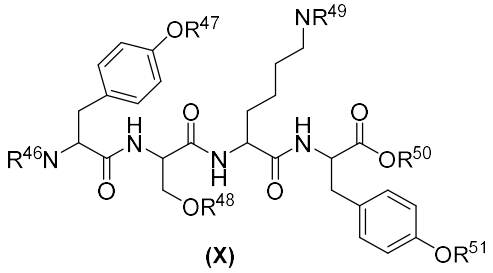
wherein R^{42} and R^{43} are protecting groups; and

- optionally removing one or more protecting groups R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, and R^{43}.

[0080] In some examples, the protecting groups are chosen from Boc, Fmoc, *tert*-butyl and trityl groups.

[0081] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 16, the method comprising: (i) conjugating a compound of Formula (IX) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 18, and (ii) conjugating the compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 19.

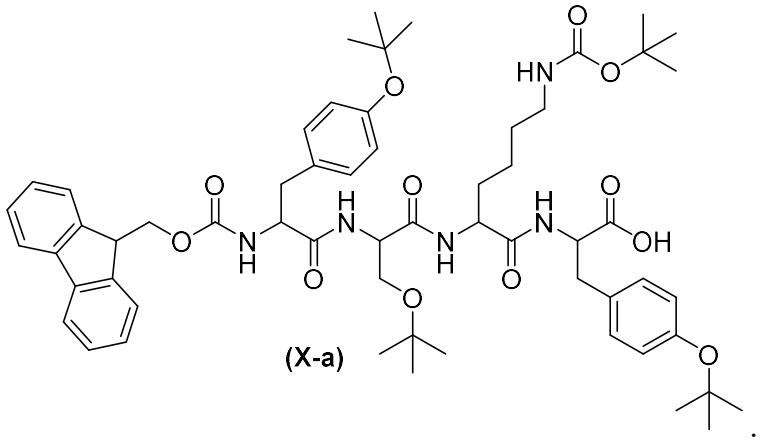
[0082] In some examples, the present disclosure describes a compound of Formula (X), or a salt, solvate, or hydrate thereof,



wherein R^{46} is H or a protecting group; R^{47} is H or a protecting group; R^{48} is H or a protecting group; R^{49} is H or a protecting group; R^{50} is H or a protecting group; and R^{51} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{46} is H or *tert*-butyl. In some examples, R^{47} is H or *tert*-butyl. In some examples, R^{48} is H or Boc. In some examples, R^{49} is H or Fmoc. In some examples, R^{50} is H or *tert*-butyl. In some examples, R^{51} is H, or *tert*-butyl. In some examples, at least one of

R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} is H. In some examples, at least one of R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51} is a protecting group.

[0083] In some examples, the compound is Formula (X) is a compound of Formula (X-a):



(X-a)

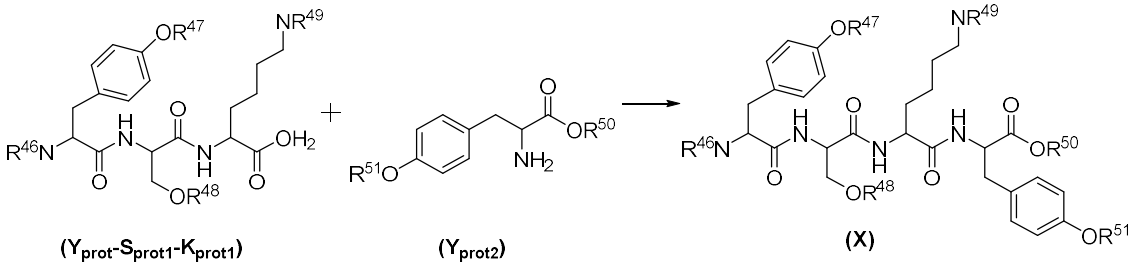
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[0084] In some examples, the compound is Formula (X) is a solvate. In some examples, the compound is a solvate produced from ethanol or isopropyl alcohol. In some examples, the compound is a de-solvate.

[0085] In some examples, the compound is Formula (X) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 18.1° and 18.7° in combination of one or more peaks chosen from 5.7°, 8.7°, 13.7°, 14.3°, 15.9°, and 16.2°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.9° and 10.5°in combination of one or more peaks chosen from 7.1°, 8.9°, 14.6°, and 16.6°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.8° and 20.3° in combination of one or more peaks chosen from 5.8°, 15.5°, and 19.5°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.9° and 7.4° in combination of one or more peaks chosen from 6.5°, 6.9°, and 14.8°.

[0086] In some examples, the present disclosure describes a method of synthesizing a compound is Formula (X), the method comprising:

- reacting the compound of formula (Y_{prot}-S_{prot1}-K_{prot1}) and a compound of formula (Y_{prot2}) to form a compound of Formula (X)



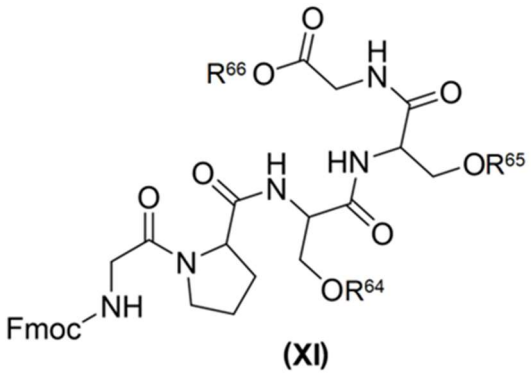
wherein R^{50} and R^{51} are protecting groups; and

- optionally removing one or more protecting groups R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, and R^{51}.

[0087] In some examples, the protecting groups are chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

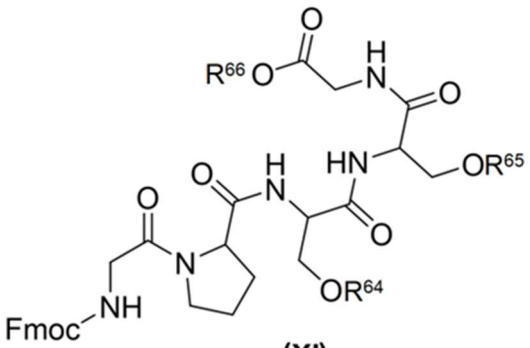
[0088] In some examples, the present disclosure describes a method of synthesizing a polypeptide of SEQ ID NO: 16, the method comprising: (i) conjugating a compound is Formula (X) via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 20, and (ii) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 21.

[0089] In some examples, the present disclosure describes a compound of Formula (XI), or a salt, solvate, or hydrate thereof,



wherein R^{64} is H or a protecting group; R^{65} is H or a protecting group; and R^{66} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, at least one of R^{64}, R^{65}, and R^{66} is H. In some examples, at least one of R^{64}, R^{65}, and R^{66} is a protecting group.

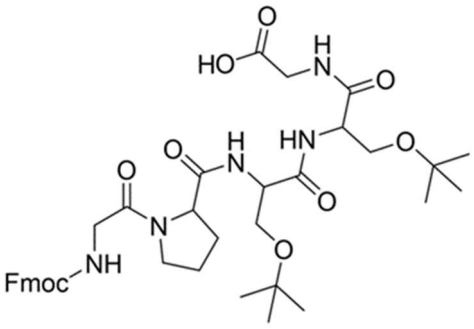
[0089a] In a seventh aspect, the present disclosure describes a compound of Formula (XI), or a salt, solvate, or hydrate thereof,



(XI)

wherein R^{64} is H or a protecting group; R^{65} is H or a protecting group; and R^{66} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0090] In some examples, the compound of Formula (XI) is a compound of the Formula:

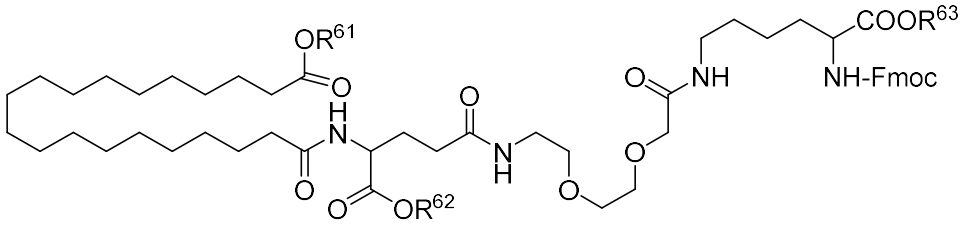


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[0091] In some examples, the compound of Formula (XI) is a solvate.

[0092] In some examples, the compound of Formula (XI) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.1° and 8.5° in combination of one or more peaks chosen from 5.8°, 16.9°, 18.5°, 18.8°, 19.3°, and 20.9.

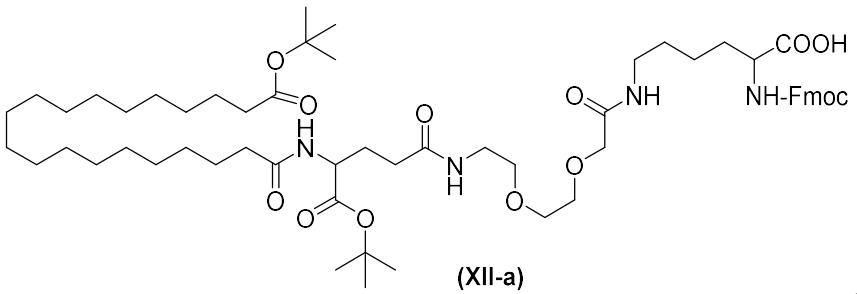
[0093] In some examples, the present disclosure describes a compound of Formula (XII), or a salt, solvate, or hydrate thereof,



(XII)

wherein R^{61} is H or a protecting group; R^{62} is H or a protecting group; and R^{63} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{61} is H or *tert*-butyl. In some examples, R^{62} is H or *tert*-butyl. In some examples, R^{63} is H or *tert*-butyl. In some examples, at least one of R^{61}, R^{62}, and R^{63} is H. In some examples, at least one of R^{61}, R^{62}, and R^{63} is a protecting group.

[0094] In some examples, the compound of Formula (XII) is a compound of Formula (XII-a):

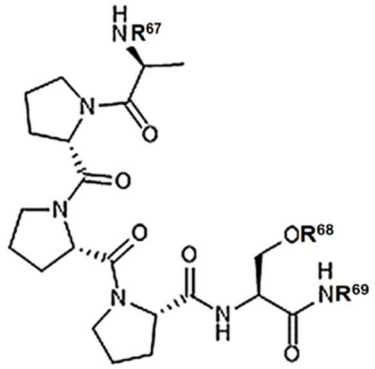


(XII-a)

[0095] In some examples, the compound of Formula (XII) is a solvate. In some examples, the compound is a de-solvate or is anhydrous.

[0096] In some examples, the compound of Formula (XII) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 11.4° in combination of one or more peaks chosen from 6.0°, 8.9°, 12.7°, 13.6°, 14.6°, 17.0°, and 18.8°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 10.6°in combination of one or more peaks chosen from 7.1°, 12.1°, 13.6°, 14.2°, 15.2°, 16.0°, and 16.8°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 10.1° and 15.5° in combination of one or more peaks chosen from 6.1°, 8.7°, 11.4°, 16.6°, and 19.2°.

[0097] In some examples, the present disclosure describes a compound of Formula (XIII), or a salt, solvate, or hydrate thereof,

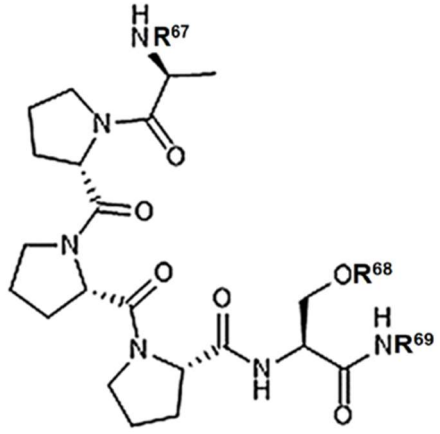


(XIII)

wherein R^{67} is H or a protecting group; R^{68} is H or a protecting group; and R^{69} is H or a protecting group. In some examples, each protecting group is independently chosen

from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{67} is H or *tert*-butyl. In some examples, R^{68} is H or *tert*-butyl. In some examples, R^{69} is H or *tert*-butyl. In some examples, at least one of R^{67}, R^{68}, and R^{69} is H. In some examples, at least one of R^{67}, R^{68}, and R^{69} is a protecting group.

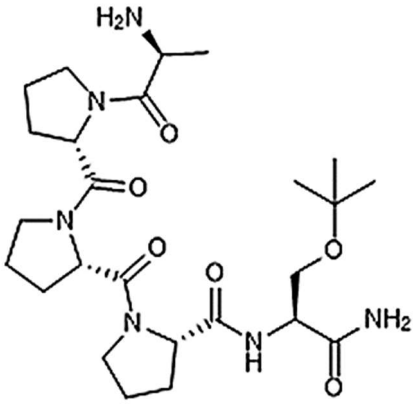
[0097a] In an eighth aspect, the present disclosure describes a compound of Formula (XIII), or a salt, solvate, or hydrate thereof,



(XIII)

wherein R^{67} is H or a protecting group; R^{68} is H or a protecting group; and R^{69} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

[0098] In some examples, the compound of Formula (XIII) is a compound of the Formula:

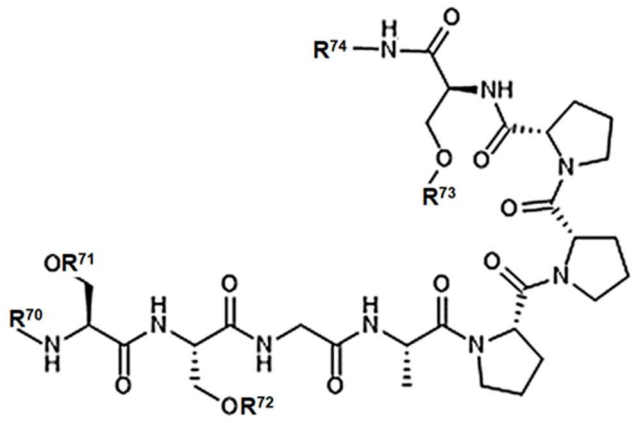


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[0099] In some examples, the compound of Formula (XIII) is a solvate. In some examples, the compound is a de-solvate or is anhydrous.

[0100] In some examples, the compound of Formula (XIII) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.0° in combination of one or more peaks chosen from 8.3, 9.7, and 11.2°. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.2°in combination of one or more peaks chosen from 5.3, 8.1, 14.4, and 16.2°.

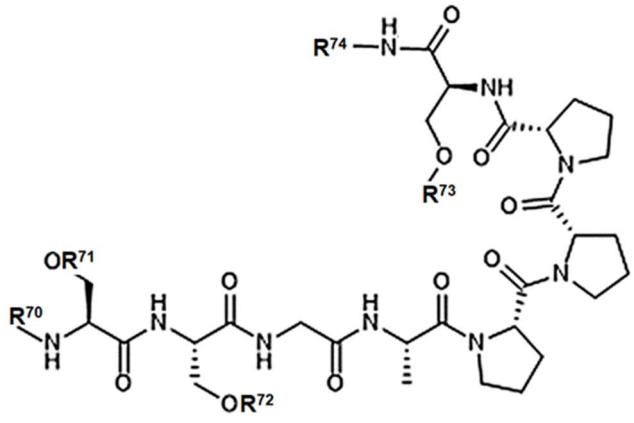
[0101] In some examples, the present disclosure describes a compound of Formula (XIV), or a salt, solvate, or hydrate thereof,



(XIV)

wherein R^{70} is H or a protecting group; R^{71} is H or a protecting group; R^{72} is H or a protecting group; R^{73} is H or a protecting group; and R^{74} is H or a protecting group. In some examples, each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups. In some examples, R^{70} is H, Fmoc, or *tert*-butyl. In some examples, R^{71} is H or *tert*-butyl. In some examples, R^{72} is H or *tert*-butyl. In some examples, R^{73} is H or *tert*-butyl. In some examples, R^{74} is H, Fmoc, or *tert*-butyl. In some examples, at least one of R^{70}, R^{71}, R^{72}, R^{73}, and R^{74} is H. In some examples, at least one of R^{70}, R^{71}, R^{72}, R^{73}, and R^{74} is a protecting group.

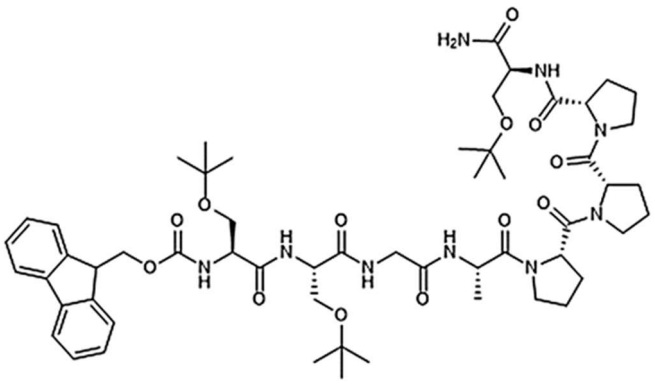
[0101a] In a ninth aspect, the present disclosure describes a compound of Formula (XIV), or a salt, solvate, or hydrate thereof,



(XIV)

wherein R^{70} is H or a protecting group; R^{71} is H or a protecting group; R^{72} is H or a protecting group; R^{73} is H or a protecting group; and R^{74} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups

[0102] In some examples, the compound of Formula (XIV) is a compound of the Formula:



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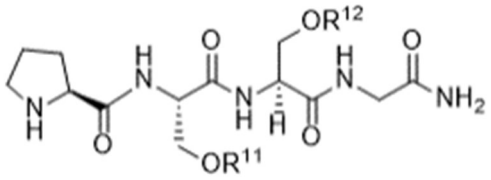
[0103] In some examples, the compound of Formula (XIV) is a solvate. In some examples, the compound is a de-solvate or is anhydrous

[0104] In some examples, the compound of Formula (XIV) is crystalline. In some examples, the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.5° in combination of one or more peaks chosen from 6.1, 8.7, 10.6, 15.0, 16.1, and 18.6°.

CLAIMS

What is claimed:

1.A compound of Formula (III), or a salt, solvate, or hydrate thereof,



(III)

wherein R^{11} is H or a protecting group; and R^{12} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

2.The compound of claim 1, wherein:

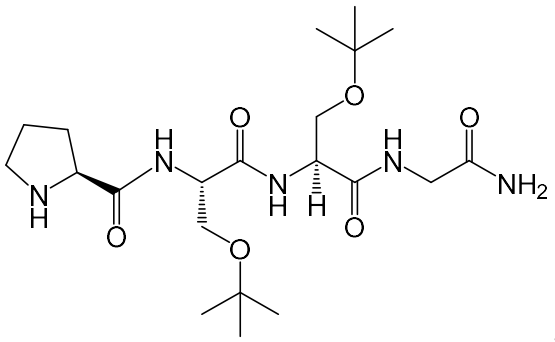
a) R^{11} is H or t-butyl;

b) R^{12} is H or t-butyl; or

c) both (a) and (b).

3.The compound of claim 1 or 2, wherein (a) at least one of R^{11} and R^{12} is a protecting group; or (b) R^{11} and R^{12} are H.

4.The compound of claim 1, wherein the compound is a compound of a formula:



.

5.The compound of any one of claims 1 to 4, wherein: (i) the compound is a solvate; or (ii) the compound is crystalline, optionally wherein:

a) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2

degrees of 8.0° in combination of one or more peaks select from 7.0°, 10.3°, 14.1°, 15.2°, 16.7°, 18.0°, 19.0°, 19.7°, 20.8°, and 21.9°;

b) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 9.0° in combination of one or more peaks select from 5.7°, 9.9°, 16.2°, 17.1°, 17.9°, 18.1°, 18.4°, 18.8°, 19.9°, 20.1°, and 22.5°;

c) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.5° in combination of one or more peaks select from 5.6°, 11.9°, 13.3°, 15.4°, 15.6°, 18.1°, 19.9°, and 21.1°;

d) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.7° in combination of one or more peaks select from 4.9°, 14.8°, 20.3°, and 21.5°;

e) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.5° in combination of one or more peaks select from 5.9°, 10.5°, 10.9°, 12.1°, 13.1°, 15.9°, 17.5°, 20.9°, 21.1°, and 21.9°;

f) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 7.8° in combination of one or more peaks select from 11.3°, 11.5°, 15.4°, 15.6°, and 21.5°;

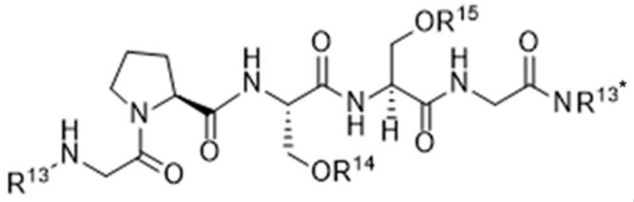
g) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 10.0° in combination of one or more peaks select from 8.1°, 12.5°, 13.5°, 14.7°, 17.8°, 18.8°, 20.0°, and 22.4°; or

h) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2

degrees of 21.1° in combination of one or more peaks select from 5.6°, 10.5°, 10.8°, 11.9°, 15.4°, and 23.8°.

6.A method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating the compound of any one of claims 1-4 via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 6 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

7.A compound of a Formula (IV), or a salt, solvate, or hydrate thereof,



(IV)

wherein R^{13} is H or a protecting group; R^{13*} is H or a protecting group; R^{14} is H or a protecting group; and R^{15} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

8.The compound of claim 7, wherein

a) R^{13} is H, Fmoc, or Boc;

b) R^{13*} is H;

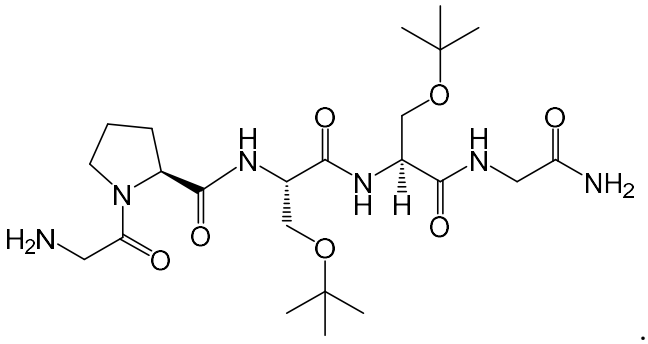
c) R^{14} is H or t-butyl;

d) R^{15} is H or t-butyl; or

e) any combination of (a)-(d).

9.The compound of claim 7 or 8, wherein (a) at least one of R^{13}, R^{13*}, R^{14} and R^{15} is a protecting group; or (b) R^{13}, R^{13*}, R^{14}, and R^{15} are H.

10. The compound of claim 7, wherein the compound is of a formula:



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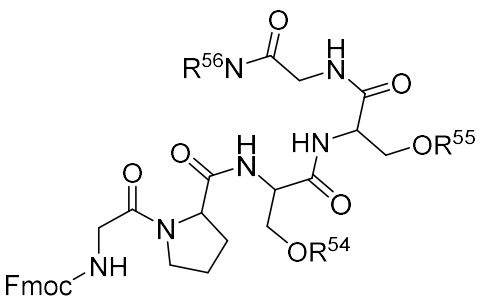
11. The compound of any one of claims 7 to 10, wherein: (i) the compound is a solvate; (ii) the compound is crystalline, optionally wherein:

    a) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.1° in combination of one or more peaks select from 4.3°, 6.1°, 8.0°, 10.1°, and 18.7°; or

    b) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2θ ± 0.2 degrees of 5.2° in combination of one or more peaks select from 6.0°, 6.7°, 10.0°, 10.3°, 16.4°, 17.8°, 18.3°, 19.4°, and 22.4°.

12. A method of synthesizing a polypeptide of SEQ ID NO: 1, the method comprising (i) conjugating the compound of any one of claims 7-10 via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 9 to form a polypeptide of SEQ ID NO: 7; and (ii) conjugating the polypeptide of SEQ ID NO: 7 via its C-terminus to the N-terminus of a polypeptide of SEQ ID NO: 8.

13. The compound of claim 7, wherein the compound is of a formula,



wherein R^{54} is H or a protecting group; R^{55} is H or a protecting group; and R^{56} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

14. The compound of claim 13, wherein:

    a) R^{54} is H or *tert*-butyl;

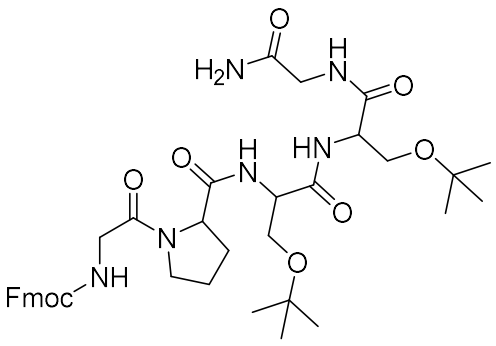
    b) R^{55} is H or *tert*-butyl;

    c) R^{56} is H or Boc; or

    d) any combination of (a)-(c).

15. The compound of claim 13 or 14, wherein: (a) at least one of R^{54}, R^{55}, and R^{56} is H; (b) at least one of R^{54}, R^{55}, and R^{56} is a protecting group; or (c) both (a) and (b).

16. The compound of claim 13, wherein the compound is of a formula:



.

17. The compound of any one of claims 13 to 16, wherein: (i) the compound is a solvate, optionally wherein the compound is a solvate produced from acetone; (ii) the compound is a de-solvate; or (iii) the compound is crystalline, optionally wherein:

    a) the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.8° and 18.5° in combination of one or more peaks chosen from 8.6°, 9.4°, 12.9°, 13.8°, 17.2°, and 19.4°;

    b) the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2

degrees of 7.0-7.1° and 7.5-7.7°in combination of one or more peaks chosen from 5.3-5.4°, 9.7-9.9°, and 14.7-14.9;

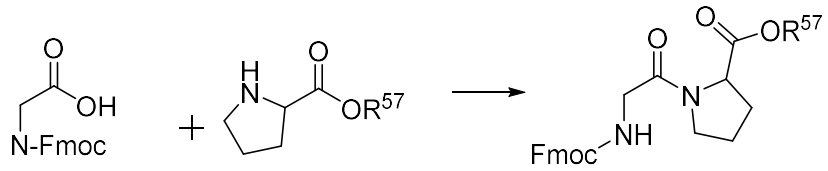
c) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 8.3° in combination of one or more peaks chosen from 6.3°, 11.4°, 14.3°, and 16.6°;

d) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.2° in combination of one or more peaks chosen from 6.8°, 8.6°, 15.8°, and 18.9°; or

e) the compound is in the form of a crystalline solid characterized by a peak in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.1° in combination of one or more peaks chosen from 6.3°, 7.8°, 10.0°, and 12.4°.

18. A method of synthesizing the compound of claim 13, the method comprising:

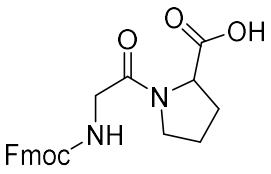
- reacting a compound of formula (Fmoc-G) and a compound of formula (P_{prot}) to form a compound of formula (Fmoc-G-P_{prot})



(Fmoc-G) **(P_{prot})** **((Fmoc-G)-P_{prot})**

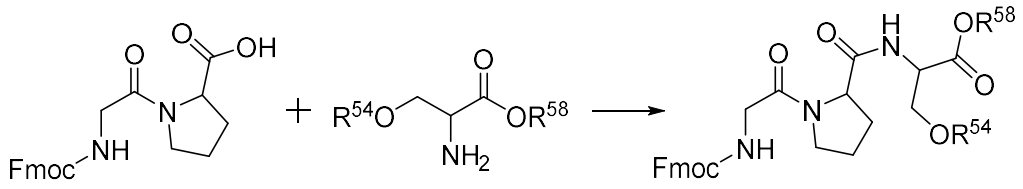
wherein R^{57} is a protecting group;

- removing the protecting group R^{57} to form a compound of (Fmoc-G-P)



(Fmoc-G-P)

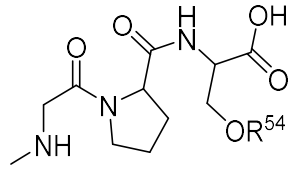
- reacting the compound of formula (Fmoc-G-P) and a compound of formula (S_{prot2}) to form a compound of a formula (Fmoc-G-P-S_{prot2})



(Fmoc-G-P) **(S_{prot2})** **(Fmoc-G-P-S_{prot2})**

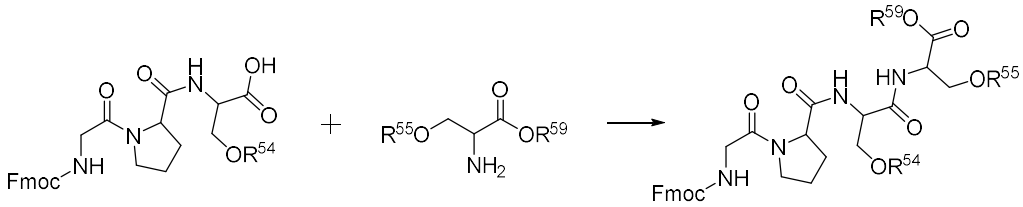
wherein R^{54} and R^{58} are protecting groups;

- removing the protecting group R^{58} to form a compound of (Fmoc-G-P-S_{prot1})



(Fmoc-G-P-S_{prot1}) ;

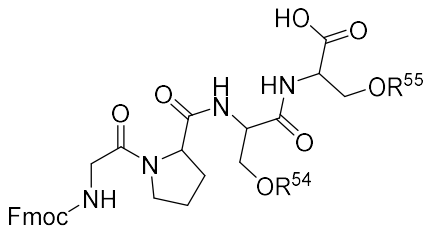
- reacting the compound of formula (Fmoc-G-P-S_{prot1}) and a compound of formula (S_{prot2}) to form a compound of formula (Fmoc-G-P-S_{prot1}-S_{prot2})



(Fmoc-G-P-S_{prot1}) **(S_{prot2})** **(Fmoc-G-P-S_{prot1}-S_{prot2})**

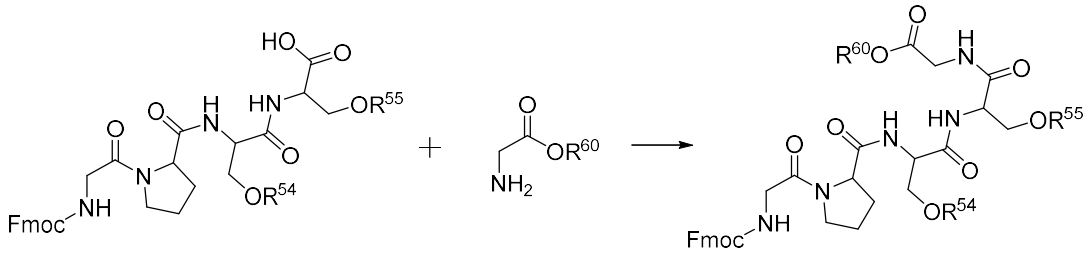
wherein R^{55} and R^{59} are protecting groups; and

- removing the protecting group R^{59} to form a compound of (Fmoc-F-G_{prot1}-S_{prot1}-S_{prot1})



(Fmoc-G-P-S_{prot1}-S_{prot1}) ;

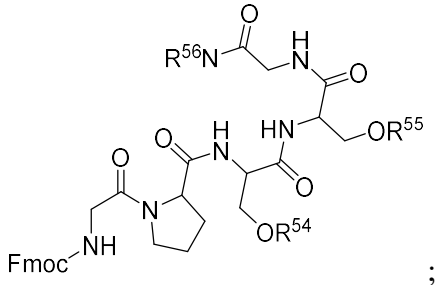
- reacting the compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}) and a compound of formula (G_{prot}) to form a compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot})



(Fmoc-G-P-S_{prot1}-S_{prot1}) (G_{prot}) (Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot})

wherein R^{60} is a protecting group;

- converting the compound of formula (Fmoc-G-P-S_{prot1}-S_{prot1}-G_{prot}) to the compound of claim 13



; and

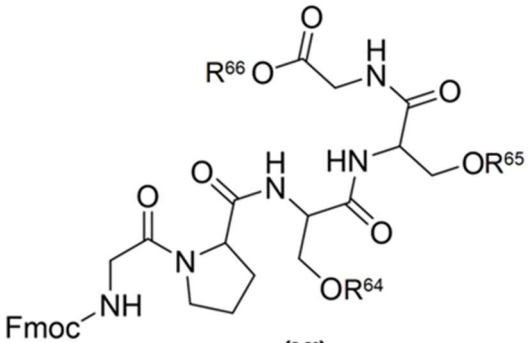
- optionally removing one or more protecting groups R^{54}, R^{55}, and R^{56}.

19. The method of claim 18, wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl and trityl groups.

20. A method of synthesizing a polypeptide, wherein: (i) the polypeptide is SEQ ID NO: 12, the method comprising: (i.1) conjugating the compound of any one of claims 13-16 via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22, and (i.2) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 23; (ii) the polypeptide is SEQ ID NO: 24, the method comprising conjugating the compound of any one of claims 13-16 via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 22; (iii) the polypeptide is SEQ ID NO: 16, the method comprising conjugating the compound of any one of claims 13-16 via the N-terminus of the compound to the C-terminus of a polypeptide of SEQ ID NO: 25; or (iv) the polypeptide is SEQ ID NO: 1, the method comprising: (iv.1) conjugating the compound of any one of claims 13-

16 via the C-terminus of the compound to the N-terminus of a polypeptide of SEQ ID NO: 8, and (iv.2) conjugating the resulting compound via its N-terminus to the C-terminus of a polypeptide of SEQ ID NO: 9.

21. A compound of Formula (XI), or a salt, solvate, or hydrate thereof,



(XI)

wherein R^{64} is H or a protecting group; R^{65} is H or a protecting group; and R^{66} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

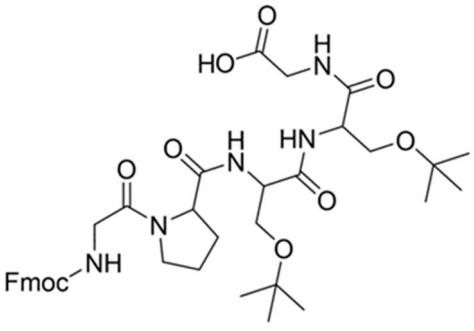
22. The compound of claim 21, wherein:

    a) (a) at least one of R^{64}, R^{65}, and R^{66} is H;

    b) (b) at least one of R^{64}, R^{65}, and R^{66} is a protecting group; or

    c) (c) both (a) and (b).

23. The compound of claim 21, wherein the compound is of the Formula:

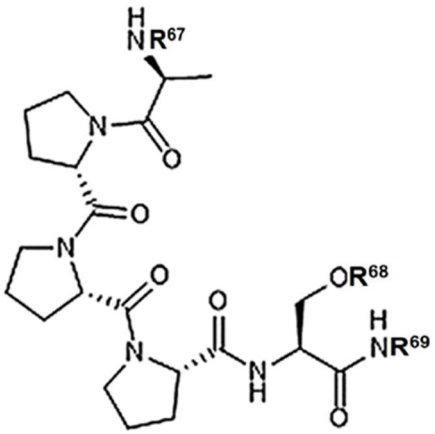


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24. The compound of any one of claims 21 to 23, wherein: (i) the compound is a solvate; or (ii) the compound is crystalline, optionally wherein the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder

diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 6.1° and 8.5° in combination of one or more peaks chosen from 5.8°, 16.9°, 18.5°, 18.8°, 19.3°, and 20.9.

25. A compound of Formula (XIII), or a salt, solvate, or hydrate thereof,



(XIII)

wherein R^{67} is H or a protecting group; R^{68} is H or a protecting group; and R^{69} is H or a protecting group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

26. The compound of claim 25, wherein:

    a) R^{67} is H or *tert*-butyl;

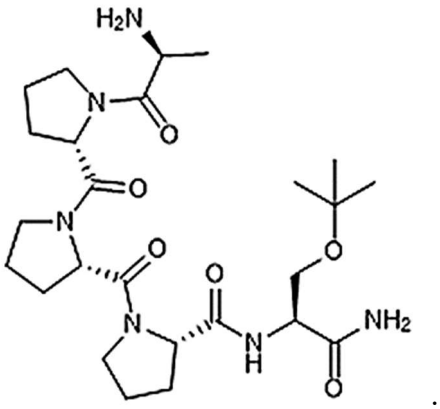
    b) R^{68} is H or *tert*-butyl;

    c) R^{69} is H or *tert*-butyl;

    d) any combination of (a)-(c).

27. The compound of claim 25 or 26, wherein: (a) at least one of R^{67}, R^{68}, and R^{69} is H; (b) at least one of R^{67}, R^{68}, and R^{69} is a protecting group; or (c) both (a) and (b).

28. The compound of claim 25, wherein the compound is of the Formula:

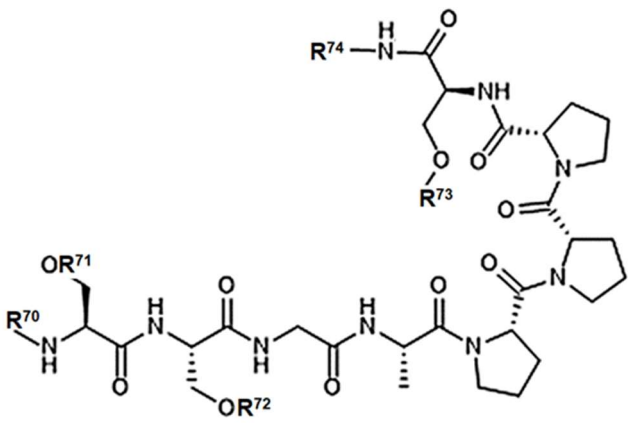


29. The compound of any one of claims 25 to 28, wherein: (i) the compound is a solvate; (ii) the compound is a de-solvate or is anhydrous; or (iii) the compound is crystalline, optionally wherein:

    a) the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 5.0° in combination of one or more peaks chosen from 8.3, 9.7, and 11.2°; or

    b) the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.2°in combination of one or more peaks chosen from 5.3, 8.1, 14.4, and 16.2°.

30. A compound of Formula (XIV), or a salt, solvate, or hydrate thereof,



(XIV)

wherein R^{70} is H or a protecting group; R^{71} is H or a protecting group; R^{72} is H or a protecting group; R^{73} is H or a protecting group; and R^{74} is H or a protecting

group; optionally wherein each protecting group is independently chosen from Boc, Fmoc, *tert*-butyl, and trityl groups.

31. The compound of claim 30, wherein:

    a) R^{70} is H, Fmoc, or *tert*-butyl;

    b) R^{71} is H or *tert*-butyl;

    c) R^{72} is H or *tert*-butyl;

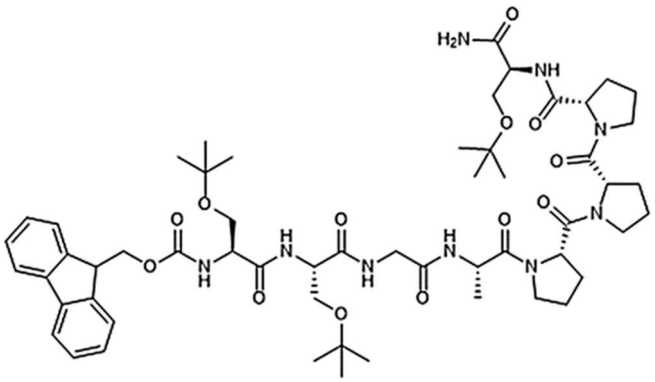
    d) R^{73} is H or *tert*-butyl;

    e) R^{74} is H, Fmoc, or *tert*-butyl;

    f) any combination of (a)-(e).

32. The compound of claim 30 or 31, wherein: (a) at least one of R^{70}, R^{71}, R^{72}, R^{73},and R^{74} is H; (b) at least one of R^{70}, R^{71}, R^{72}, R^{73},and R^{74} is a protecting group; or (c) both (a) and (b).

33. The compound of claim 30, wherein the compound is of the Formula:



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34. The compound of any one of claims 30 to 33, wherein: (i) the compound is a solvate; (ii) the compound is a de-solvate or is anhydrous; or (iii) the compound is crystalline, optionally wherein the compound is in the form of a crystalline solid characterized by peaks in the X-ray powder diffraction pattern at diffraction angle 2-theta ± 0.2 degrees of 7.5° in combination of one or more peaks chosen from 6.1, 8.7, 10.6, 15.0, 16.1, and 18.6°.