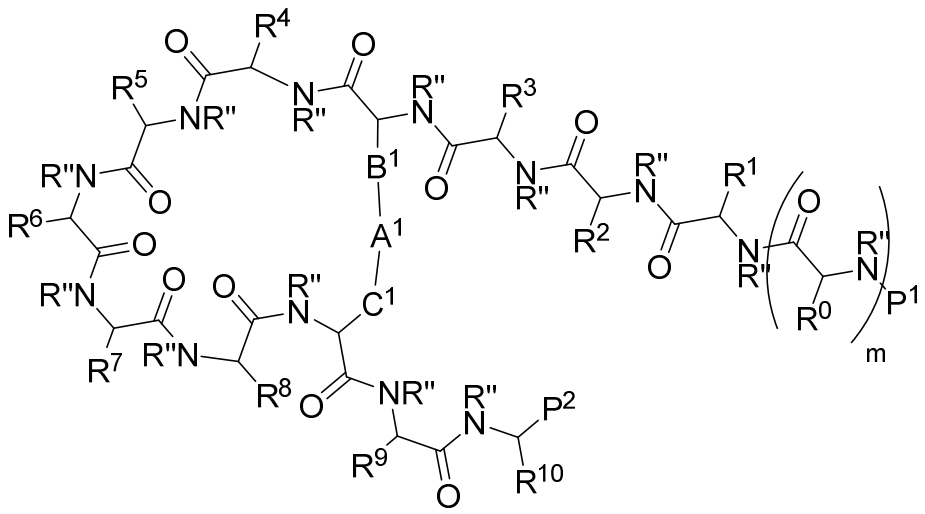
CLAIMS

1. A cyclic peptide of Formula B:

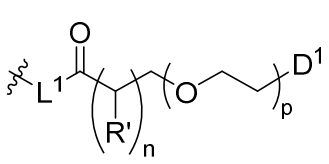


(B),

or a pharmaceutically acceptable salt thereof,

wherein:

P^1 is selected from: -L^1-Chelator,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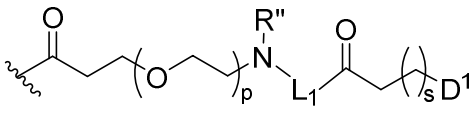
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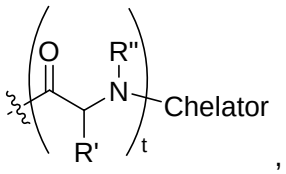
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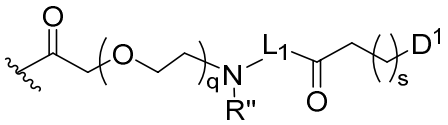
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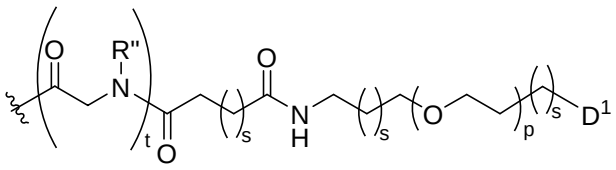
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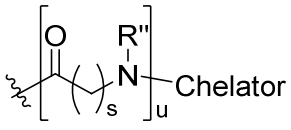
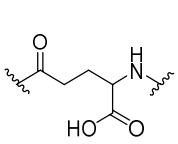

;

D^1 is -NR"-Chelator;

L^1 is absent or selected from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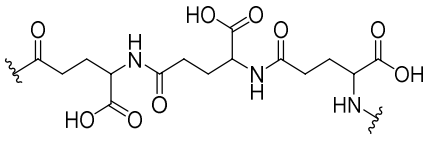
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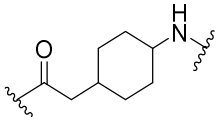
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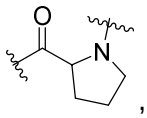
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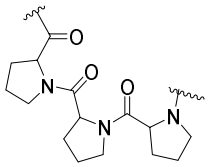
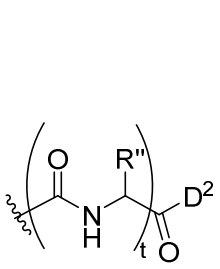

;

wherein the amino group of L^1 connects to the carbonyl group of P^1 or Chelator to form an amide bond;

P^2 is selected from $C(O)NH_2$, C(O)OH,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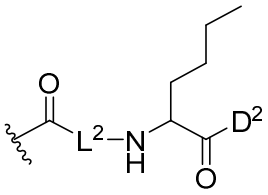
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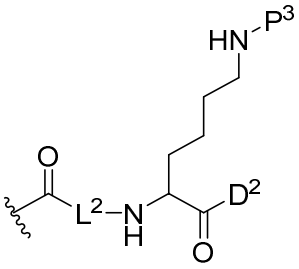
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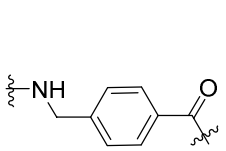
D^2 is OH or NH_2;

L^2 is absent or selected from: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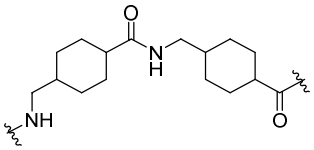
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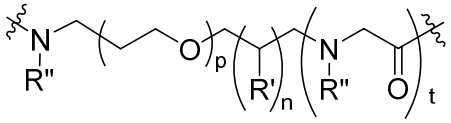
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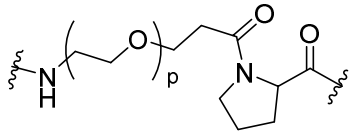
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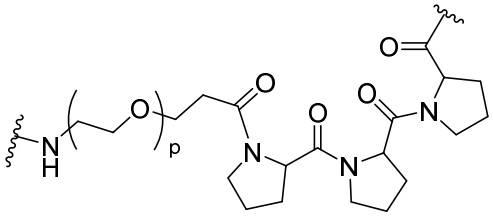
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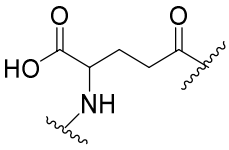
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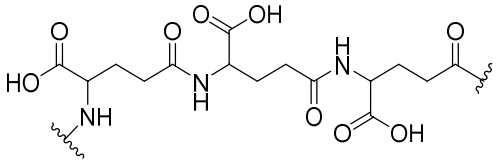
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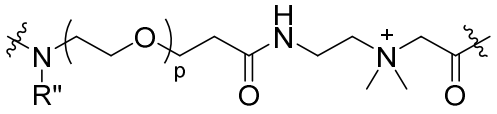
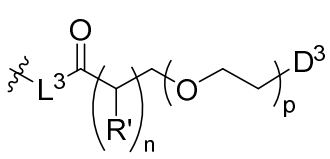

;

wherein the amino group of L^2 connects to the carbonyl group of P^2 to form an amide bond;

P^3 is selected from H,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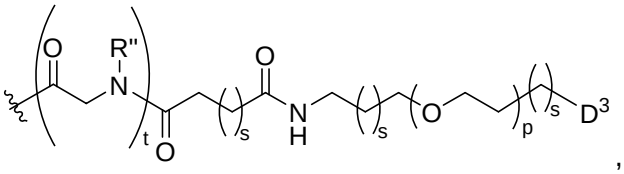
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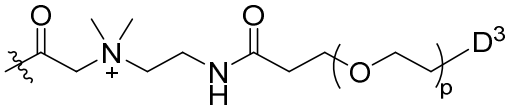
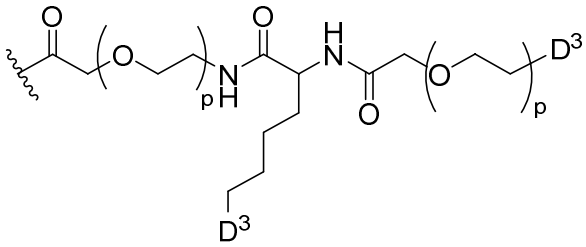
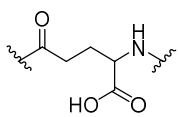
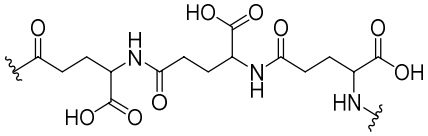
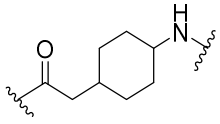
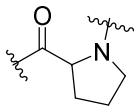
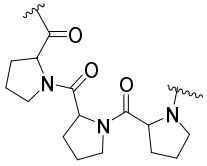
 , and  ;

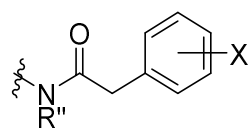
L^3 is absent or independently selected from

 ,  ,  ,  , and

 ;

wherein the carbonyl group of L^3 connects to an amine group of P^2 to form an amide bond;

D^3 is independently selected from: CH_3, C(O)OH, and

 ;

X is halogen;

R^0 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

R^1 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

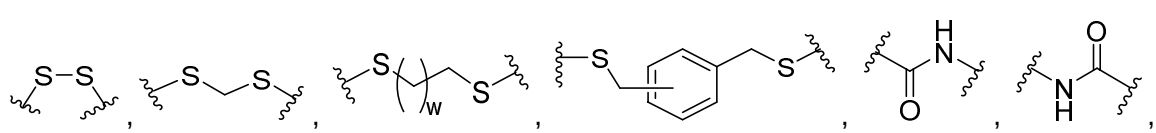
R^2 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

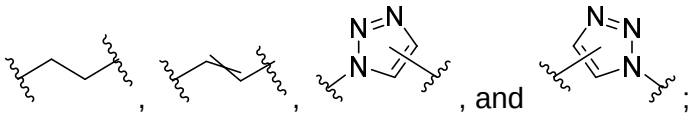
R^3 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

B^1 is C_{1-6} alkylene;

C^1 is C_{1-6} alkylene;

A^1 is selected from:




, and ;

wherein w is selected from 1, 2, or 3;

R^4 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid, both of which are optionally substituted with $CH_2C(O)OH$ or $C(O)(CH_2CH_2O)_p(CH_2)_2N(CH_3)_3^+$;

R^5 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

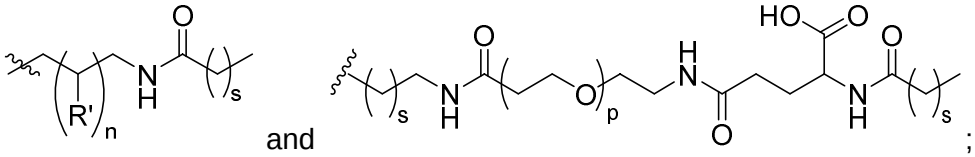
R^6 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

R^7 is selected from:

(i) an amino acid side chain of a natural amino acid,

(ii) an amino acid side chain of an unnatural amino acid, or

(iii) selected from the group consisting of:


and ;

R^8 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

R^9 is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

R^{10} is an amino acid side chain of a natural amino acid or an amino acid side chain of an unnatural amino acid;

m is 0 or 1;

each n, q, and u are independently an integer from 0 to 16;

each p is independently an integer from 0 to 24;

each s is independently an integer from 0 to 16;

each t is independently 1, 2, 3, 4, 5, or 6;

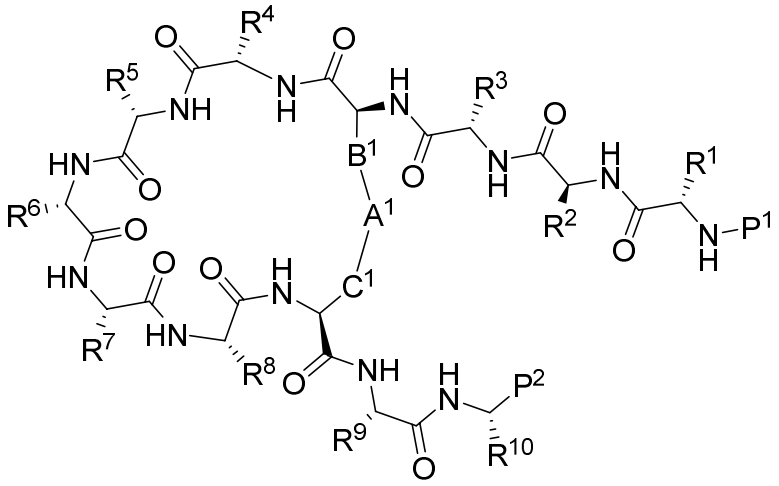
each R' is independently selected from H, C(O)OH, (CH_2)OH, and NHAc; and

each R" is independently selected from H and CH_3;

wherein when a variable group R^0, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, or R^{10} is defined as the amino acid side chain of a cyclic amino acid, the corresponding amino acid nitrogen of the peptide backbone of the generic formula forms part of the cyclic group; and

and wherein the cyclic peptide optionally comprises a radionuclide.

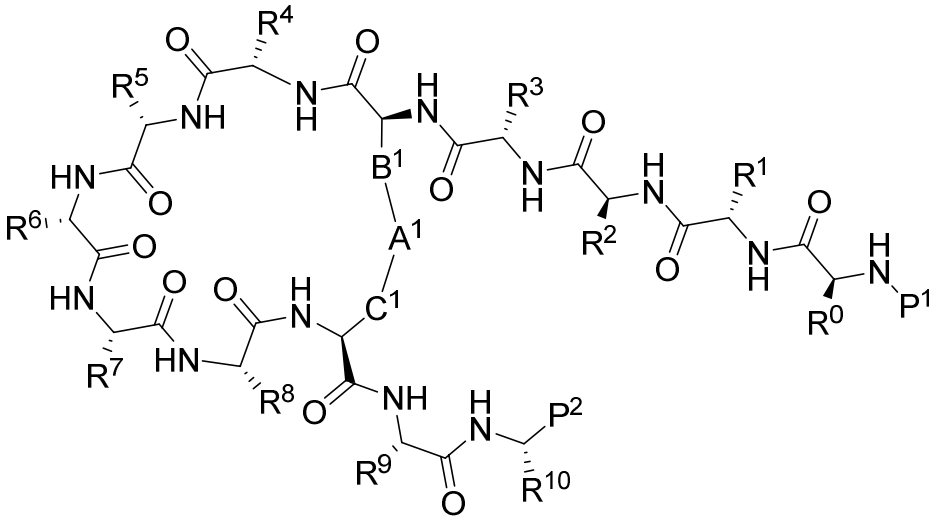
2. The cyclic peptide of claim 1, wherein the cyclic peptide of Formula B is a cyclic peptide of Formula Ia:



(Ia),

or a pharmaceutically acceptable salt thereof.

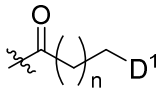
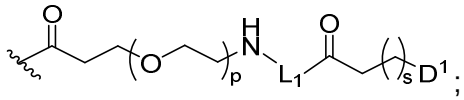
3. The cyclic peptide of claim 1, wherein the cyclic peptide of Formula B is a cyclic peptide of Formula Ib:



(Ib),

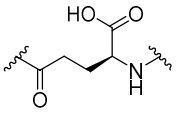
or a pharmaceutically acceptable salt thereof.

4. The cyclic peptide of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein:

P^1 is selected from  , -L^1-Chelator, and  ;

wherein:

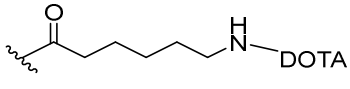
D^1 is NR''-Chelator;

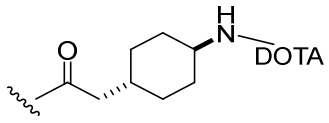
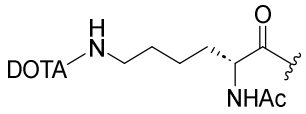
L^1 is absent or  ;

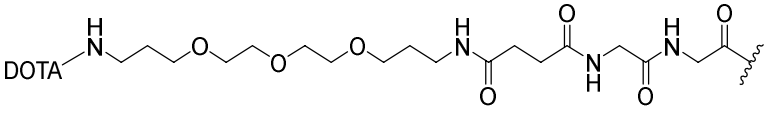
n and s are independently an integer from 2 to 15; and

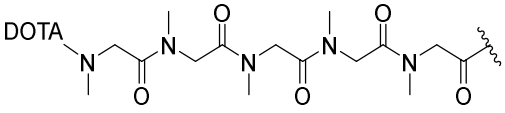
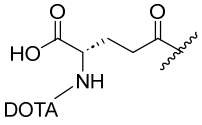
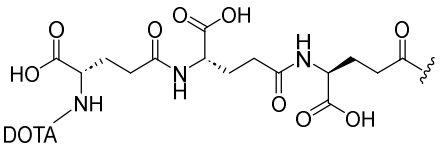
p is 8, 9, 10, 11, or 12.

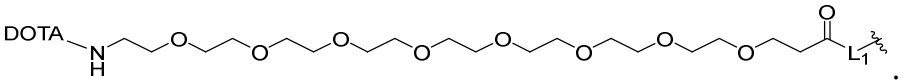
5. The cyclic peptide of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein P^1 is -L^1-Chelator.

6. The cyclic peptide of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein P^1 is selected from DOTA,  ,

 ,  ,

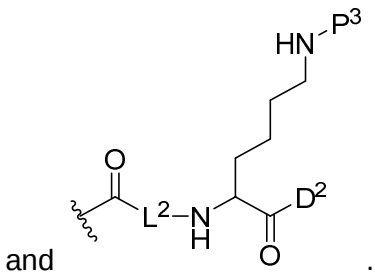
 ,

 ,  ,  ,

and  .

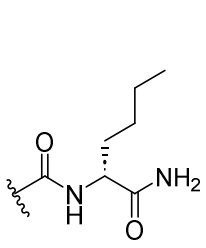
7. The cyclic peptide of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein P^2 is $C(O)NH_2$ or C(O)OH.

8. The cyclic peptide of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein P^2 is selected from $C(O)NH_2$, C(O)OH,



and .

9. The cyclic peptide of claim 8, or a pharmaceutically acceptable salt thereof, wherein P^2 is selected from $C(O)NH_2$, C(O)OH,



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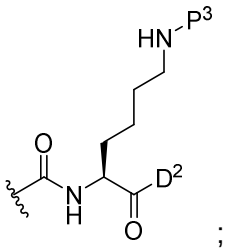
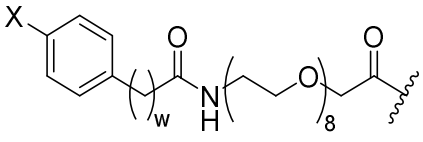


;

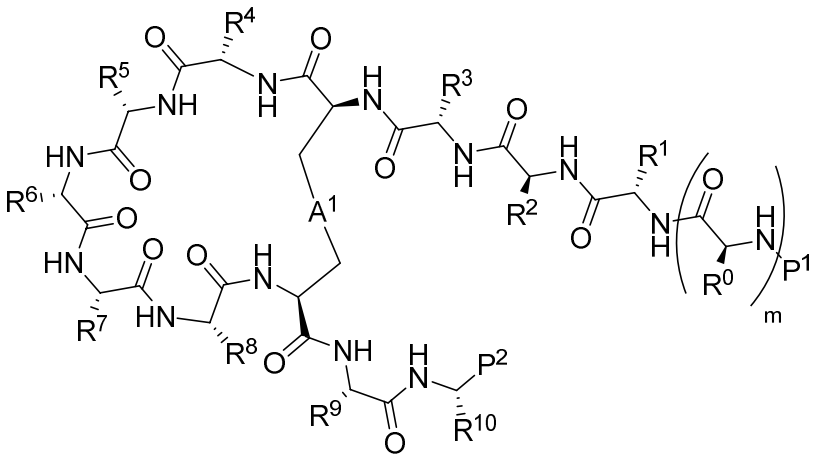
P^3 is Ac or



; and

X is halo.

10. The cyclic peptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein the cyclic peptide of Formula B is a cyclic peptide of Formula II:



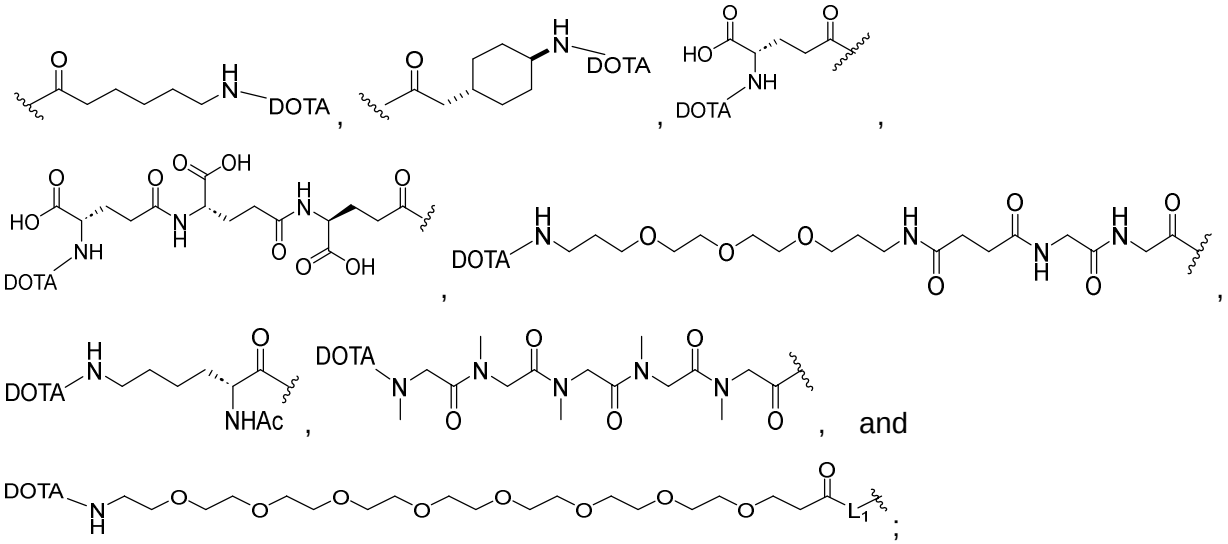
(II),

or a pharmaceutically acceptable salt thereof,

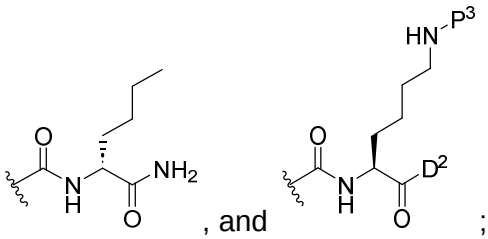
wherein P^2 is $C(O)NH_2$ or C(O)OH.

11. The cyclic peptide of claim 1, or a pharmaceutically acceptable salt thereof, wherein m is 0;

P^1 is selected from DOTA,

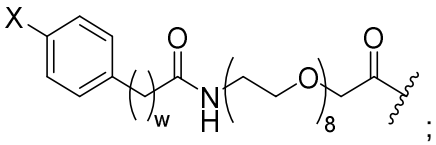


P^2 is selected from $C(O)NH_2$, C(O)OH,



; and

P^3 is Ac or



;

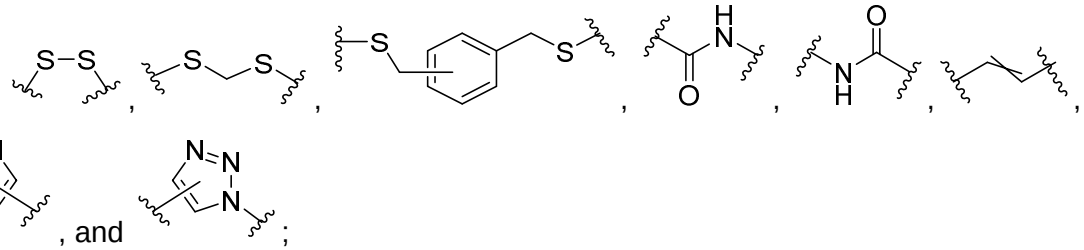
X is halo;

R^1 is selected from the group consisting of an amino acid side chain of Trp, 2Nal, 1Nal, 4CF_3-Phe, 7Aza-Trp, 1Me-Trp, 5OH-Trp, BIP, 5OMe-Trp, 4F-Phe, 3Pya, 4Pya, PAF, MAF, OAF, 5Qui, 7MeO-Trp, 7Me-Trp, 5F-Trp, 7Cl-Trp, D-Ala, Ala, alpha-Me-Trp, and NMe-Trp;

R^2 is selected from the group consisting of an amino acid side chain of Thr, D-Ala, Ala, alpha-Me-Thr, Lys, and NMe-Thr;

R^3 is selected from the group consisting of an amino acid side chain of Ile, Env, CHA, CBA, Nle, Tbg, THPG, Chg, 2Nal, 1Nal, 2CF_3-Phe, 2PhEt-Ala, D-Ala, Ala, Leu, t-Bu-Ala, NMe-Nle, α-tert-amylGly, Allo-Ile, Lys(C12), Lys(C14), Lys(C16), alpha-Me-Ile, and NMe-tBuAla;

A^1 is selected from the group consisting of:



, and ;

R^4 is selected from the group consisting of an amino acid side chain of Asn, D-Ala, Ala, DAB-4-NHCOC_5H_{11}, DAB-4-NHCOC_7H_{15}, Asp, Ser, Lys, 3-(4-piperidinyl)-Ala, 3-(1-morpholinyl)-Ala, 3Pya, 4Pya, Glu, NMe-Asn, PipA(acetic), and Pip(PegNMe_3)Ala;

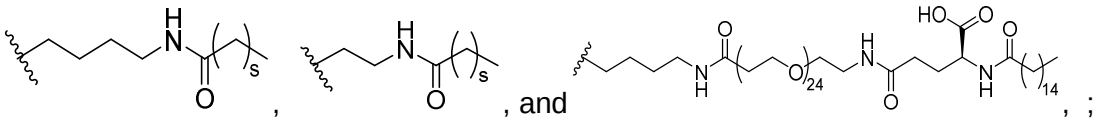
R^5 is selected from the group consisting of an amino acid side chain of Asn, Ala, D-Ala, Trp, Asp, Lys, 3Pya, 4Pya, 3-(4-piperidinyl)-Ala, 3-(1-morpholinyl)-Ala, Glu, NMe-Asn, and Ser;

R^6 is selected from the group consisting of an amino acid side chain of Trp, 4CF_3-Phe, 1Me-Trp, 7Aza-Trp, BIP, 2Nal, 1Nal, alpha-Me-Trp, D-Ala, Ala, 4F-Phe, , 5F-Trp, 5Ome-Trp, Asn, 5OH-Trp, 7Me-Trp, 7MeO-Trp, 7Cl-Trp, and NMe-Trp;

R^7 is:

(i) selected from the group consisting of an amino acid side chain of 3Pya, 4Pya, Lys(Me)3, His, Ala, D-Ala, Gln, Lys, Glu, Arg, Orn, NMe-His, and Ser; or

(ii) selected from the group consisting of:



, , and , ;

each s is independently 3, 5,10, 12, or 14;

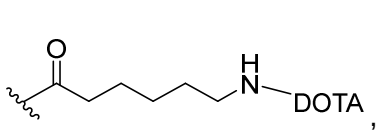
R^8 is selected from the group consisting of an amino acid side chain of Asp, D-Ala, Ala, Asn, Thr, NMe-Asp, and alpha-Me-Asp;

R^9 is selected from the group consisting of an amino acid side chain of Trp, 7Aza-Trp, 1Me-Trp, D-Ala, Ala, 4F-Phe, 1Nal, 2Nal, 5F-Trp, 5Ome-Trp, alpha-Me-Trp, 7Cl-Trp, 5OH-Trp, 7Me-Trp, 7MeO-Trp, and NMe-Trp; and

R^{10} is selected from the group consisting of an amino acid side chain of Pro, D-Ala, Ala, alpha-Me-Pro, trans4Fluoro-Pro, cis4Fluoro-Pro, trans4OH-Pro, cis4OH-Pro, Pip, 5,5-diMe-Pro, NMe-Ser, trans4NH2-Pro, cis4NH2-Pro, Sar, Aze, NMe-Ala, NMe-Leu, R-3Me-Aze, alpha-Me-Aze, ACI, and 3Me2-Aze.

12. The cyclic peptide of claim 1 or 3, or a pharmaceutically acceptable salt thereof, wherein m is 1;

P^1 is selected from DOTA,



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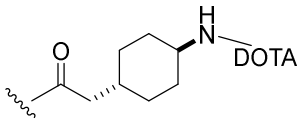

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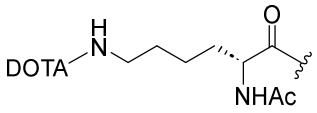

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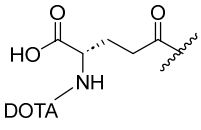

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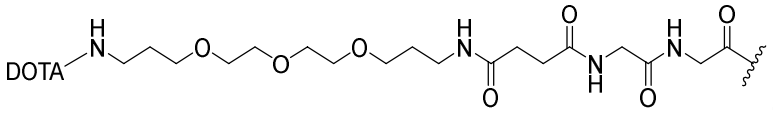

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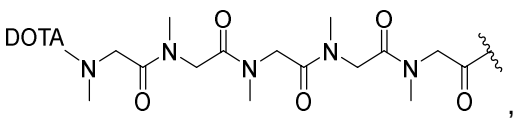

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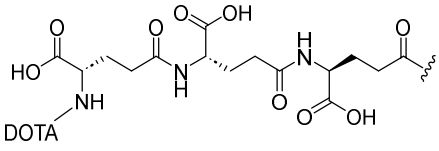

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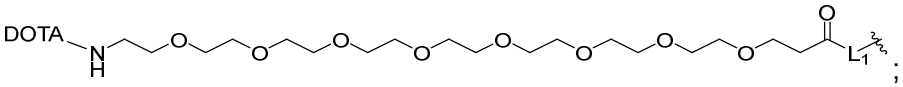
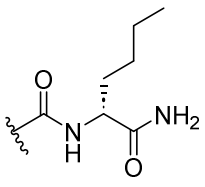
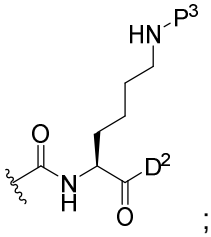


;

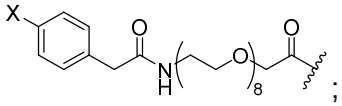
P^2 is selected from $C(O)NH_2$, C(O)OH,



, and


;

P^3 is selected from Ac and



X is halo;

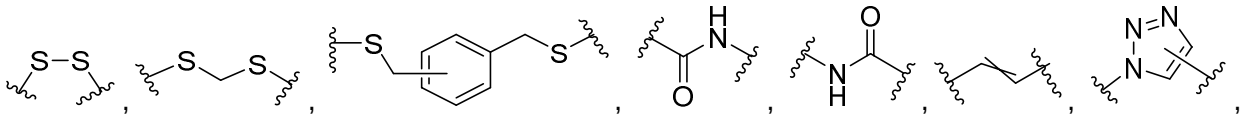
R^0 is selected from the group consisting of an amino acid side chain of Gly, Met, D-Ala, Ala, Nle, and Nva;

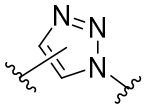
R^1 is selected from the group consisting of an amino acid side chain of Trp, 2Nal, 1Nal, 4CF_3-Phe, 7Aza-Trp, 1Me-Trp, 5OH-Trp, BIP, 5Ome-Trp, 4F-Phe, 3Pya, 4Pya, PAF, MAF, OAF, 5Qui, 7MeO-Trp, 7Me-Trp, 5F-Trp, 7Cl-Trp, D-Ala, Ala, alpha-Me-Trp, and NMe-Trp;

R^2 is selected from the group consisting of an amino acid side chain of Thr, D-Ala, Ala, alpha-Me-Thr, Lys, and NMe-Thr;

R^3 is selected from the group consisting of an amino acid side chain of Ile, Env, CHA, CBA, Nle, Tbg, THPG, Chg, 2Nal, 1Nal, 2CF_3-Phe, 2PhEt-Ala, D-Ala, Ala, Leu, t-Bu-Ala, NMe-Nle, α-tert-amylGly, Allo-Ile, Lys(C12), Lys(C14), Lys(C16), alpha-Me-Ile, and NMe-tBuAla;

A^1 is selected from the group consisting of



and  ;

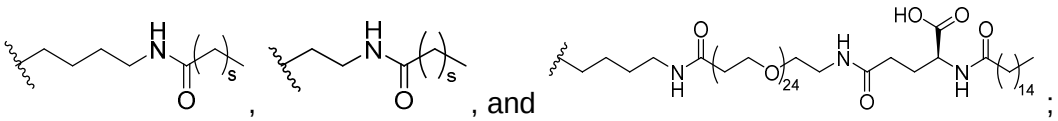
R^4 is selected from the group consisting of an amino acid side chain of Asn, D-Ala, Ala, DAB-4-NHCOC_5H_{11}, DAB-4-NHCOC_7H_{15}, Asp, Ser, Lys, 3-(4-piperidinyl)-Ala, 3-(1-morpholinyl)-Ala, 3Pya, 4Pya, Glu, and NMe-Asn;

R^5 is selected from the group consisting of an amino acid side chain of Asn, Ala, D-Ala, Trp, Asp, Lys, 3Pya, 4Pya, 3-(4-piperidinyl)-Ala, 3-(1-morpholinyl)-Ala, Glu, NMe-Asn, and Ser;

R^6 is selected from the group consisting of an amino acid side chain of Trp, 4CF_3-Phe, 1Me-Trp, 7Aza-Trp, BIP, 2Nal, 1Nal, alpha-Me-Trp, D-Ala, Ala, 4F-Phe, , 5F-Trp, 5Ome-Trp, Asn, 5OH-Trp, 7Me-Trp, 7MeO-Trp, 7Cl-Trp, and NMe-Trp;

R^7 is selected from the group consisting of an amino acid side chain of 3Pya, 4Pya, Lys(Me)3, His, Ala, D-Ala, Gln, Lys, Glu, Arg, Orn, NMe-His, and Ser; or

R^7 is selected from the group consisting of



each s is independently 3, 5,10, 12, or 14;

R^8 is selected from the group consisting of an amino acid side chain of Asp, D-Ala, Ala, Asn, Thr, NMe-Asp, and alpha-Me-Asp;

R^9 is selected from the group consisting of an amino acid side chain of Trp, 7Aza-Trp, 1Me-Trp, D-Ala, Ala, 4F-Phe, 1Nal, 2Nal, 5F-Trp, 5Ome-Trp, alpha-Me-Trp, 7Cl-Trp, 5OH-Trp, 7Me-Trp, 7MeO-Trp, and NMe-Trp; and

R^{10} is selected from the group consisting of an amino acid side chain of Pro, D-Ala, Ala, alpha-Me-Pro, trans4Fluoro-Pro, cis4Fluoro-Pro, trans4OH-Pro, cis4OH-Pro, Pip, 5,5-diMe-Pro, NMe-Ser, trans4NH2-Pro, cis4NH2-Pro, Sar, Aze, NMe-Ala, NMe-Leu, R-3Me-Aze, alpha-Me-Aze, ACI, and 3Me2-Aze.

13. The cyclic peptide of any one of claims 1 to 9, 11, and 12, or a pharmaceutically acceptable salt thereof, wherein

B^1 is CH_2 or $C(CH_3)_2$; and

C^1 is CH_2 or $C(CH_3)_2$.

14. The cyclic peptide of any one of claims 1 to 9, 11, and 12, or a pharmaceutically acceptable salt thereof, wherein

B^1 is CH_2; and

C^1 is CH_2.

15. The cyclic peptide of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein Chelator is independently selected from a group consisting of ethylenediamine tetraacetic acid (EDTA), diethylenetriamine pentaacetic acid (DTPA), 1,4,7,10-tetra-azacylcododecane-N,N′,N″,N‴-tetraacetic acid (DOTA), 6-((16-((6-Carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)-4-isothiocyanatopicolinic acid (Macropa), Macrodipa, 2,2',2'',2'''-(1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-4,7,13,16-tetrayl)tetraacetic acid) (Crown), 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid, α-(2-carboxyethyl) (DOTAGA), 1,4,7-Triazacyclononane-N,N′,N″-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (TETA), 1,4,7,10,13-pentaazacyclopentadecane-N,N′,N″,N‴,N⁗-pentaacetic acid (PEPA), and 1,4,7,10,13,16-hexaazacyclohexadecane-N,N′,N″,N‴,N⁗,N⁗′-hexaacetic acid (HEHA).

16. The cyclic peptide of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein Formula B is substituted by at least one chelator.

17. The cyclic peptide of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein the cyclic peptide of Formula B is selected from a cyclic peptide in Table A.

18. The cyclic peptide of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein the cyclic peptide of Formula B is selected from a cyclic peptide in Table B.

19. The cyclic peptide of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein the cyclic peptide further comprises a radioisotope.

20. The cyclic peptide of claim 19, or a pharmaceutically acceptable salt thereof, wherein the radioisotope is selected from a radioisotope in Table 3.

21. A pharmaceutical composition comprising the cyclic peptide of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

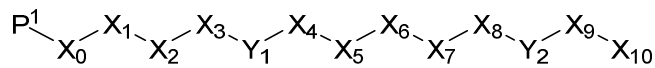
22. Use of the cyclic peptide of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

23. The use of claim 22, wherein the cancer is a DLL3-mediated cancer.

24. The use of claim 22 or 23, wherein the cancer is a neuroendocrine neoplasm, melanoma, or primary brain cancer.

25. The use of claim 24, wherein the neuroendocrine neoplasm is selected from small cell lung cancer (SCLC), medullary thyroid carcinoma (MTC), large cell neuroendocrine cancer (LCNEC), gastroenteropancreatic neuroendocrine carcinoma (GEP NEC), neuroendocrine prostate cancer (NEPC), small cell prostate cancer (SCPC), Merkel cell carcinoma (MCC), neuroendocrine cervical carcinoma, and Grade 3 neuroendocrine tumors (NETs).

26. A peptide having binding specificity for DLL3, wherein the peptide binds to one or more amino acids of A81, L83, G106, A85, and R61 of a DLL3 amino acid sequence of SEQ ID NO: 1, wherein the peptide comprises the amino acid sequence of Formula A:



(**A**),

or a pharmaceutically acceptable salt thereof,

wherein:

X_0 is any natural or unnatural amino acid or X_0 is absent;

X_1 is selected from Trp, 7Aza-Trp, 1Me-Trp, 5OH-Trp, 5OMe-Trp, 7OMe-Trp, 7Me-Trp, 5F-Trp, 7Cl-Trp, alpha-Me-Trp, and NMe-Trp;

X_2 and X_3 are each independently any natural or unnatural amino acids;

Y_1 is Cys;

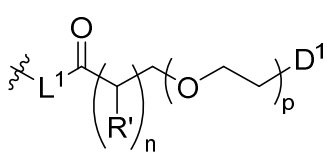
X_4, X_5, X_6, X_7 and X_8 are each independently any natural or unnatural amino acids;

Y_2 is Cys;

X_9 is selected from Trp, 7Aza-Trp, 1Me-Trp, 5OH-Trp, 5OMe-Trp, 7OMe-Trp, 7Me-Trp, 5F-Trp, 7Cl-Trp, alpha-Me-Trp, and NMe-Trp;

X_{10} is selected from Pro, alpha-Me-Pro, trans4Fluoro-Pro, cis4Fluoro-Pro, trans4OH-Pro, cis4OH-Pro, 5,5-diMe-Pro, trans4NH2-Pro, and cis4NH2-Pro;

P^1 is selected from: -L^1-Chelator,



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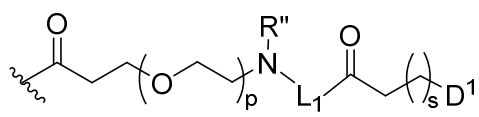

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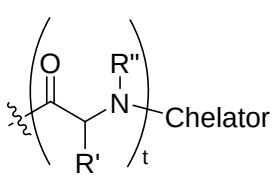

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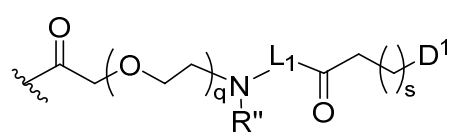

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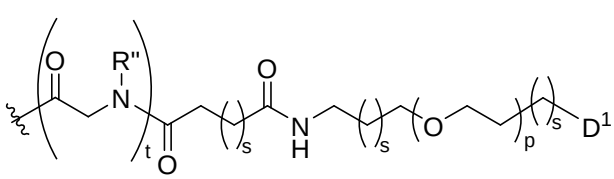

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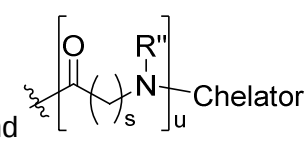
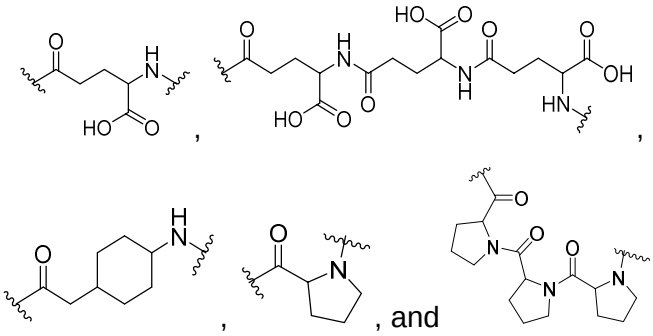


;

D^1 is -NR”-Chelator;

L^1 is absent or selected from



wherein the amino group of L^1 connects to the carbonyl group of P^1 or Chelator to form an amide bond;

each n, q, and u are independently an integer from 0 to 16;

each p is independently an integer from 0 to 24;

each s is independently an integer from 0 to 16;

each t is independently 1, 2, 3, 4, 5, or 6;

each R' is independently selected from H, C(O)OH, (CH_2)OH, and NHAc; and

each R" is independently selected from H and CH_3;

wherein the cyclic peptide is cyclized via a linker between Y_1 and Y_2; and

wherein the cyclic peptide binds to DLL3.

27. The peptide of claim 26, binding to amino acids A81, L83, G106, A85, and R61 of a DLL3 amino acid sequence of SEQ ID NO: 1.

28. The peptide of claim 26 or 27, binding to main chain atoms of amino acids A81, L83, G106, and A85 of a DLL3 amino acid sequence of SEQ ID NO: 1.

29. The peptide of any one of claims 26 to 28, binding to side chain atoms of amino acid R61 of a DLL3 amino acid sequence of SEQ ID NO: 1.

30. The peptide of any one of claims 26 to 29, binding to main chain atoms of amino acids A81, L83, G106, and A85 of a DLL3 amino acid sequence of SEQ ID NO: 1, and binding to side chain atoms of amino acid R61 of a DLL3 amino acid sequence of SEQ ID NO: 1.

31. The peptide of any one of claims 26 to 30, capable of binding DLL3 with an SPR K_D value of about 1×10^{-8} M to about 1×10^{-10} M.

32. The peptide of any one of claims 26 to 31, comprising an amino acid sequence of WTACANAKDCWP, or a derivative thereof comprising one or more unnatural amino acids.

33. The peptide of 32, wherein amino acids W1, A3, A7, and W11 bind to DLL3.

34. A pharmaceutical composition comprising the peptide of any one of claims 26 to 33 and a pharmaceutically acceptable carrier.

35. Use of the peptide of any one of claims 26 to 33 or the pharmaceutical composition of claim 34 in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

36. The use of claim 35, wherein the cancer is a DLL3-mediated cancer.

37. The use of claim 35 or 36, wherein the cancer is a neuroendocrine neoplasm, melanoma, or primary brain cancer.

38. The use of claim 37, wherein the neuroendocrine neoplasm is selected from small cell lung cancer (SCLC), medullary thyroid carcinoma (MTC), large cell neuroendocrine cancer (LCNEC), gastroenteropancreatic neuroendocrine carcinoma (GEP NEC), neuroendocrine prostate cancer (NEPC), small cell prostate cancer (SCPC), Merkel cell carcinoma (MCC), neuroendocrine cervical carcinoma, and Grade 3 neuroendocrine tumors (NETs).

39. The use of claim 24 or 37, wherein the neuroendocrine neoplasm is extrapulmonary neuroendocrine carcinoma (NEC) of the cervix.

40. The cyclic peptide of claim 17, wherein the cyclic peptide is radiolabeled with F-18, Ga-68, In-111, Lu-177, or Ac-225, and pharmaceutically acceptable salts and solvates thereof.

41. The cyclic peptide of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, the pharmaceutical composition of claim 21, the peptide of any one of claims 26 to 33 or the pharmaceutical composition of claim 34 for use in therapy.