

comorbidity (e.g., obesity, non-alcoholic fatty liver disease, bone fracture and cognitive dysfunction). See, e.g., Sieno at page 108.

SUMMARY

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt and/or hydrate and/or prodrug of the compound) that modulate (e.g., agonize or partially agonize or antagonize) glucagon-like peptide-1 receptor ("GLP-1R") and/or the gastric inhibitory polypeptide receptor ("GIPR"). The chemical entities are useful, e.g., for treating a subject (e.g., a human) having a disease, disorder, or condition in which modulation (e.g., agonism, partial agonism or antagonism) of GLP-1R and/or GIPR activities is beneficial for the treatment or prevention of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some examples, the modulation results in an enhancement of (e.g., an increase in) existing levels (e.g., normal, or below normal levels) of GLP-1R and/or GIPR activity (e.g., signaling). In some examples, the chemical entities described herein further modulate (e.g., attenuate, uncouple) β -arrestin signaling relative to what is observed with the native ligand. This disclosure also features compositions as well as other methods of using and making the said chemical entities.

An "agonist" of GLP-1R includes compounds that, at the protein level, directly bind or modify GLP-1R such that an activity of GLP-1R is increased, e.g., by activation, stabilization, altered distribution, or otherwise relative to GLP-1R activity in absence of ligand.

Certain compounds described herein that agonize GLP-1R to a lesser extent (partial agonists) than a GLP-1R full agonist (e.g., native GLP-1) can function in assays as antagonists as well as agonists. These compounds antagonize activation of GLP-1R by a GLP-1R full agonist because they prevent the full effect of GLP-1R interaction. However, the compounds also, on their own, activate some GLP-1R activity, typically less than a corresponding amount of the GLP-1R full agonist. Such compounds are sometimes referred to herein as "partial agonists of GLP-1R".

An “antagonist” of GLP-1R includes compounds that, at the protein level, directly bind or modify GLP-1R such that an activity of GLP-1R is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise relative to GLP-1R activity in absence of ligand.

5 In some examples, the compounds described herein are agonists (e.g., full agonists) of GLP-1R. In other examples, the compounds described herein are partial agonists or antagonists of GLP-1R.

 An "agonist" of GIPR includes compounds that, at the protein level, directly bind or modify GIPR such that an activity of GIPR is increased, e.g., by activation, stabilization,
10 altered distribution, or otherwise relative to GIPR activity in absence of ligand.

 Certain compounds described herein that agonize GIPR to a lesser extent than native GIP (s full agonist) can function as antagonists as well as agonists. These compounds are partial antagonists as they reduce activation of GIPR by native GIP because they reduce the full effect of native GIP. However, the compounds also, on their own, activate some
15 GIPR activity, typically less than a corresponding amount of native GIP. Such compounds are sometimes referred to herein as "partial agonists of GIPR".

 An “antagonist” of GIPR includes compounds that, at the protein level, directly bind or modify GIPR such that an activity of GIPR is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise
20 relative to GIPR activity in absence of ligand.

 In some examples, the compounds described herein are agonists (e.g., full agonists) of GIPR. In other examples, the compounds described herein are partial agonists of GIPR. In still other examples, the compounds described herein are or antagonists of GIPR.

 In some examples, the compounds described herein are full agonists of both GLP-
25 1R and GIPR. In some examples, the compounds described herein are partial agonists of both GLP-1R and GIPR. This disclosure also contemplates chemical entities that (i) agonize one of GLP-1R and GIPR (e.g., GLP-1R); and antagonize the other of GLP-1R and GIPR (e.g., GIPR). For example, this disclosure contemplates chemical entities that (i) fully agonize one of GLP-1R and GIPR (e.g., GLP-1R); and partially agonize or

antagonize the other of GLP-1R and GIPR (e.g., GIPR). In certain examples, the chemical entities that are full agonists of GLP-1R and partial agonists or antagonists of GIPR; or that are partial agonists or antagonists of GLP-1R and full agonists of GIPR.

Generally, a receptor exists in an active (Ra) and an inactive (Ri) conformation. Certain compounds that affect the receptor can alter the ratio of Ra to Ri (Ra/Ri). For example, a full agonist increases the ratio of Ra/Ri and can cause a "maximal", saturating effect. A partial agonist, when bound to the receptor, gives a response that is lower than that elicited by a full agonist (e.g., an endogenous agonist). Thus, the Ra/Ri for a partial agonist is less than for a full agonist. However, the potency of a partial agonist may be greater or less than that of the full agonist.

In some examples, the chemical entities described herein further modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) β -arrestin coupling and/or b-arrestin signaling, and GLP-1R and/or GIPR internalization. In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) recruitment of β -arrestin to a G-protein coupled receptor (e.g., GLP-1R). In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) formation of a complex ("coupling") (e.g., a signaling complex) between β -arrestin and a G-protein coupled receptor (e.g., GLP-1R or GIPR). The effects of the chemical entities described herein on β -arrestin signaling and associated downstream processes (e.g., those delineated above) can be assessed using conventional methods, e.g., PathHunter β -arrestin Assay for determining β -arrestin coupling (see Examples section). By way of example, a value of β -arrestin (GLP-1R) $EC_{50} < 1 \mu M$ in the aforementioned assay indicates a compound that induces β -arrestin recruitment to GLP-1R. GLP-1, the native ligand for GLP-1R, and therapeutic analogs thereof, such a liraglutide, are potent recruiters of β -arrestin. As another example, a value of β -arrestin (GLP1R) $EC_{50} > 1 \mu M$ (e.g., $> 10 \mu M$) indicates a compound that does not substantially induce β -arrestin recruitment to GLP-1R. Therapeutic agents that modulate G-protein coupled receptors (e.g., GLP-1R and/or GIPR) can produce a variety of effects depending on the degree of cAMP activation versus β -arrestin -based signaling. It has been shown that b-arrestin coupling is a key step in

receptor internalization and subsequent de-sensitization and attenuation of signaling. Both GLP-1 (and the liraglutide analog) and GIP have been shown to produce rapid receptor internalization. Thus, compounds that activate GLP-1R and/or GIPR cAMP signaling but do not substantially couple to β -arrestin have the potential to prolong receptor signaling and extend pharmacological benefits. In some examples, the chemical entities described herein exhibit relatively strong GLP-1R and/or GIPR mediated cAMP activation with minimal or no detectable β -arrestin coupling. In some examples, the chemical entities described herein exhibit relatively strong GLP-1R mediated cAMP activation and no or little GIPR mediated cAMP activation with minimal or no detectable β -arrestin coupling.

In some examples, the compounds described herein show reduced activity in a rodent aversion model, while maintaining a relatively high potency in glucose clearance assay. Aversion models, such as conditioned taste aversion, are commonly used to identify compounds with adverse effects such as nausea. Nausea causing agents, such as Exendin-4 and liraglutide, are known to have a strong signal in conditioned taste aversion models. Advantageously, some of the chemical entities described herein are therefore expected to have a reduced likelihood of producing unwanted side effects, such as nausea, when administered to a patient, while maintaining full pharmacological benefit.

Accordingly, in one example, this disclosure features peptide-based chemical entities (e.g., N-protected peptide-based chemical entities; e.g., peptide-based chemical entities having from 30-50 amino acids, 30-45 amino acids, 30-40 amino acids, 35-40 amino acids; e.g., an N-protected peptide-based chemical entities having from 30-50 amino acids, 30-45 amino acids, 30-40 amino acids, 35-40 amino acids). The peptide-based chemical entities modulate (e.g., agonize or partially agonize or antagonize) glucagon-like peptide-1 receptor ("GLP-1R") and/or the gastric inhibitory polypeptide receptor ("GIPR") and optionally further modulate (e.g., uncouple, attenuate,) β -arrestin signaling and/or aversion as described herein.

In some examples, the peptide-based chemical entities agonize or partially agonize GLP-1R.

In some examples, the peptide-based chemical entities agonize or partially agonize or antagonize GIPR.

5 In some examples, said peptide-based chemical entities reduce (e.g., uncouple, attenuate, inhibit) β -arrestin signaling; e.g., reduce (e.g., uncouple, attenuate, inhibit) the recruitment of β -arrestin to a G-protein coupled receptor (e.g., GLP-1R); e.g., reduce (e.g., attenuate, disrupt, inhibit) the formation of a complex (e.g., a signaling complex) between β -arrestin and a G-protein coupled receptor (e.g., GLP-1R).

10 In certain examples, the peptide-based chemical entities:

- agonize or partially agonize GLP-1R;
- agonize or partially agonize or antagonize GIPR;
- reduce (e.g., uncouple, attenuate, inhibit) β -arrestin signaling; e.g., reduce (e.g., attenuate, disrupt, inhibit) the recruitment of β -arrestin to a G-protein coupled receptor (e.g., GLP-1R and/or GIPR); e.g., reduce (e.g., attenuate, disrupt, inhibit) the formation of a complex (e.g., a signaling complex) between β -arrestin and a G-protein coupled receptor (e.g., GLP-1R and/or GIPR); and
- 20 • stimulate glucose clearance in vivo (GTT test) without causing aversion.

In some examples, the peptide-based chemical entities exhibit a value of cAMP (GLP1R) EC50 of less than about 10 nM, 5 nM, or 1 nM (e.g., less than about 1 nM).

25 In some examples, the peptide-based chemical entities exhibit a value of cAMP (GIPR) EC50 of less than about 100 nM, 50 nM, or 10 nM (e.g., less than about 10 nM).

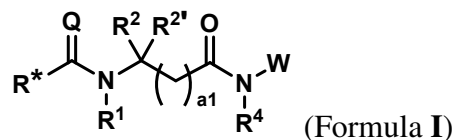
In some examples, the peptide-based chemical entities inhibit GIP induced cAMP production (GIPR antagonism).

In some examples, the compounds described herein exhibit a value of β -arrestin (GLP1R) EC₅₀ > 1 μ M.

In some examples, the peptide-based chemical entities:

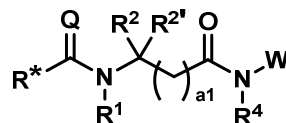
- exhibit a value of cAMP (GLP1R) EC₅₀ of less than about 10 nM, 5 nM, or 1 nM (e.g., less than about 1 nM);
- exhibit a value of cAMP (GIPR) EC₅₀ of less than about 100 nM, 50 nM, or 10 nM (e.g., less than about 10 nM) or are GIPR antagonists;
- exhibit a value of β -arrestin (GLP1R) EC₅₀ > 1 μ M; and
- stimulate glucose clearance in vivo (GTT test) without causing aversion (nausea)

In one example, the featured peptide-based chemical entities include compounds of Formula (I), or a pharmaceutically acceptable salt thereof:



in which **R***, **R¹**, **R²**, **R^{2'}**, **a₁**, **R⁴**, and **W** can be as defined anywhere herein.

In one aspect, the present disclosure refers to a compound of Formula (I):



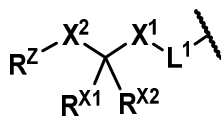
Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

Q is O or S;

R* is as defined in (i), (ii), or (iii), below:

(i)

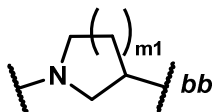


Formula (A)

5 wherein:

L^1 is selected from the group consisting of:

- C_{1-10} alkylene optionally substituted with 1-3 substituents each independently selected from the group consisting of: halo; C_{1-4} alkoxy; -OH; phenyl; and $NR'R''$; and



- , wherein $m1$ is 0, 1, 2, 3, or 4;

X^1 is selected from the group consisting of: $C(=O)$; $C(=S)$; $S(O)_{1-2}$; $C(=O)N(R')^*$; $C(=S)N(R')^*$; $S(O)_{1-2}N(R')^*$; $N(R')C(=O)^*$; $N(R')C(=S)^*$; and $N(R')S(O)_{1-2}^*$, wherein * represents the point of attachment to L^1 ;

R^{X1} and R^{X2} are each defined according to (AA) or (AB):

(AA)

R^{X1} and R^{X2} are each independently selected from the group consisting of:

- -H, -F;
- C_{1-8} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1-3 R^a ; and

- C_{3-8} cycloalkyl which is optionally substituted with 1-3 R^b ;

(AB)

R^{X1} and R^{X2} taken together with the carbon atom to which each is attached form a saturated or partially unsaturated ring having 3-10 ring atoms, wherein 0-2 ring atoms are heteroatoms each independently selected from the group consisting of: O, N, N(H), $N(R^c)$, and $S(O)_{0-2}$, wherein the ring is optionally substituted at one or more ring carbon atoms with 1-3 R^b ;

X^2 is a bond; and

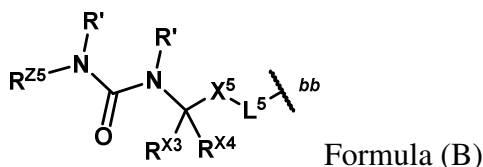
R^Z is selected from the group consisting of:

- H;
- C_{1-6} alkyl optionally substituted with 1-6 R^a ;
- $-R^{ZA}$; and
- $-L^{ZA}-R^{ZA}$;

L^{ZA} is C_{1-6} alkylene optionally substituted with 1-3 independently selected R^a ; and

R^{ZA} is R^c ;

(ii)



wherein:

L^5 is C_{1-10} alkylene optionally substituted with 1-3 substituents each independently selected from the group consisting of: halo; C_{1-4} alkoxy; -OH; phenyl; and $NR'R''$;

X^5 is selected from the group consisting of: a bond; $C(=O)$; $C(=S)$; $S(O)_{1-2}$; $C(=O)N(R')^*$; $C(=S)N(R')^*$; and $S(O)_{1-2}N(R')^*$, wherein * represents the point of attachment to L^5 ;

R^{X3} and R^{X4} are each defined according to (BA) or (BB):

(BA)

R^{X3} and R^{X4} are each independently selected from the group consisting of:

- -H, -F;
- C_{1-8} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1-3 R^a ; and
- C_{3-6} cycloalkyl which is optionally substituted with 1-3 R^b ;

(BB)

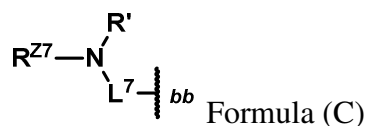
R^{X3} and R^{X4} taken together with the carbon atom to which each is attached form a saturated or partially unsaturated ring having 3-10 ring atoms, wherein 0-2 ring atoms are heteroatoms each independently selected from the group consisting of: O, N,

N(H), N(R^c), and S(O)₀₋₂, wherein the ring is optionally substituted at one or more ring carbon atoms with 1-3 R^b; and

R^{Z5} is selected from the group consisting of: -R^{ZE}; -L^{ZE}-R^{ZE}; and C₁₋₆ alkyl optionally substituted with 1-6 R^a;

5 L^{ZE} is C₁₋₆ alkylene optionally substituted with 1-3 independently selected R^a; and R^{ZE} is R^e;

(iii)



10 L⁷ is C₁₋₁₀ alkylene optionally substituted with 1-3 substituents each independently selected from the group consisting of: halo; C₁₋₄ alkoxy; -OH; phenyl; and NR'R''; and

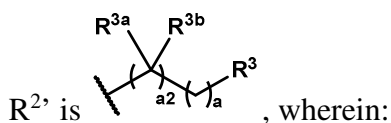
R^{Z7} is -L^{ZG}-R^{ZG};

L^{ZG} is C₁₋₆ alkylene optionally substituted with 1-3 independently selected R^a;

R^{ZG} is R^e;

15 each of R¹ and R² is independently selected from the group consisting of H and C₁₋₃ alkyl;

a₁ is 0, 1, 2, 3, or 4;



R³ is -C(O)OH, -C(O)OR^{4a}, -CH(C(O)OH)₂, or a carboxylic acid isostere;

a is 0, 1, 2, 3, 4, or 5; a₂ is 0 or 1;

20 each of R^{3a} and R^{3b} is independently H or C₁₋₃ alkyl; and

R^{4a} is -(C₀₋₃ alkylene)-R^e or C₁₋₆ alkyl optionally substituted with 1-6 R^a

-N(R⁴)-W has Formula WD:

*GT(Xaa3)(Xaa4)SD(Xaa7)SI(Xaa10)LD(Xaa13)(Xaa14)A(Xaa16)(Xaa17)(Xaa18)F(Xaa20)(Xaa21)(Xaa22)L(Xaa24)(Xaa25)GGPSSGAPPPS(Xaa37)-

25 R⁶ (SEQ ID NO: 4),

wherein:

Xaa3 is F, F* , F† , or F‡;

Xaa4 is T, A or V;

Xaa7 is Y, or K*;

Xaa10 is Y, L*, or Aib;

Xaa13 is K, Orn, or R;

5 Xaa14 is Q, I, or K*;

Xaa16 is A, or Q;

Xaa17 is Aib, or K*;

Xaa18 is A, or E;

Xaa20 is V or I;

10 Xaa21 is N, Q, K*, or dE;

Xaa22 is W or Y;

Xaa24 is I or L;

Xaa25 is A or E;

Xaa37 is absent;

15 R⁶ is -NH₂ or -OH;

wherein -N(R⁴)-W is attached to the remainder of Formula (I) by the amino group of N-terminal amino acid *G;

each occurrence of R^a is independently selected from the group consisting of: halo; -OH; -N(R^f)(R'); C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -OC(=O)(C₁₋₆ alkyl); -C(=O)O(C₁₋₆ alkyl);
20 -C(=O)OH, -C(=O)N(R')(R''), -S(O)₁₋₂(C₁₋₆ alkyl); and cyano;

each occurrence of R^b is independently selected from the group consisting of: C₁₋₆ alkyl optionally substituted with 1-6 R^a; C₂₋₆ alkenyl; C₂₋₆ alkynyl; -OH; oxo; -halo; -N(R^f)(R'); C₁₋₄ alkoxy; C₁₋₄ haloalkoxy; -C(=O)(C₁₋₄ alkyl); -C(=O)O(C₁₋₆ alkyl); -C(=O)OH; -C(=O)N(R')(R''); -S(O)₁₋₂N(R')(R''); -S(O)₁₋₂(C₁₋₆ alkyl); -SF₅; -NO₂; and
25 cyano;

each occurrence of R^c is independently selected from the group consisting of: C₁₋₆ alkyl; C₁₋₆ haloalkyl; -C(=O)(C₁₋₆ alkyl); -C(=O)O(C₁₋₆ alkyl); -C(=O)N(R')(R''); and -S(O)₁₋₂(C₁₋₆ alkyl);

each occurrence of R^d is independently selected from the group consisting of: -R^e,
30 -(C₁₋₃ alkylene)-R^e, -O-(C₀₋₃ alkylene)-R^e, -C(=O)(C₀₋₃ alkylene)-R^e, and -C(=O)(C₀₋₃ alkylene)O-R^e;

each occurrence of R^e is independently selected from the group consisting of:

(i) C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with 1-4 independently selected R^b ;

5 (ii) heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of N, N(H), $N(R^c)$, O, and $S(O)_{0-2}$, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^b at one or more ring carbon atoms;

(iii) C_{6-10} aryl, wherein the aryl is optionally substituted with 1-5 independently selected R^b ; and

10 (iv) heteroaryl including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, N(H), $N(R^c)$, O, and $S(O)_{0-2}$, wherein the heteroaryl is optionally substituted with 1-3 independently selected R^b at one or more ring carbon atoms;

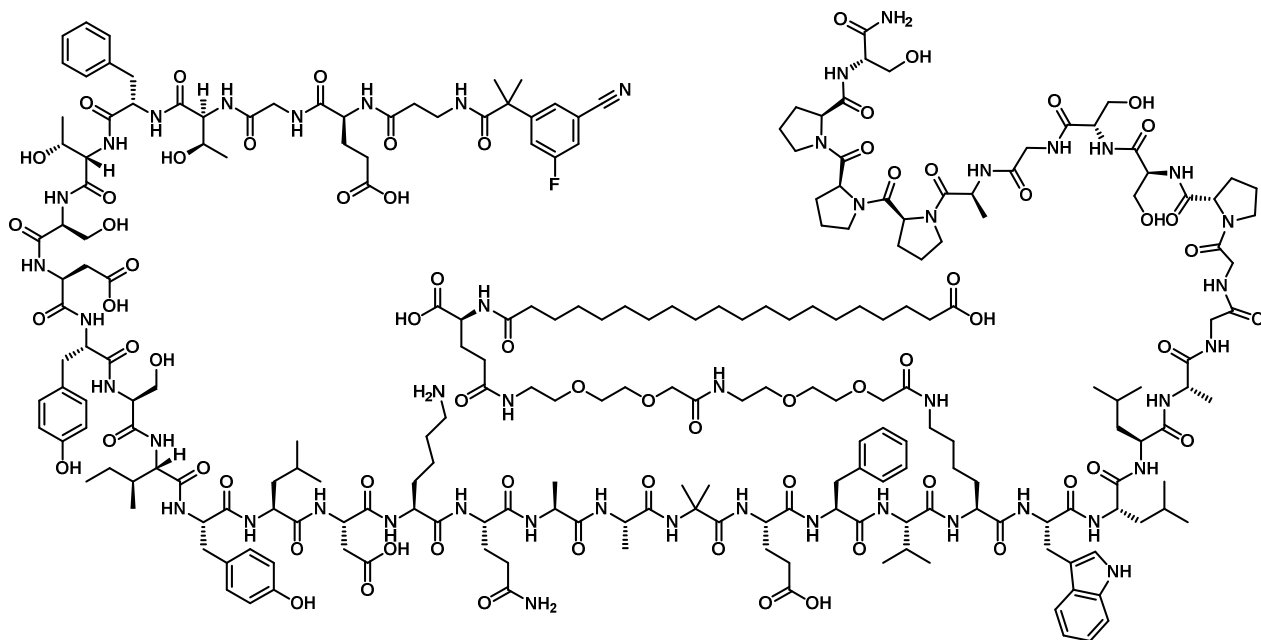
each occurrence of R^f is independently selected from the group consisting of: H;
15 C_{1-4} alkyl; C_{3-6} cycloalkyl; $-C(=O)(C_{1-6} \text{ alkyl})$; $-C(=O)O(C_{1-6} \text{ alkyl})$; and $-S(O)_{1-2}(C_{1-6} \text{ alkyl})$; and

each occurrence of R' and R'' is independently selected from the group consisting of: H and C_{1-6} alkyl.

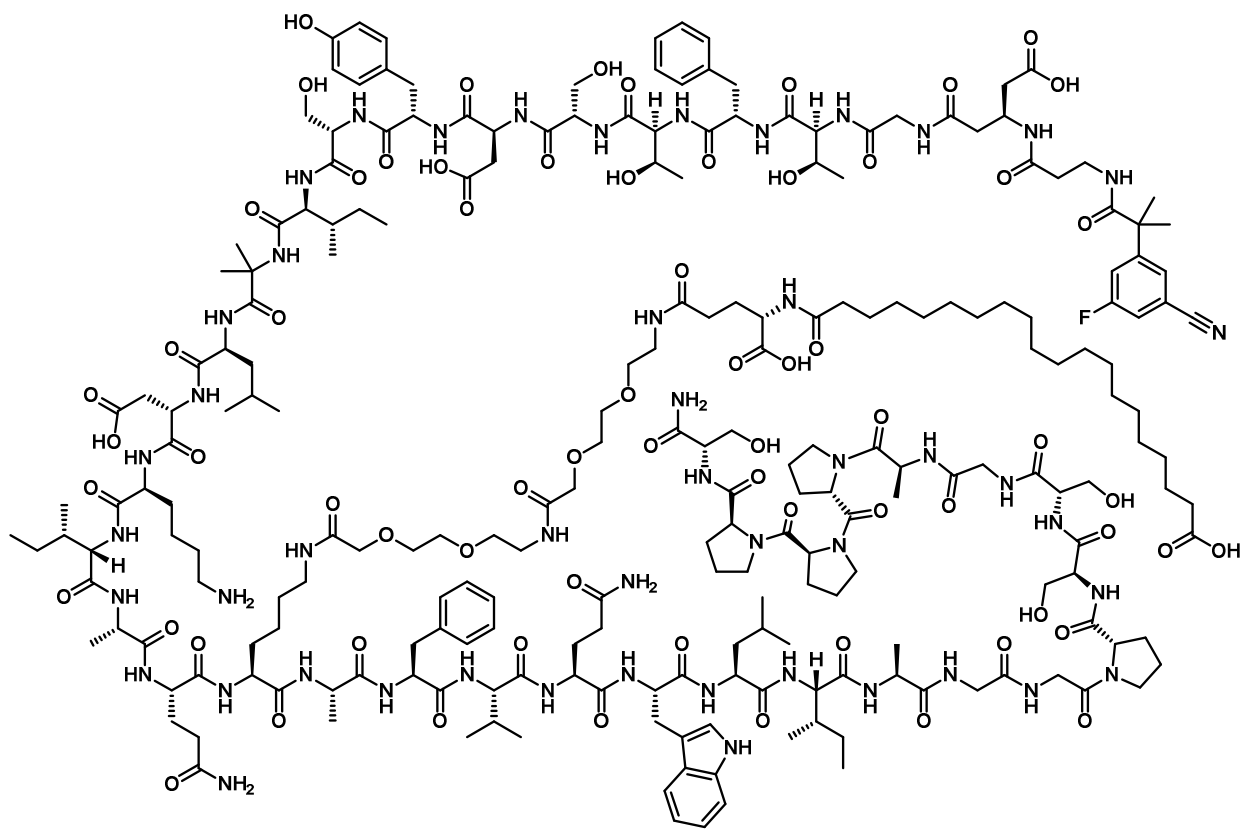
In one aspect, the present disclosure refers to a compound, or pharmaceutically
20 acceptable salt thereof, wherein the compound is selected from the group consisting of:

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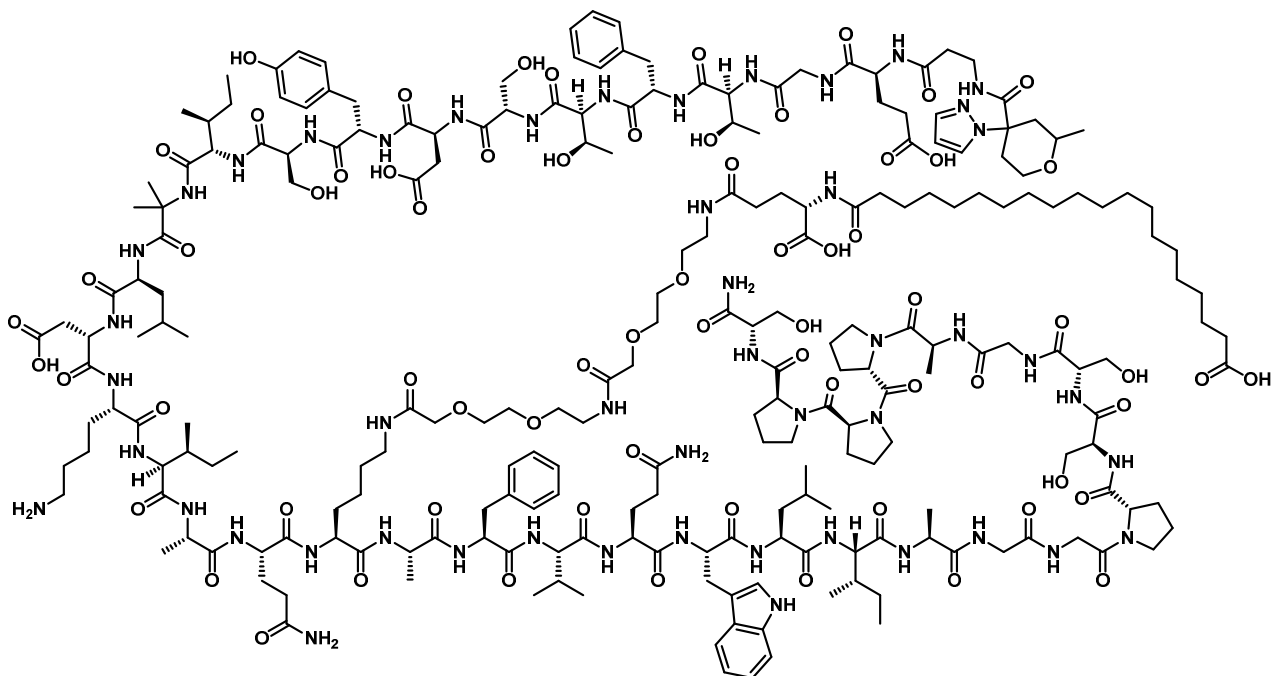
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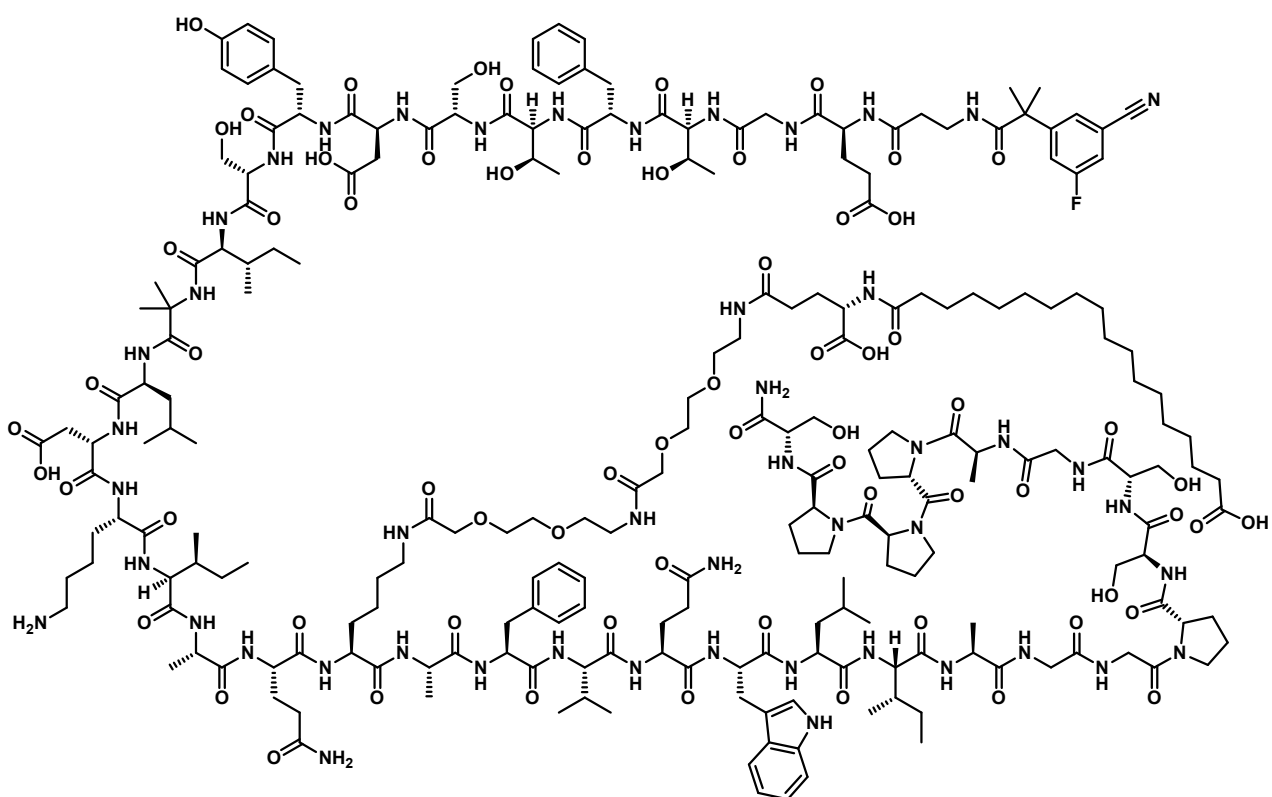
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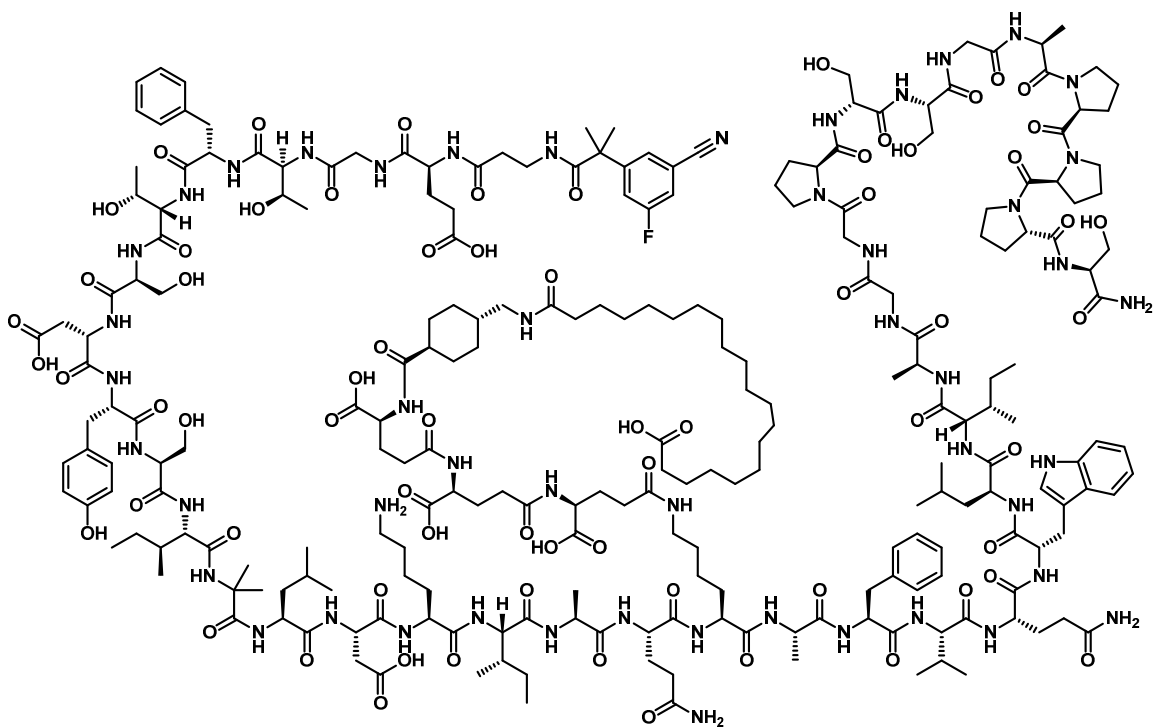
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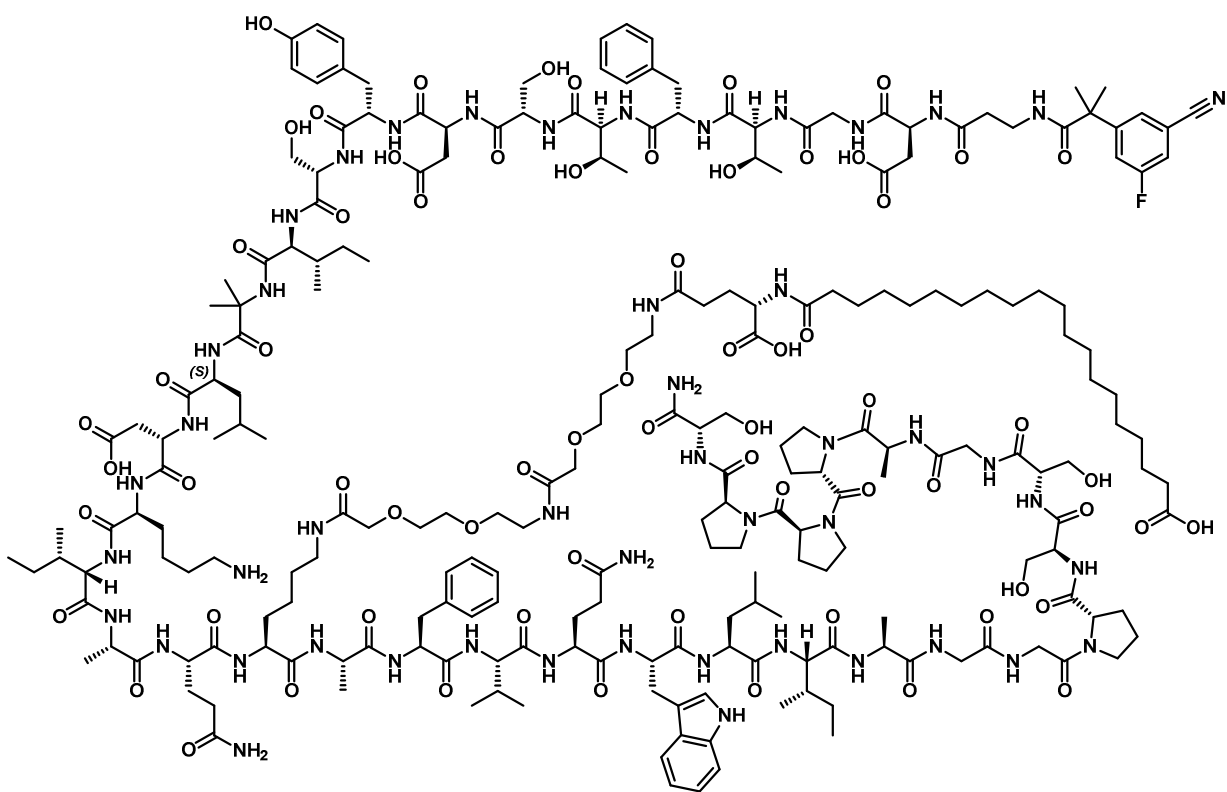
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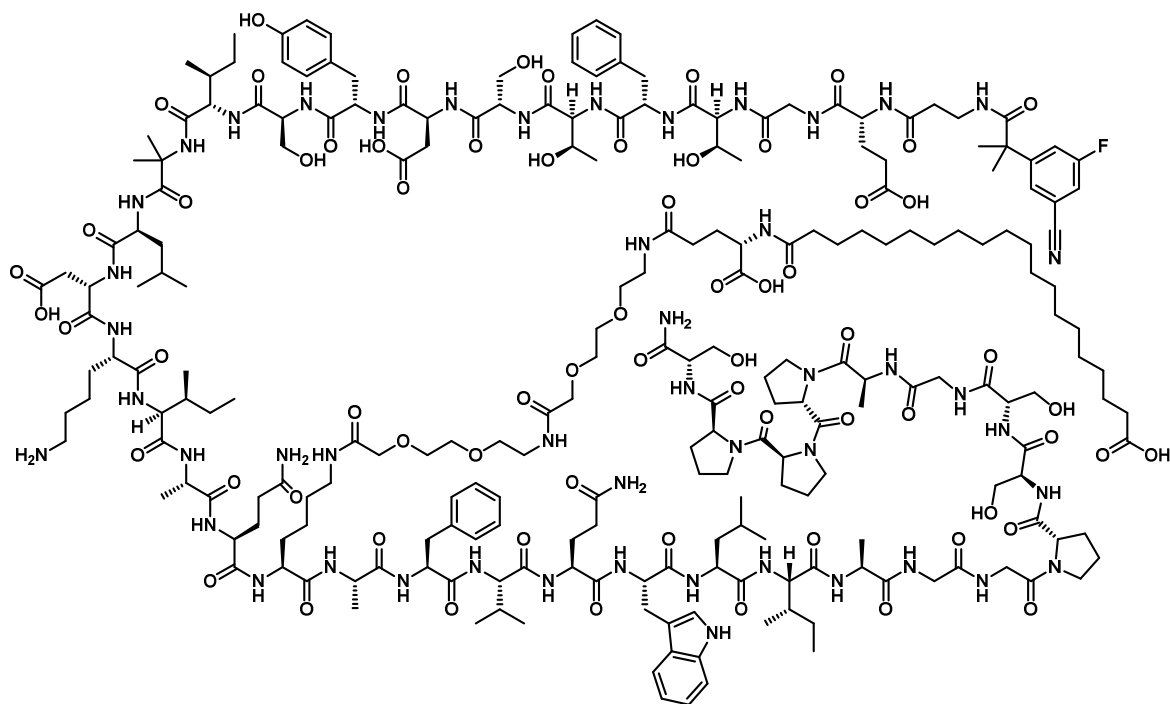
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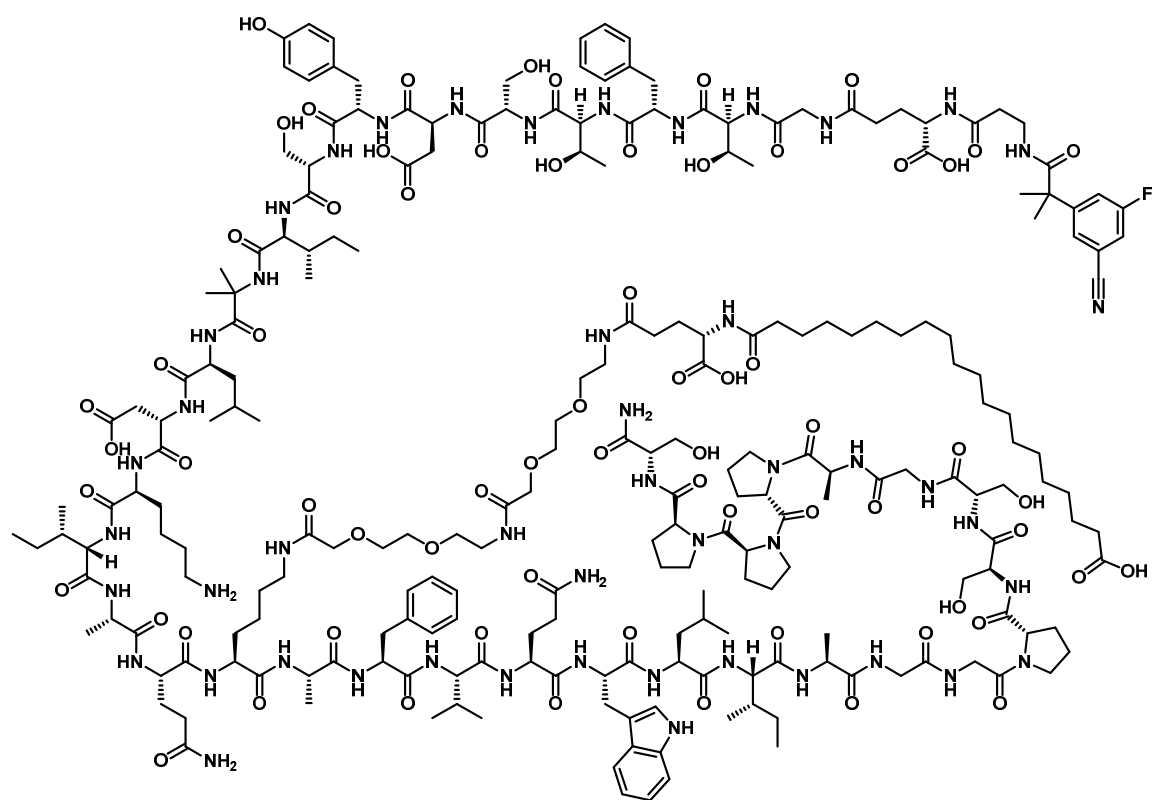
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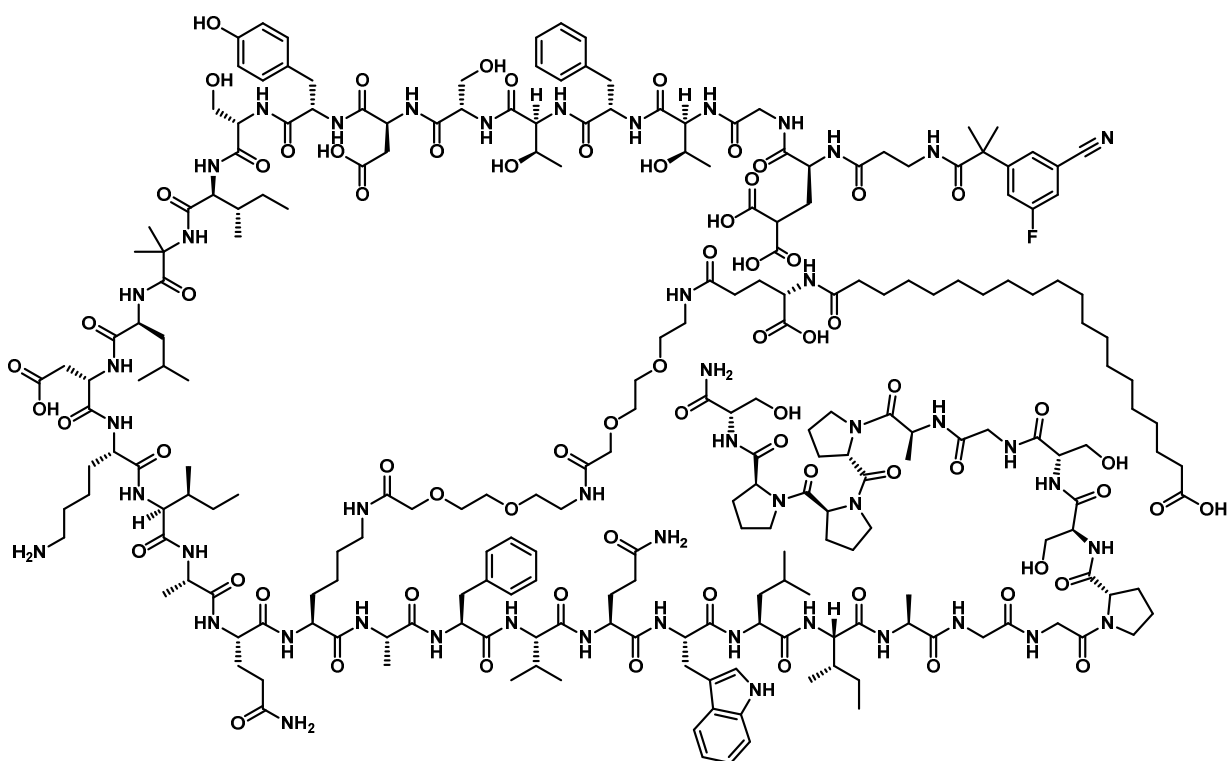
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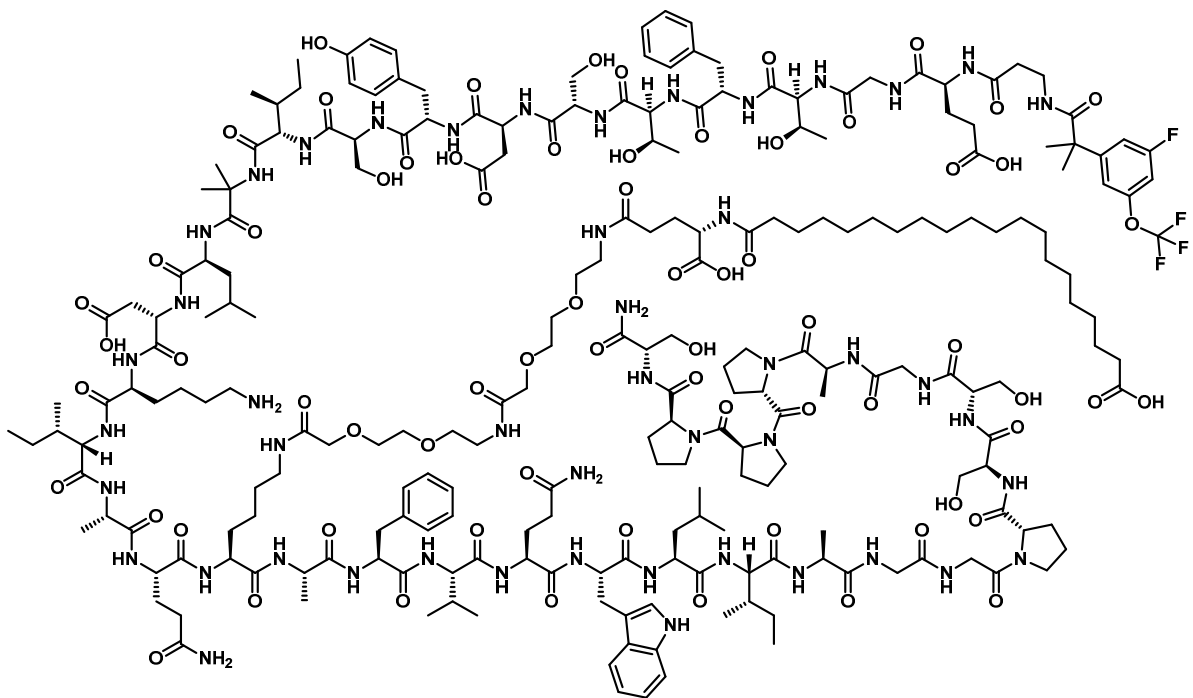
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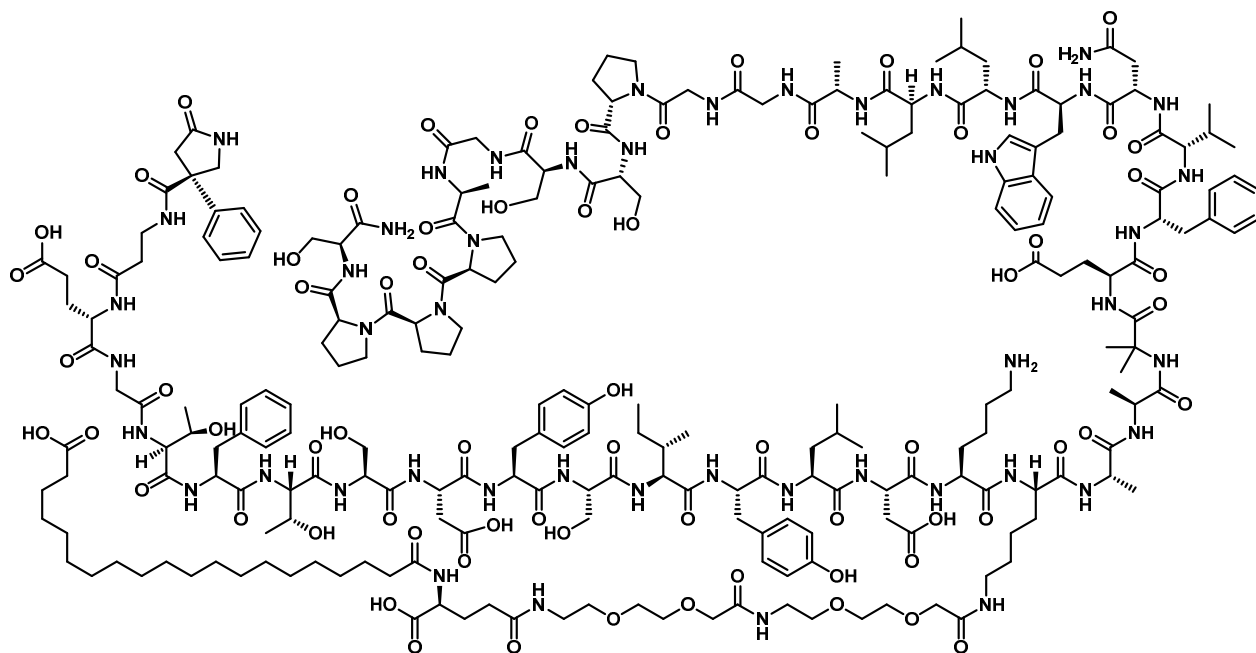
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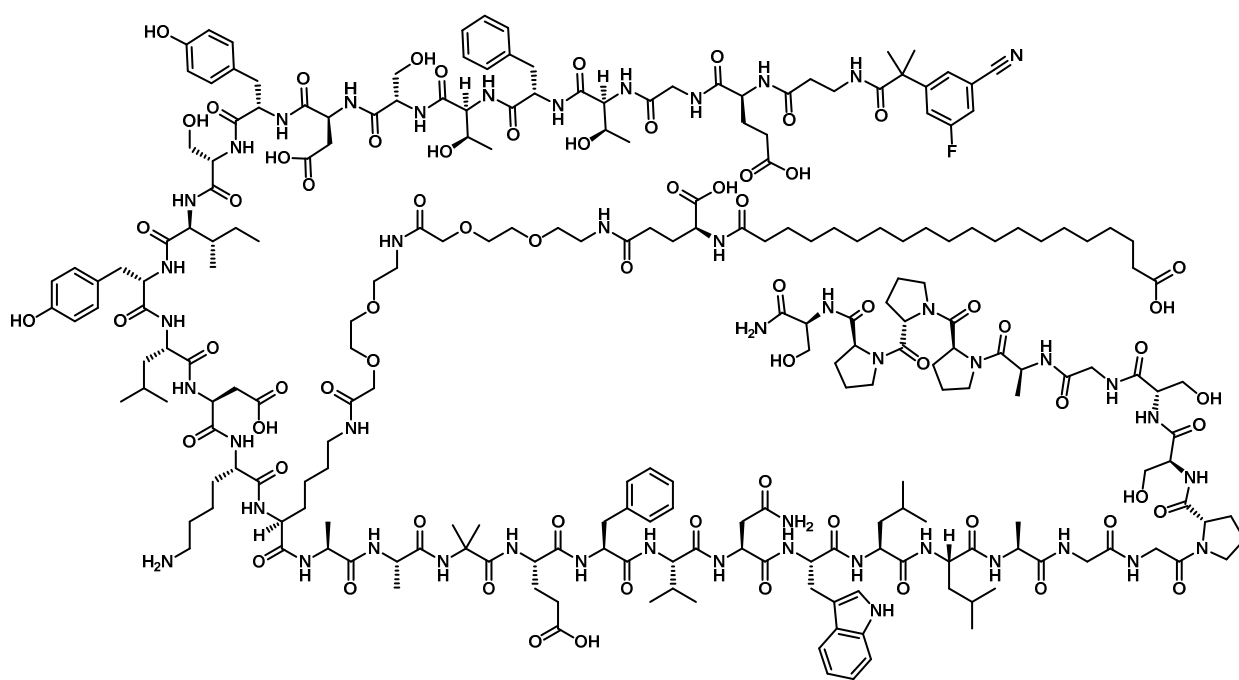
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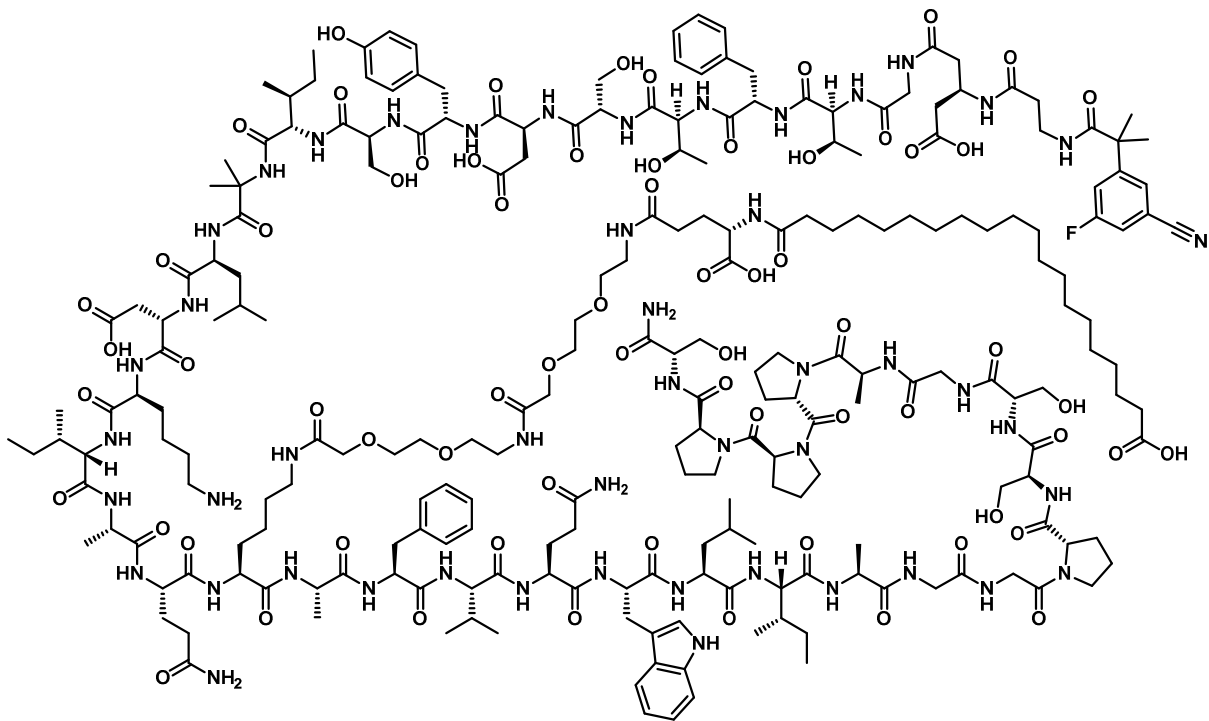
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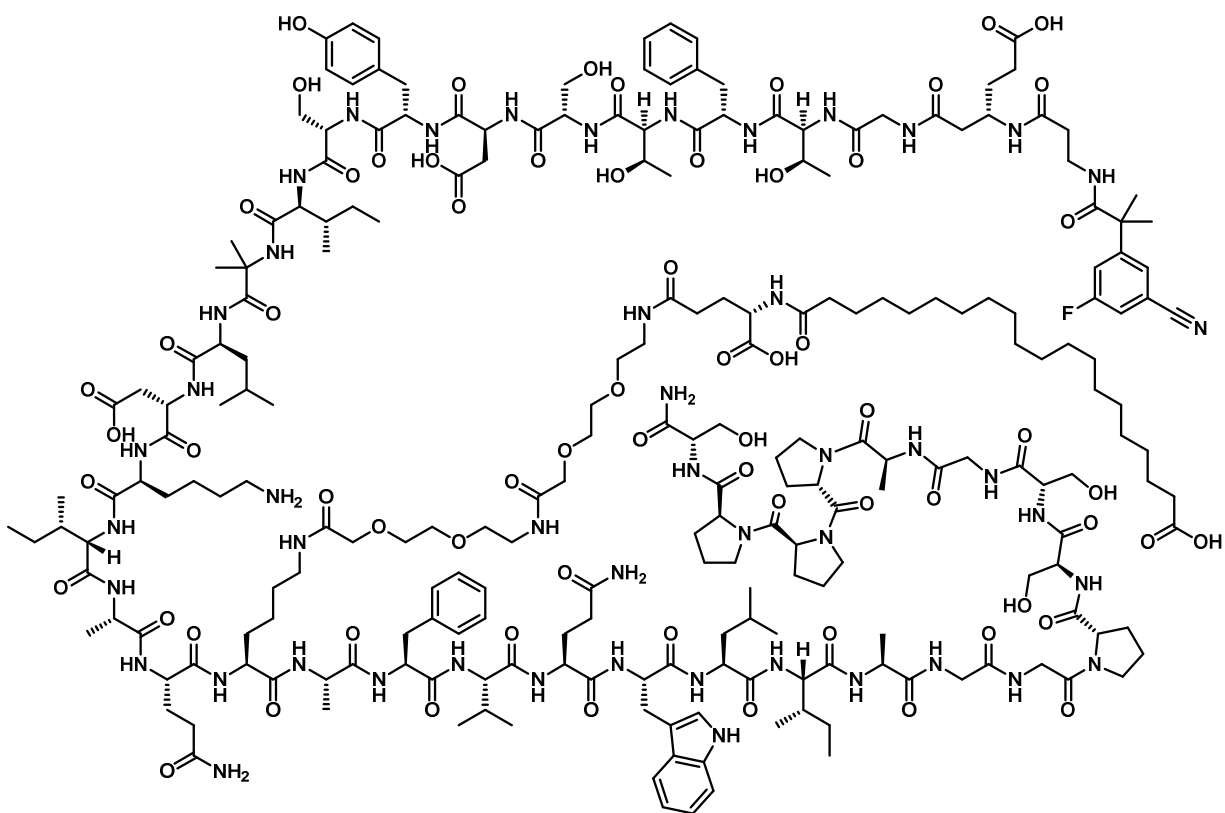
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Compound 114,



Compound 115,



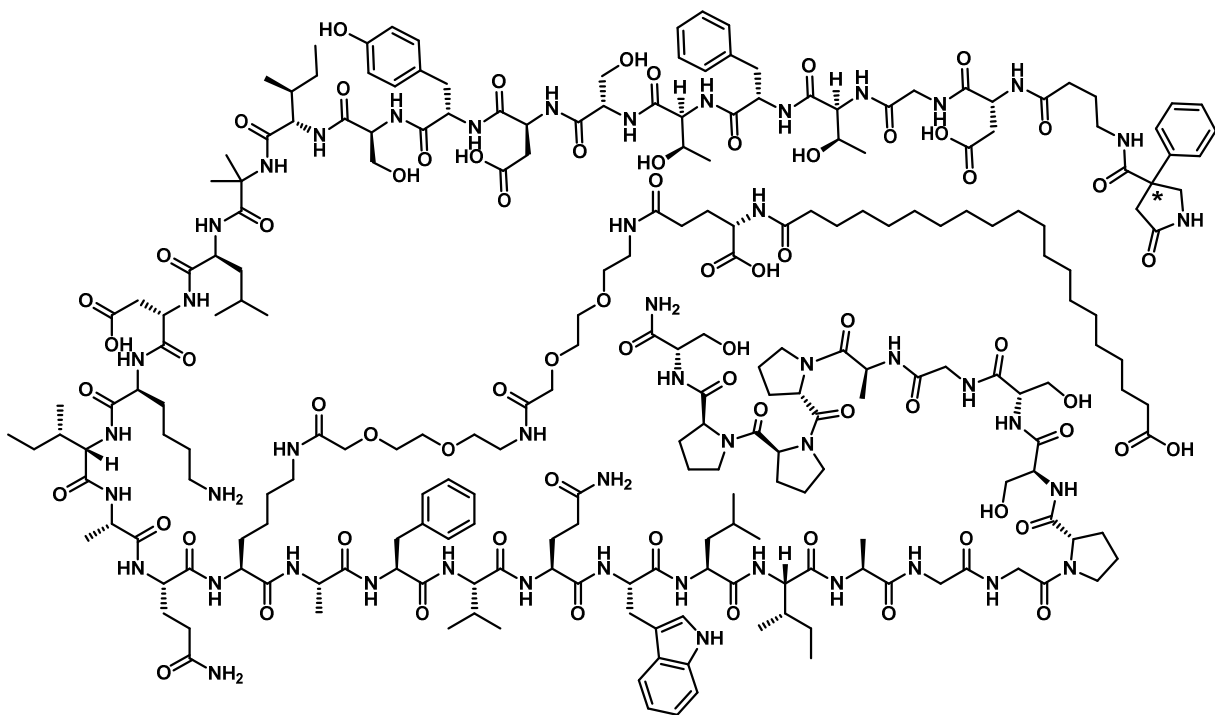
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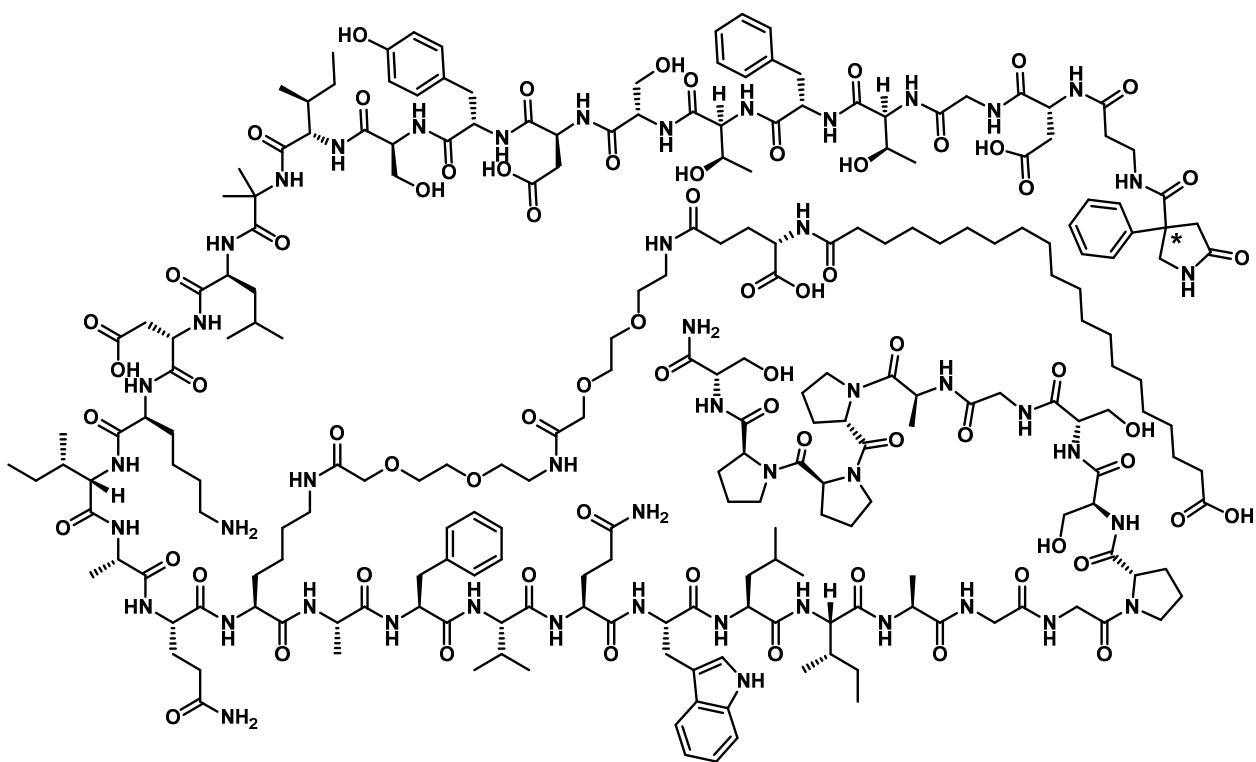
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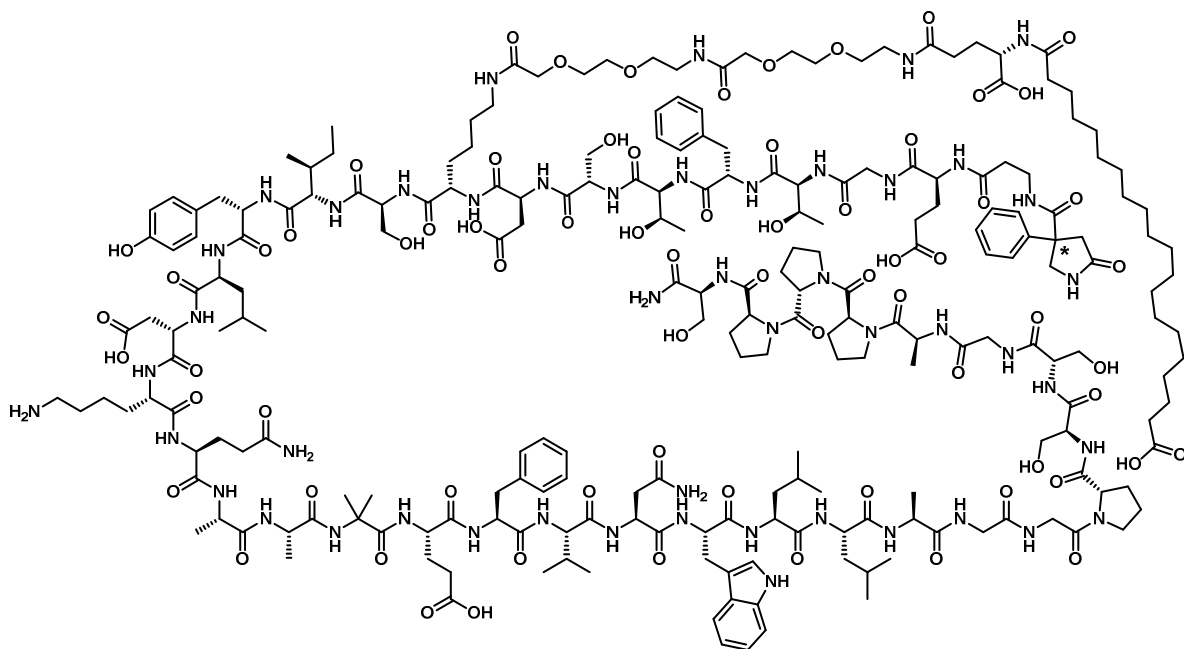
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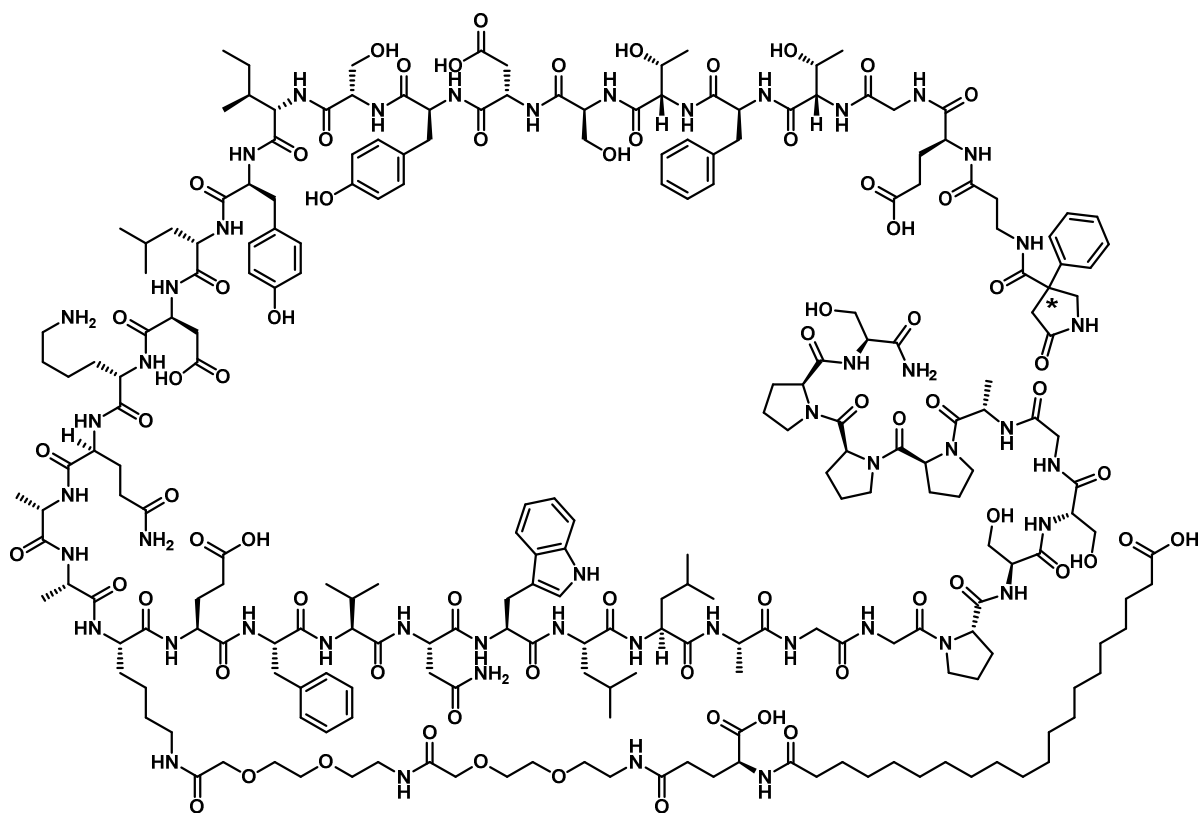
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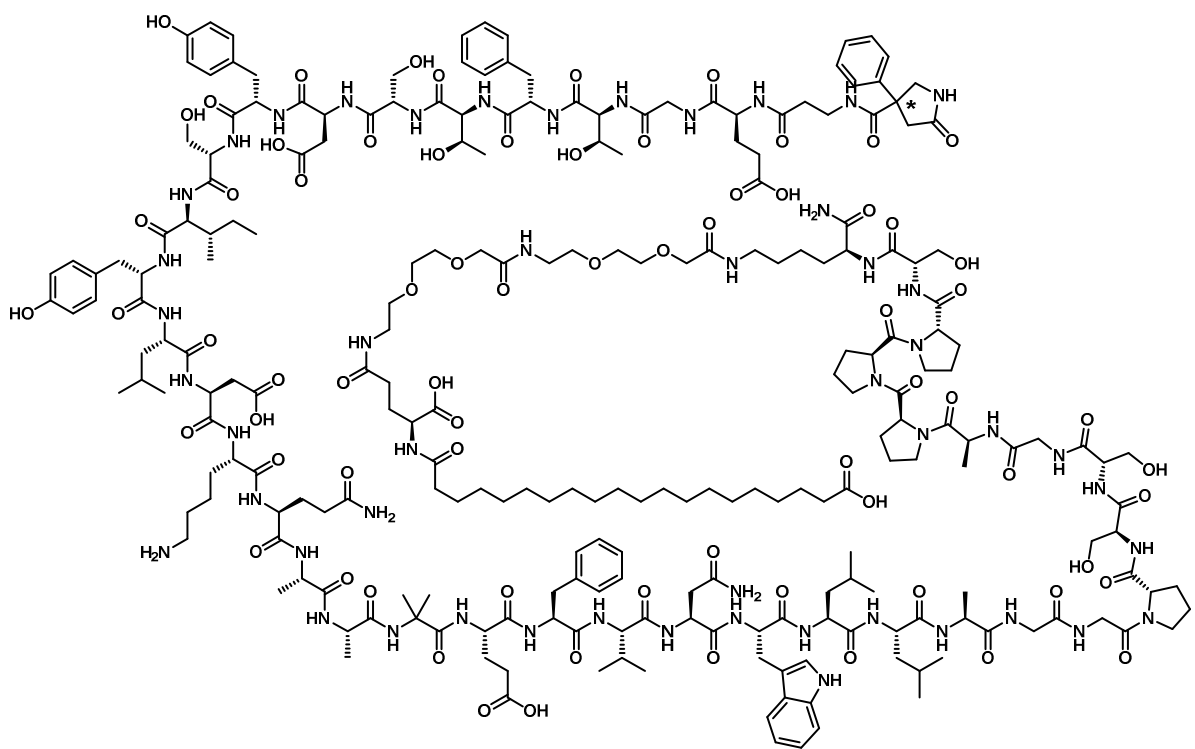
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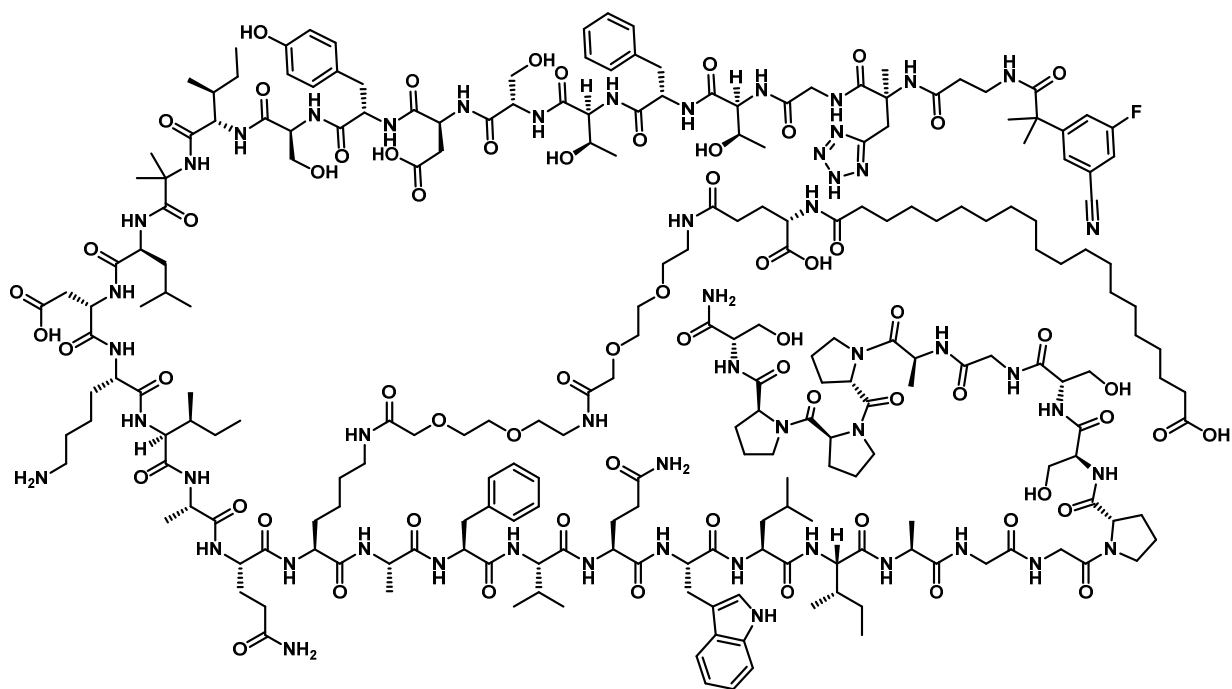
Compound 123,



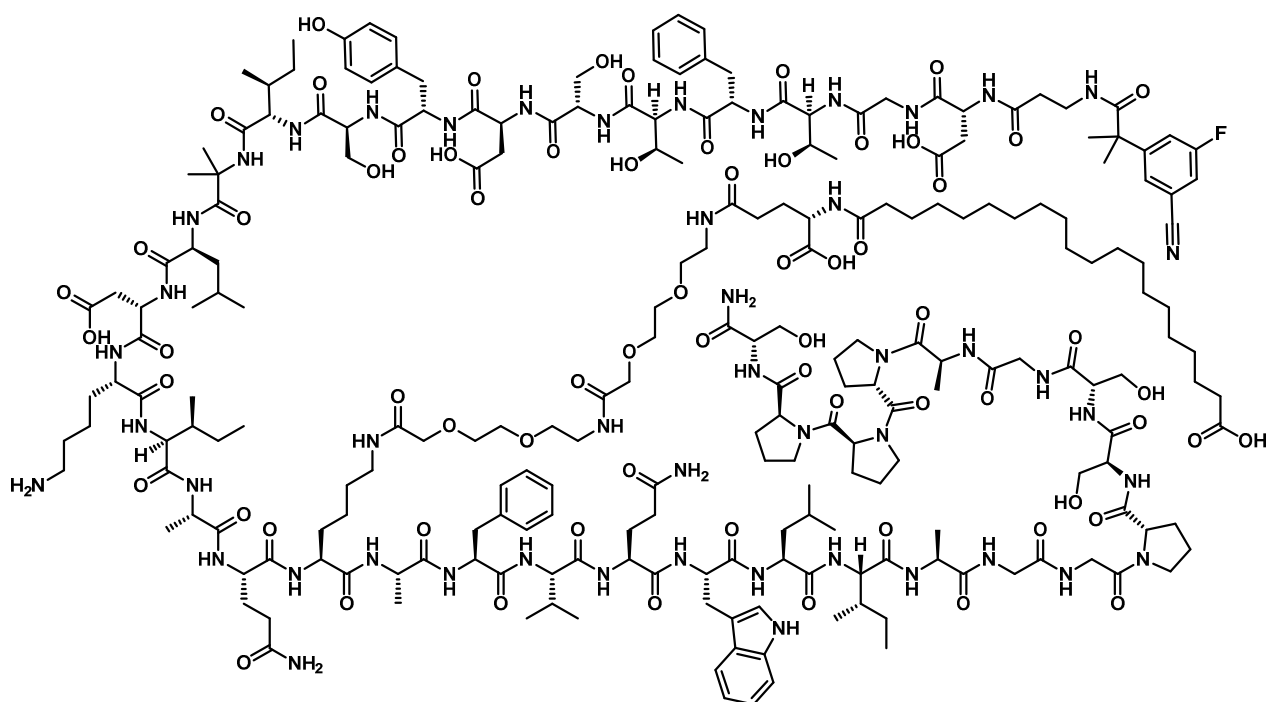
Compound 124,



Compound 125,

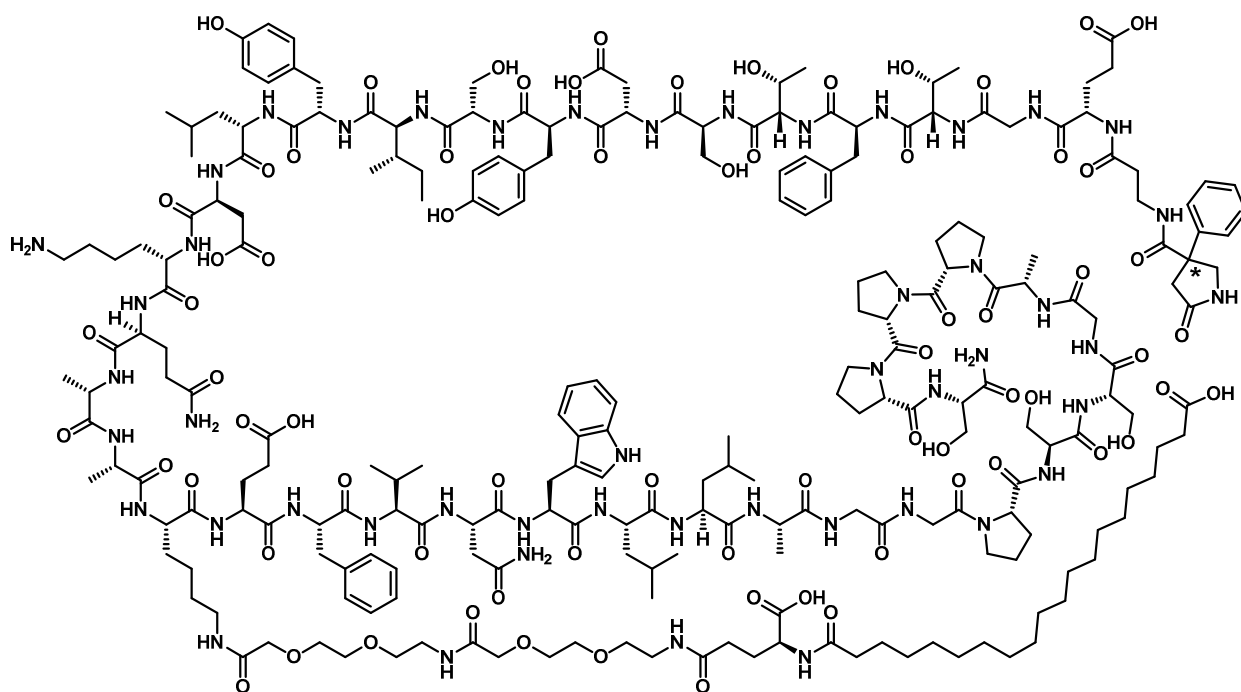


Compound 126,

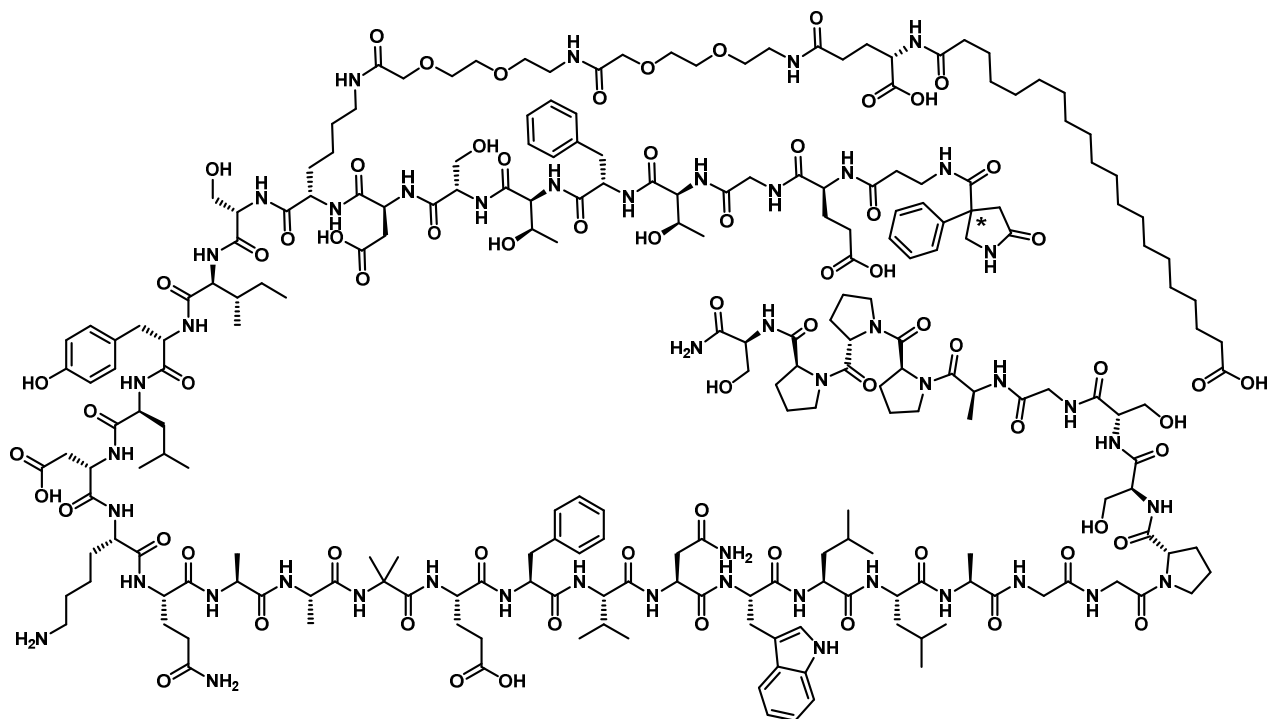


Compound 127,

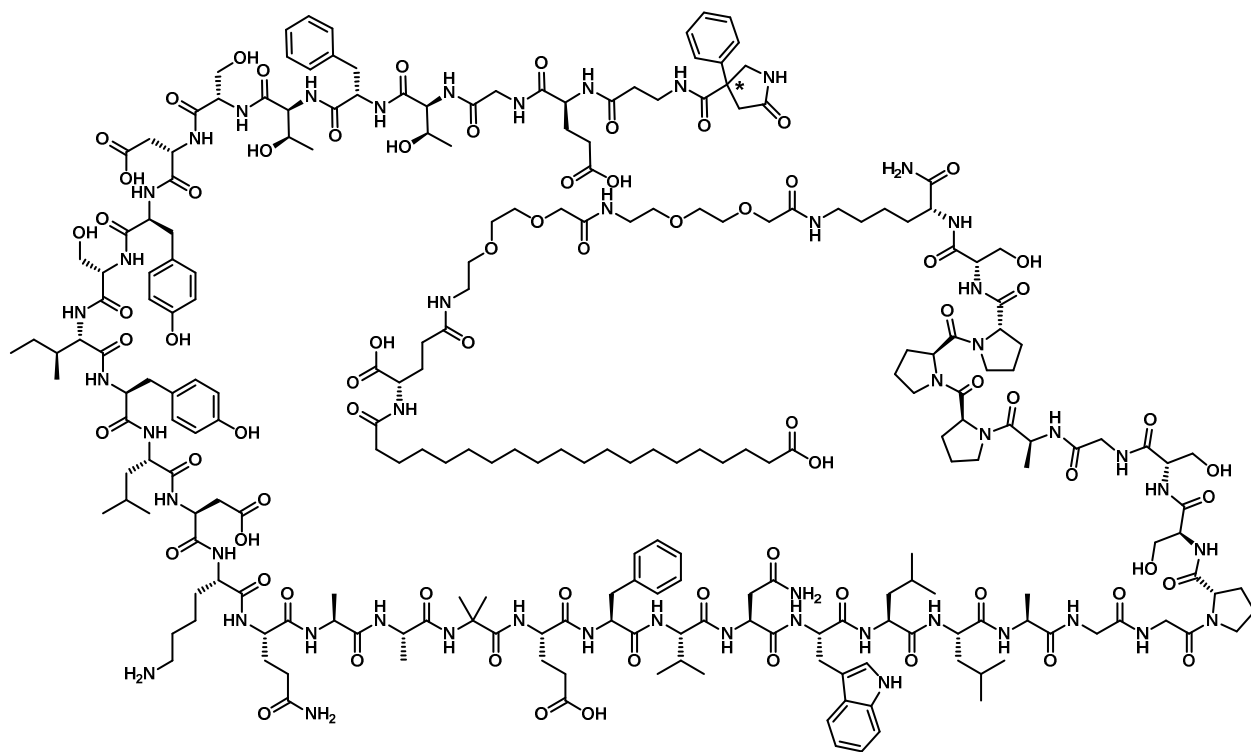
5



Compound 128,



Compound 129,



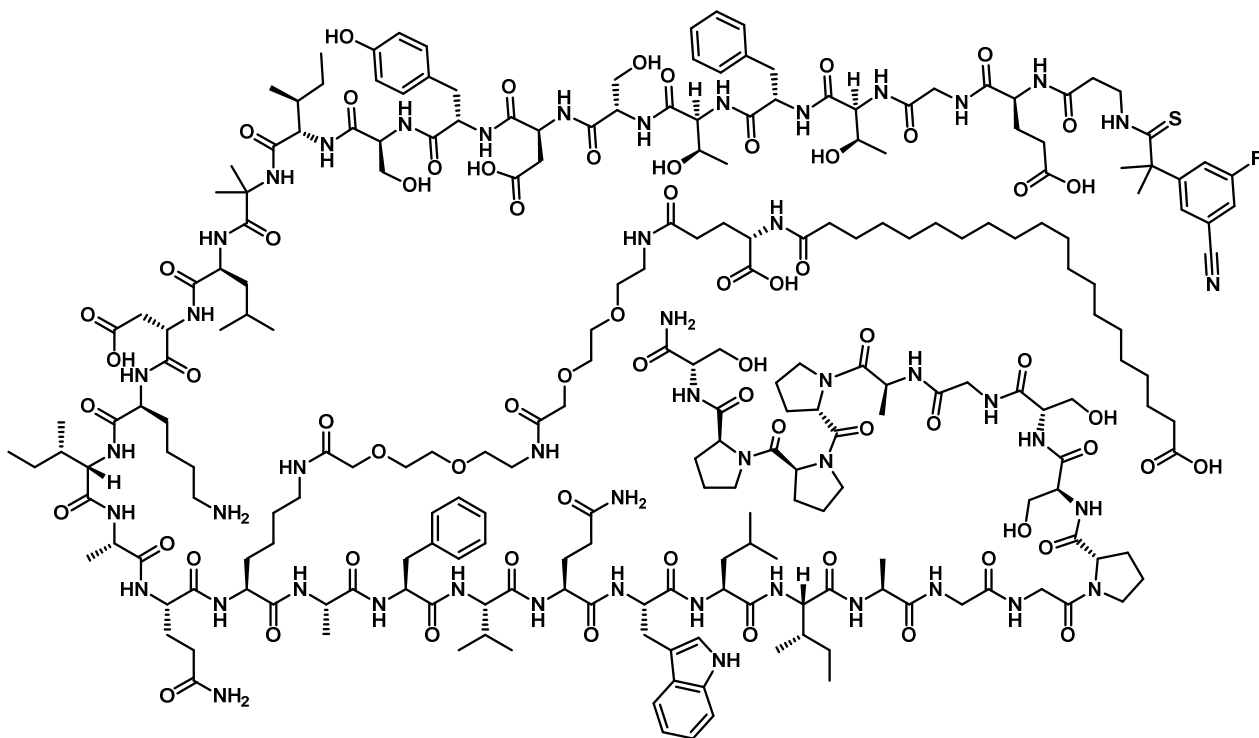
Compound 130,

[illegible]

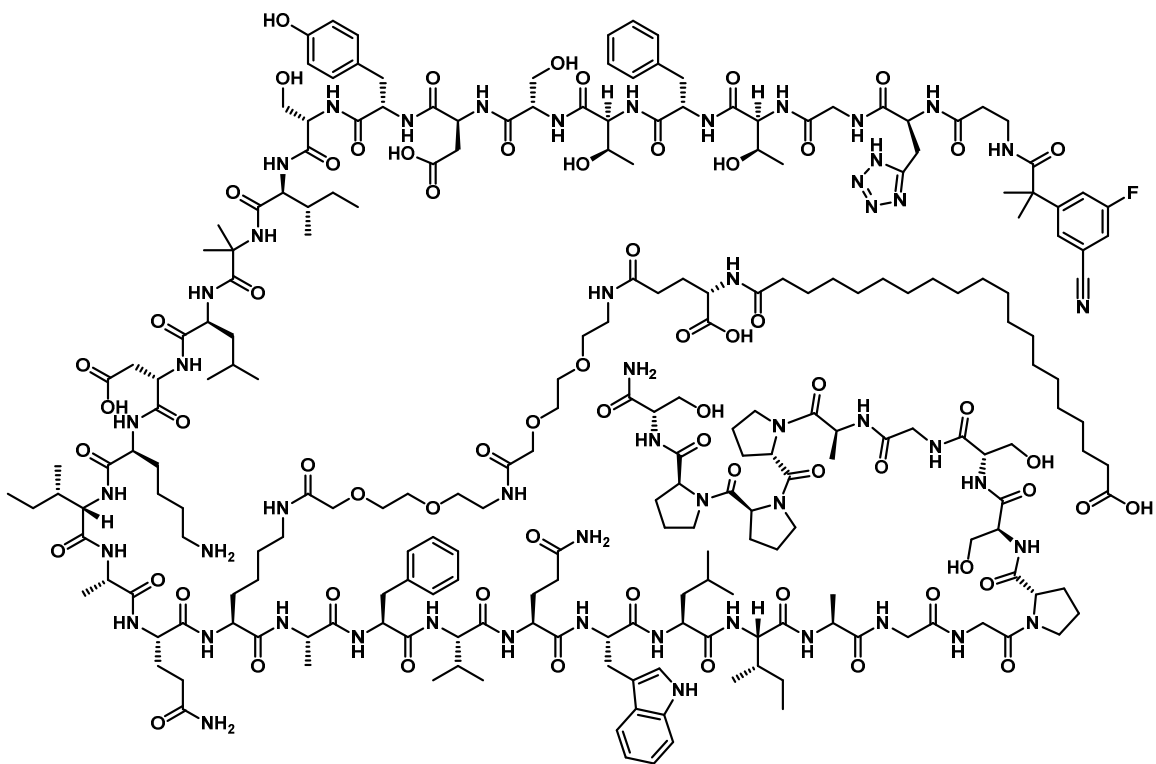
Compound 132,

[illegible]

Compound 134,



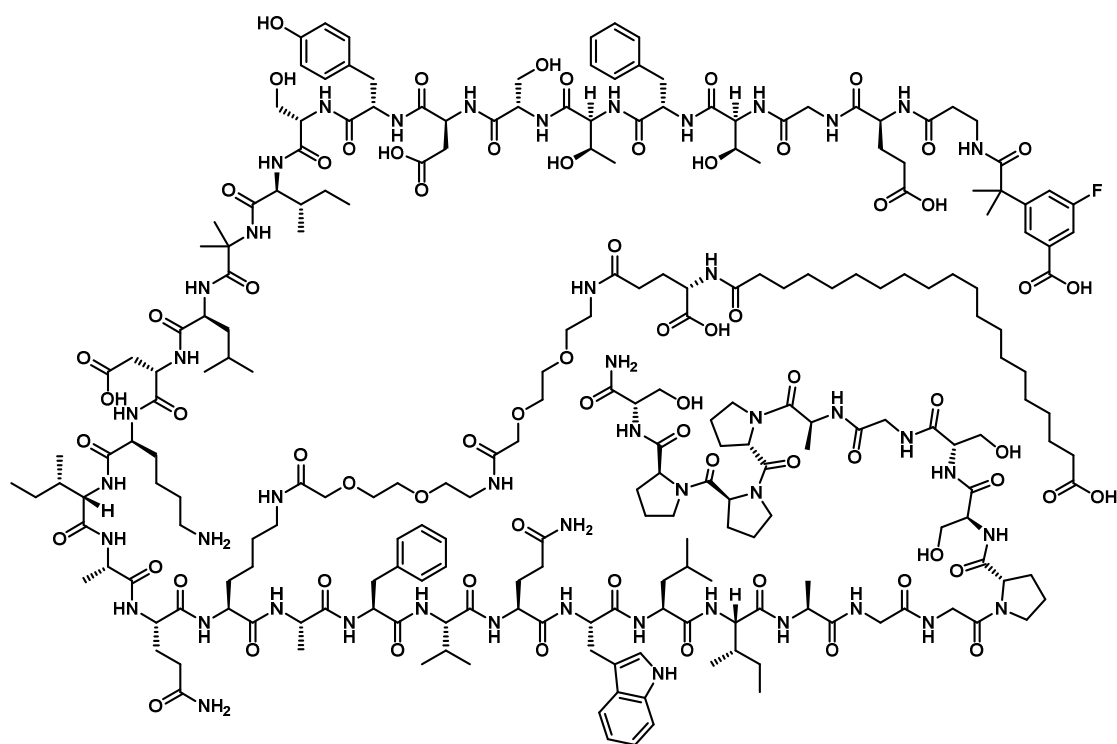
Compound 135,

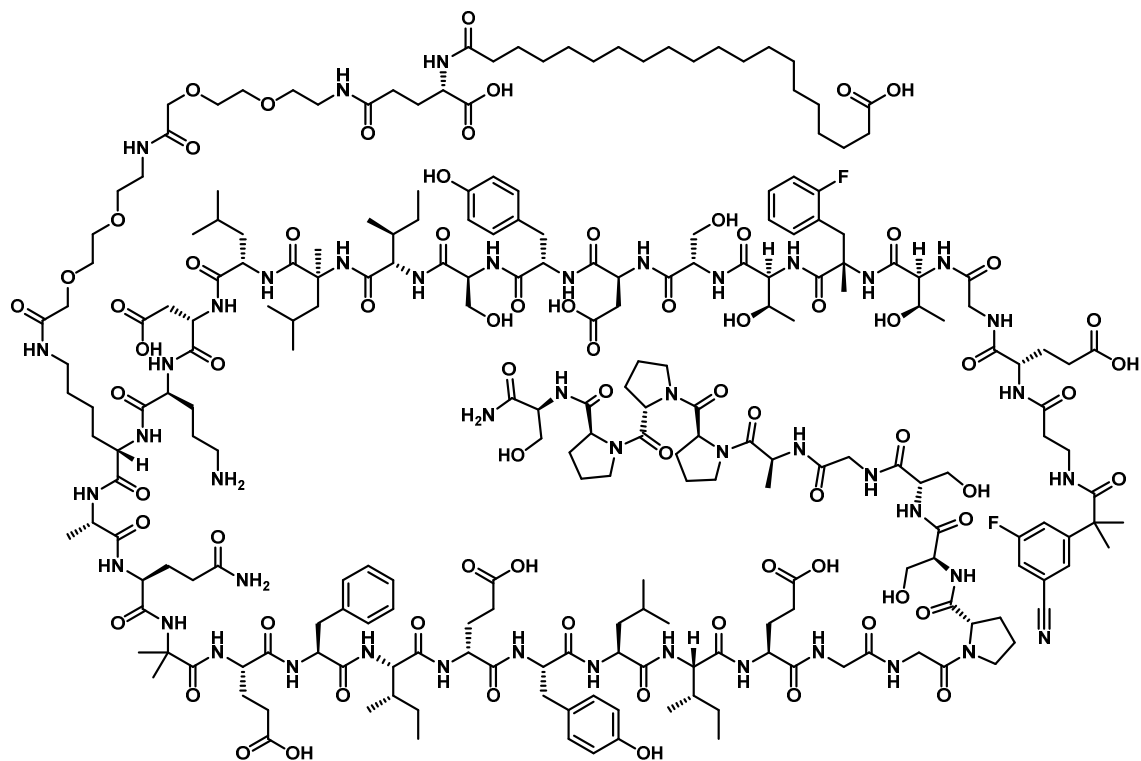


Compound 136,

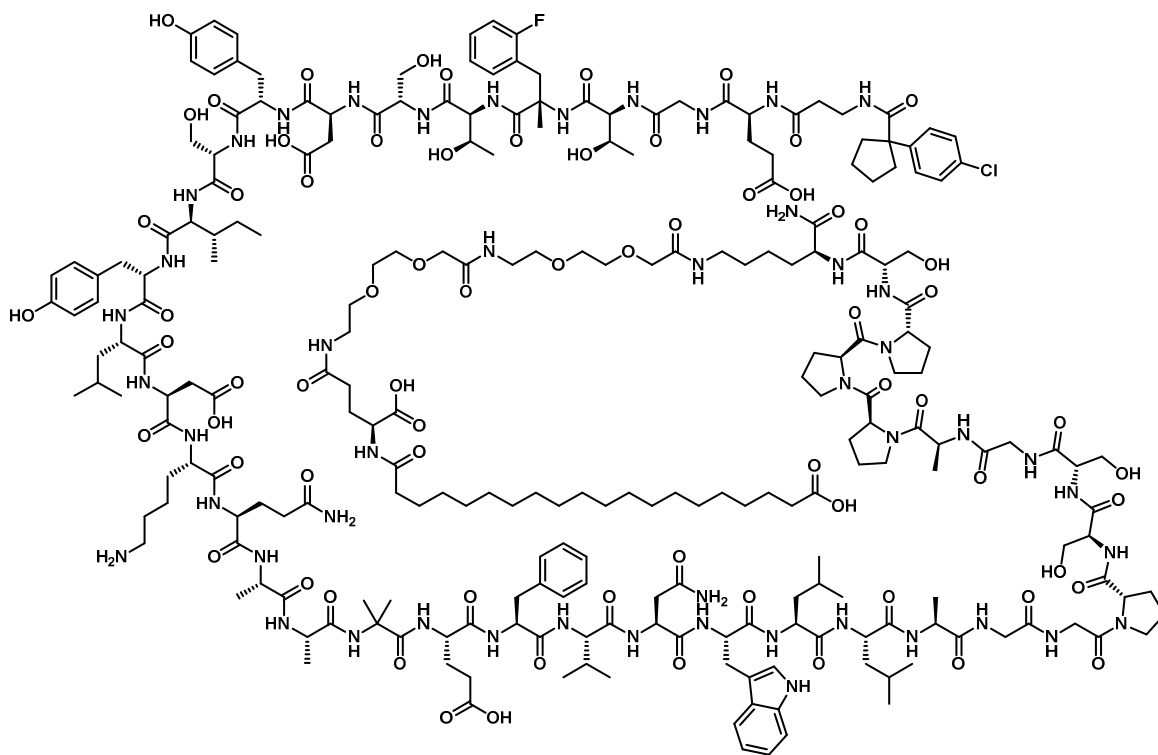
[illegible]

Compound 138,



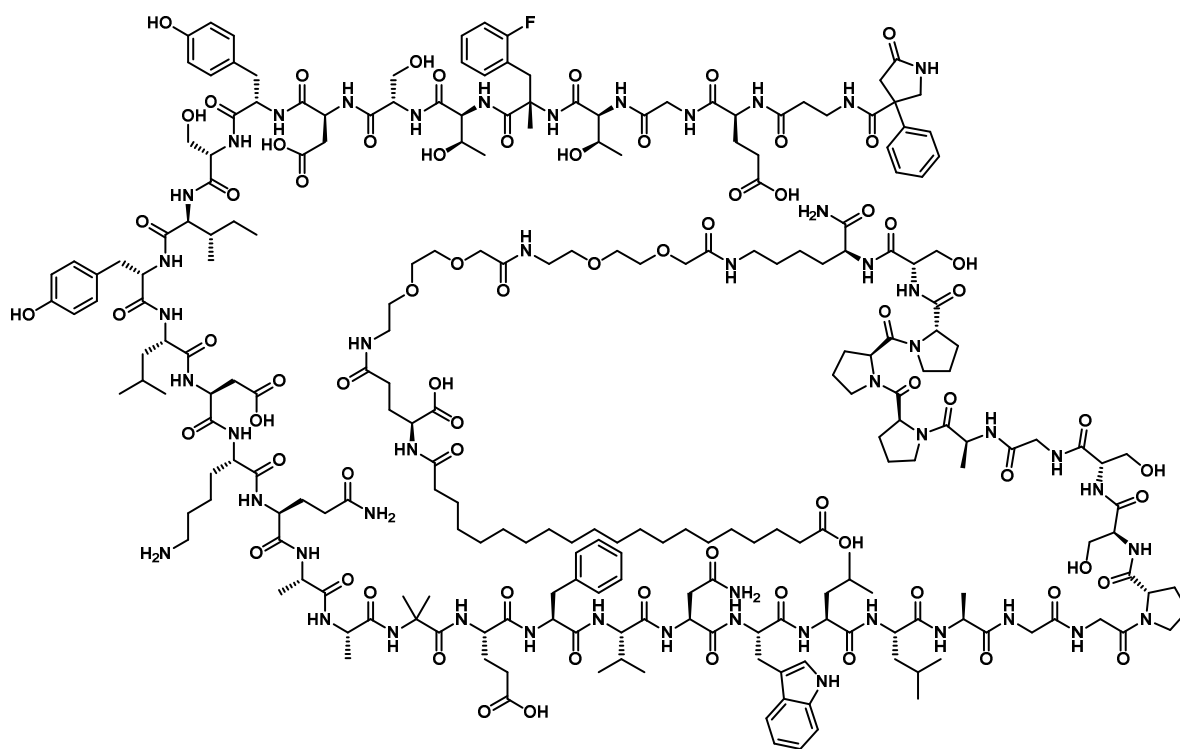


Compound 140,

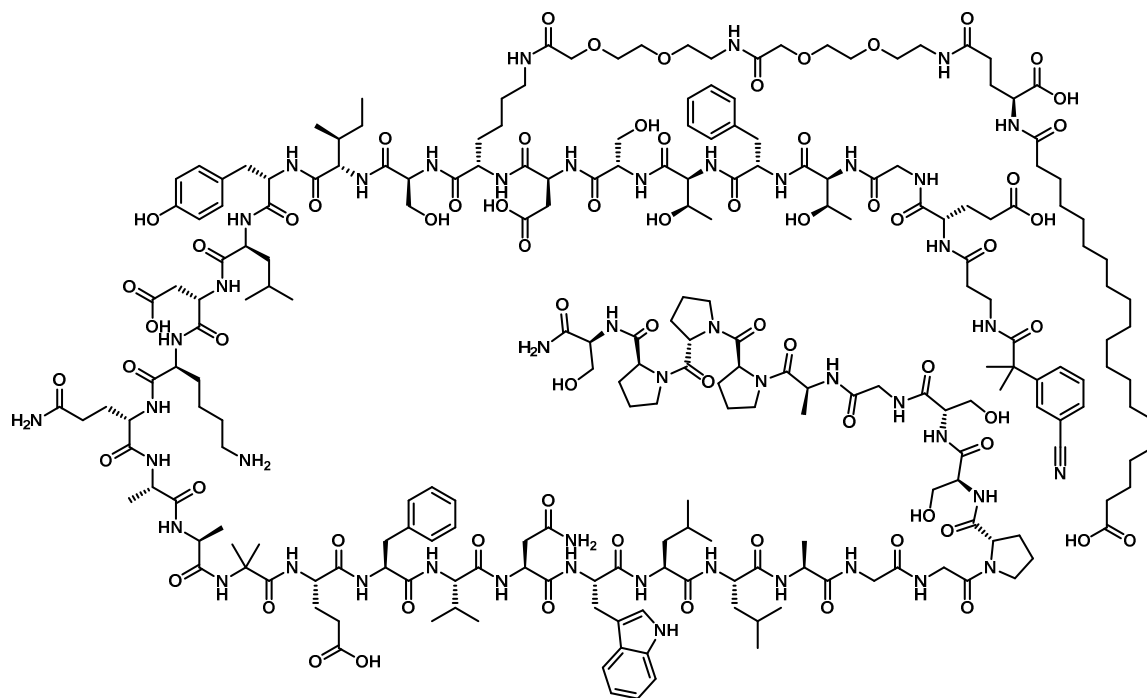


Compound 141,

8aa

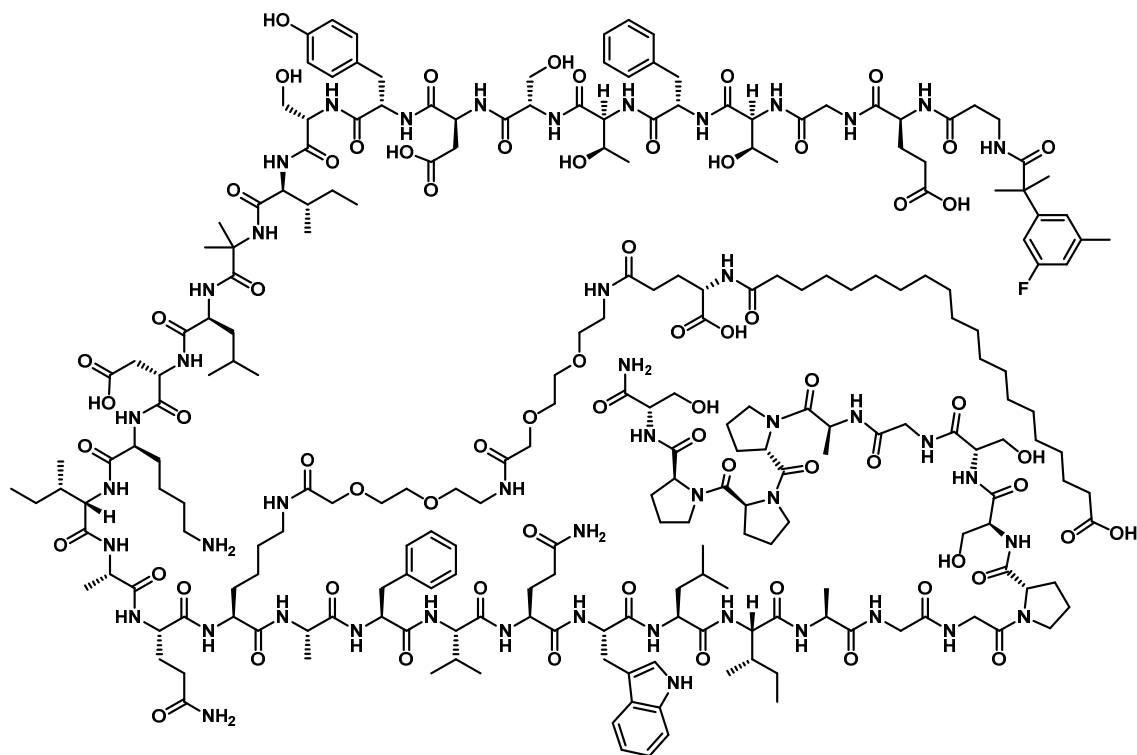


Compound 142,

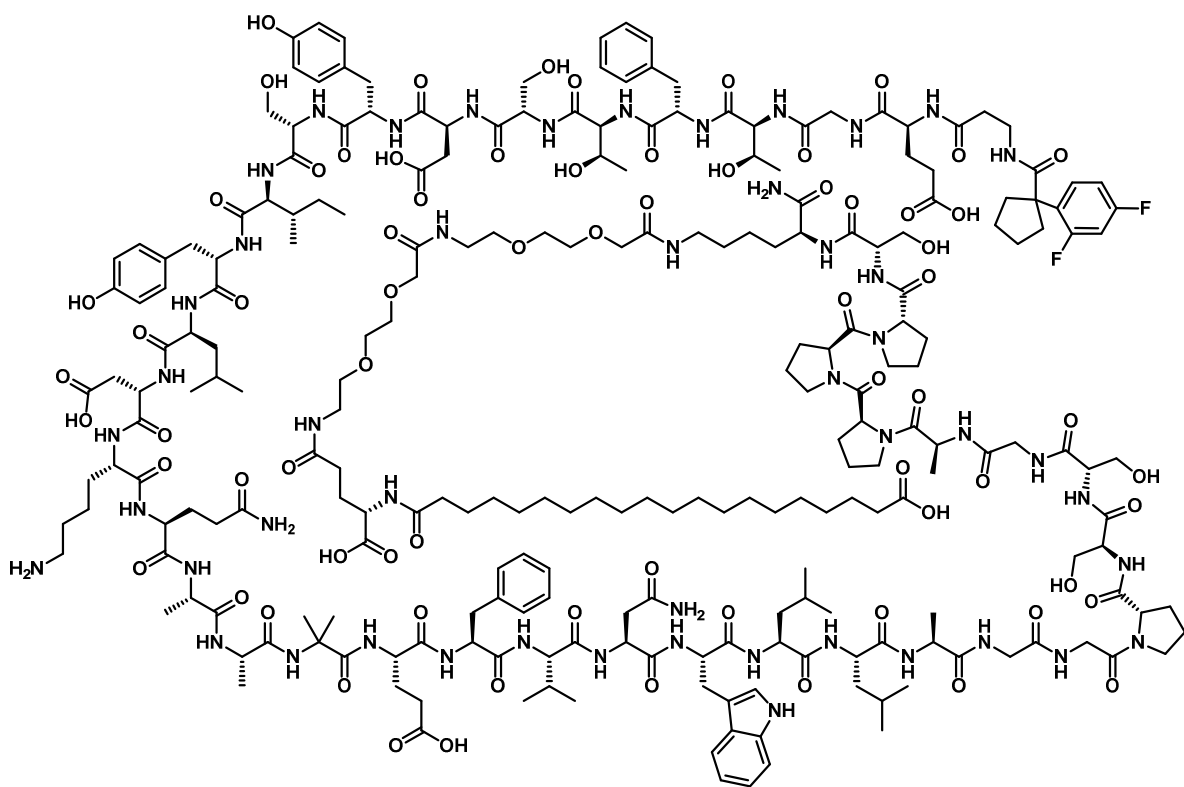


Compound 143,

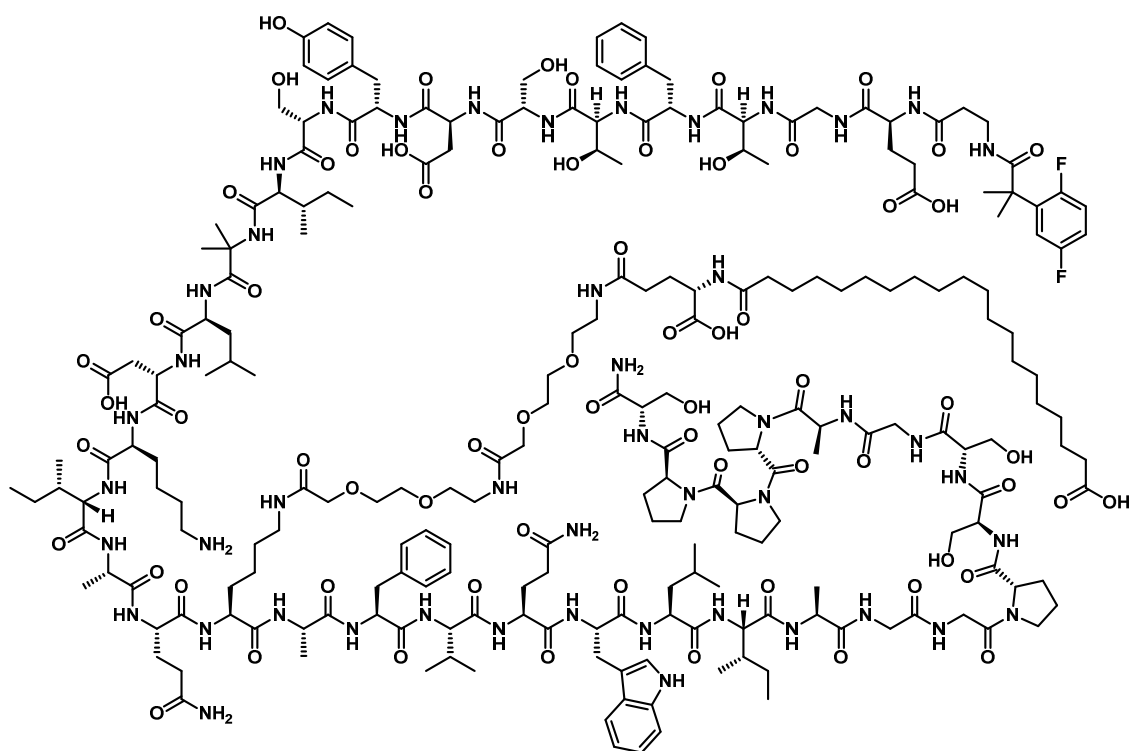
8bb



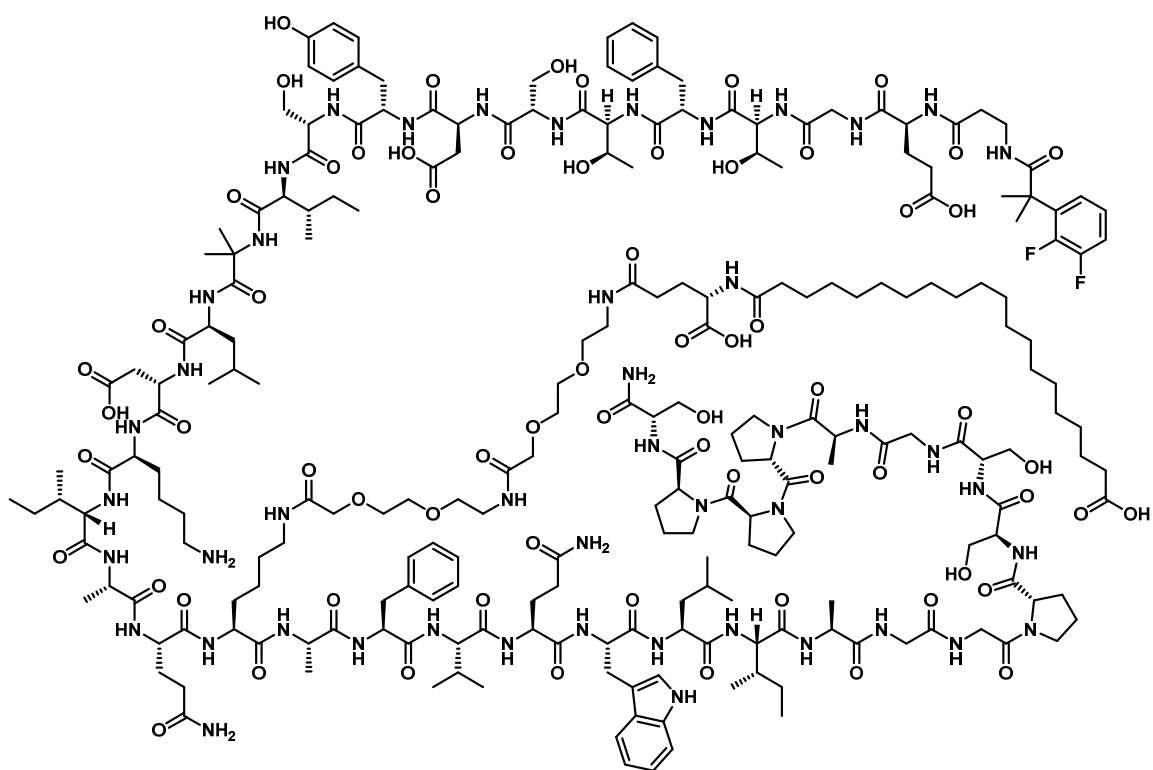
Compound 144,



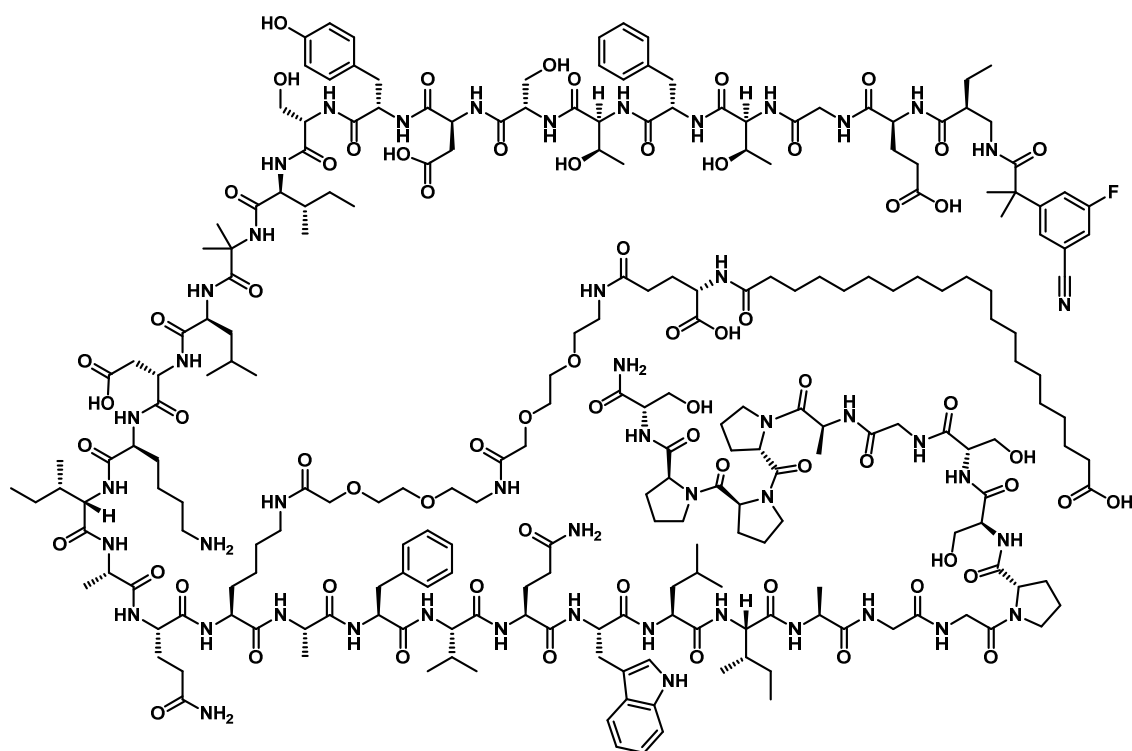
Compound 145,



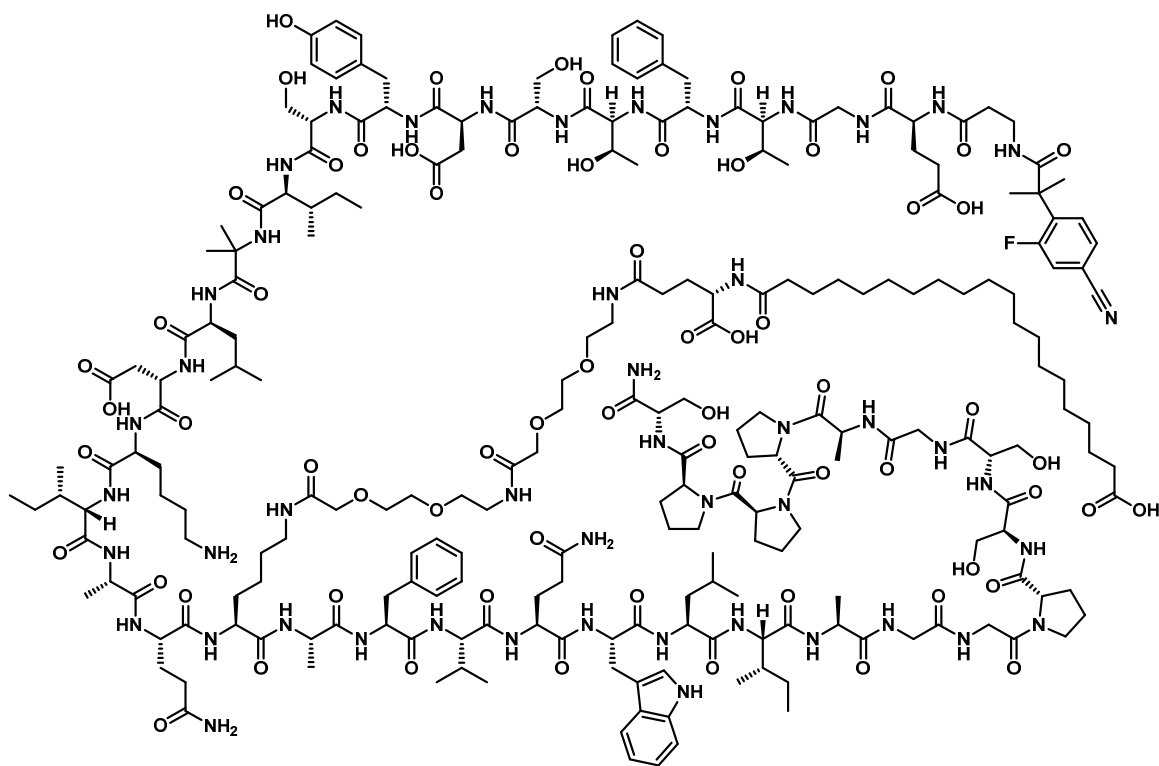
Compound 146,



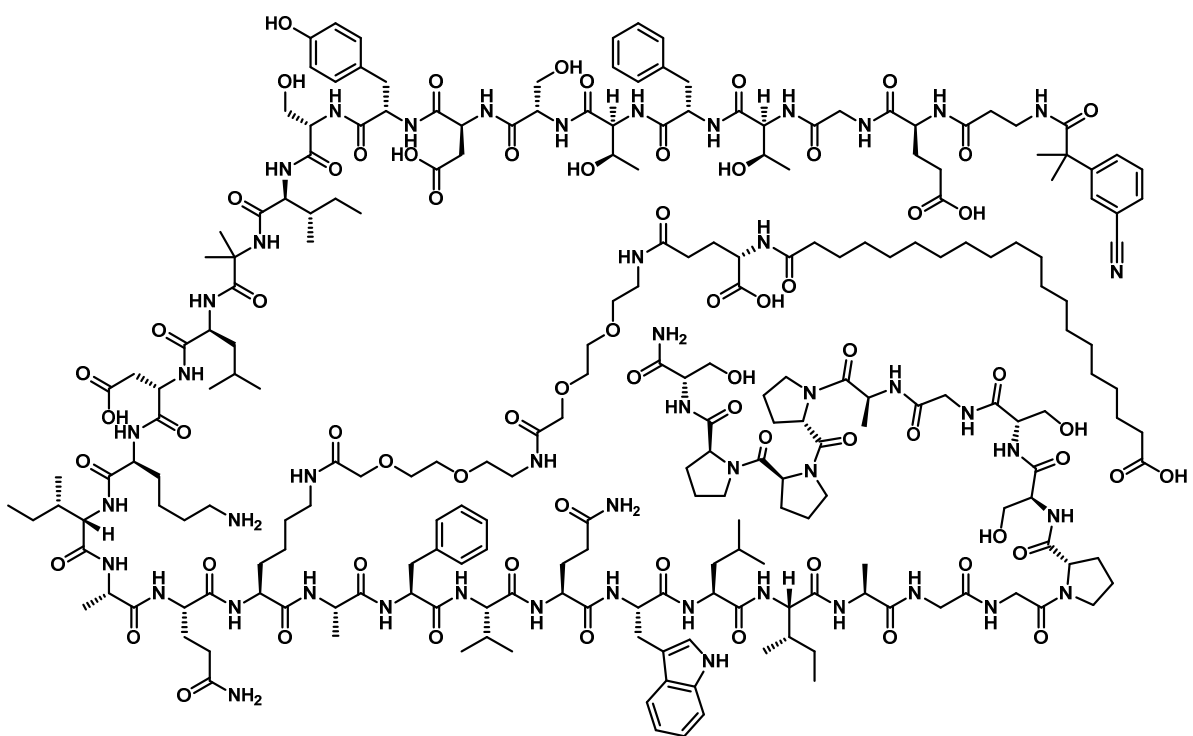
Compound 147,



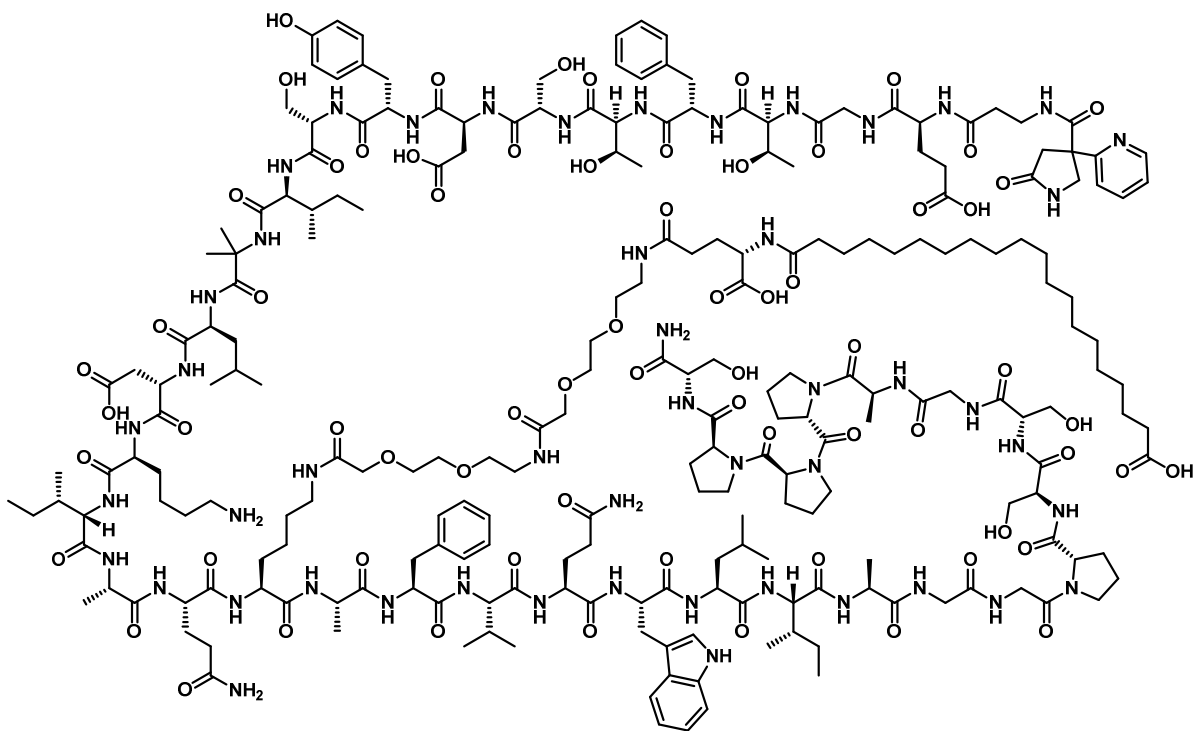
Compound 148,



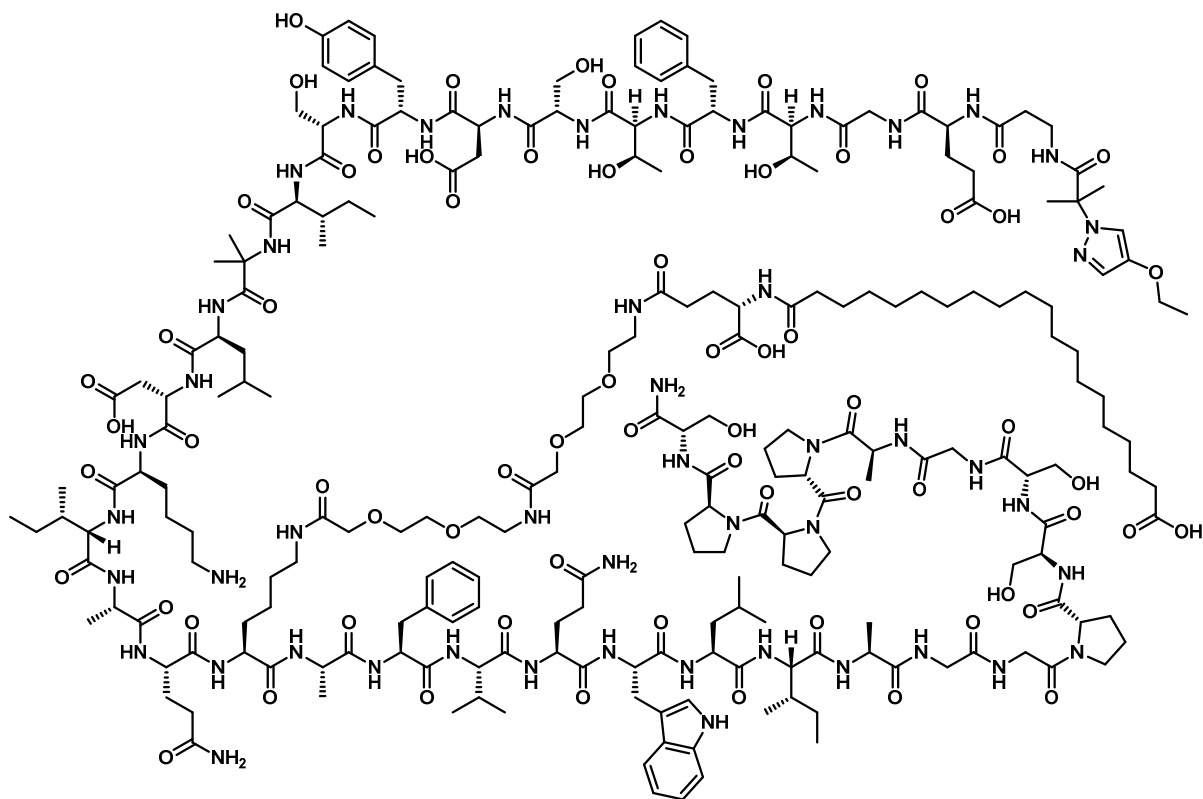
Compound 149,



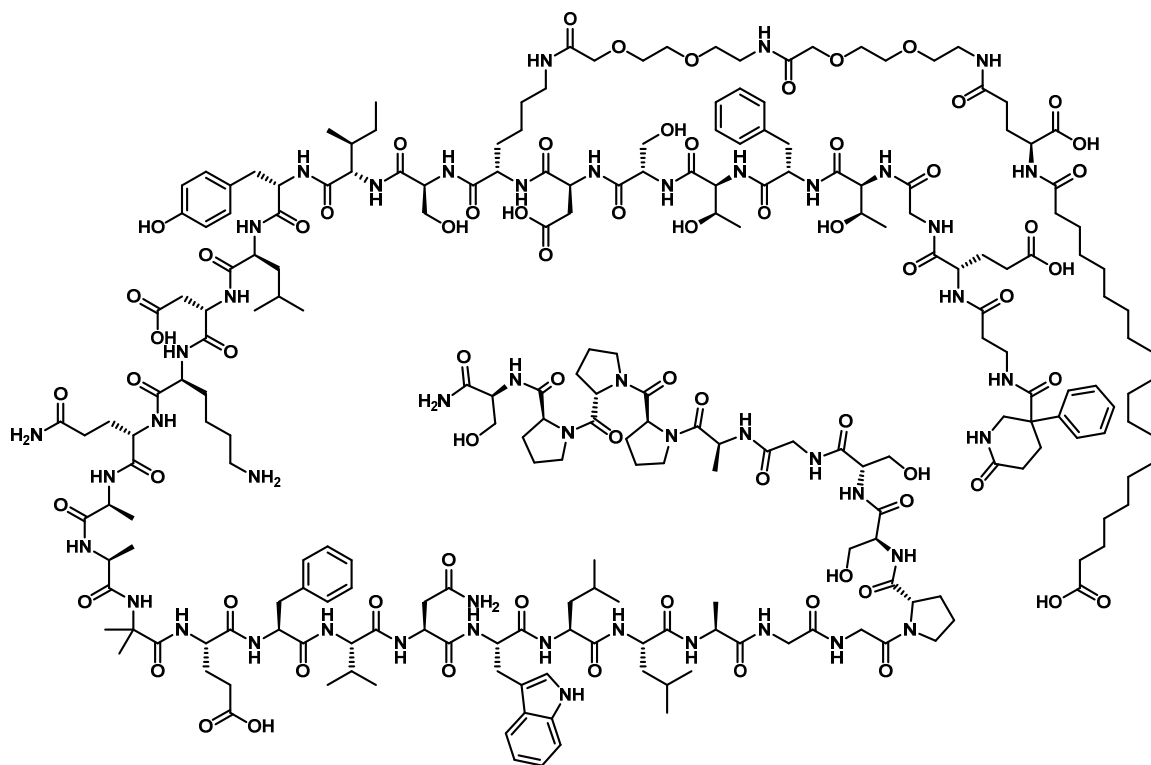
Compound 150,



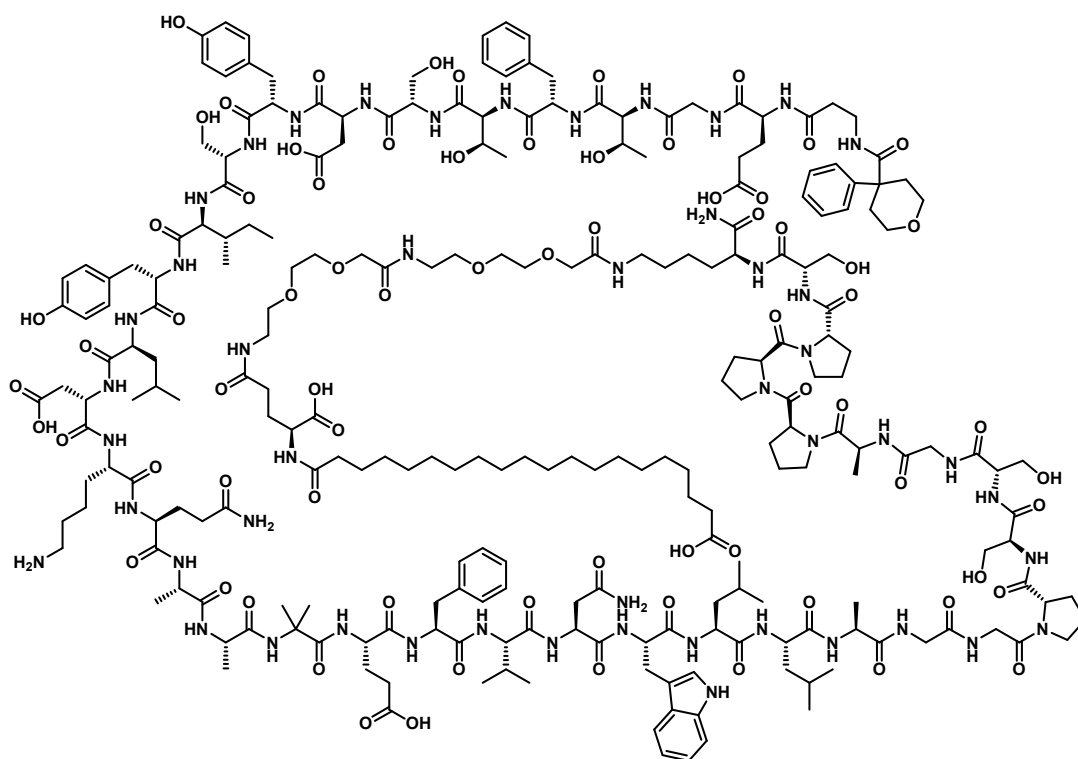
Compound 151,



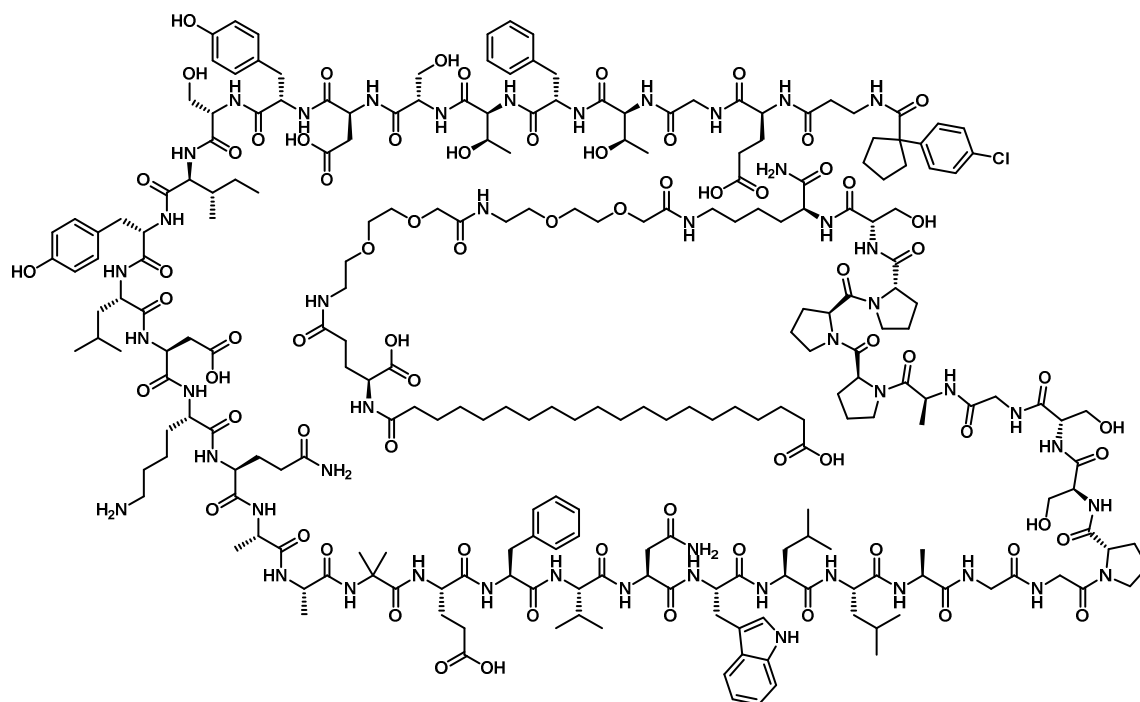
Compound 152,



Compound 153,

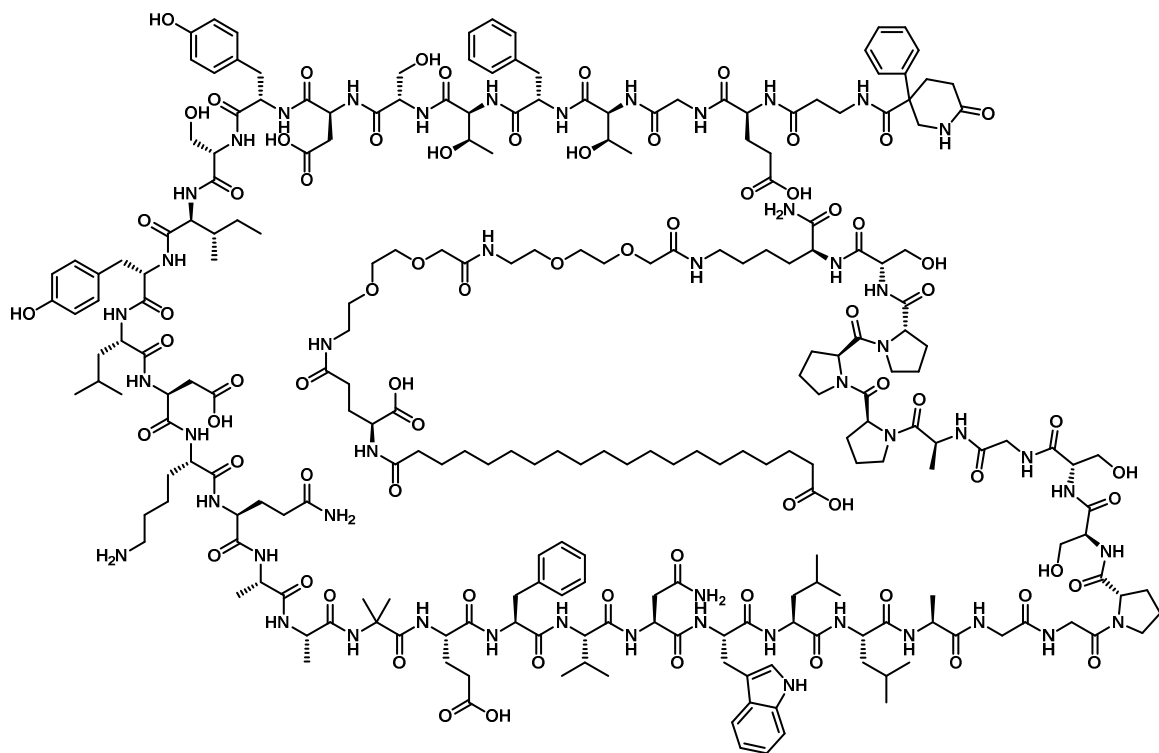


Compound 154,

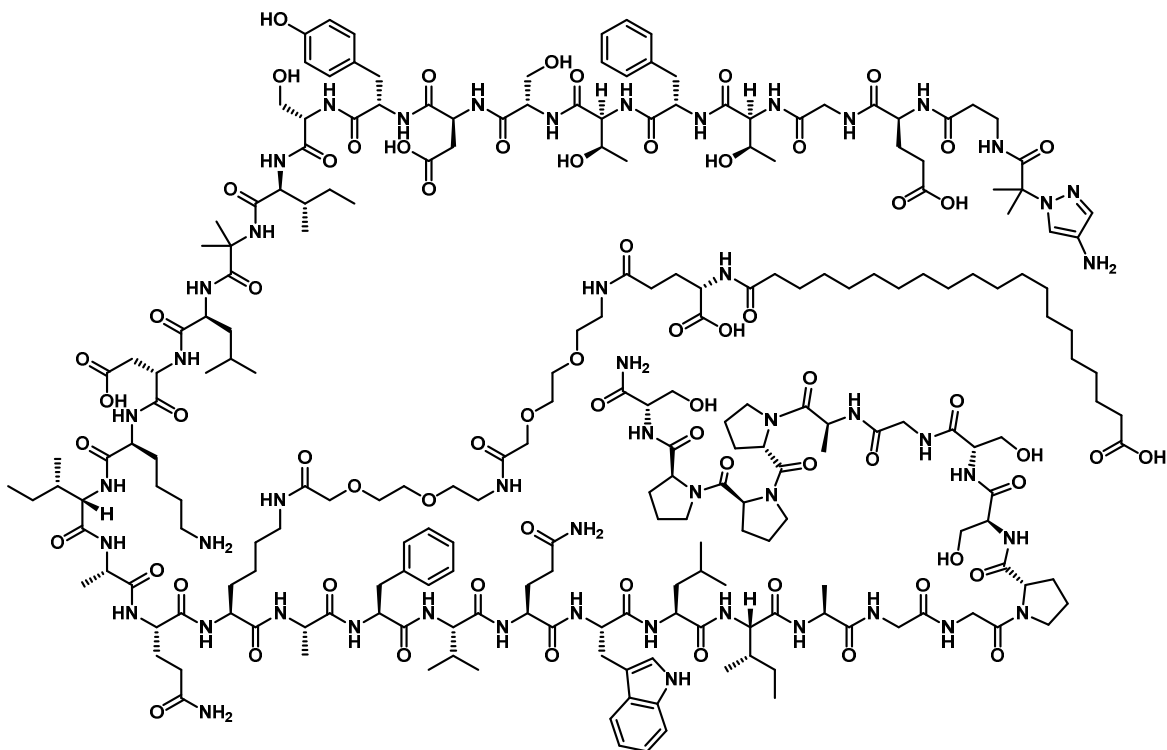


Compound 155,

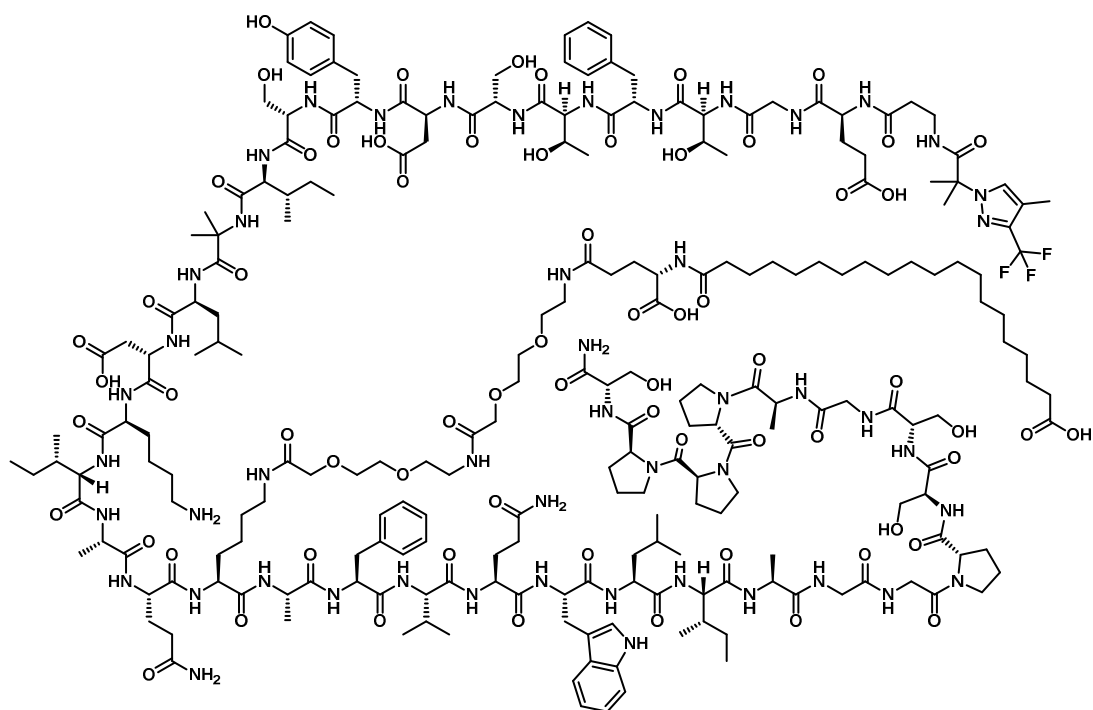
8hh



Compound 156,



Compound 157,

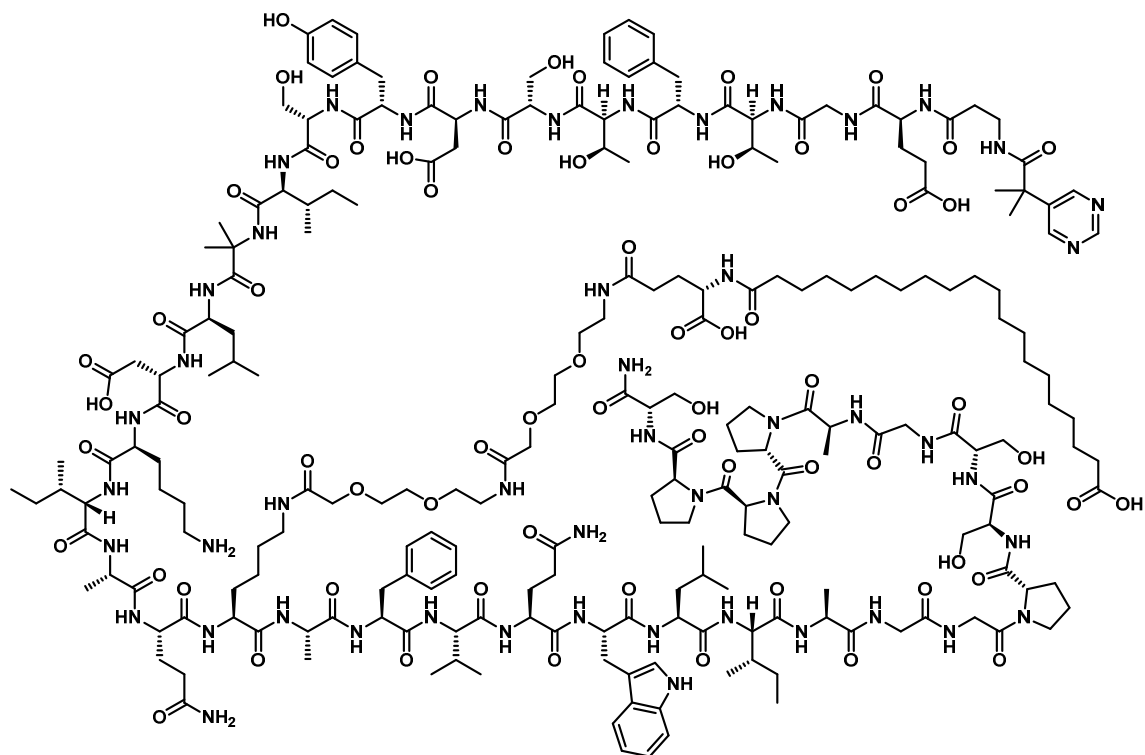


Compound 158,

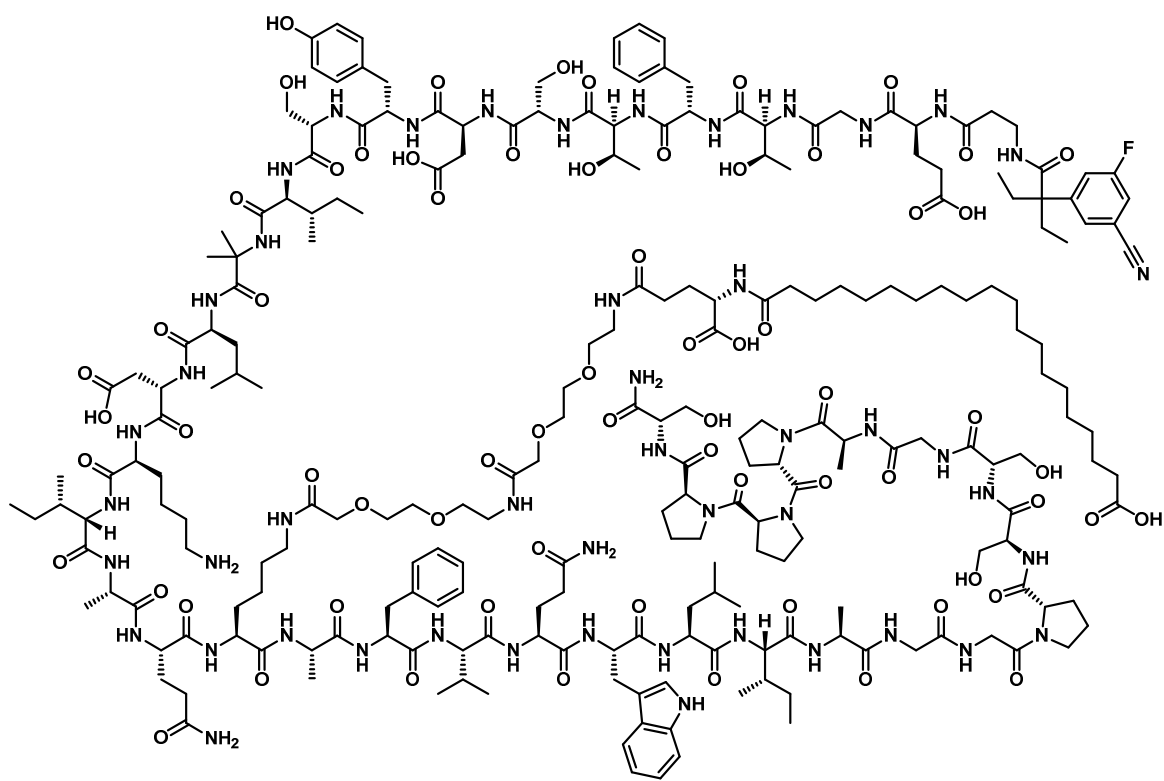
[illegible][illegible]

Compound 160,

8kk



Compound 161,

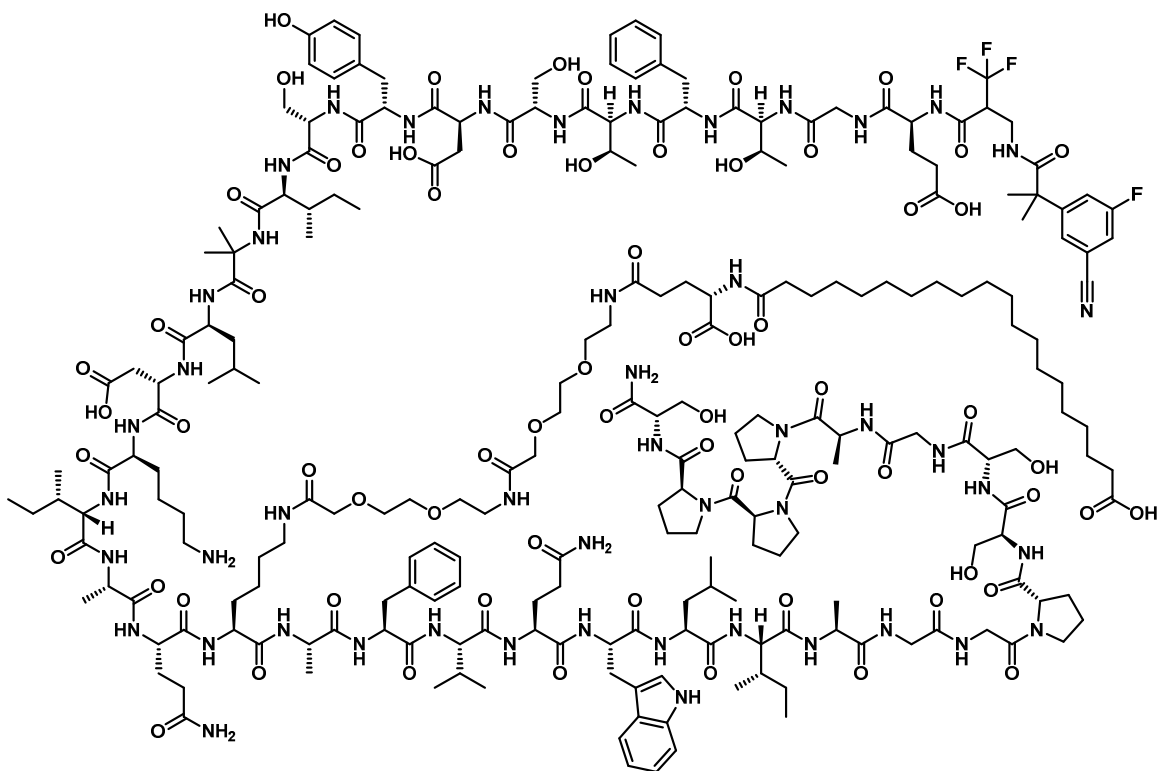


Compound 162,

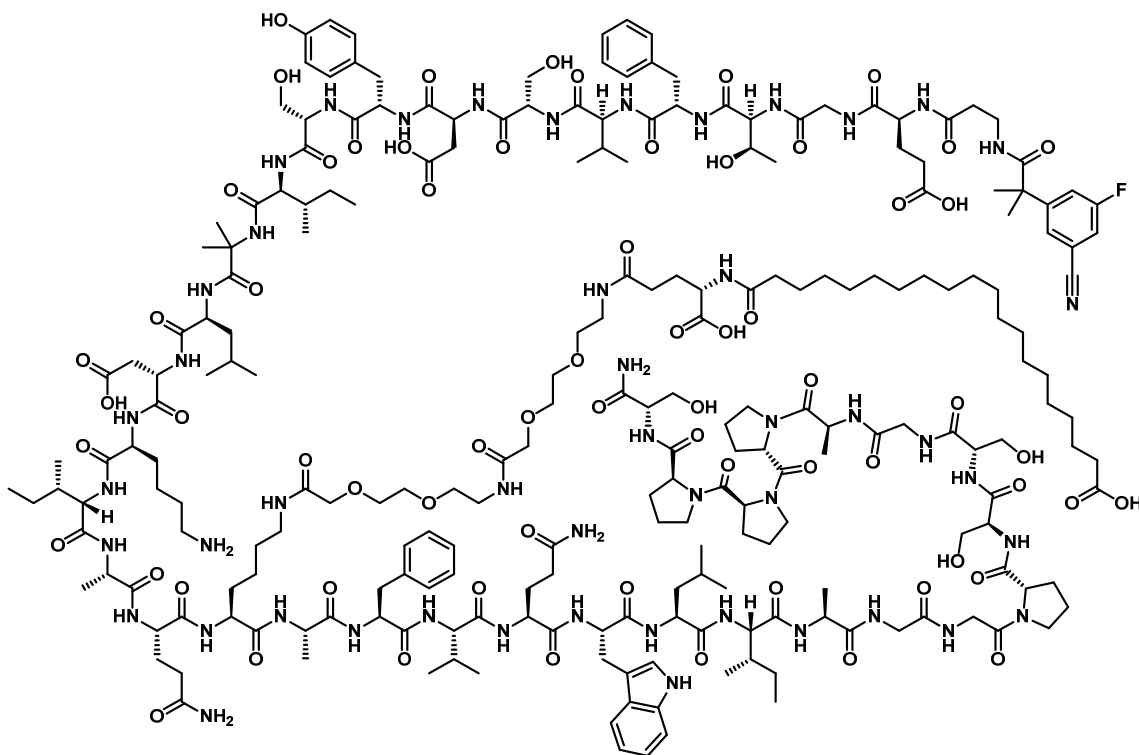
The image displays a complex macrocyclic peptide structure. The backbone is a long chain of amino acids linked by amide bonds, forming a large ring. The side chains are diverse, including a fluorinated phenyl group, a nitrile group, a long alkyl chain, and a nitrile group. The structure is highly detailed, showing the stereochemistry of the amino acids and the specific functional groups.

Compound 164,

8mm

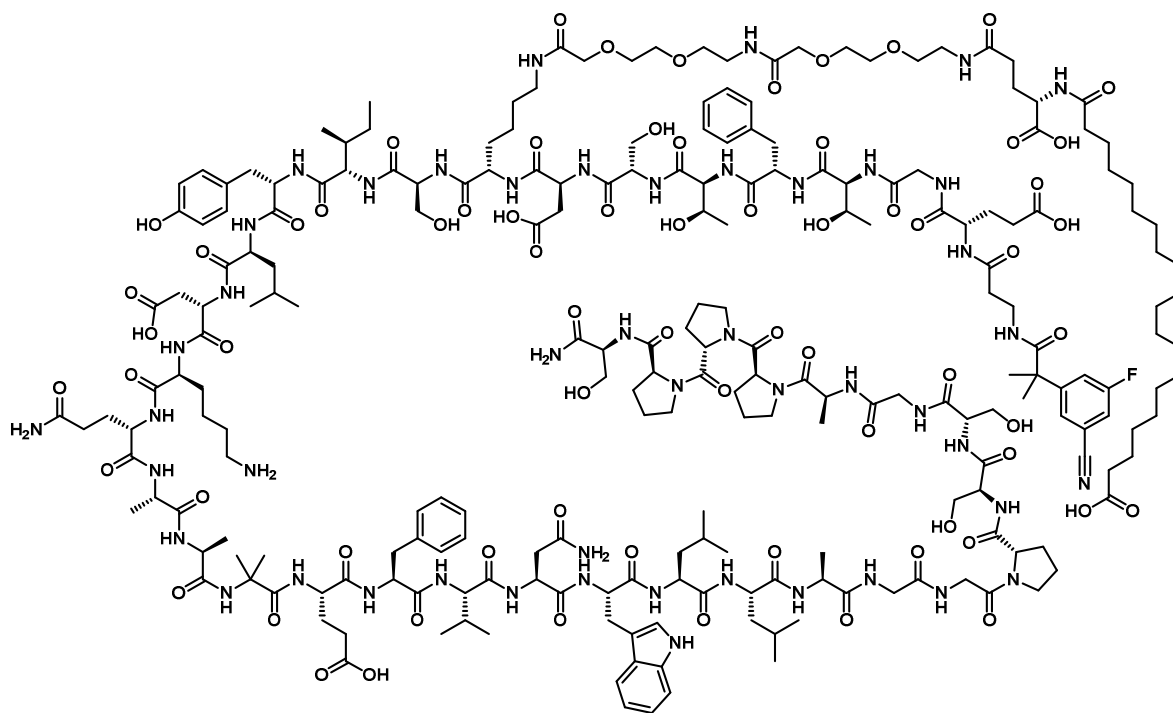


Compound 165,

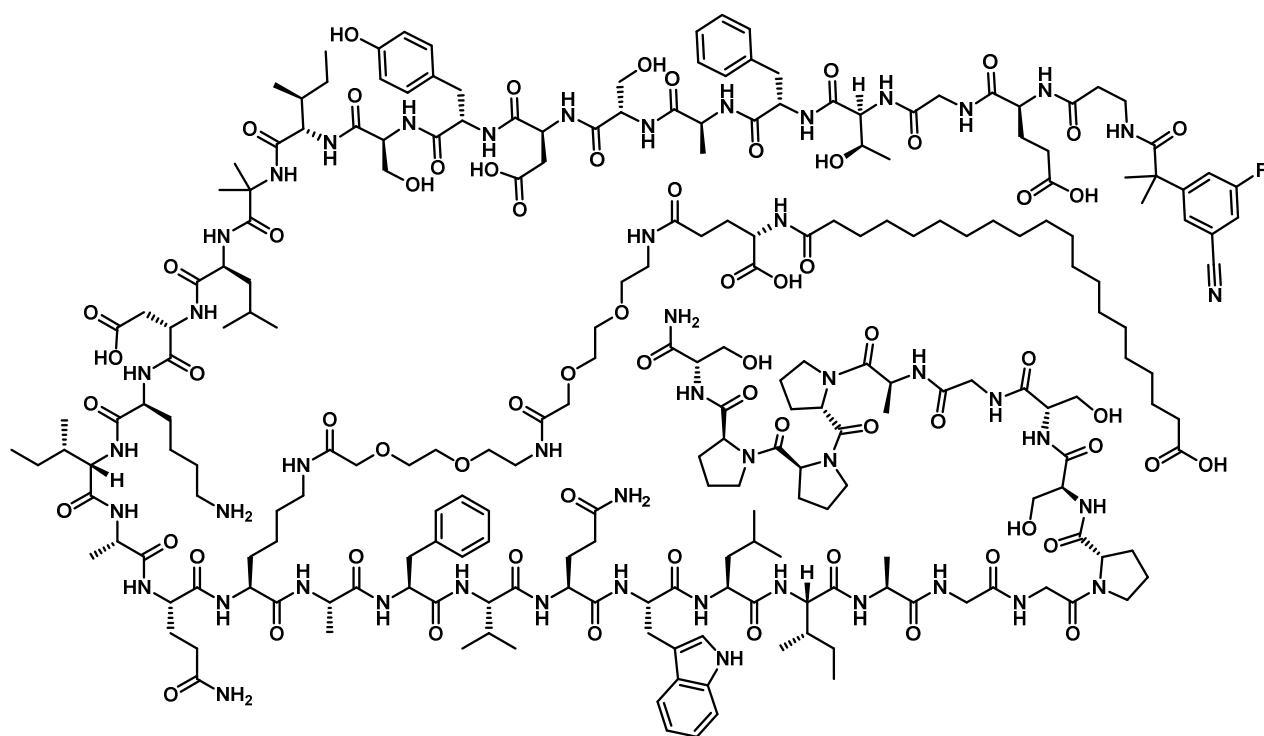


Compound 166,

8nm



Compound 167,



Compound 168,

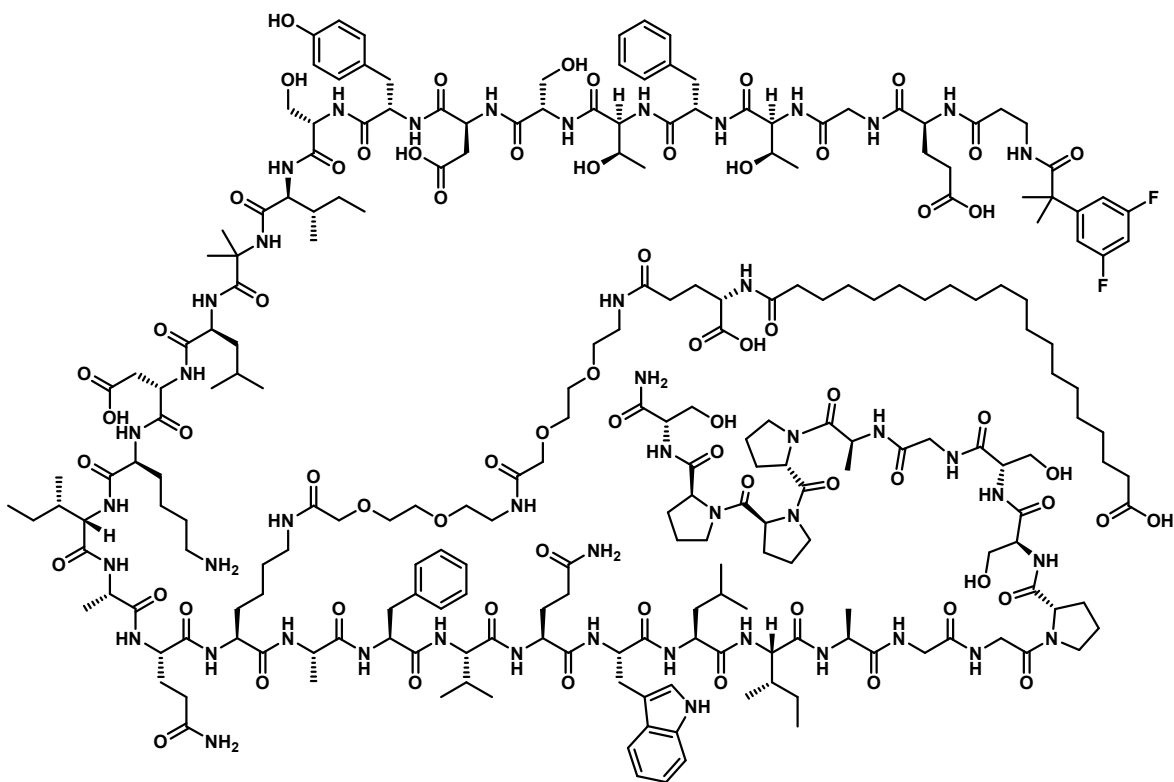
[illegible]

Compound 170,

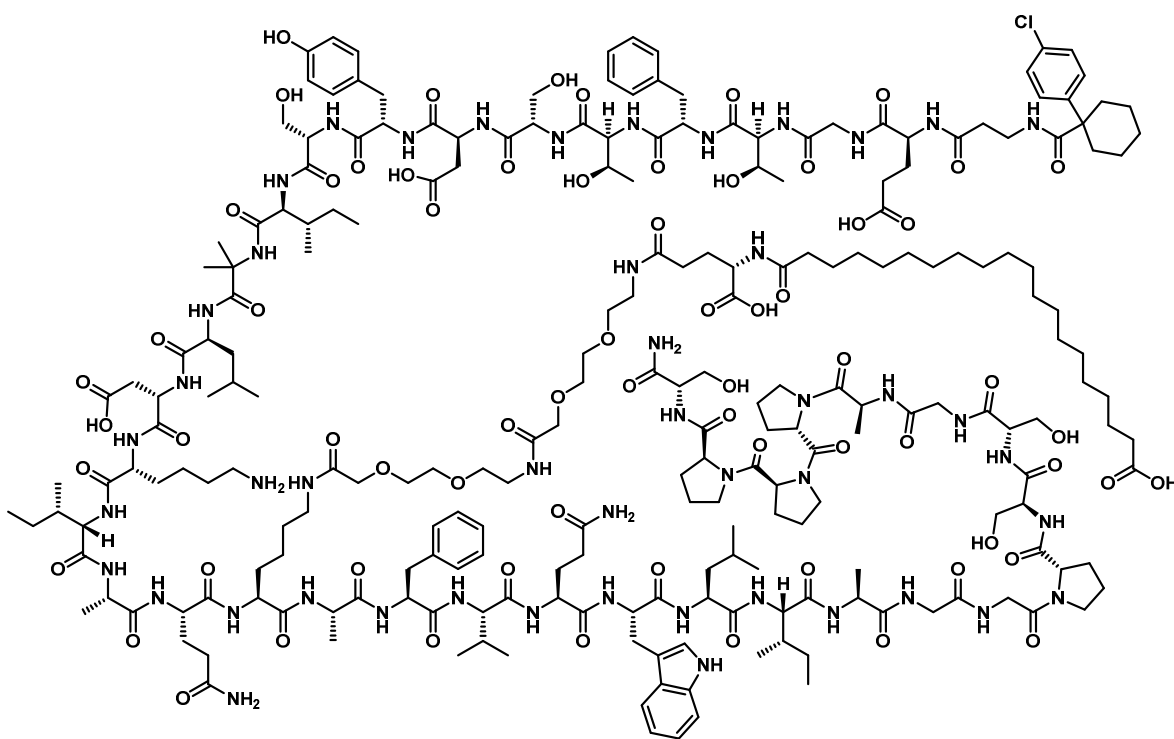
[illegible][illegible]

Compound 172,

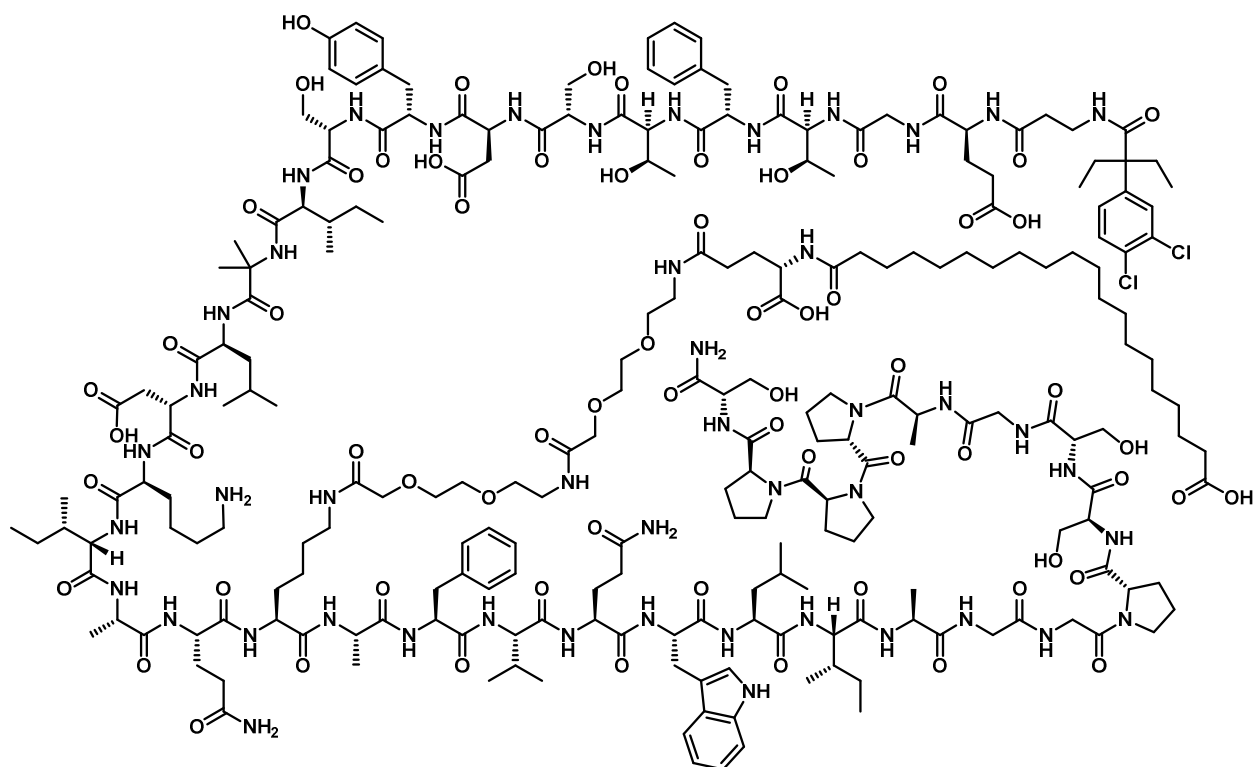
8qq



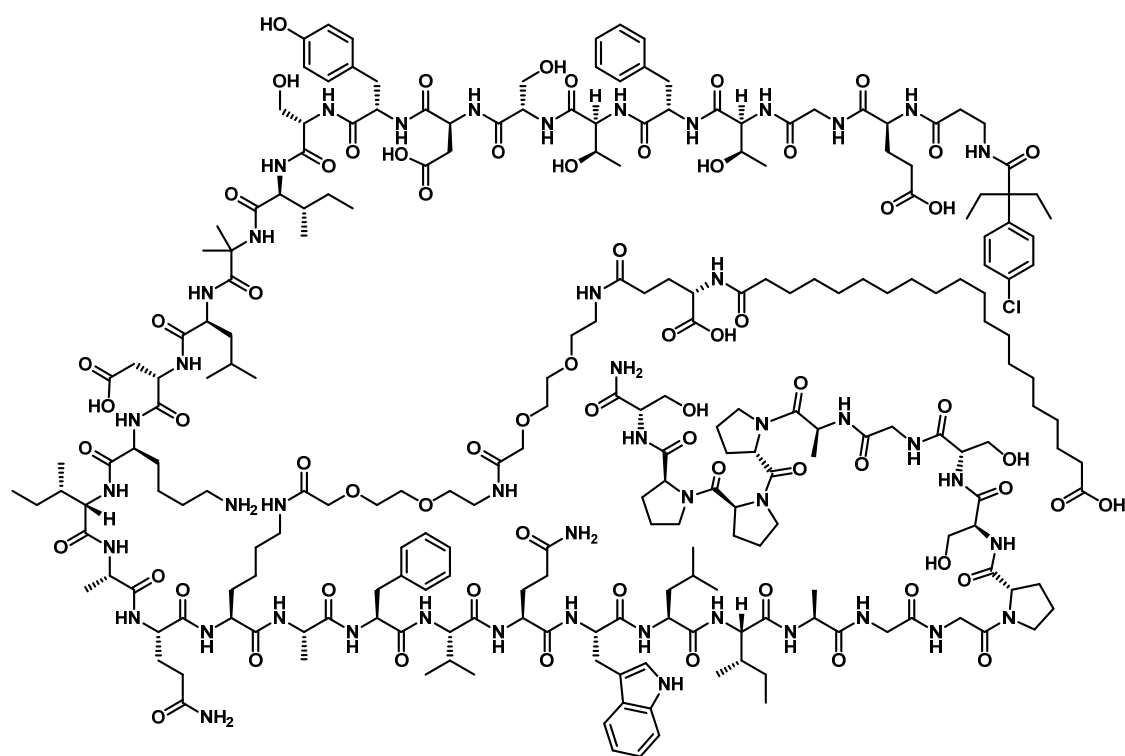
Compound 173,



Compound 174,



Compound 175,

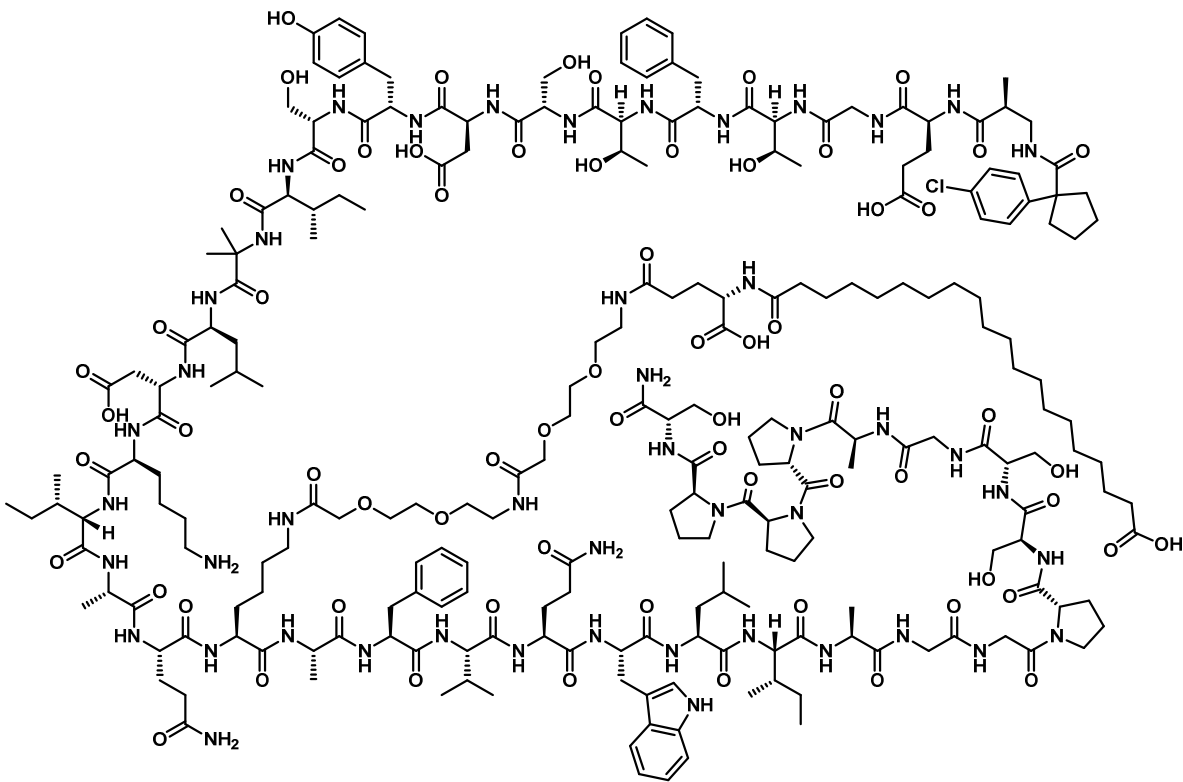


Compound 176,

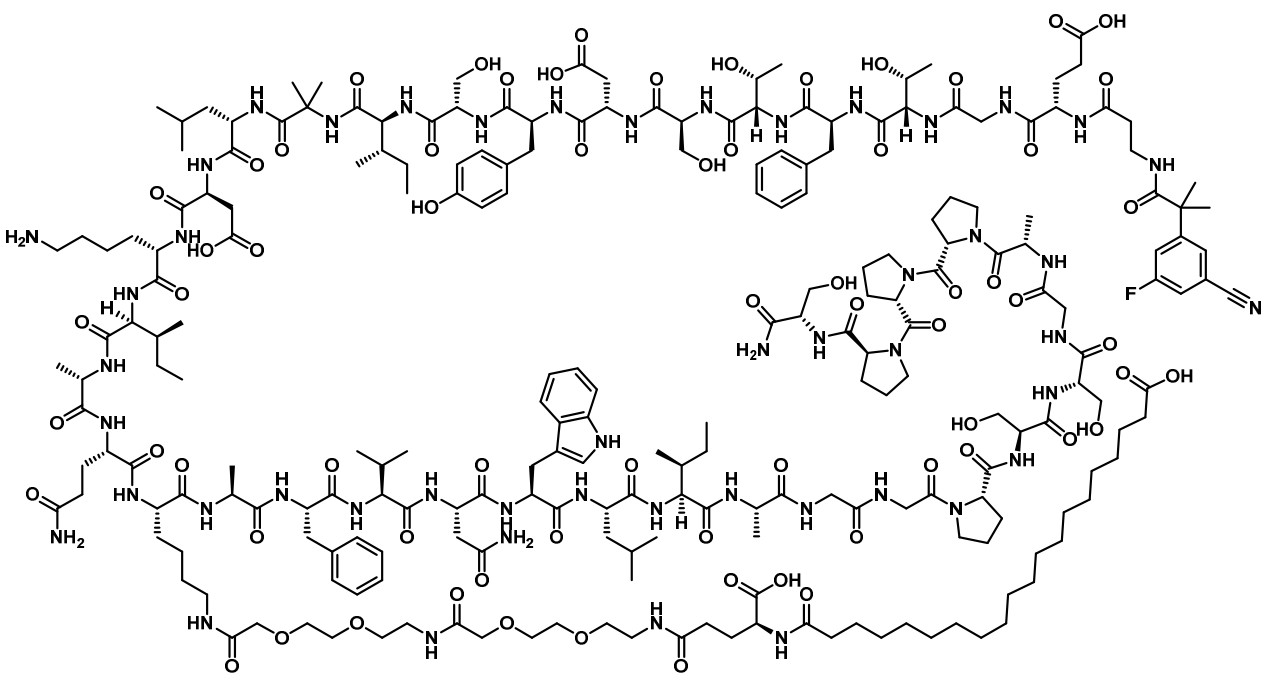
[illegible]

[illegible]

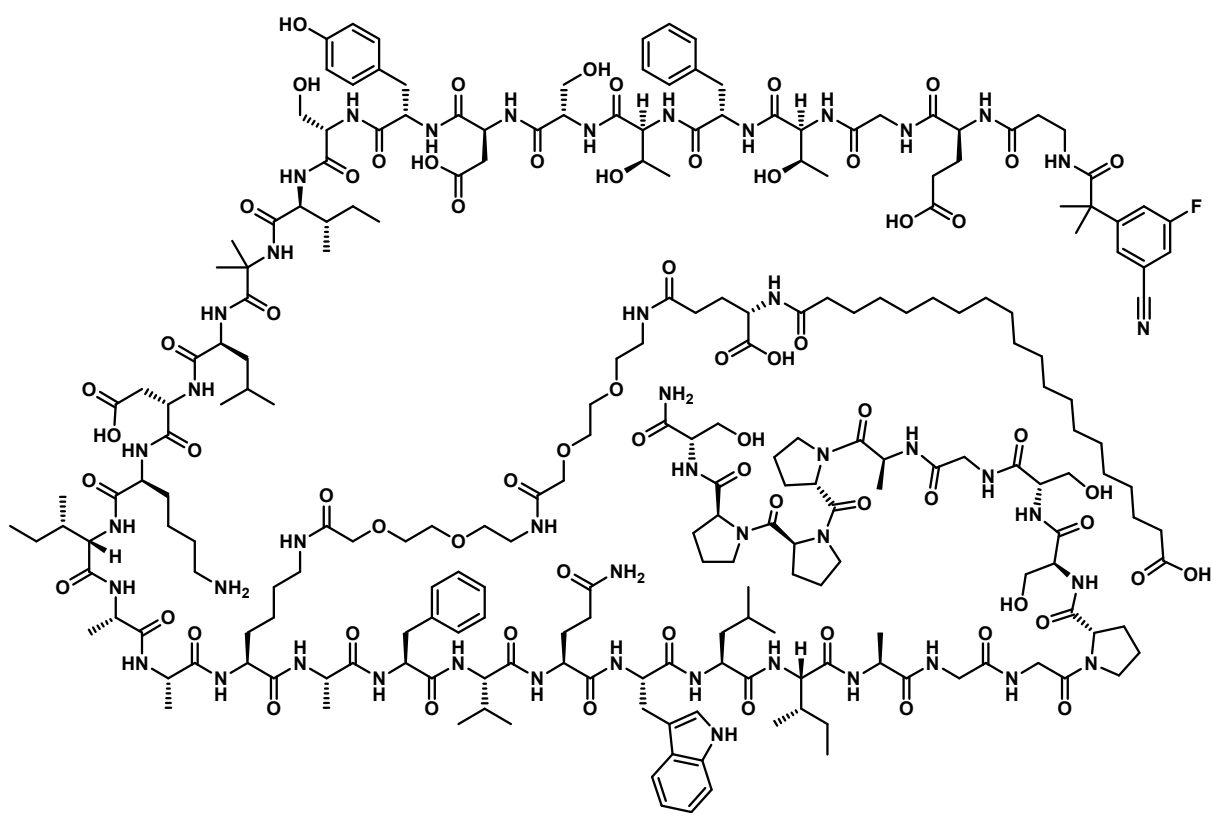
Compound 180,



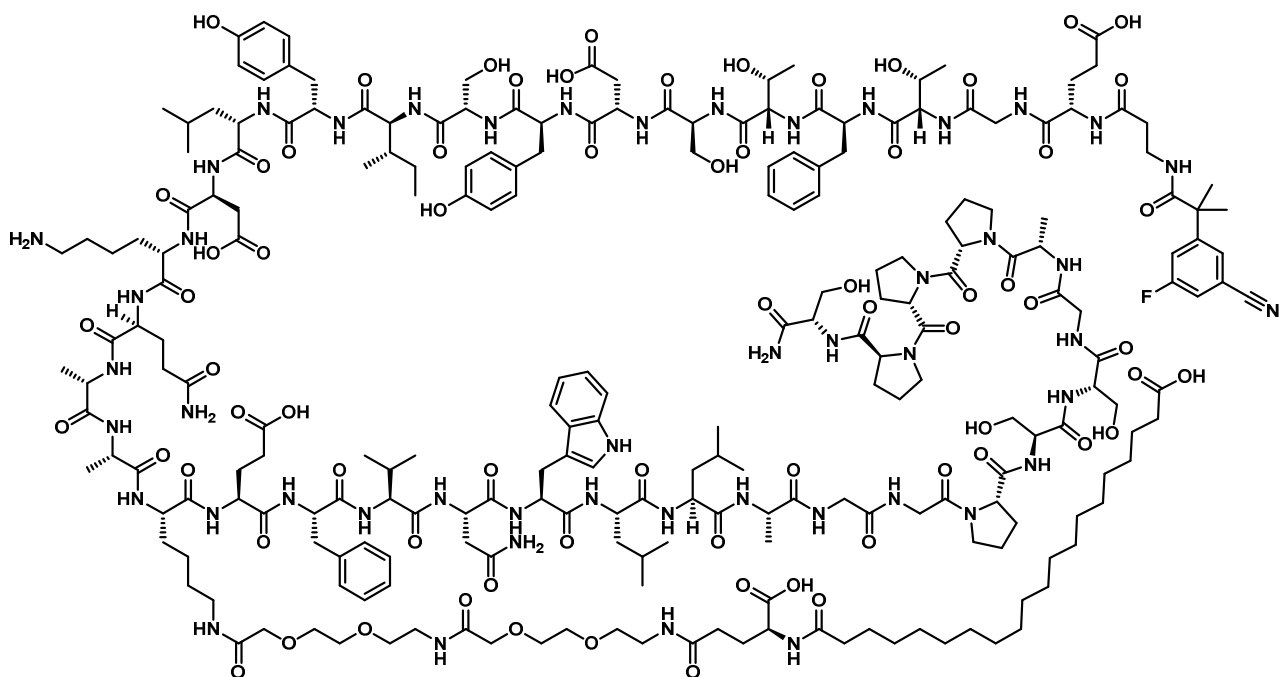
Compound 181,



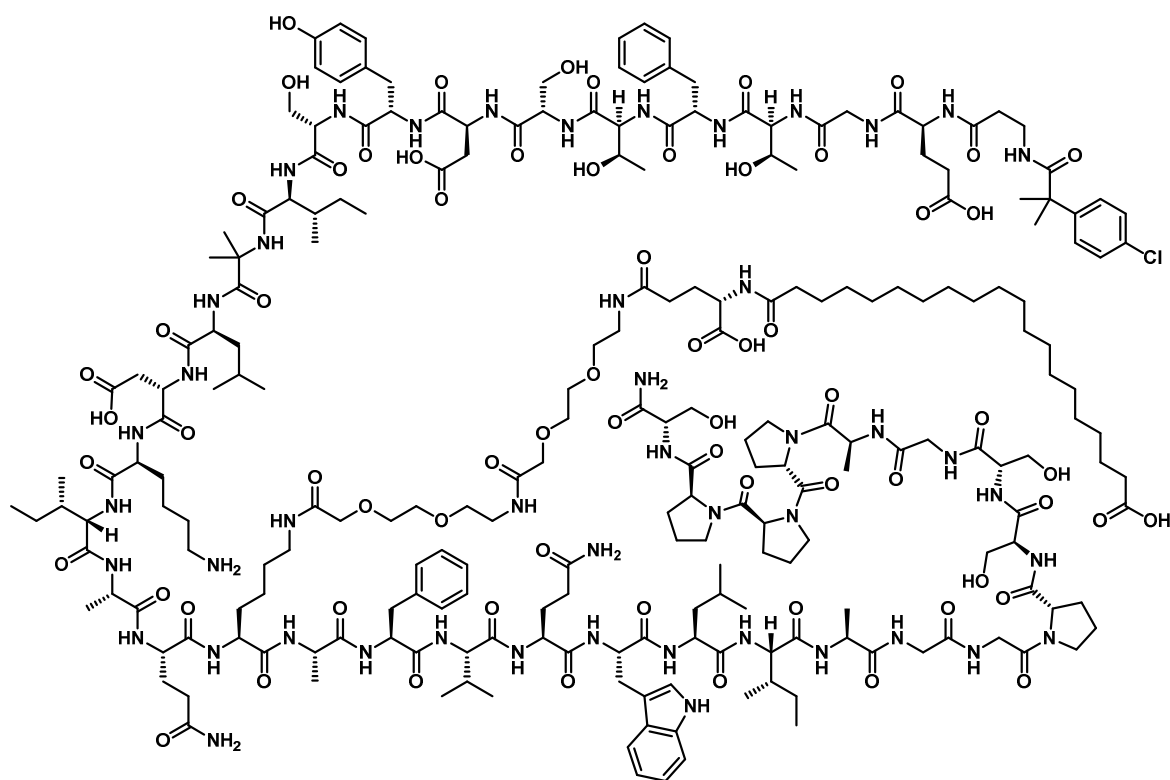
Compound 182,



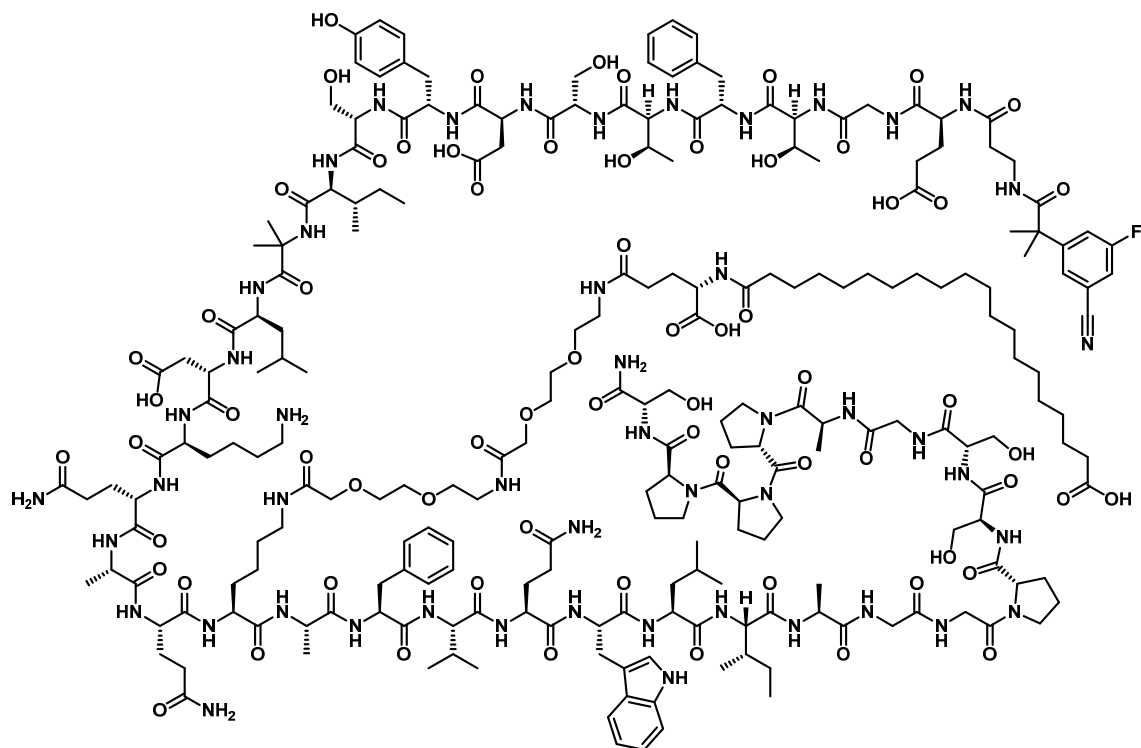
Compound 183,



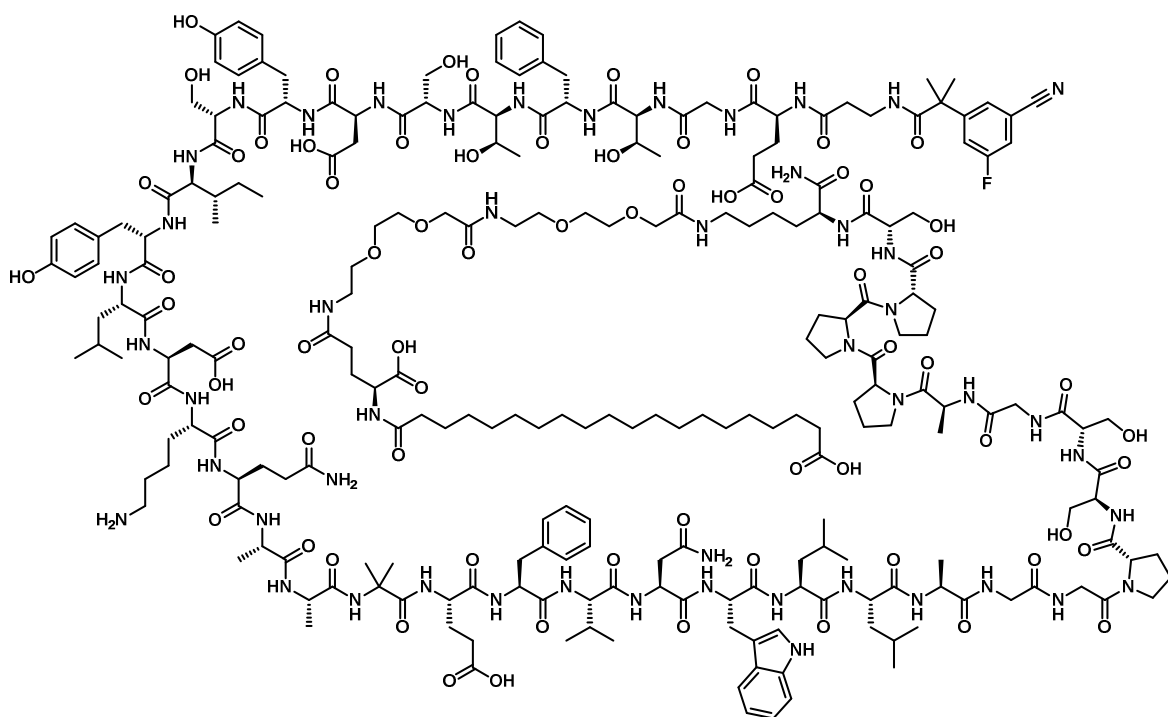
Compound 184,



Compound 185,

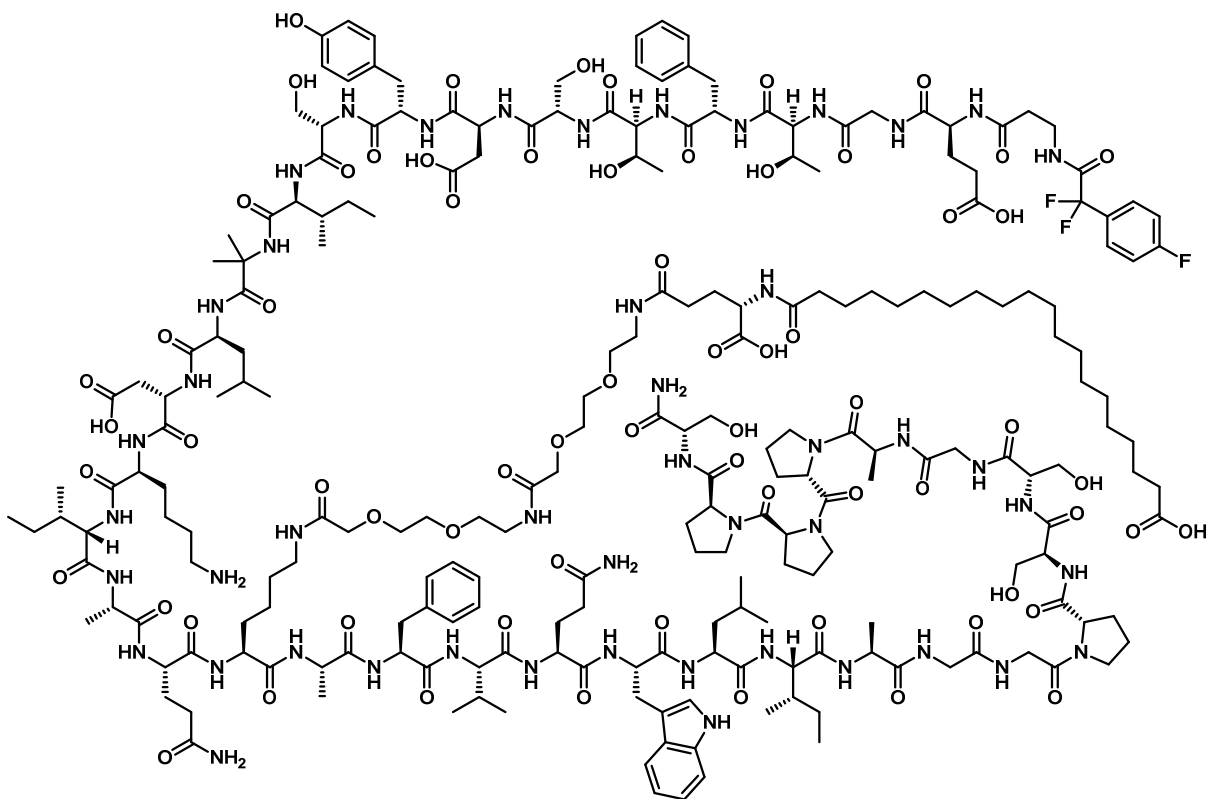


Compound 186,

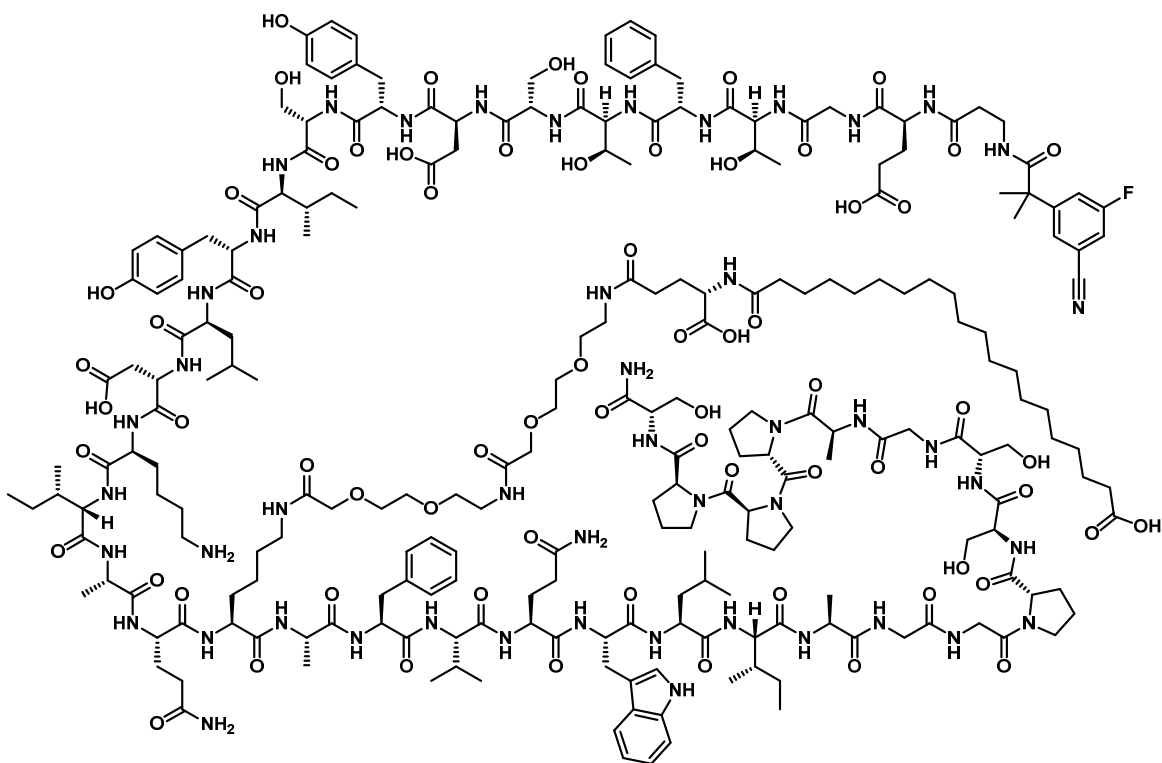


Compound 187,

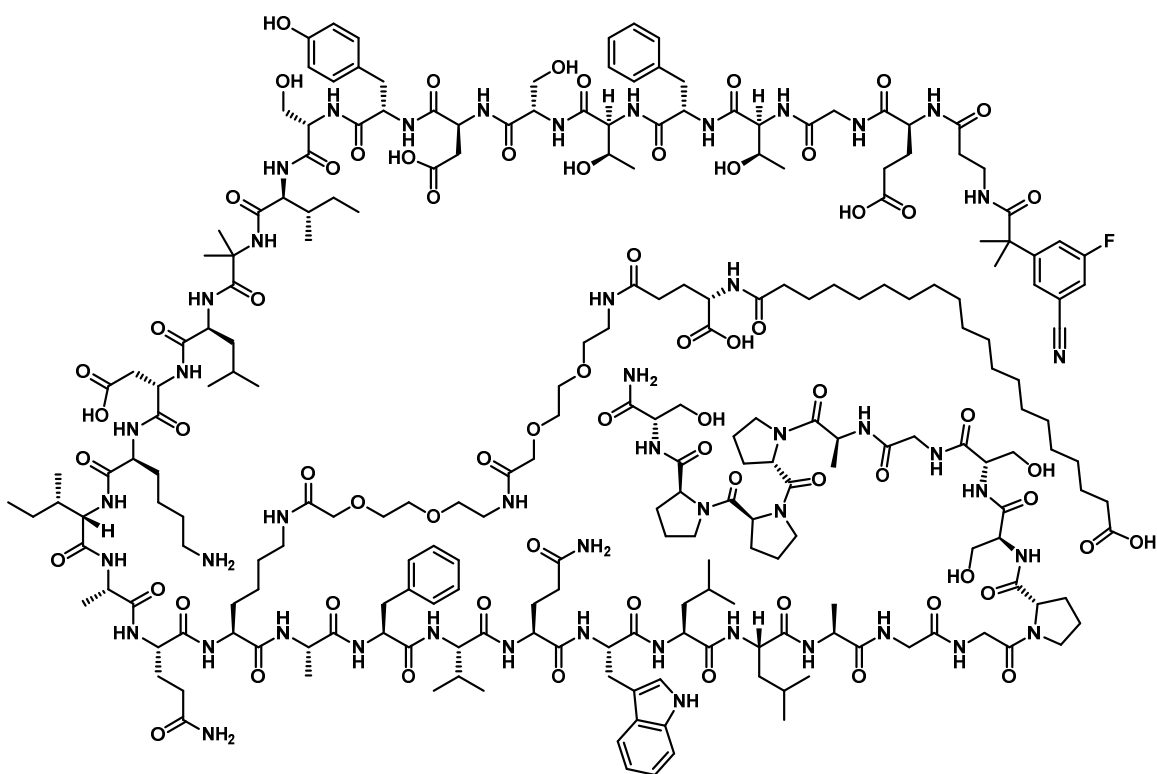
8yy



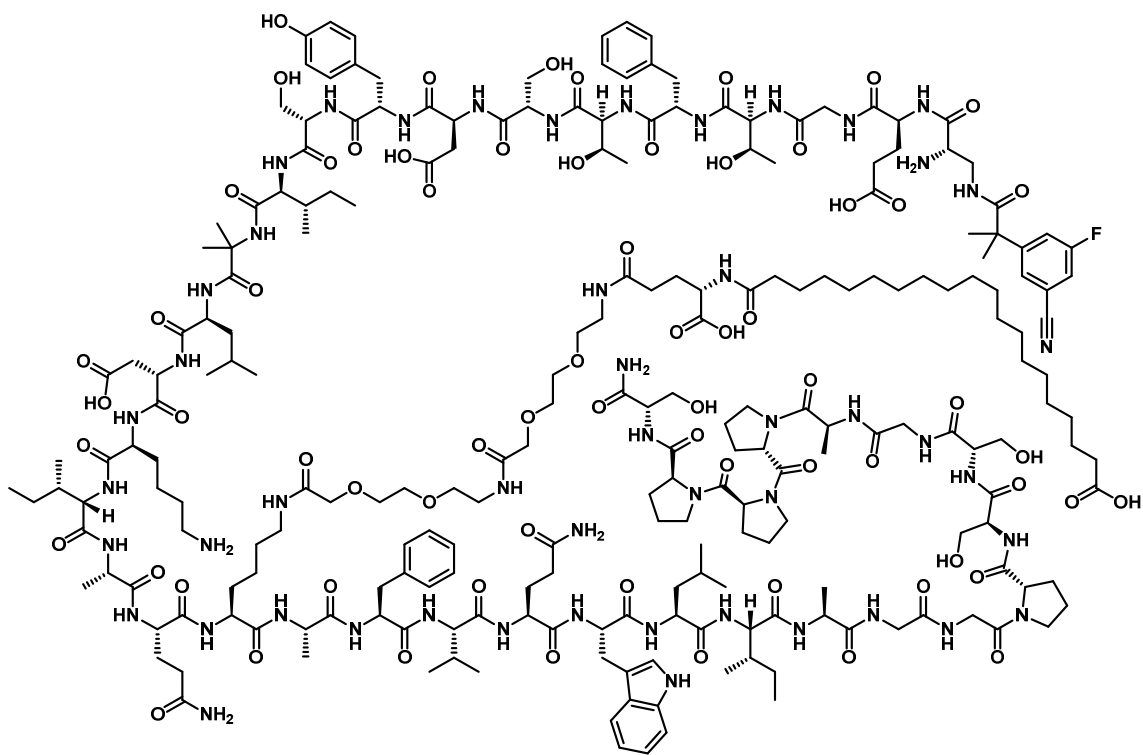
Compound 188,



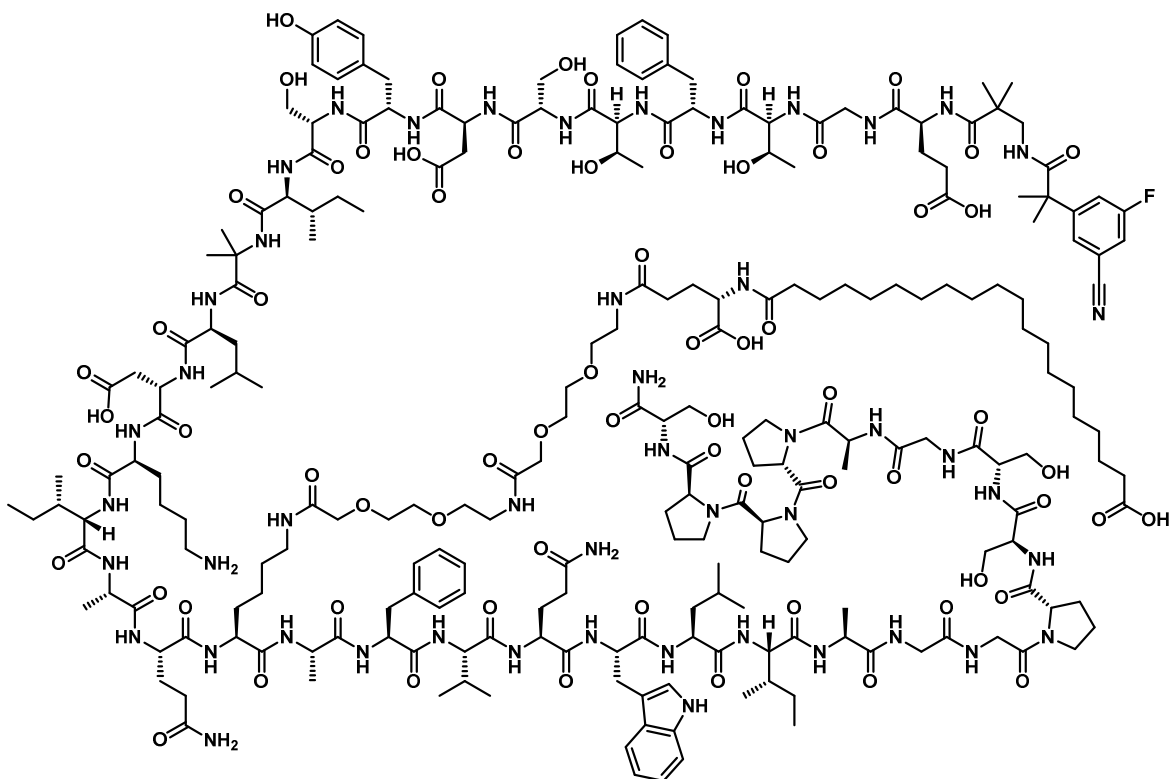
Compound 189,



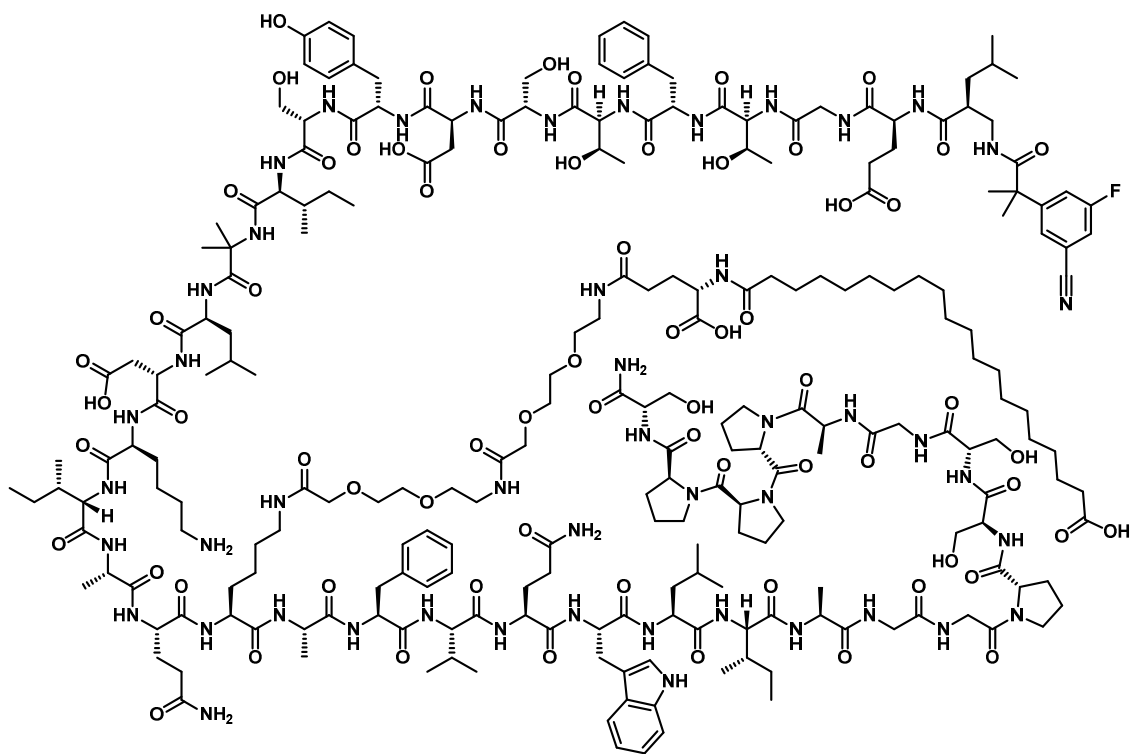
Compound 190,



Compound 191,

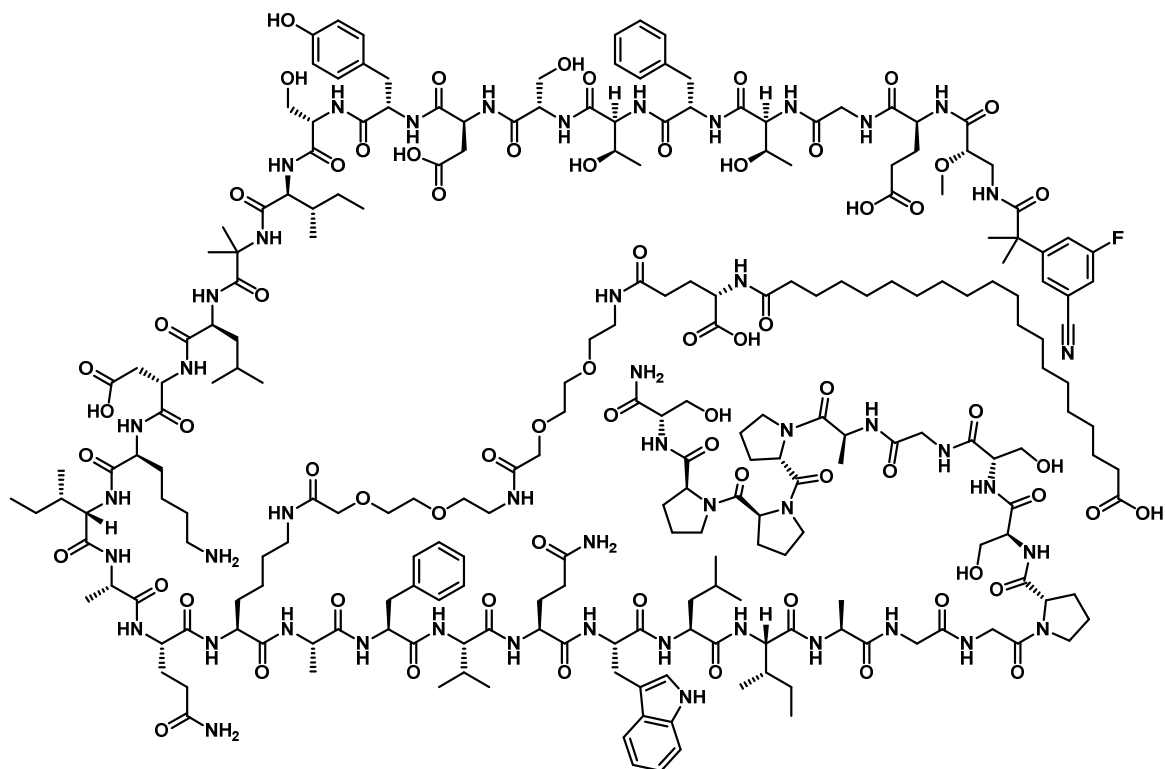


Compound 192,

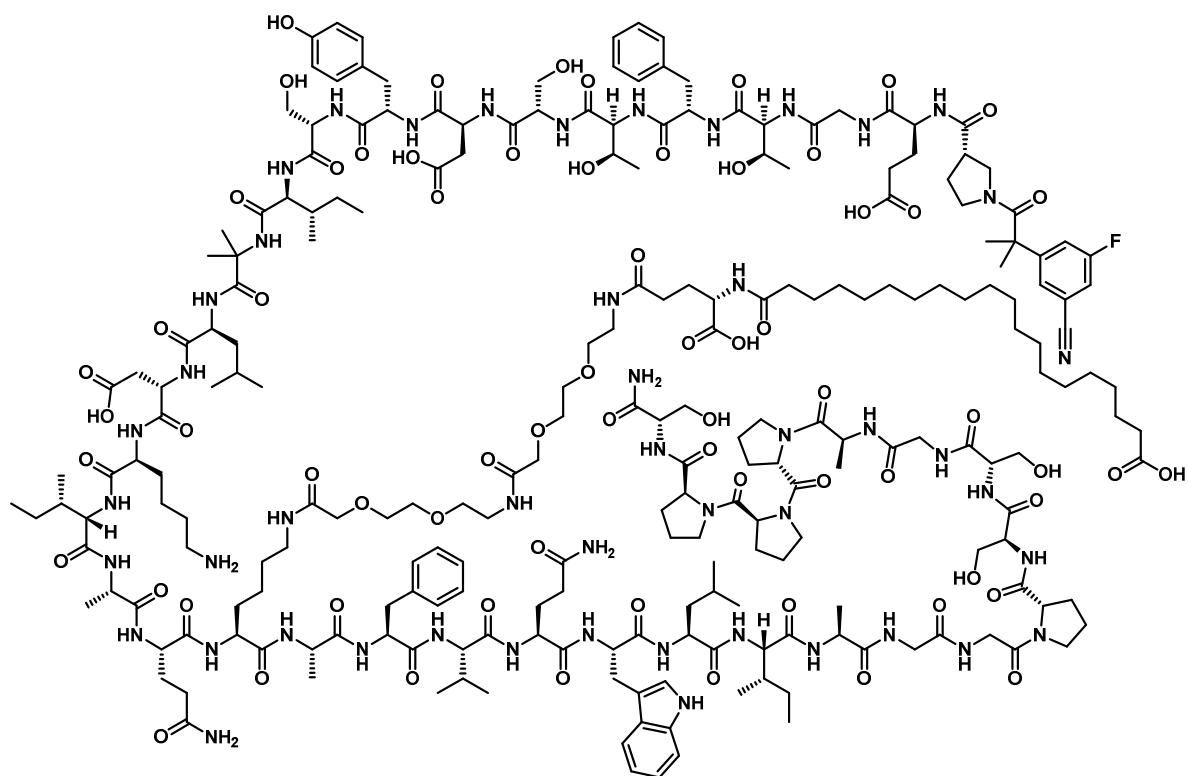


Compound 193,

8bbb



Compound 194,

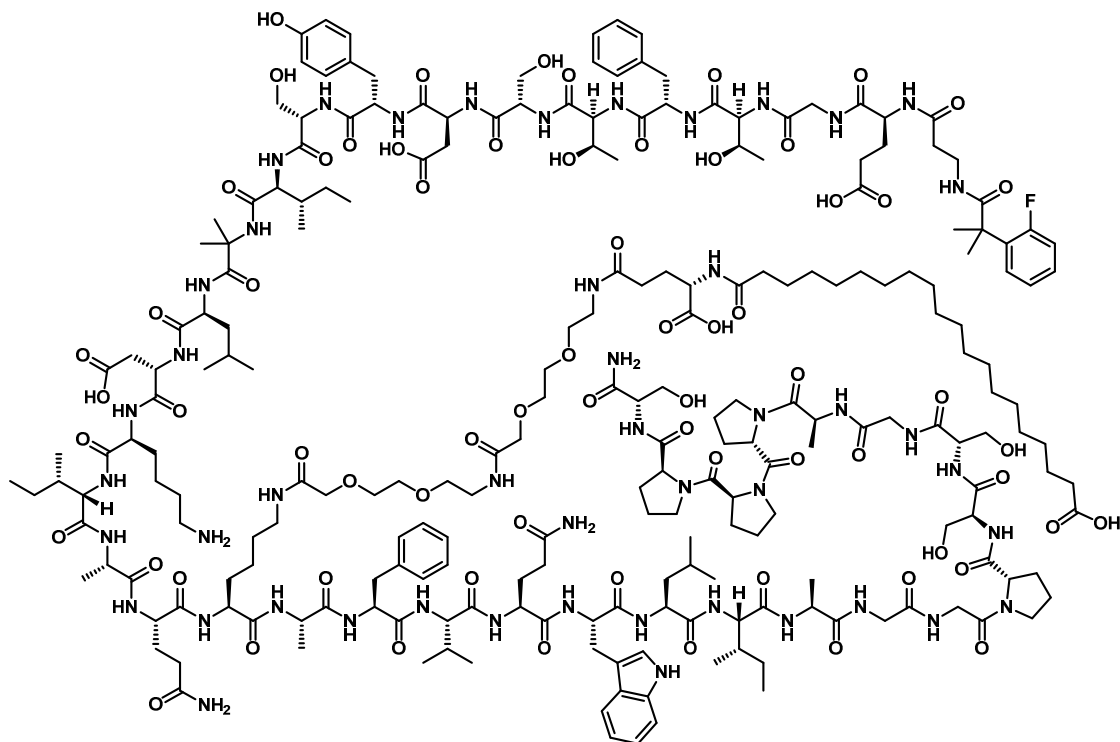


Compound 195,

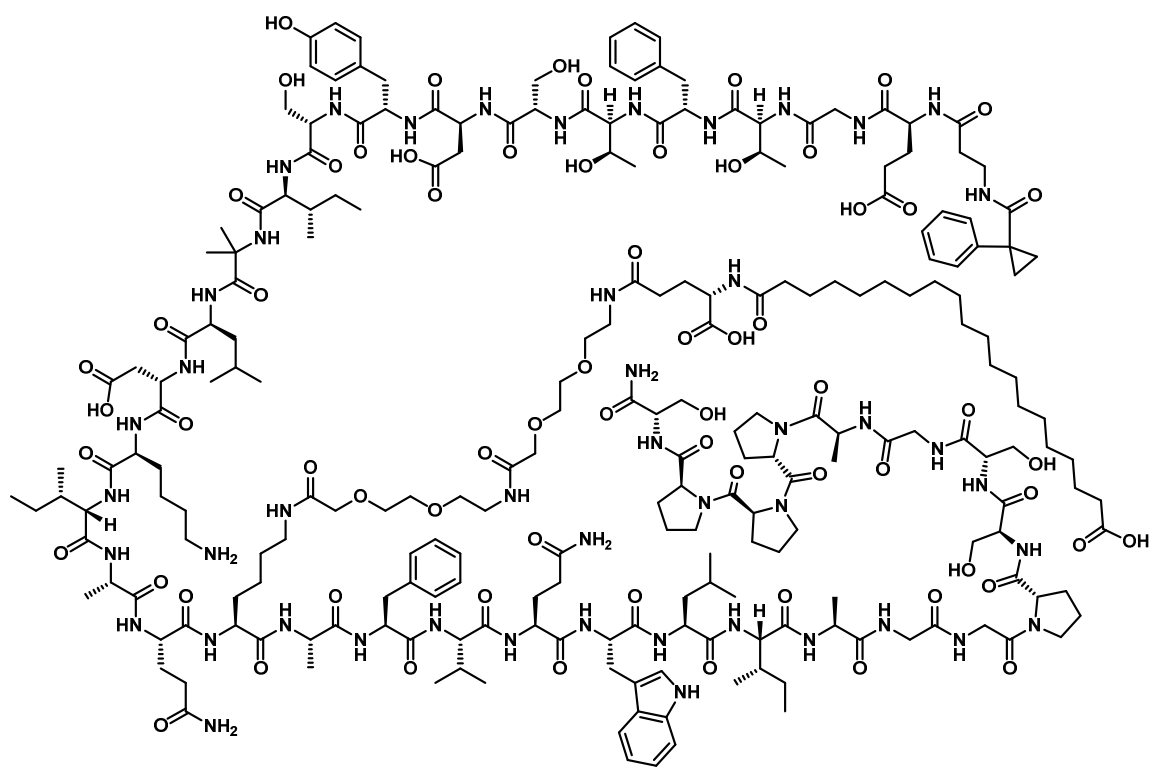
[illegible][illegible]

Compound 197,

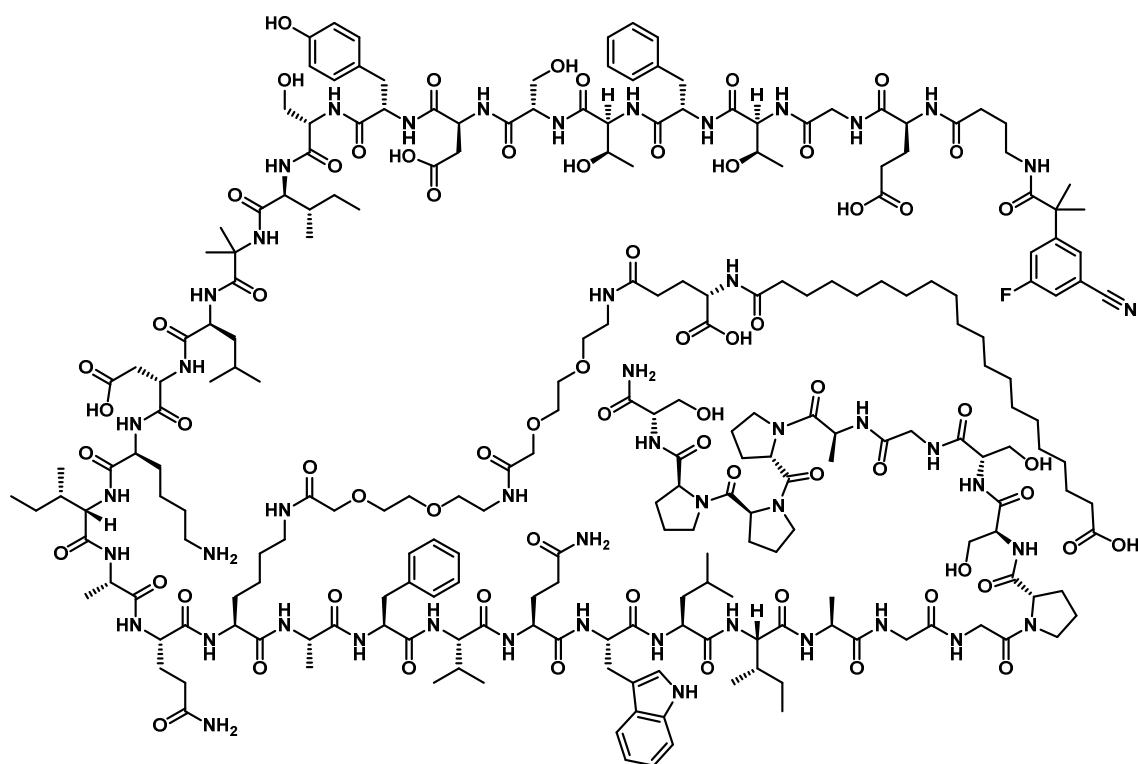
8ddd



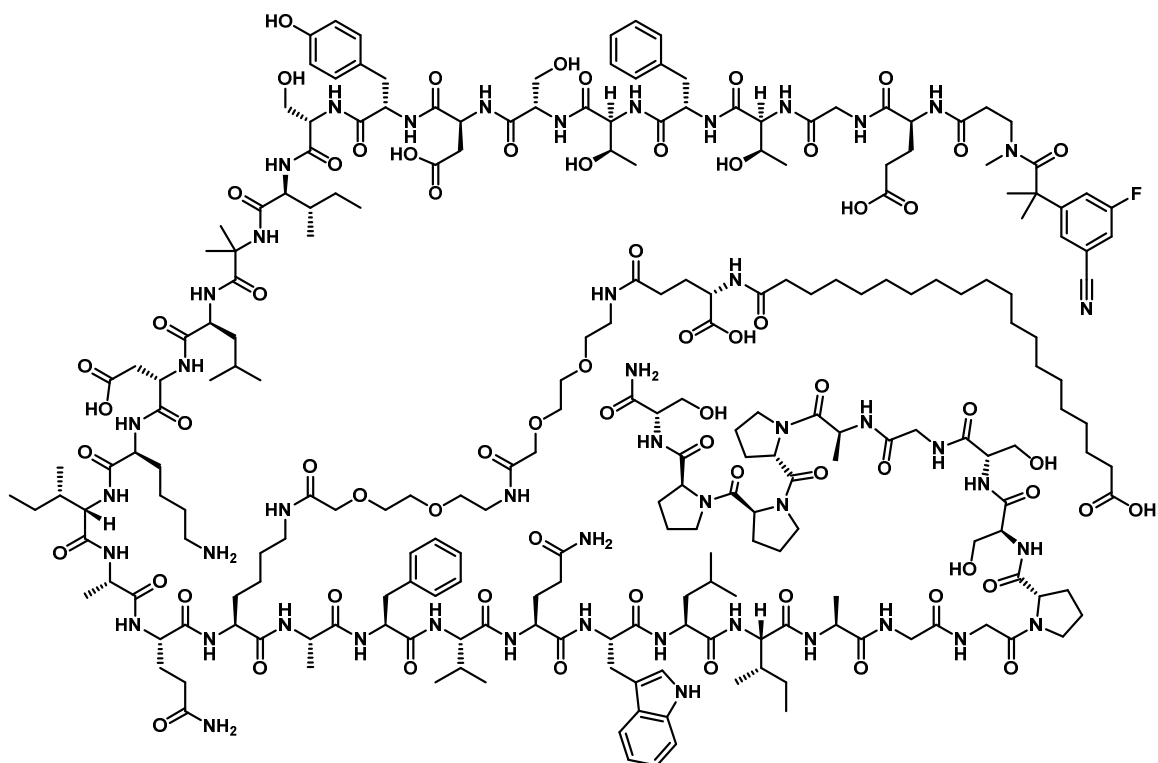
Compound 198,



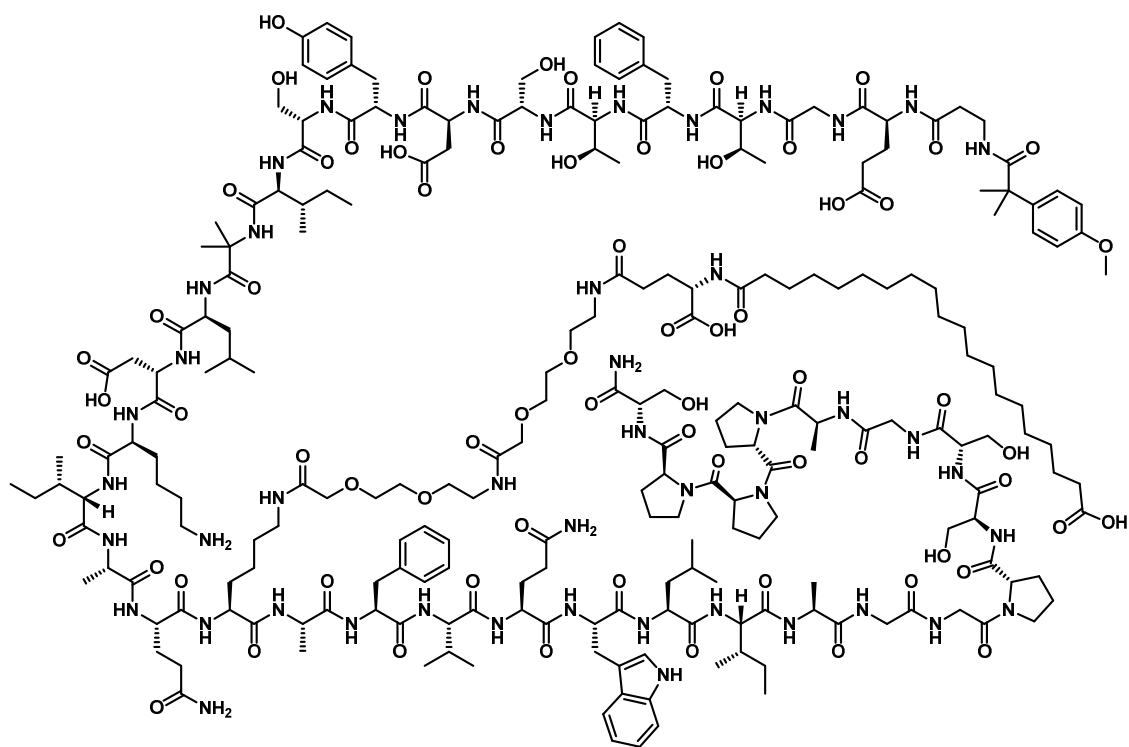
Compound 199,



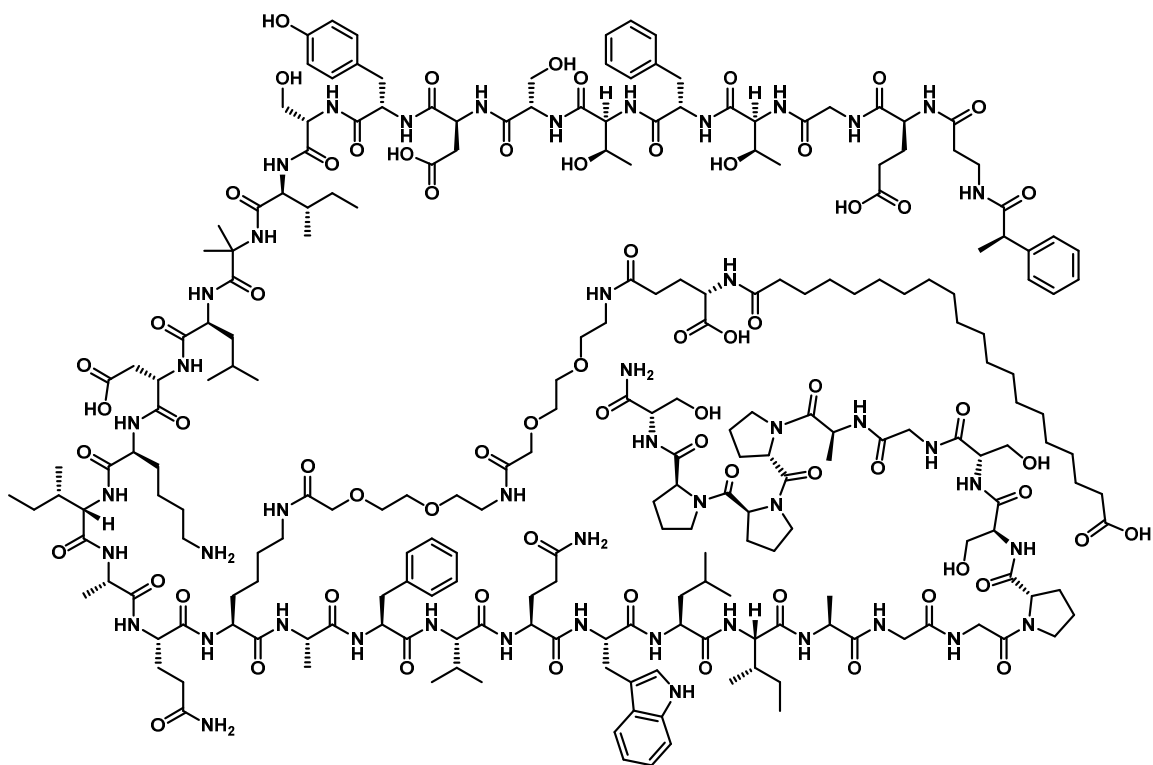
Compound 200,



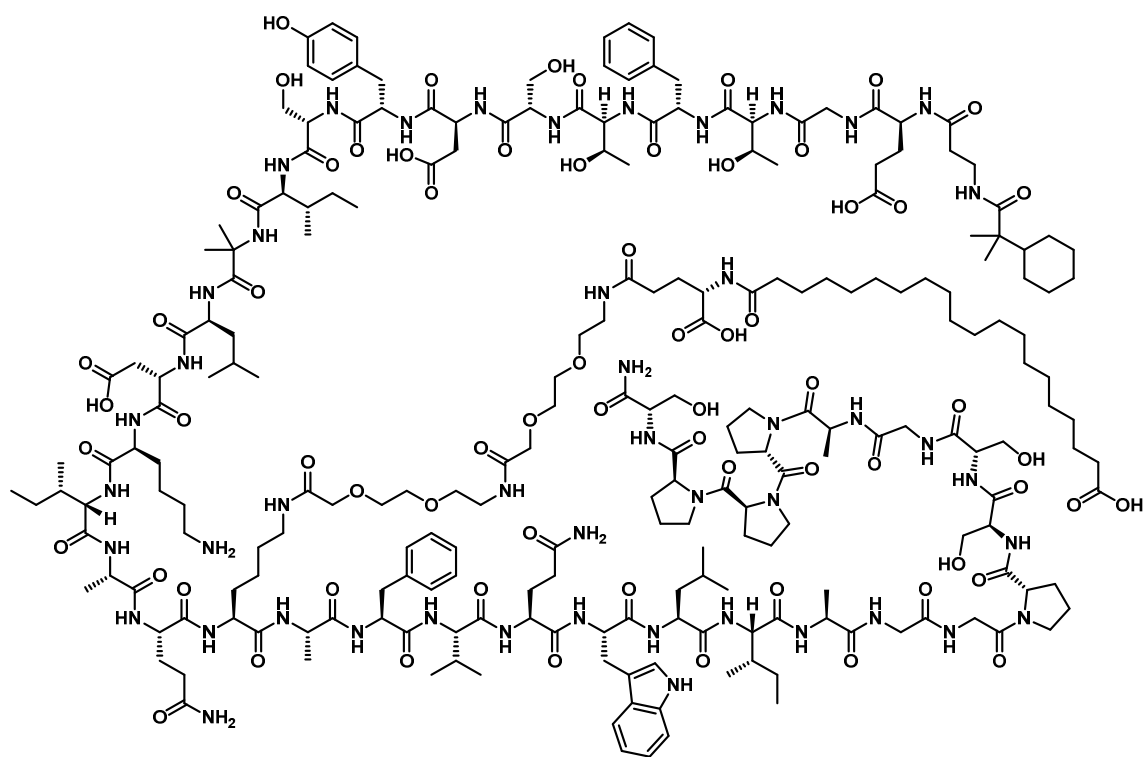
Compound 201,



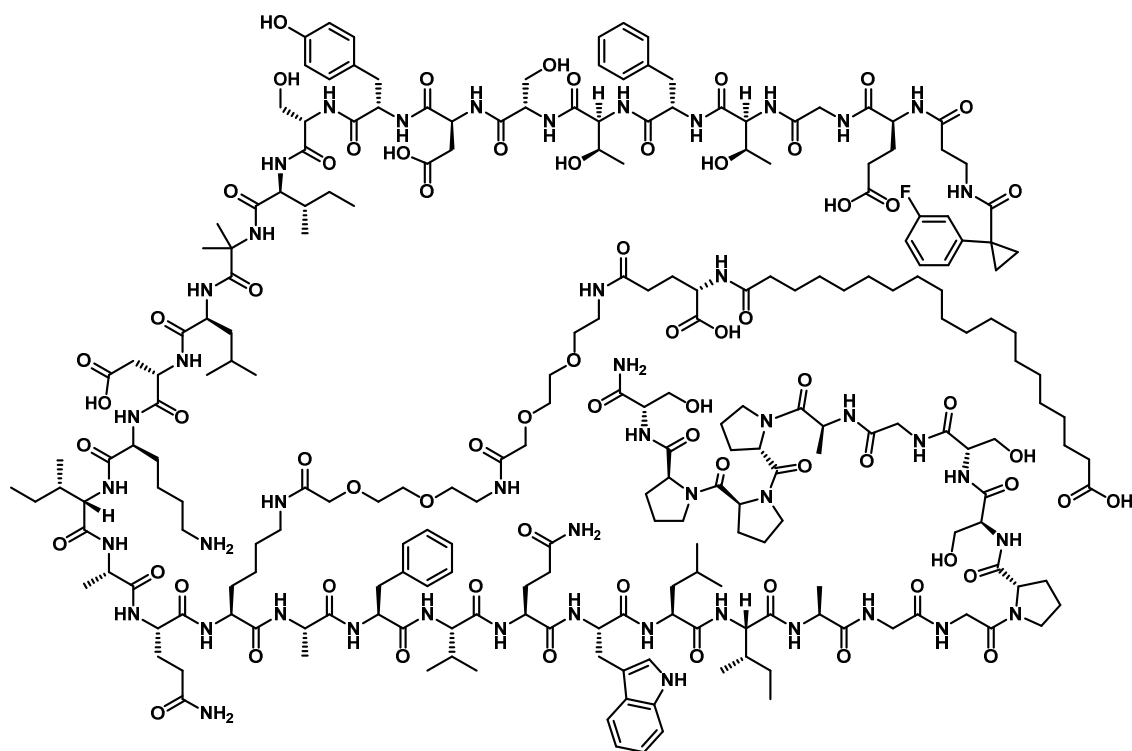
Compound 203,



Compound 204,

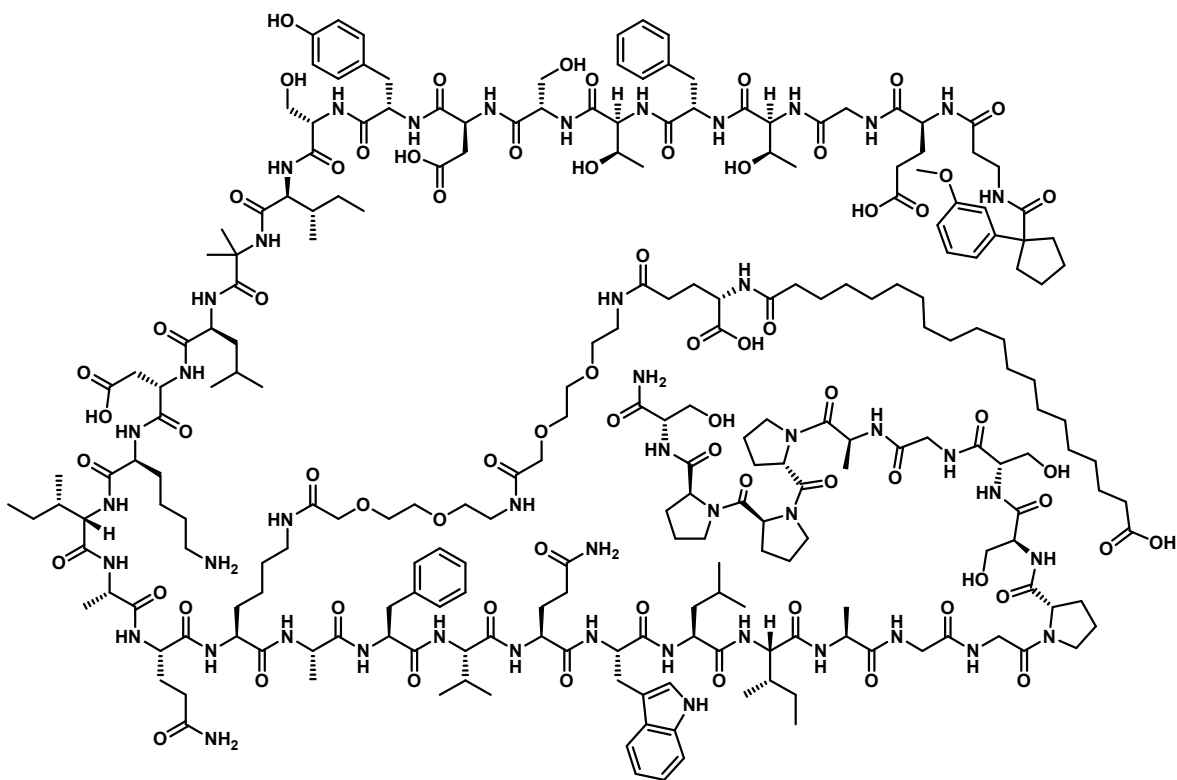


Compound 205,

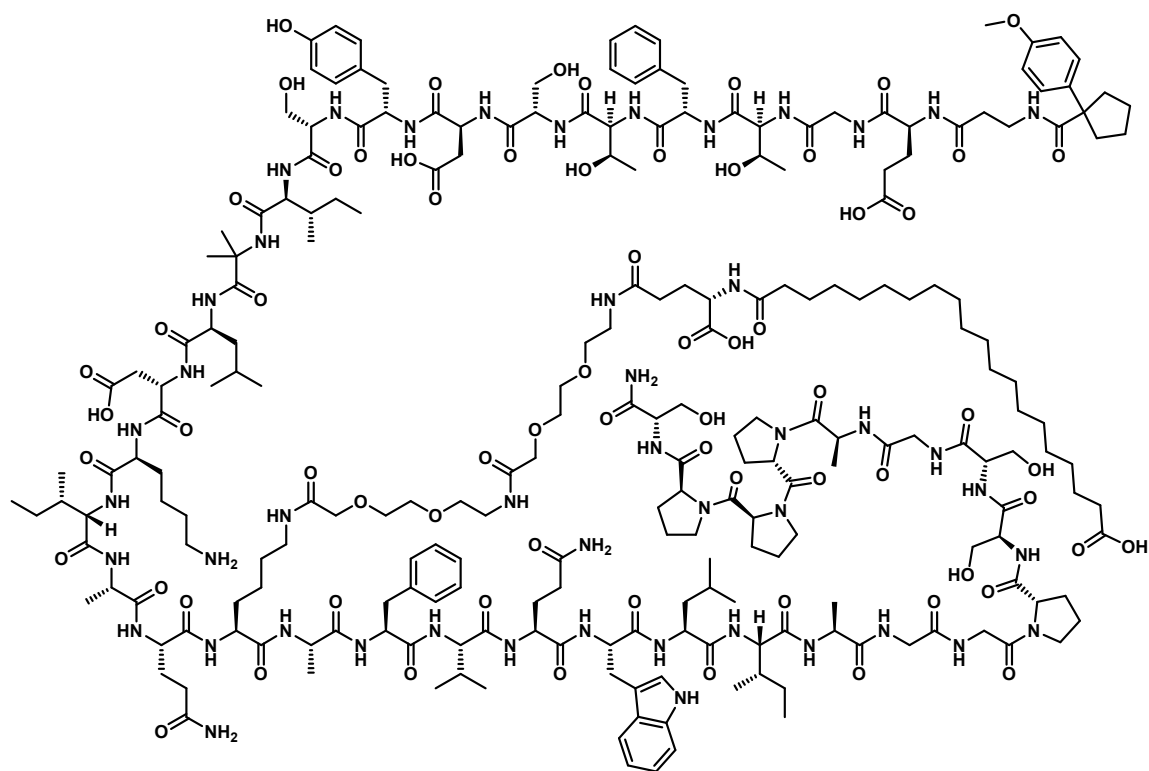


Compound 206,

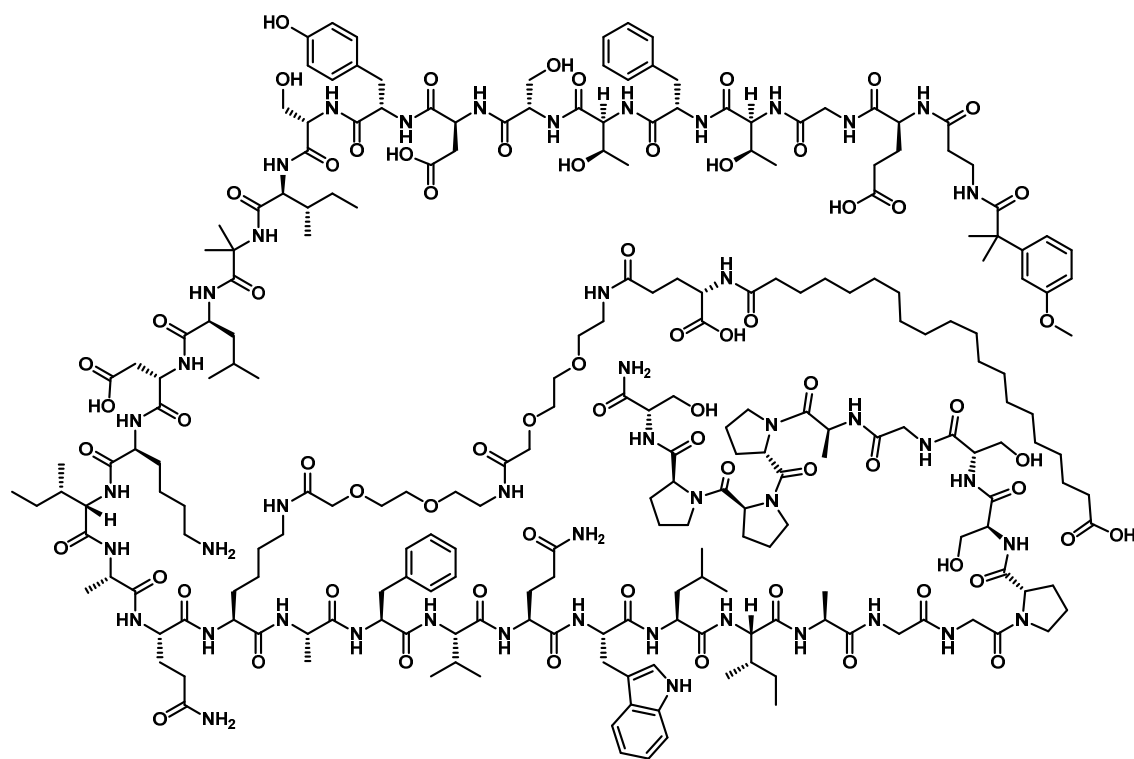
8hhh



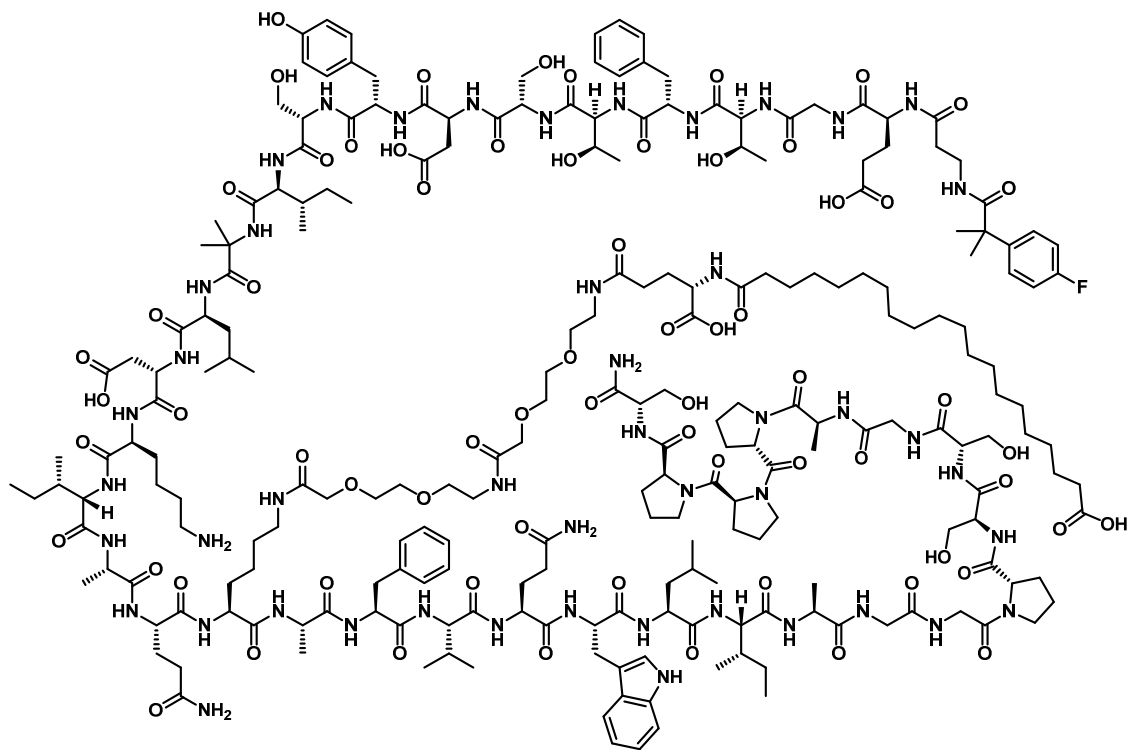
Compound 207,



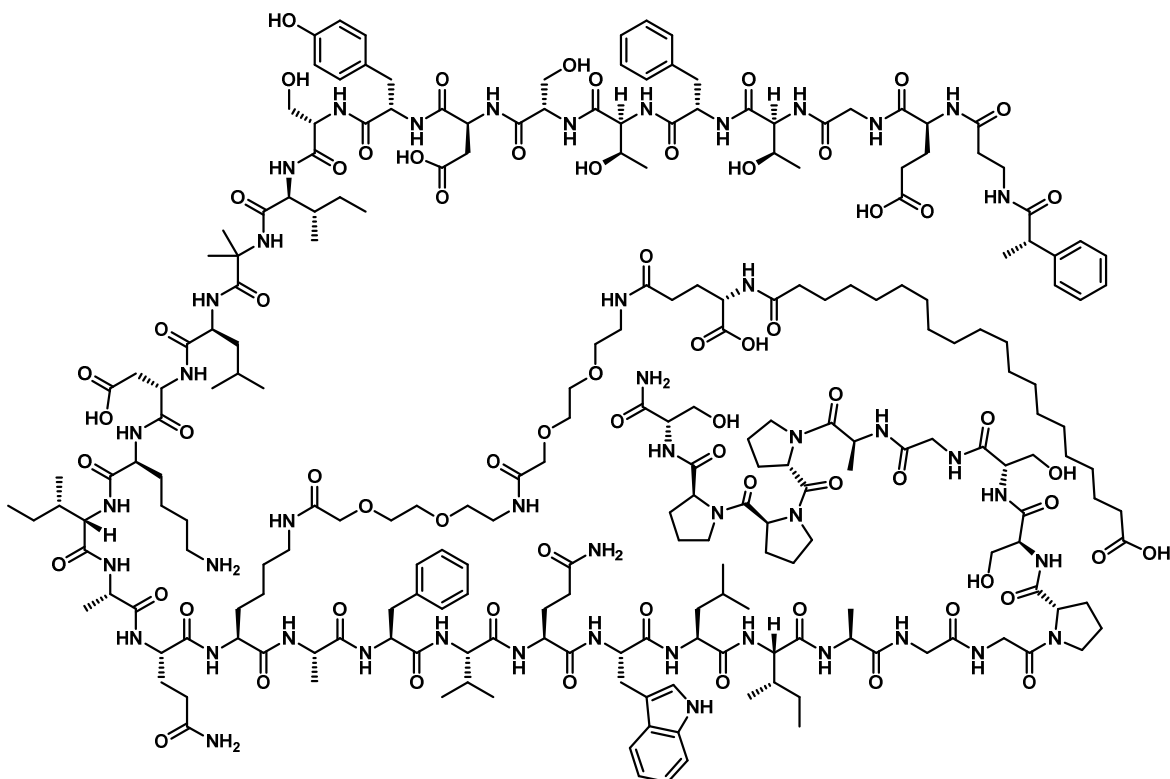
Compound 208,



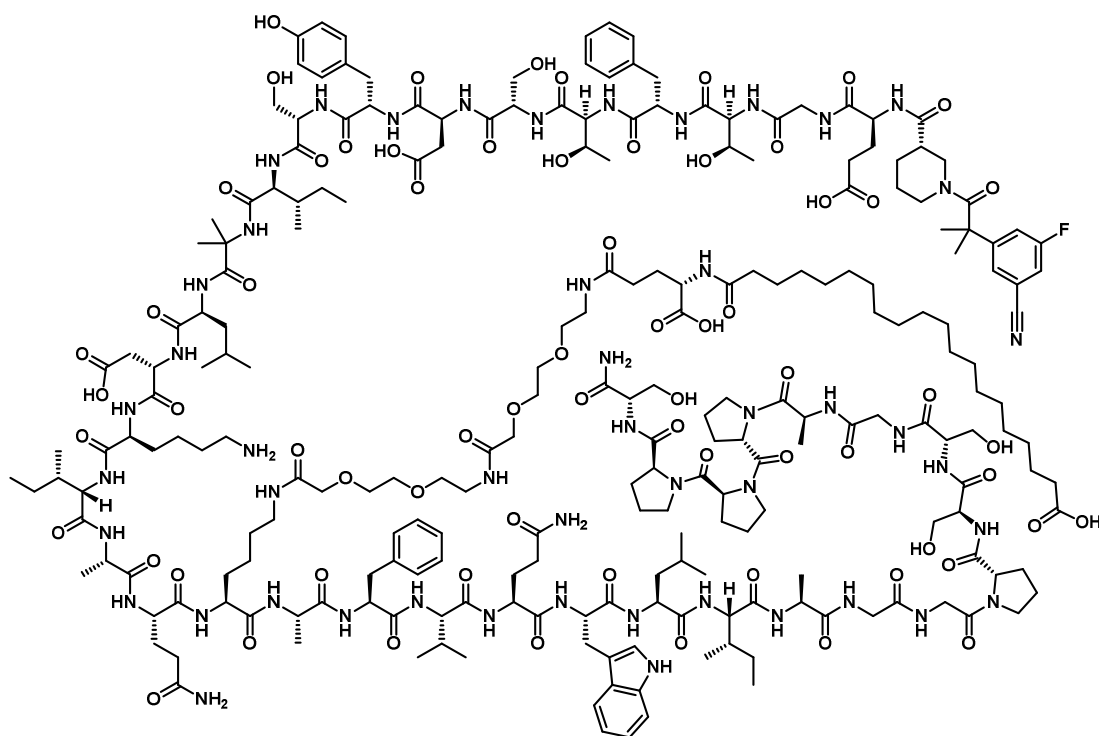
Compound 209,



Compound 210,

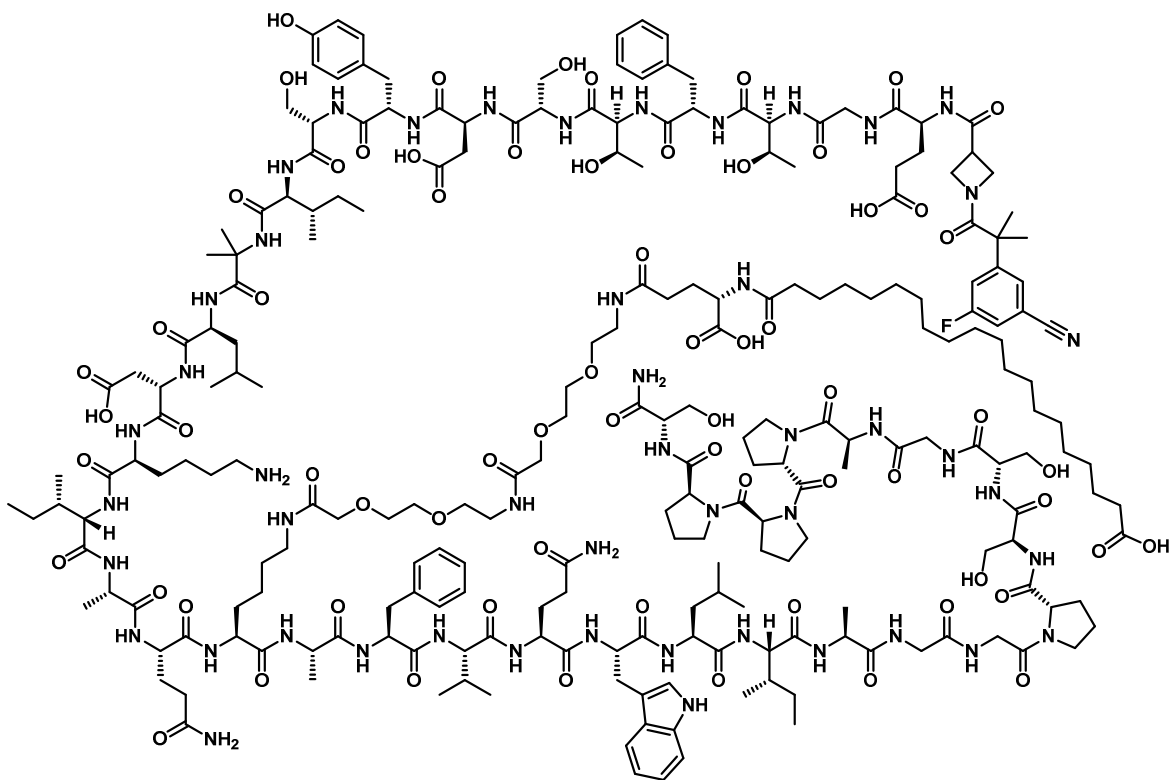


Compound 211,

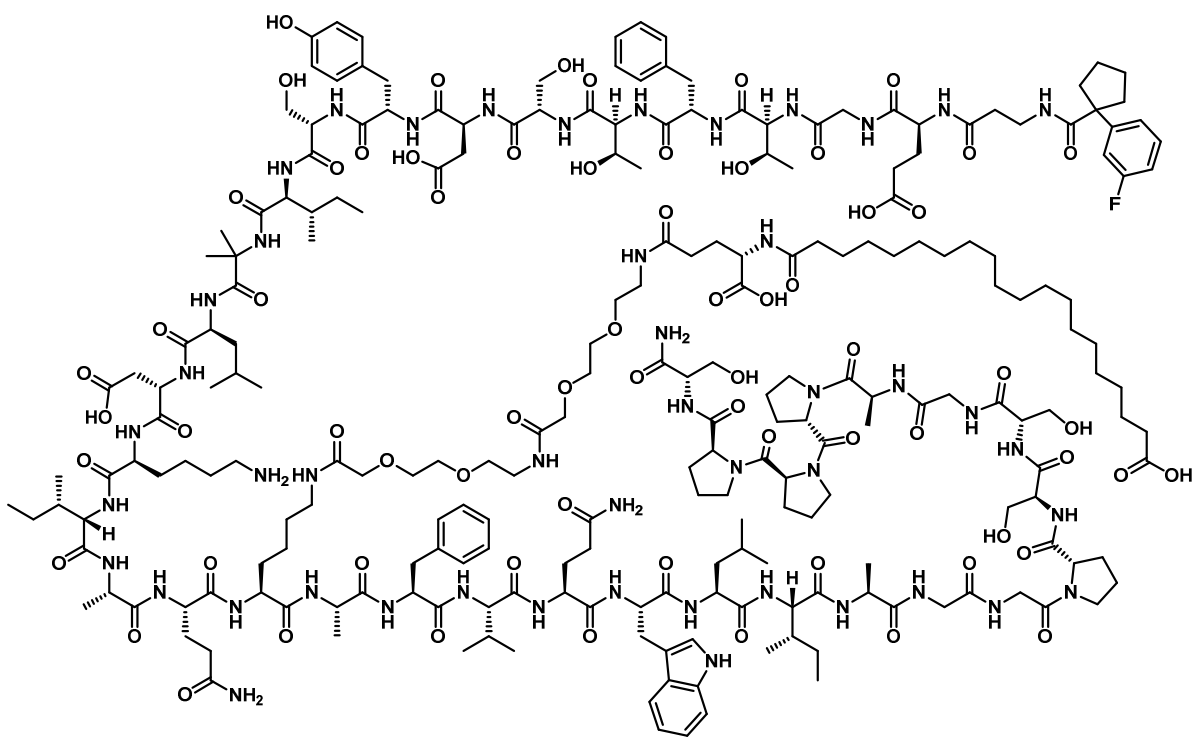


Compound 212,

8kkk



Compound 213,

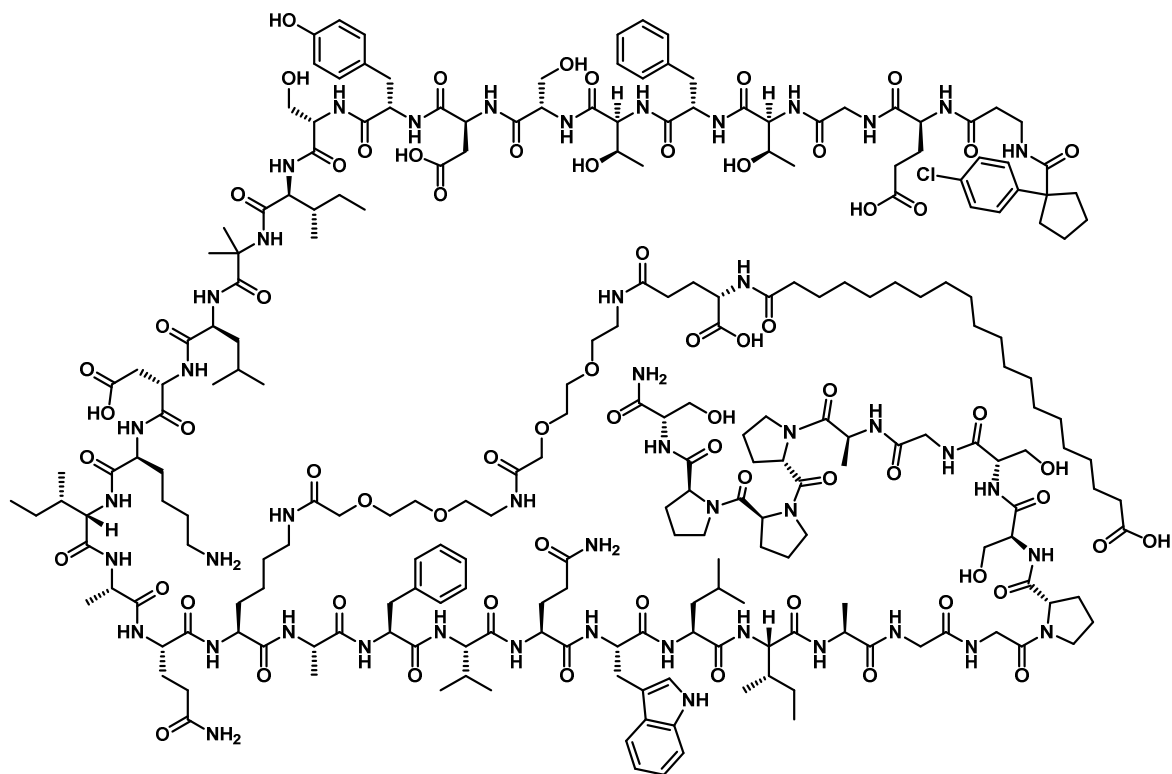


Compound 214,

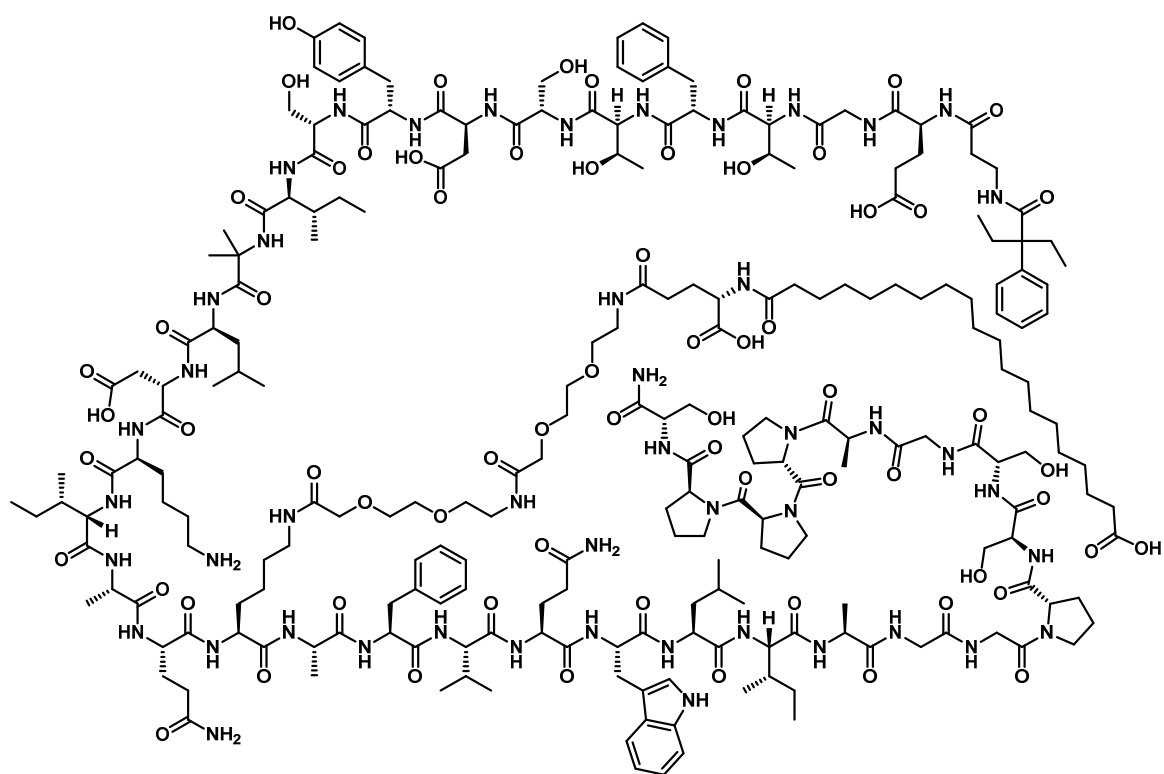
[illegible]

Compound 216,

8mm

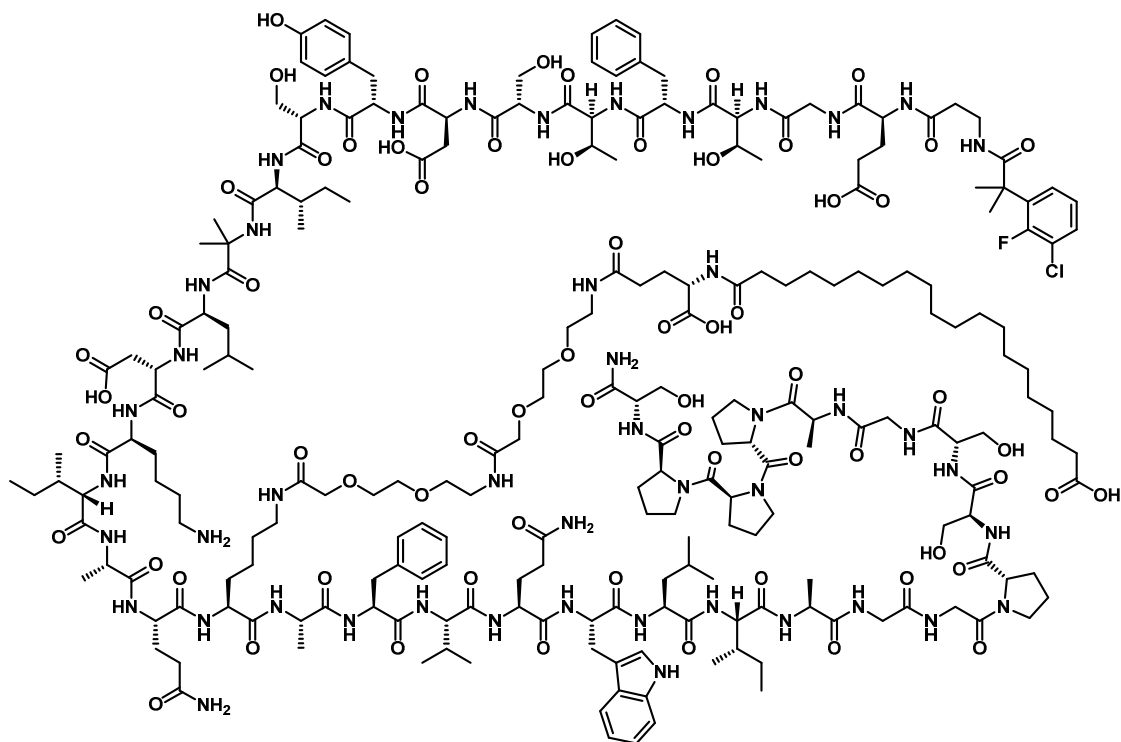


Compound 217,

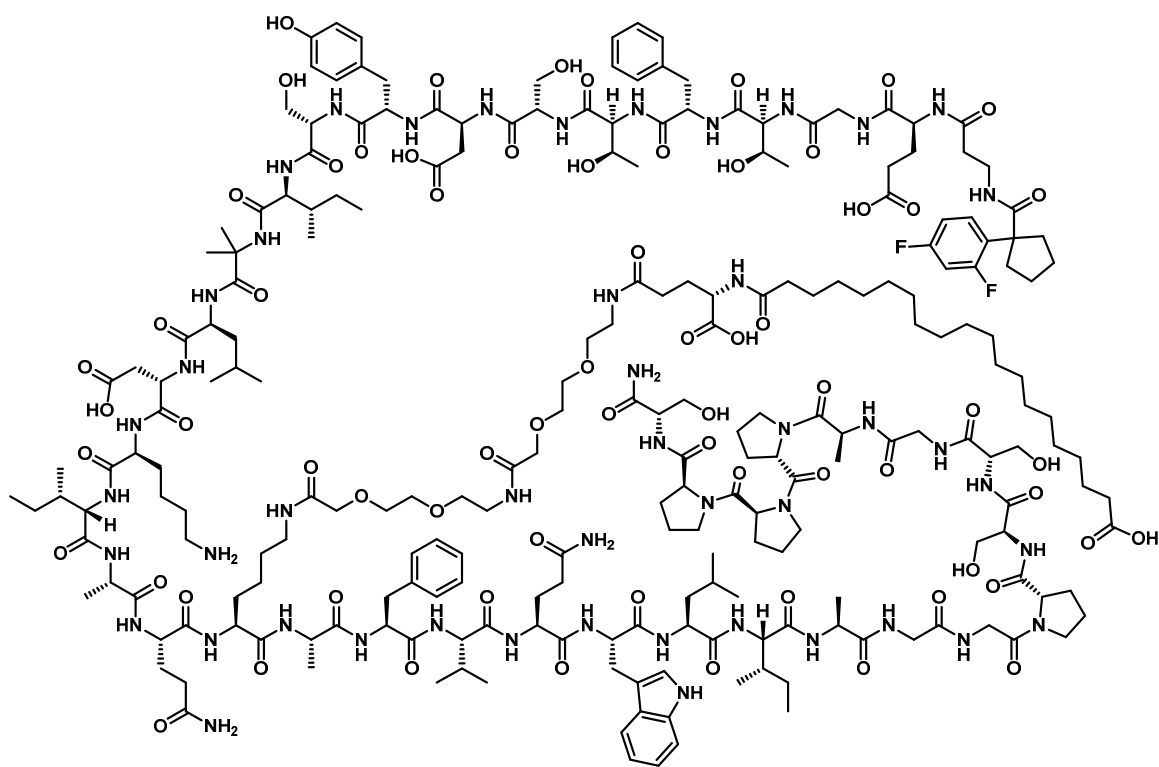


Compound 218,

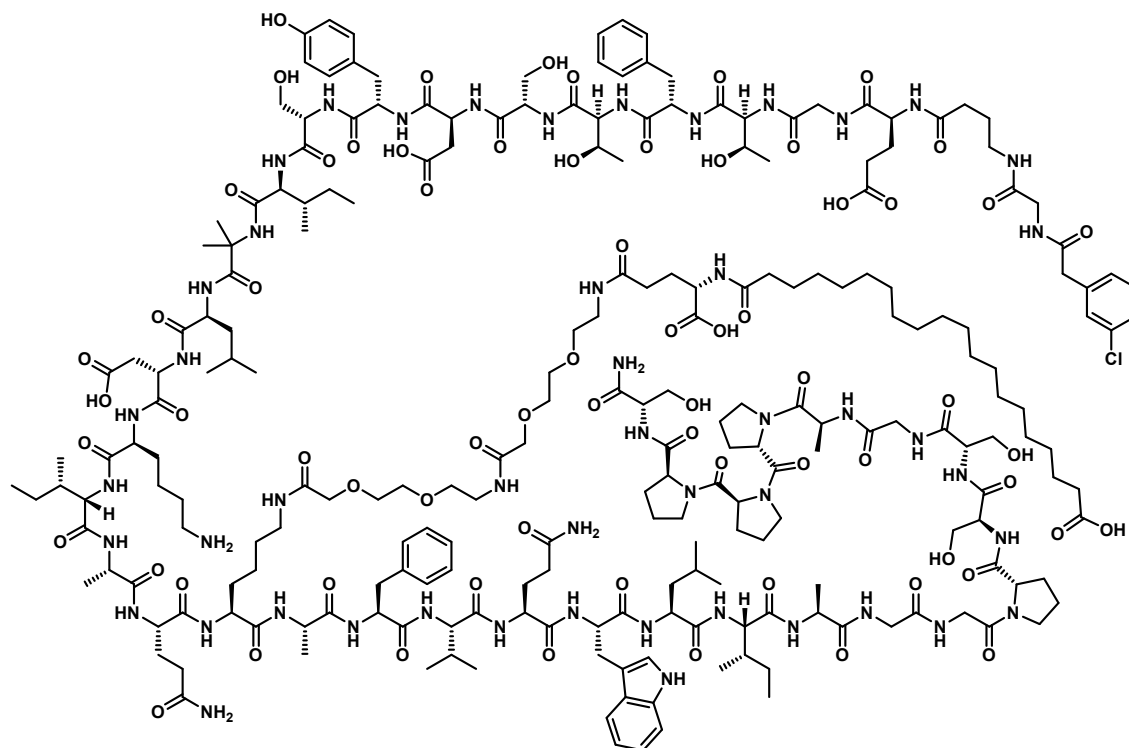
8nnn



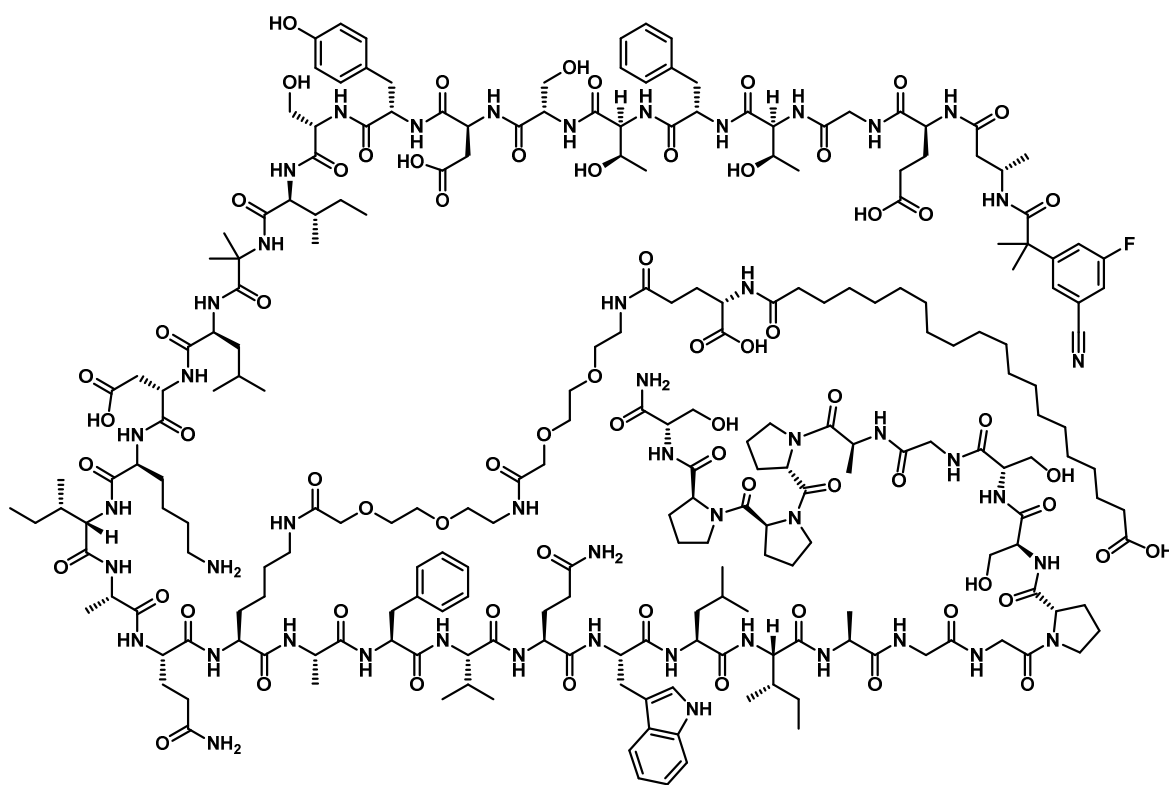
Compound 219,



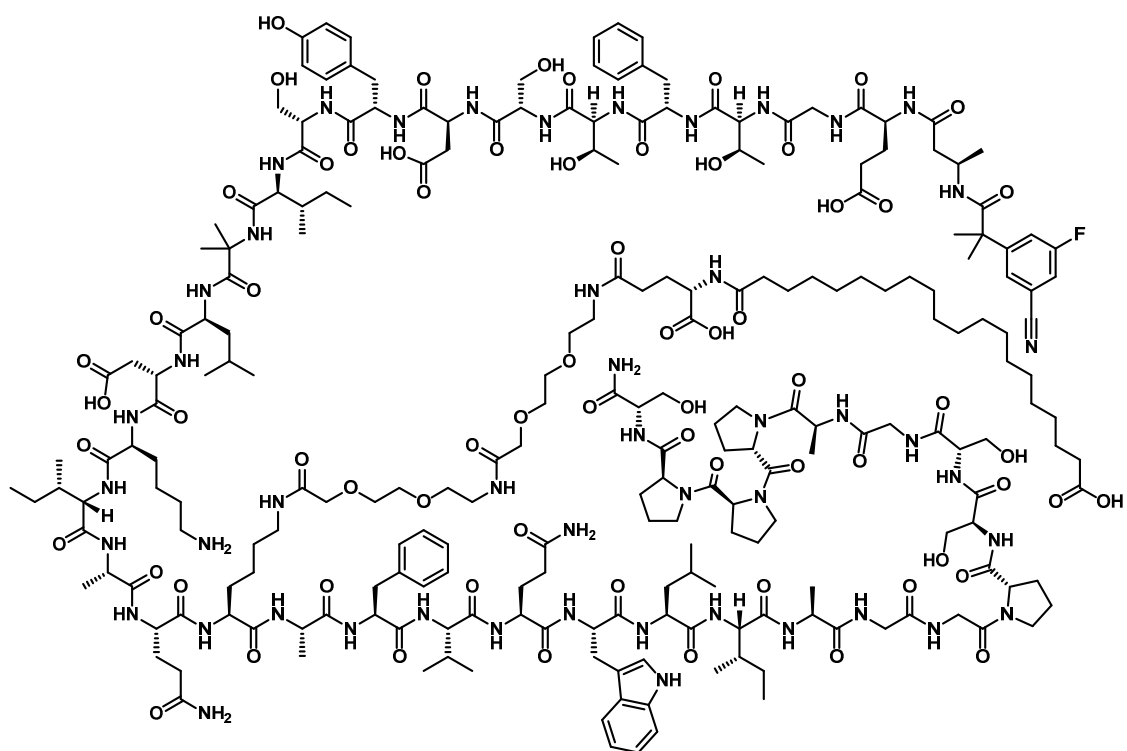
Compound 220,



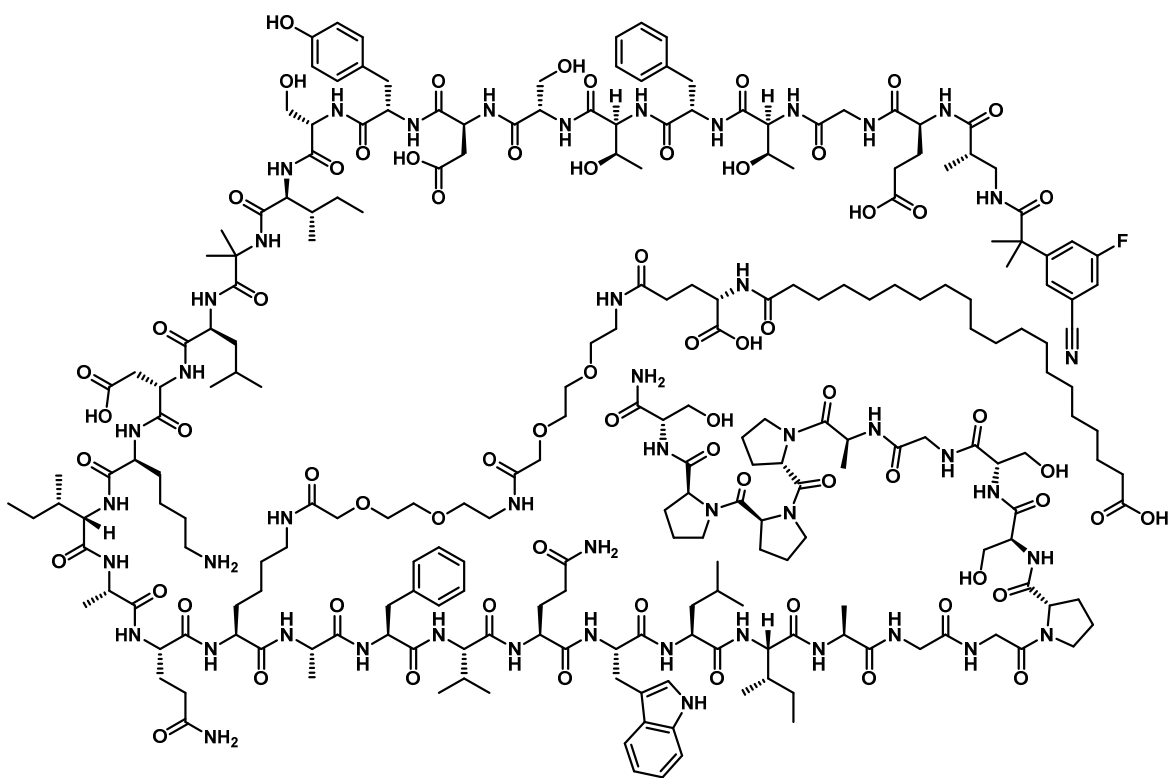
Compound 221,



Compound 222,

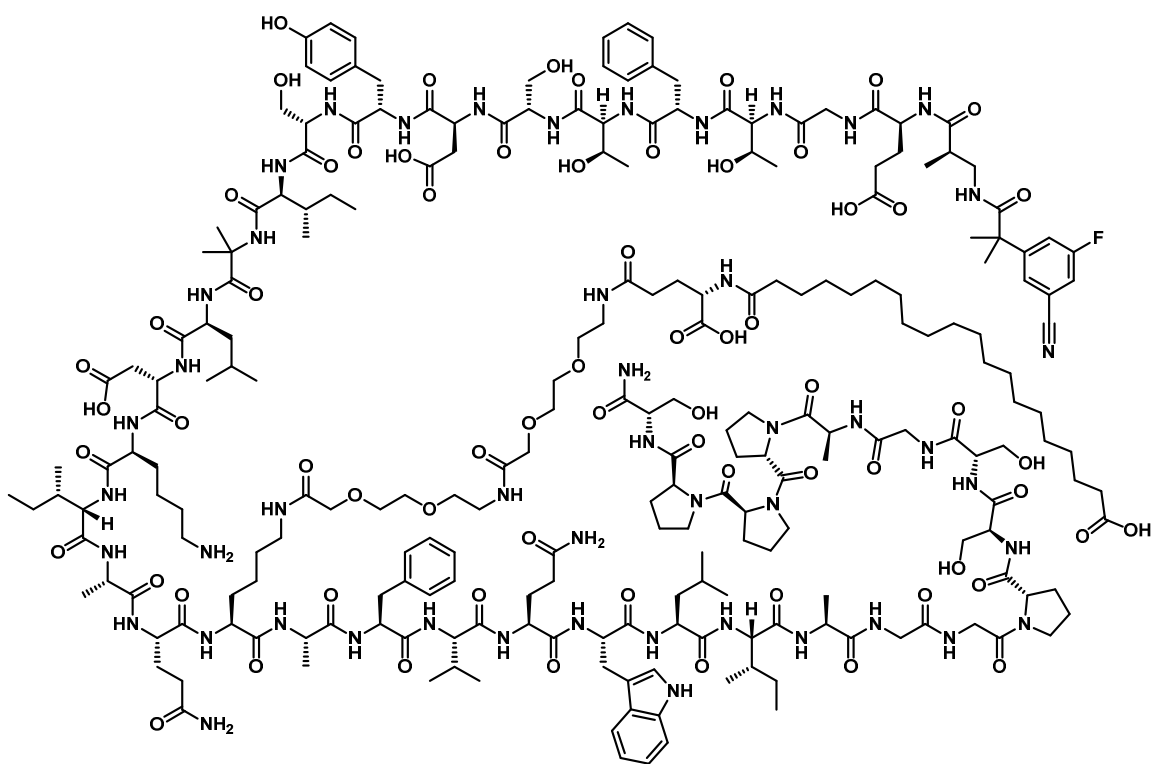


Compound 223,

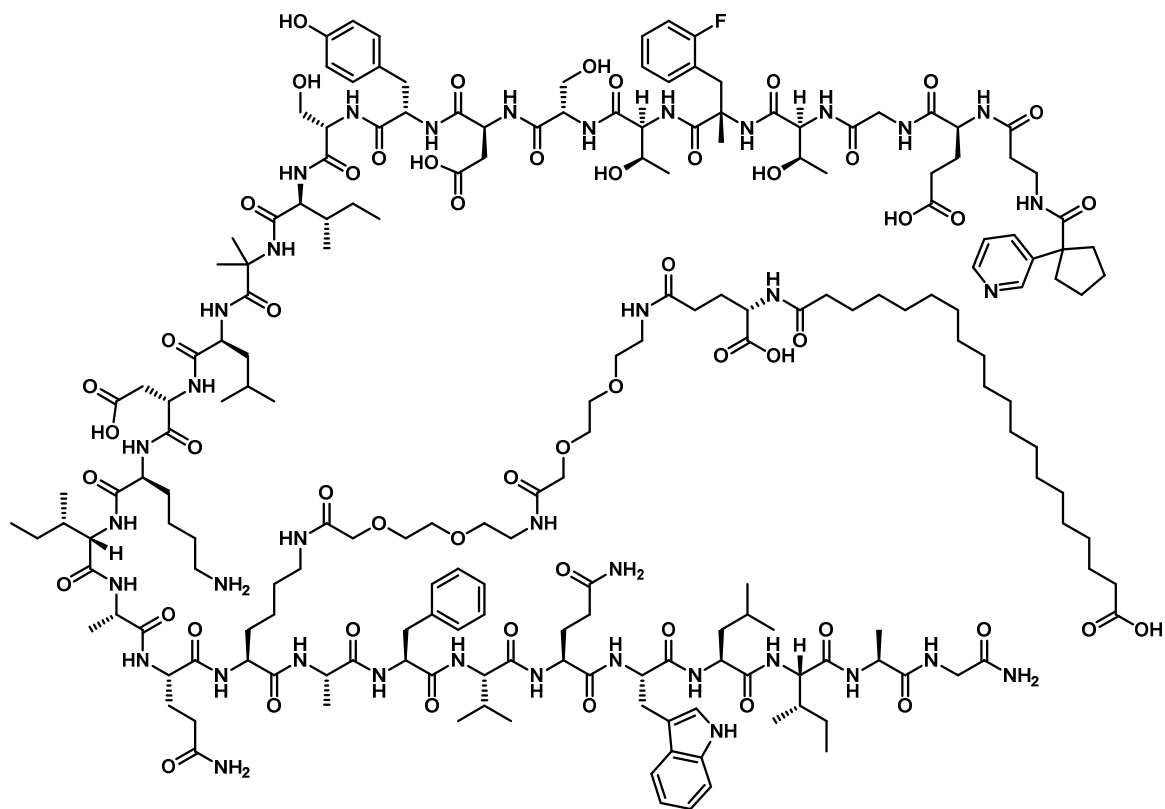


Compound 224,

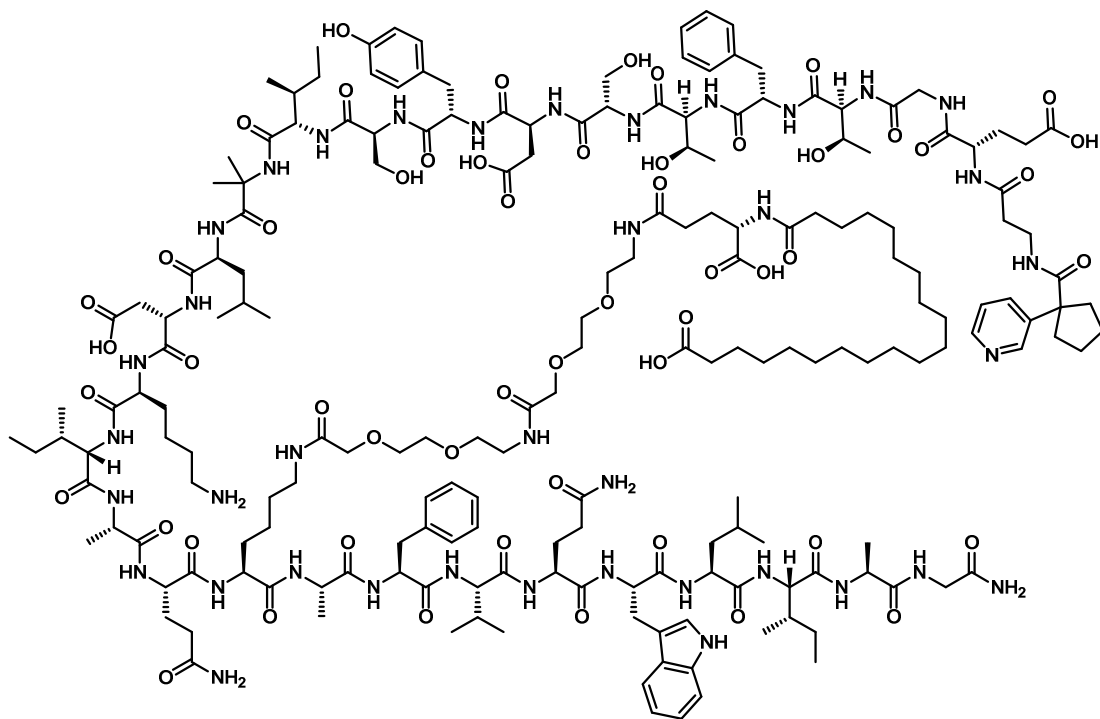
8qqq



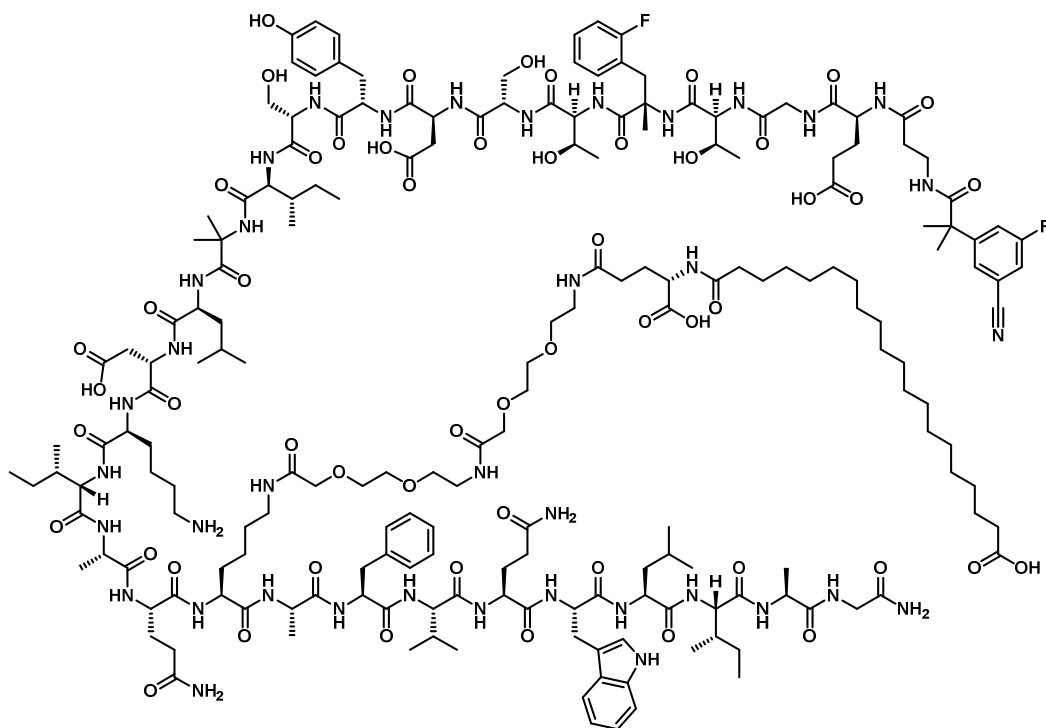
Compound 225,



Compound 226,

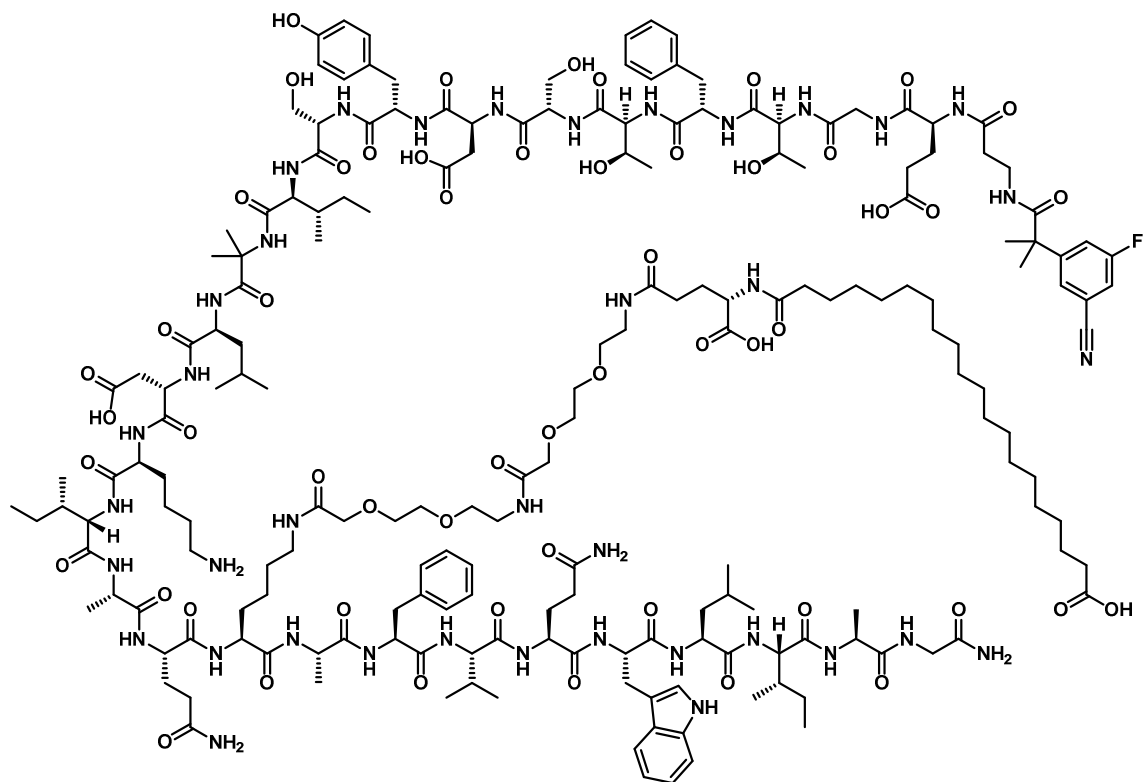


Compound 227,

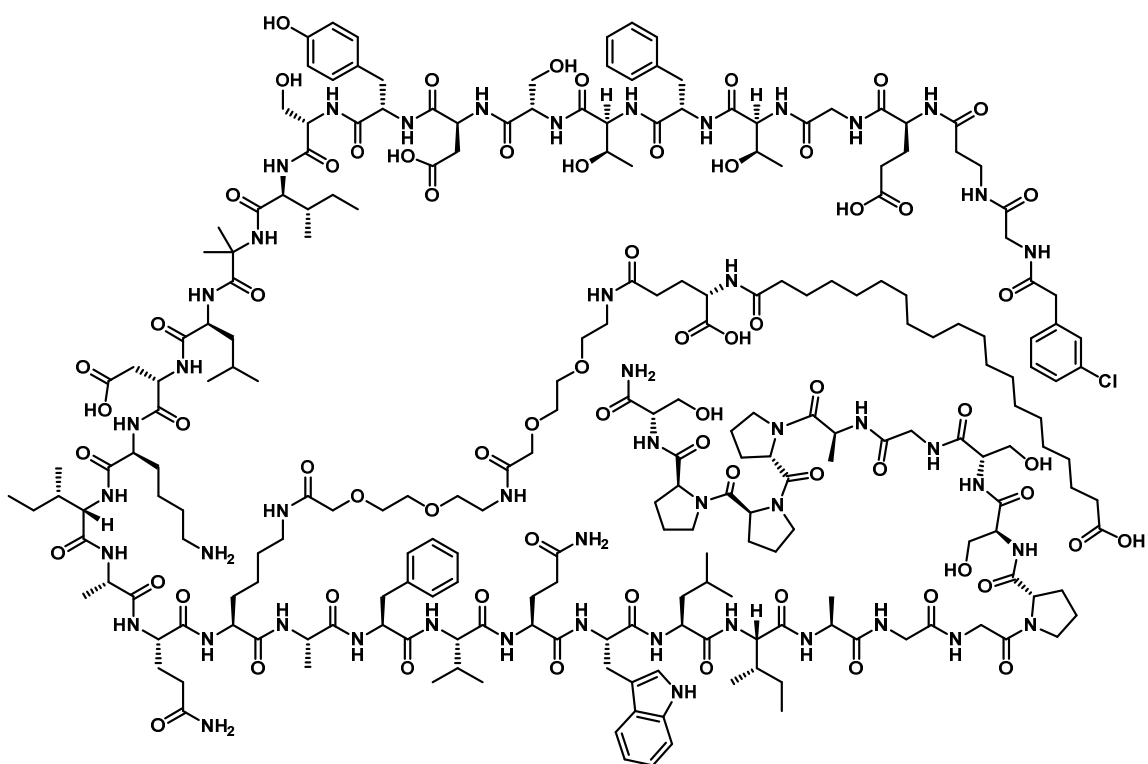


Compound 228,

8ttt

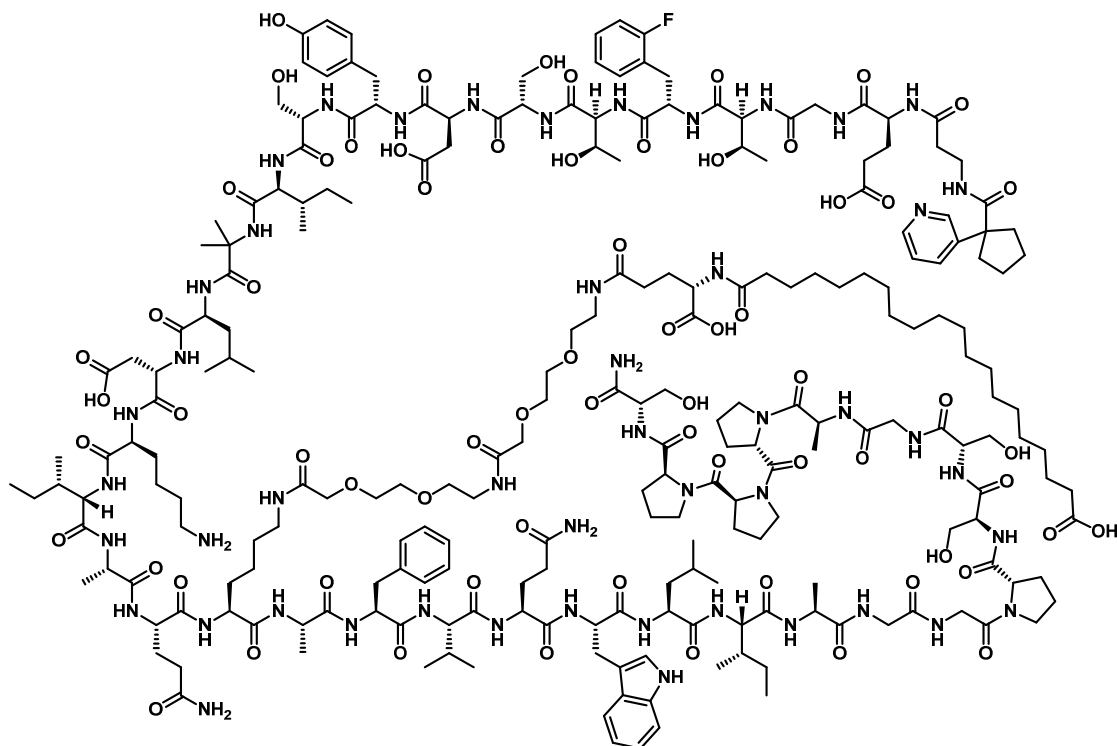


Compound 229,

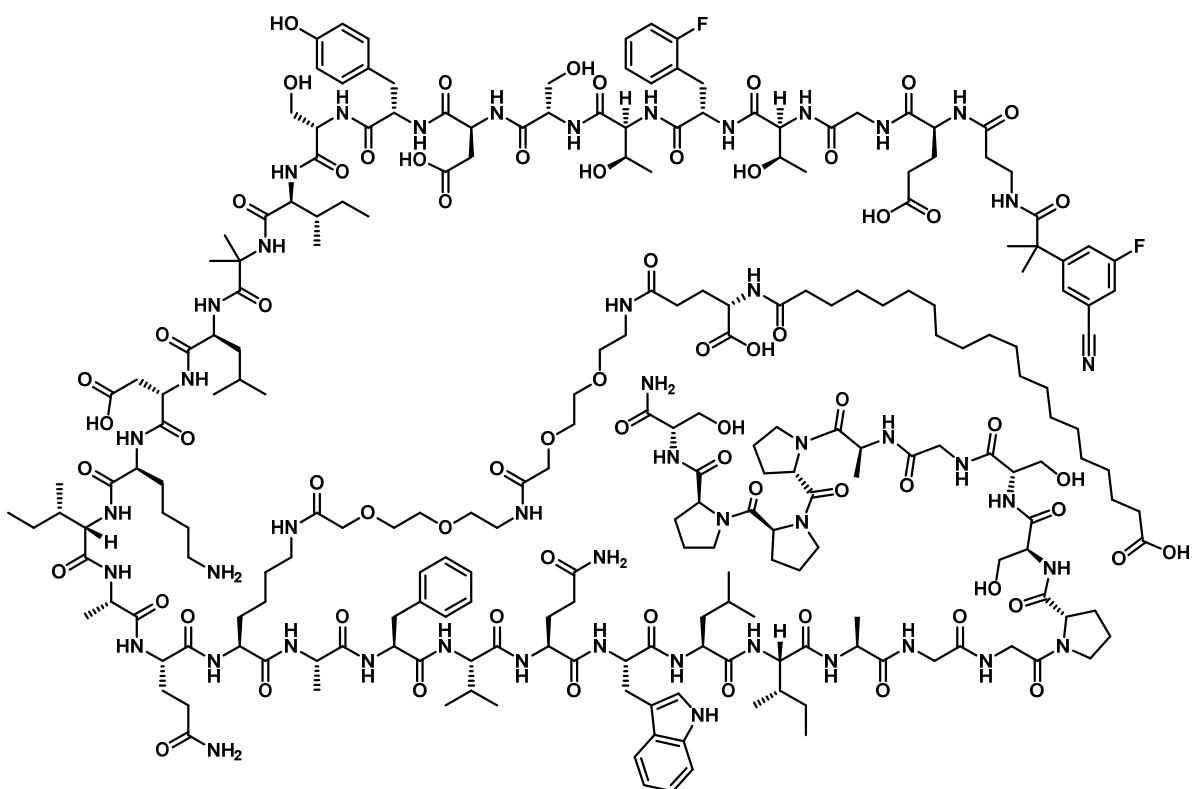


Compound 230,

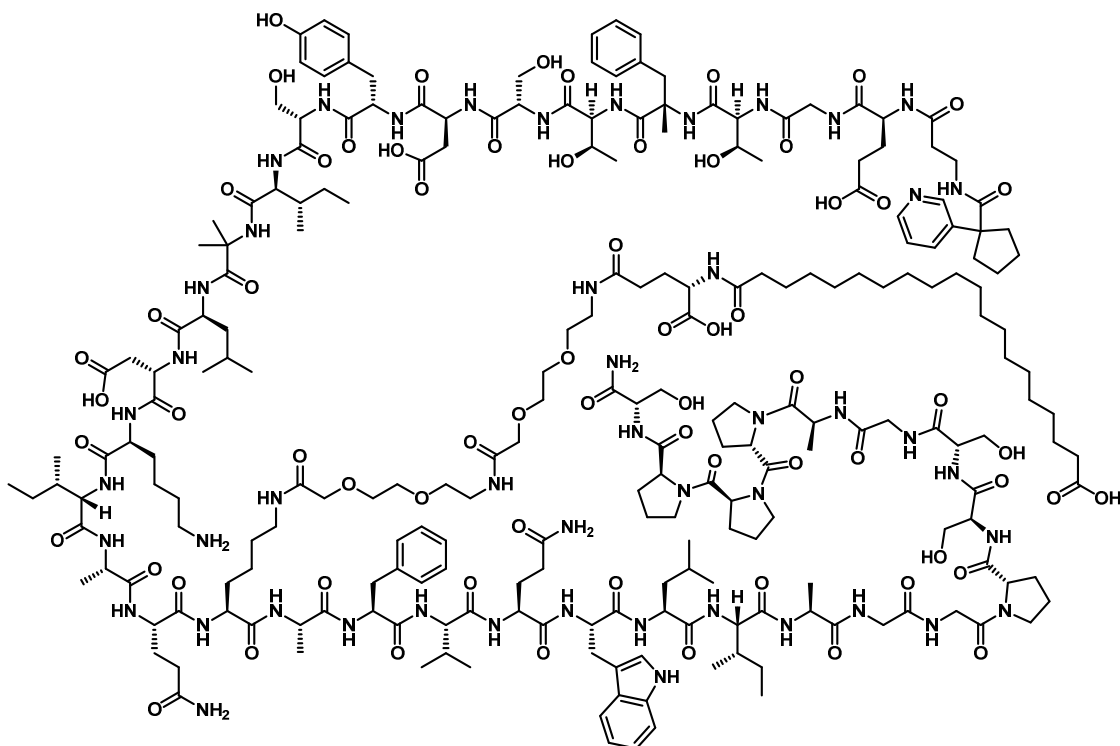
8uuu



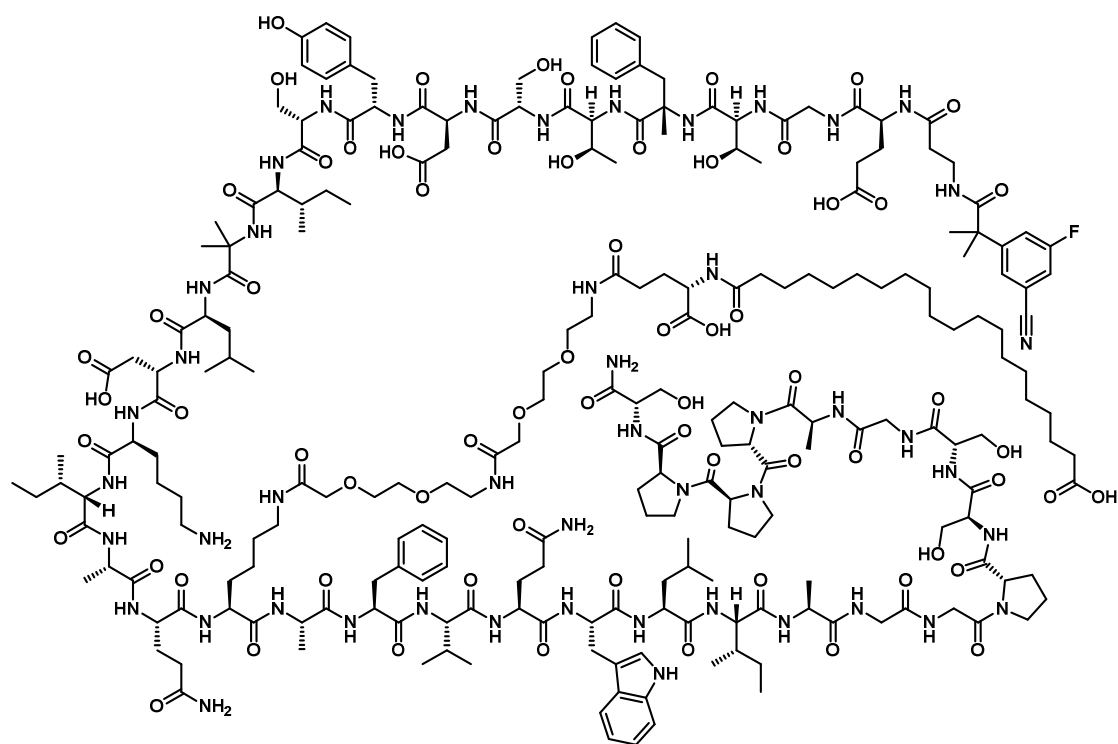
Compound 231,



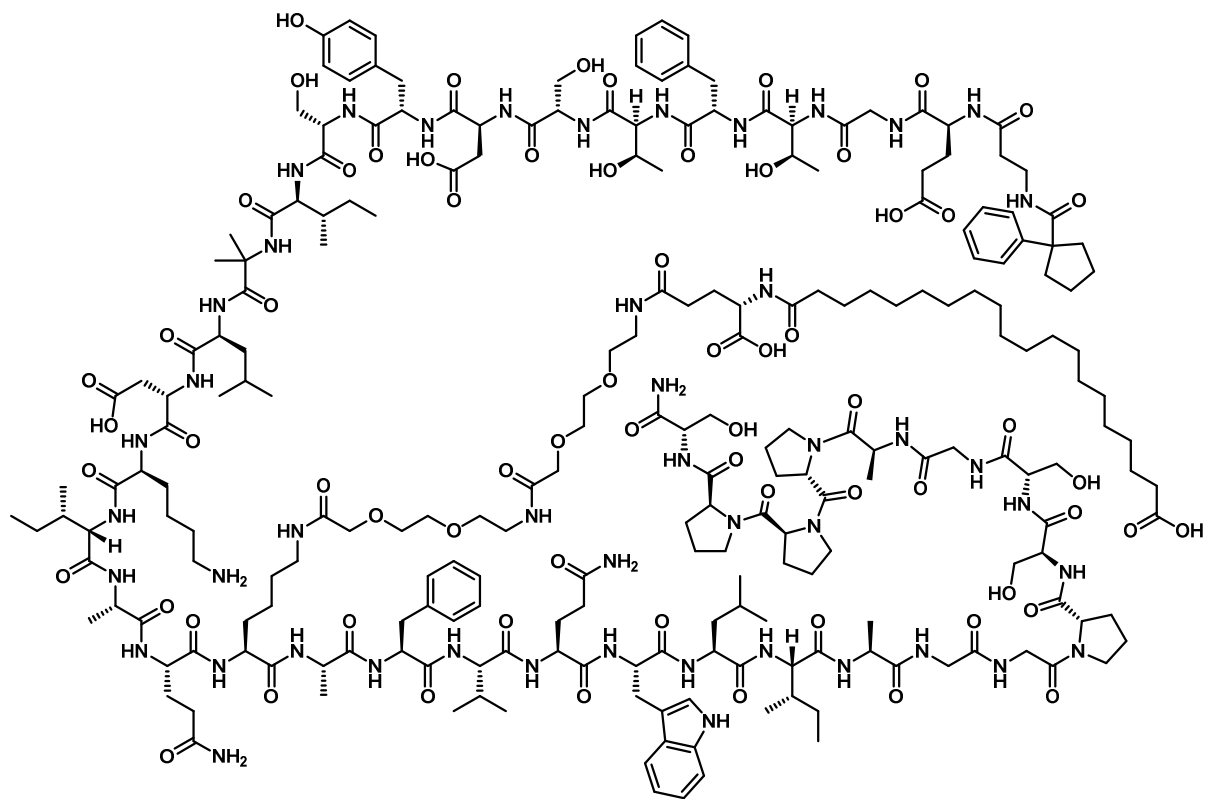
Compound 233,



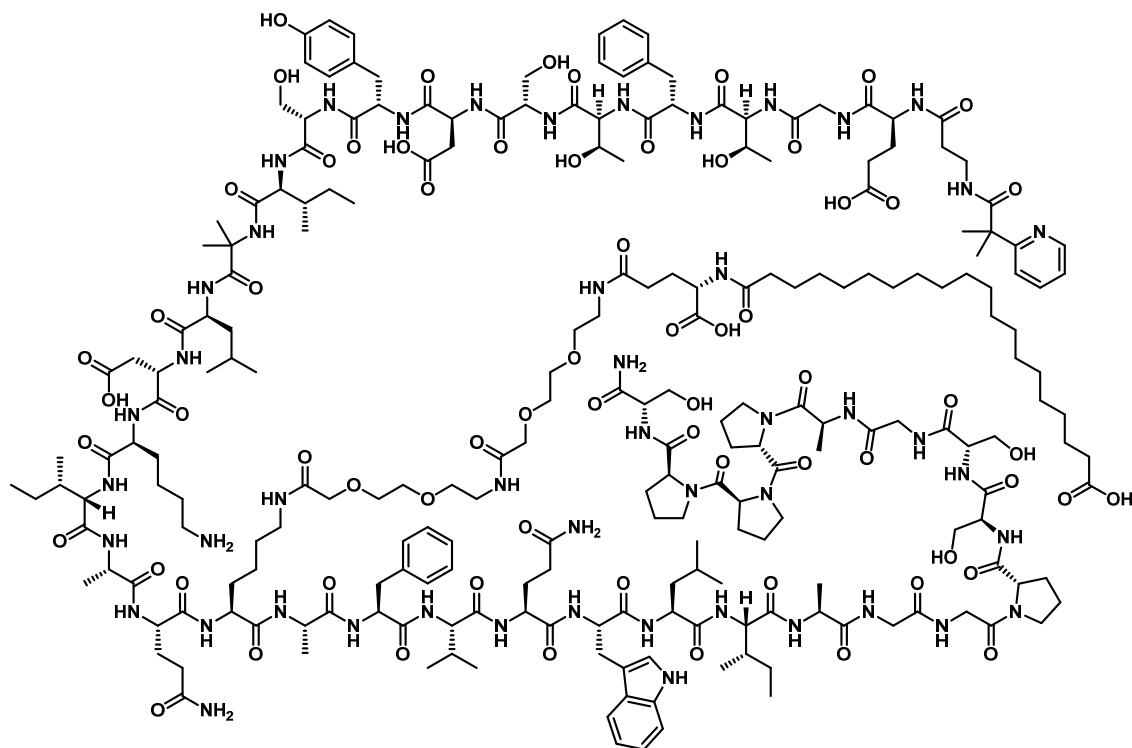
Compound 234,



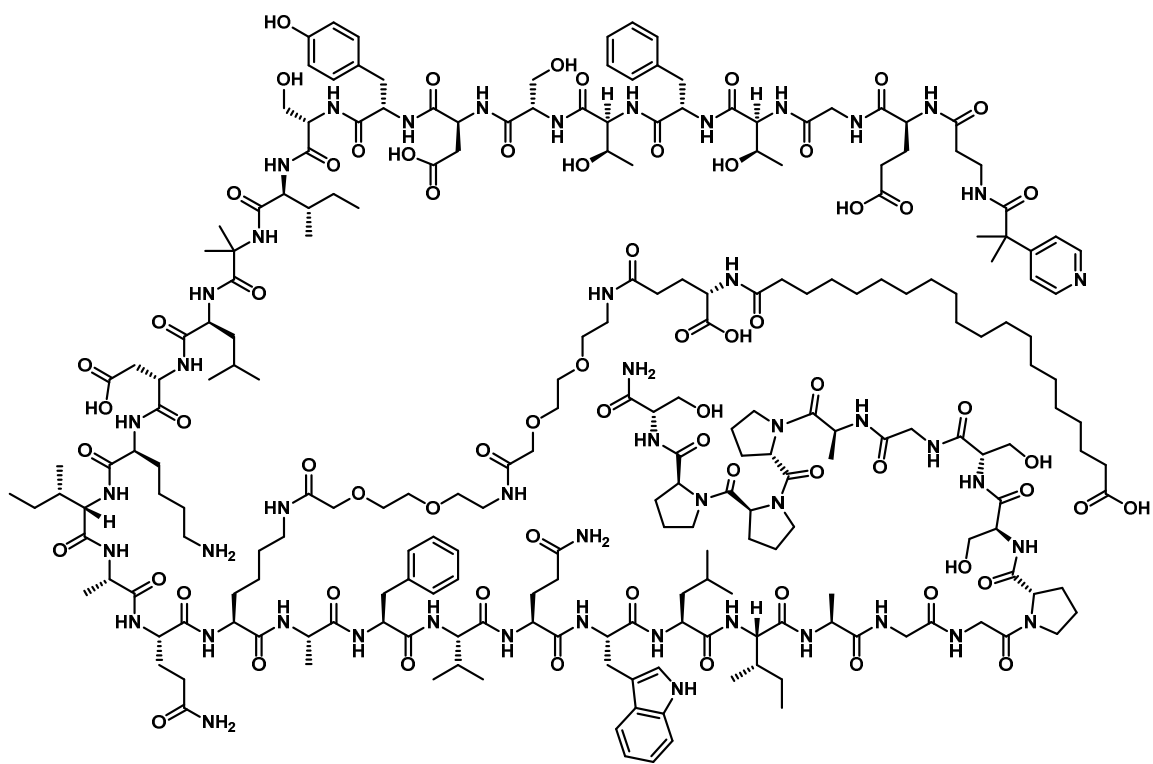
Compound 235,



Compound 236,

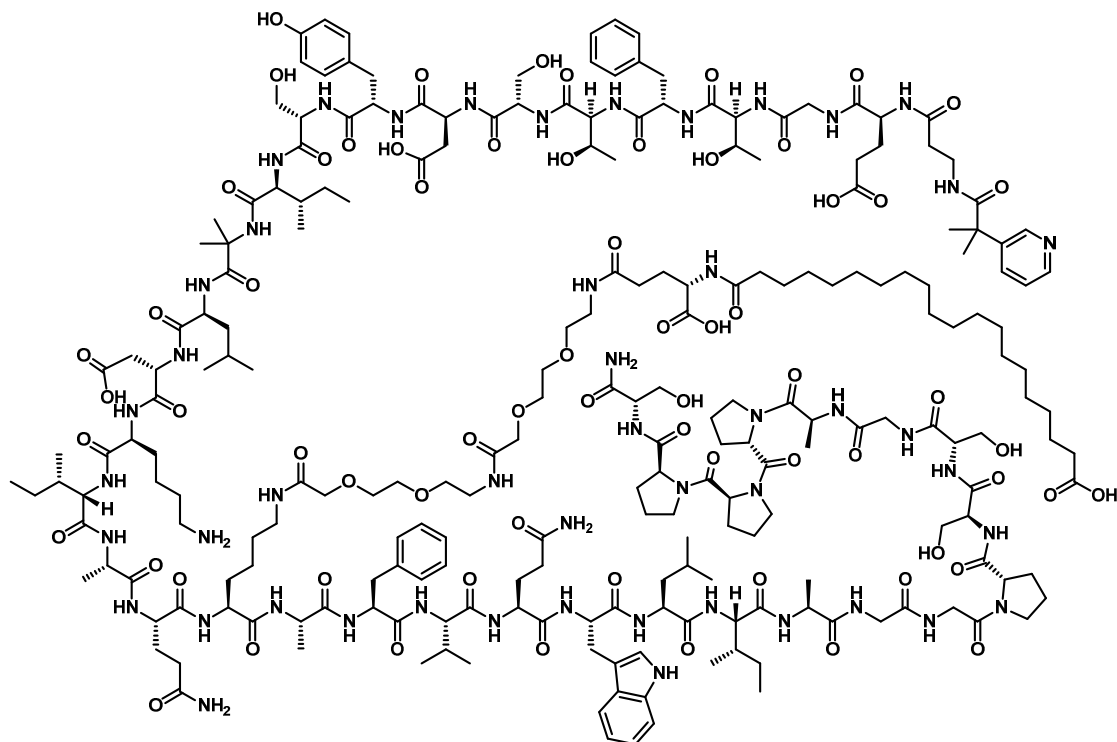


Compound 237,



Compound 238,

8yyy

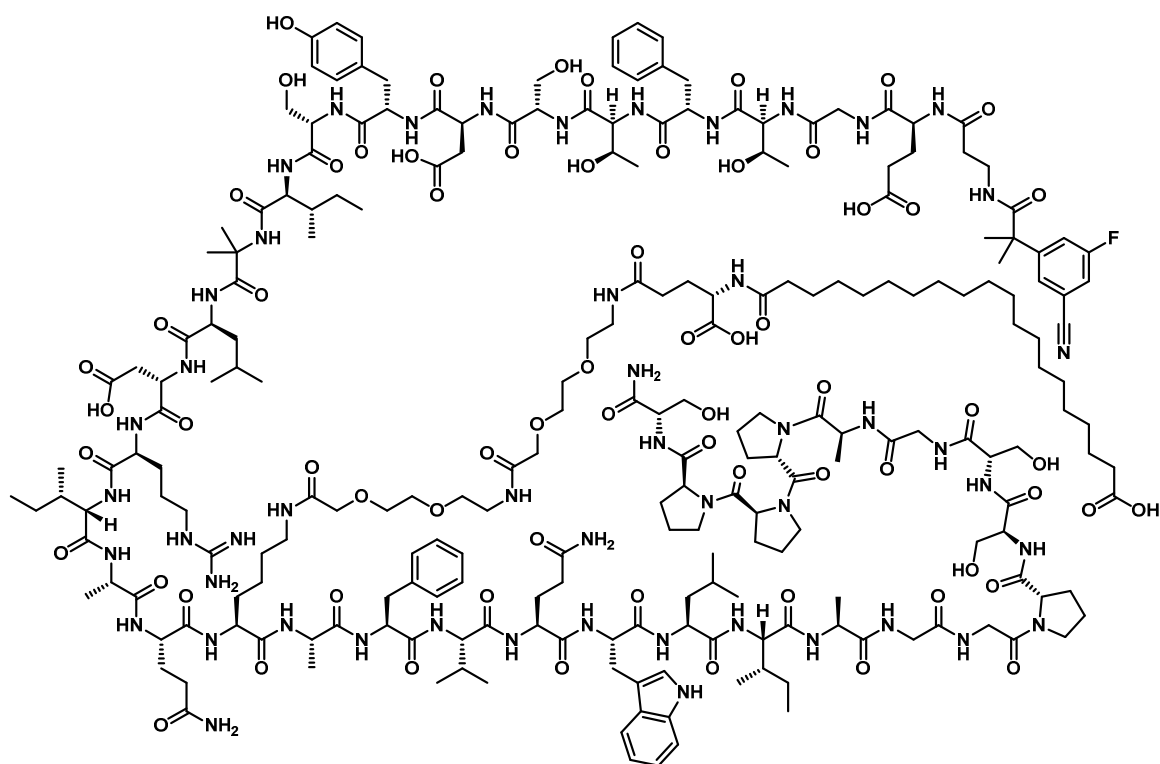


Compound 239,

[illegible]

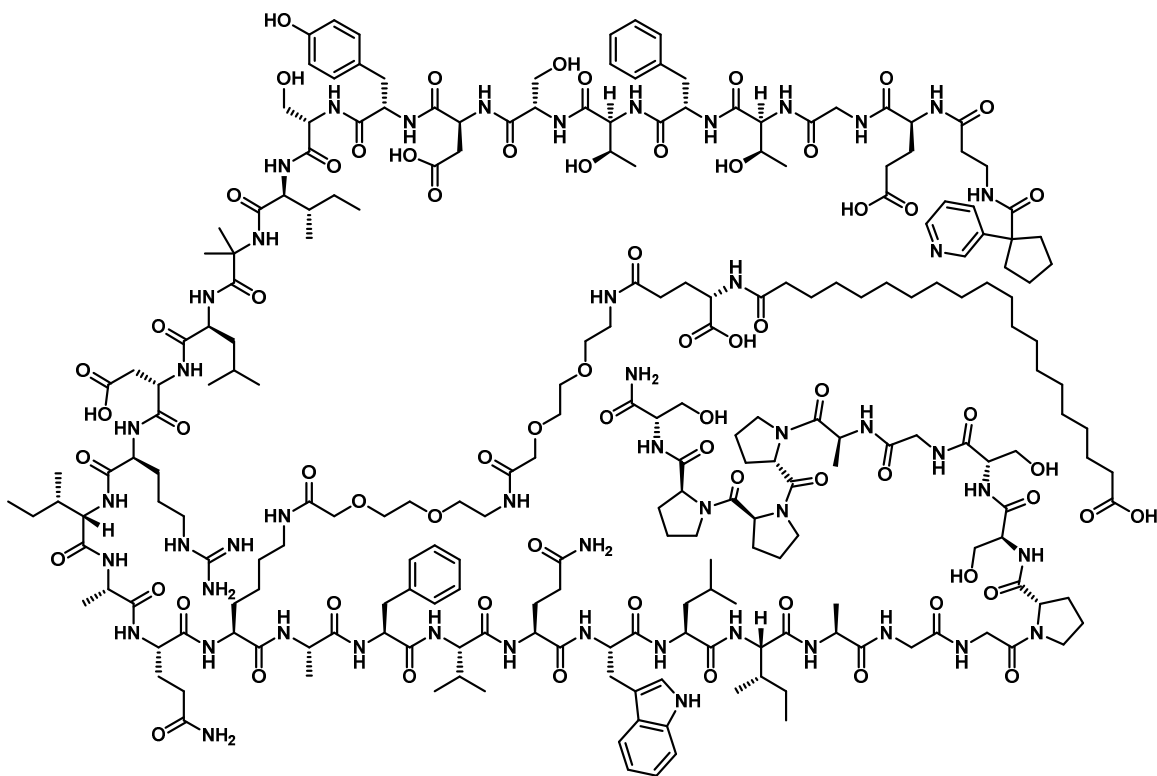
Compound 241,

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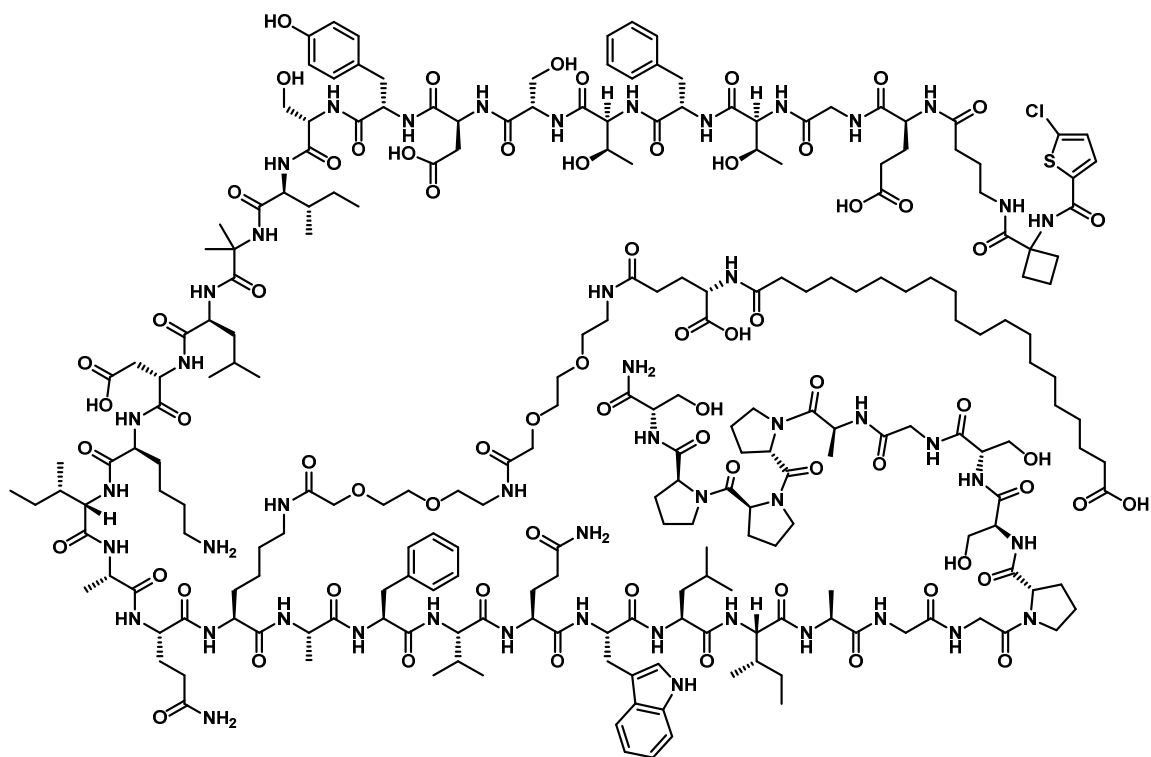
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8bbbb

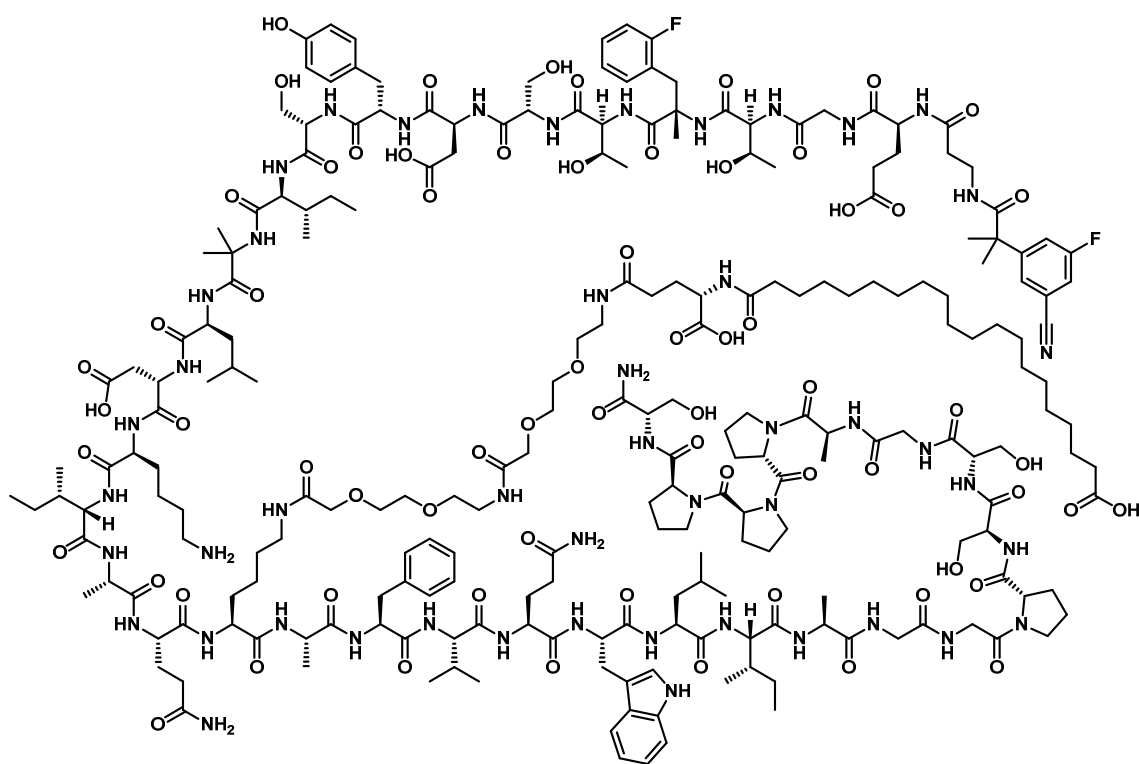


Compound 243,

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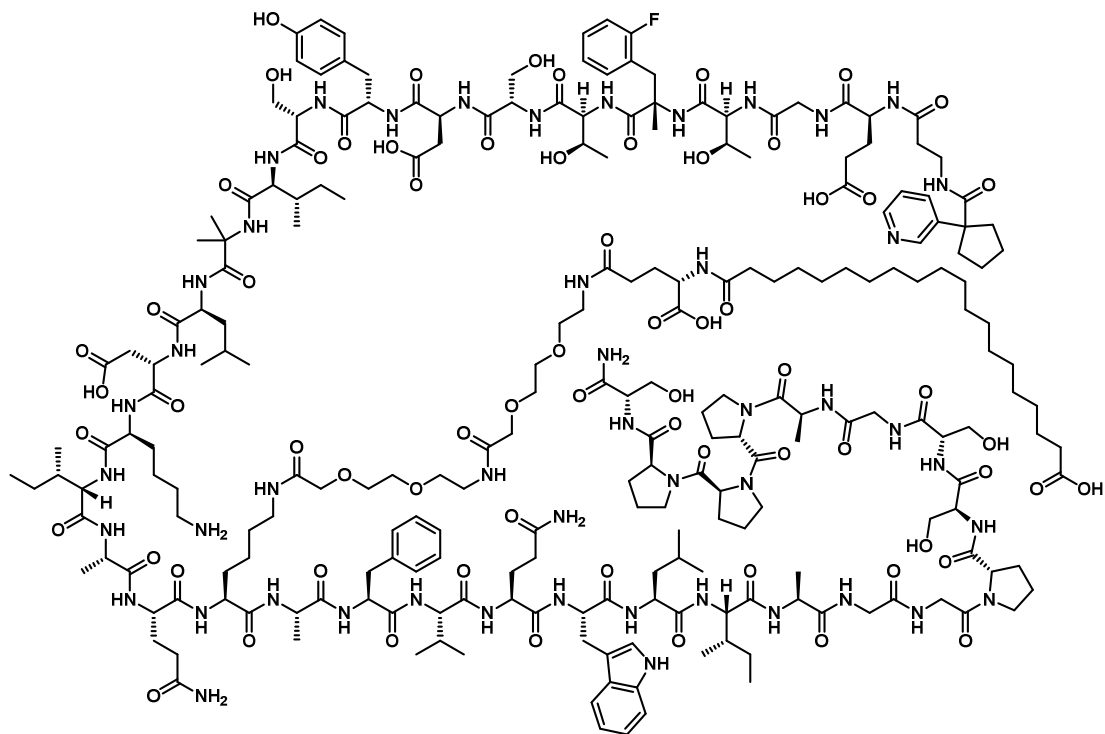


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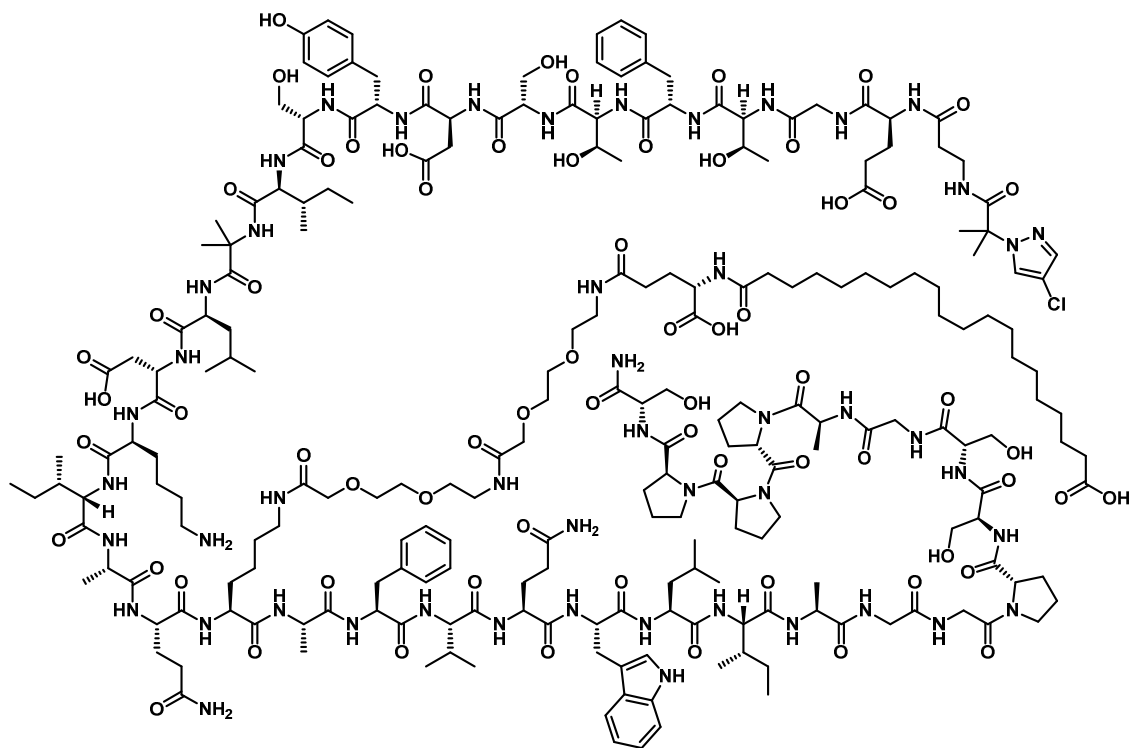


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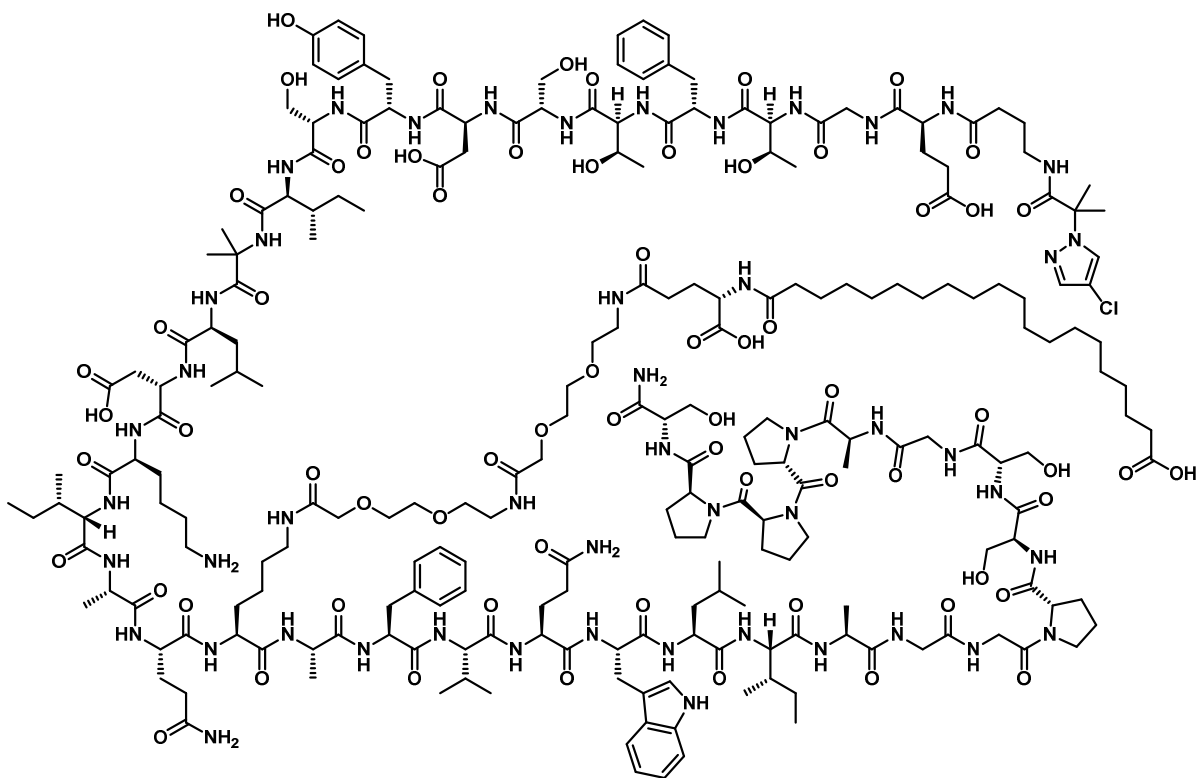
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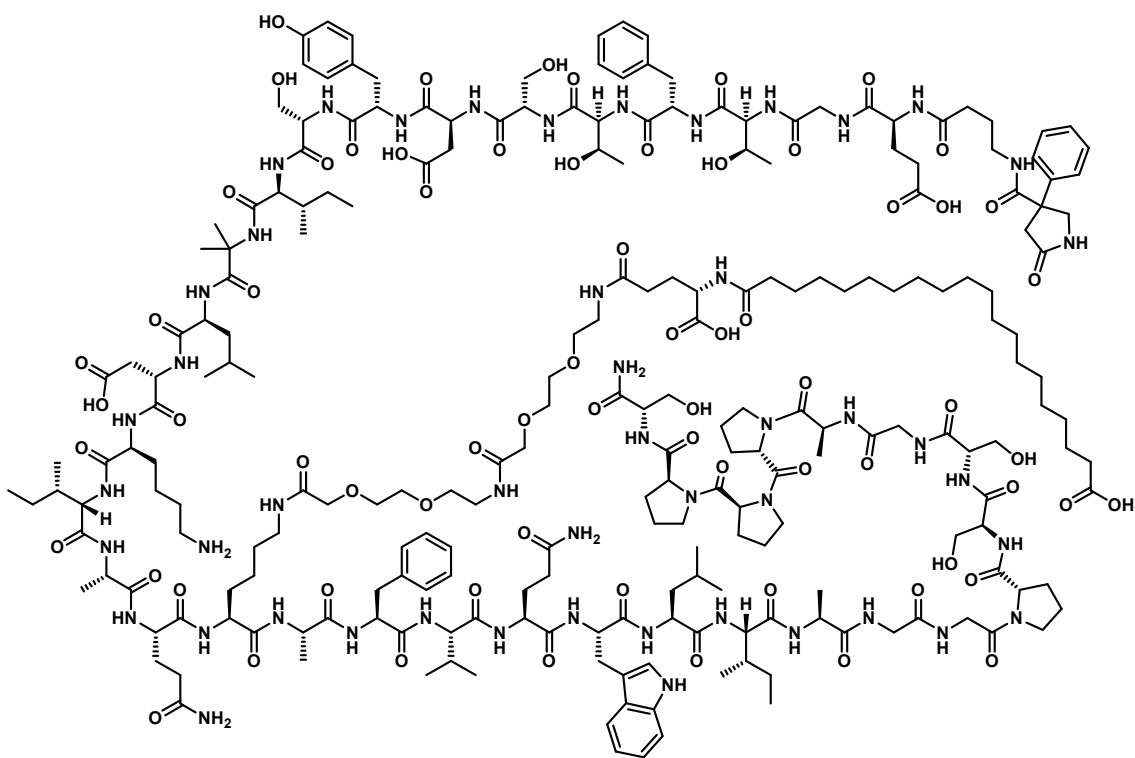
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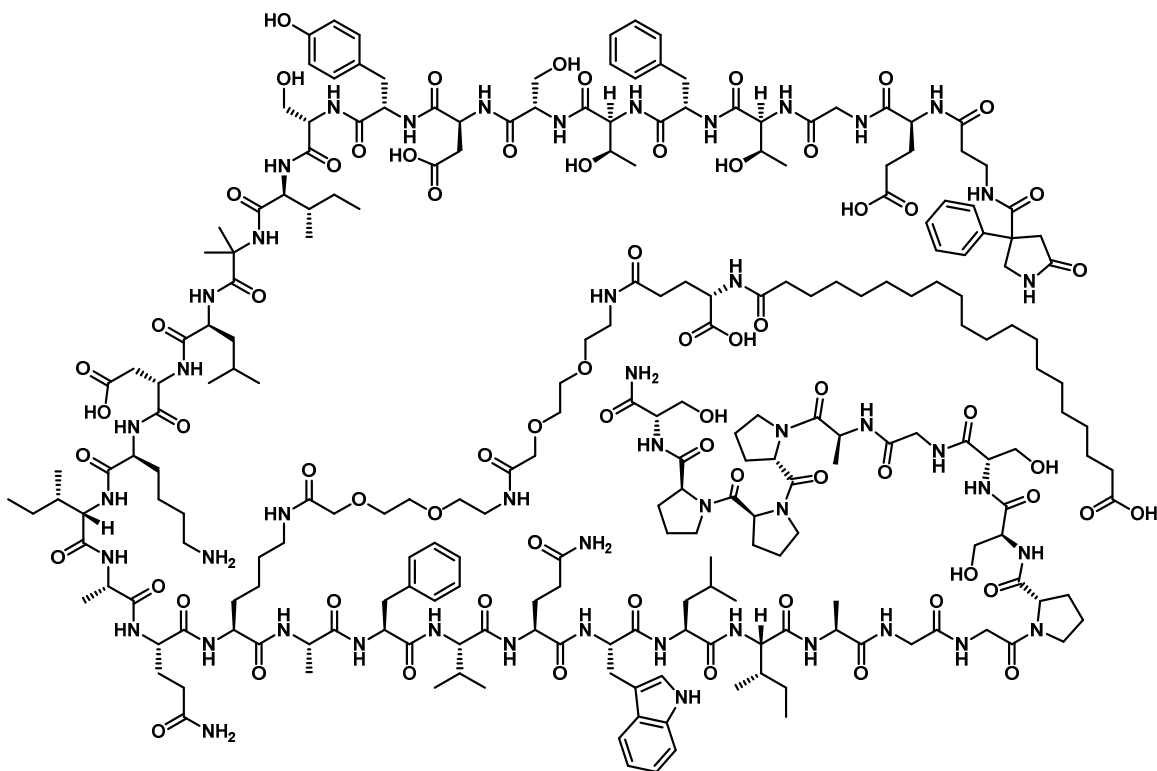
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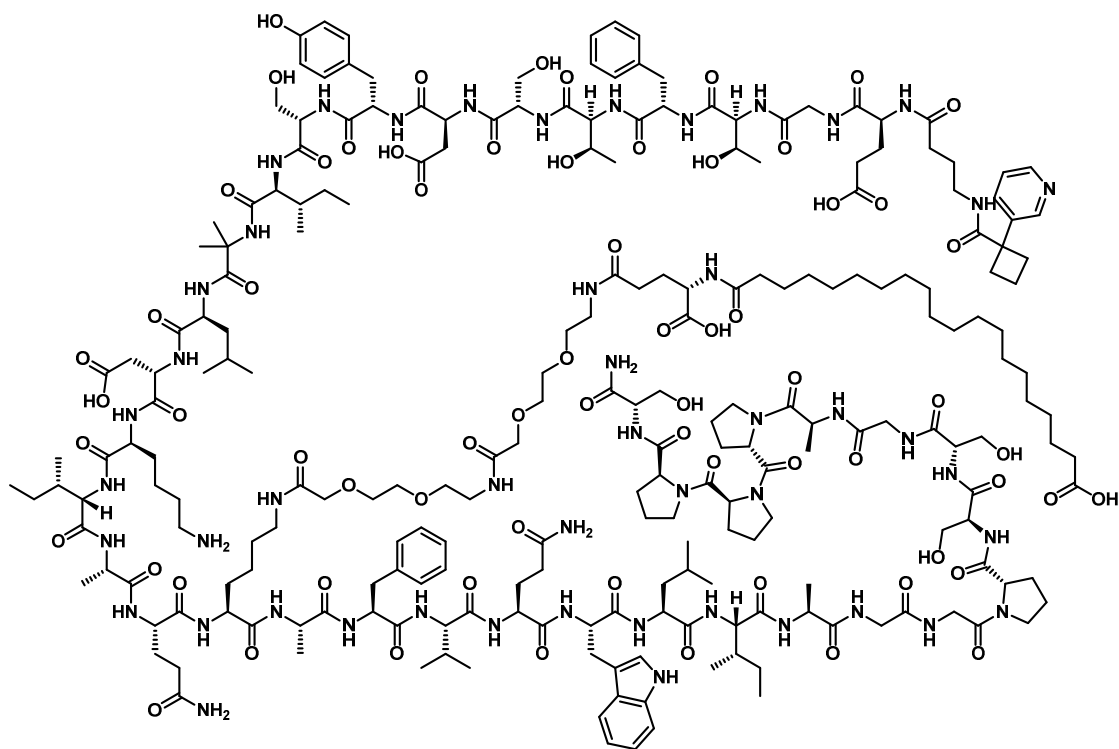
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Compound 249,



Compound 250,

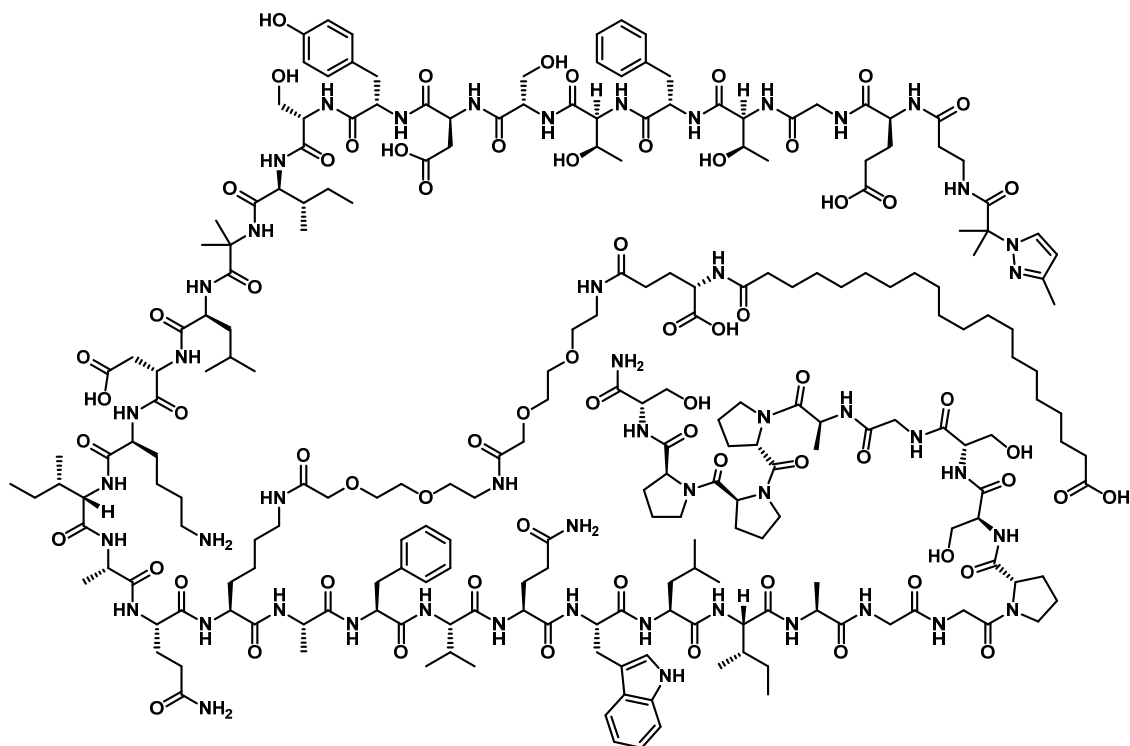


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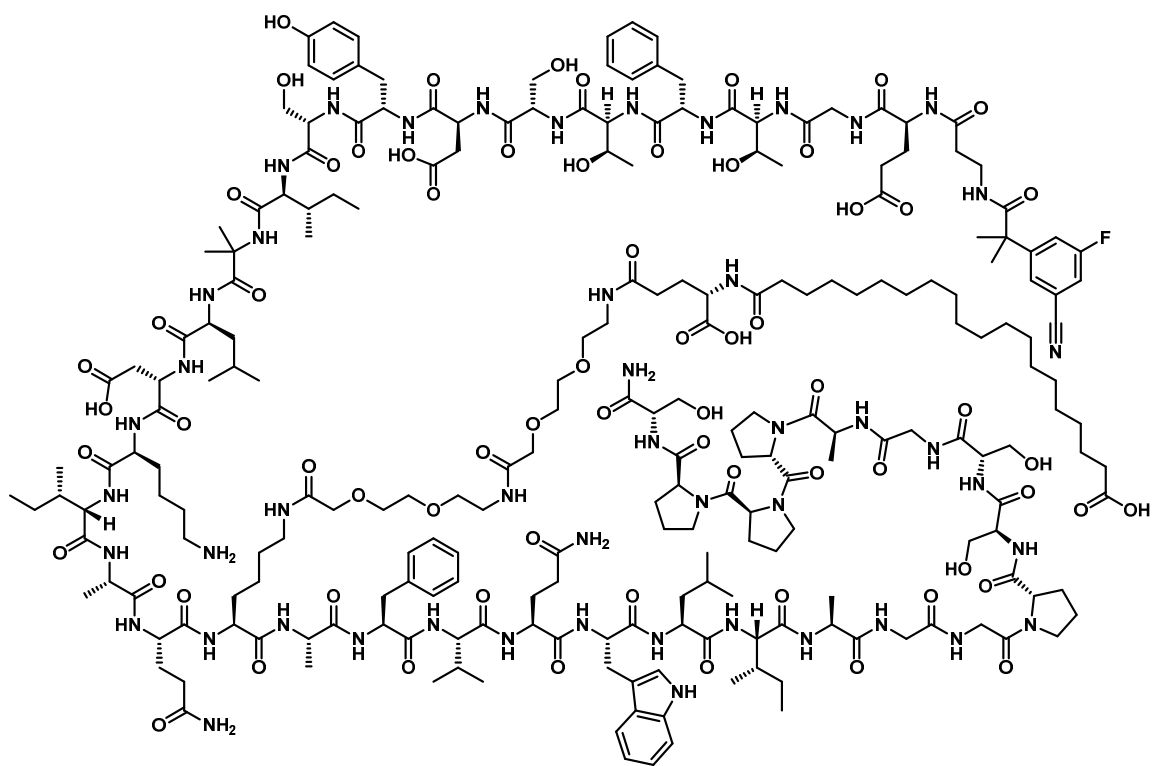
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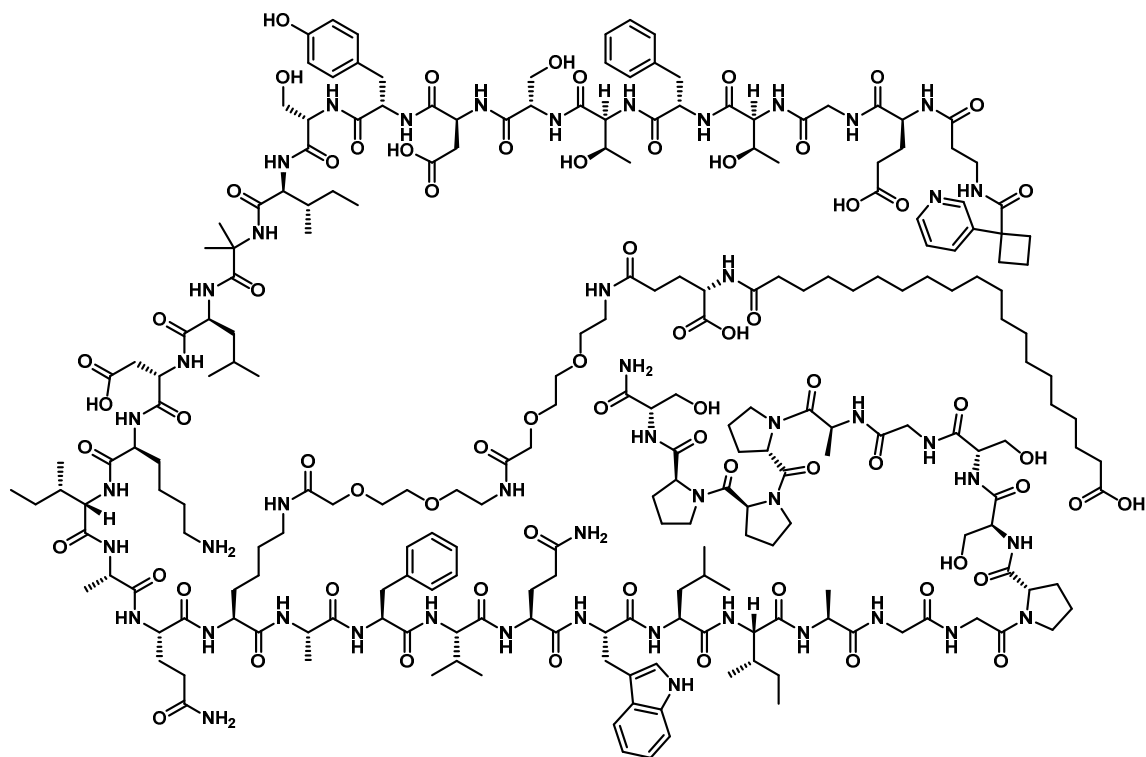
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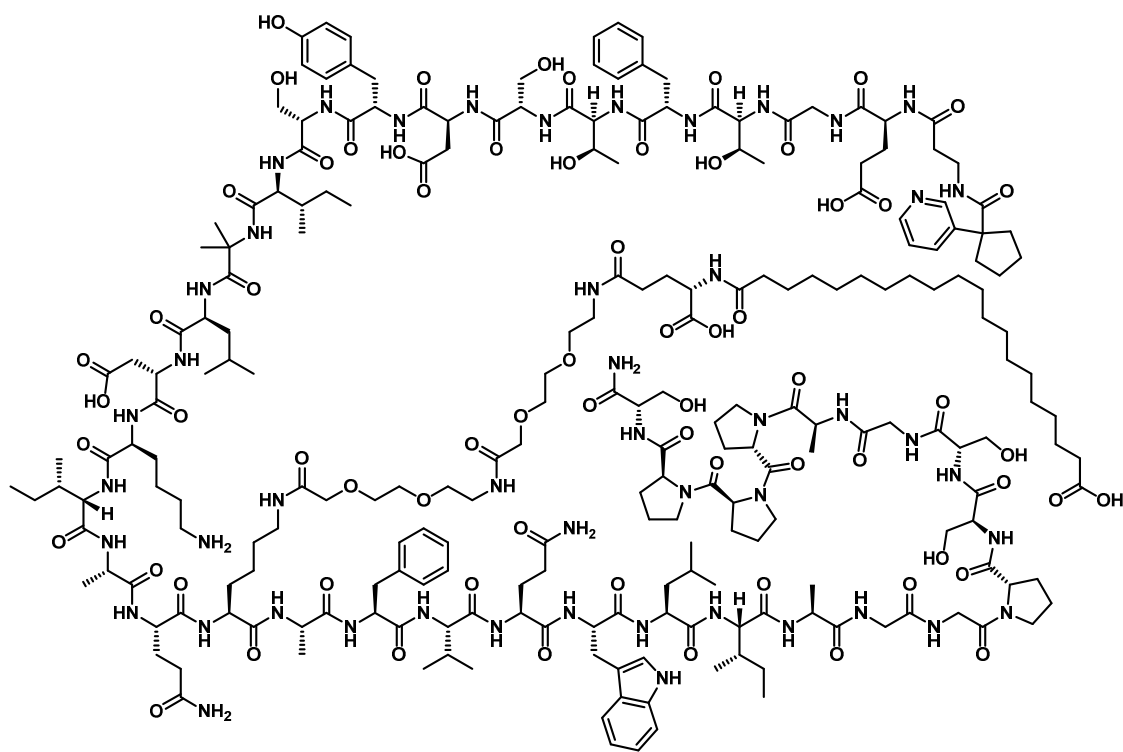
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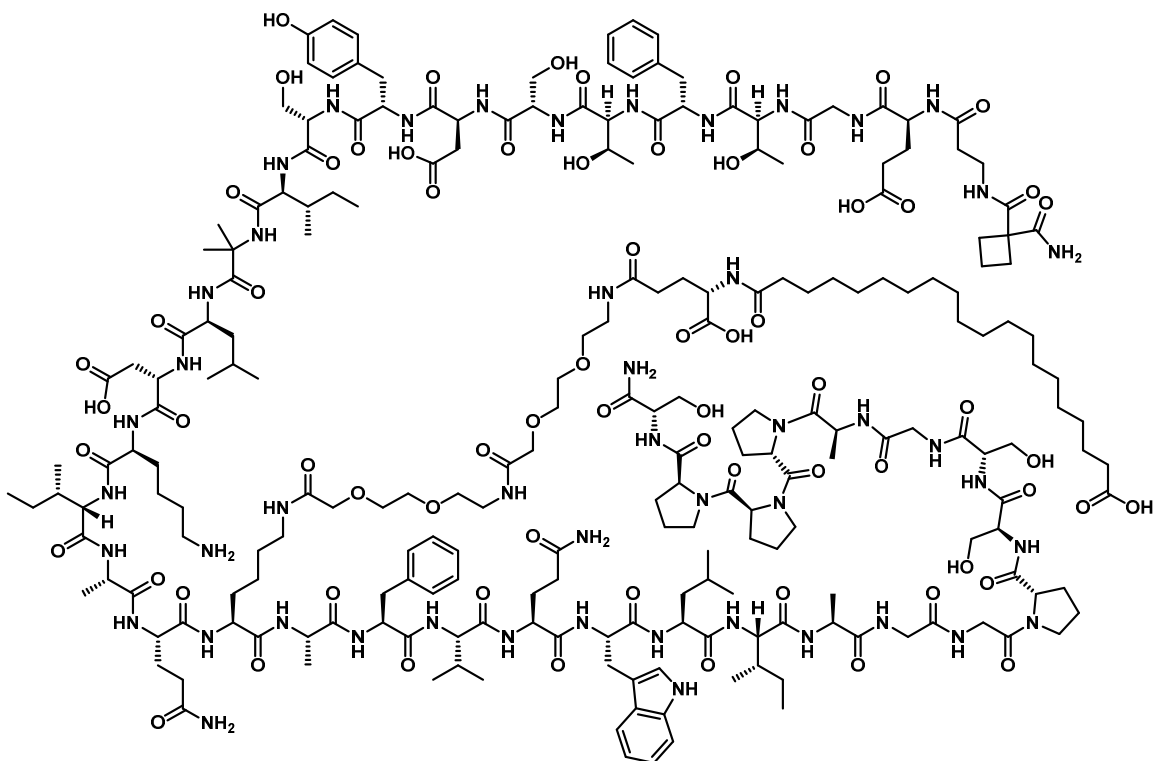
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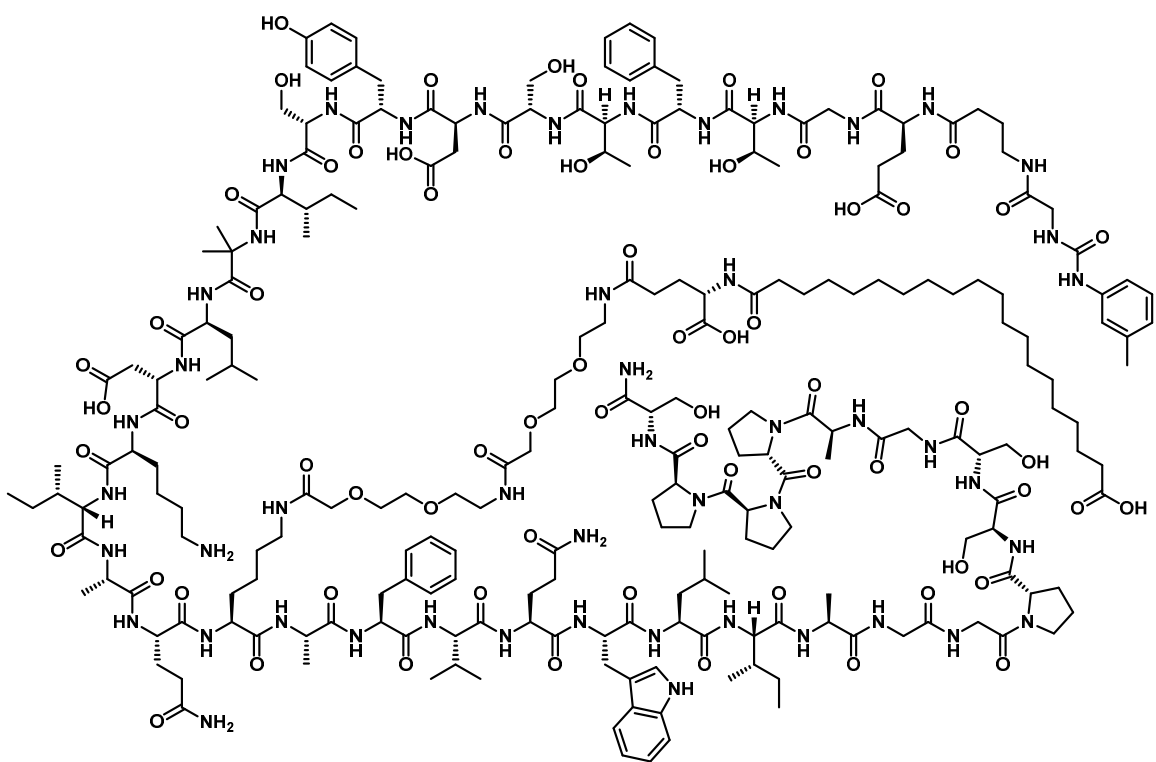
Compound 255,



Compound 256,

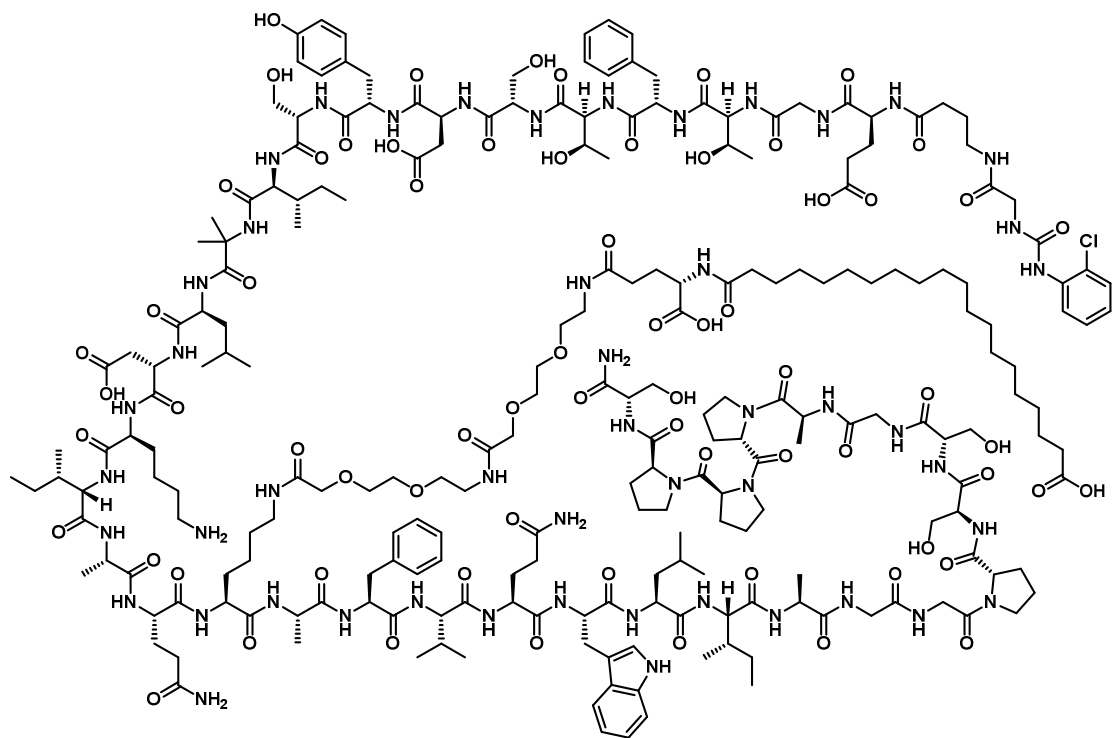


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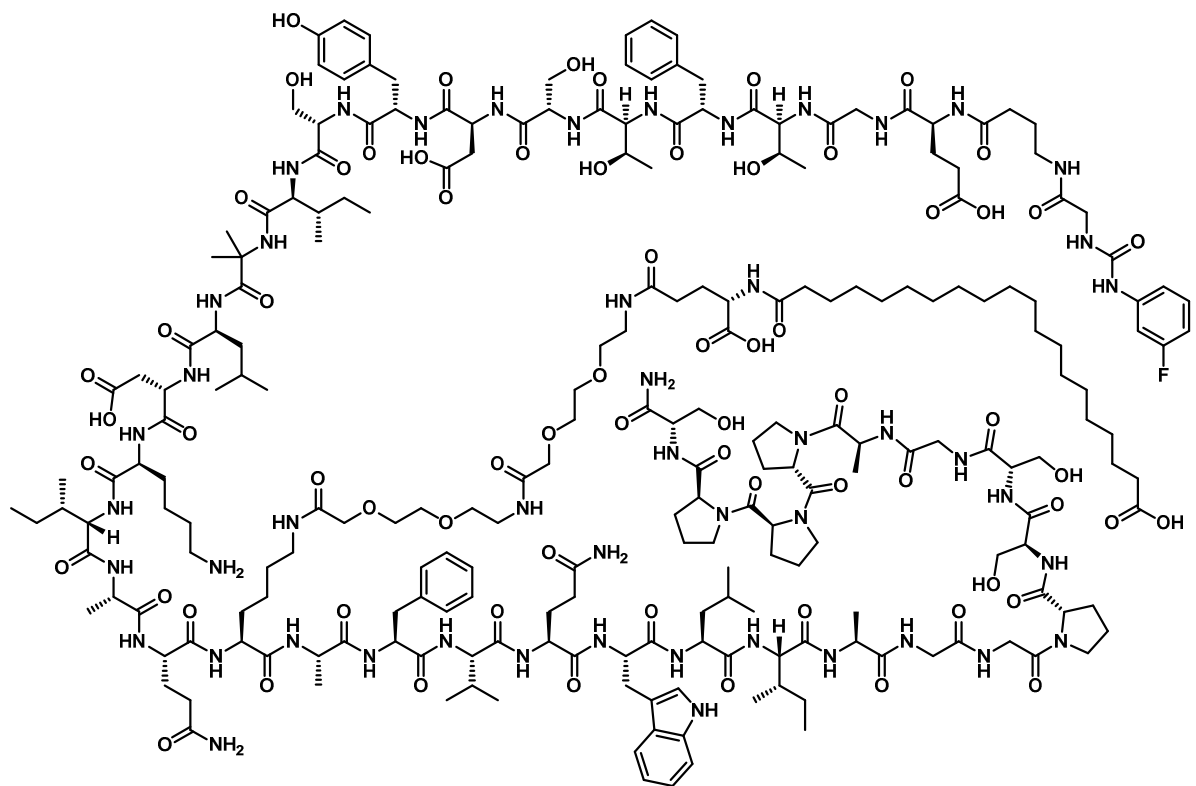


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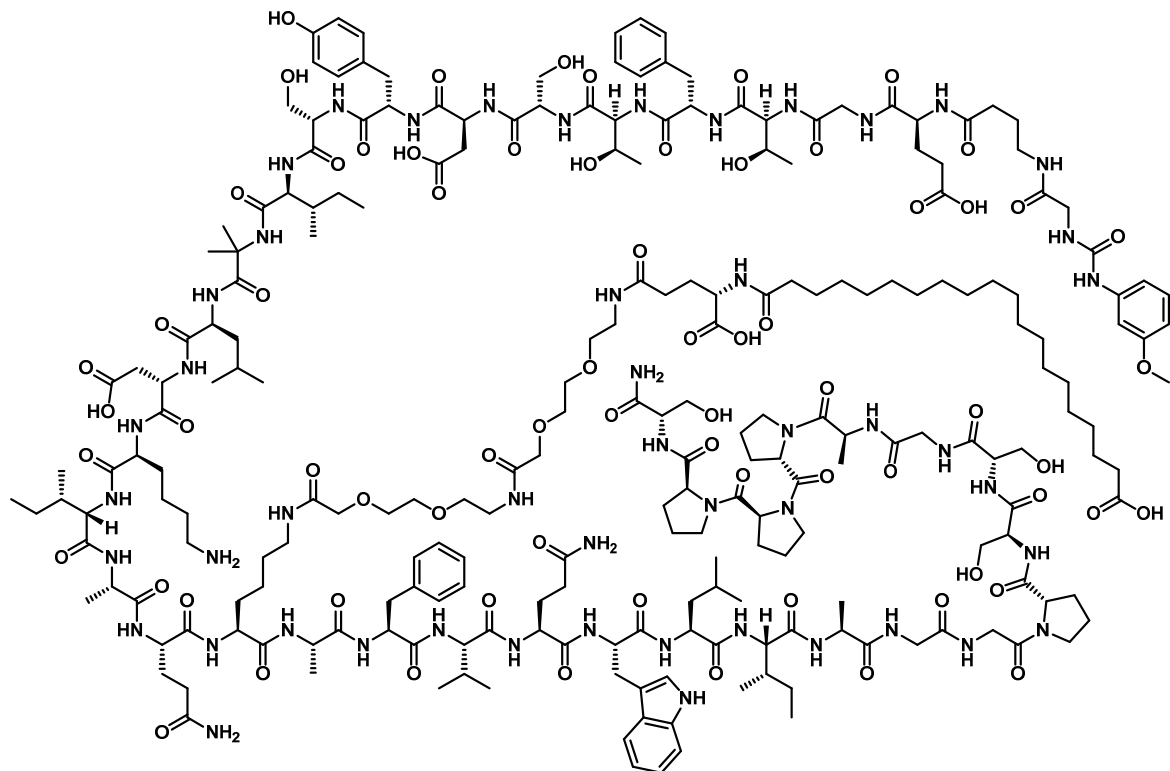
8kkkk



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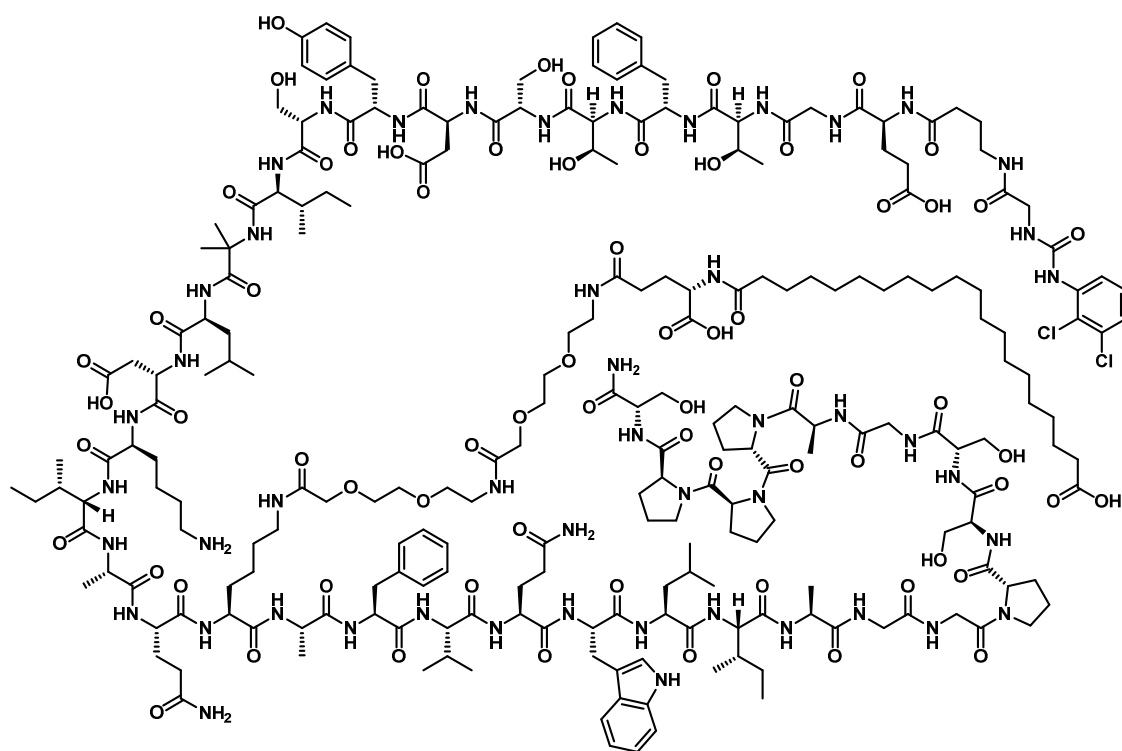


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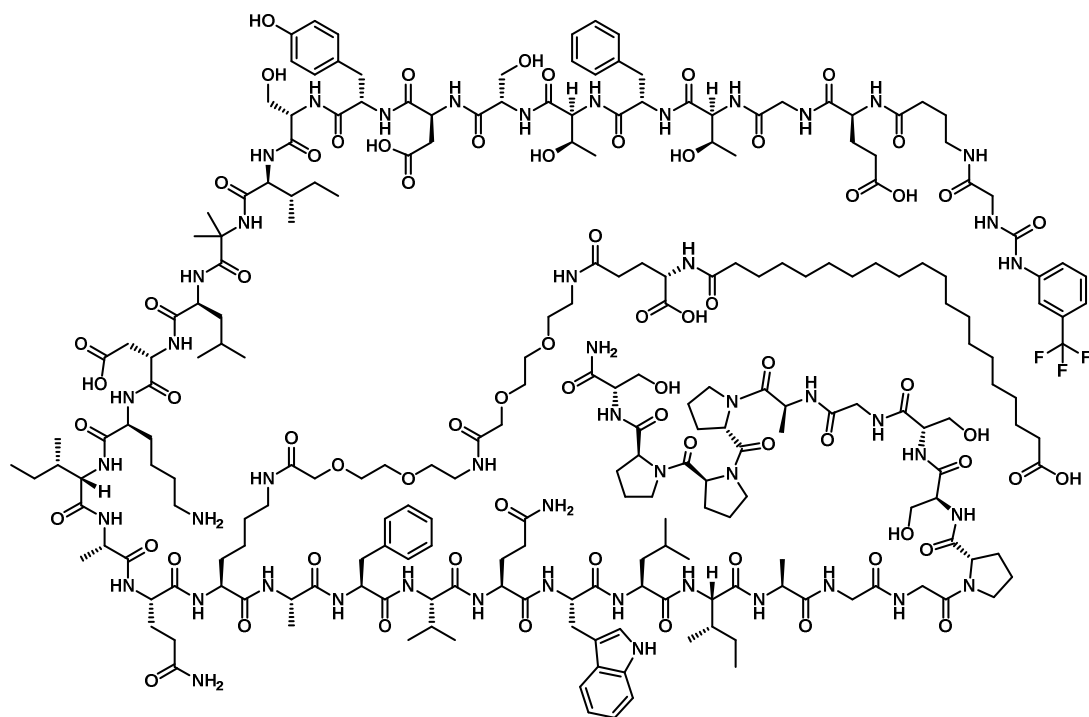


Compound 261,

8mmmm

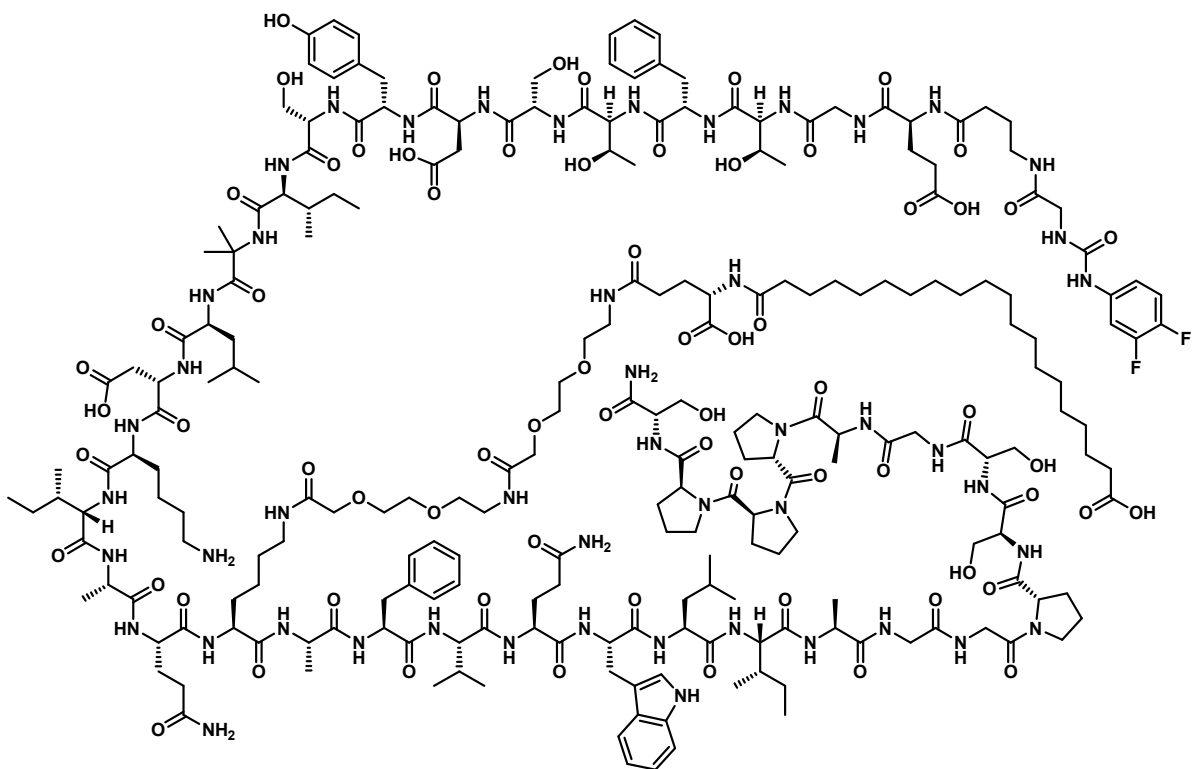


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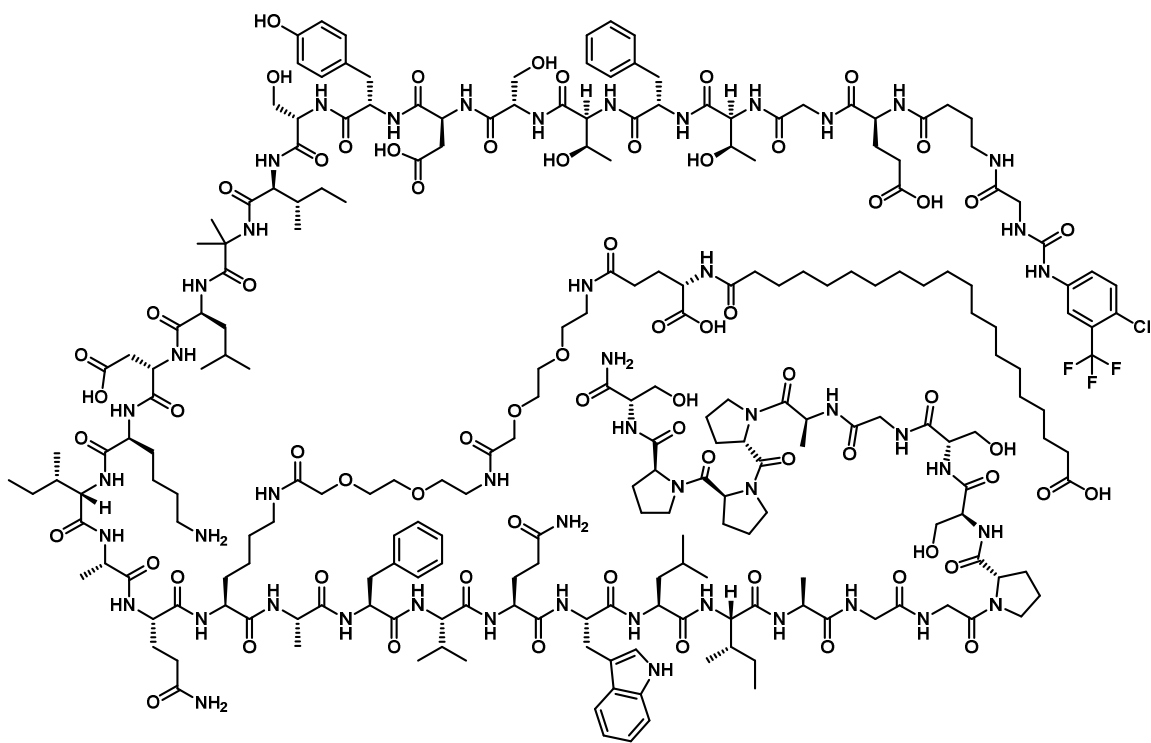


Compound 263,

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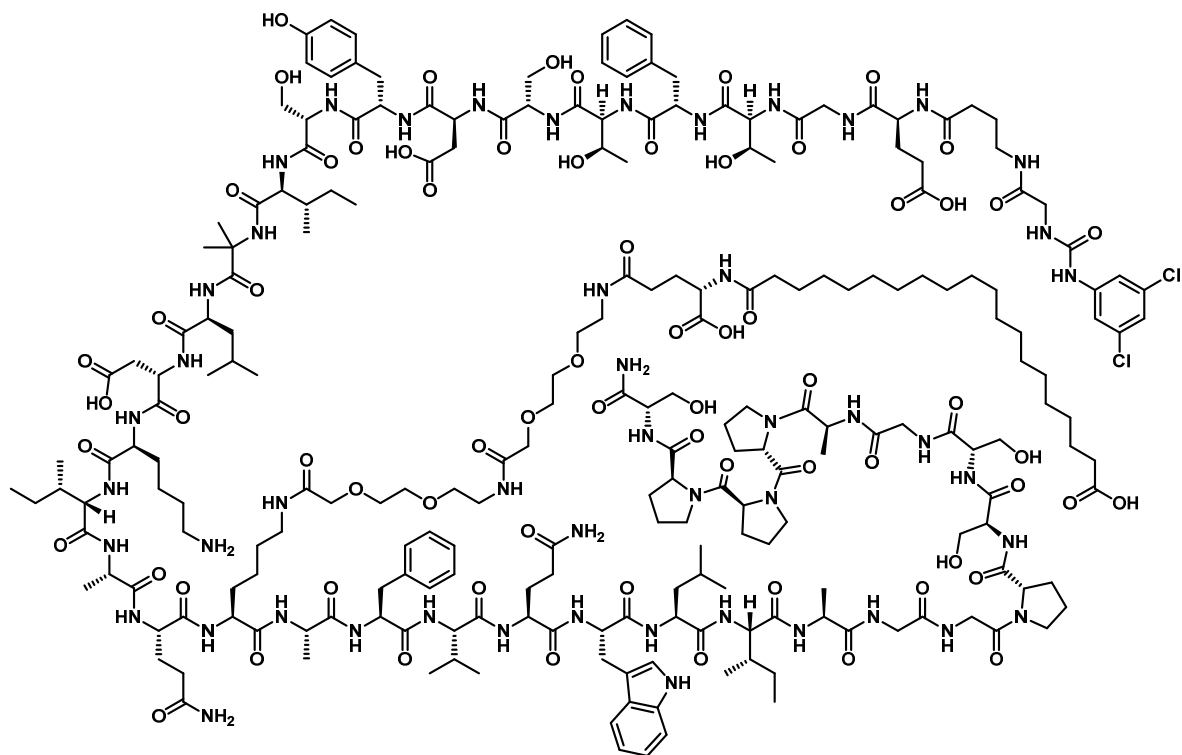


Compound 264,



Compound 265,

80000

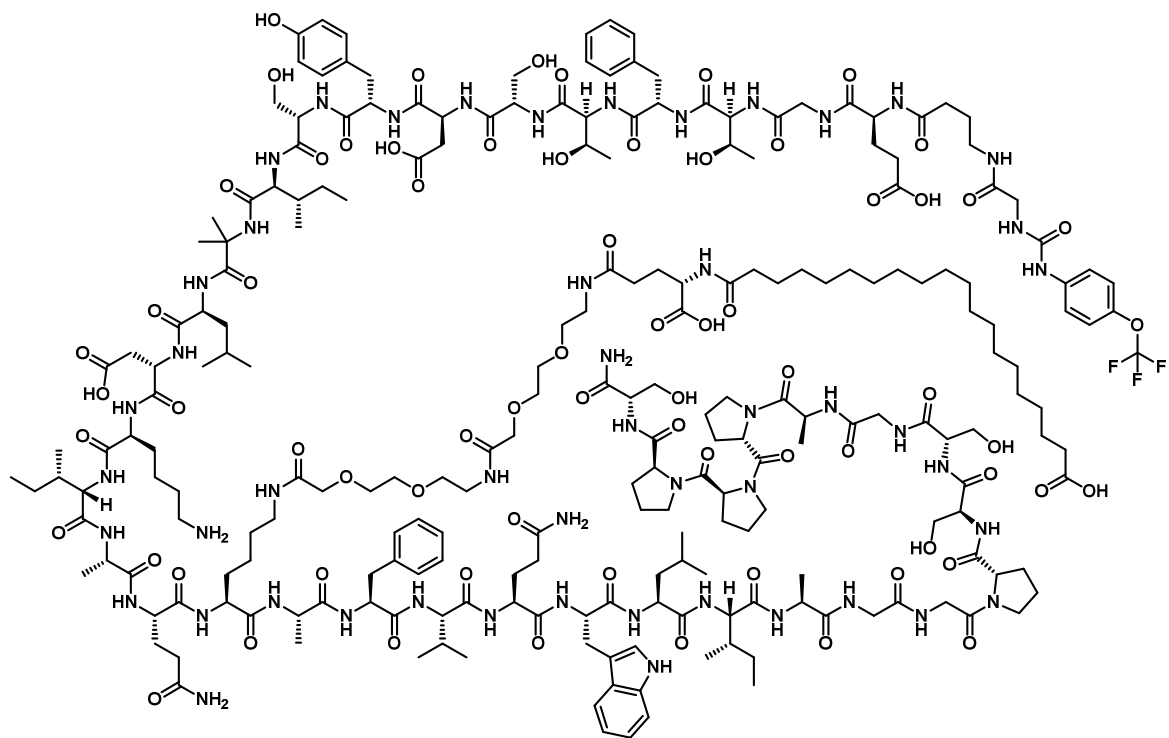


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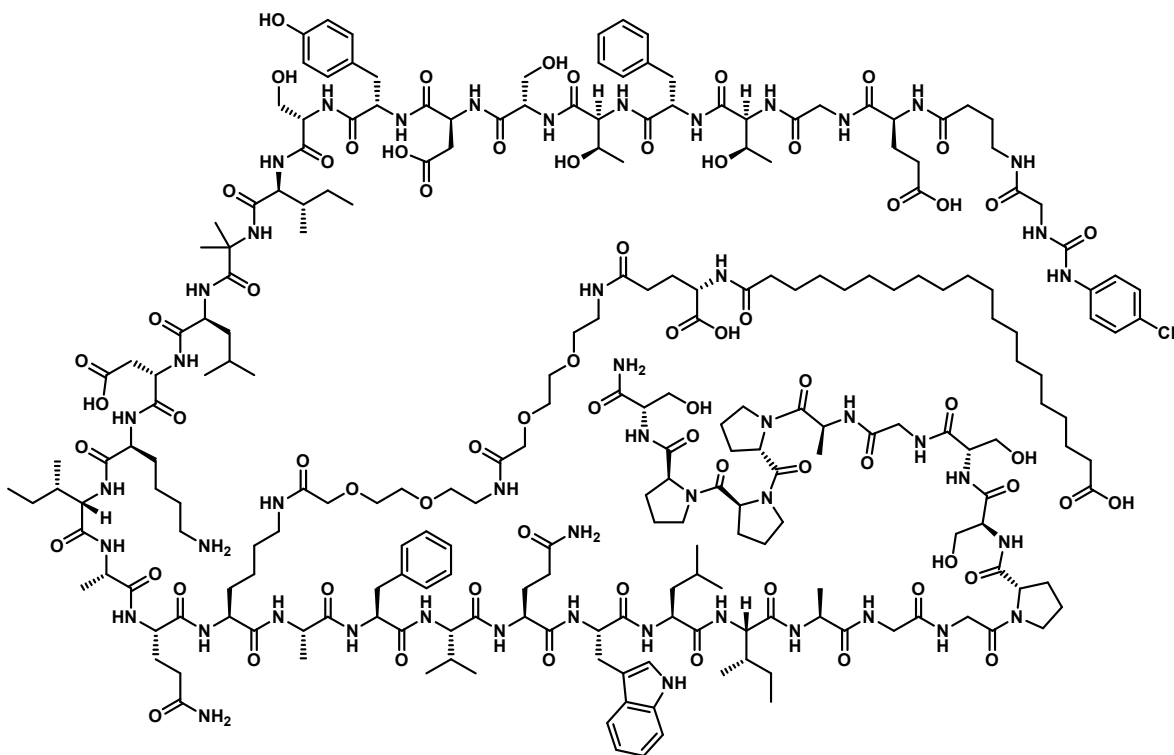
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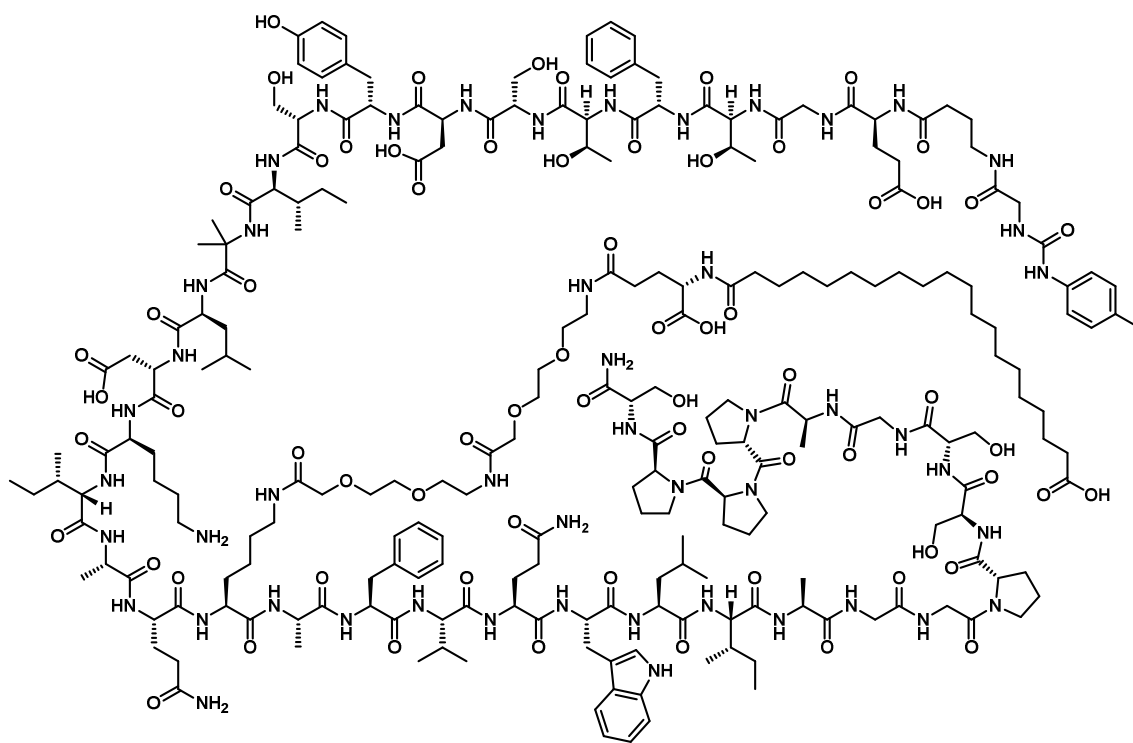
8qqqq



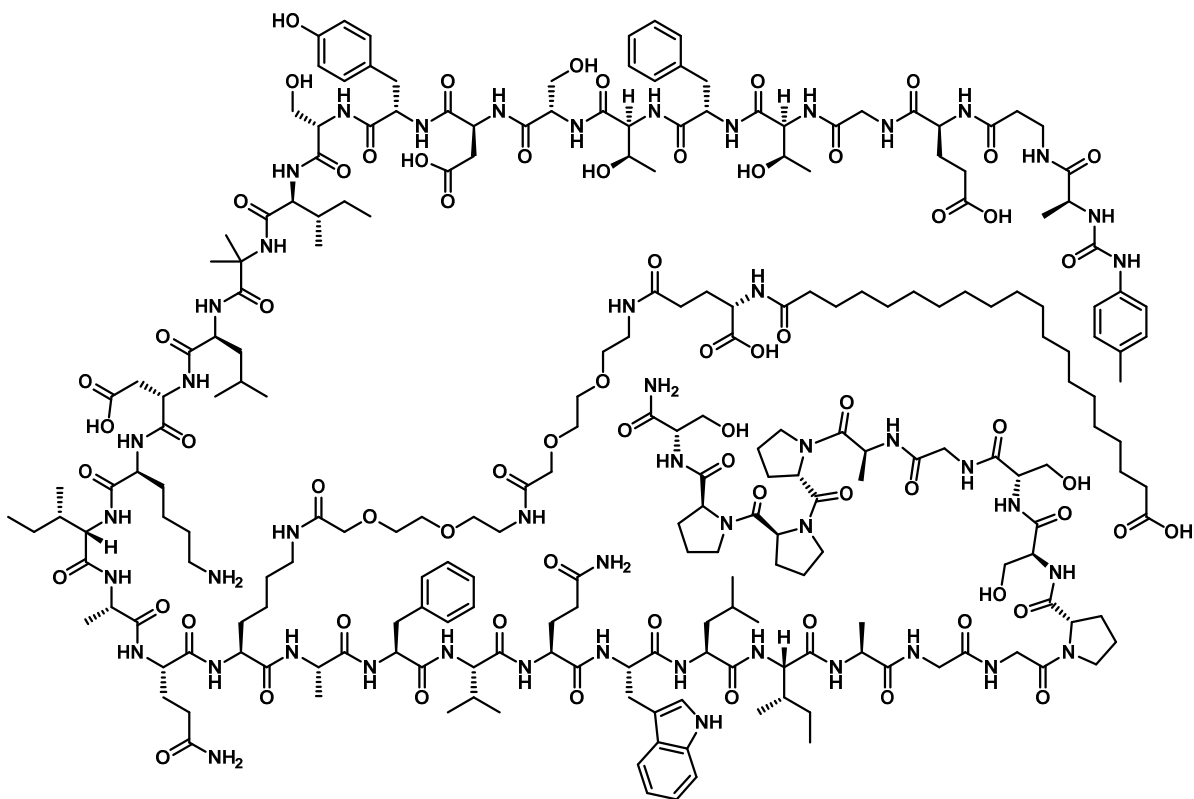
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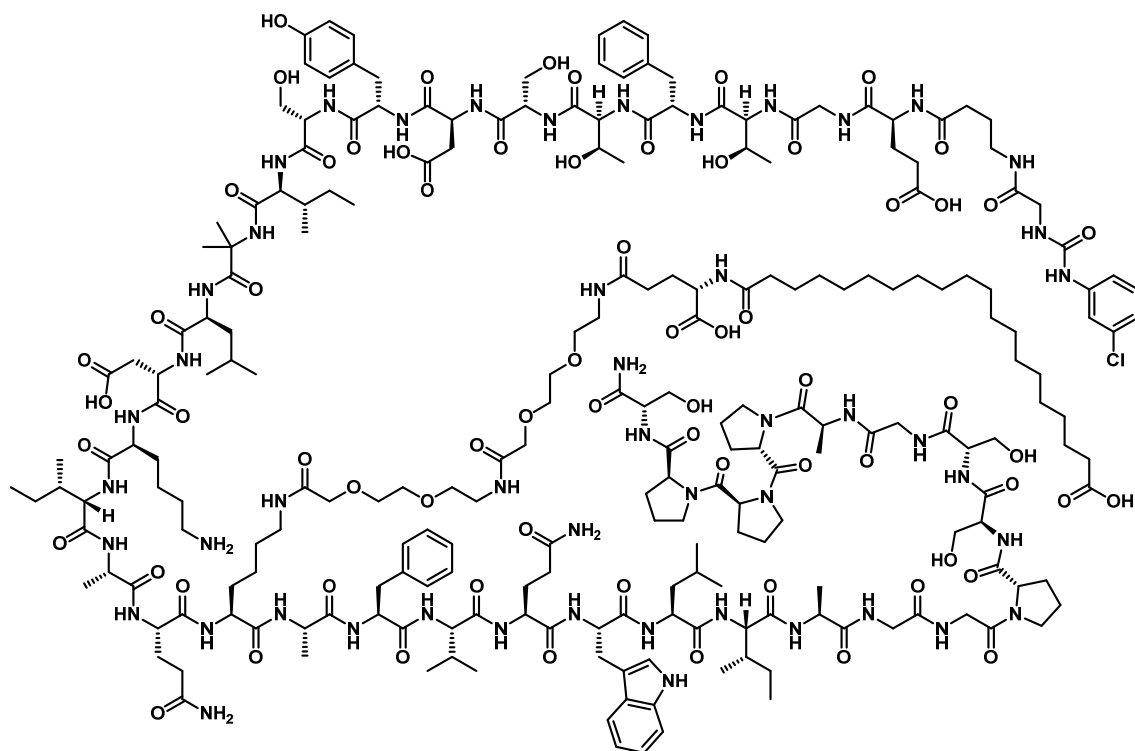
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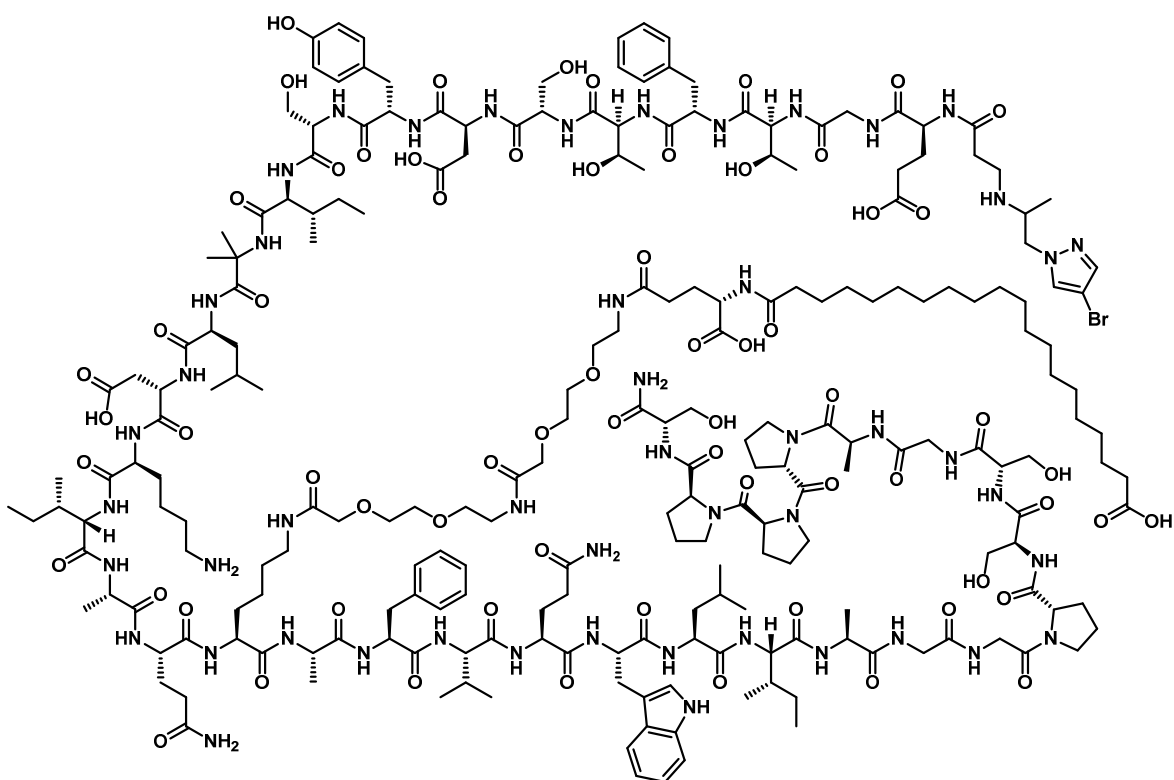


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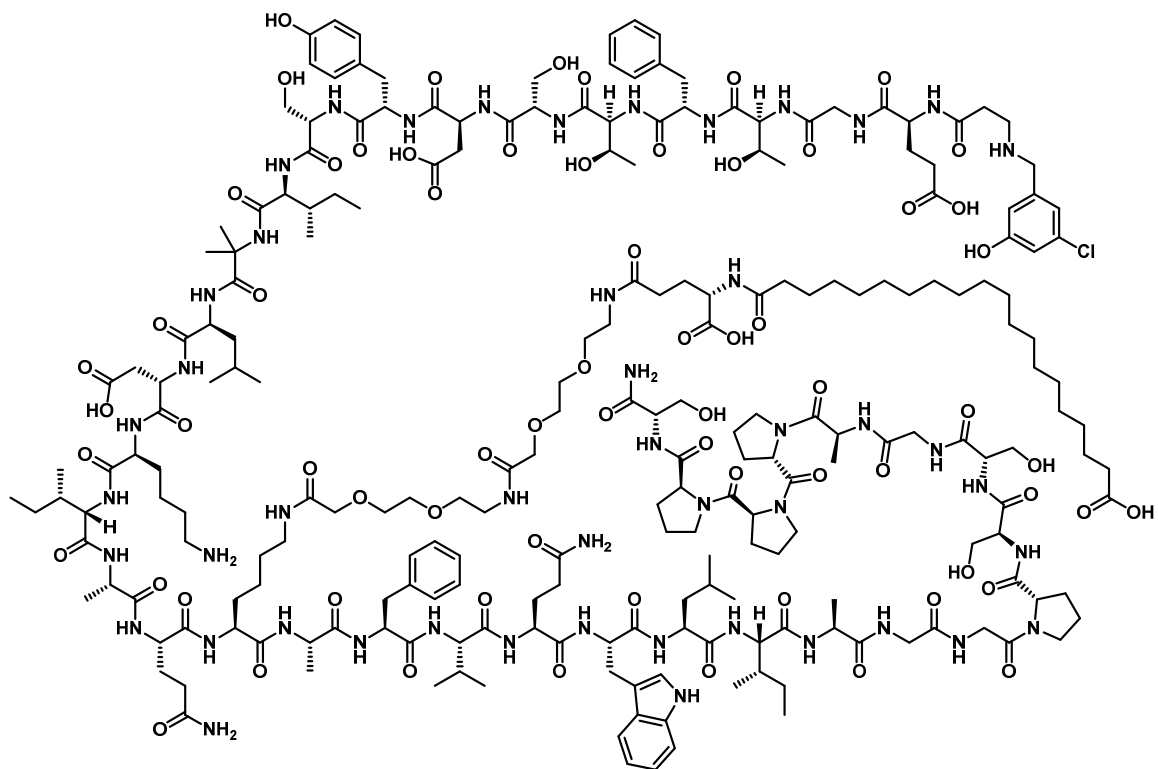
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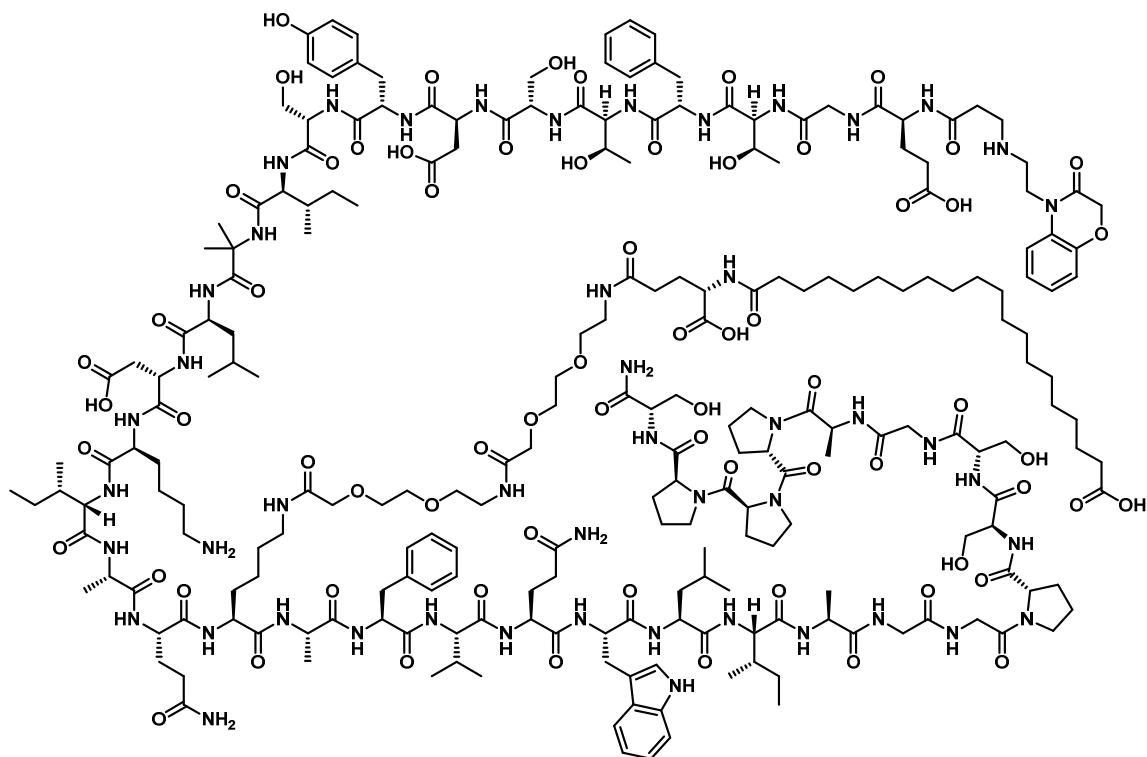


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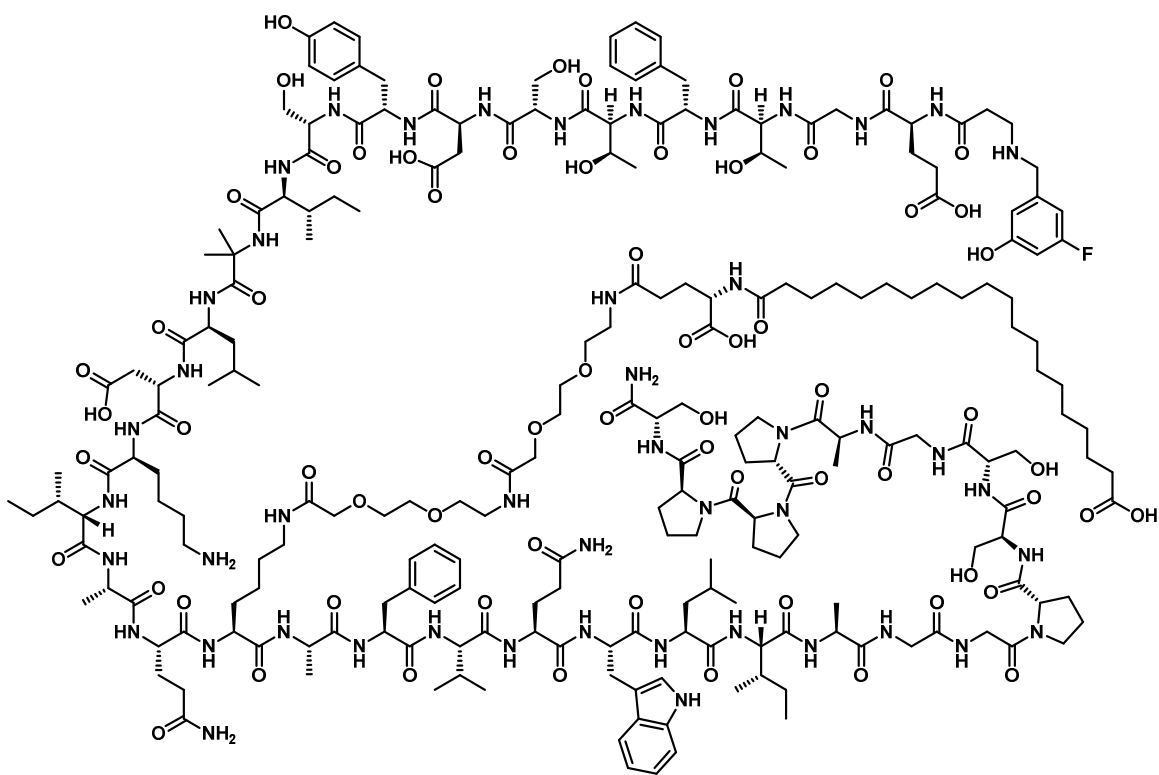
8uuuu



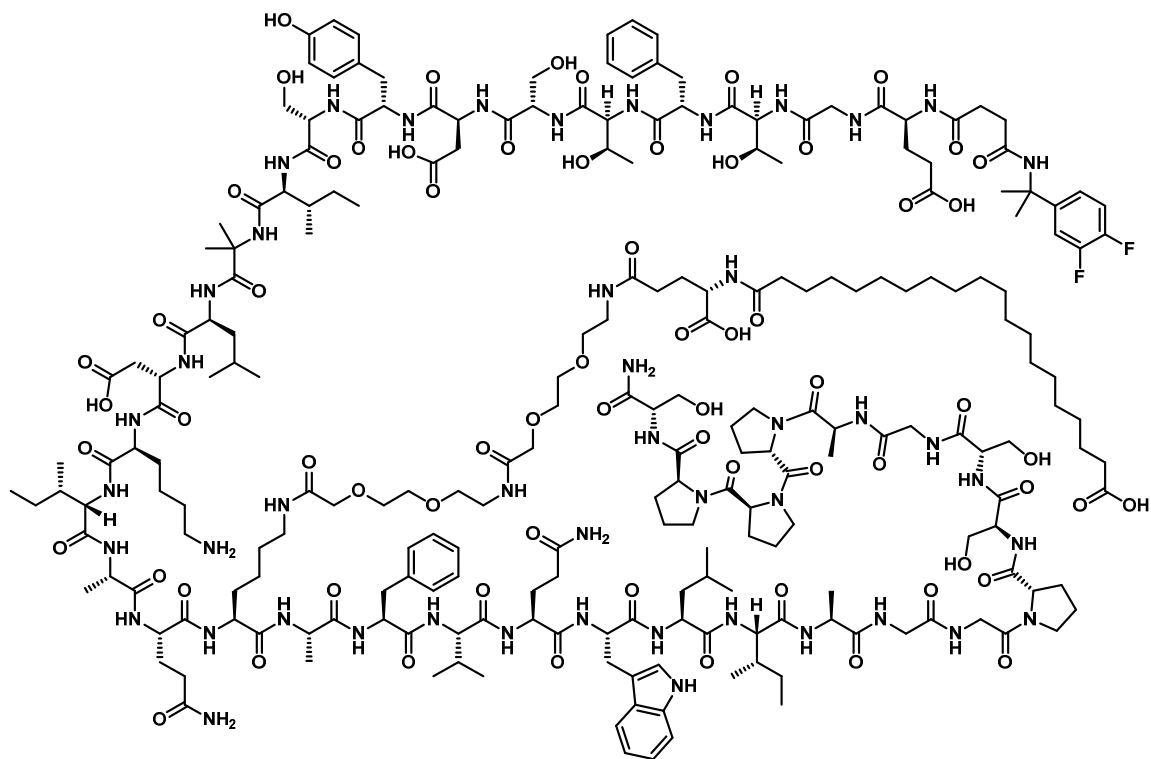
Compound 275,



Compound 276,

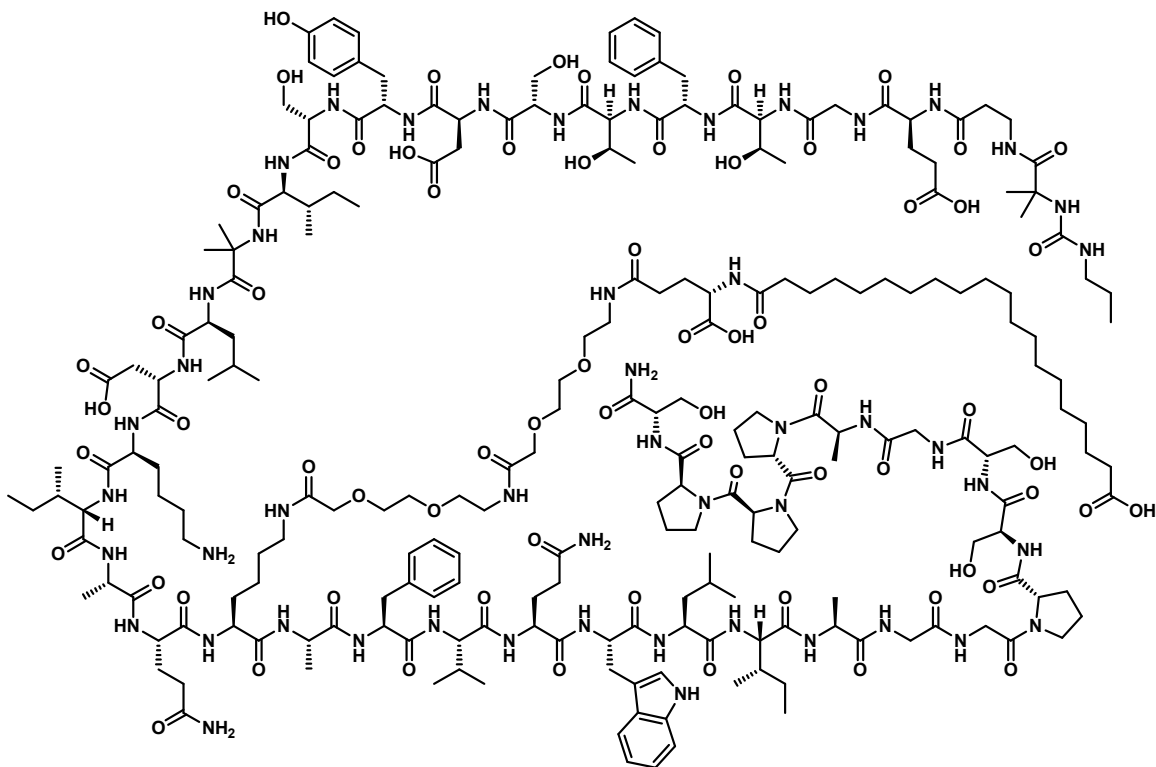


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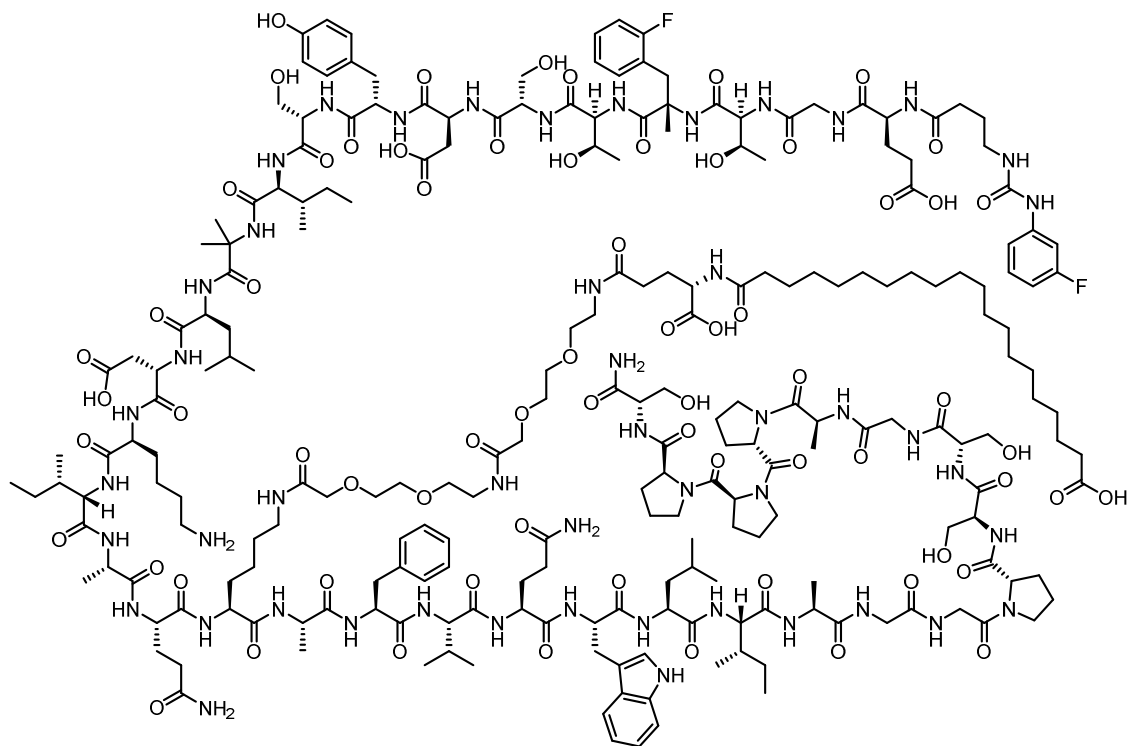


Compound 280,

8xxxx

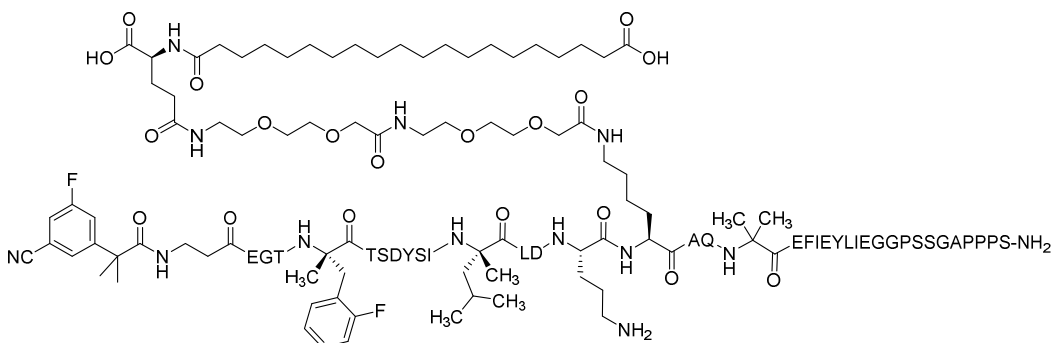
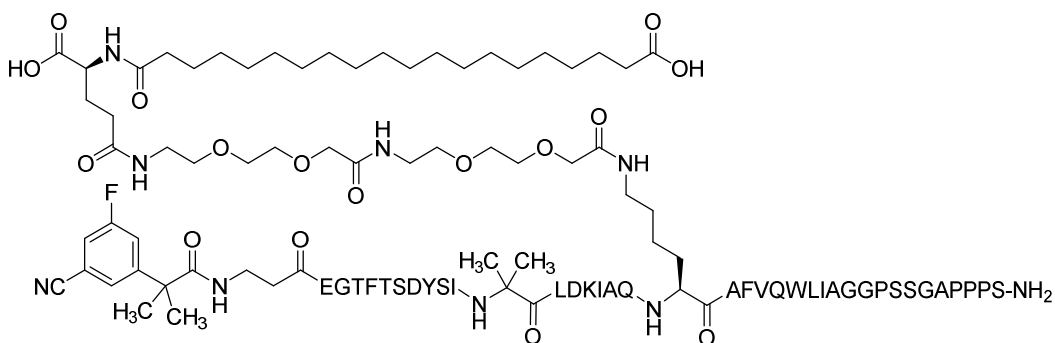
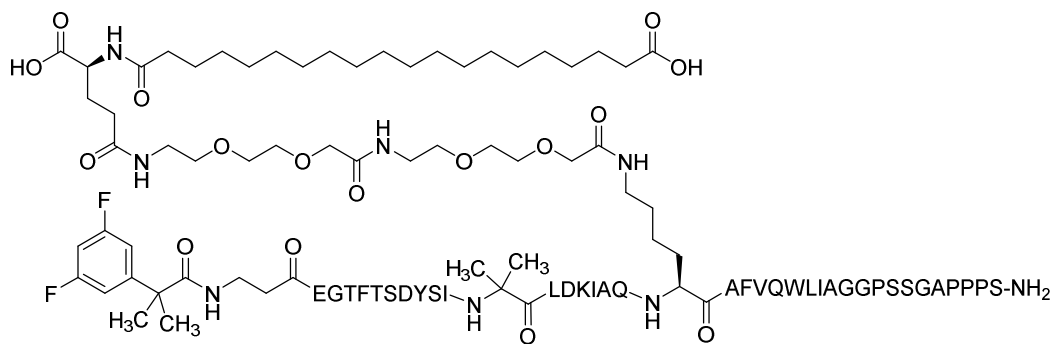
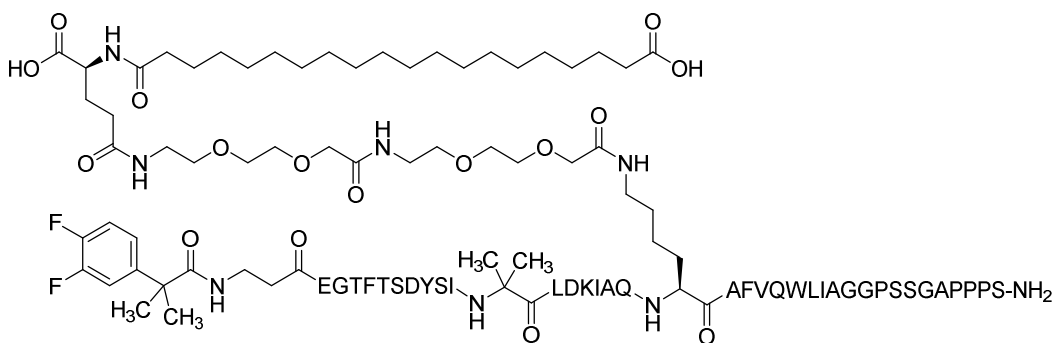


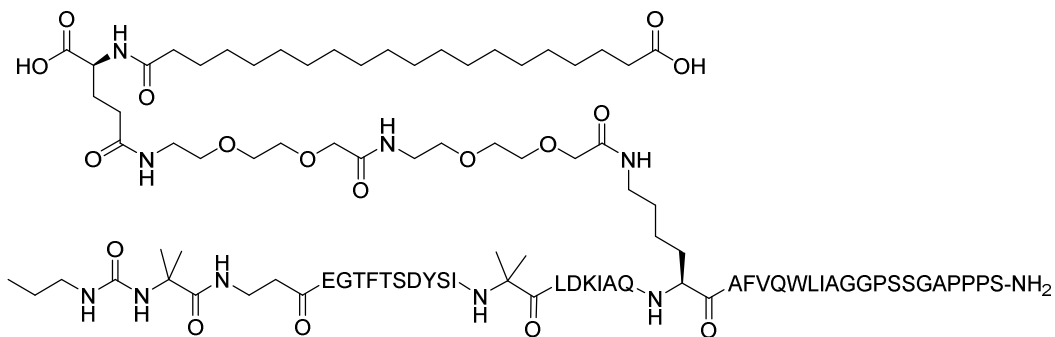
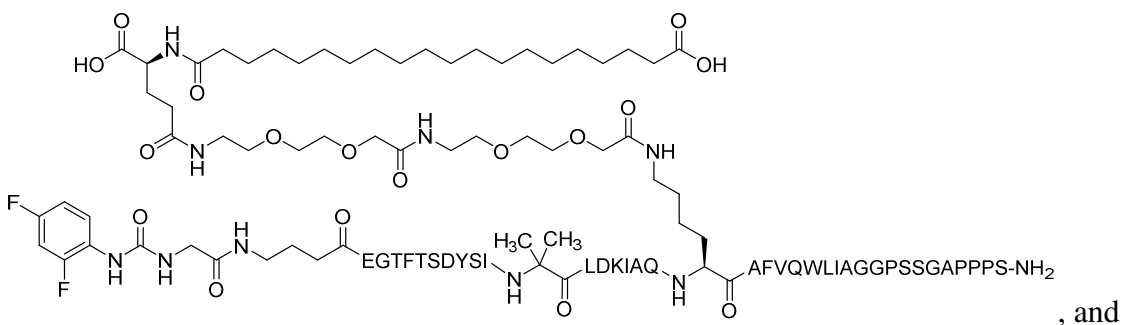
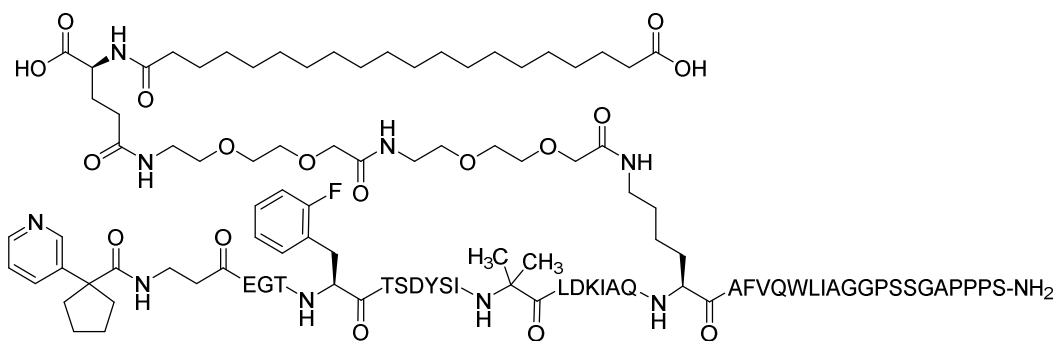
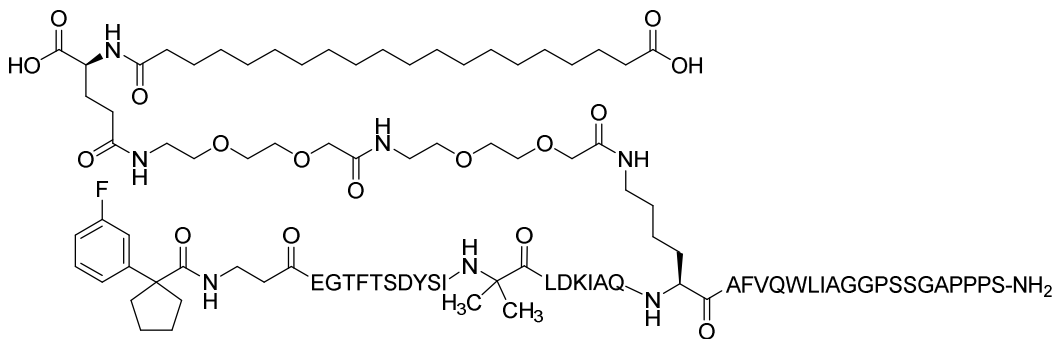
Compound 281, and



Compound 282.

In one aspect, the present disclosure refers to a compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:





In one example, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or

more pharmaceutically acceptable excipients. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, disclosed herein and one or more pharmaceutically acceptable excipients.

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In one example, methods for modulating (e.g., agonizing, partially agonizing, or antagonizing) GLP-1R and/or GIPR activities are featured that include contacting GLP-1R and/or GIPR with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). In one aspect, the present disclosure refers to a method of modulating GLP-1R or GIPR activity, comprising contacting GLP-1R or GIPR with the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein. Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells, each independently comprising one or more of GLP-1R and/or GIPR with the chemical entity. Methods can also include *in vivo* methods;

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e.g., administering the chemical entity to a subject (e.g., a human) having a disease, disorder, or condition in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition (e.g., diabetes; e.g., NASH; e.g., obesity). *In vivo* methods include, but are not limited to modulating (e.g., increasing) insulin levels and modulating (e.g., decreasing) glucose levels in a subject (e.g., a human). In some of the foregoing examples, said methods of modulating are achieved without substantially stimulating β -arrestin signaling; e.g., without stimulating the recruitment of β -arrestin to a G-protein coupled receptor (e.g., GLP-1R); e.g., without stimulating the formation of a complex (e.g., a signaling complex) between β -arrestin and a G-protein coupled receptor (e.g., GLP-1R). In some of the foregoing examples, said methods of modulating are achieved without causing aversion or nausea.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for modulating GLP-1R and/or GIPR activity in a subject without inducing aversion, nausea, or vomiting in the subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for increasing insulin levels or decreasing glucose levels in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for improving glycemic control in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for reducing body weight in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In a further example, methods of treatment of a disease, disorder, or condition are featured, in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same).

In another example, this disclosure features methods of treating a subject having a disease, disorder, or condition in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof or compositions containing the same) in an amount effective to treat the disease, disorder, or condition.

In a further example, methods of treatment are featured that include administering to a subject chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing

the same). The methods include administering the chemical entity in an amount effective to treat a disease, disorder, or condition, wherein modulation of GLP-1R and/or GIPR is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition, thereby treating the disease, disorder, or condition.

In another example, methods of treatment can further include:

(i) administering a first therapeutic agent that modulates (e.g., agonizes, partially agonizes, or antagonizes) GLP-1R and/or GIPR to a subject as defined anywhere herein;

(ii) determining that the subject is suffering from one or more side effects (e.g., aversion, nausea or vomiting); and

(iii) ceasing administration of the first therapeutic agent and administering a chemical entity as described herein (e.g., a compound having Formula (I)).

Non-limiting examples of such diseases, disorders, and conditions include metabolic syndrome; diabetes (e.g., type 2 diabetes); obesity; obesity-related disorders; impaired glucose tolerance; insulin resistance; non-alcoholic steatohepatitis (NASH); fatty liver disease; steatohepatitis; and other forms of inflammation in metabolically important tissues including, liver, fat, pancreas, kidney, and gut.

Other non-limiting examples of such diseases, disorders, and conditions include neurological disorders include brain insulin resistance, mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, dementia (e.g., senile dementia), traumatic brain injury, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, brain trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis (ALS), glaucoma, and apoptosis-mediated degenerative diseases of the central nervous system (e.g., Creutzfeldt-Jakob Disease, bovine spongiform encephalopathy (mad cow disease), and chronic wasting syndrome).

Still other non-limiting examples of such diseases, disorders, and conditions include bone disorder characterized by altered bone metabolism, such as osteoporosis, including post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodystrophy in liver disease and the altered bone metabolism caused by renal failure or hemodialysis, bone fracture, bone surgery, aging, pregnancy, protection against bone fractures, and malnutrition.

In certain examples, the disease, disorder, or condition is diabetes.

In other examples, the disease, disorder, or condition is NASH.

In still other examples, the disease, disorder, or condition is obesity.

In other examples, the disease, disorder, or condition is Alzheimer's disease (AD) or Parkinson's disease (PD).

In still other examples, the disease, disorder, or condition is a bone disorder characterized by altered bone metabolism, such as osteoporosis, including post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodystrophy in liver disease and the altered bone metabolism caused by renal failure or hemodialysis, bone fracture, bone surgery, aging, or pregnancy.

In certain examples, the chemical entities described herein are useful for protection against bone fractures.

The methods described herein can further include treating one or more conditions associated, co-morbid or sequela with any one or more of the conditions described herein. By way of non-limiting example, the methods can further include treating one or more conditions that are co-morbid or sequela with diabetes (e.g., type 2 diabetes), such as obesity, obesity-related disorders, metabolic syndrome, impaired glucose tolerance; insulin resistance; cardiovascular risk factors. (e.g., coronary artery disease, peripheral artery disease, cerebrovascular disease, hypertension, and risk factors related to unmanaged cholesterol and/or lipid levels, and/or inflammation), retinopathy, nephropathy, neuropathy, NASH, bone fracture and cognitive dysfunction.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating obesity in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating diabetes in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In one aspect, the present disclosure refers to use of the compound or pharmaceutically acceptable salt thereof disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating metabolic syndrome, impaired glucose tolerance, insulin resistance, non-alcoholic steatohepatitis (NASH), fatty liver disease, steatohepatitis, mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, dementia, traumatic brain injury, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, brain trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis (ALS), glaucoma, Creutzfeldt-Jakob Disease, bovine spongiform encephalopathy, chronic wasting syndrome, osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, or osteodystrophy in liver disease; or altered bone metabolism caused by renal failure or hemodialysis, bone fracture, bone surgery, aging, pregnancy, and malnutrition in a subject, wherein the medicament is to be subcutaneously administered to the subject in need thereof.

In another example, this disclosure features methods for screening a candidate compound for treatment of a disease, disorder, or condition, in which modulation of GLP-1R and/or GIPR is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition; the method comprising:

(a) contacting the candidate compound with (i) a β -Arrestin-coupled GPCR receptor signaling complex or (ii) one or more GPCR receptor signaling complexes that are not complexed with β -arrestin (e.g., uncoupled GLP-1R and/or uncoupled GIPR); and

(b) detecting (i) the disruption of the β -arrestin coupled complex; or (ii) detecting the formation of the signaling complex in the absence of β -arrestin coupling; wherein the candidate compound modulates (e.g., agonizes, partially agonizes) GLP-1R and/or GIPR.

In certain examples, the methods further include selecting a candidate compound that exhibits a value of β -arrestin (GLP-1R) $EC_{50} > 1 \mu M$.

The methods can further include identifying the subject.

The methods can further include administering one or more other therapeutic agents (e.g., in combination with a chemical entity described herein).

Examples can include one of more of the following advantageous properties.

In some examples, the compounds described herein exhibit a value of AUC Score of 0-25% of vehicle, which corresponds to a finding of maximal decrease in glucose excursion compared to control.

In some examples, the compounds described herein exhibit a value of cAMP (GLP-1R) EC_{50} of less than about 1 nM, which is indicative that the compound is a relatively potent GLP-1R agonist.

In some examples, the compounds described herein exhibit a value of cAMP (GLP-1R) E_{max} of greater than about 80%, which is indicative that the compound is an agonist that can fully activate GLP-1R.

In some examples, the compounds described herein exhibit a value of cAMP (GIPR) EC₅₀ of less than about 10 nM, which is indicative that the compound is a relatively potent GIPR agonist.

In some examples, the compounds described herein exhibit a value of cAMP (GIPR) EC₅₀ of less than about 10 nM, which is indicative that the compound is a relatively potent GIPR antagonist.

GLP-1 and GIP are susceptible to rapid degradation by dipeptidyl peptidase-IV (DPP-IV) (see, e.g., Deacon, et al. Journal of Clinical Endocrinology & Metabolism, 1995, 80, 952-957). As such, GLP-1 and GIP have been shown to exhibit relatively short half-life times in human due to DPP-IV degradation. Advantageously, the compounds described herein exhibit relatively long half-life times in the presence of DPP-IV when compared to those of GLP-1 and GIP.

In some examples, the compounds described herein exhibit a value of β -arrestin coupling (GLP-1R) EC₅₀ > 1 μ M in a β -arrestin (GLP1R) assay that measures the formation of a complex between GLP-1R and β -arrestin in cells. A value of β -arrestin (GLP1R) EC₅₀ > 1 μ M indicates a compound that does not substantially induce β -arrestin recruitment to GLP-1R.

In some examples, the compounds described herein exhibit a value of conditioned taste aversion ("CTA") = 0.6-1.0, which indicates no measurable aversion to a compound, which is desired. A value of CTA = 0.0-0.6 indicates significant aversion to a compound. The conditioned taste aversion assay measures the preference for a dilute saccharin solution that is associated with compound administration.

In some examples, the compounds described herein have a reduced likelihood of producing unwanted side effects when administered to a patient. A non-limiting example of such a side effect is nausea.

Other examples include those described in the Detailed Description, drawings, and/or in the claims.