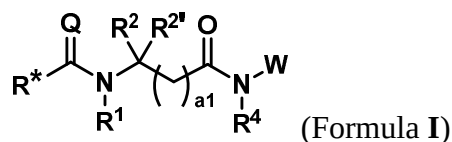


In some examples, the compounds described herein exhibit a value of β -arrestin (GLP1R) EC₅₀ > 1 μ M.

In some examples, the peptide-based chemical entities:

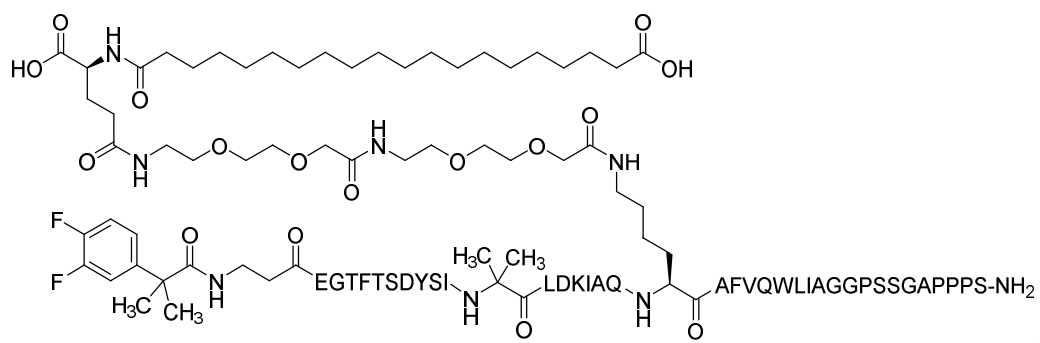
- exhibit a value of cAMP (GLP1R) EC₅₀ of less than about 10 nM, 5 nM, or 1 nM (e.g., less than about 1 nM);
- exhibit a value of cAMP (GIPR) EC₅₀ of less than about 100 nM, 50 nM, or 10 nM (e.g., less than about 10 nM) or are GIPR antagonists;
- exhibit a value of β -arrestin (GLP1R) EC₅₀ > 1 μ M; and
- 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:

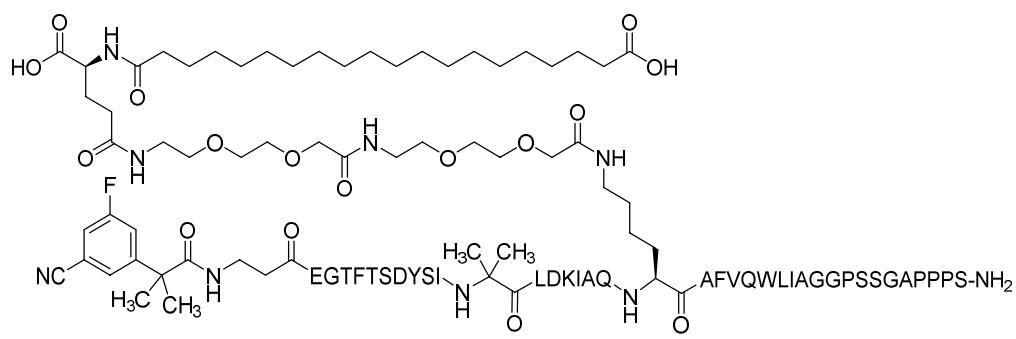
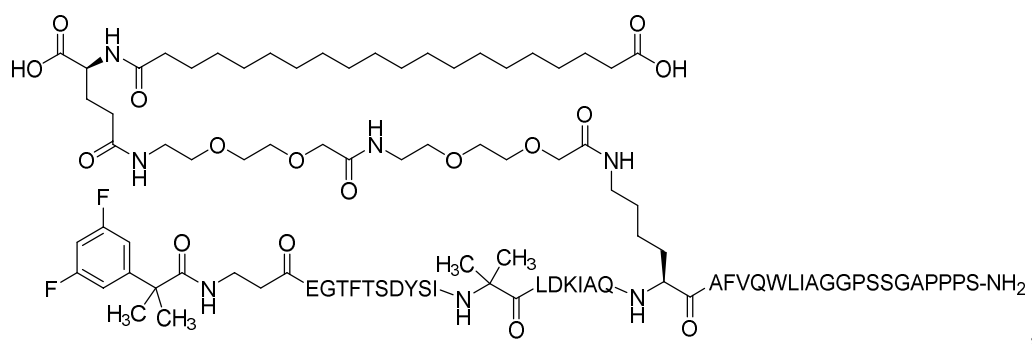


in which **R***, **R¹**, **R²**, **R^{2'}**, **a1**, **R⁴**, and **W** can be as defined anywhere herein.

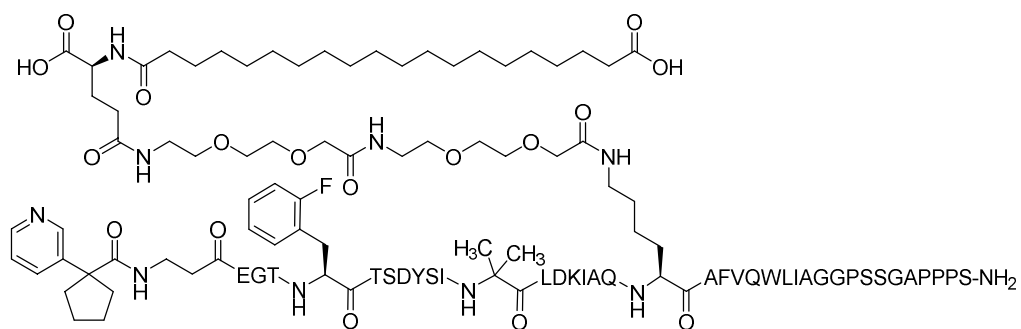
In one aspect, the present disclosure refers to a compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



8b

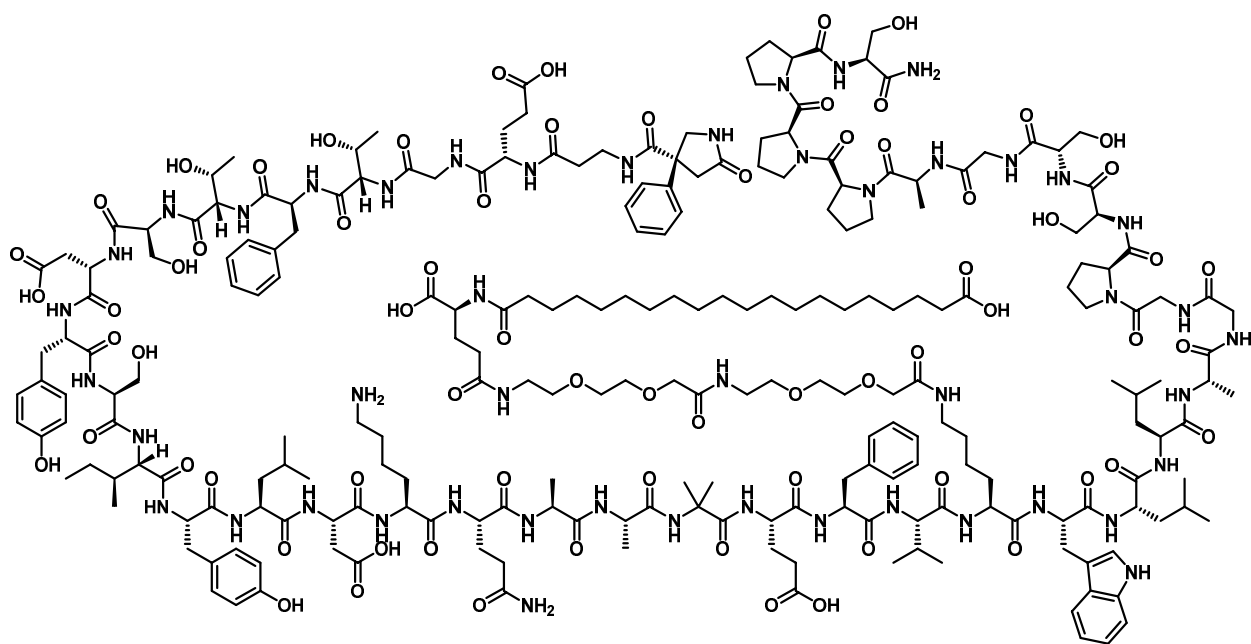






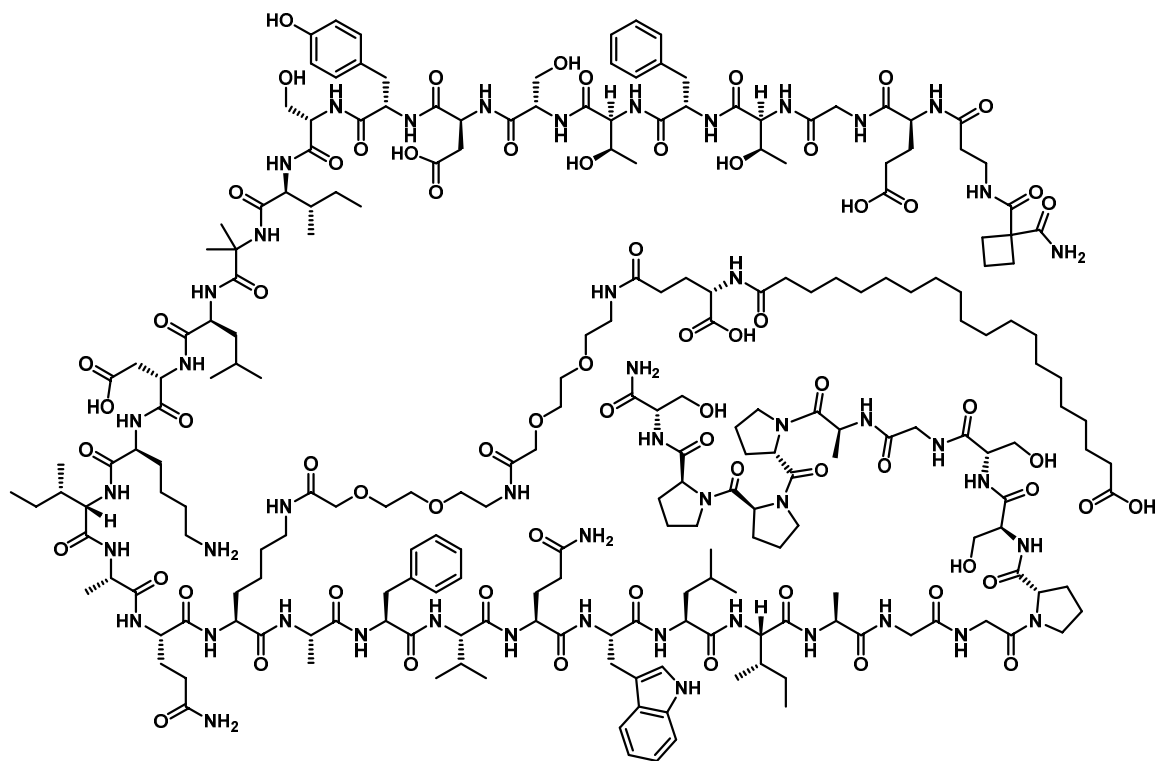
In one aspect, the present disclosure refers to a compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

Compound 101,



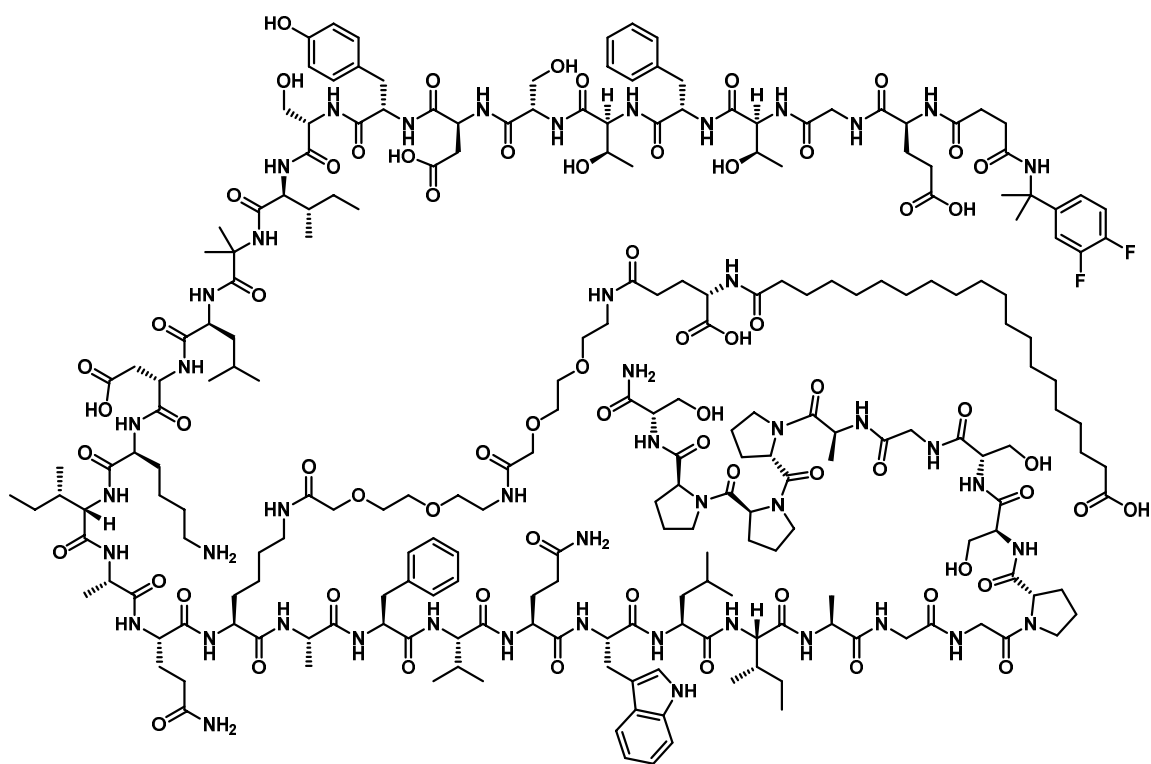
Compound 102,

8jjjj



Compound 257, and

8kkkk



Compound 280.

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.

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, wherein the method is carried out *in vitro*. 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;

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 improving glycemic control in a subject with type 2 diabetes mellitus, 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

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.

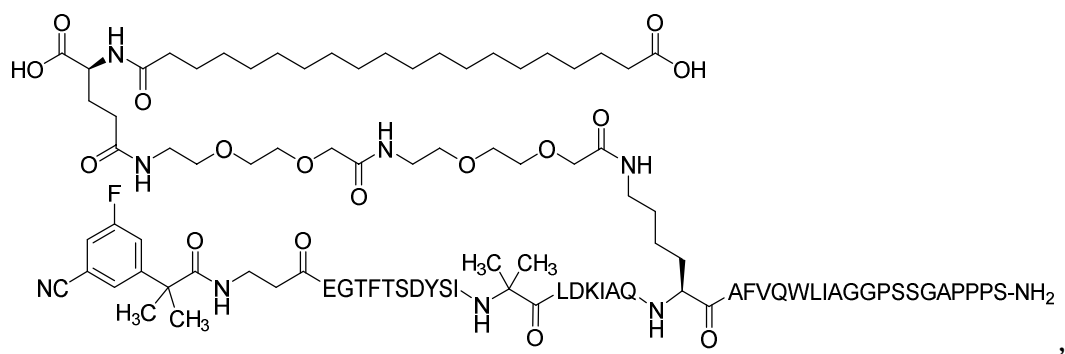
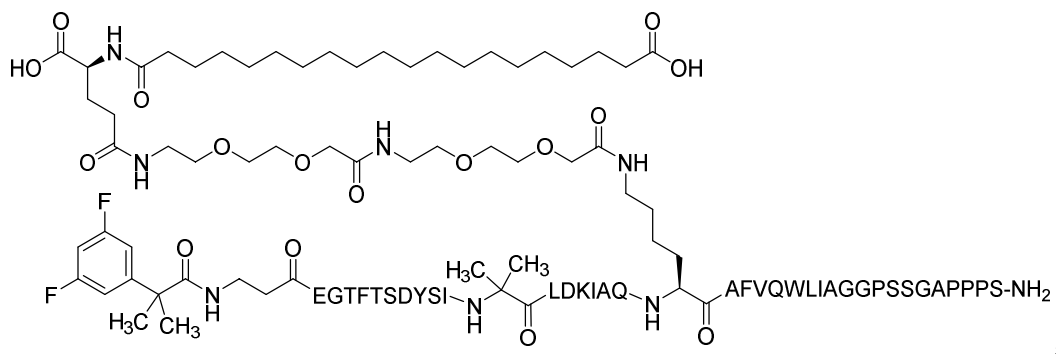
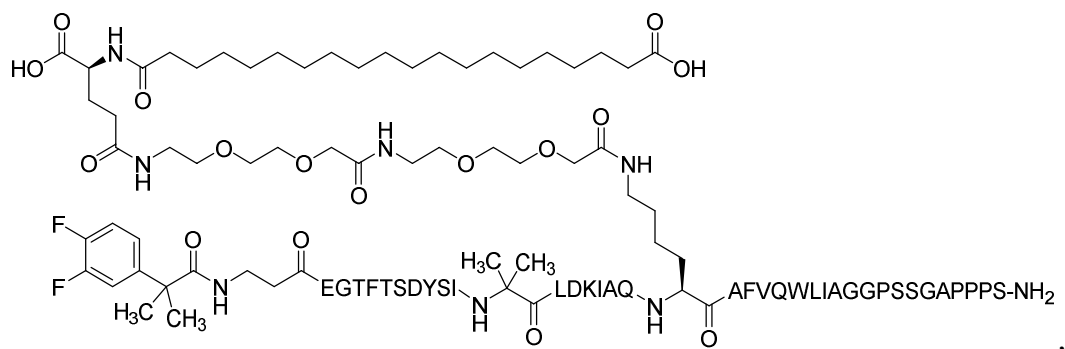
In some examples, the compounds described herein exhibit a value of AUC Score of 0-25% of vehicle, which corresponds to a finding of maximal decrease in glucose excursion compared to control.

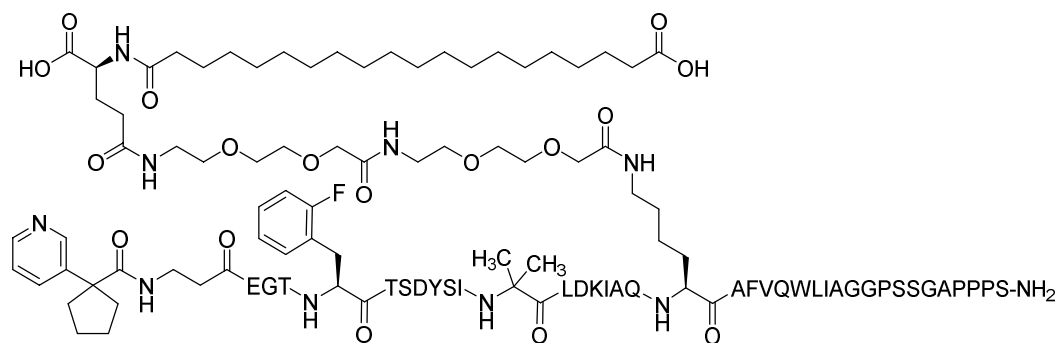
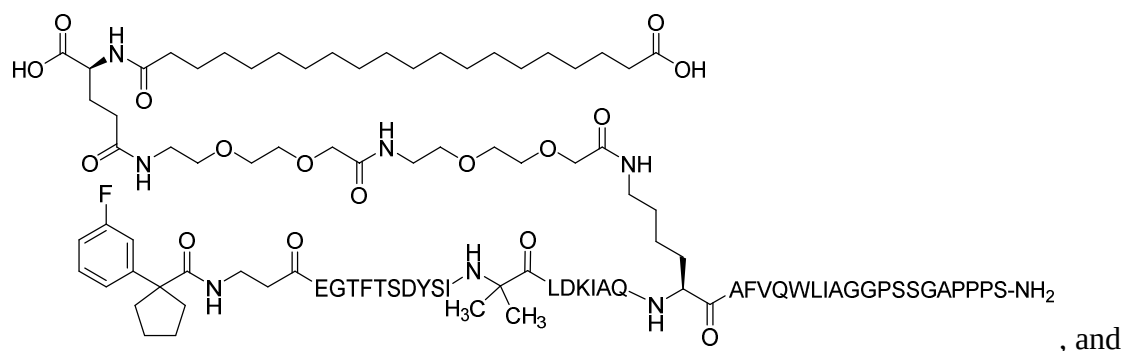
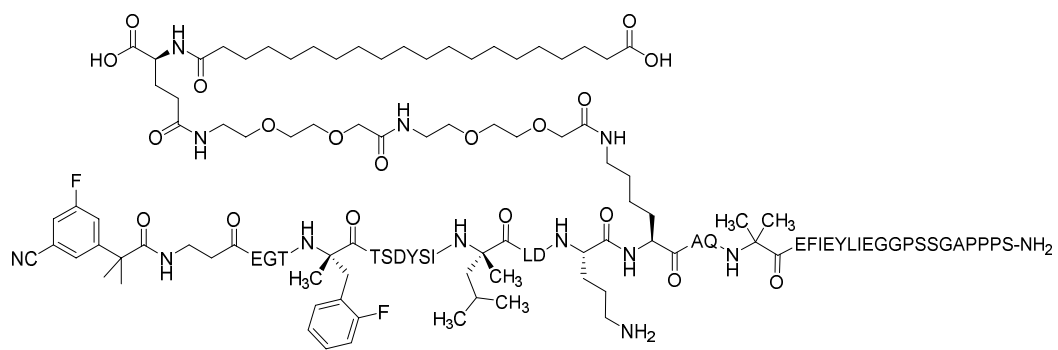
In some examples, the compounds described herein exhibit a value of cAMP (GLP-1R) EC_{50} of less than about 1 nM, which is indicative that the compound is a relatively potent GLP-1R agonist.

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.

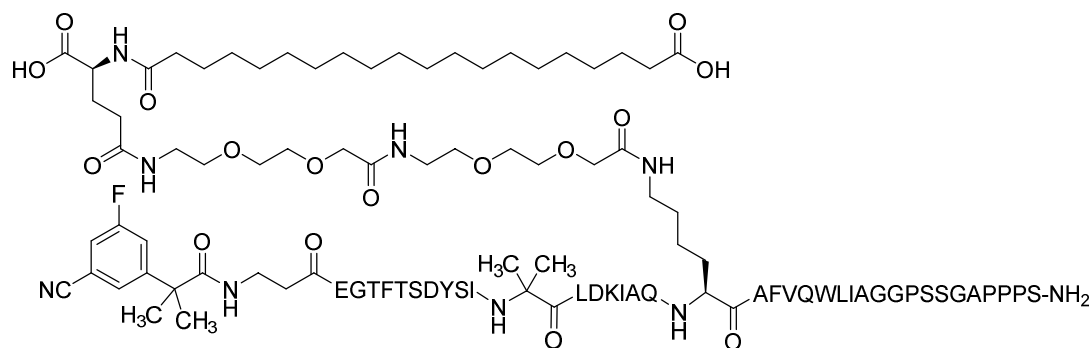
WHAT IS CLAIMED IS:

1. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

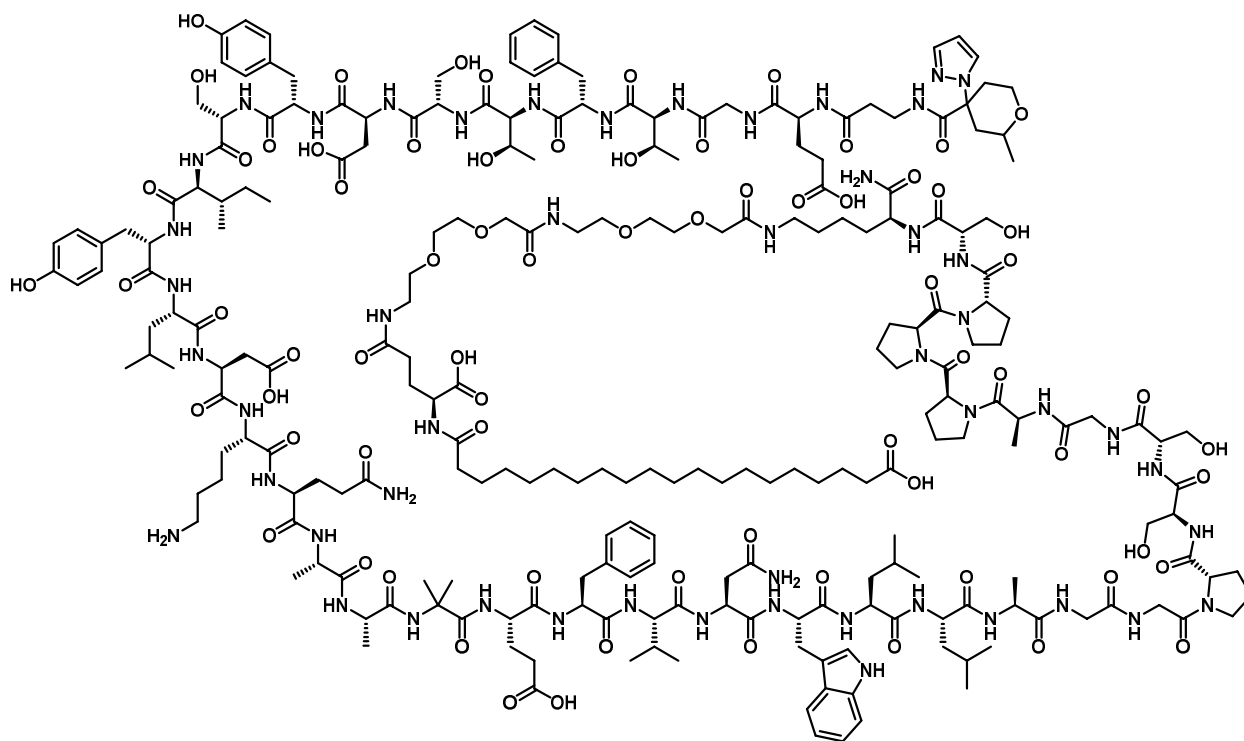




- 5 2. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is:

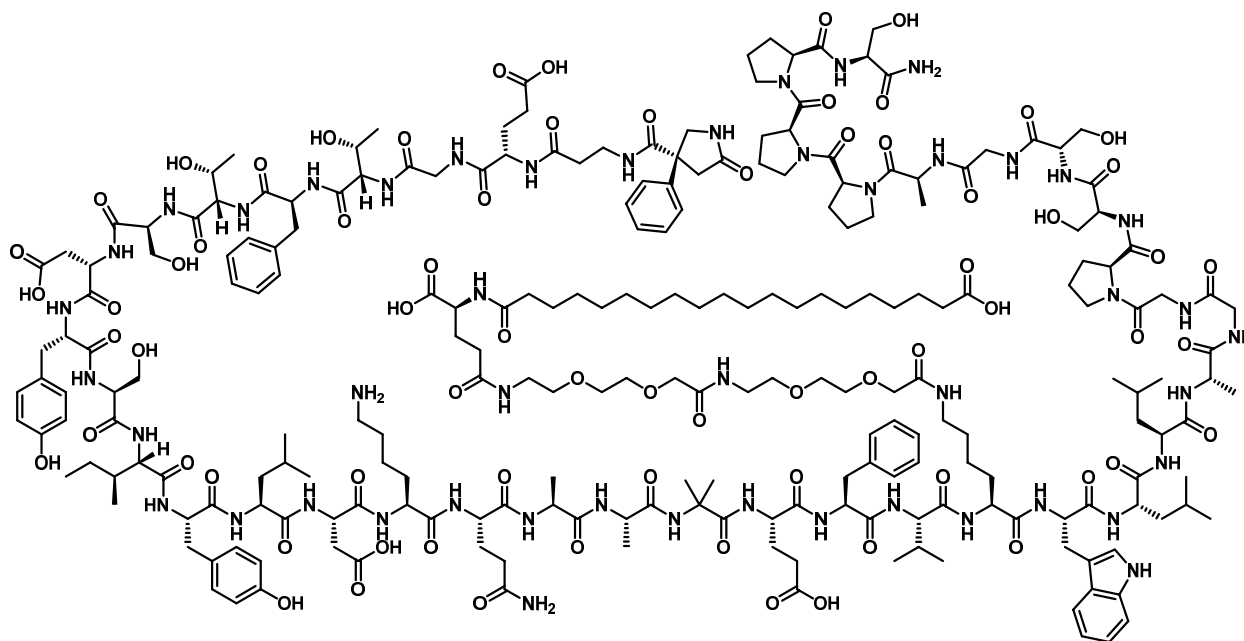


3. A compound, or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

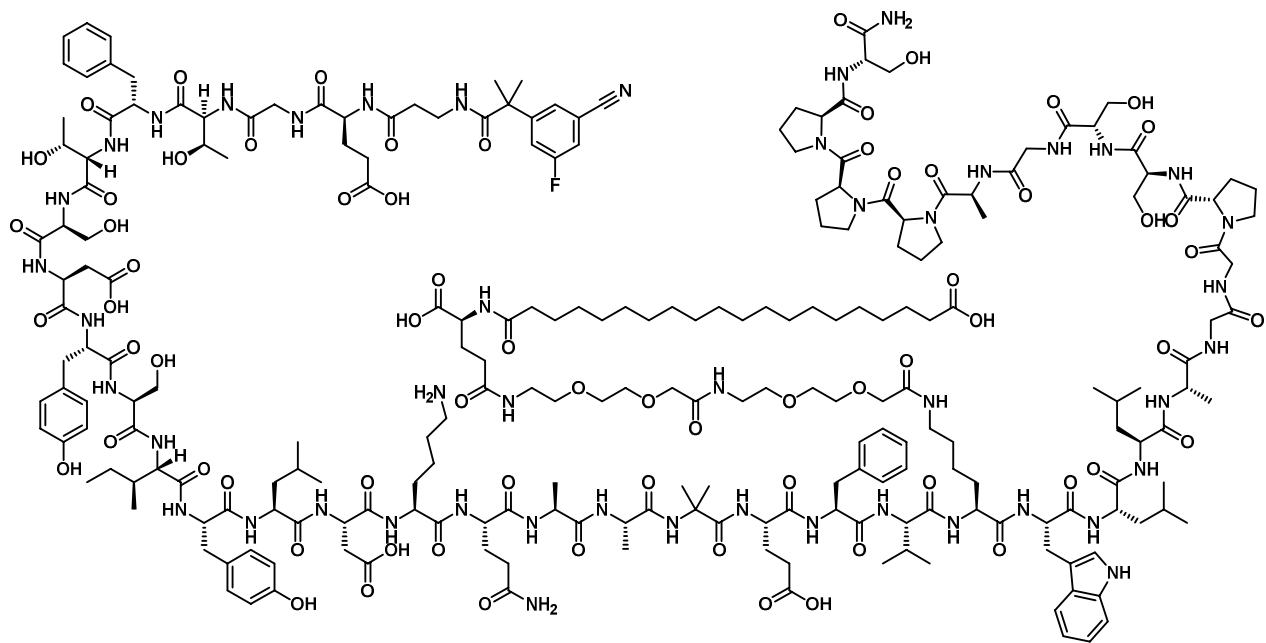


Compound 101,

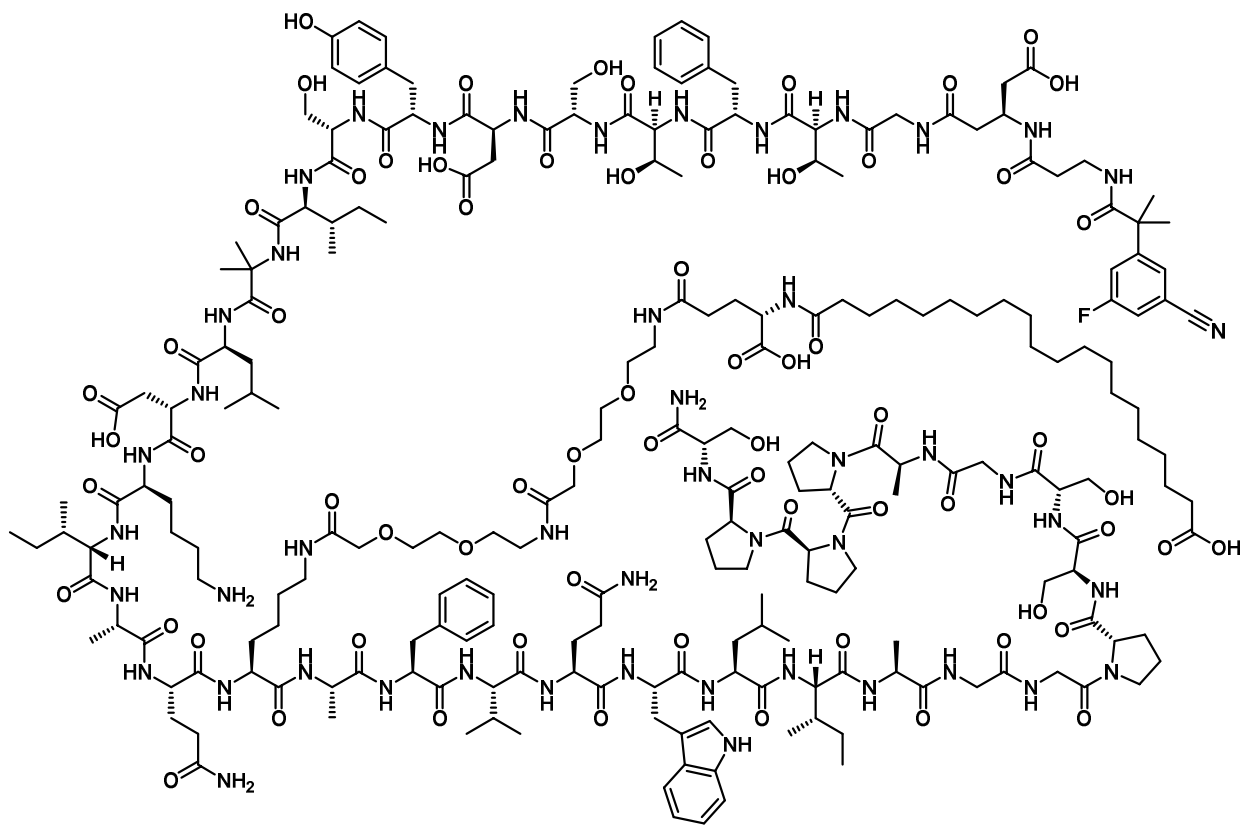
5



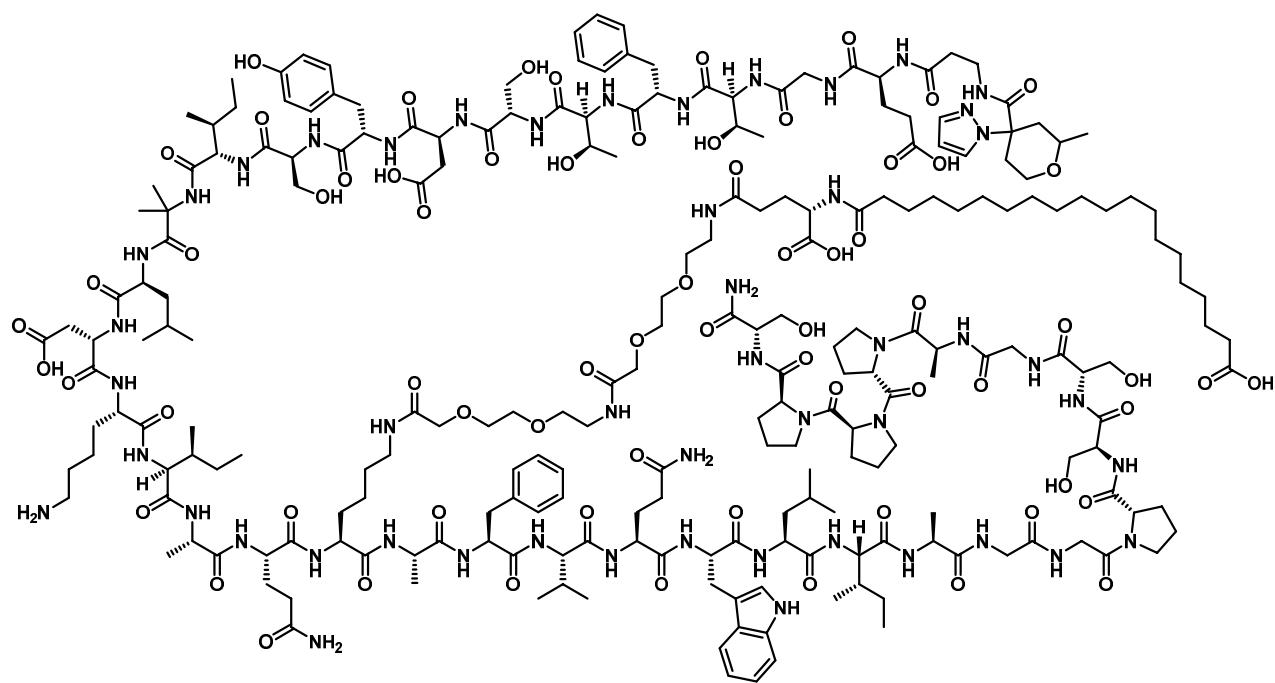
Compound 102,



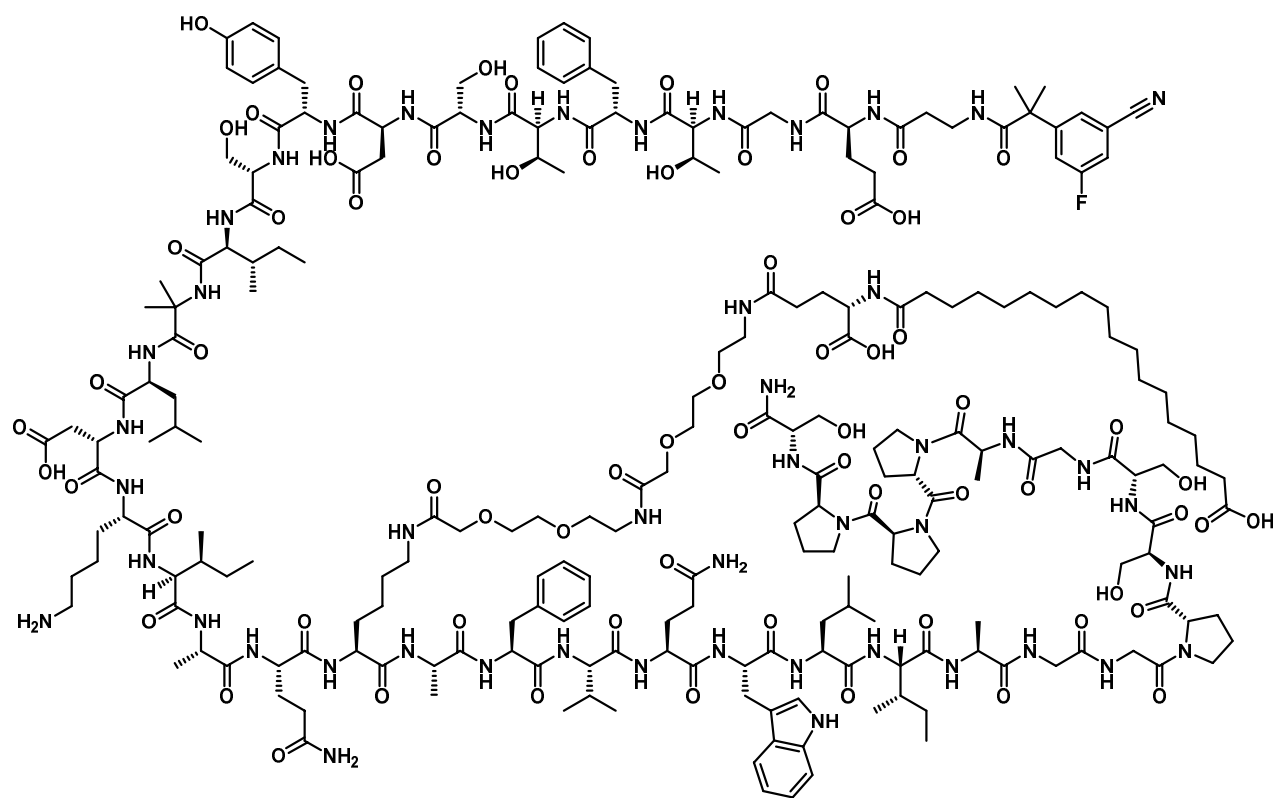
Compound 103,



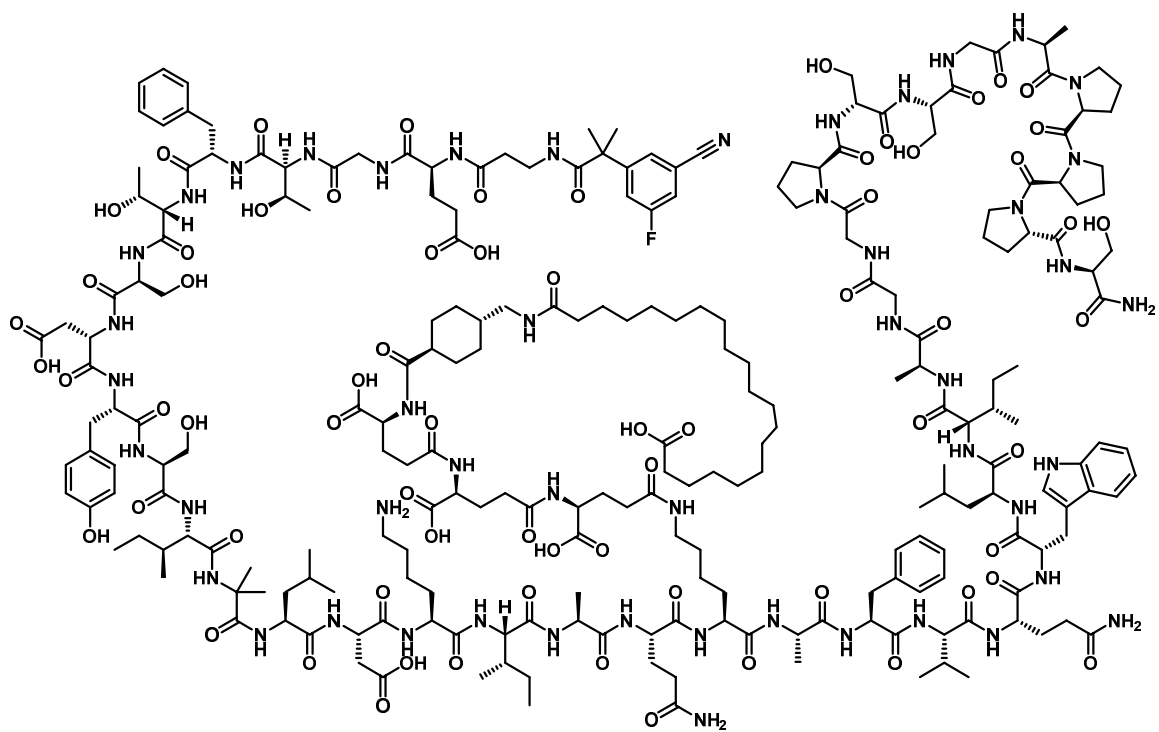
Compound 104,



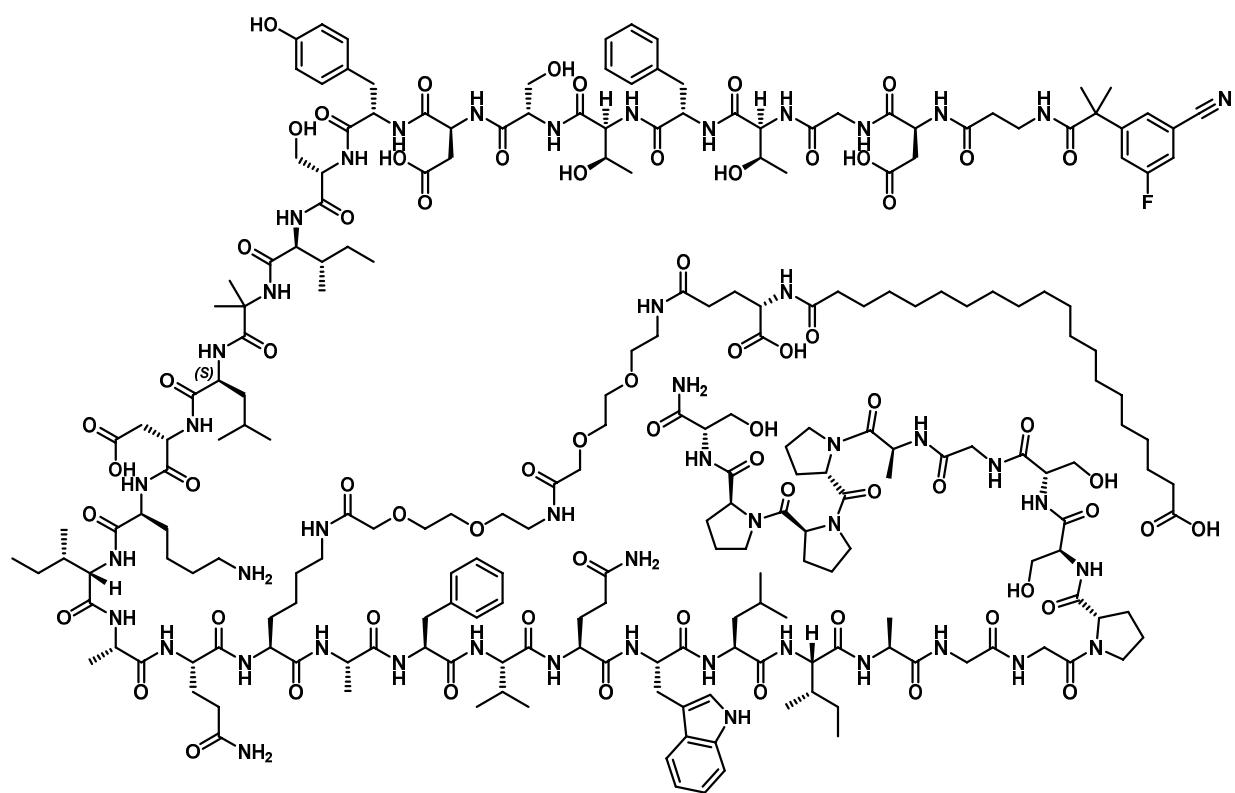
Compound 105,



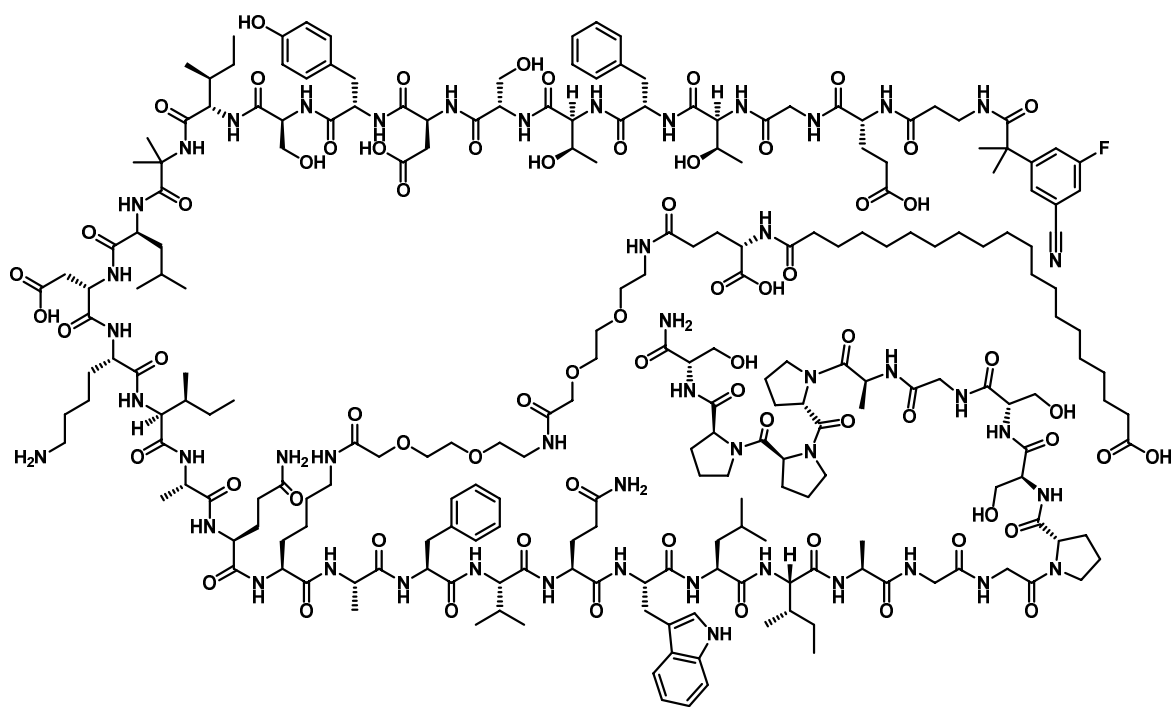
Compound 106,



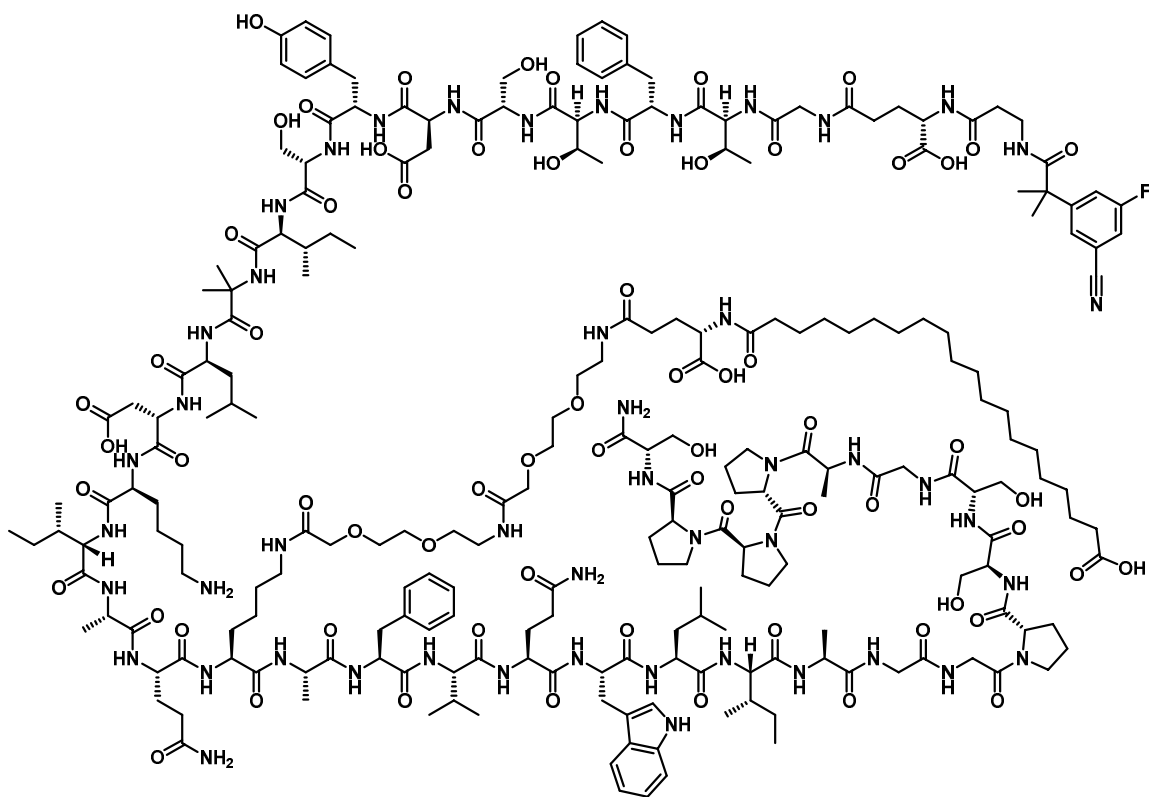
Compound 107,



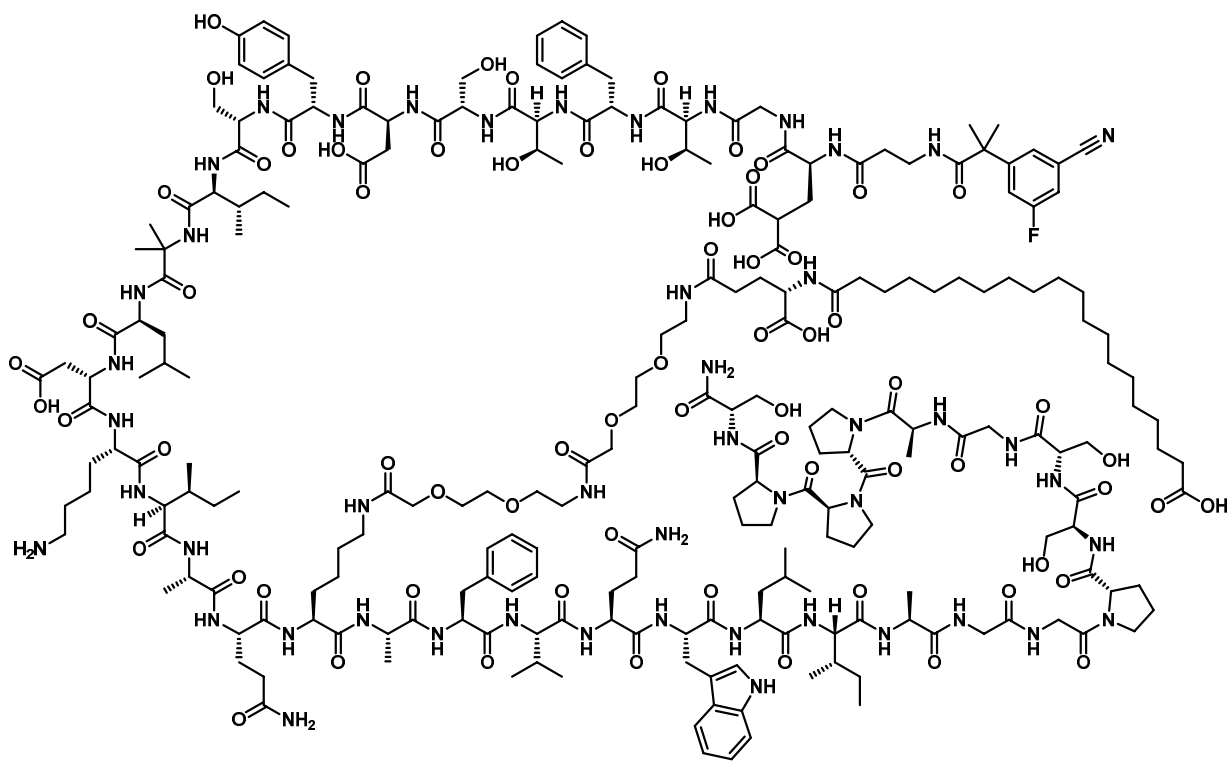
Compound 108,



Compound 109,

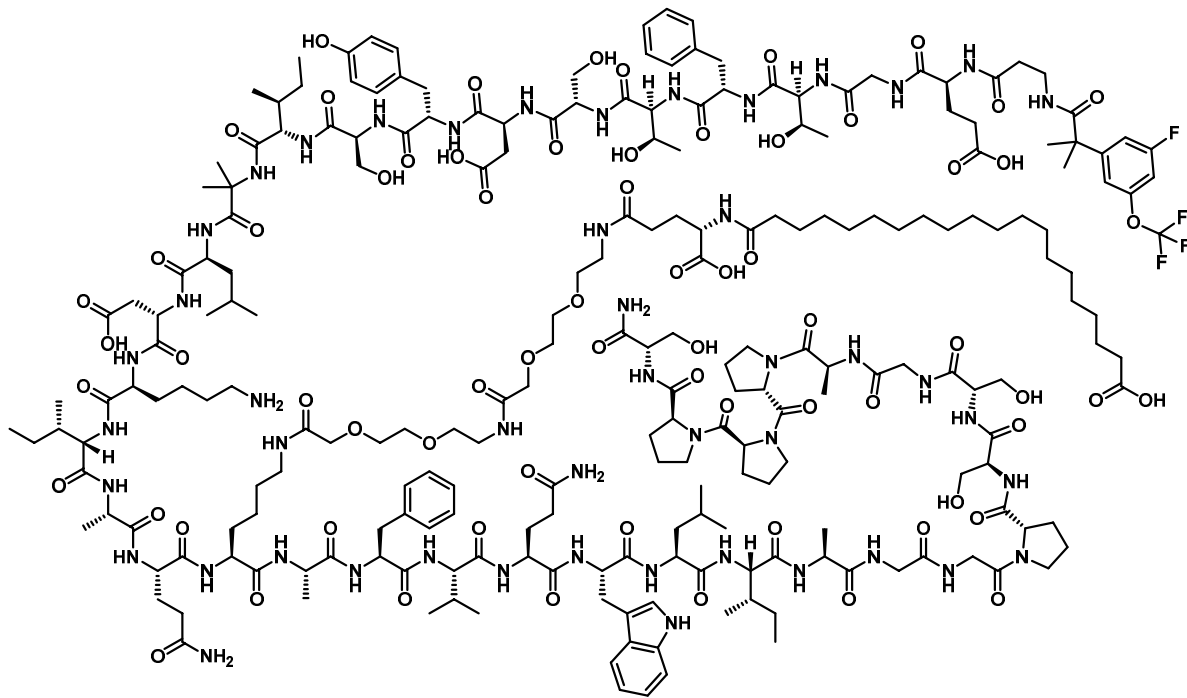


Compound 110,

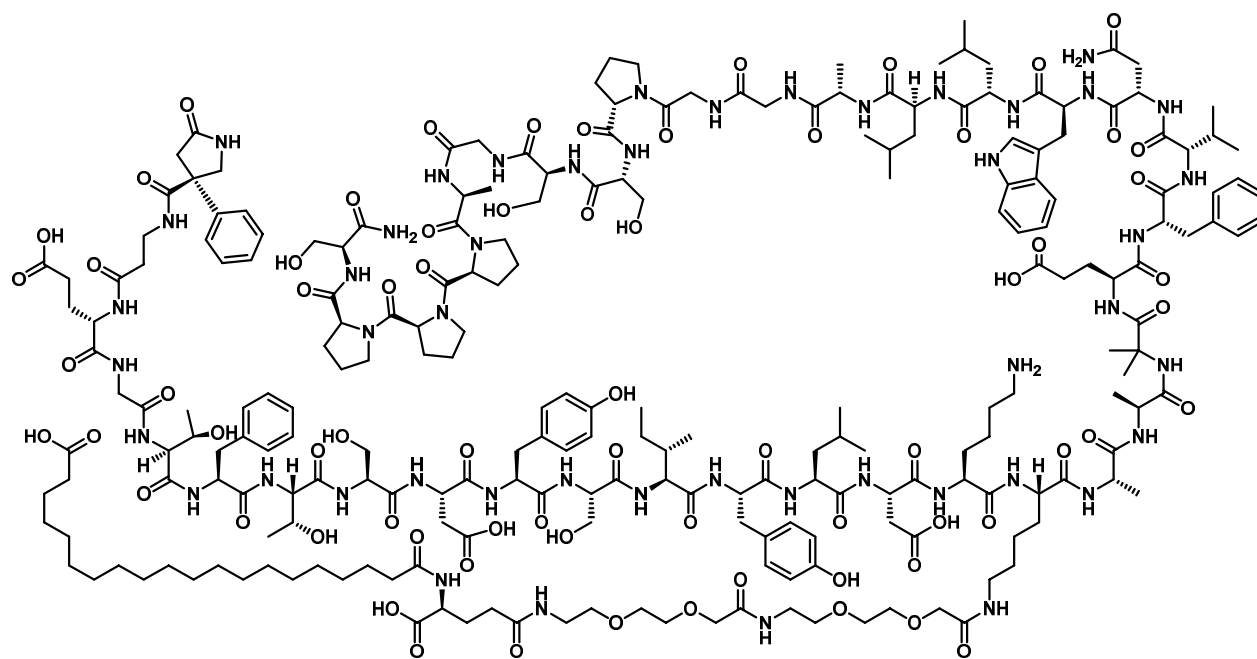


Compound 111,

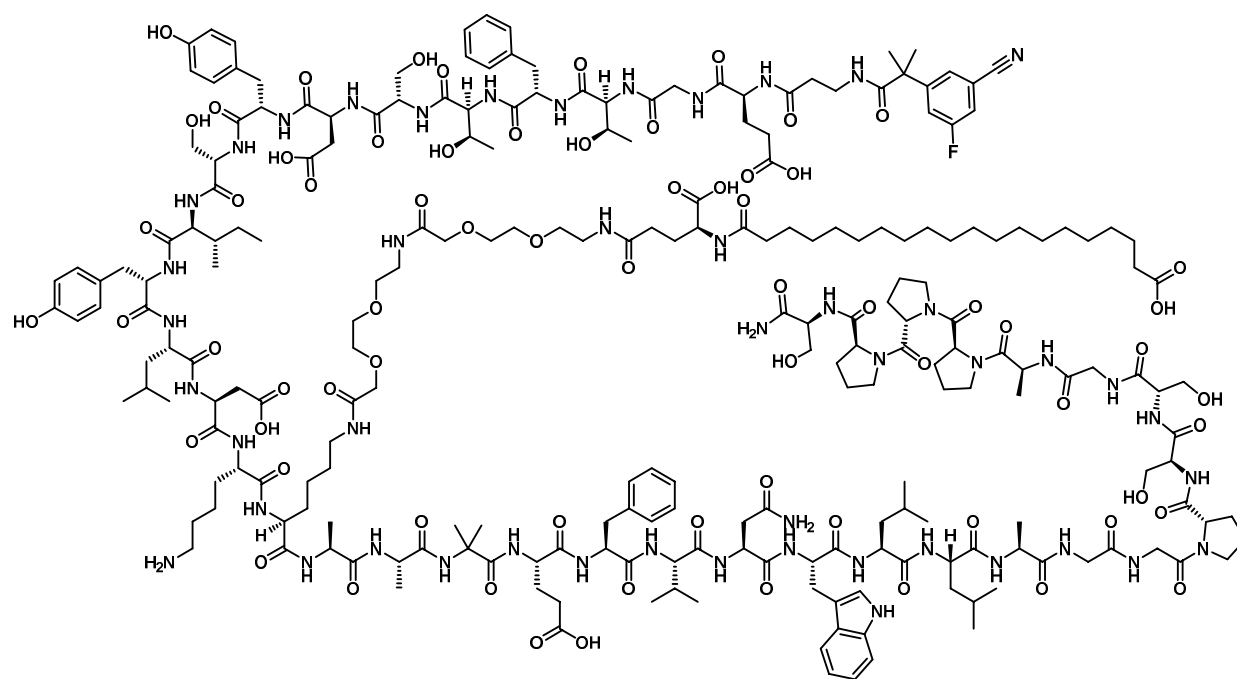
5



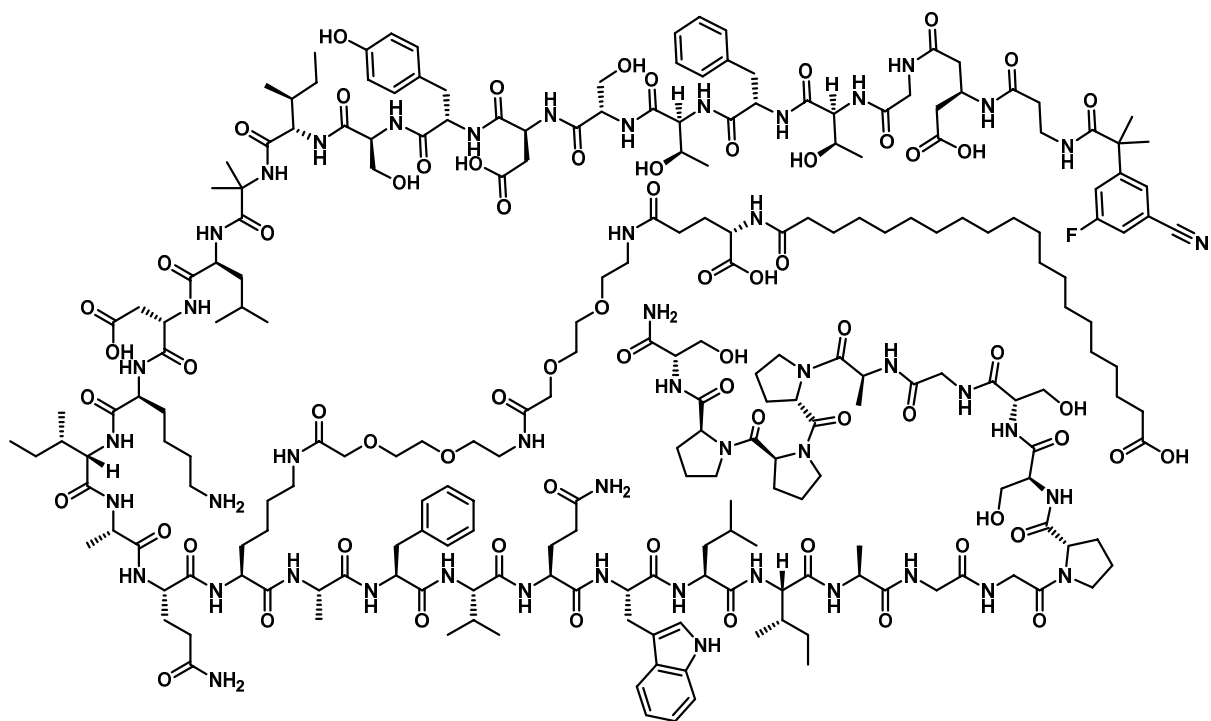
Compound 112,



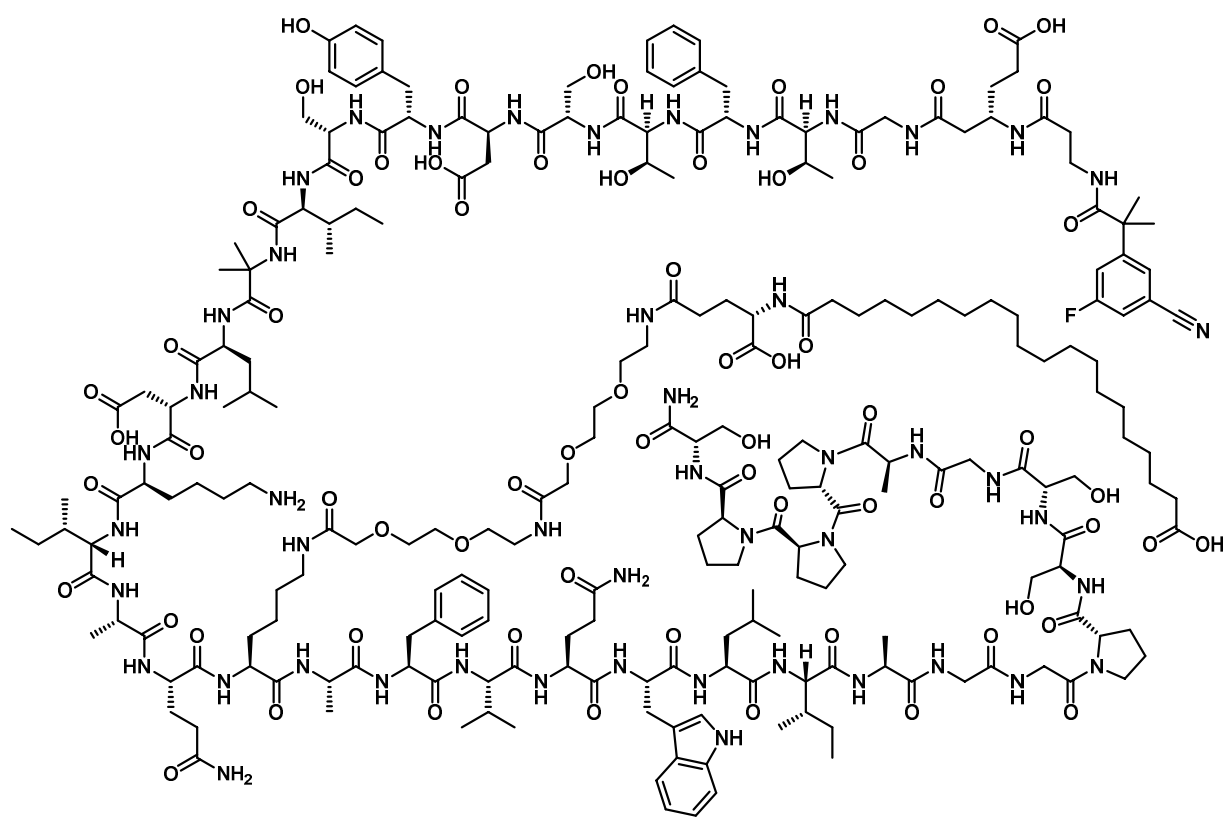
Compound 113,



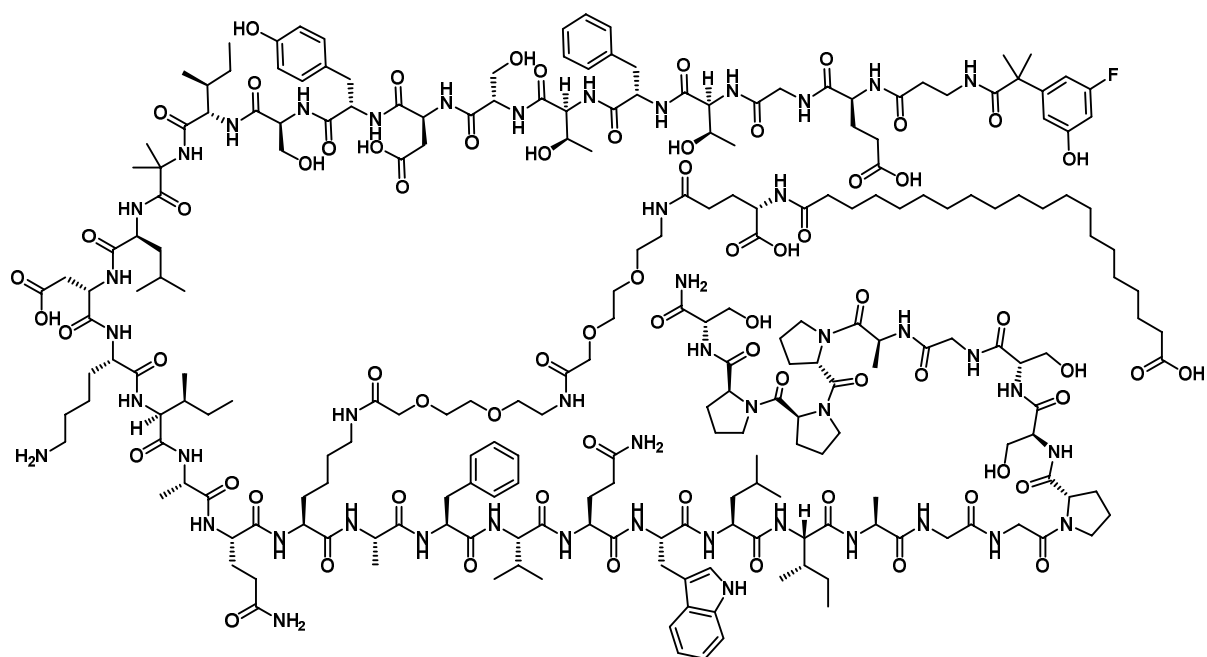
Compound 114,



Compound 115,

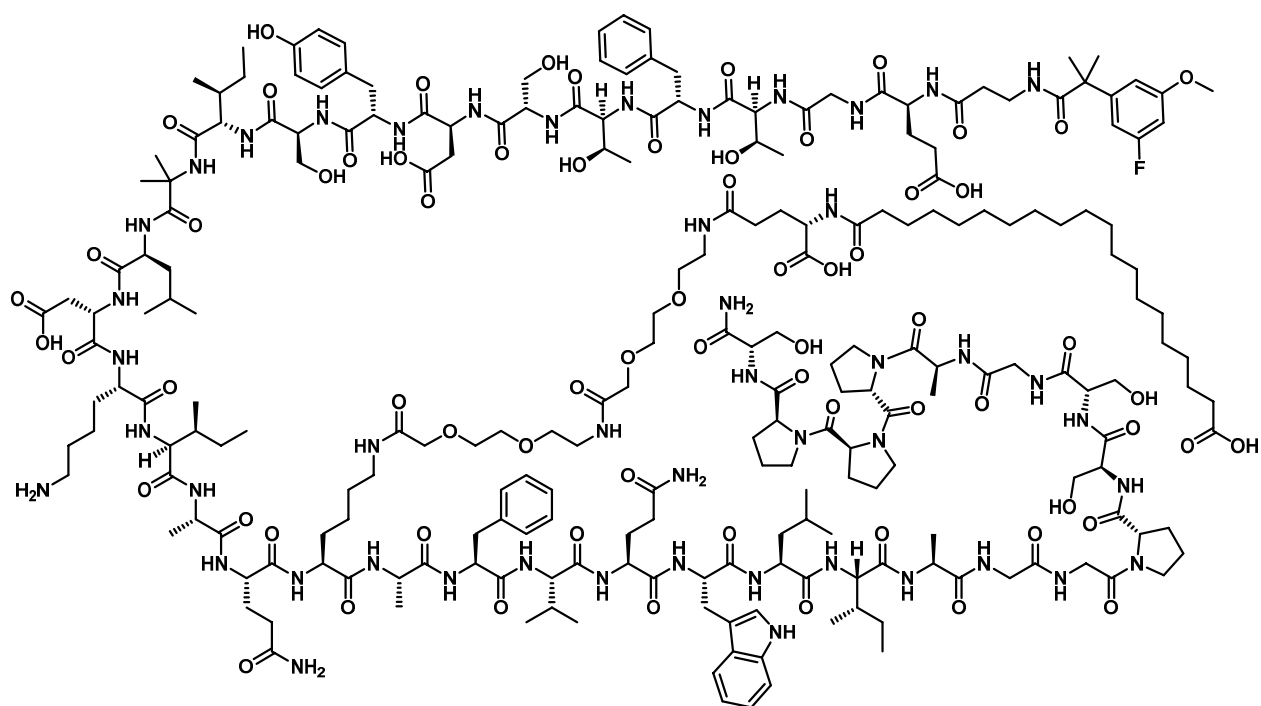


Compound 116,



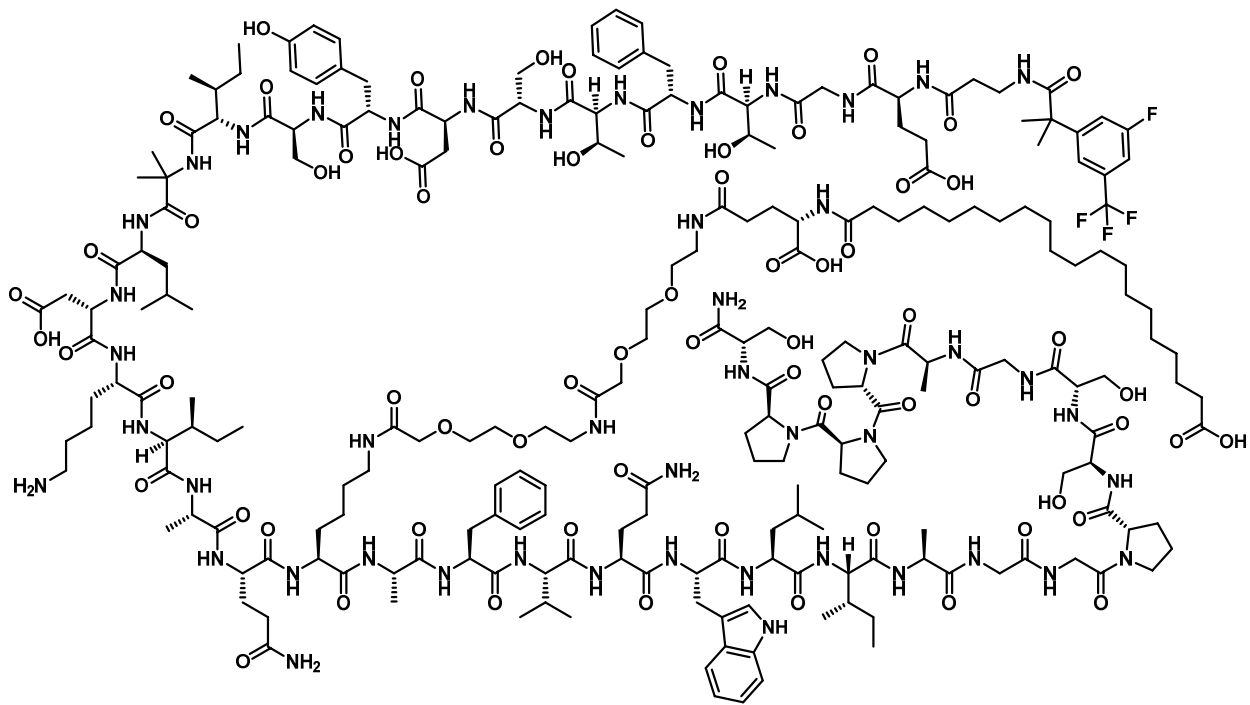
Compound 117,

5



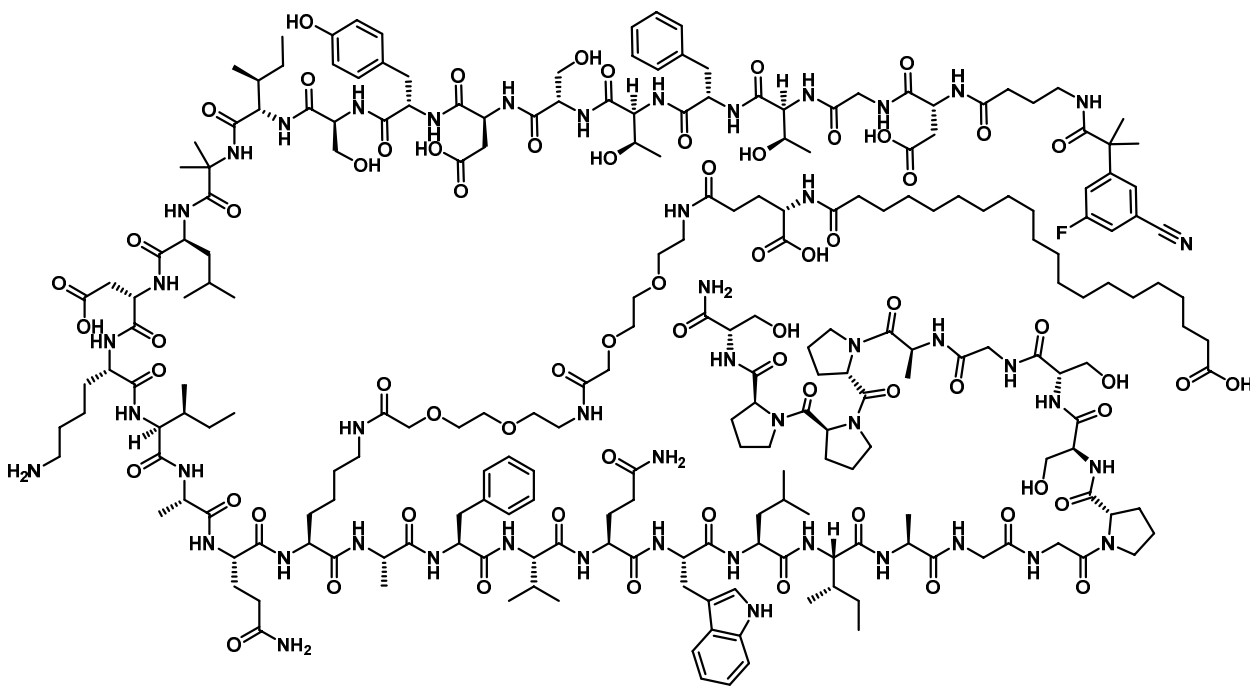
Compound 118,

10



Compound 119,

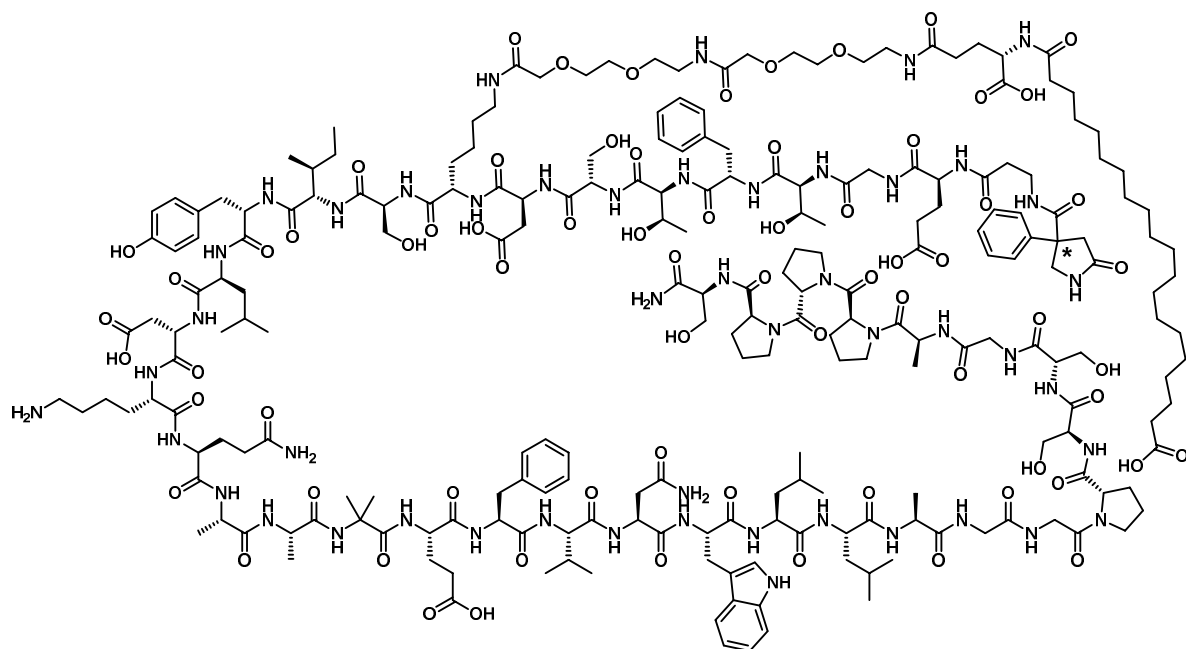
5



Compound 120,

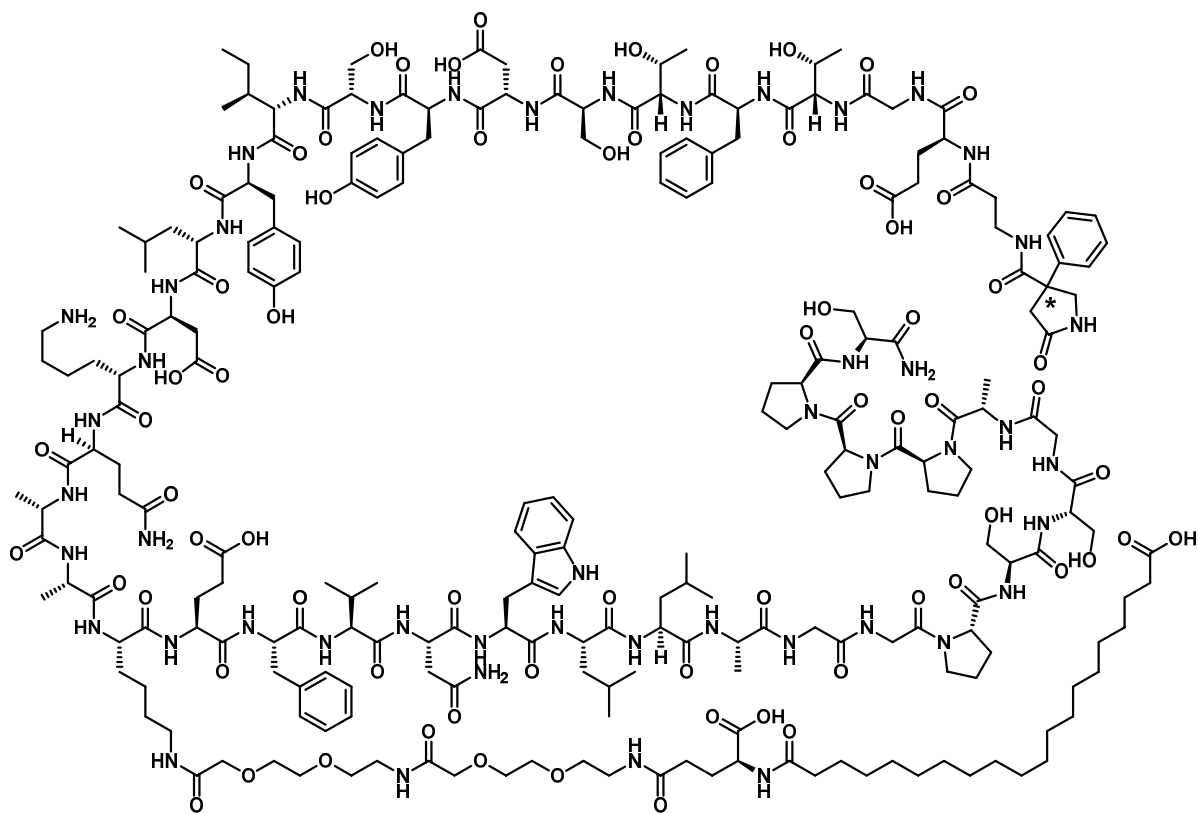
[illegible]

Compound 122,

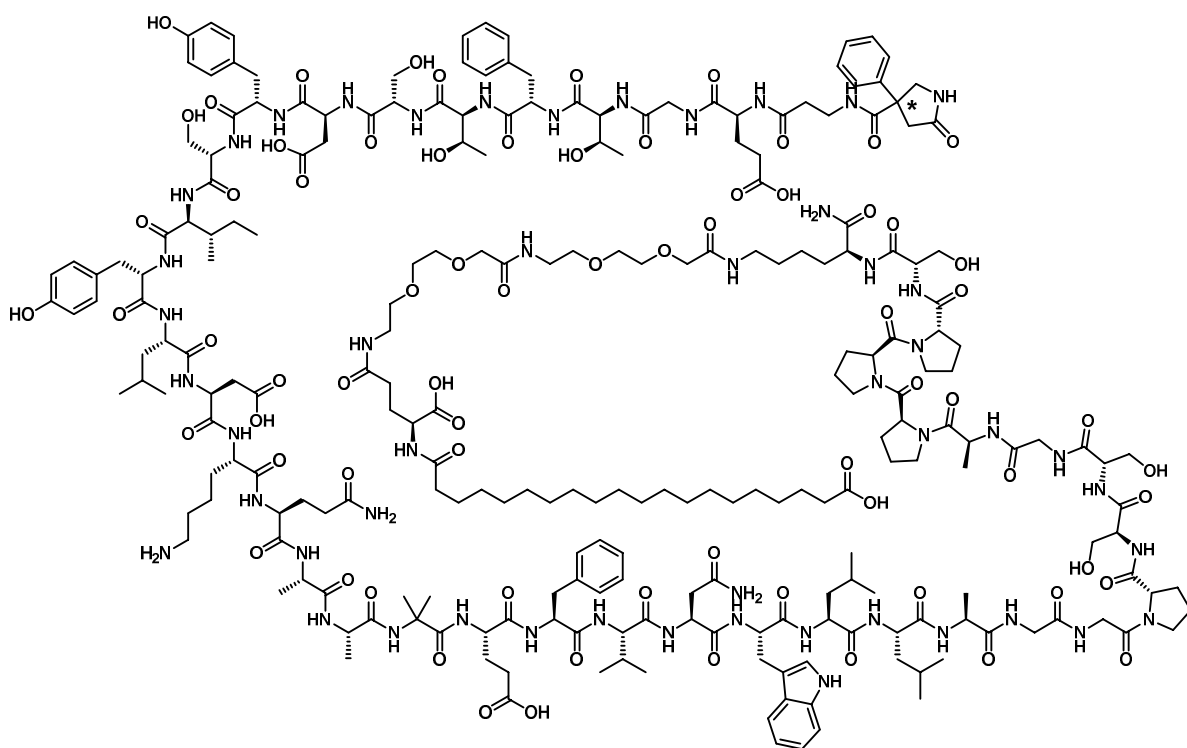


Compound 123,

5

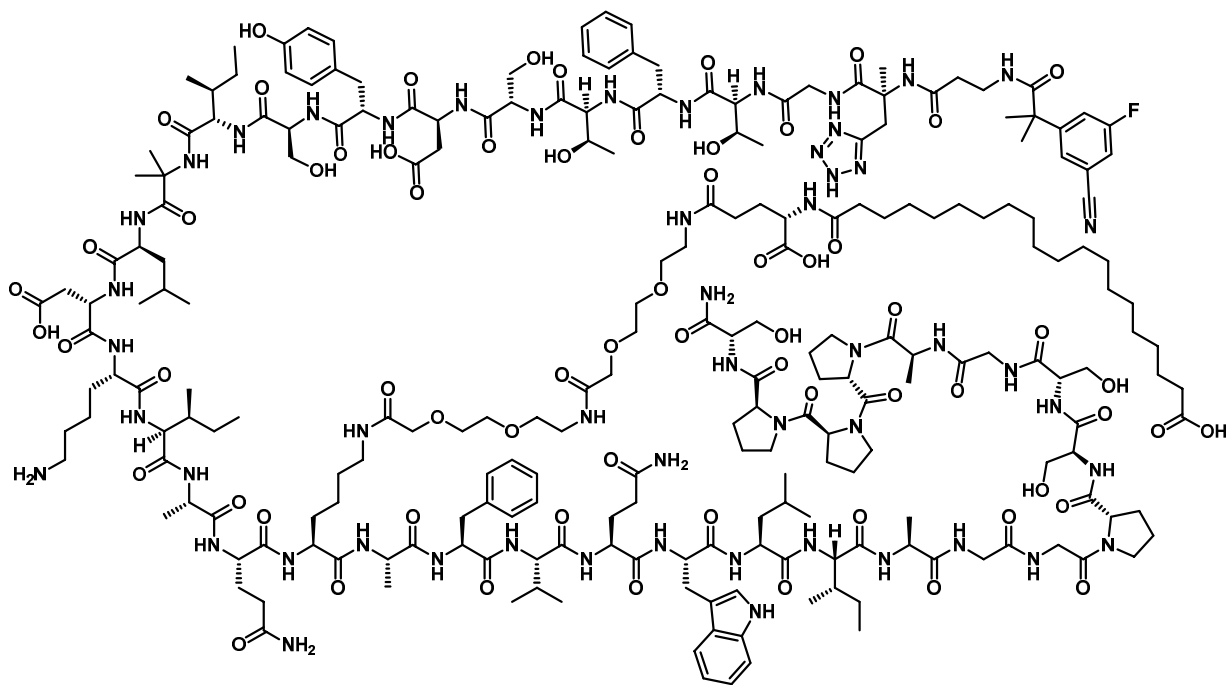


Compound 124,



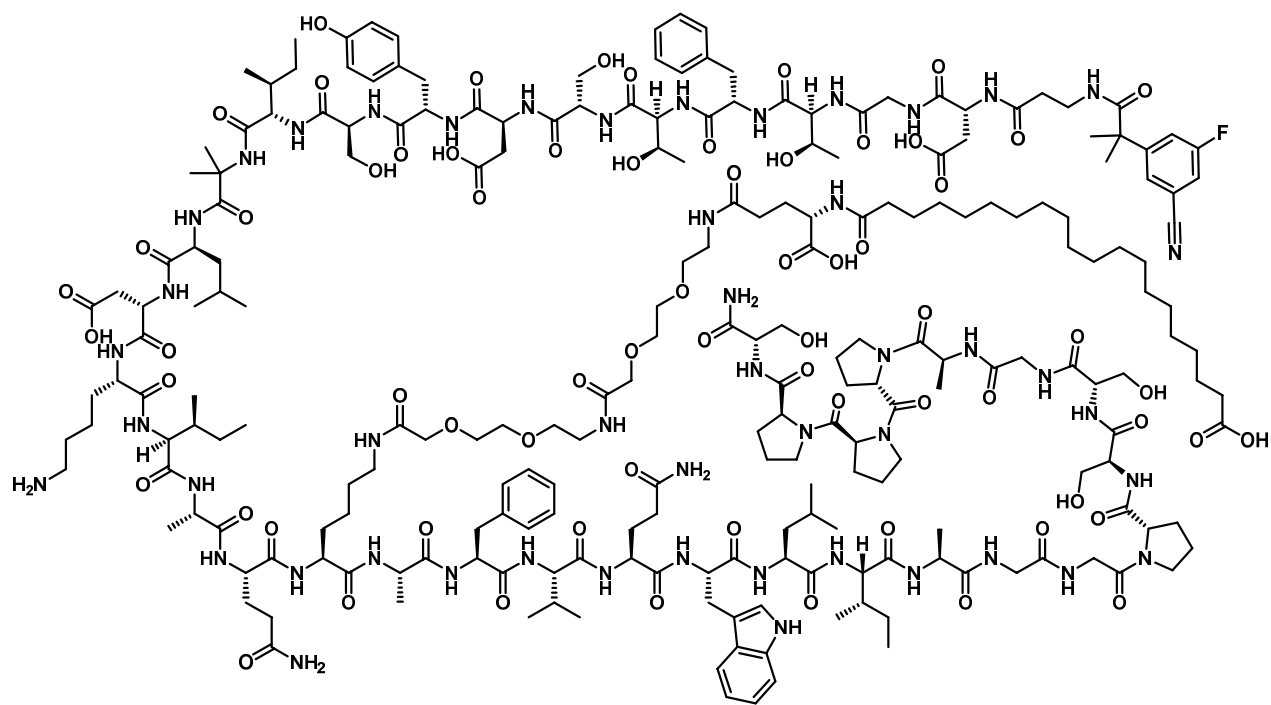
Compound 125,

5

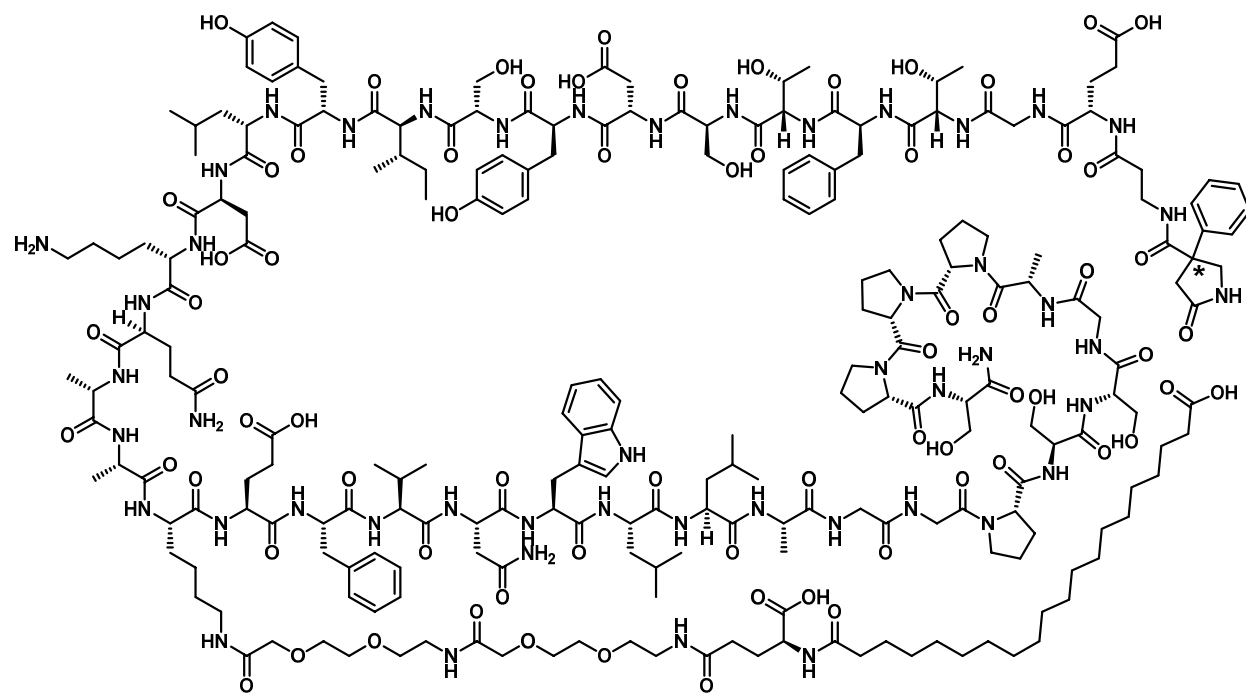


Compound 126,

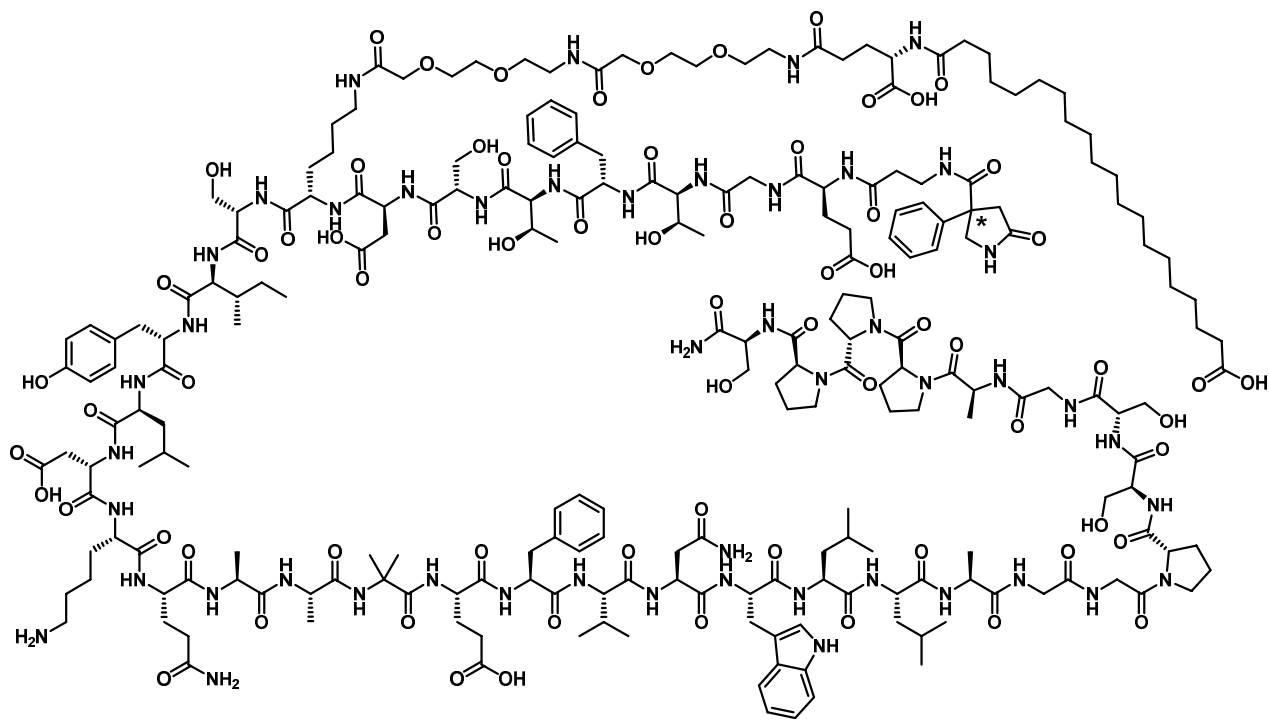
10



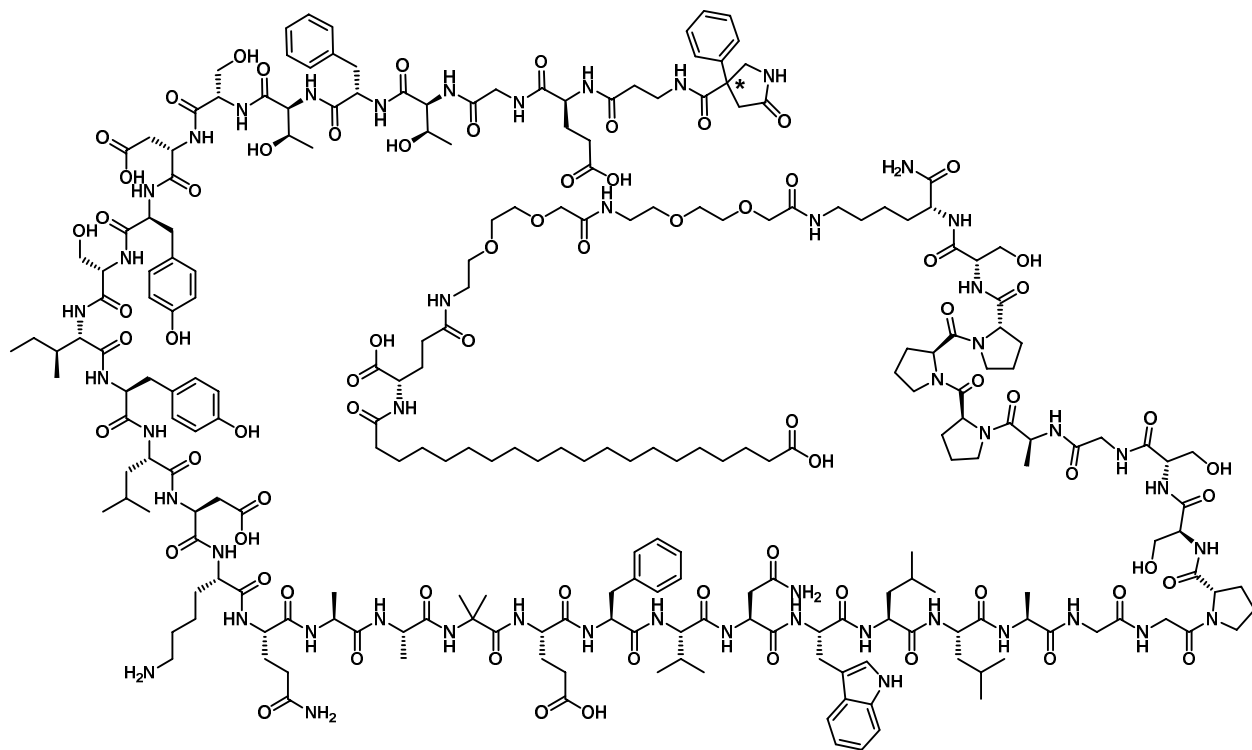
Compound 127,



Compound 128,



Compound 129,



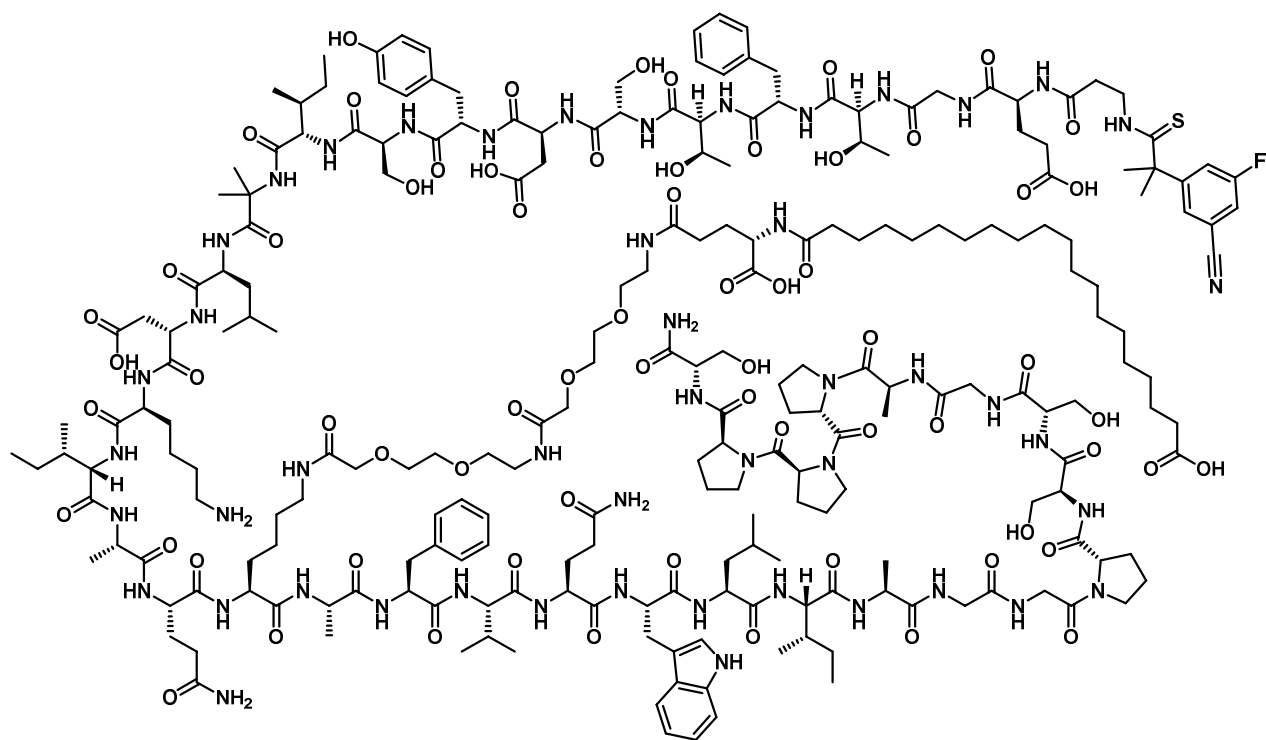
Compound 130,

[illegible]

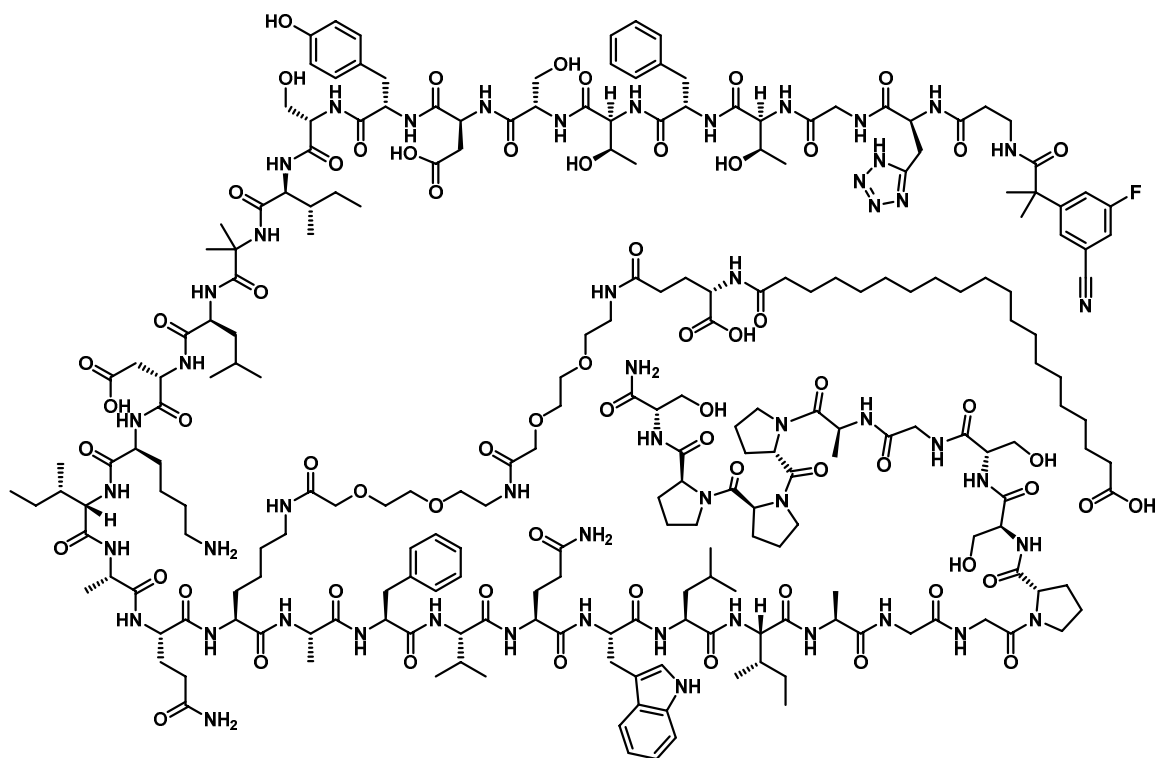
5

[illegible]

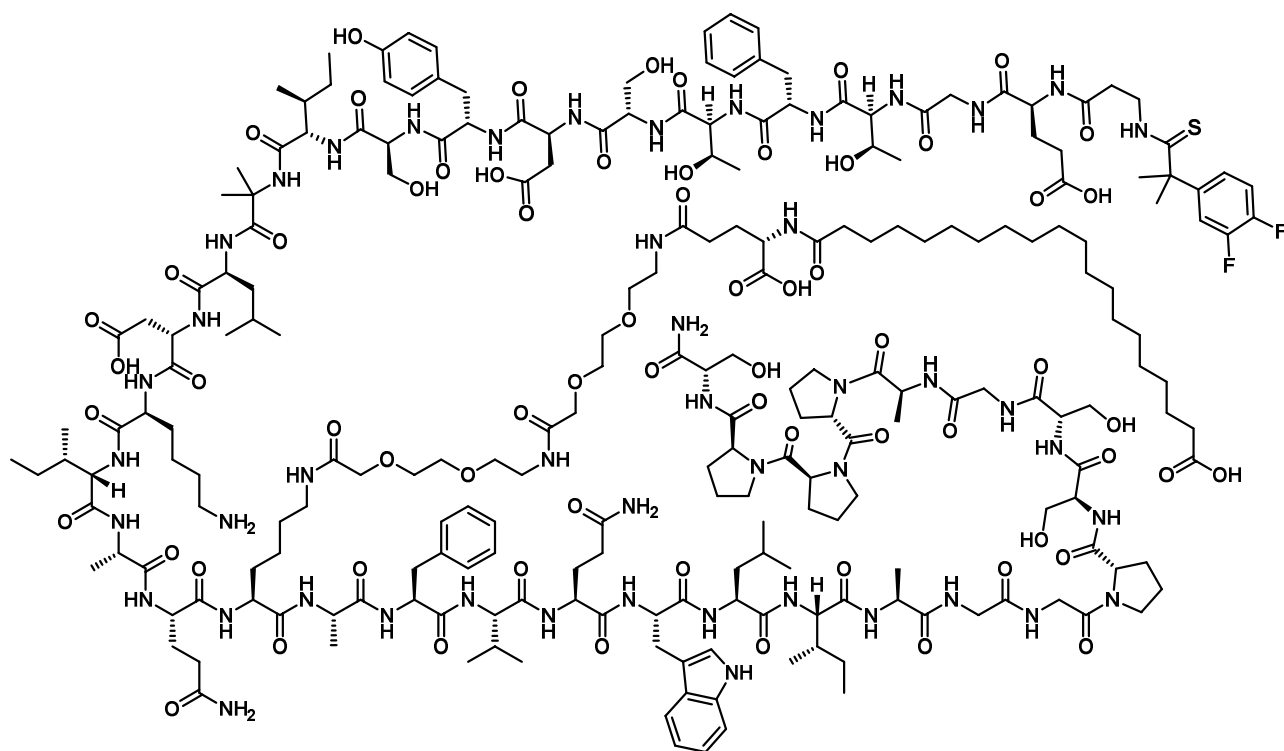
Compound 134,



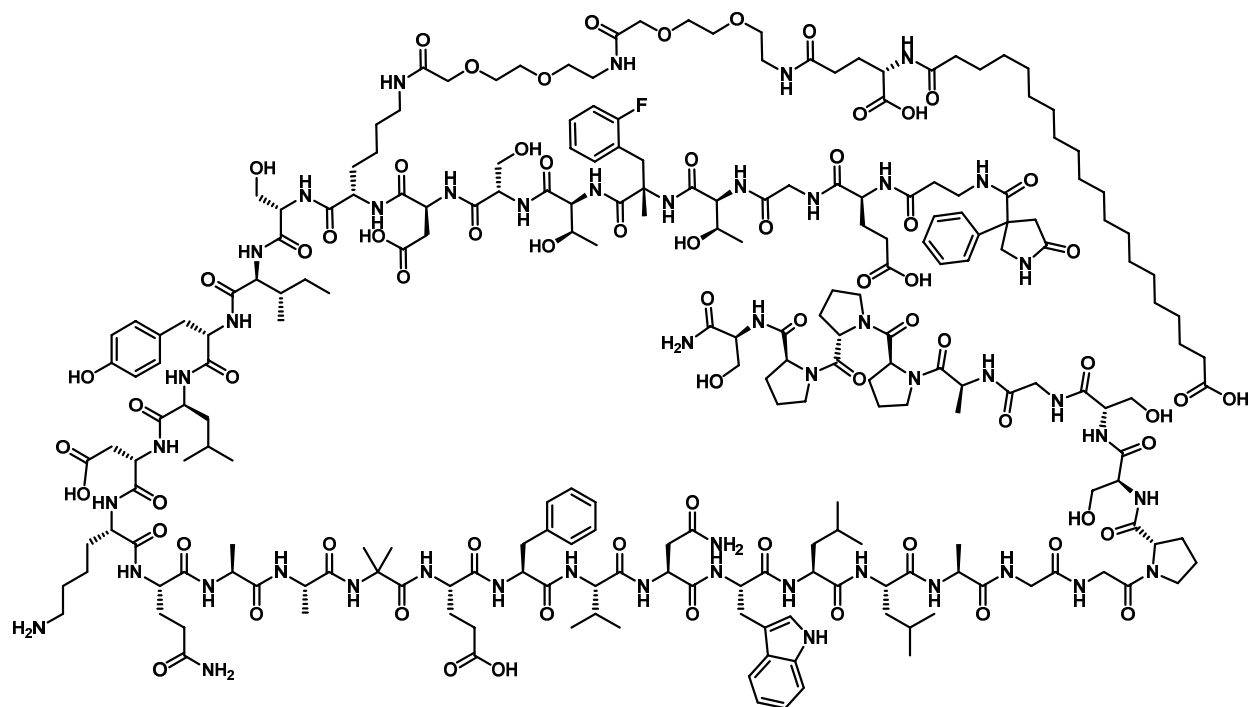
Compound 135,



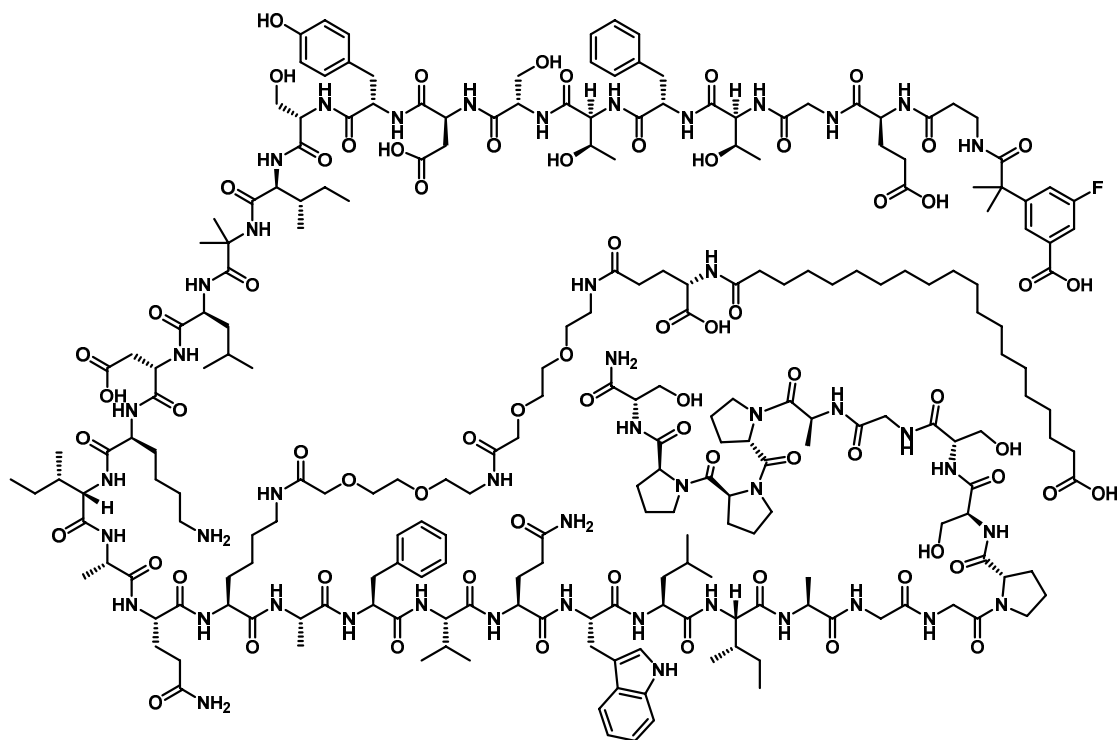
Compound 136,



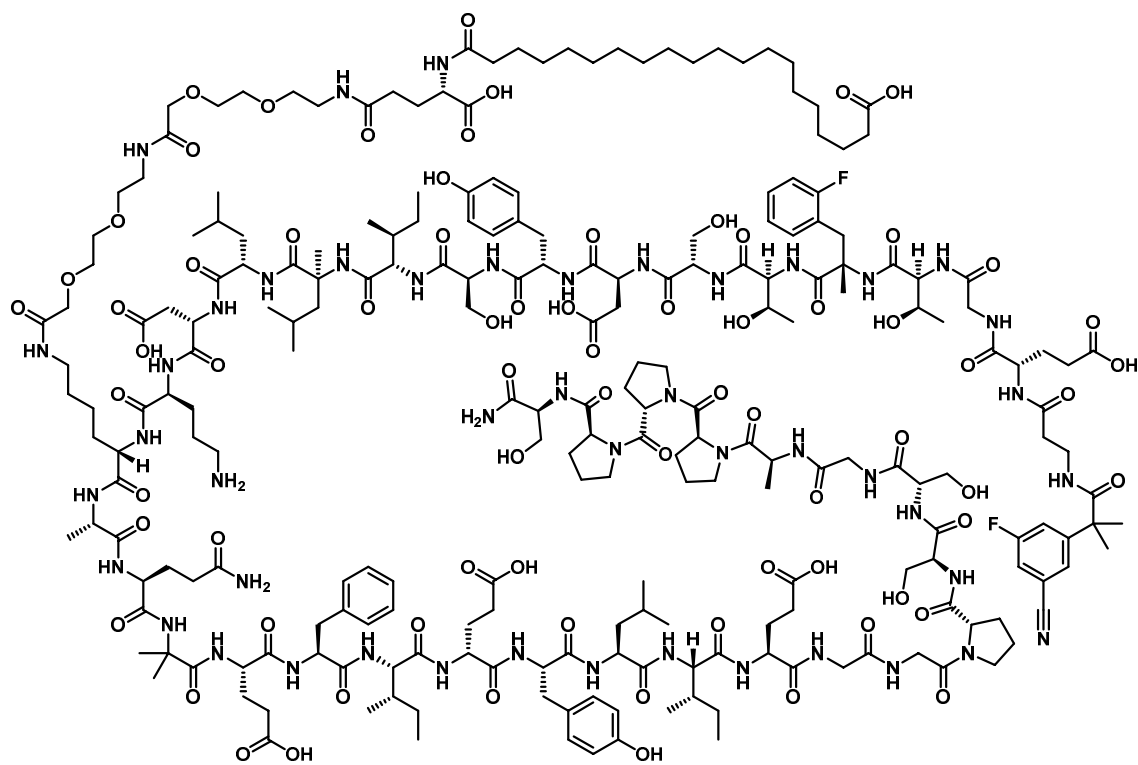
Compound 137,



Compound 138,



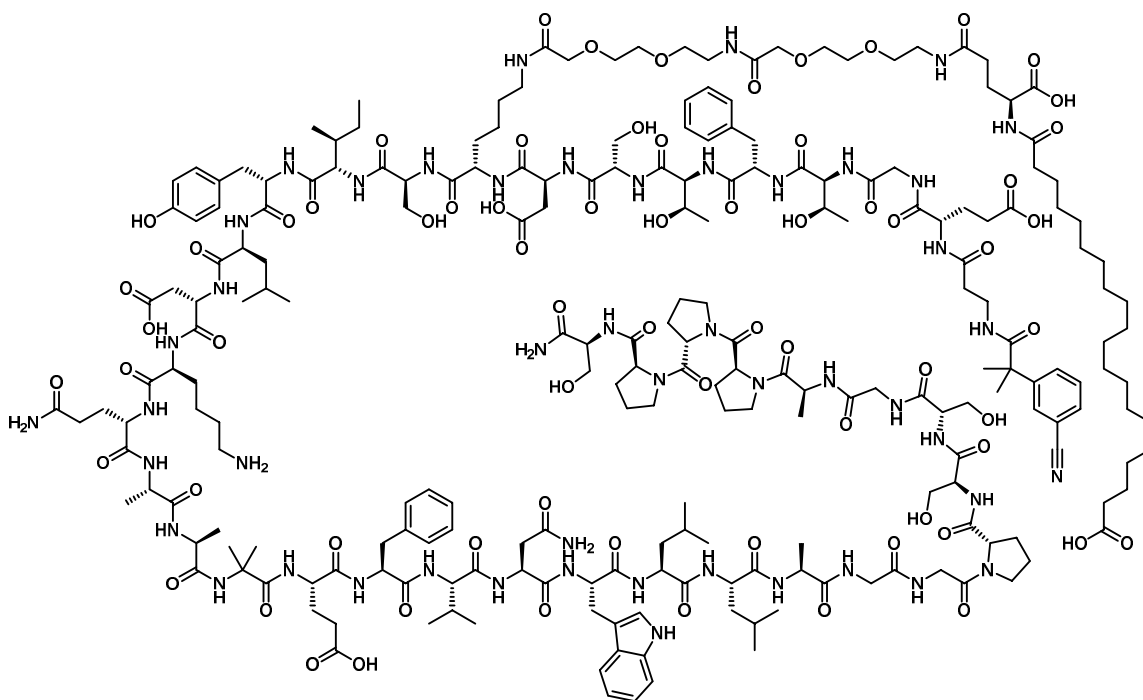
Compound 139,



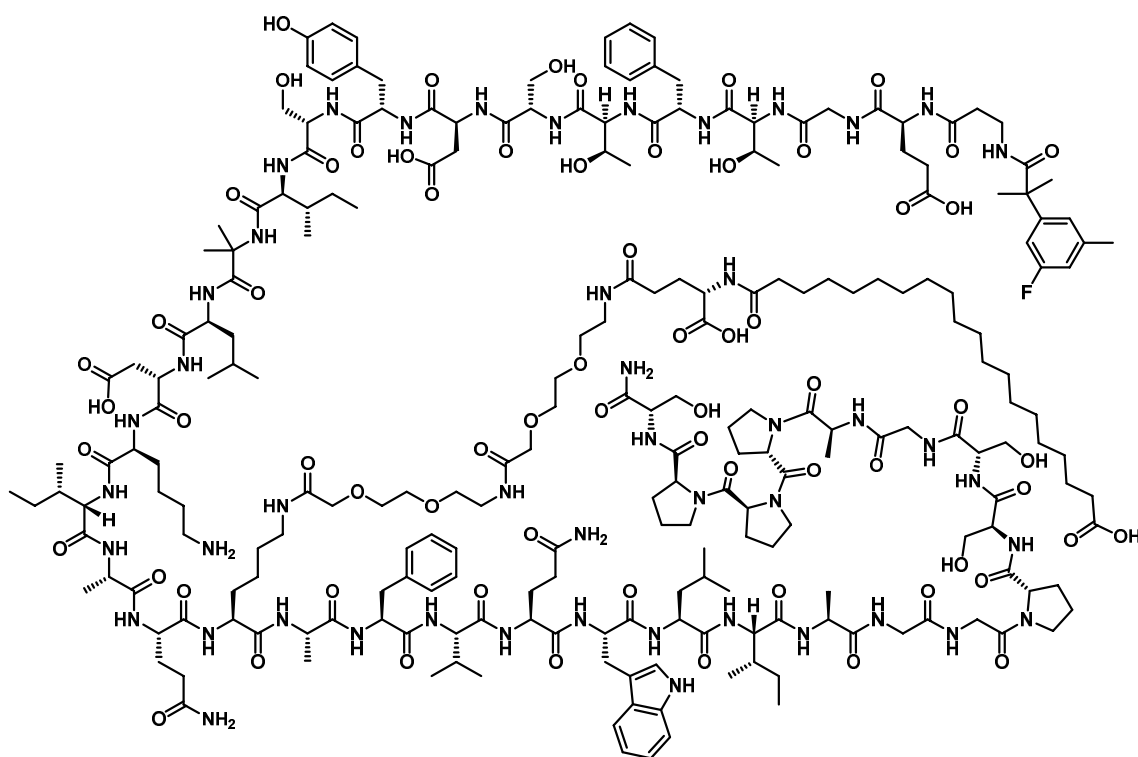
Compound 140,

[illegible]

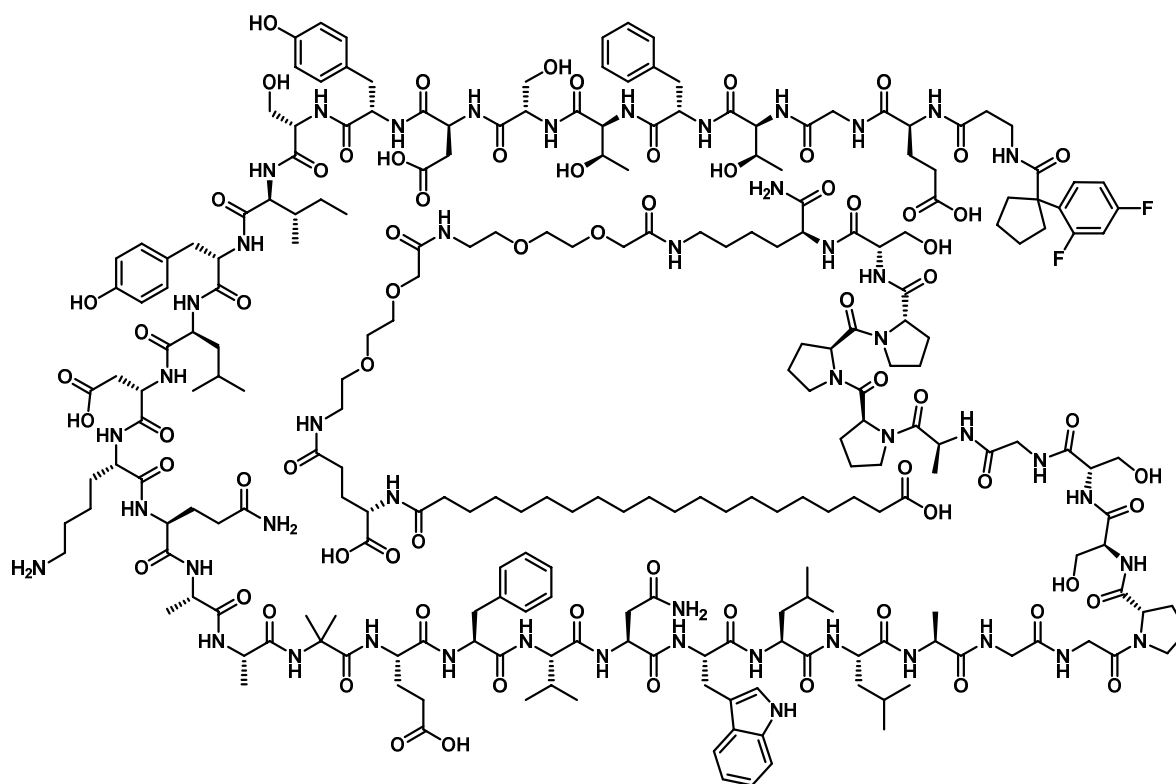
Compound 142,



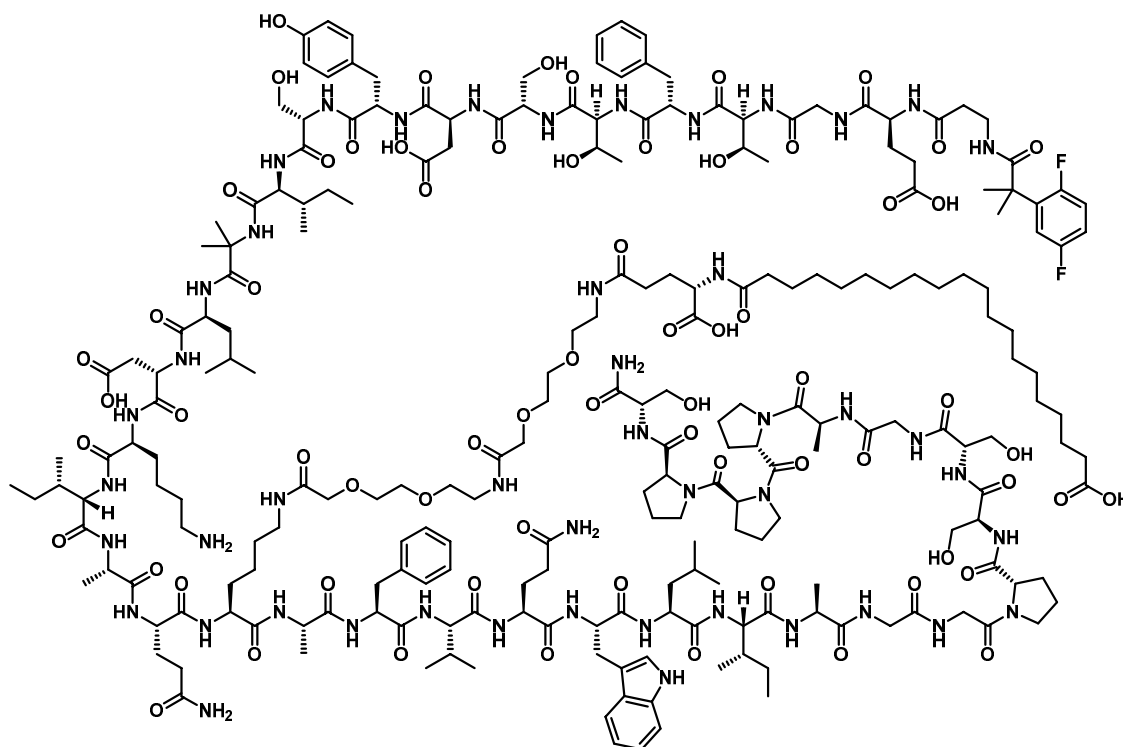
Compound 143,



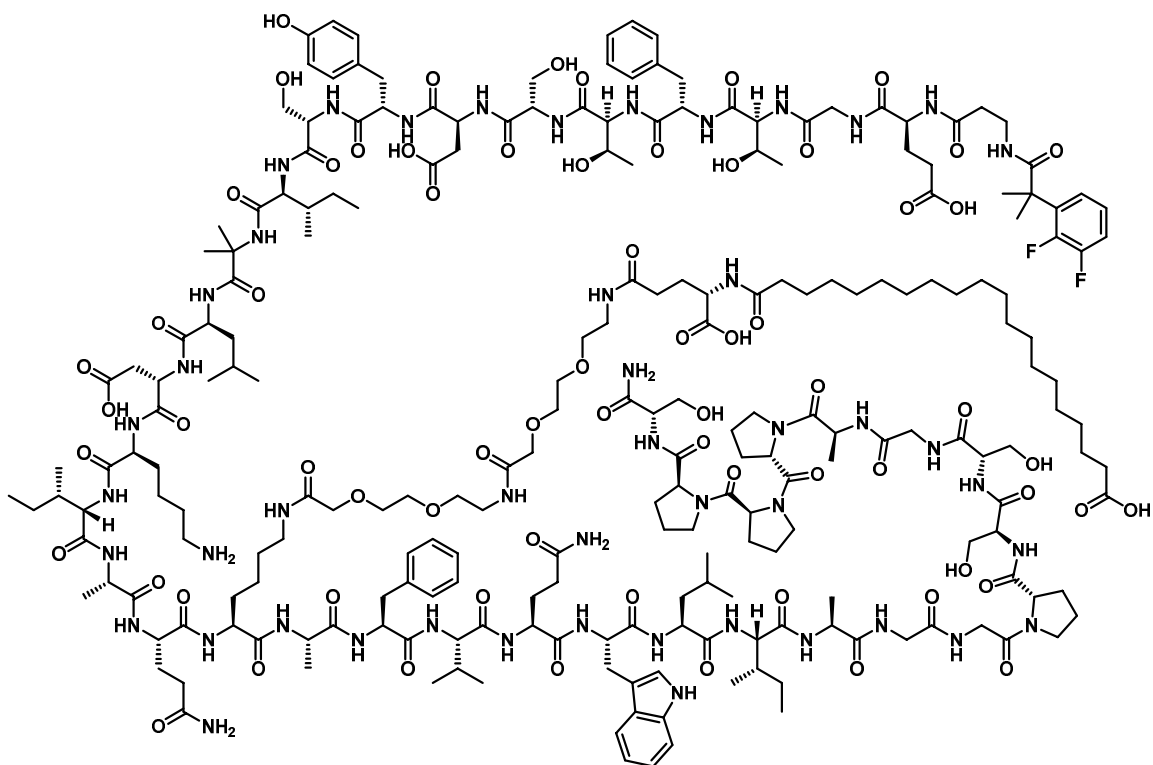
Compound 144,



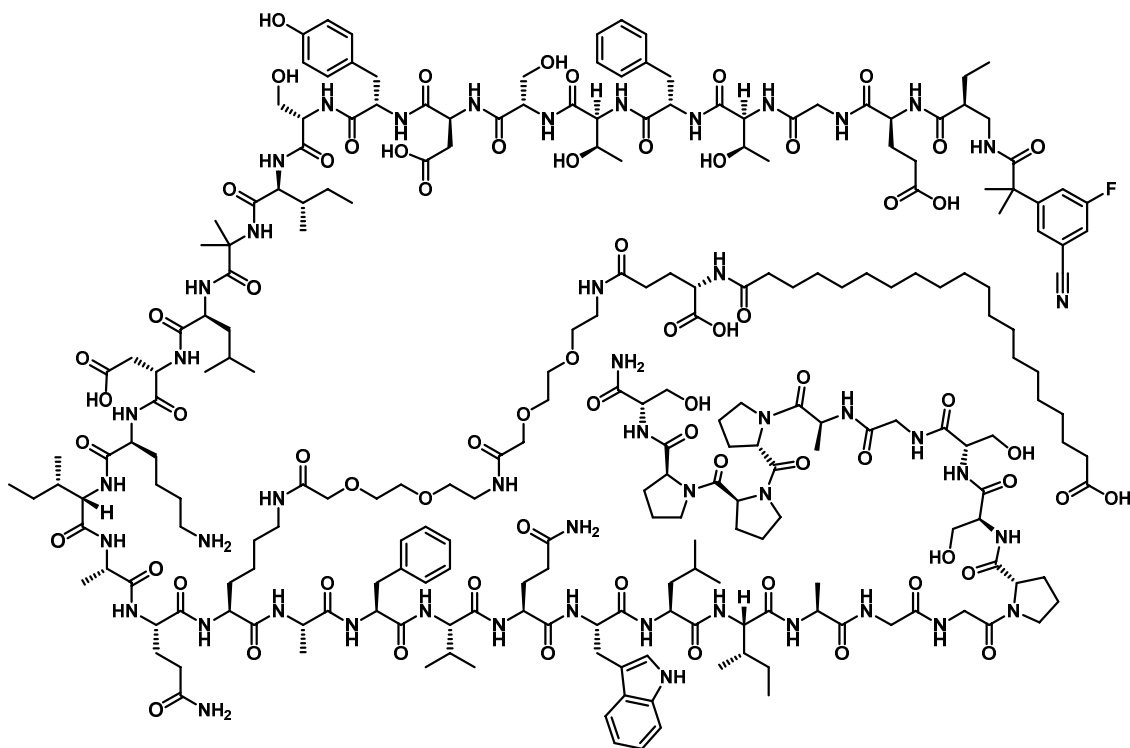
Compound 145,



Compound 146,



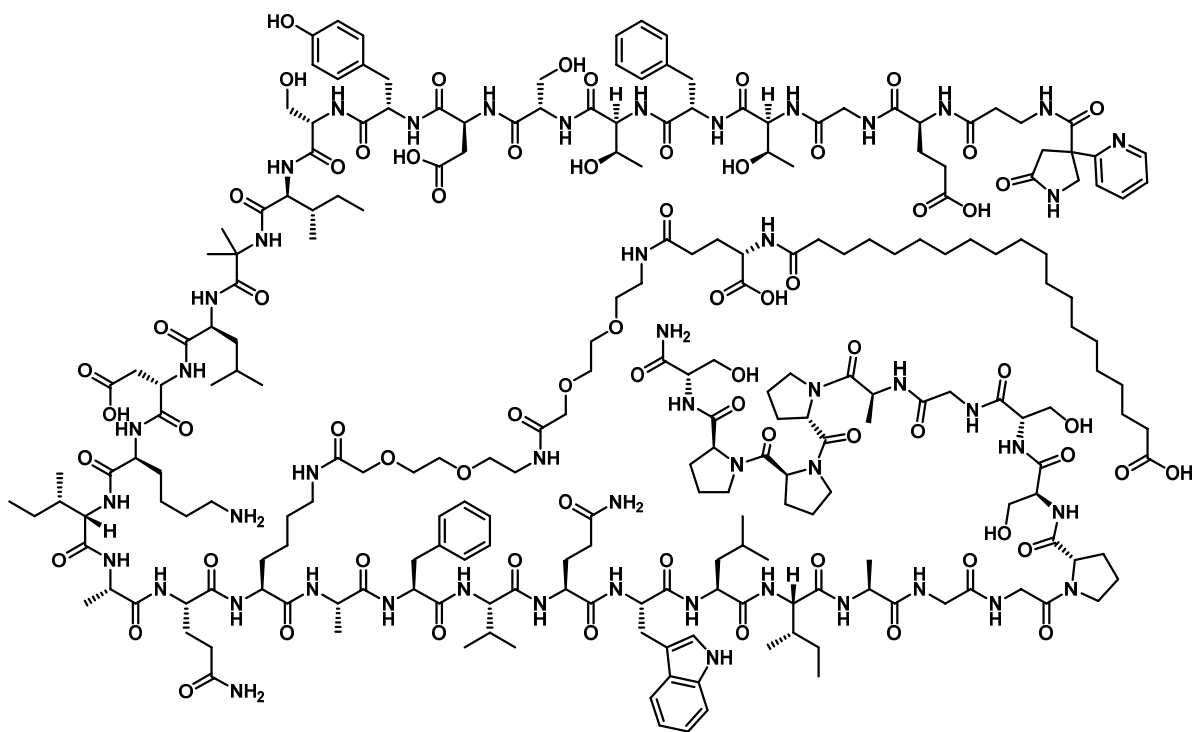
Compound 147,



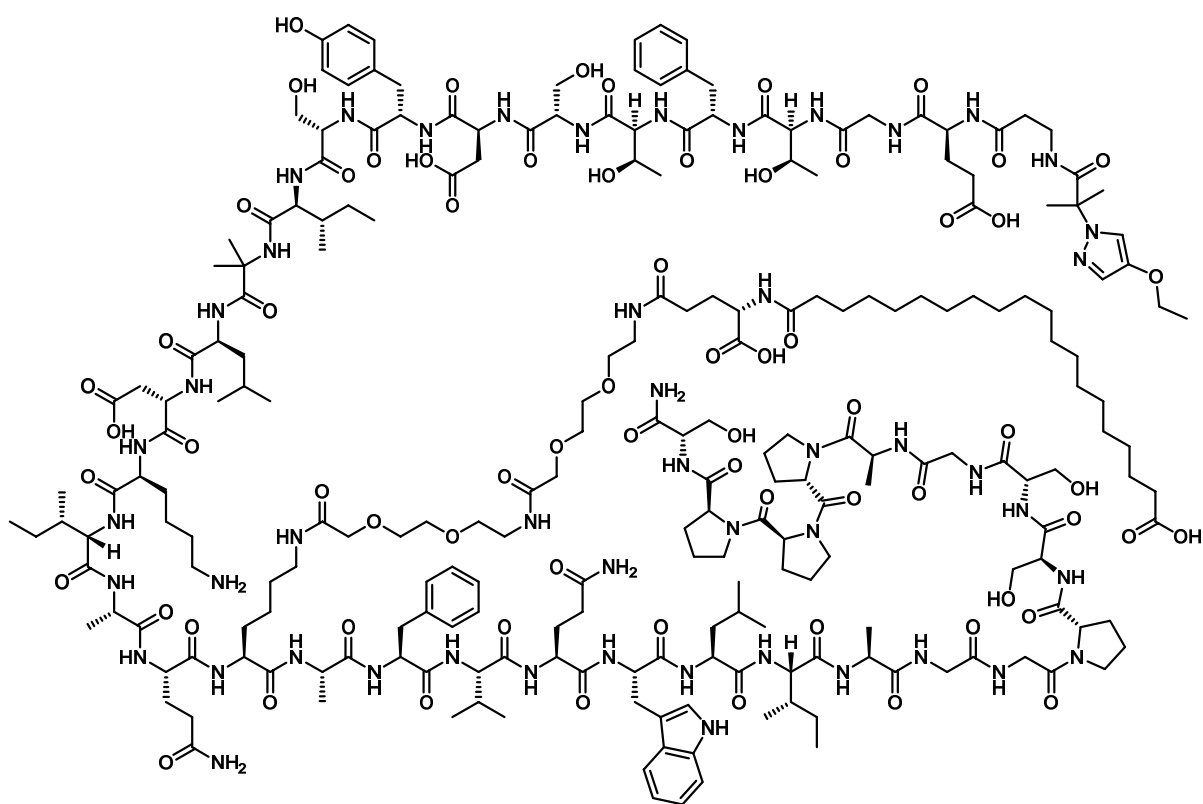
Compound 148,

[illegible]

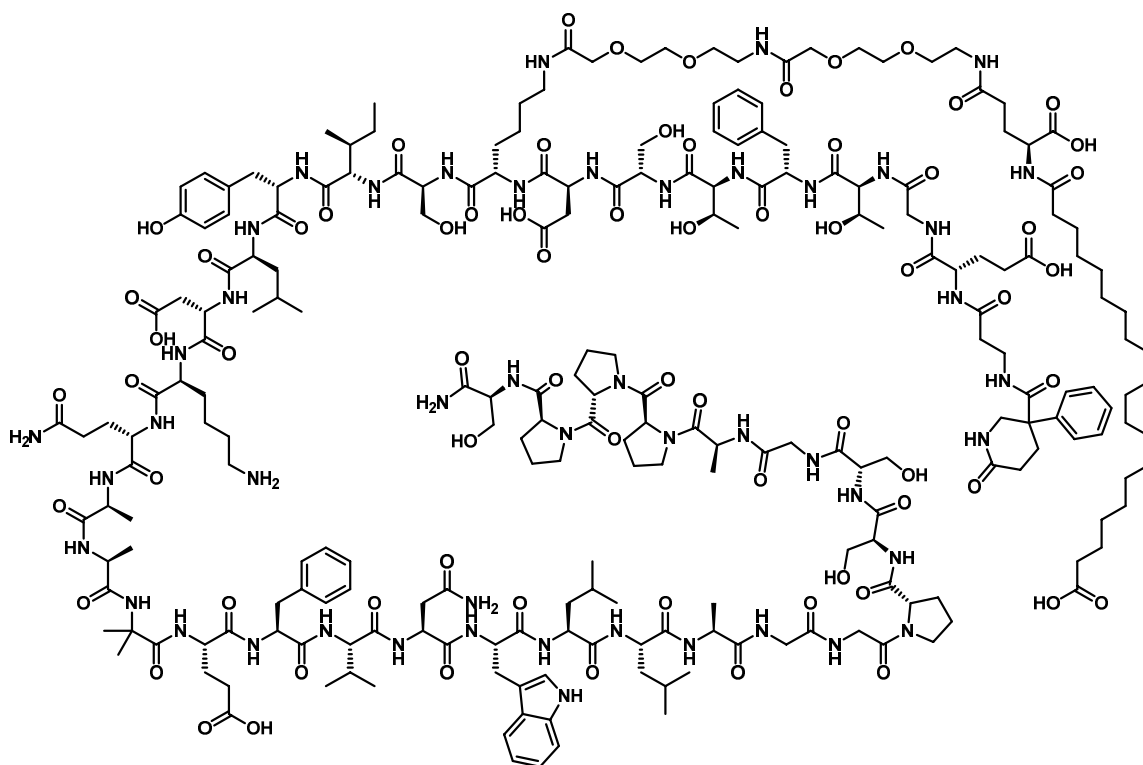
Compound 150,



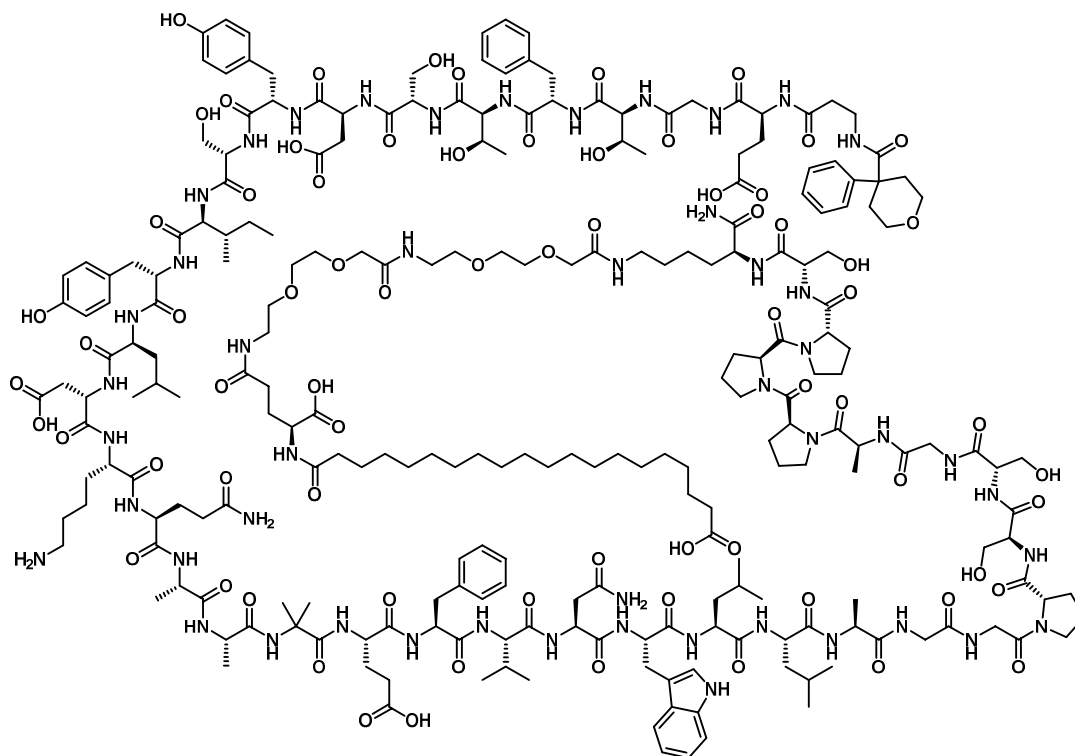
Compound 151,



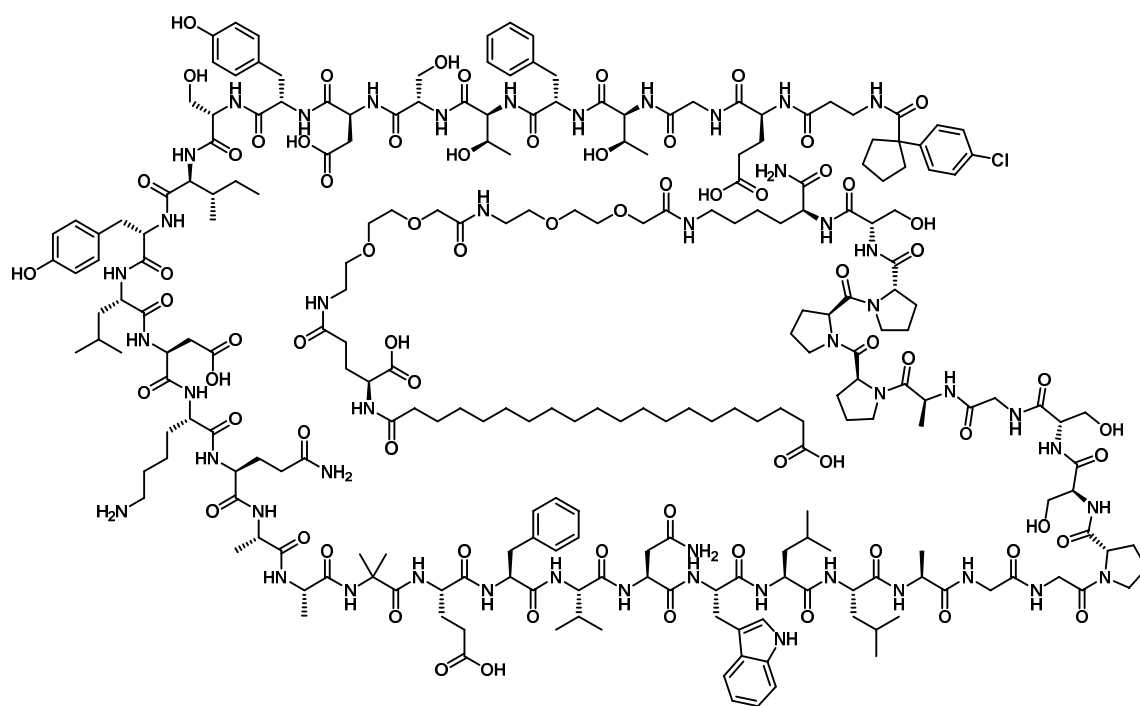
Compound 152,



Compound 153,

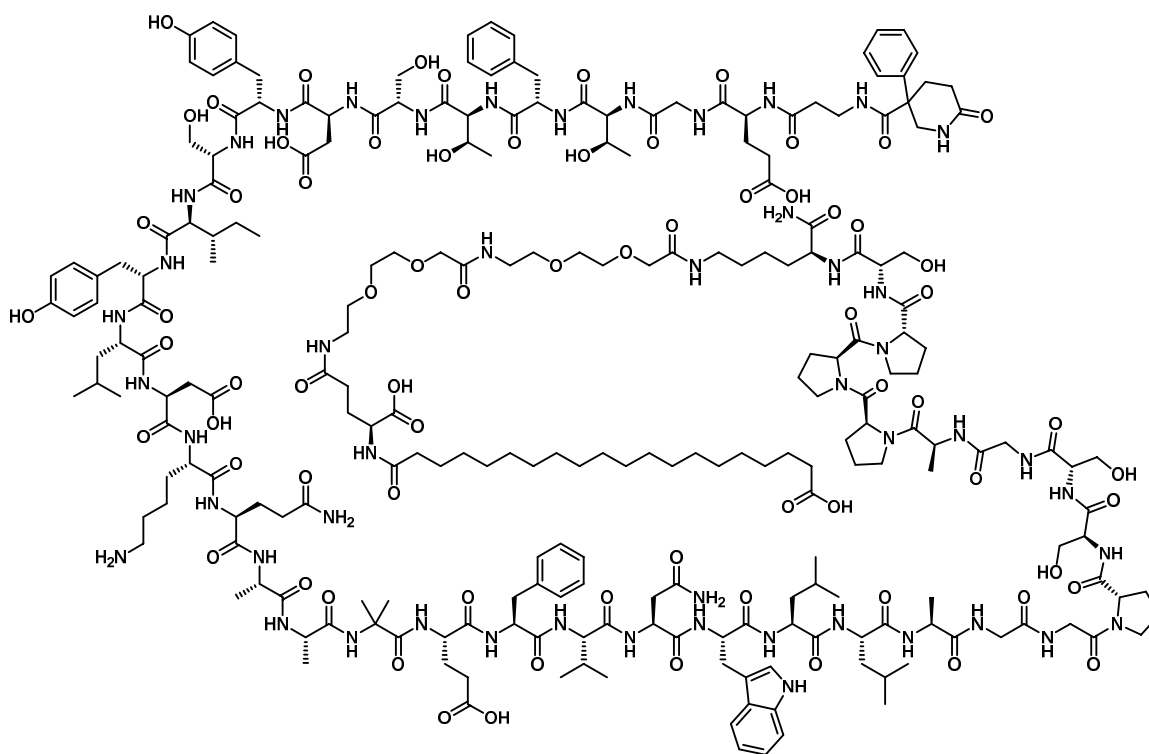


Compound 154,

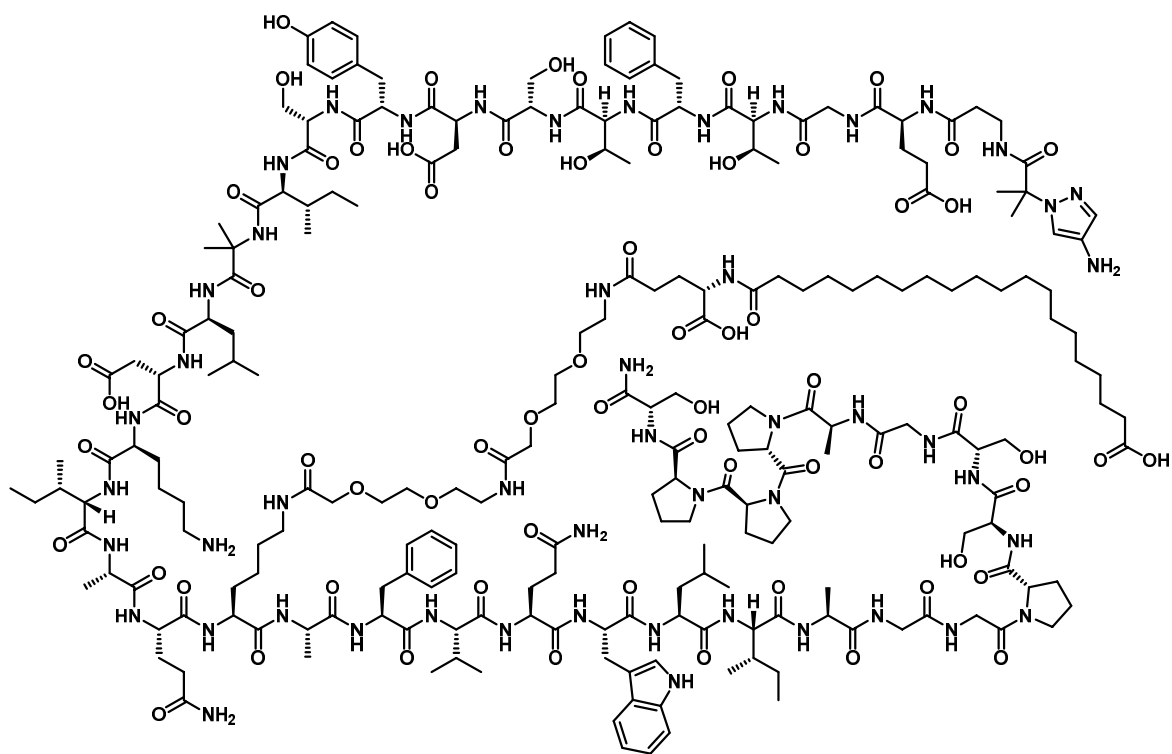


Compound 155,

5

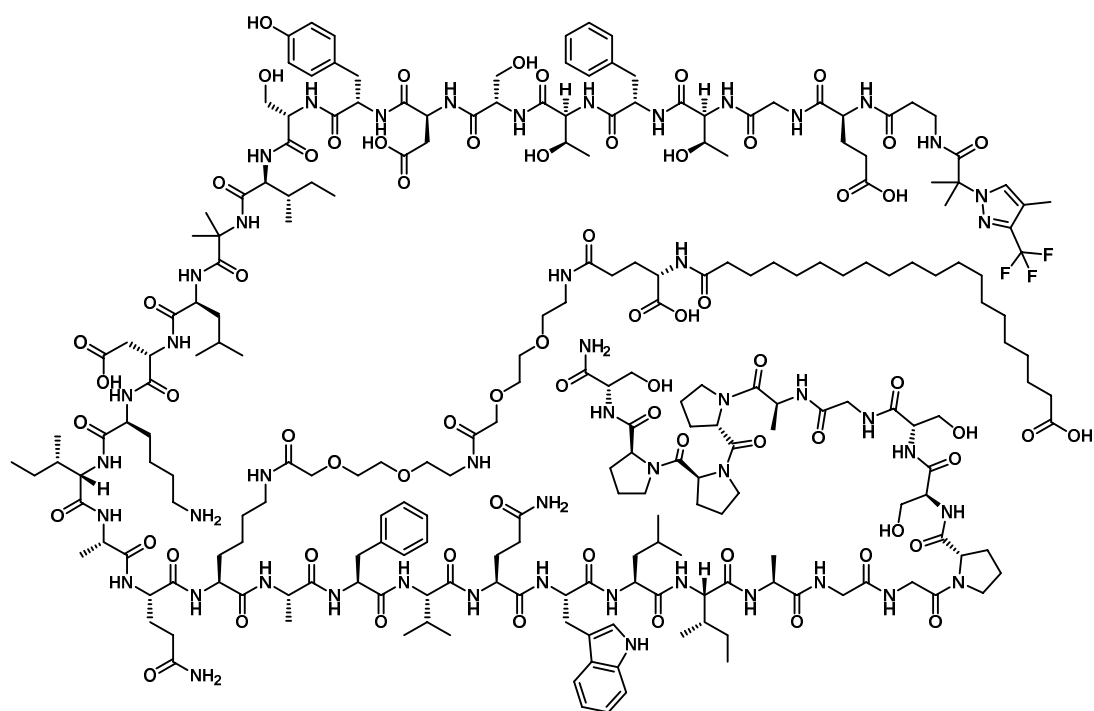


Compound 156,

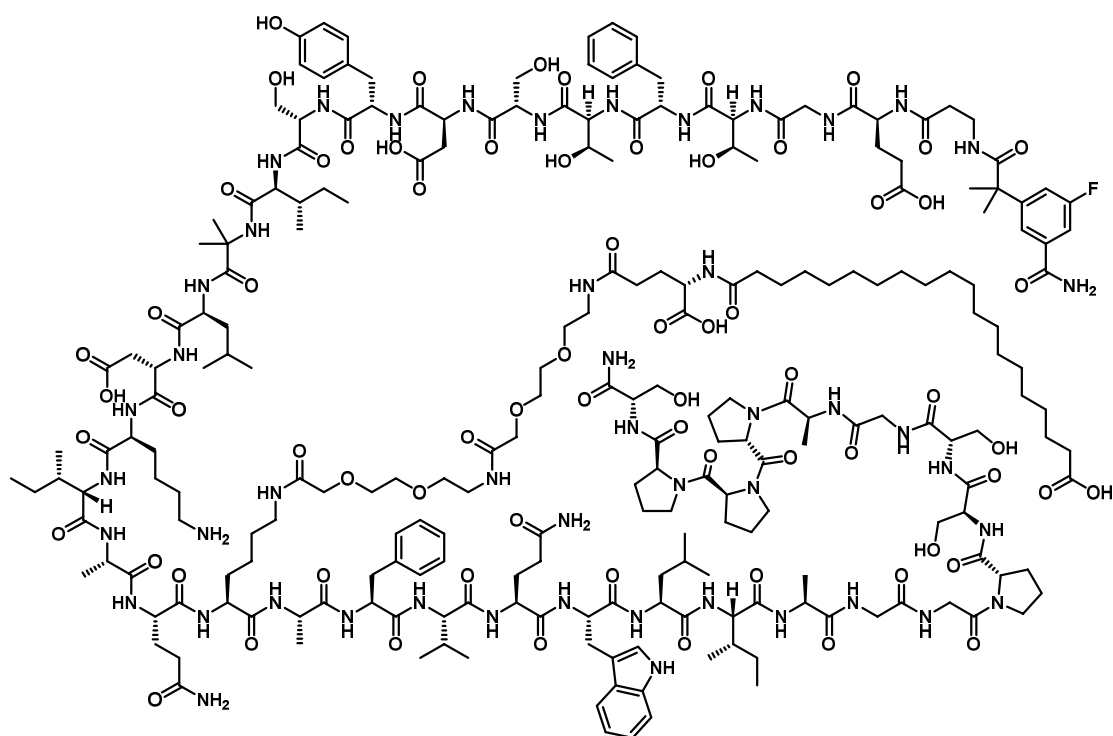


5

Compound 157,

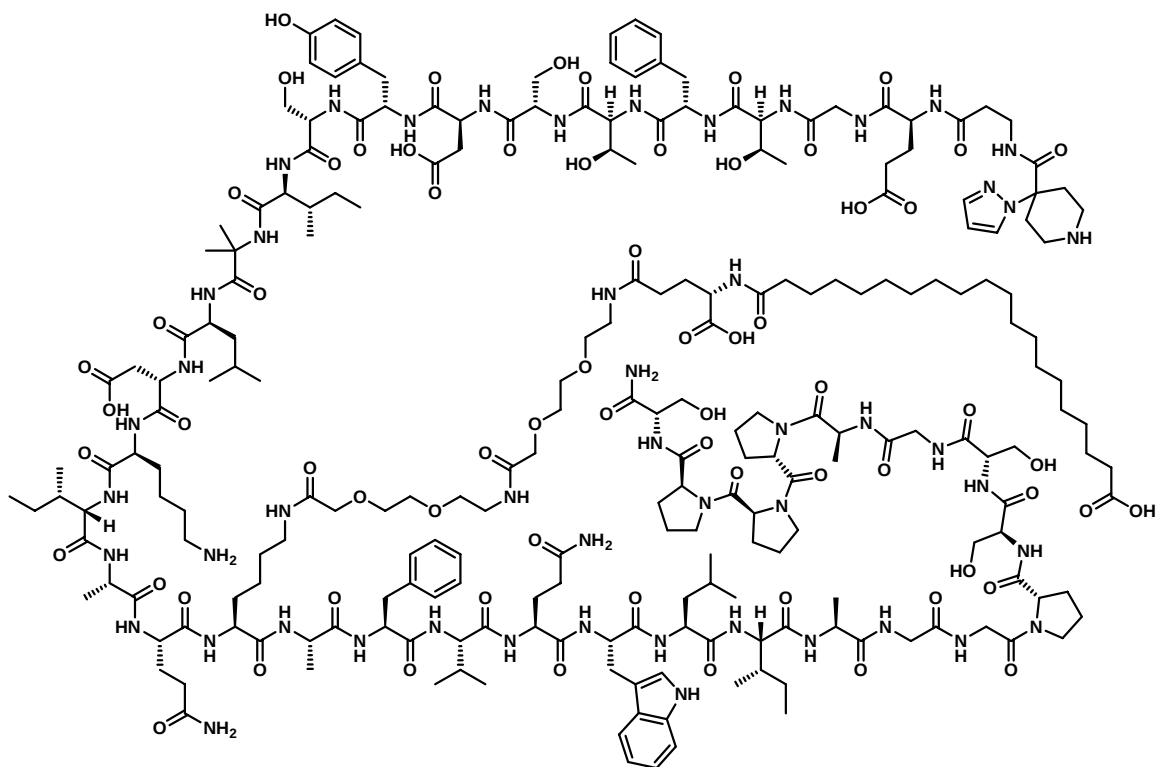


Compound 158,

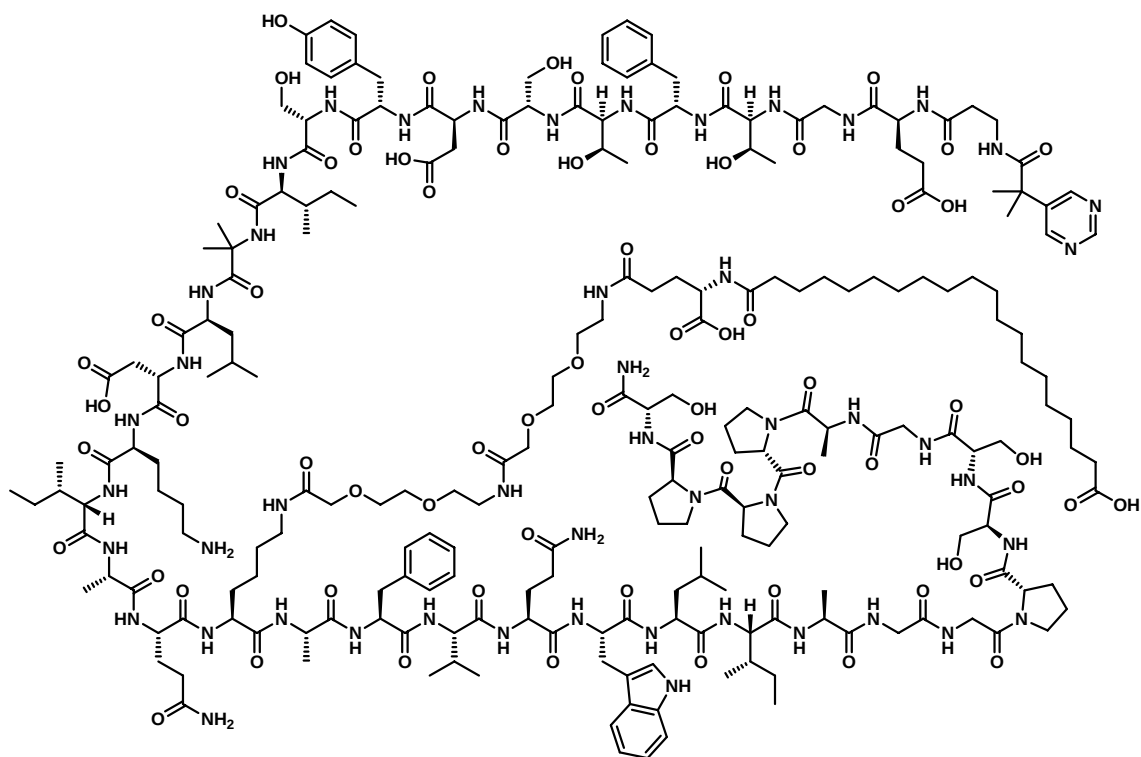


Compound 159,

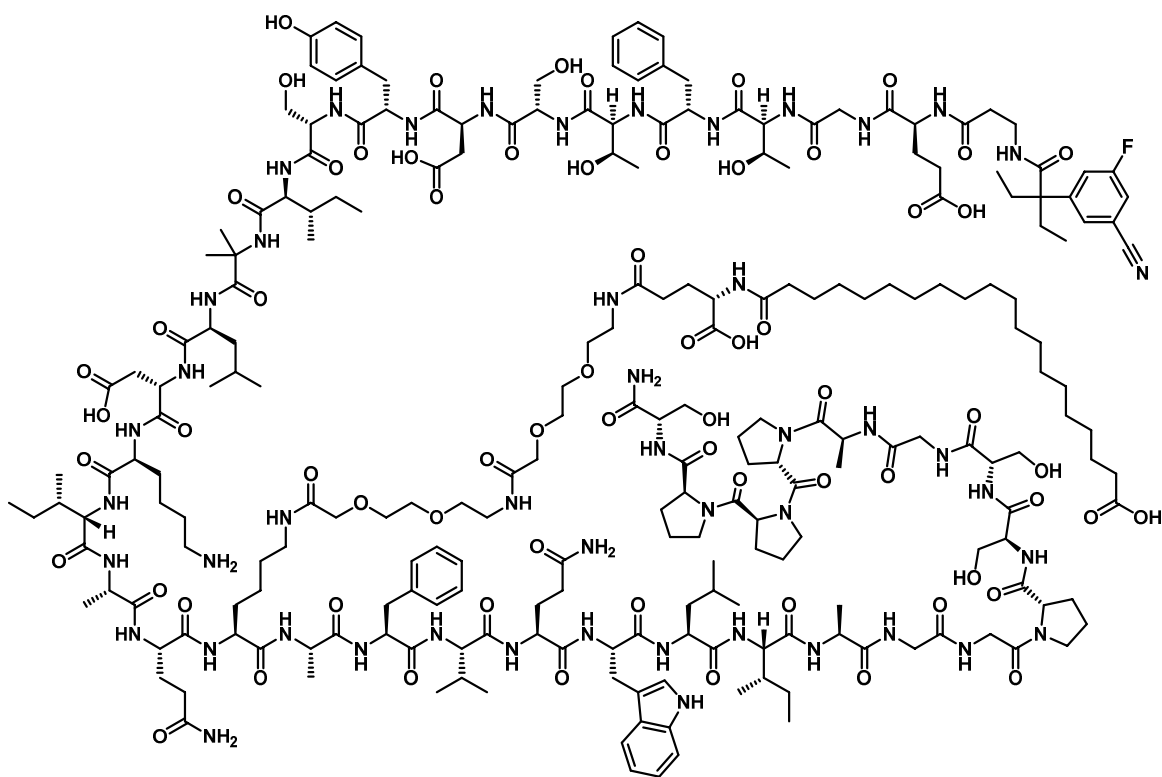
5



Compound 160,



Compound 161,



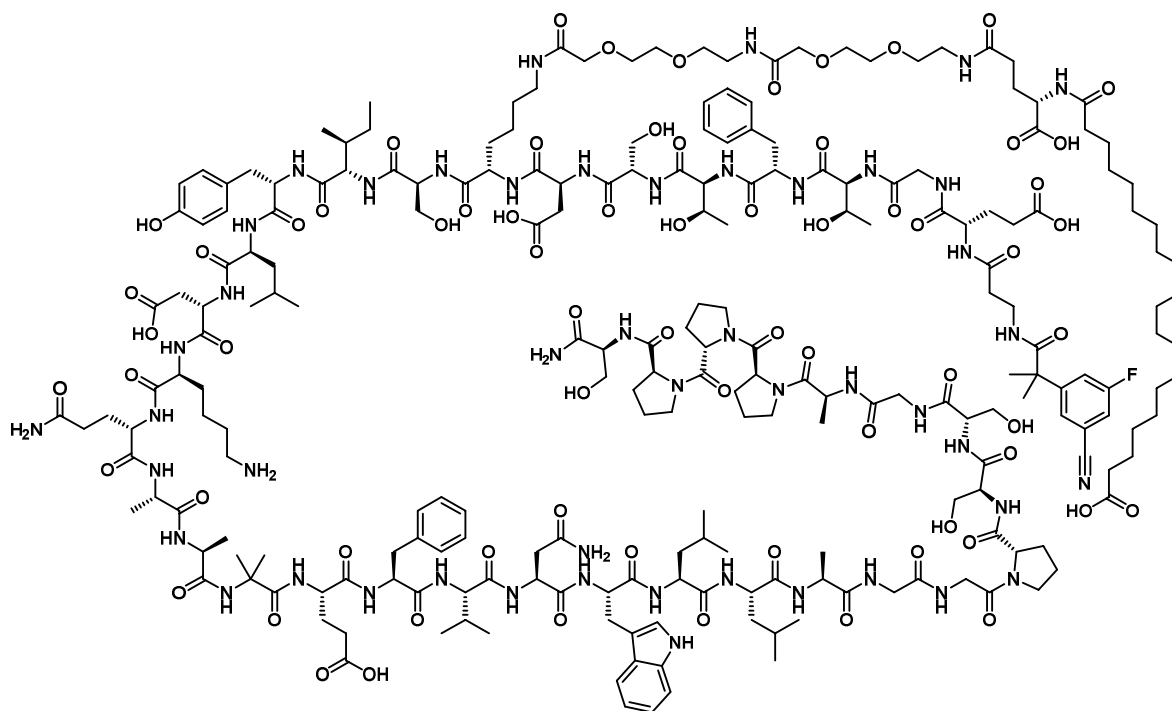
Compound 162,

[illegible]

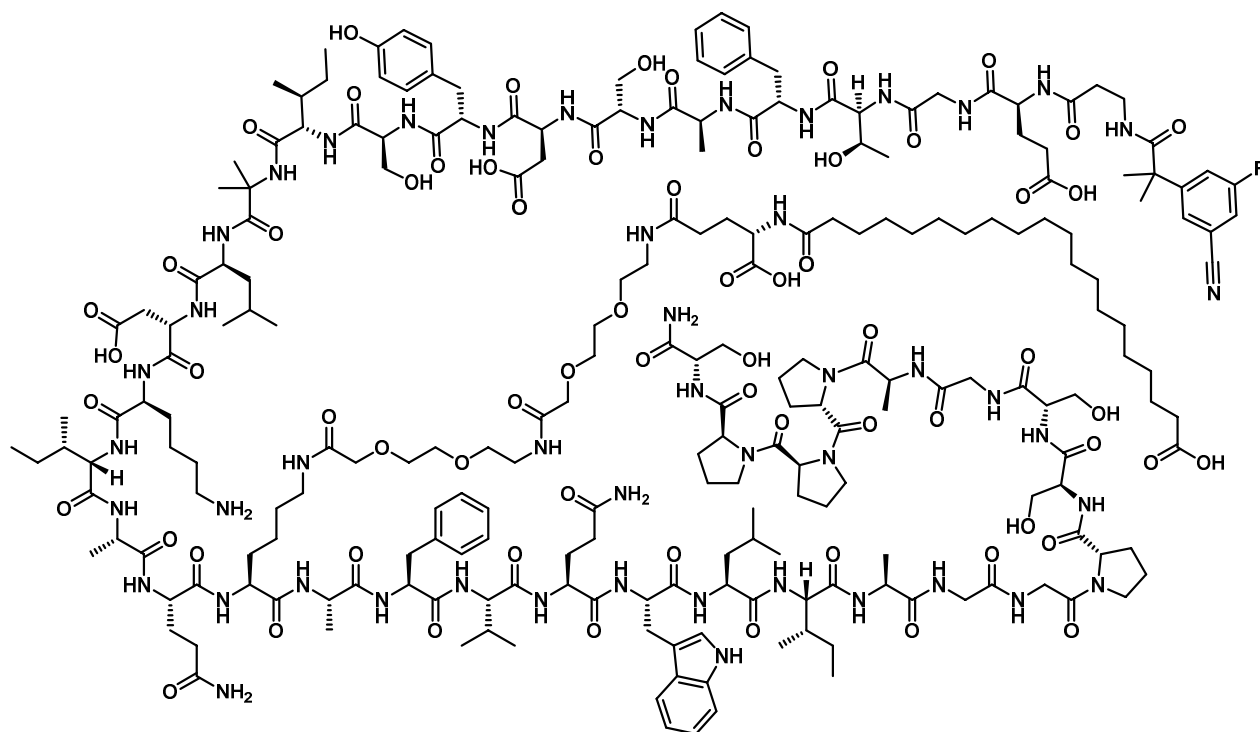
Compound 164,

[illegible]

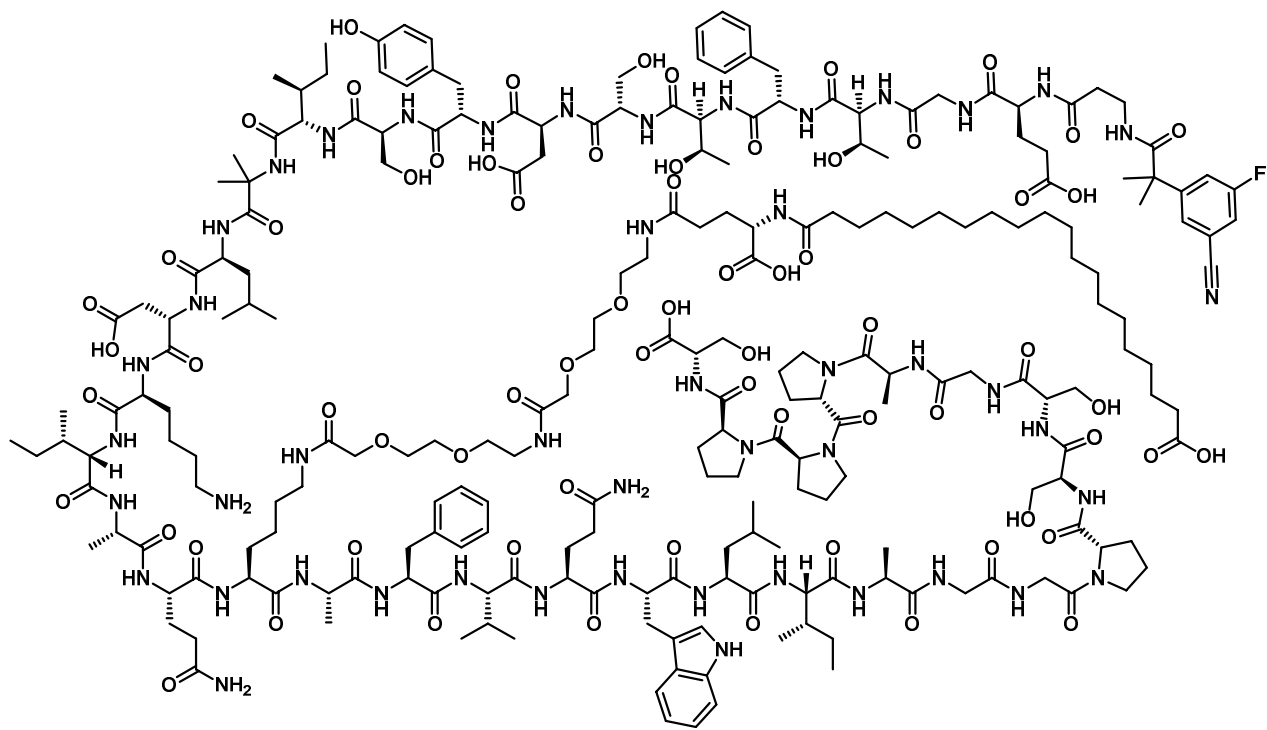
Compound 166,



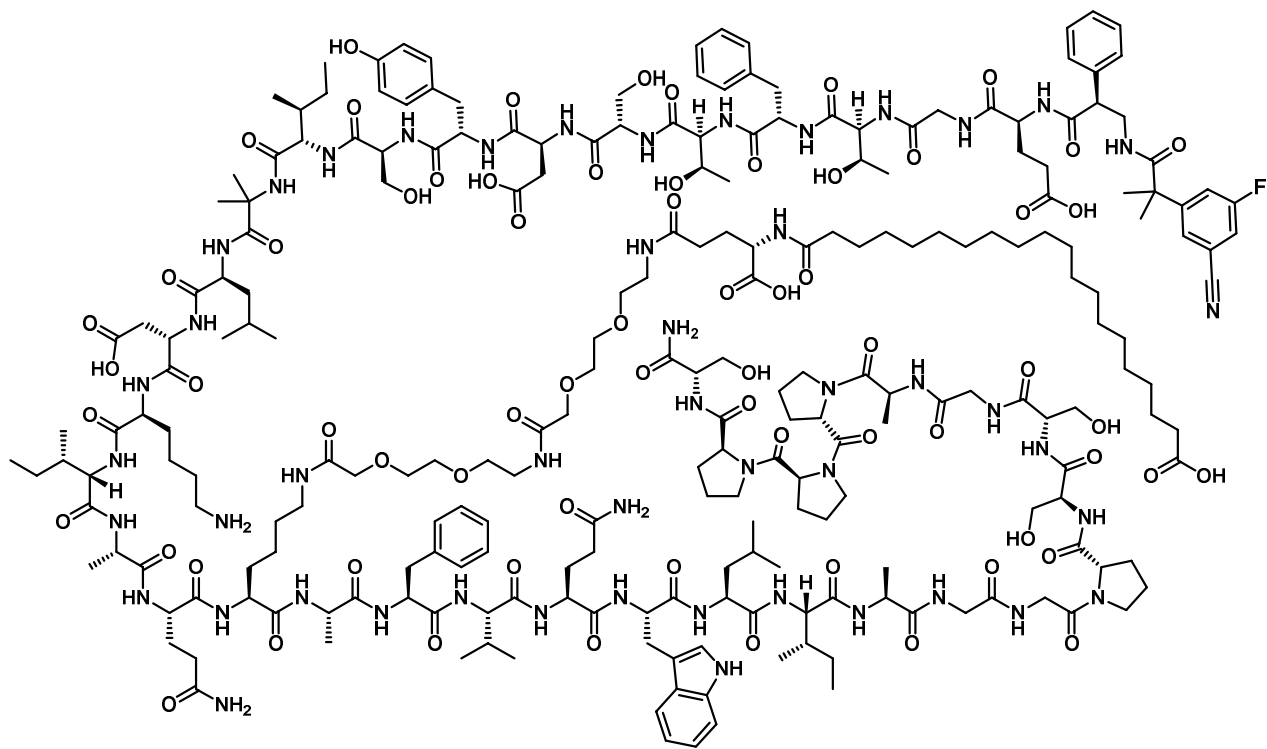
Compound 167,



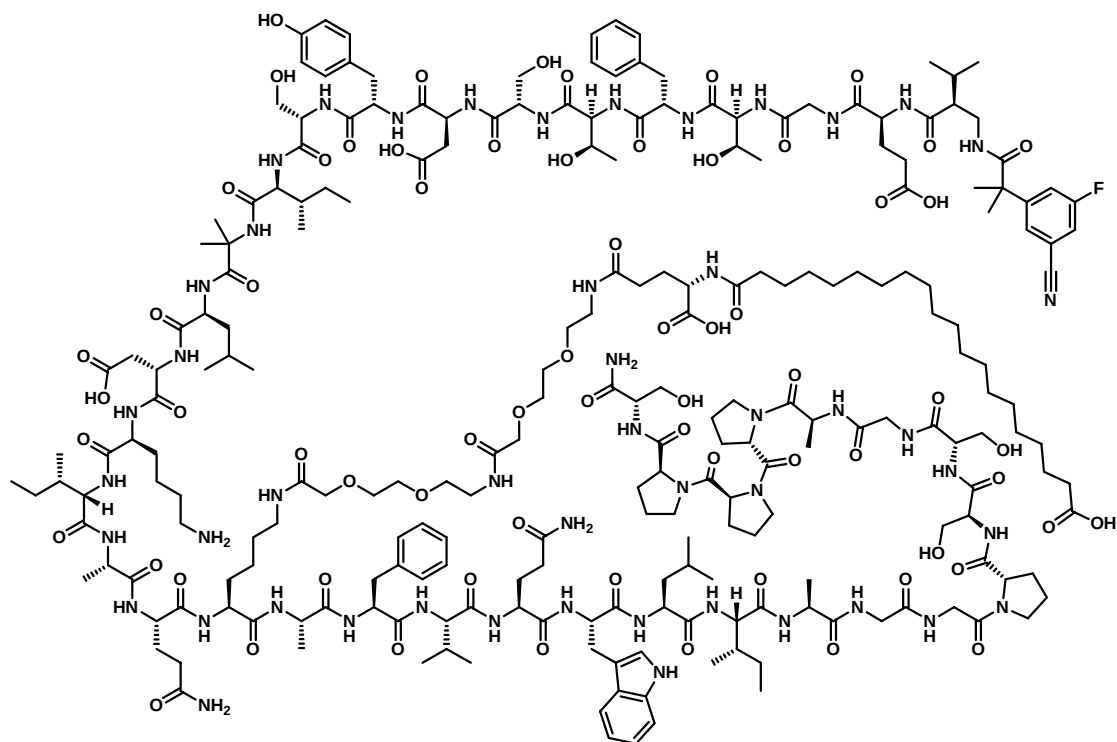
Compound 168,



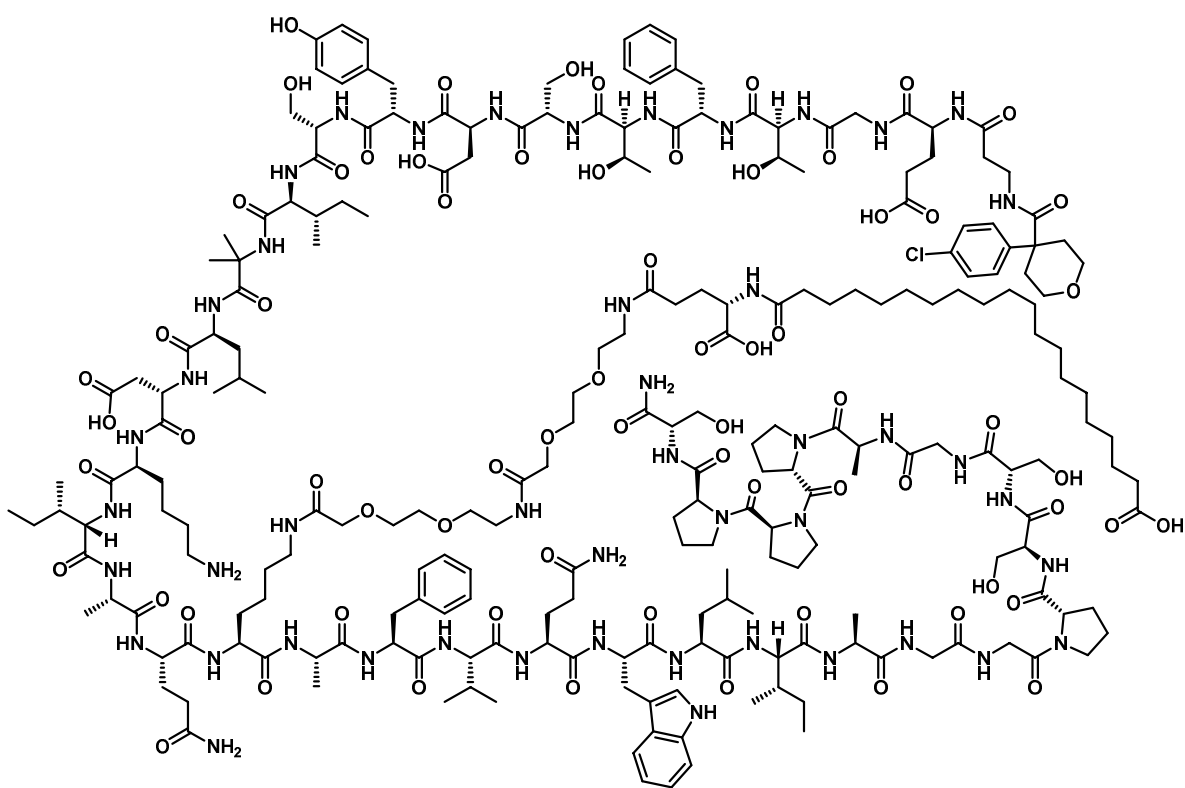
Compound 169,



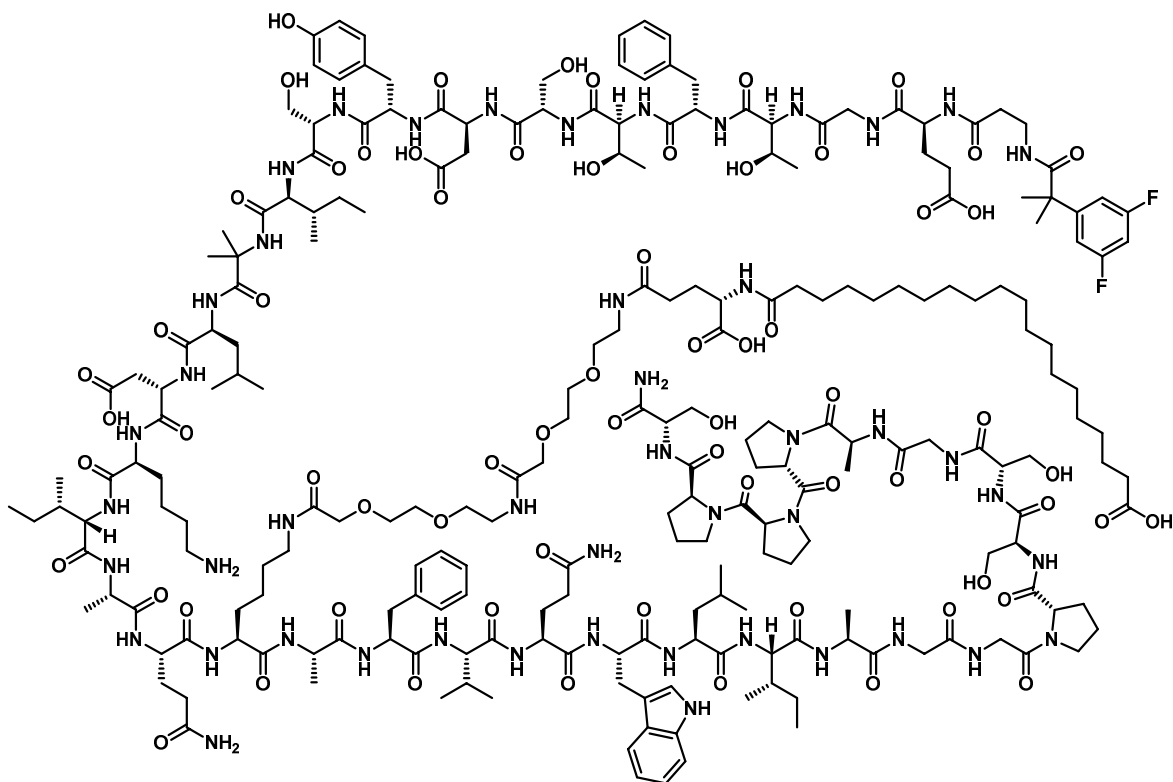
Compound 170,



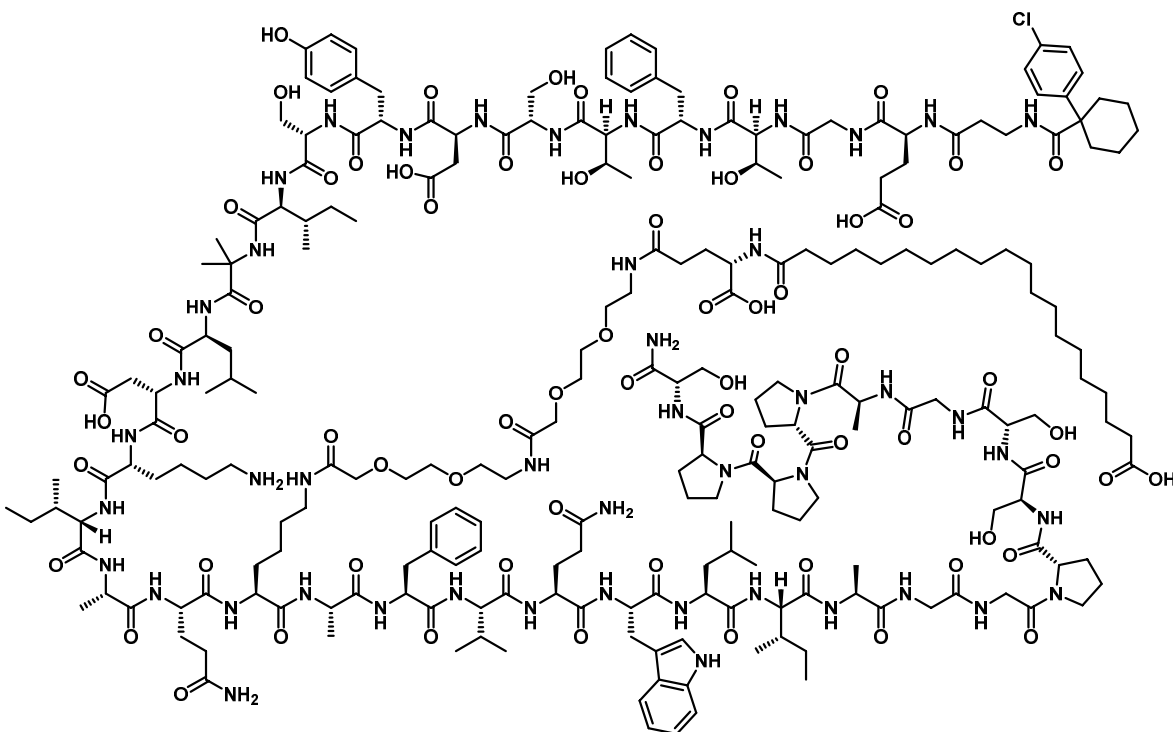
Compound 171,



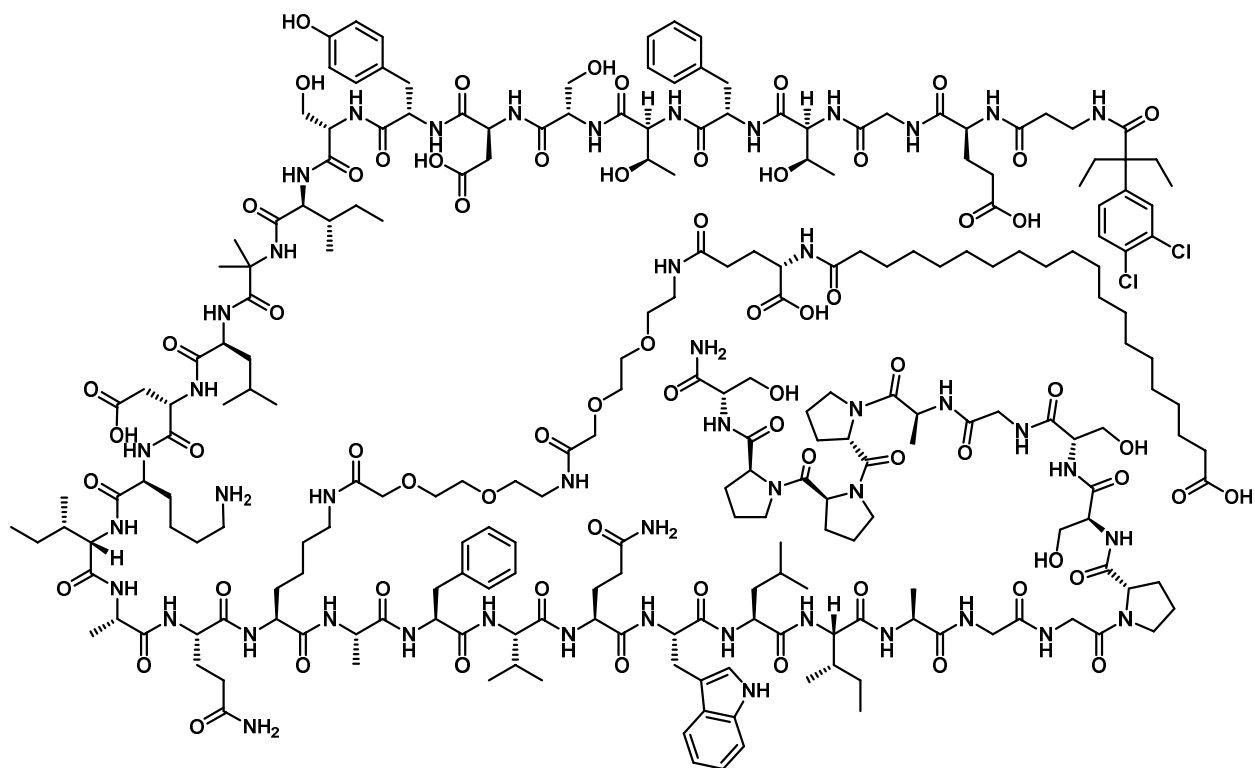
Compound 172,



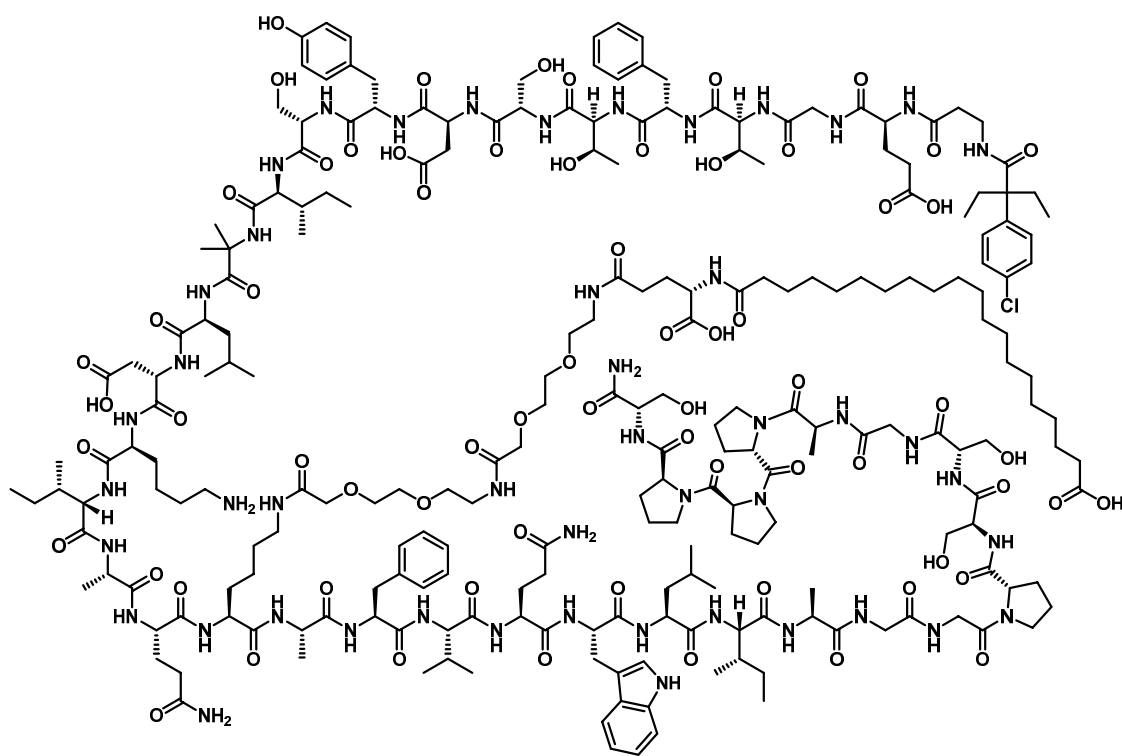
Compound 173,



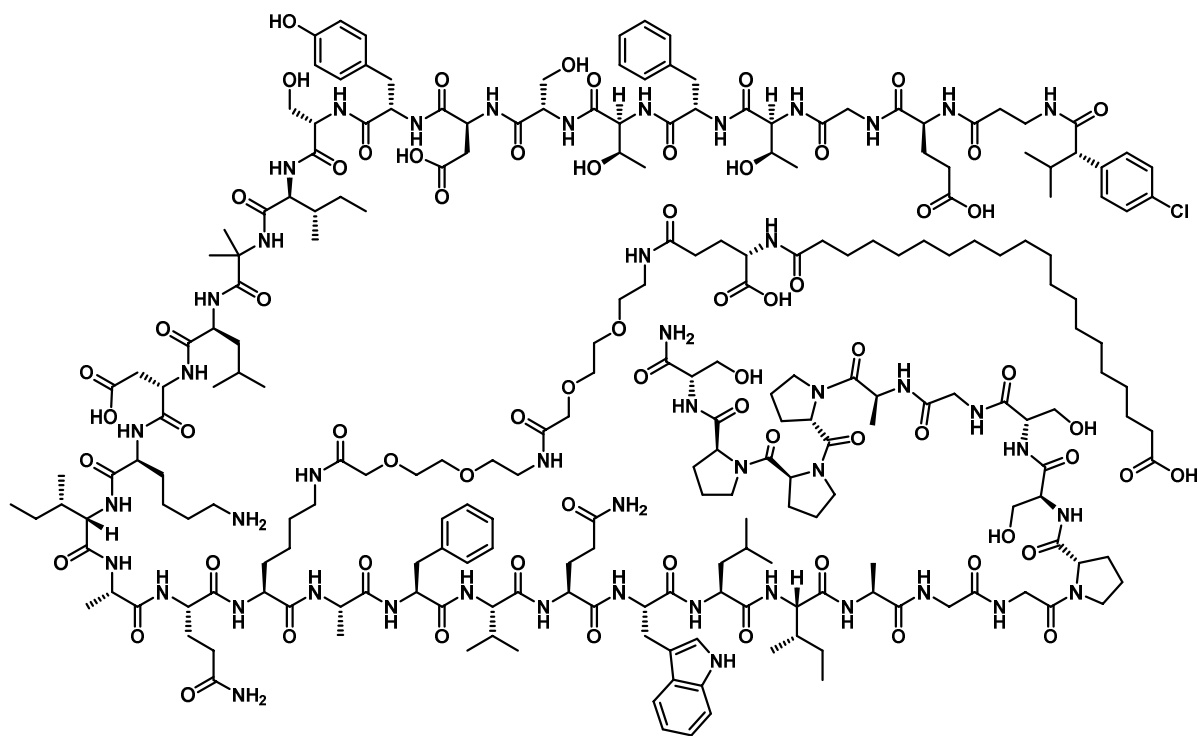
Compound 174,



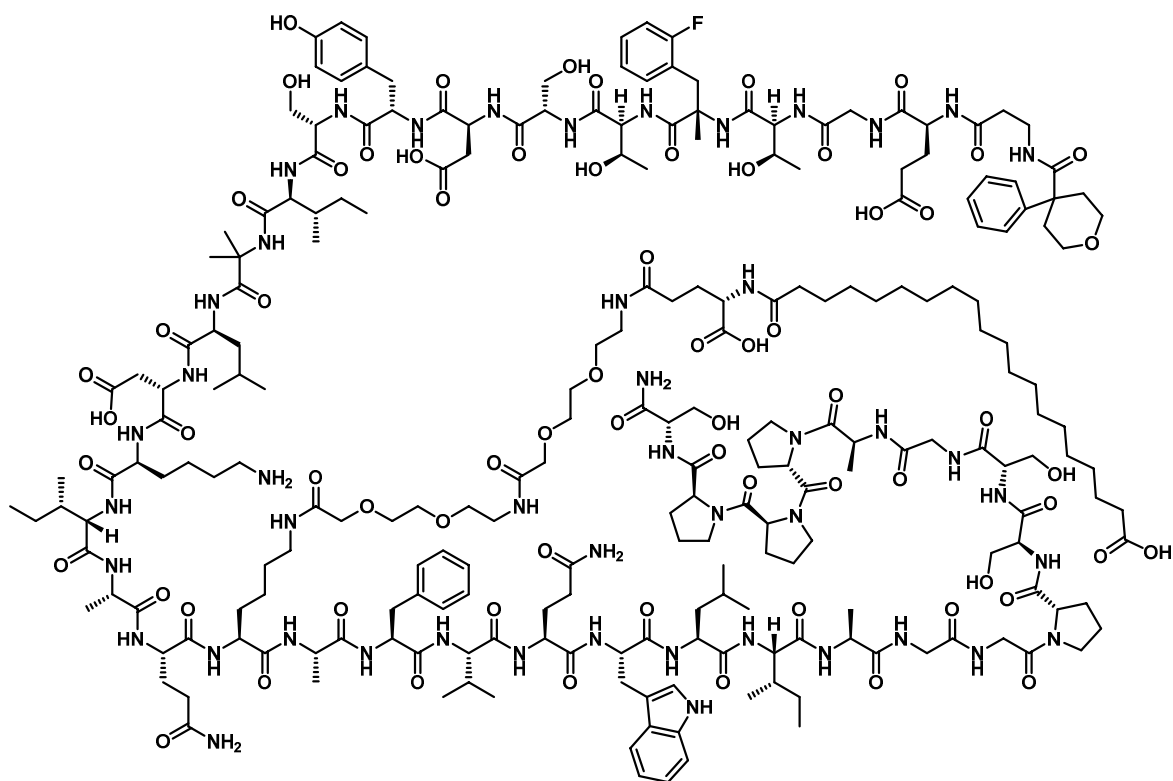
Compound 175,



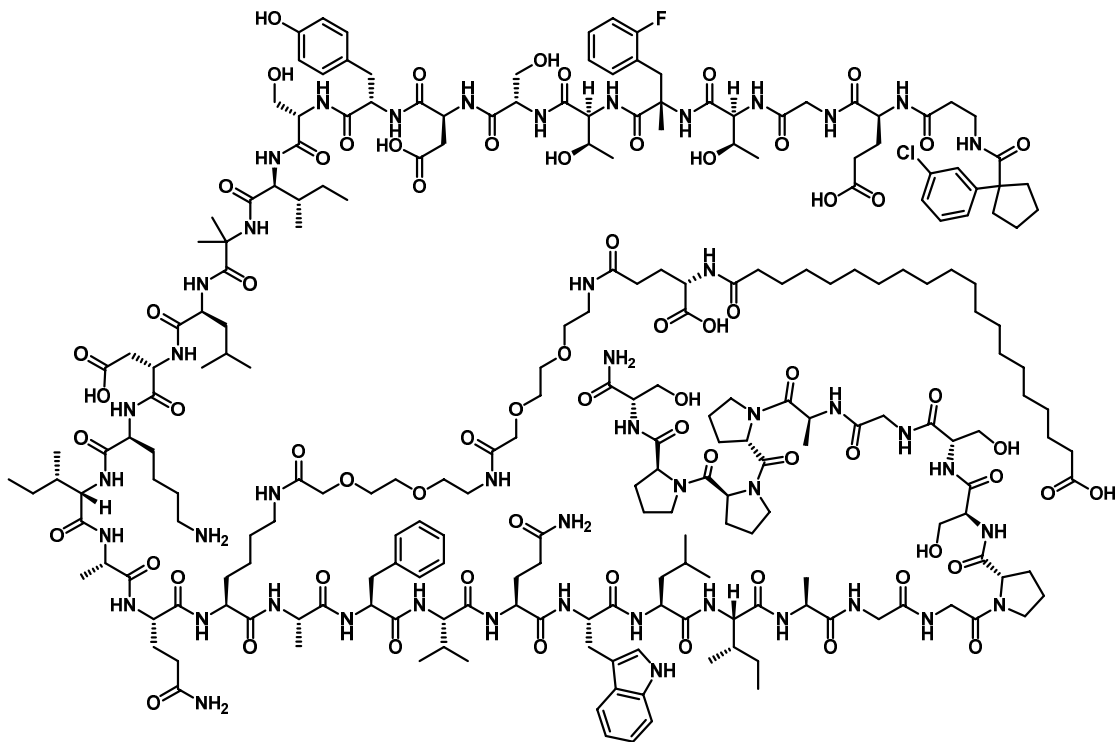
Compound 176,



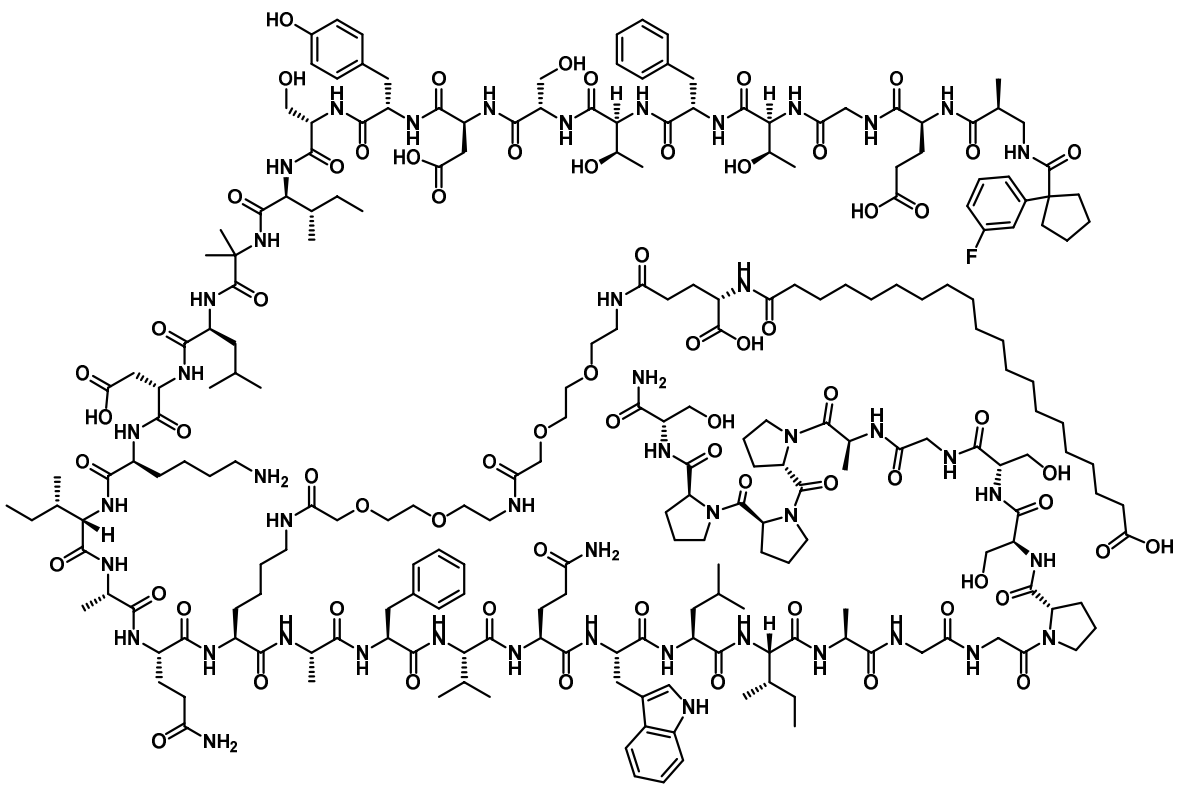
Compound 177,



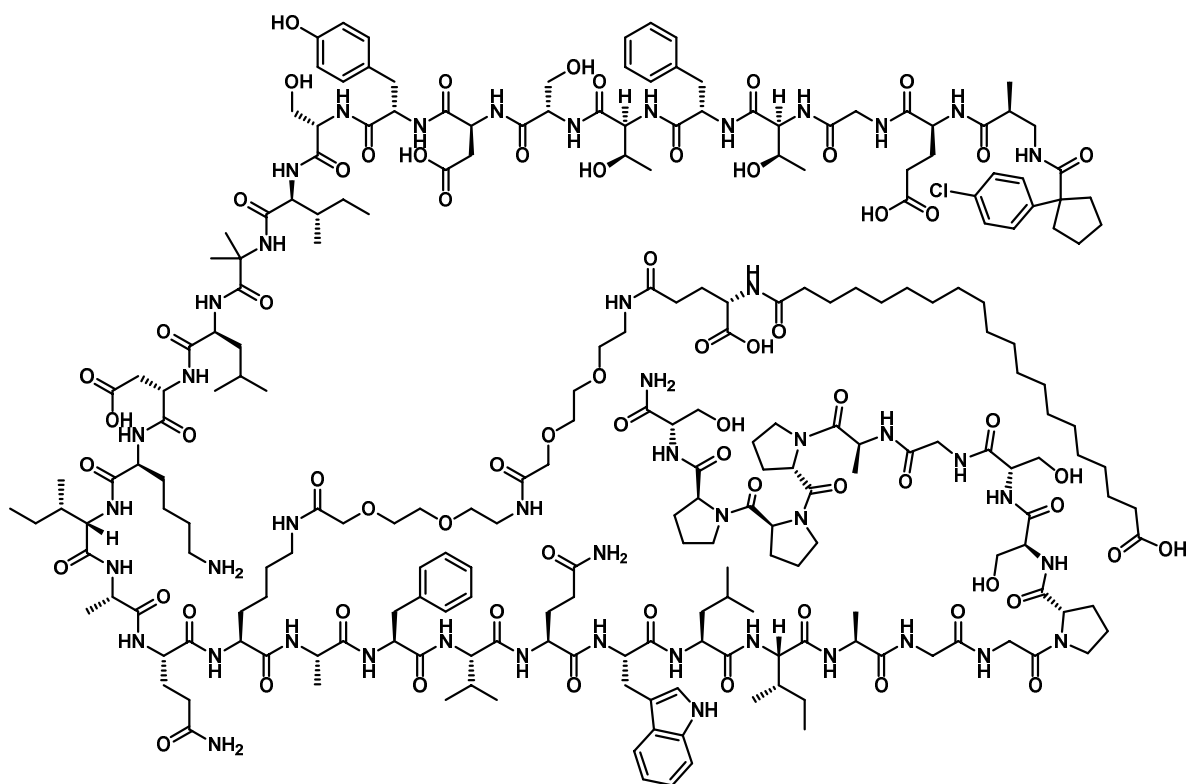
Compound 178,



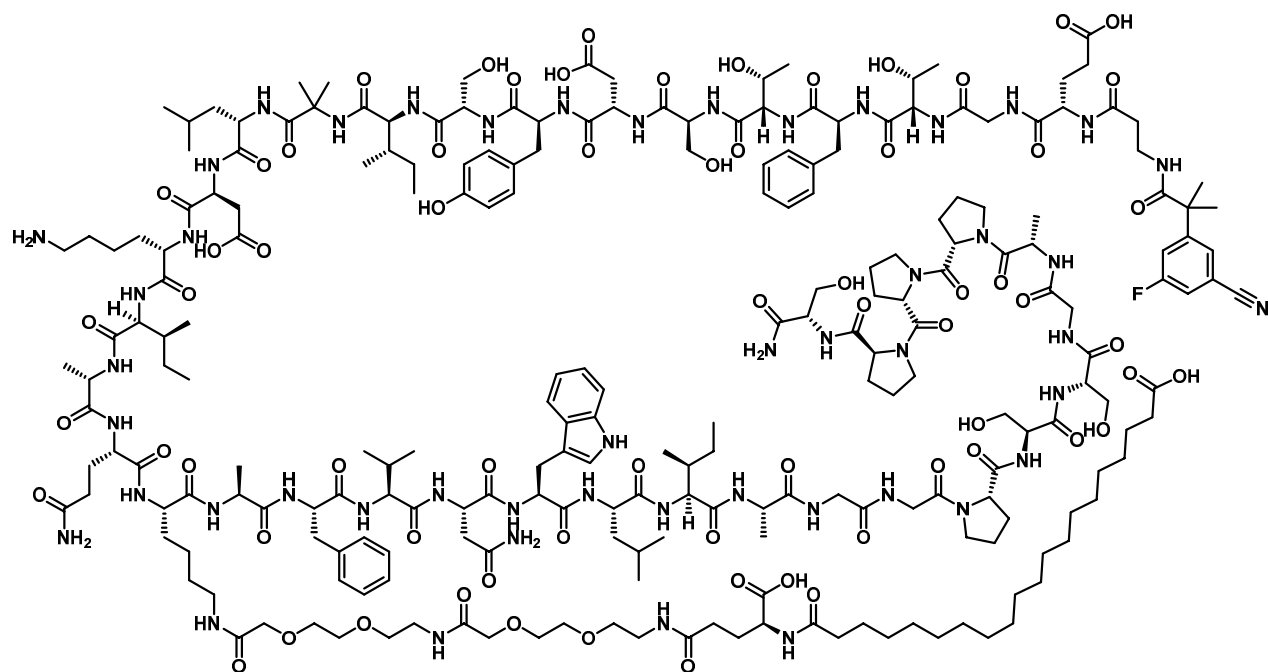
Compound 179,



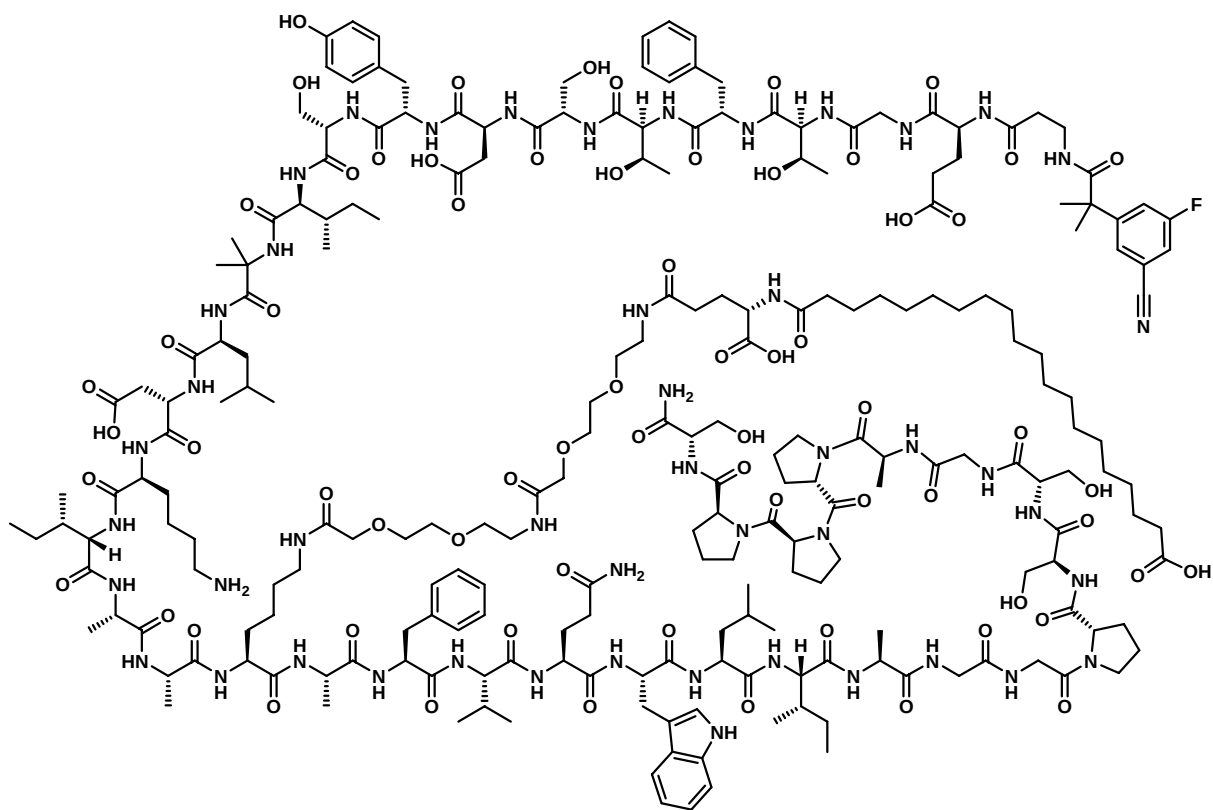
Compound 180,



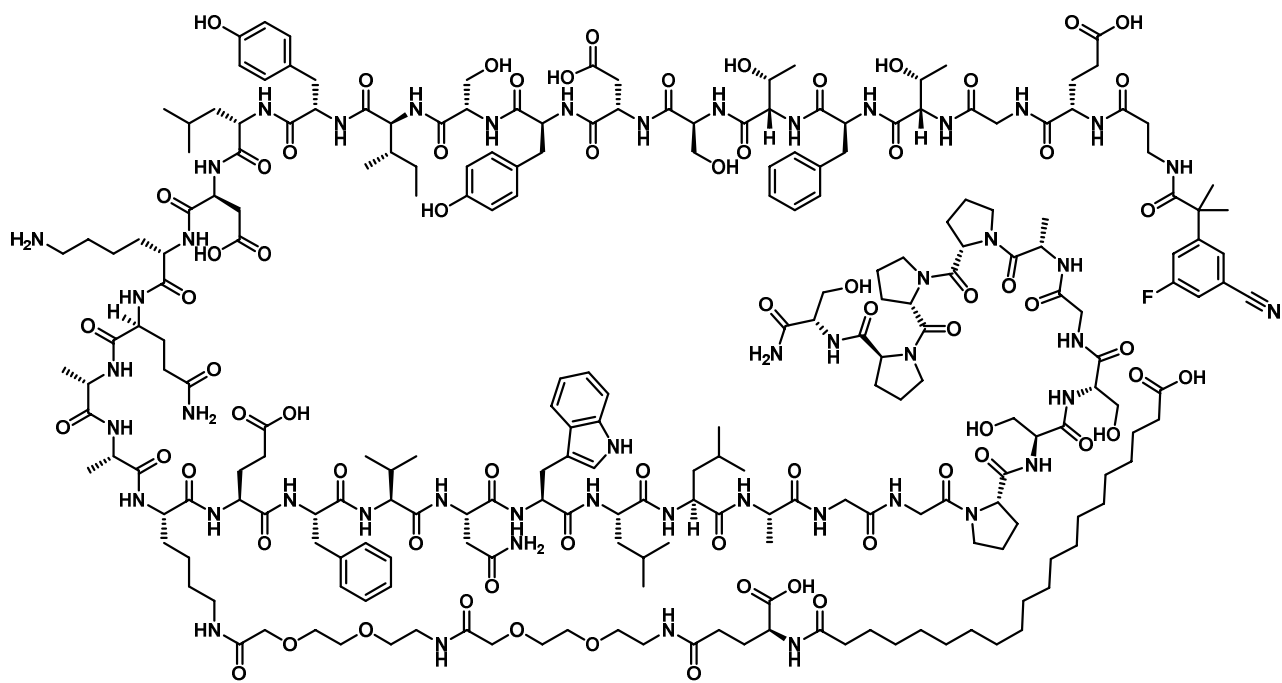
Compound 181,



Compound 182,



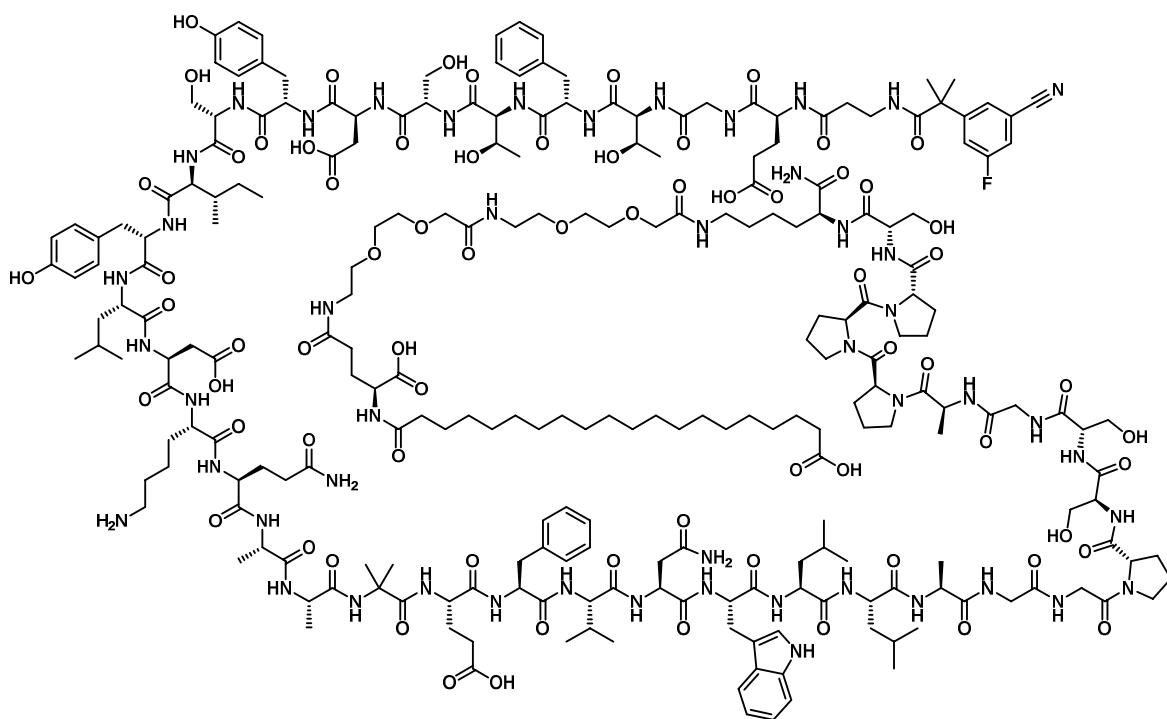
Compound 183,



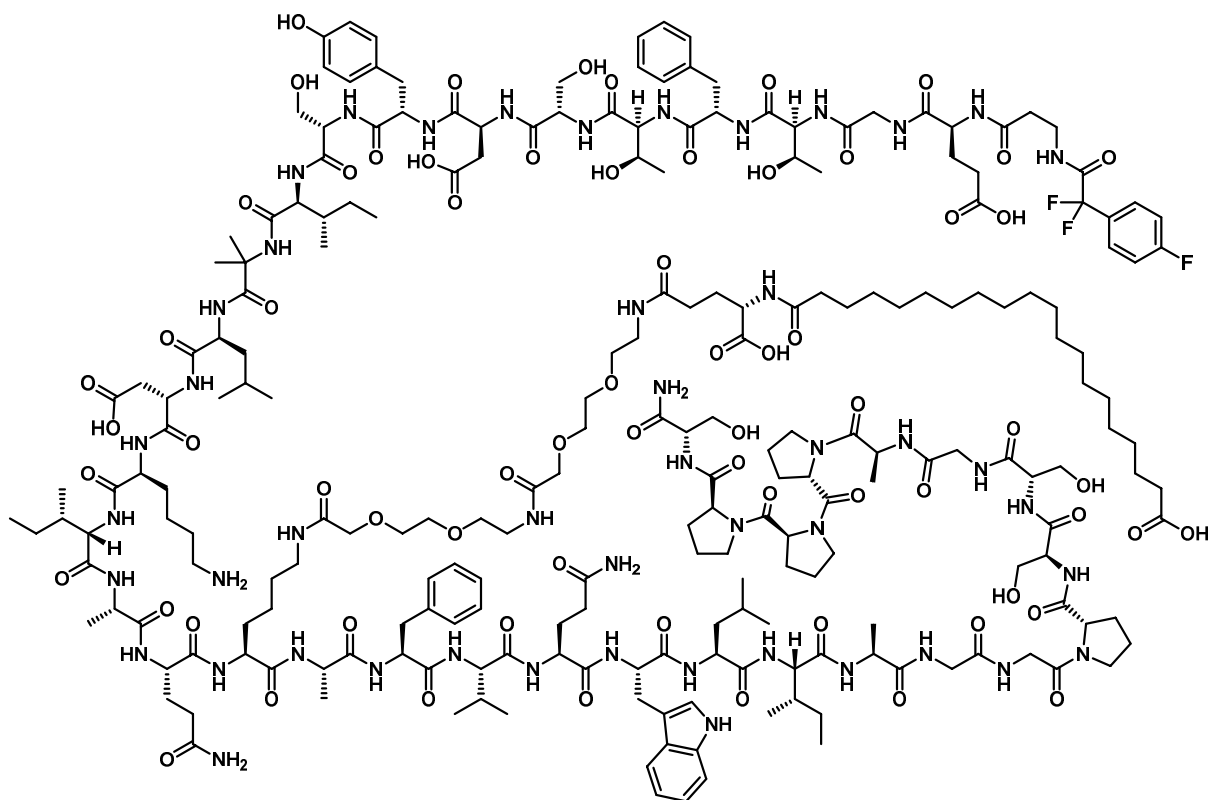
Compound 184,

[illegible]

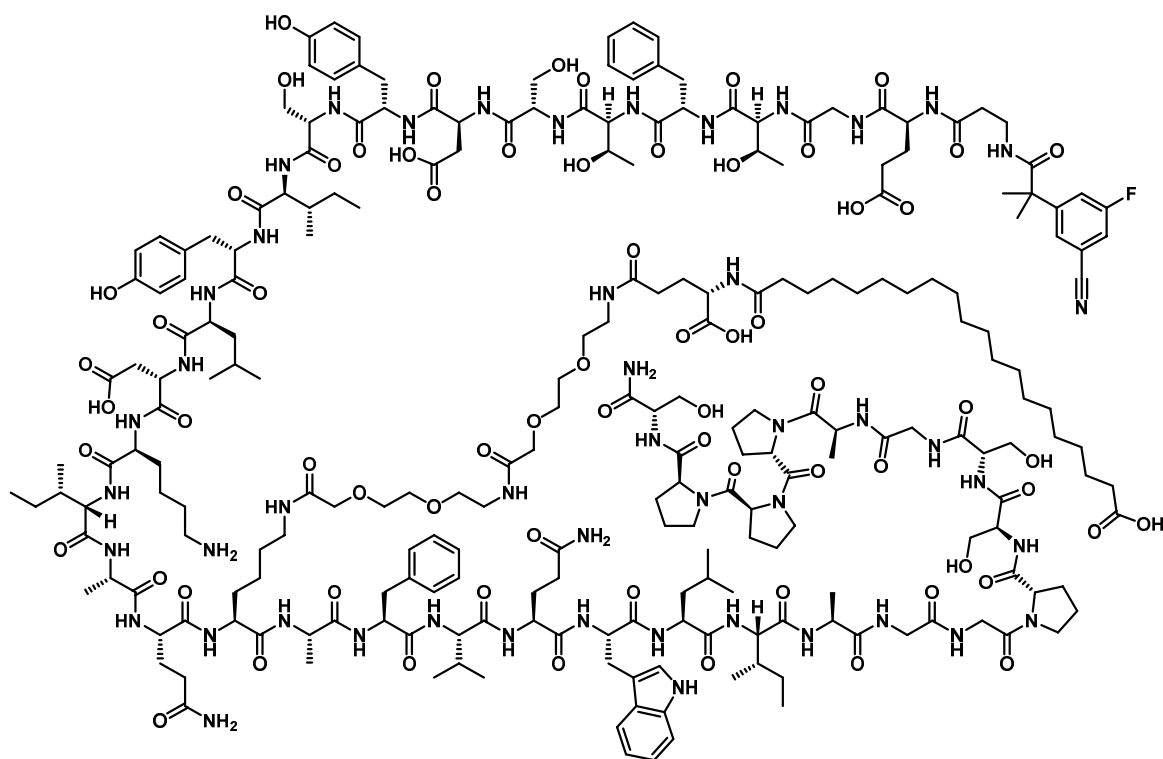
5



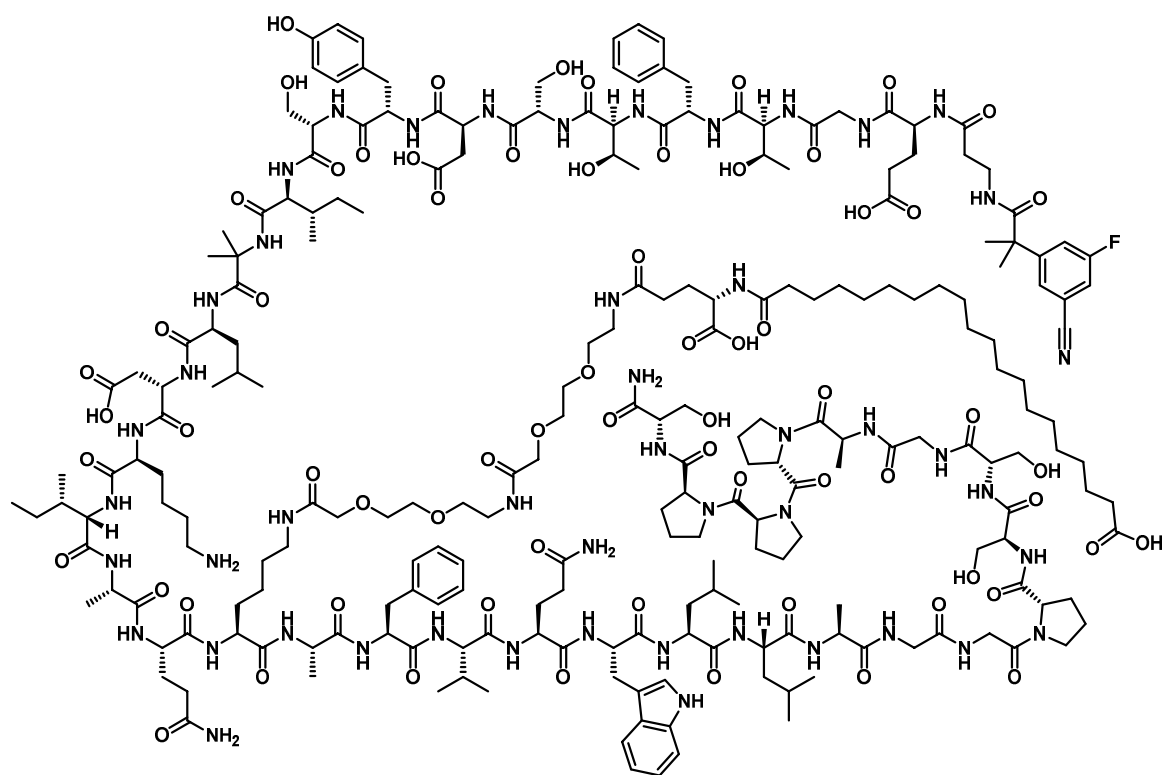
Compound 187,



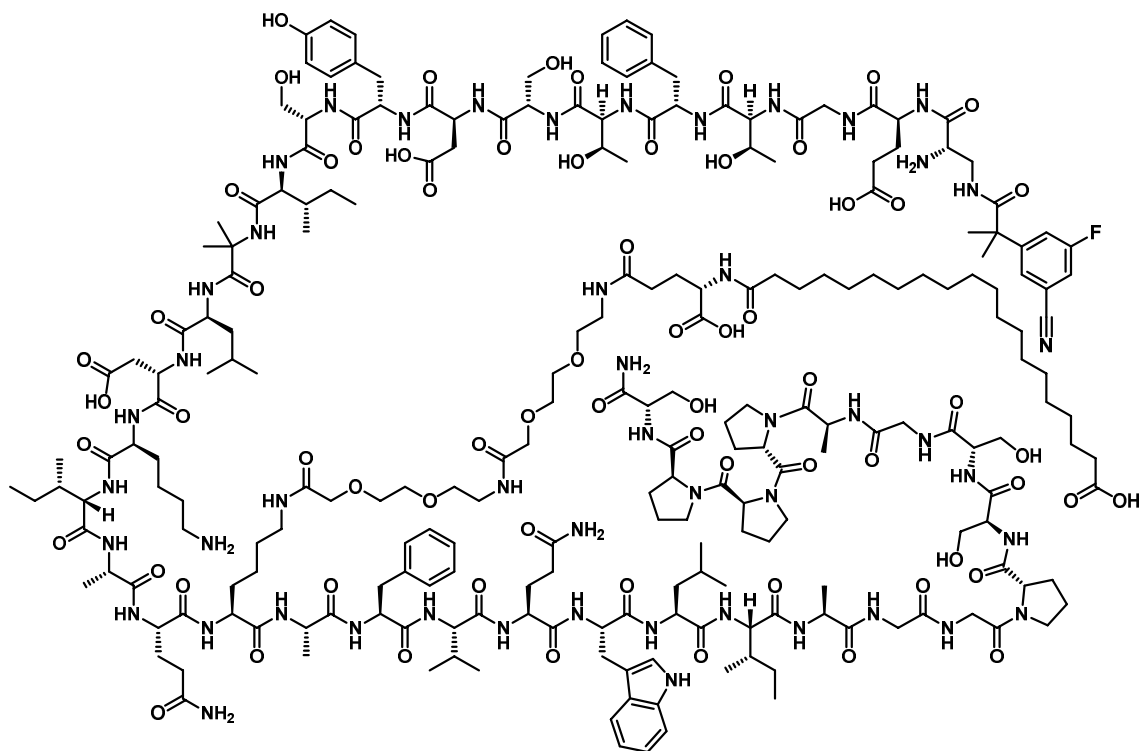
Compound 188,



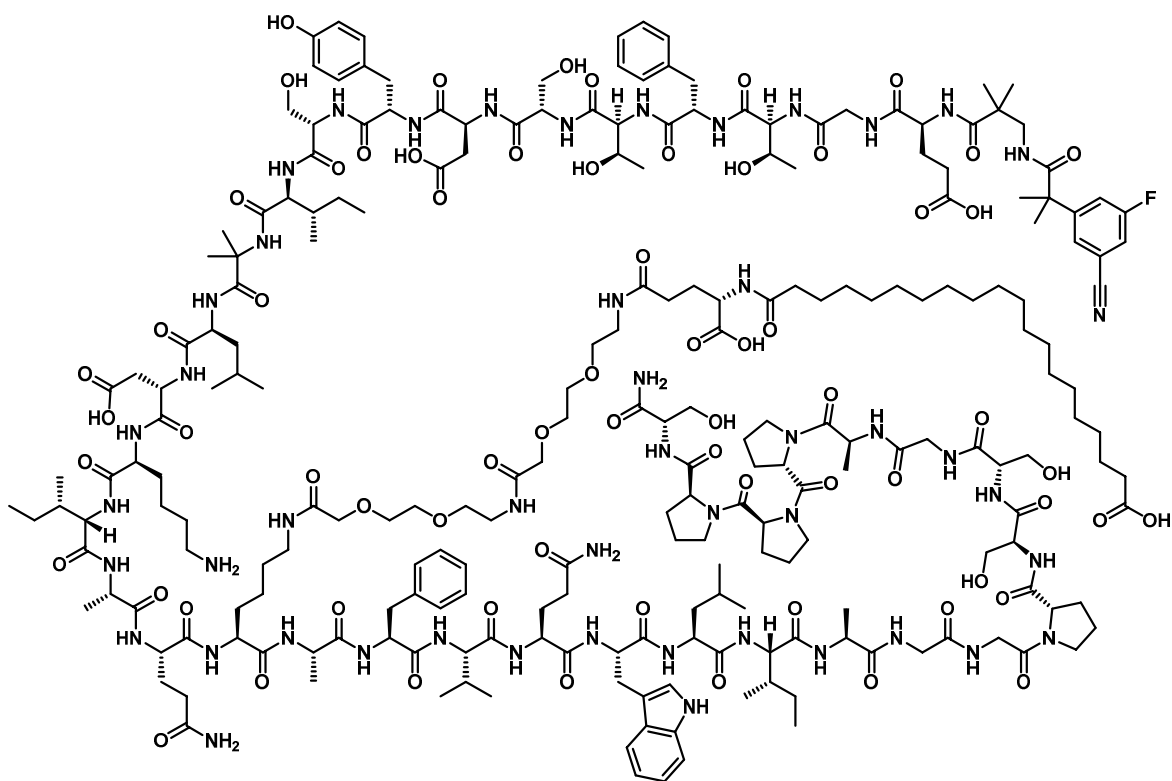
Compound 189,



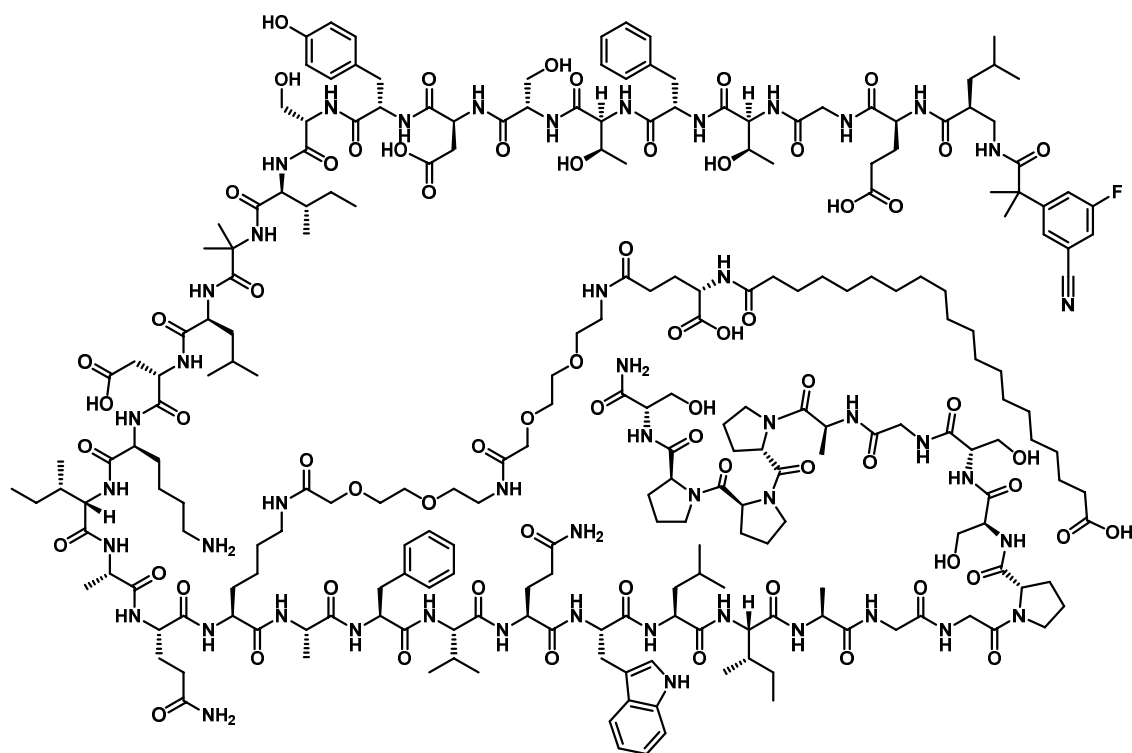
Compound 190,



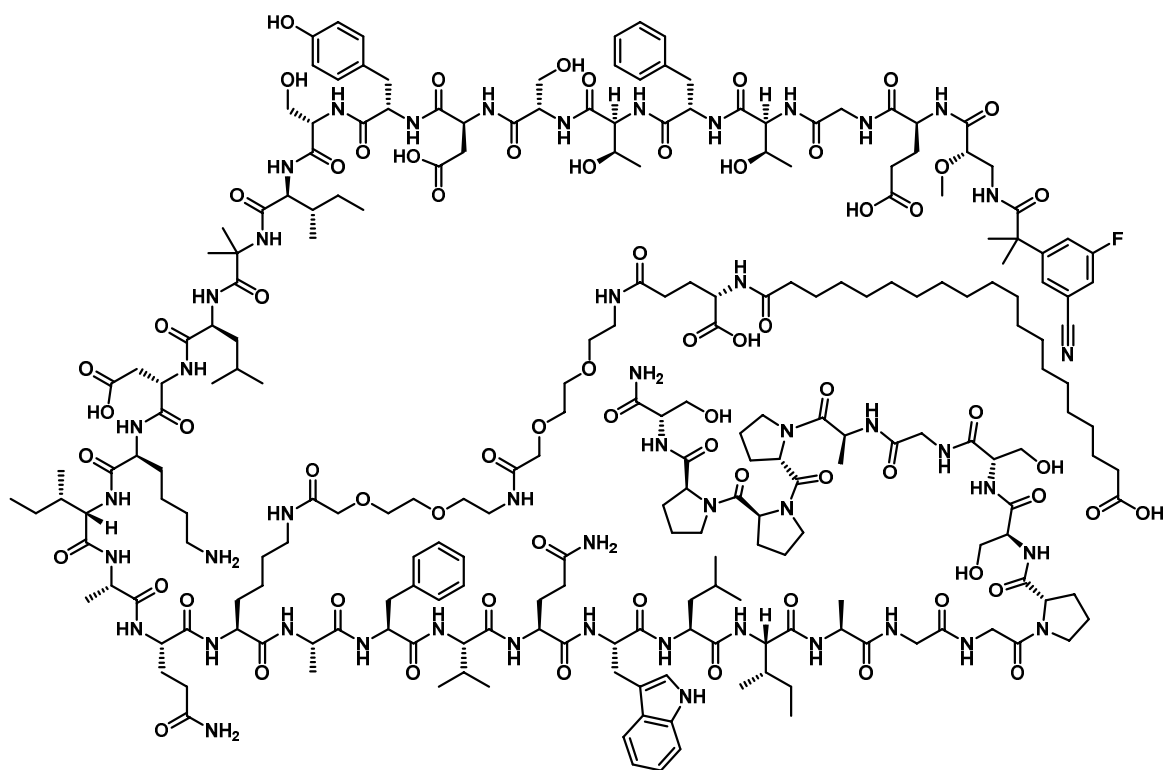
Compound 191,



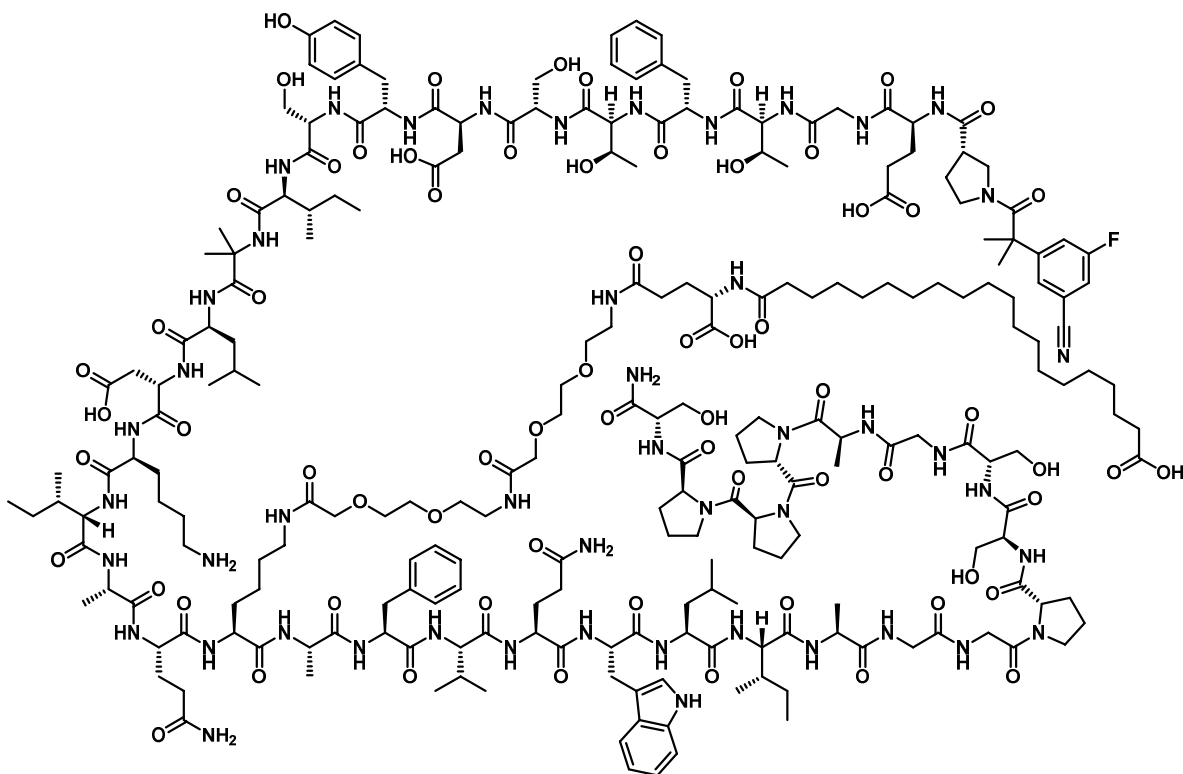
Compound 192,



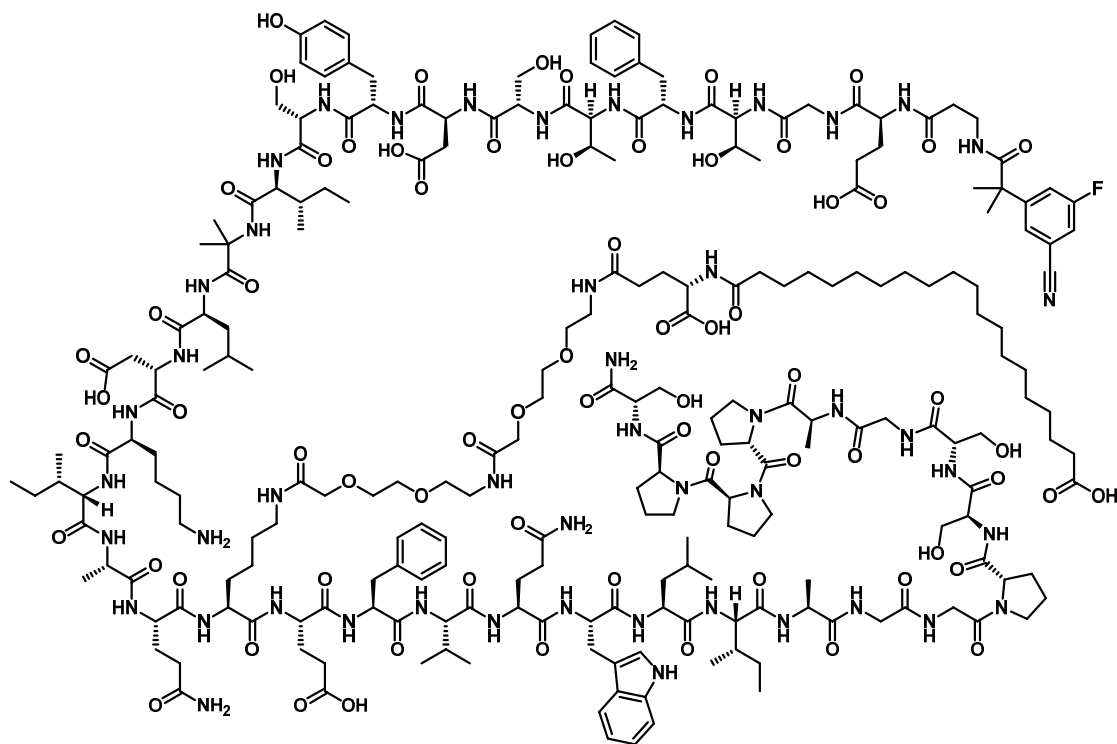
Compound 193,



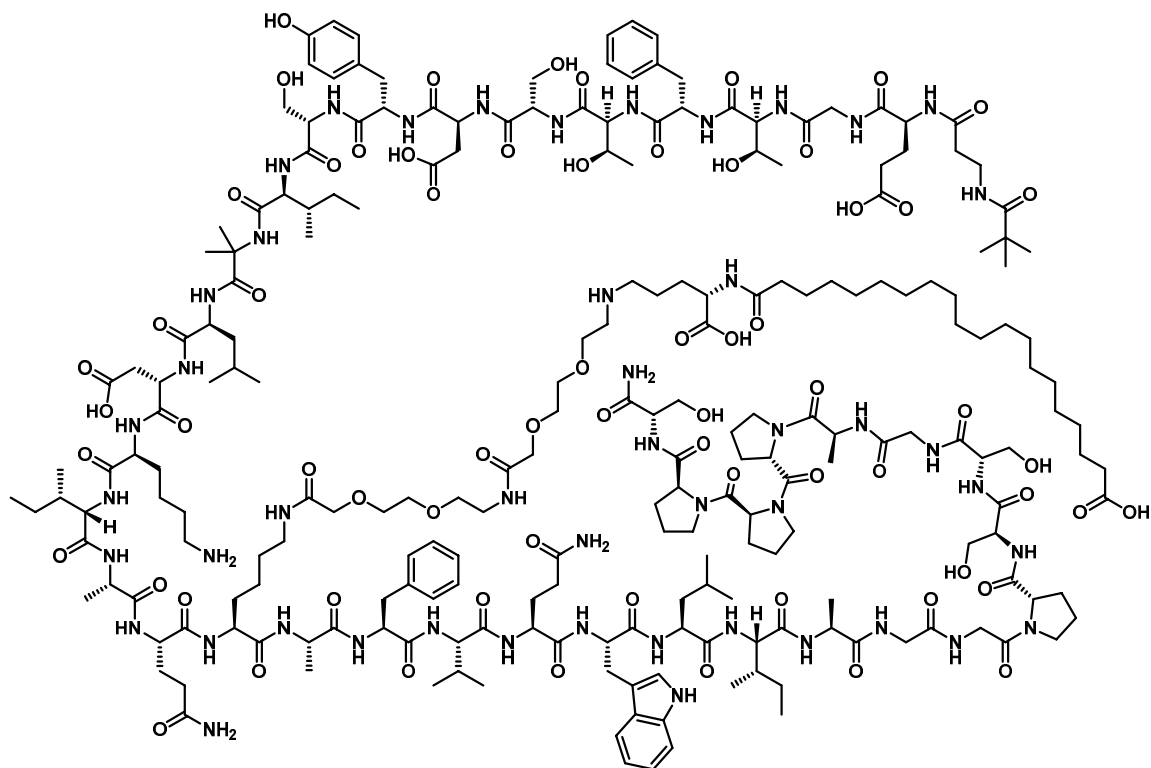
Compound 194,



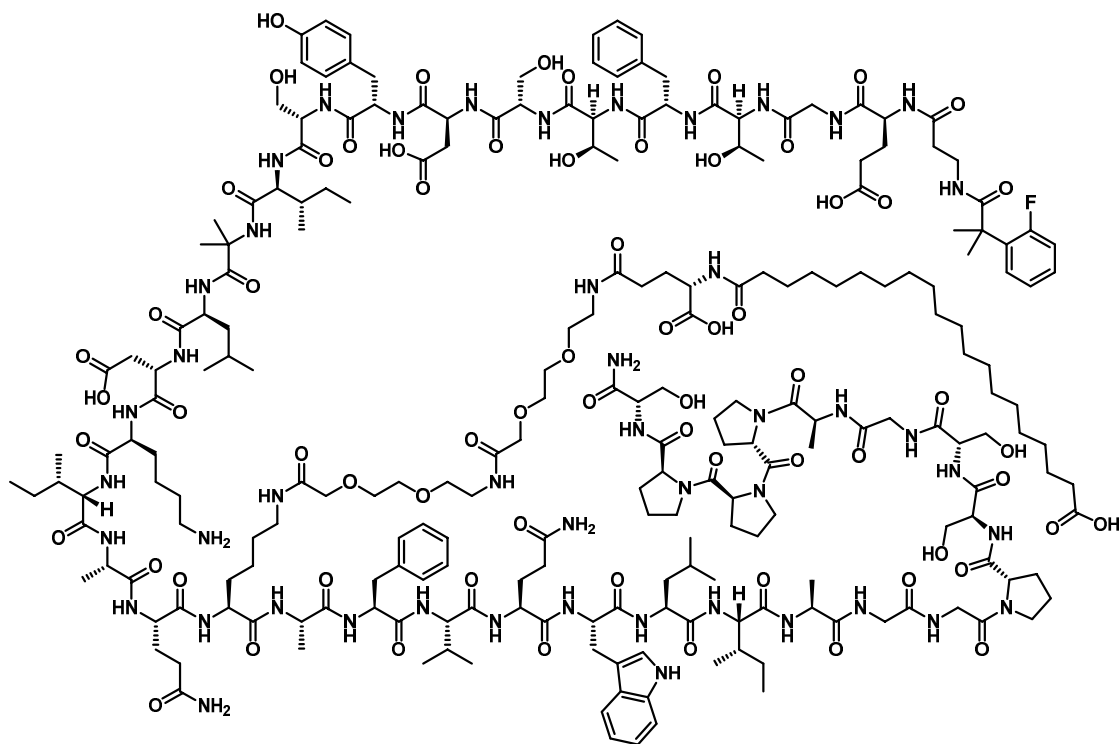
Compound 195,



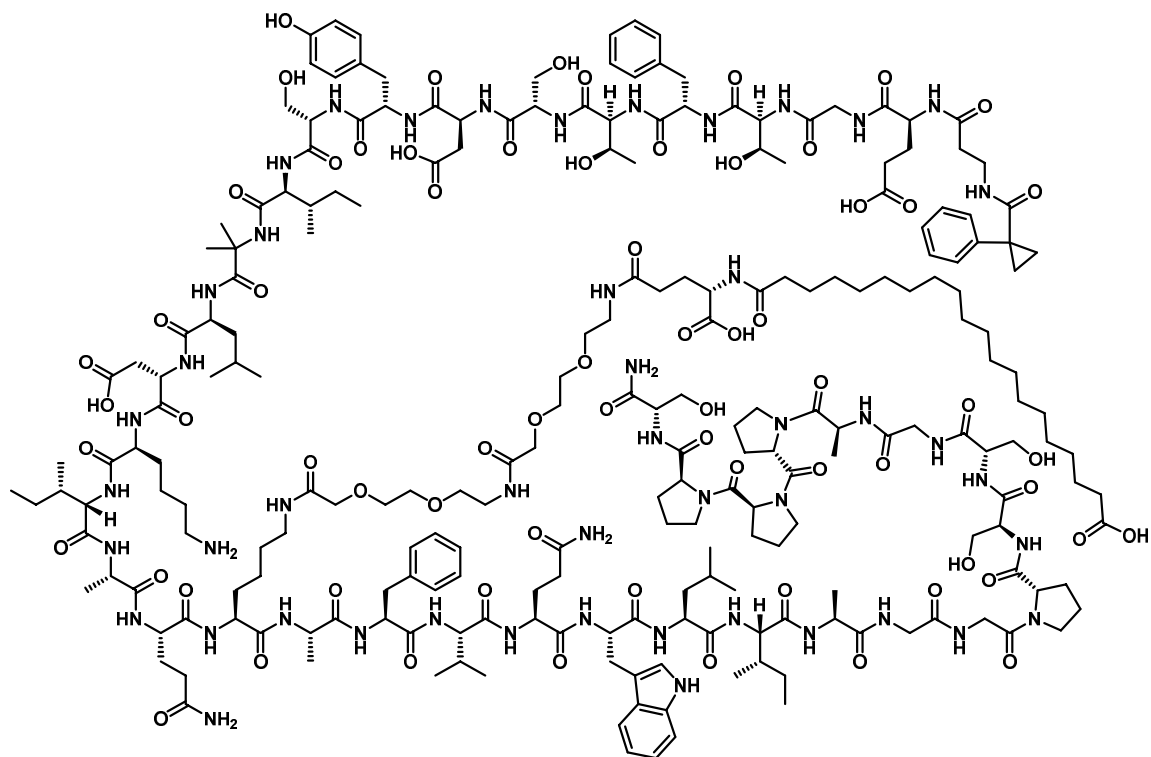
Compound 196,



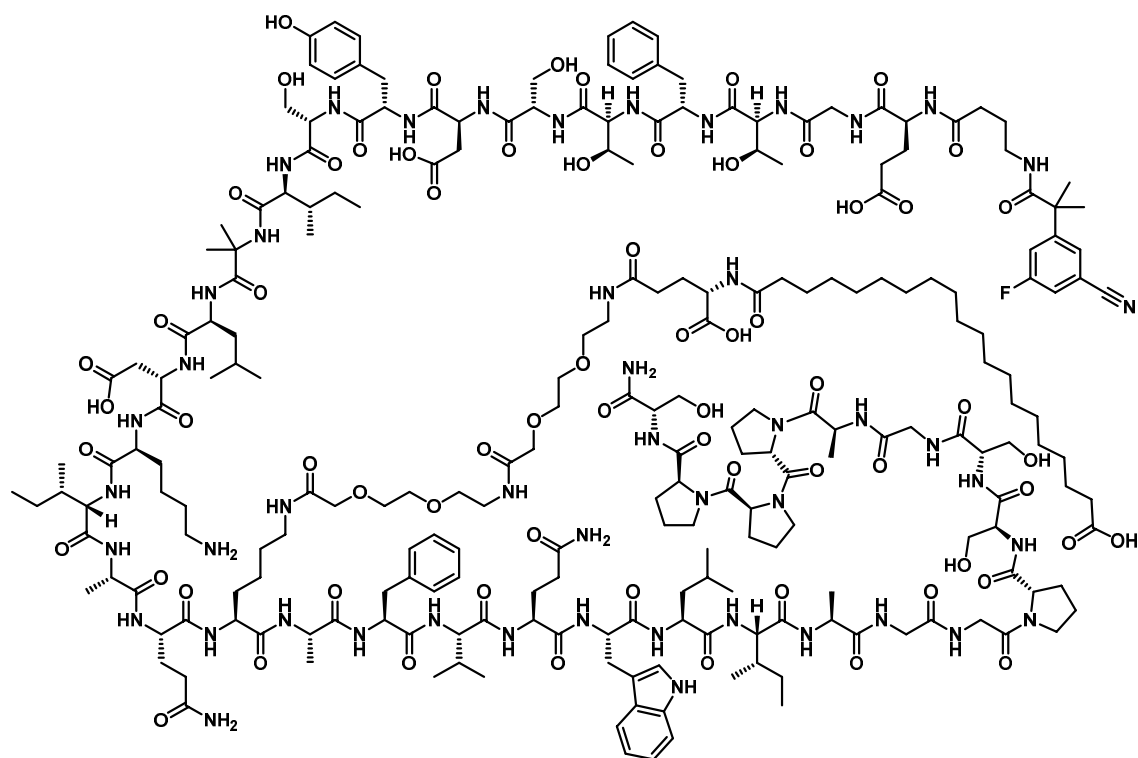
Compound 197,



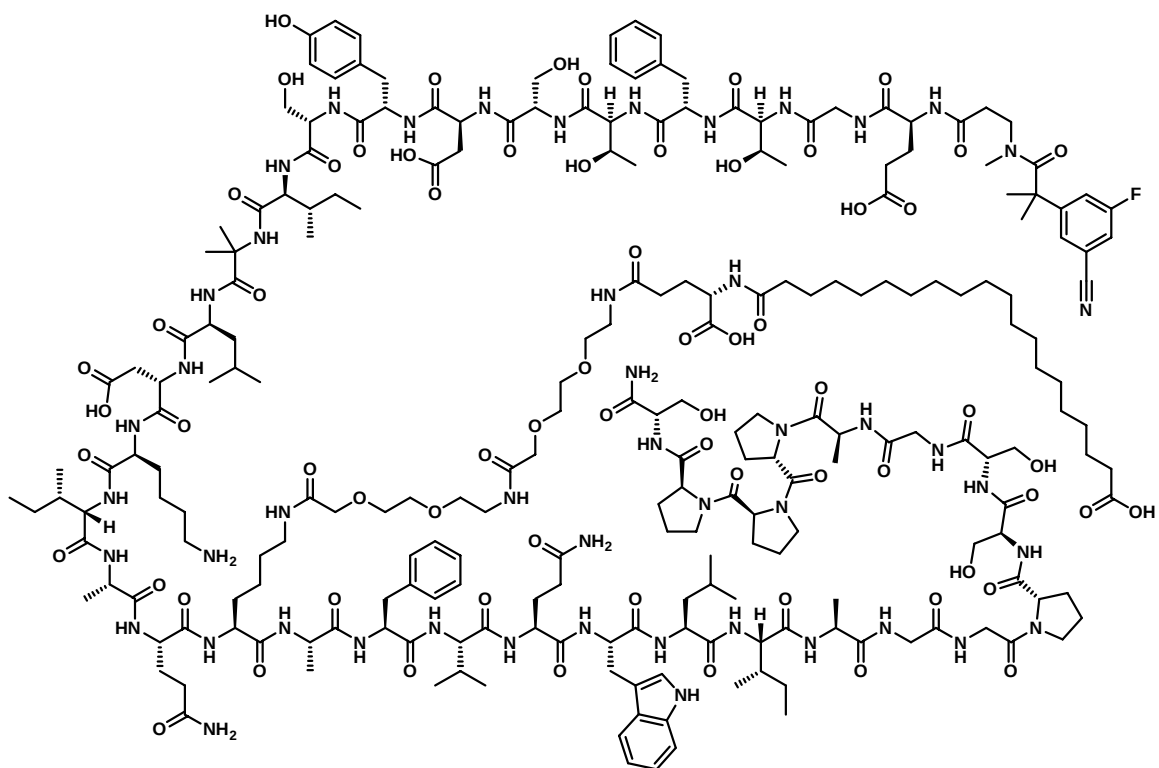
Compound 198,



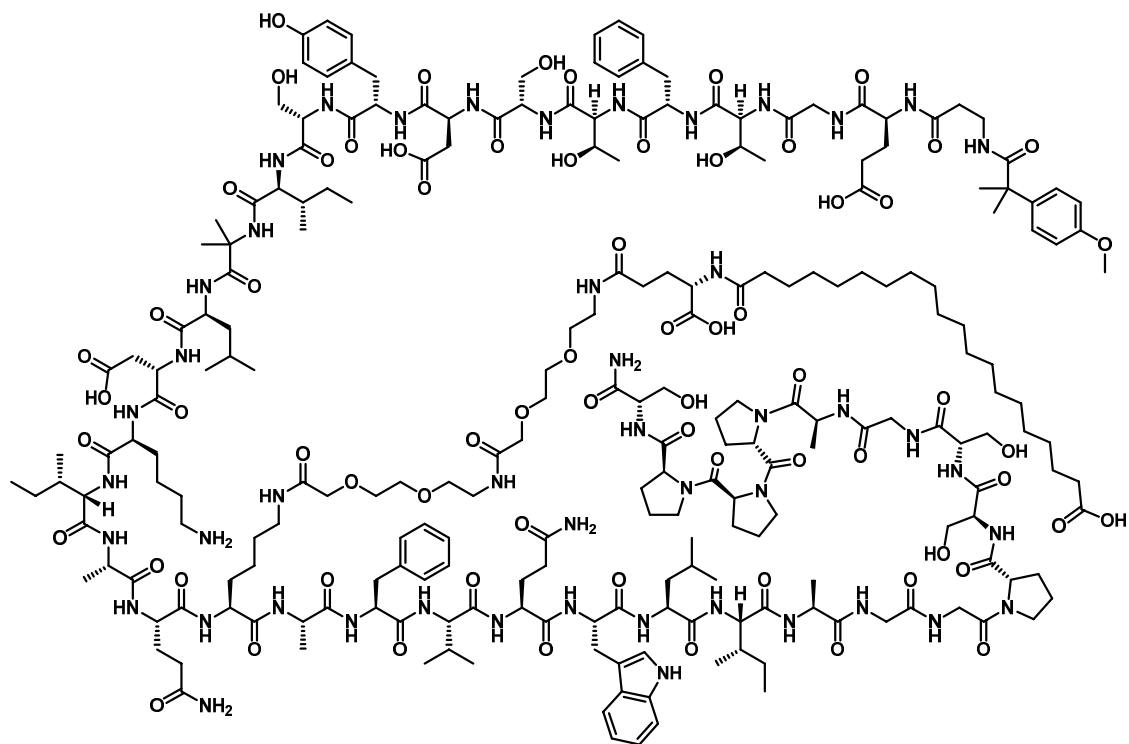
Compound 199,



Compound 200,



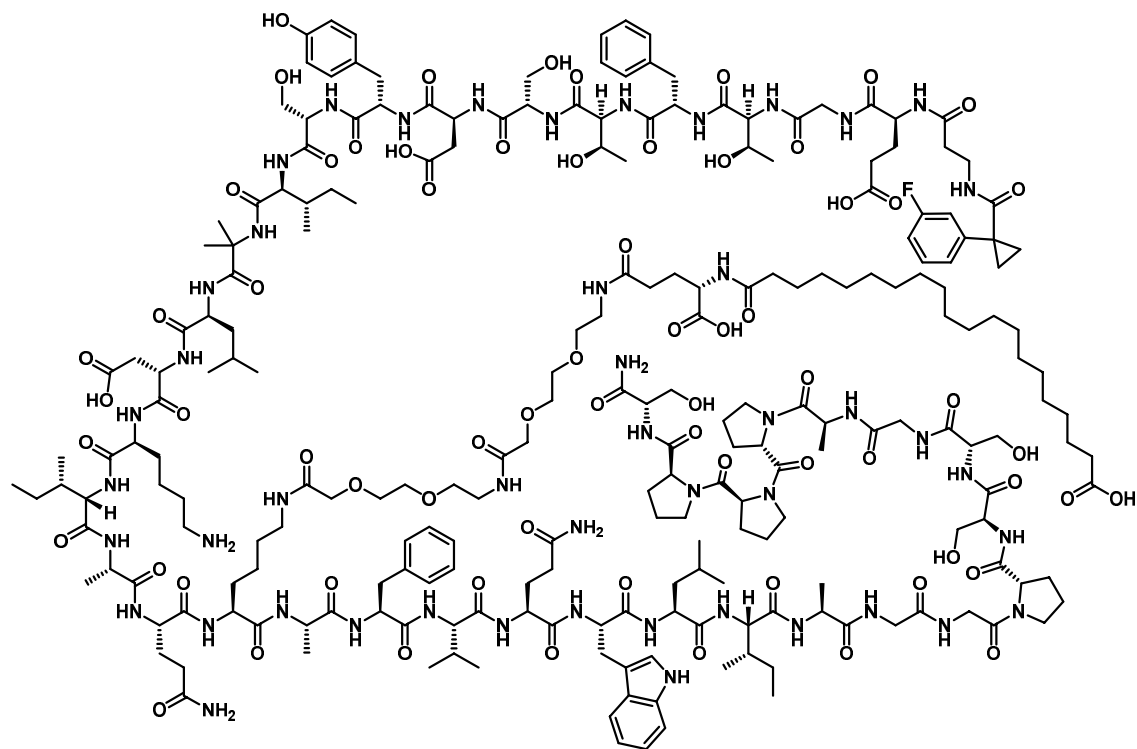
Compound 201,



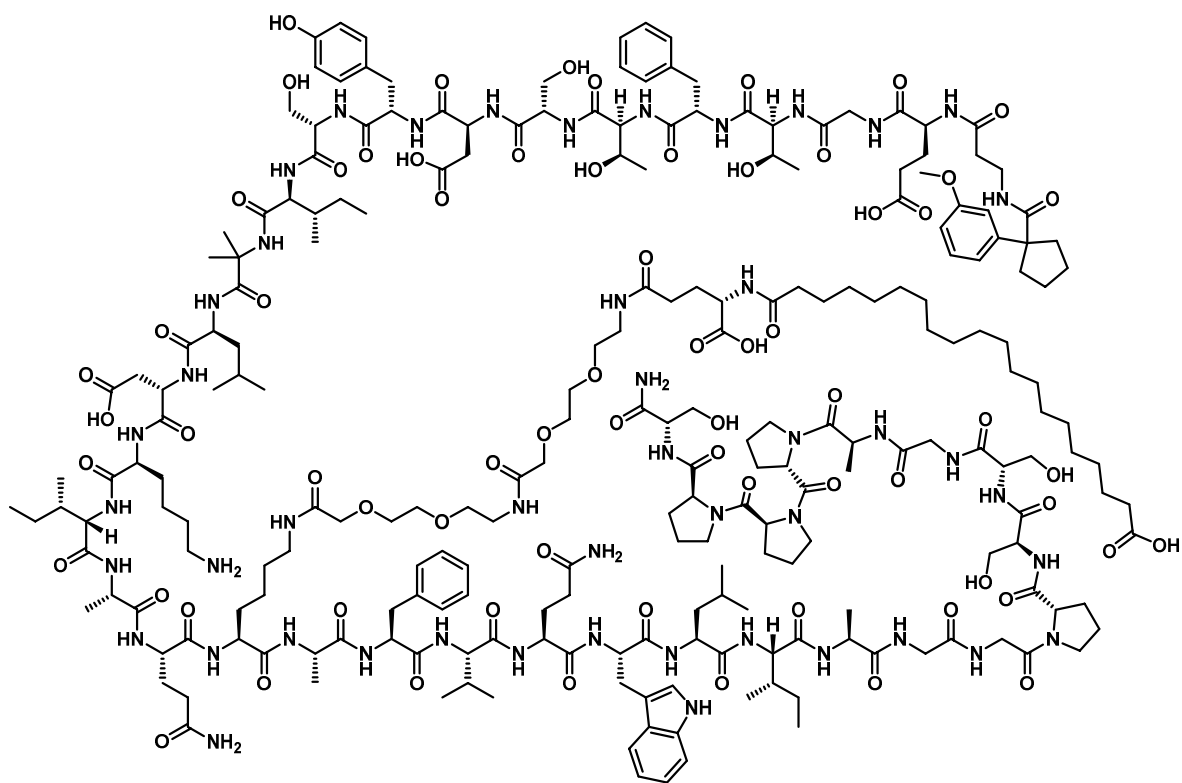
Compound 203,

[illegible]

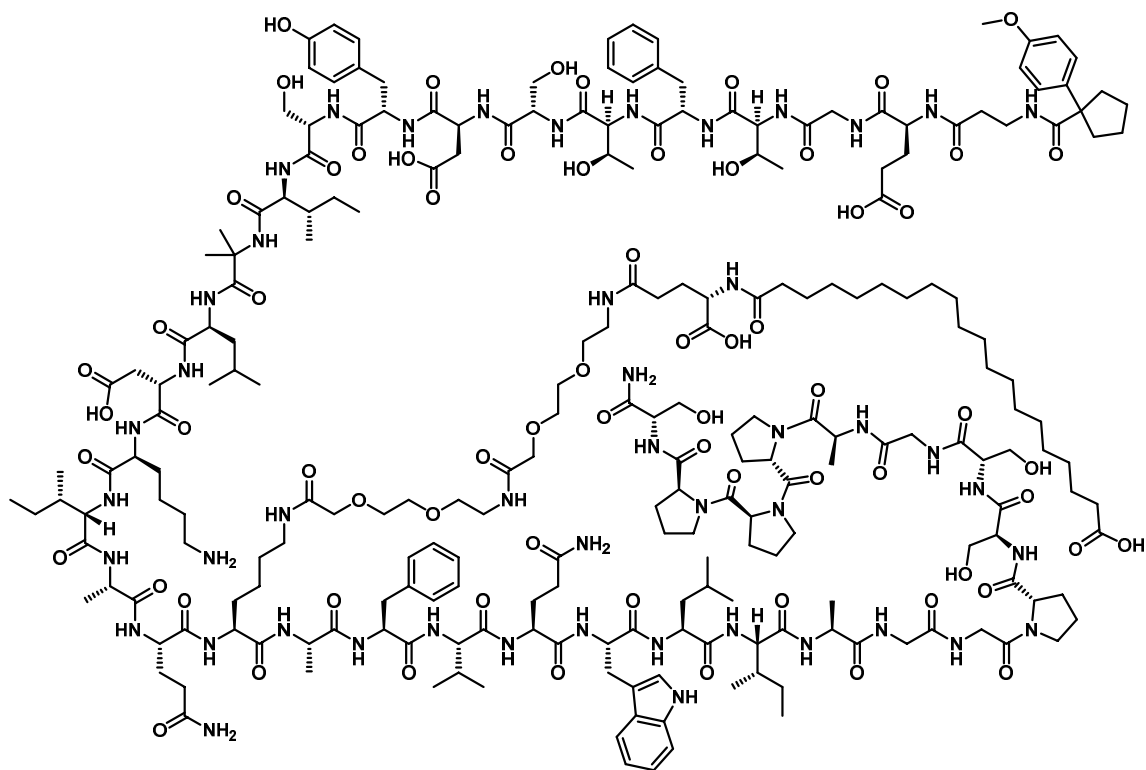
Compound 205,



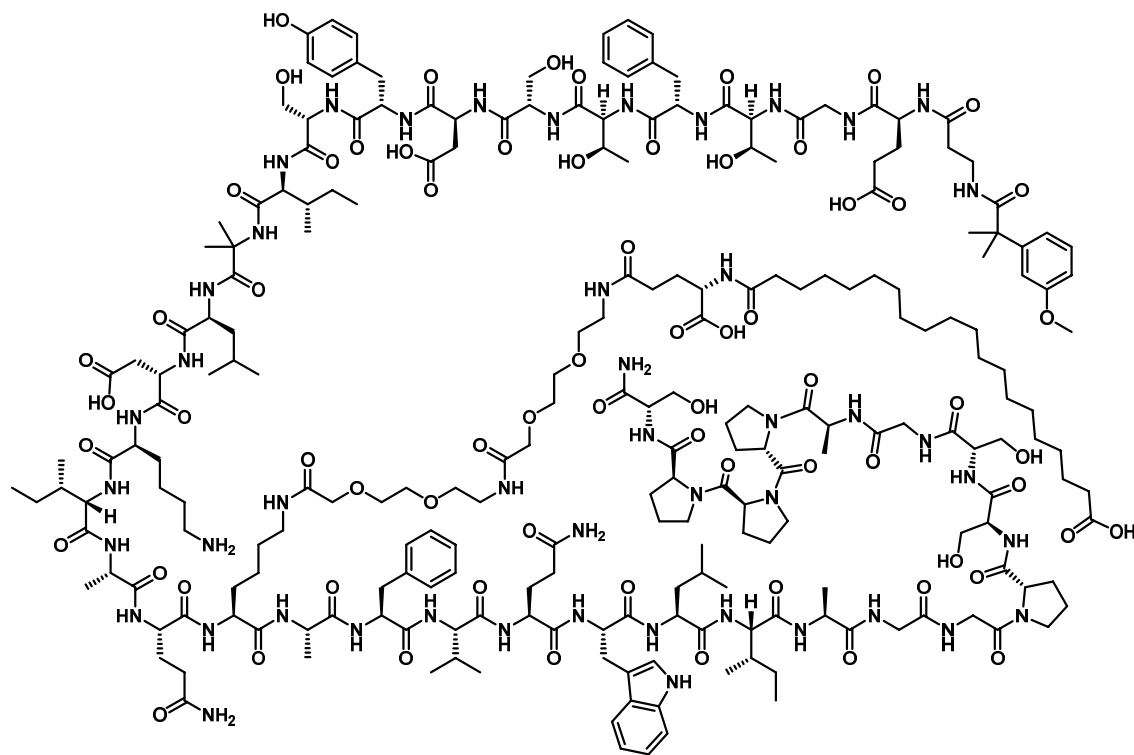
Compound 206,



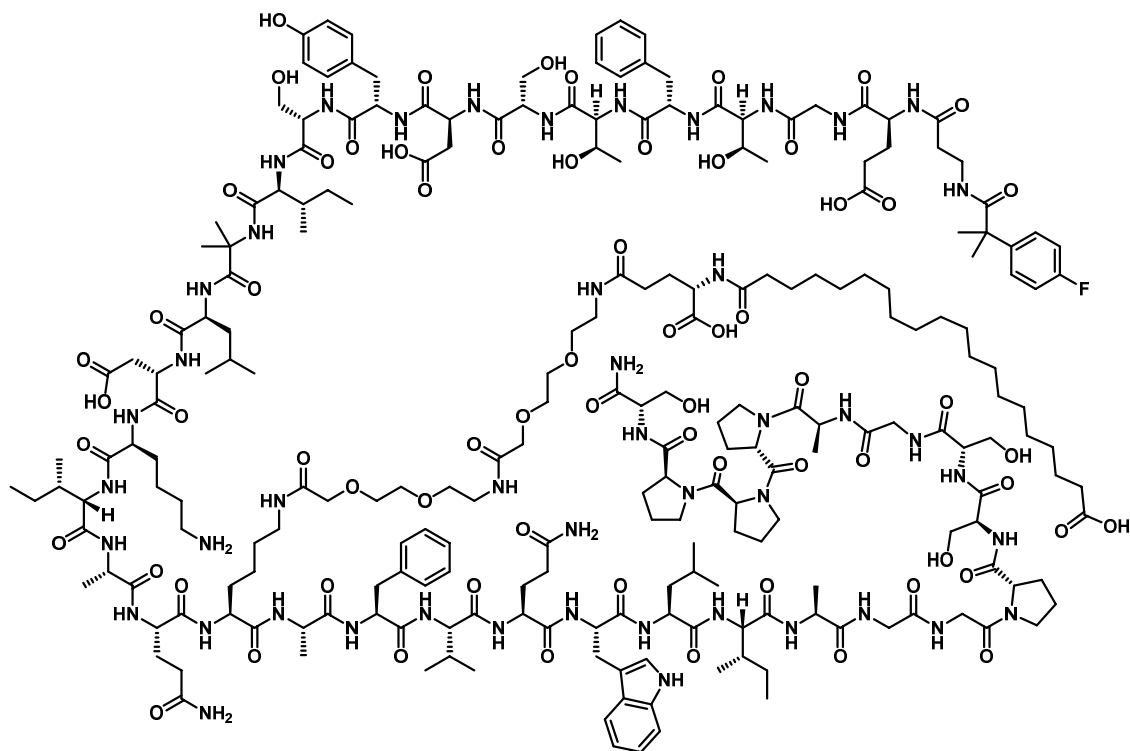
Compound 207,



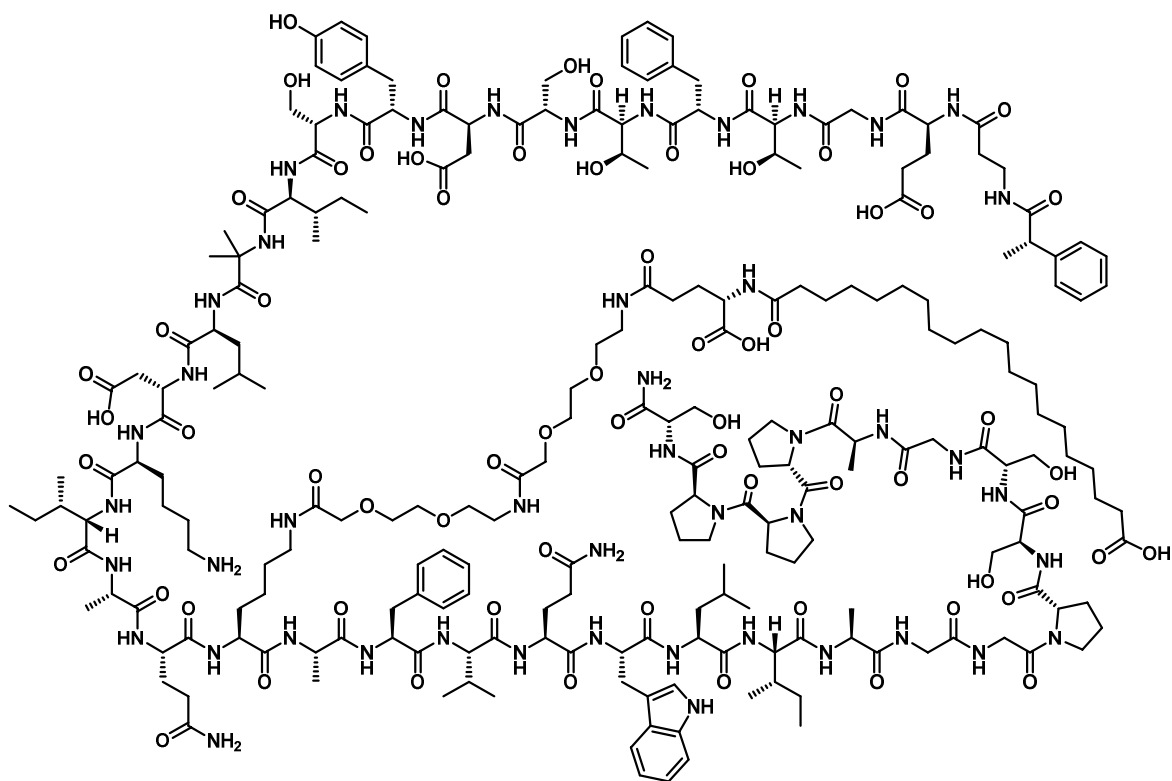
Compound 208,



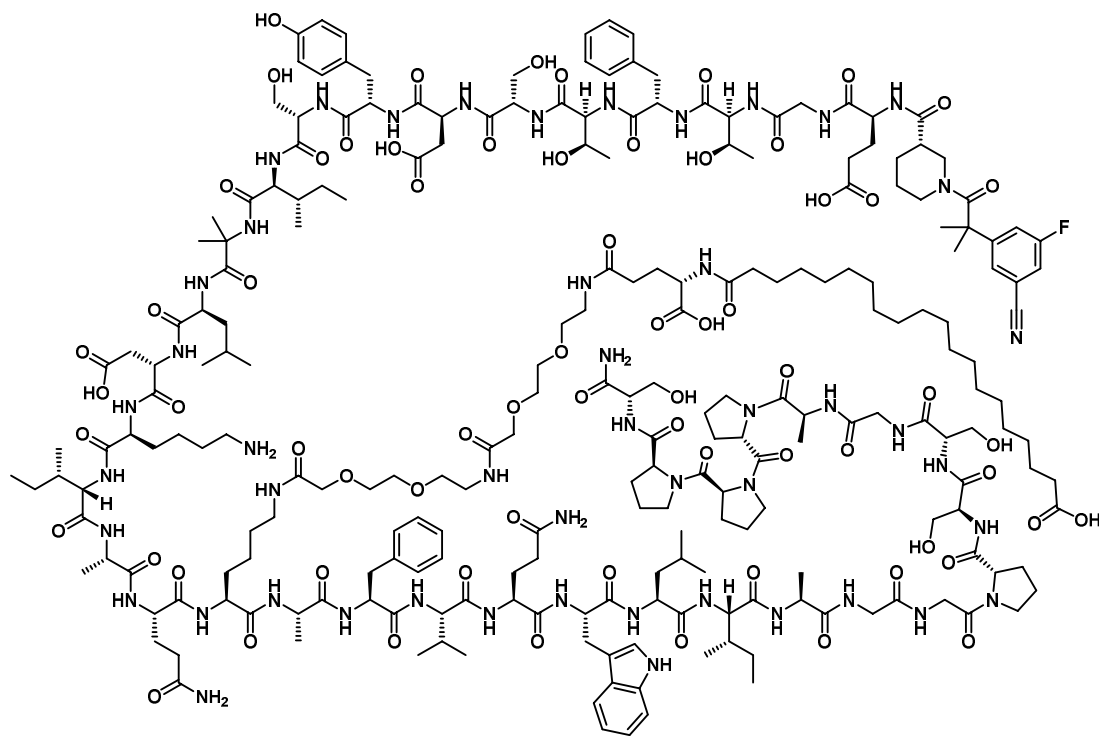
Compound 209,



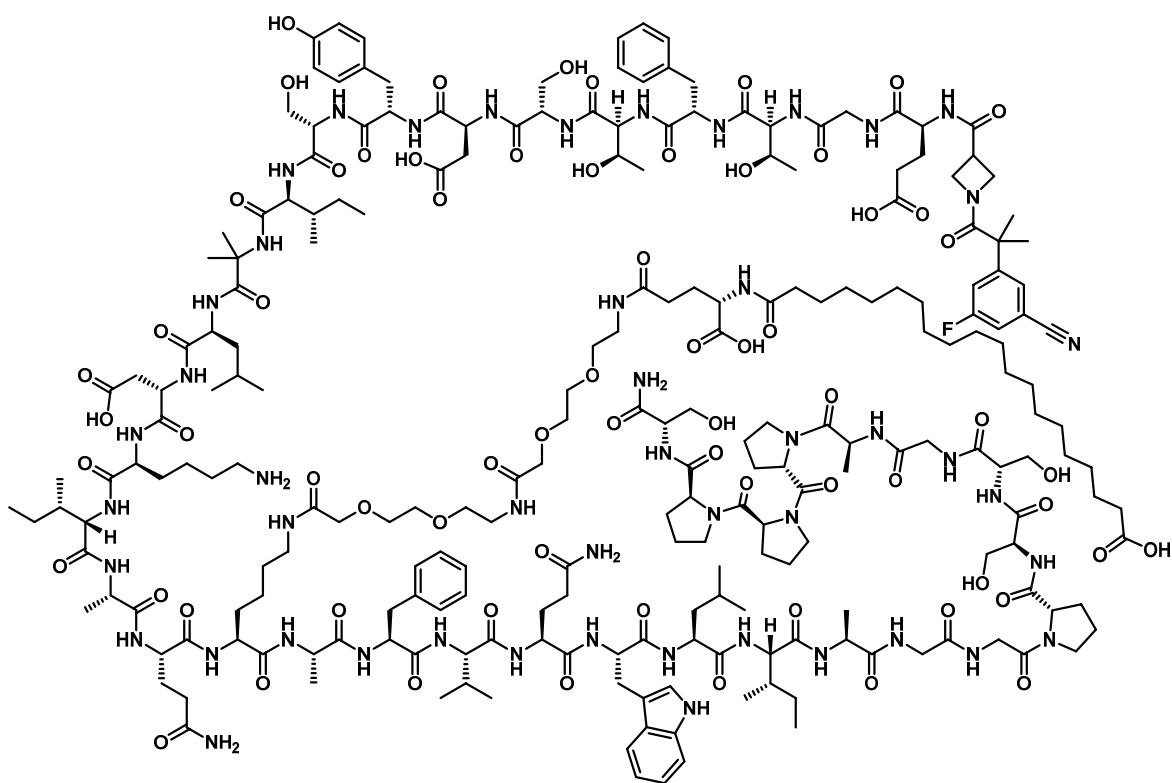
Compound 210,



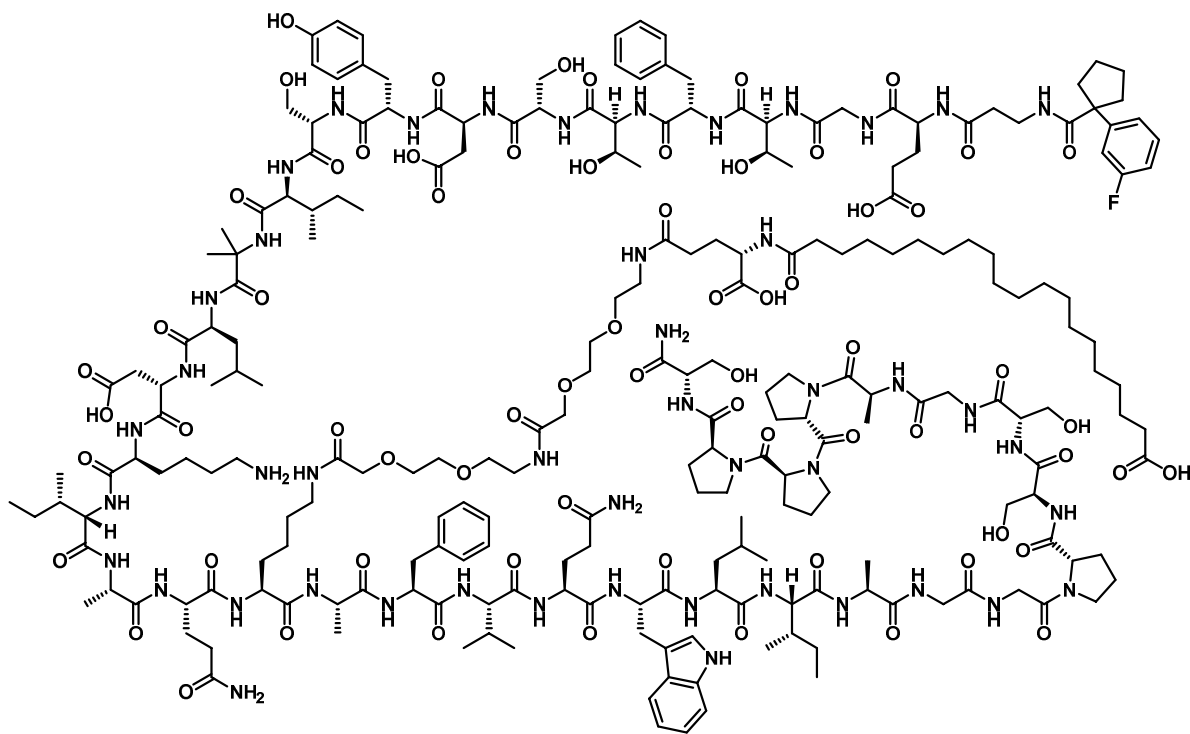
Compound 211,



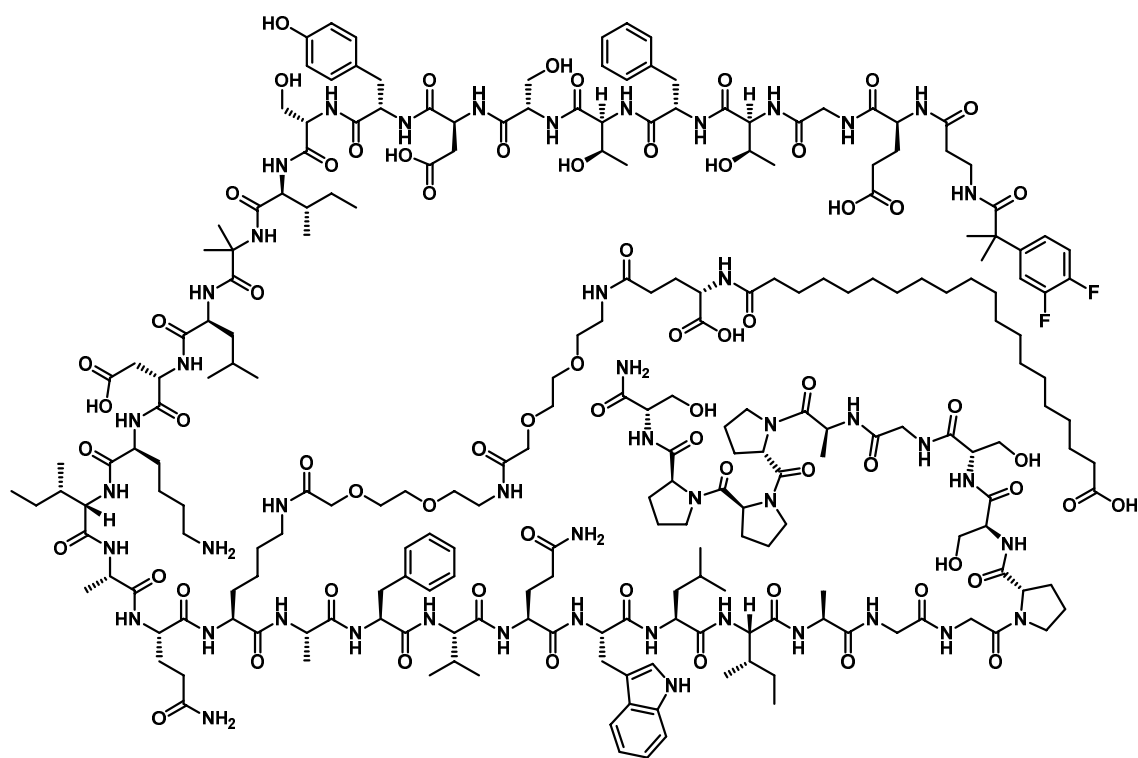
Compound 212,



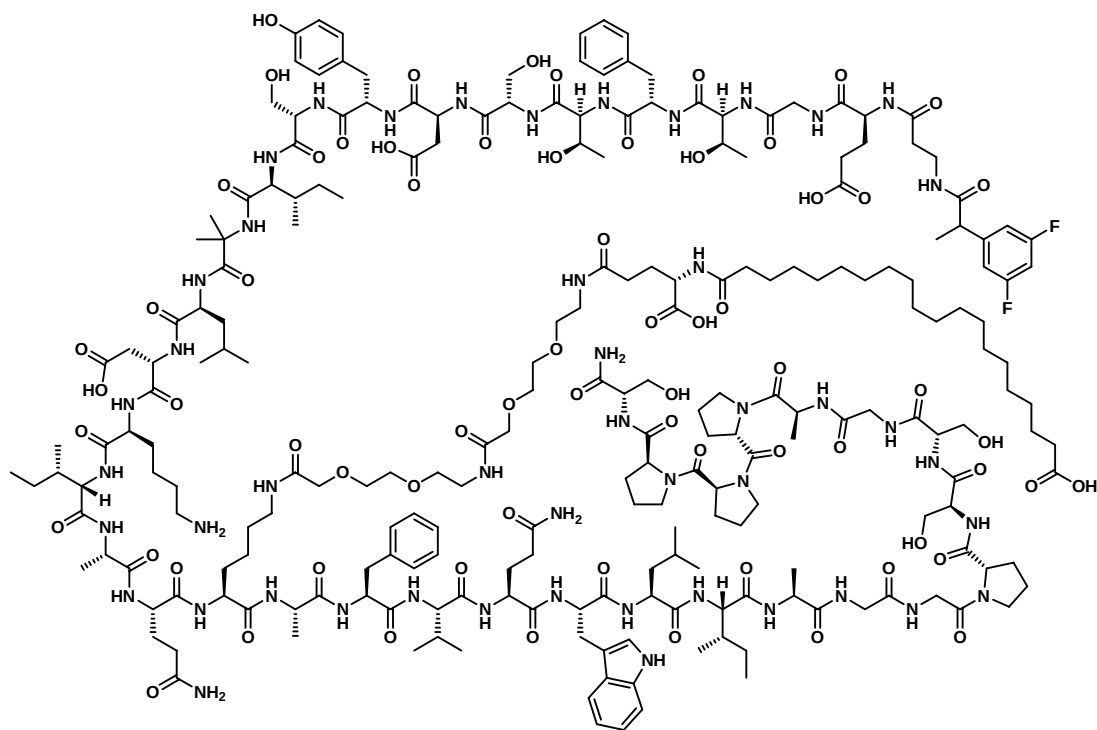
Compound 213,



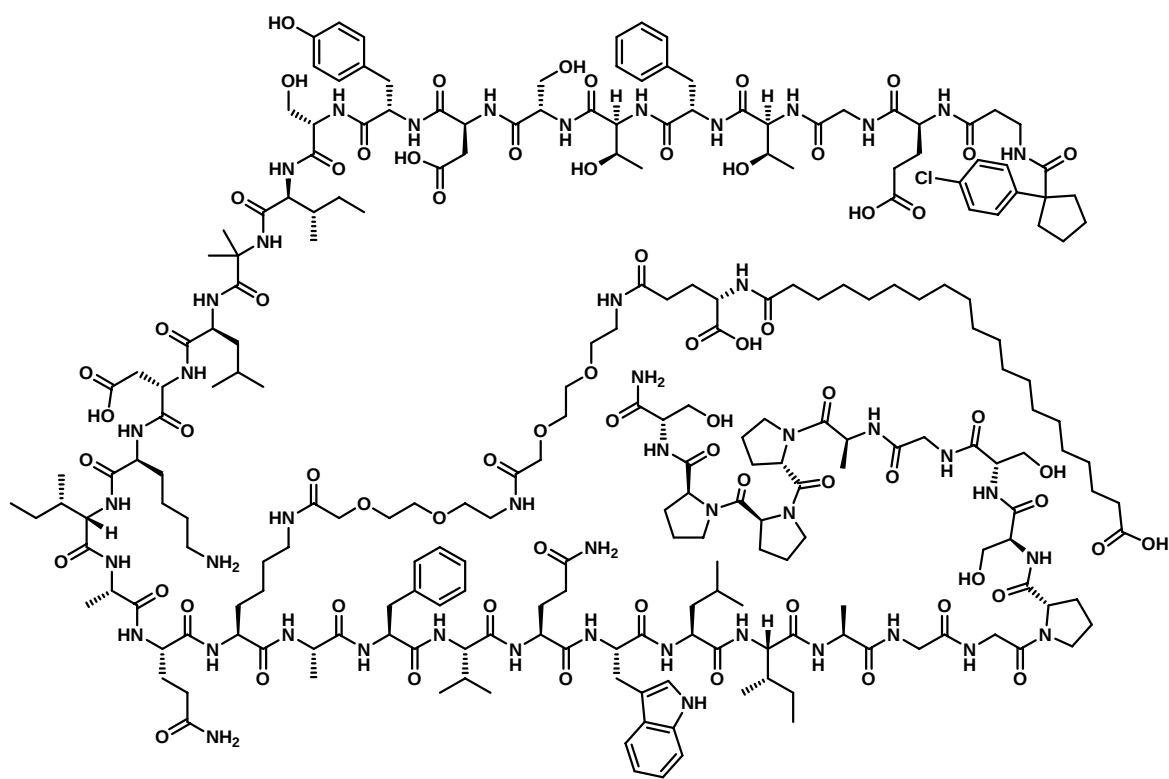
Compound 214,



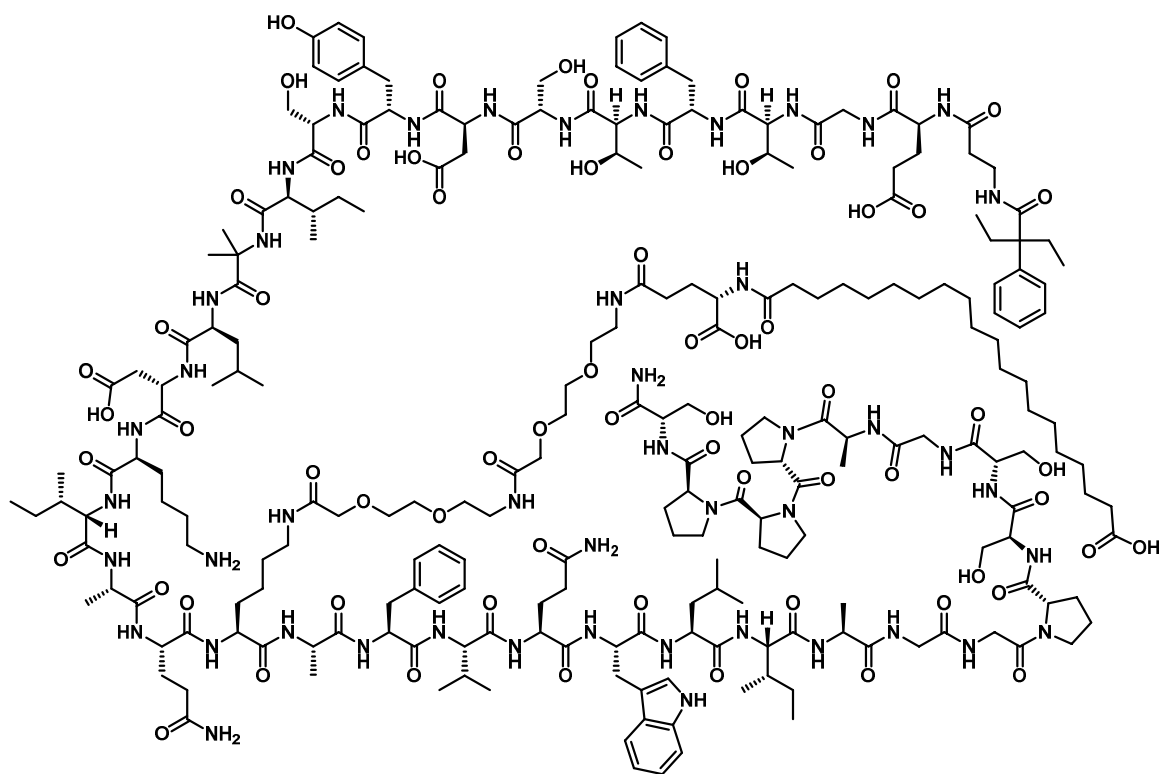
Compound 215,



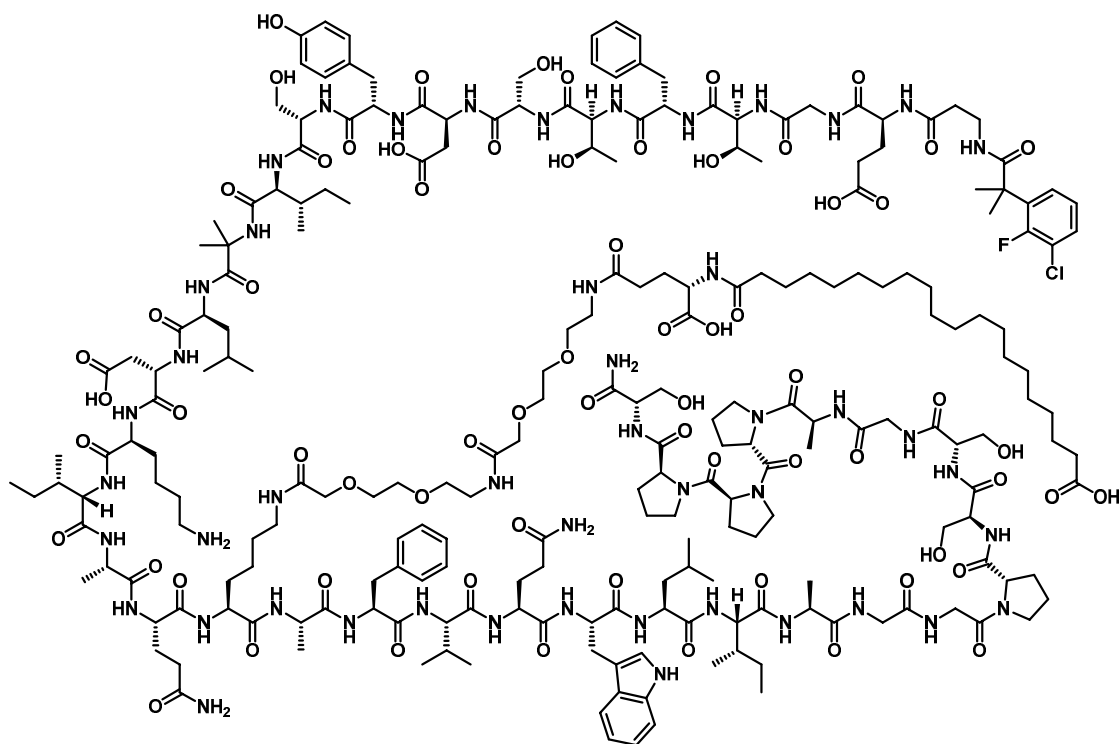
Compound 216,



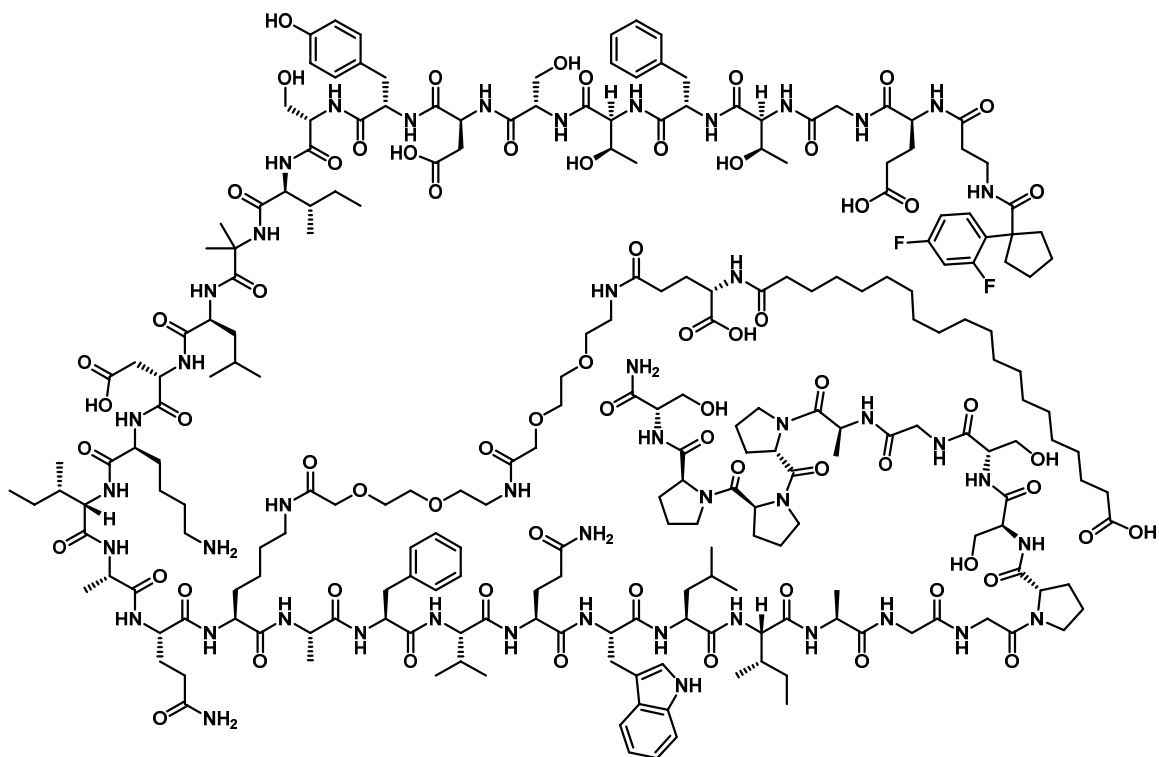
Compound 217,



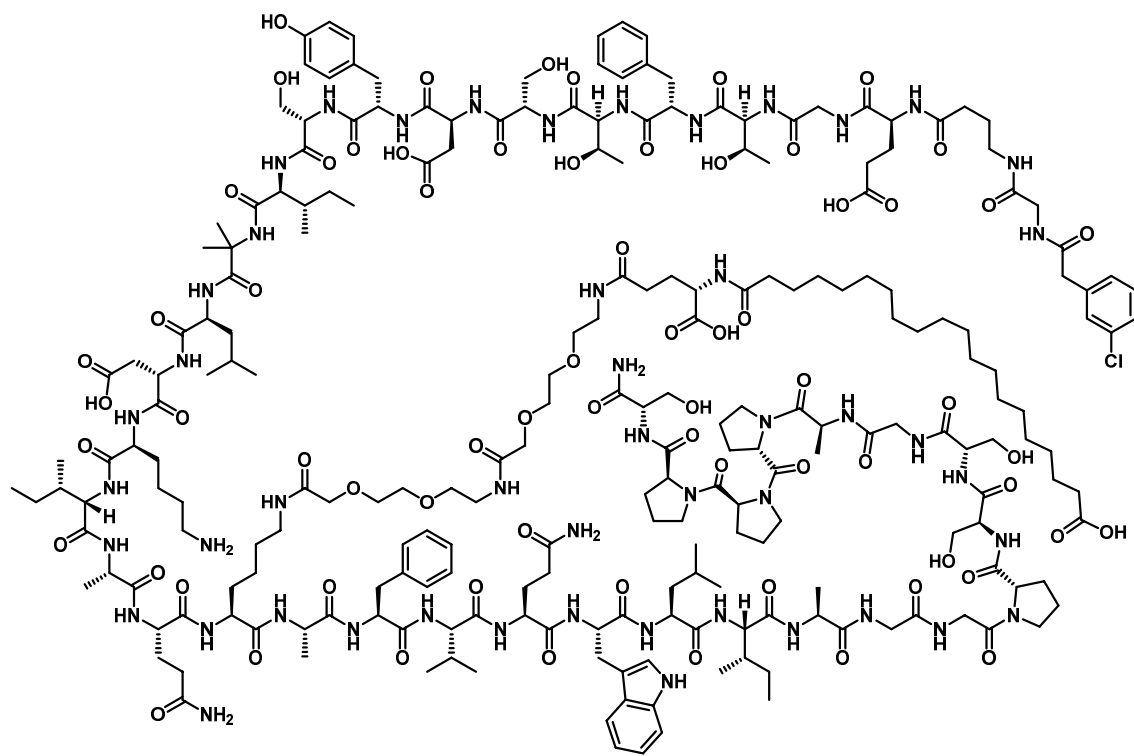
Compound 218,



Compound 219,



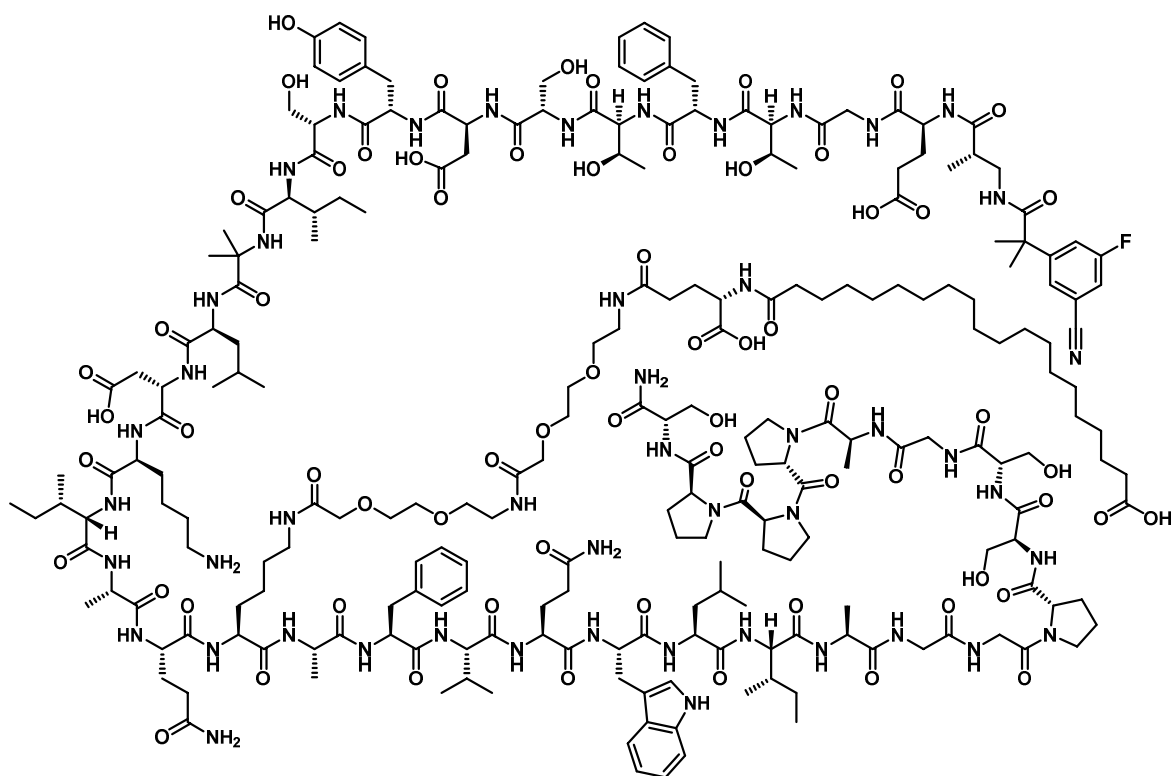
Compound 220,



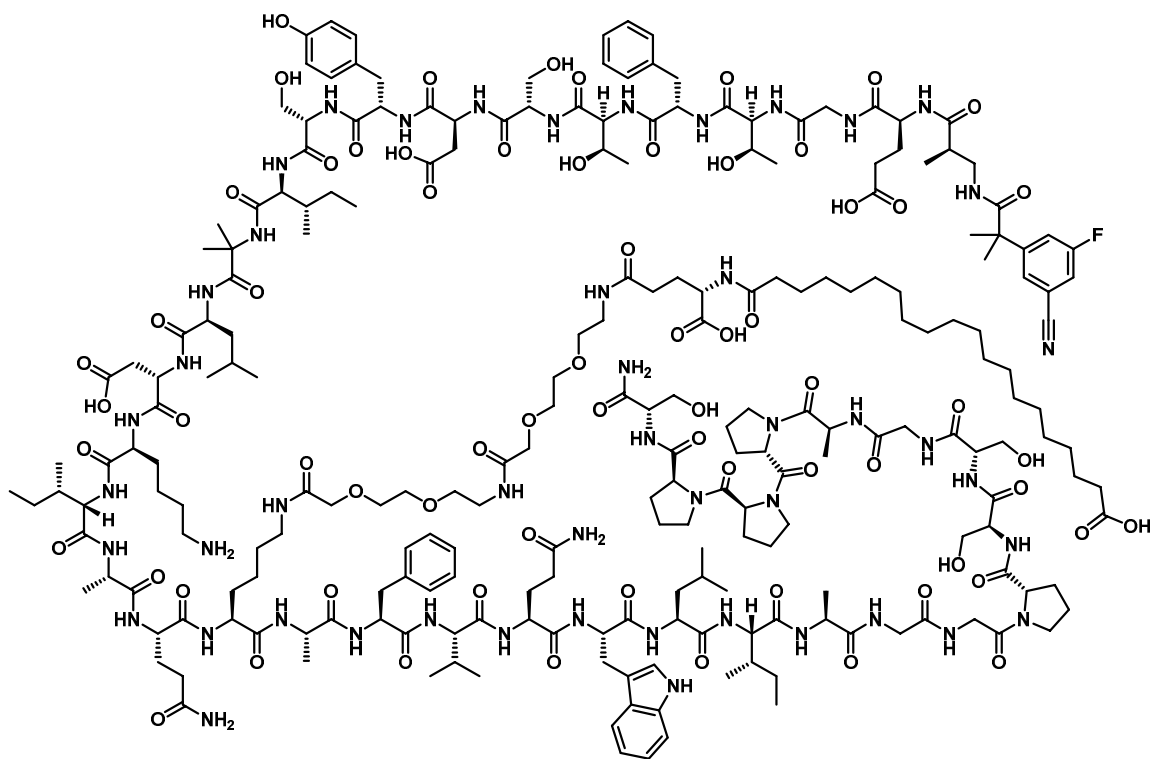
Compound 221,

[illegible]

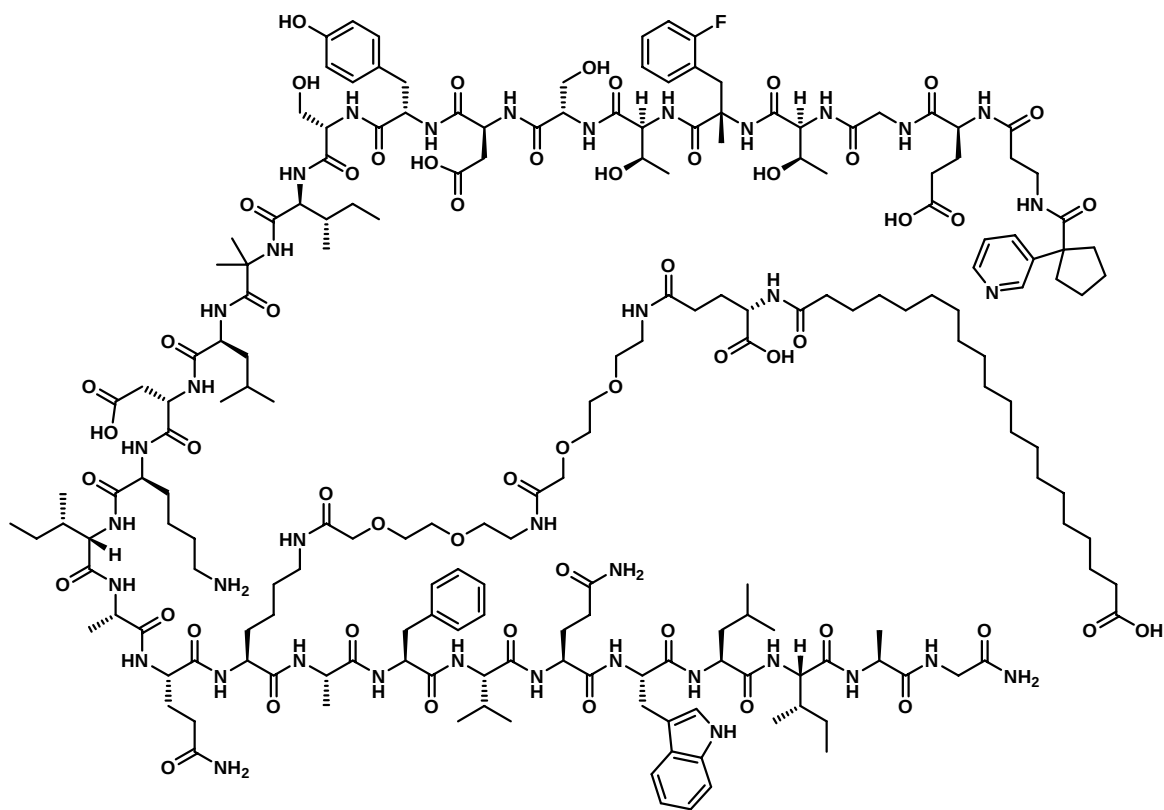
Compound 223,



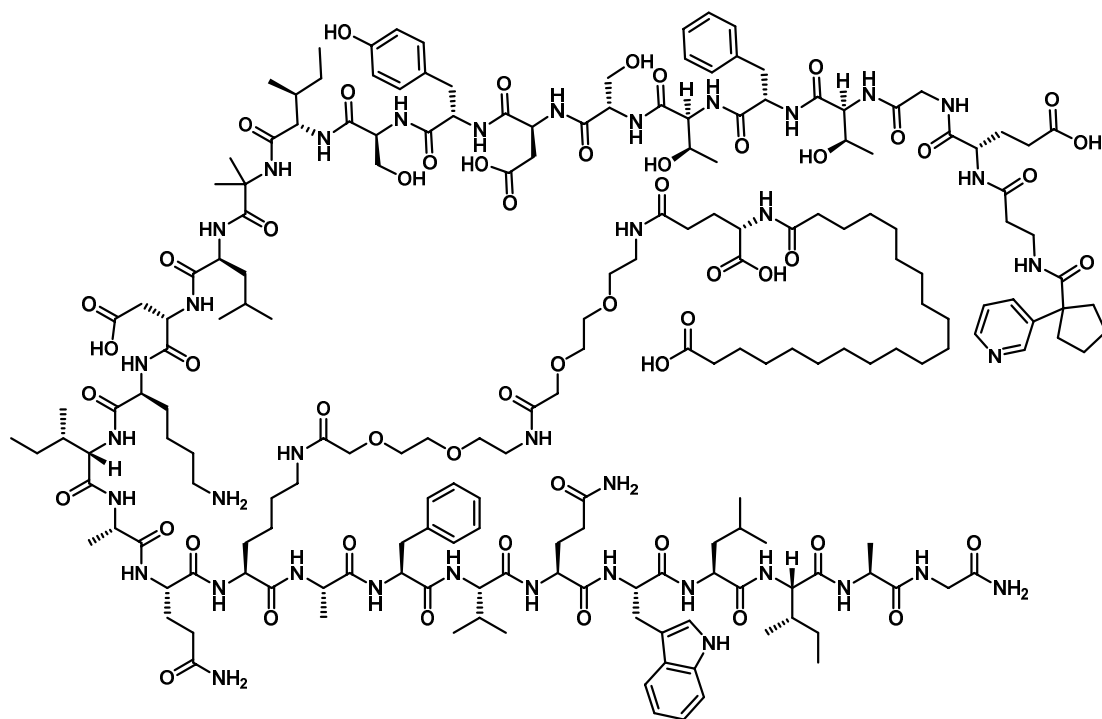
Compound 224,



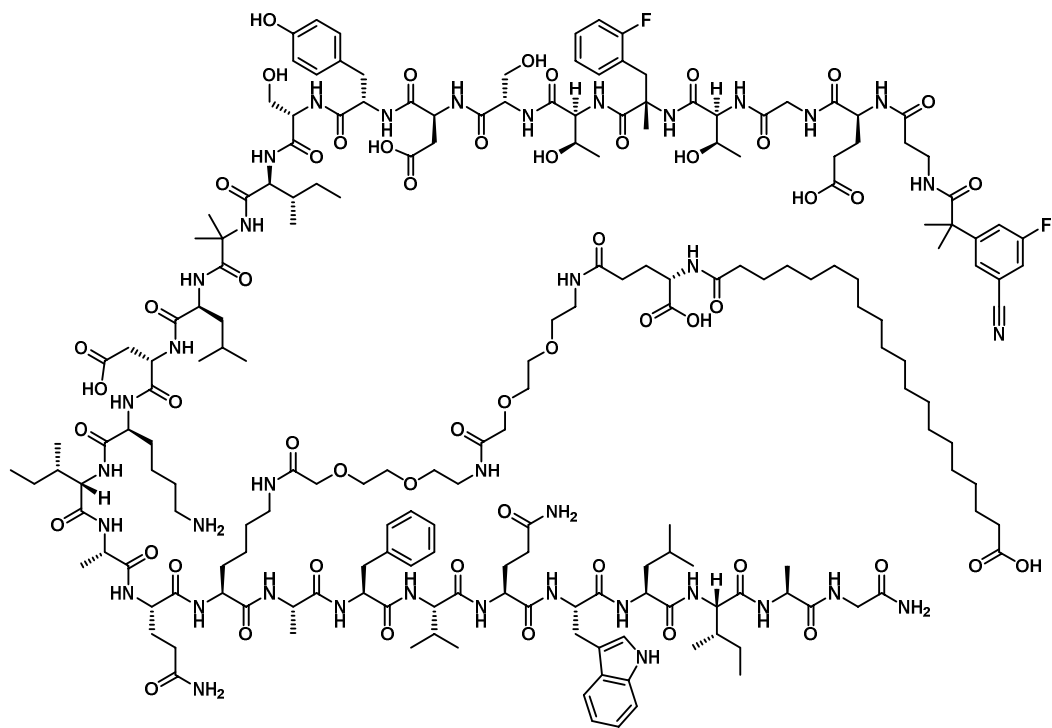
Compound 225,



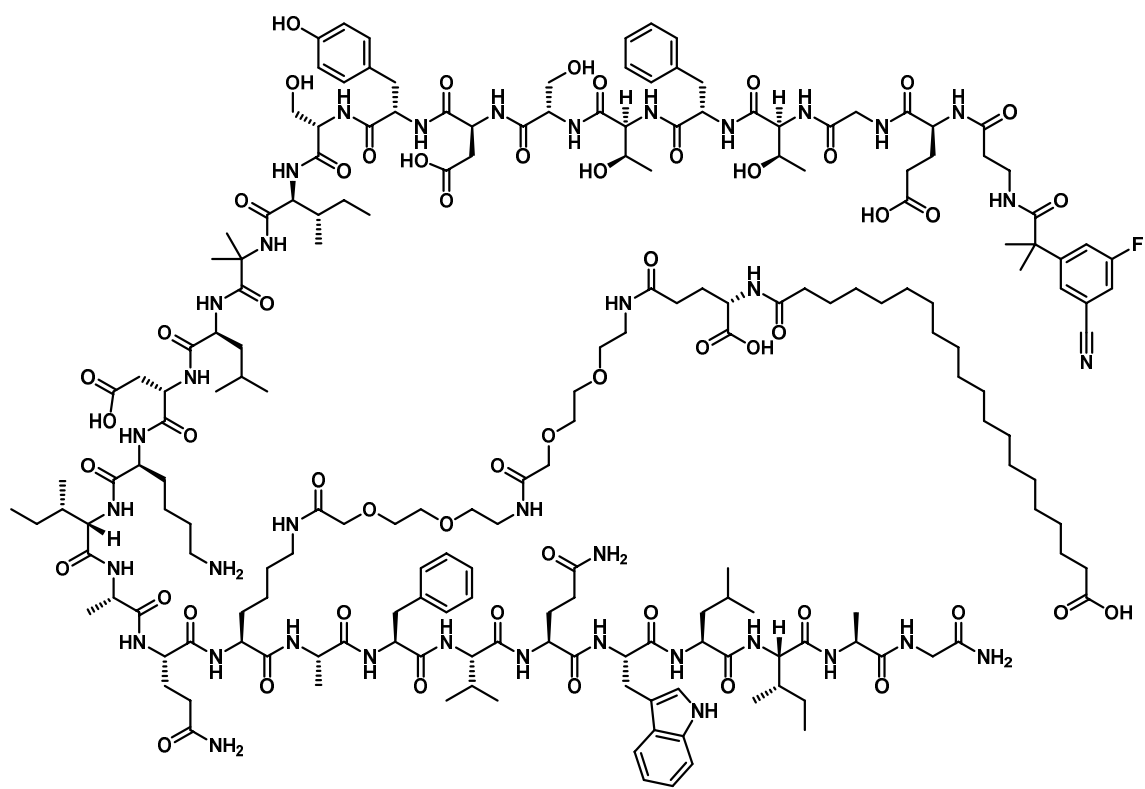
Compound 226,



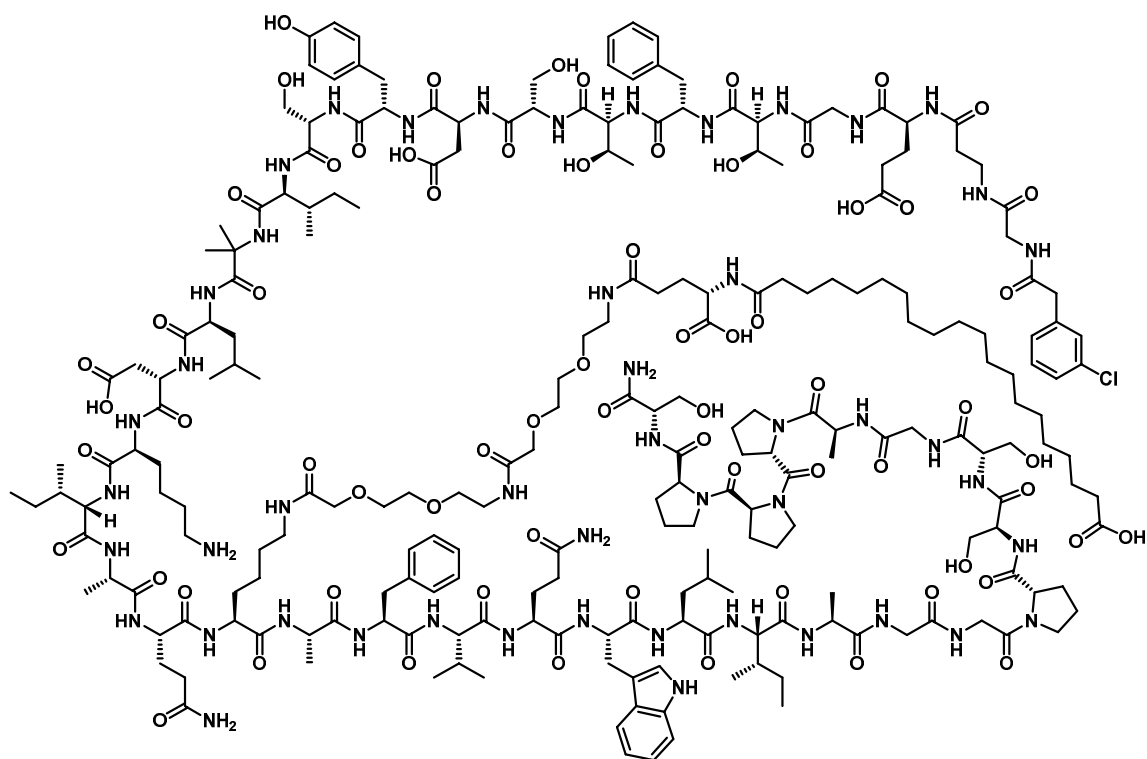
Compound 227,



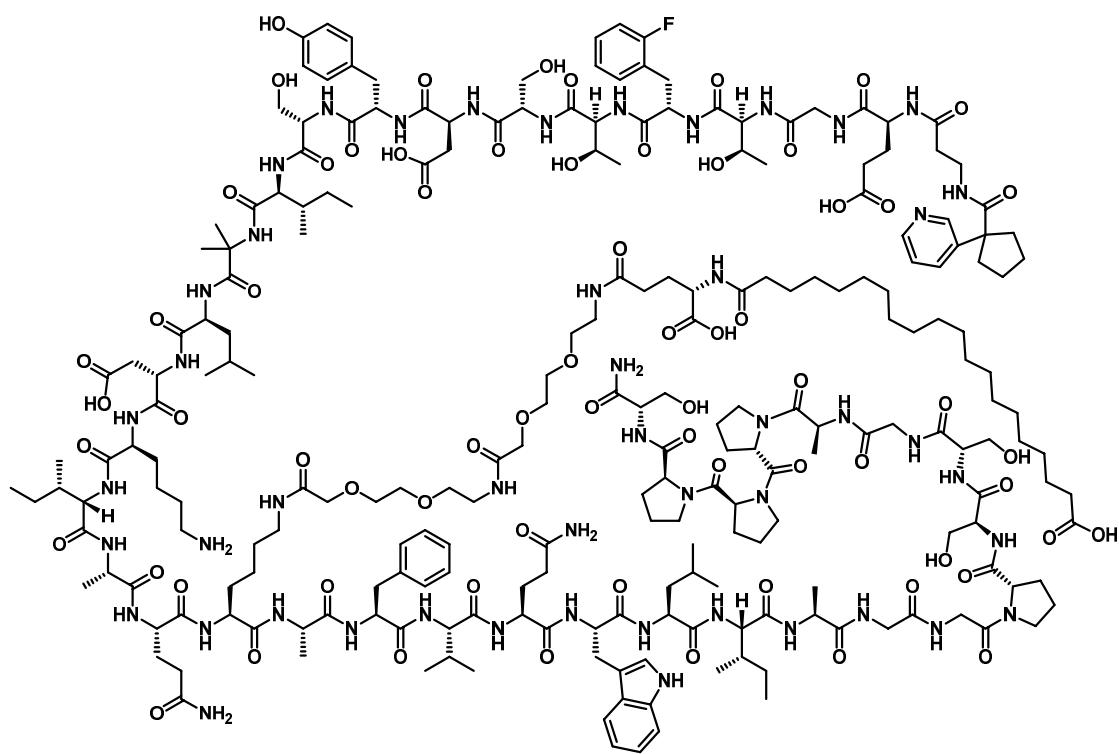
Compound 228,



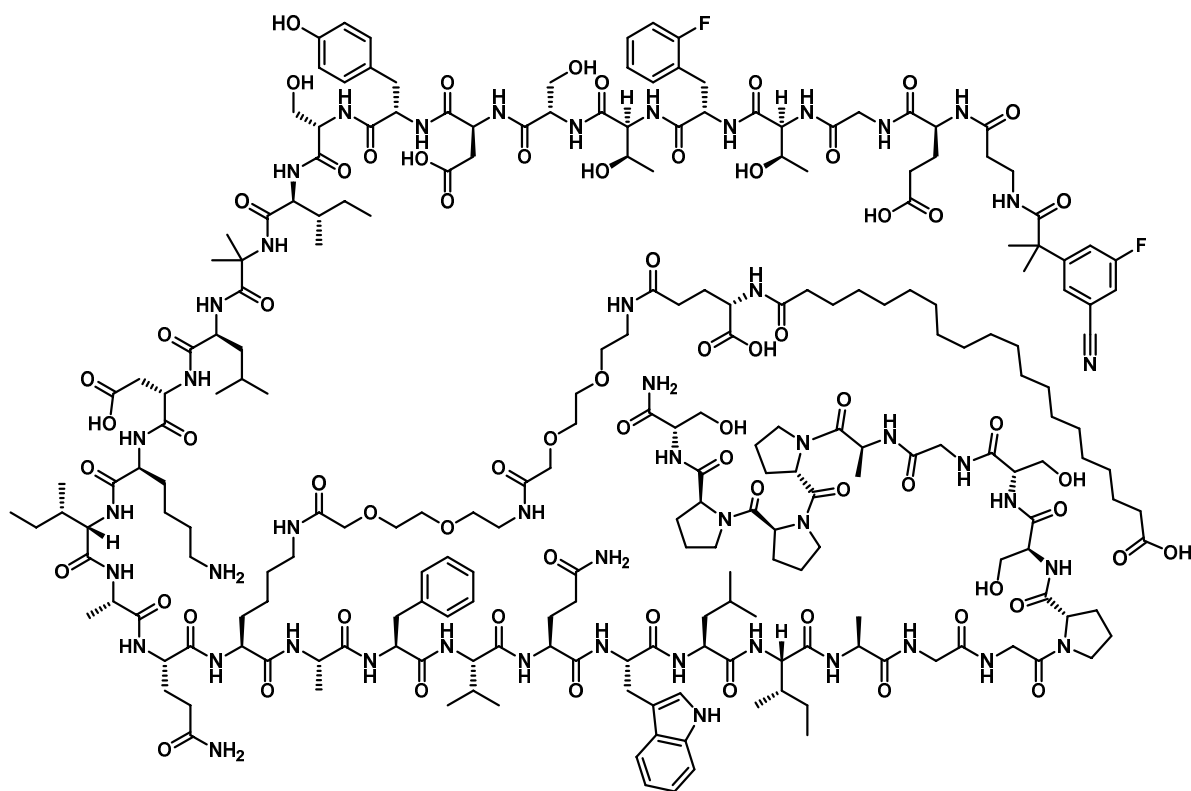
Compound 229,



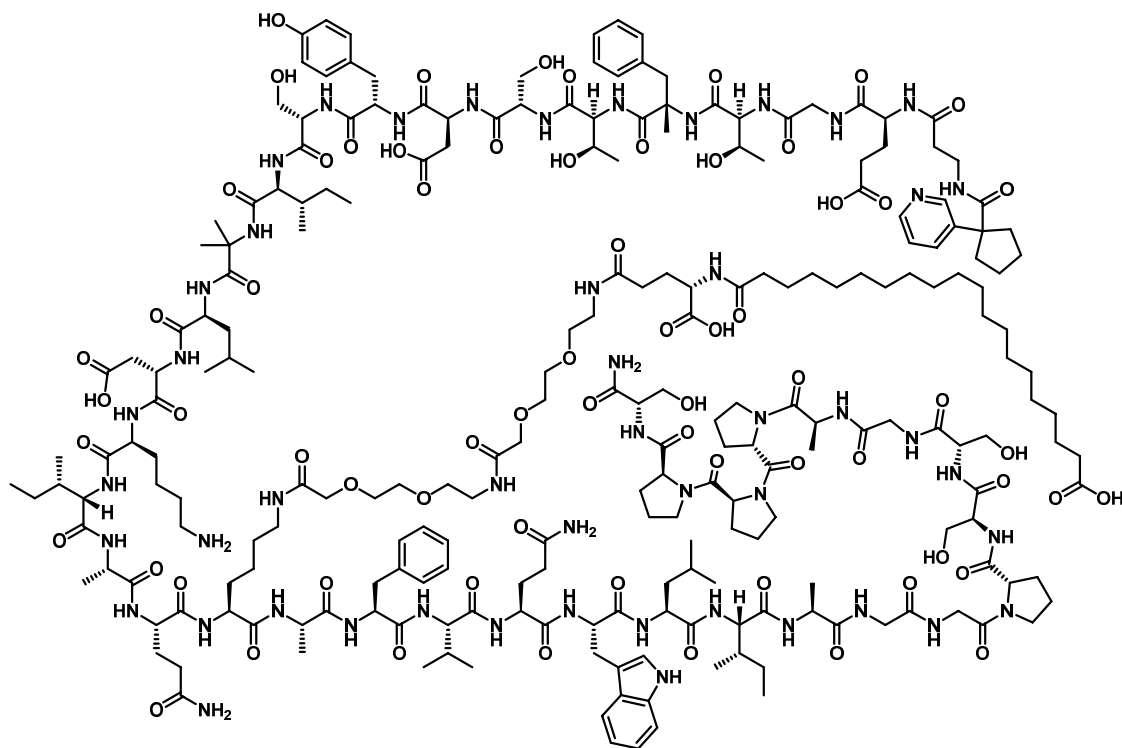
Compound 230,



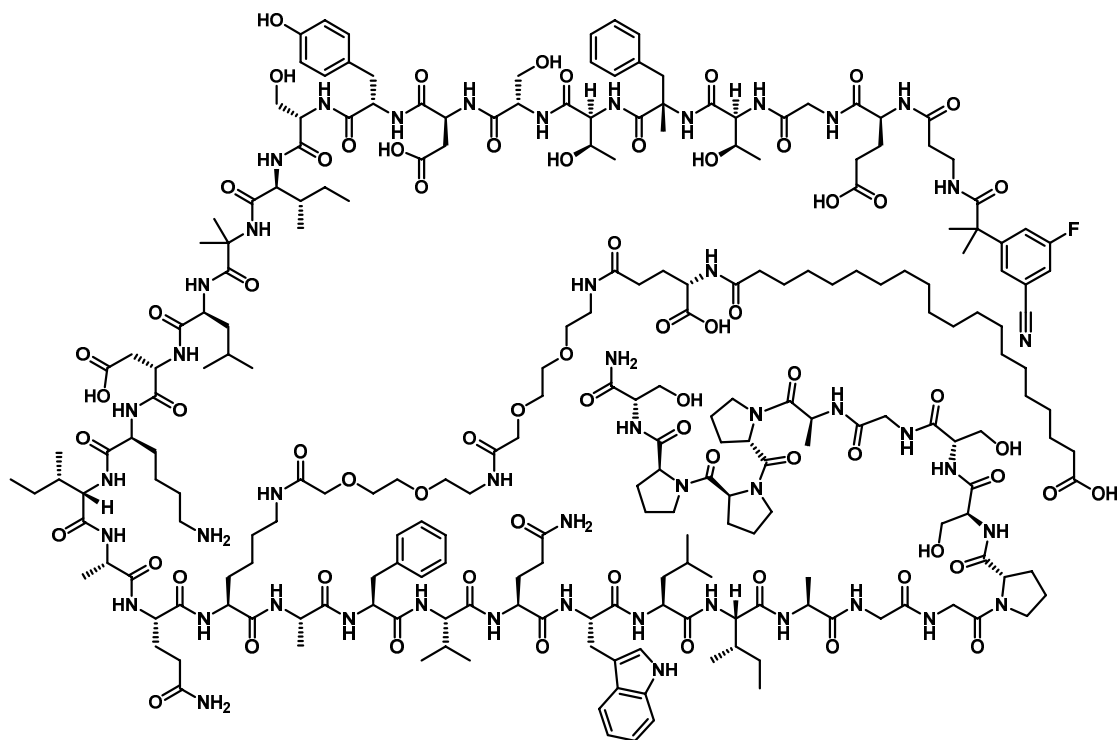
Compound 231,



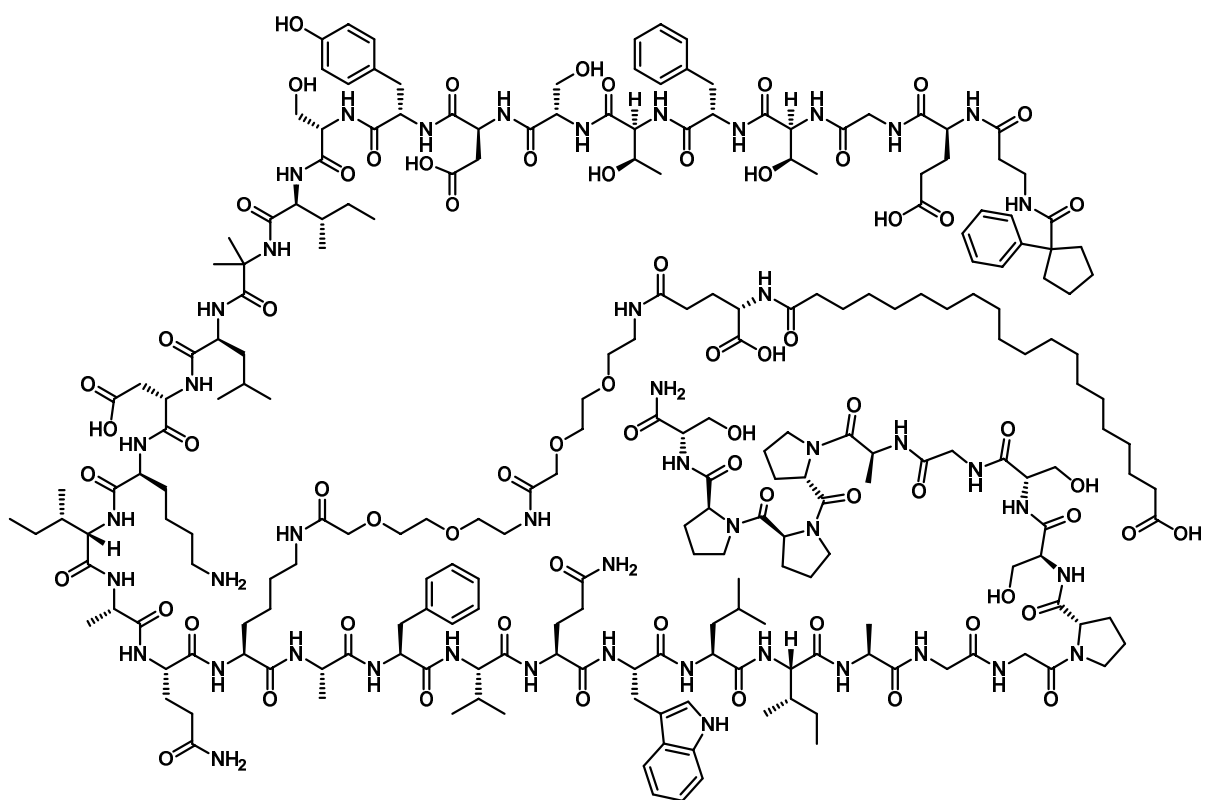
Compound 233,



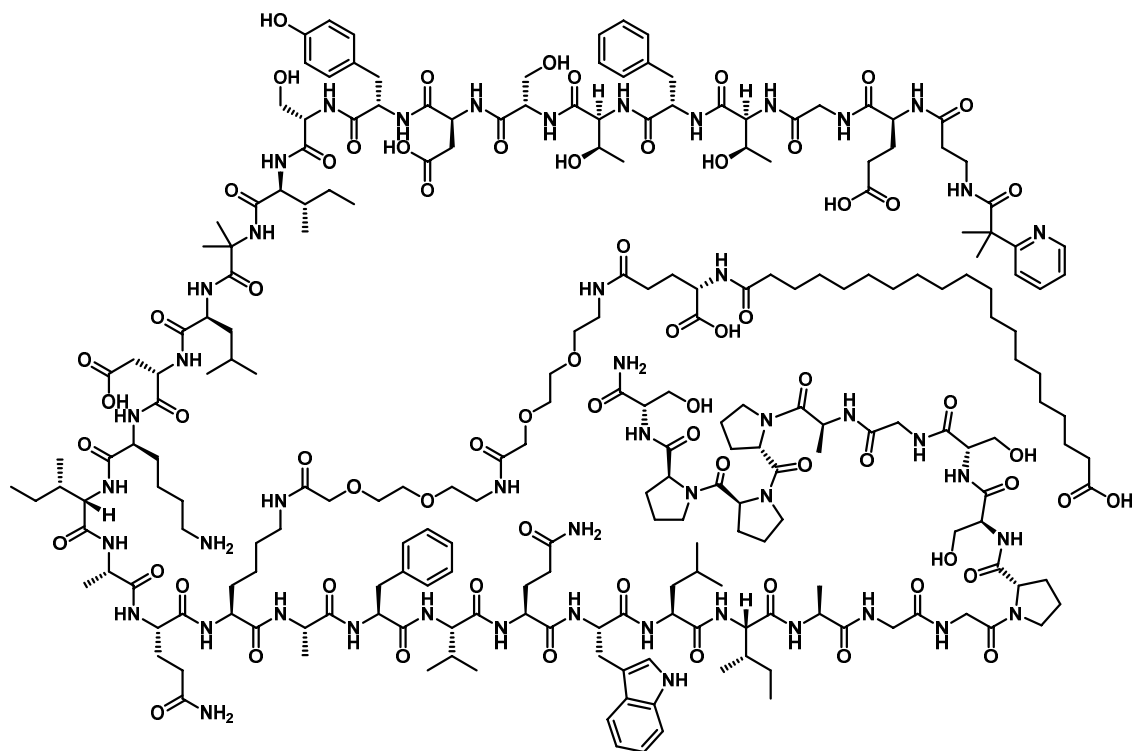
Compound 234,



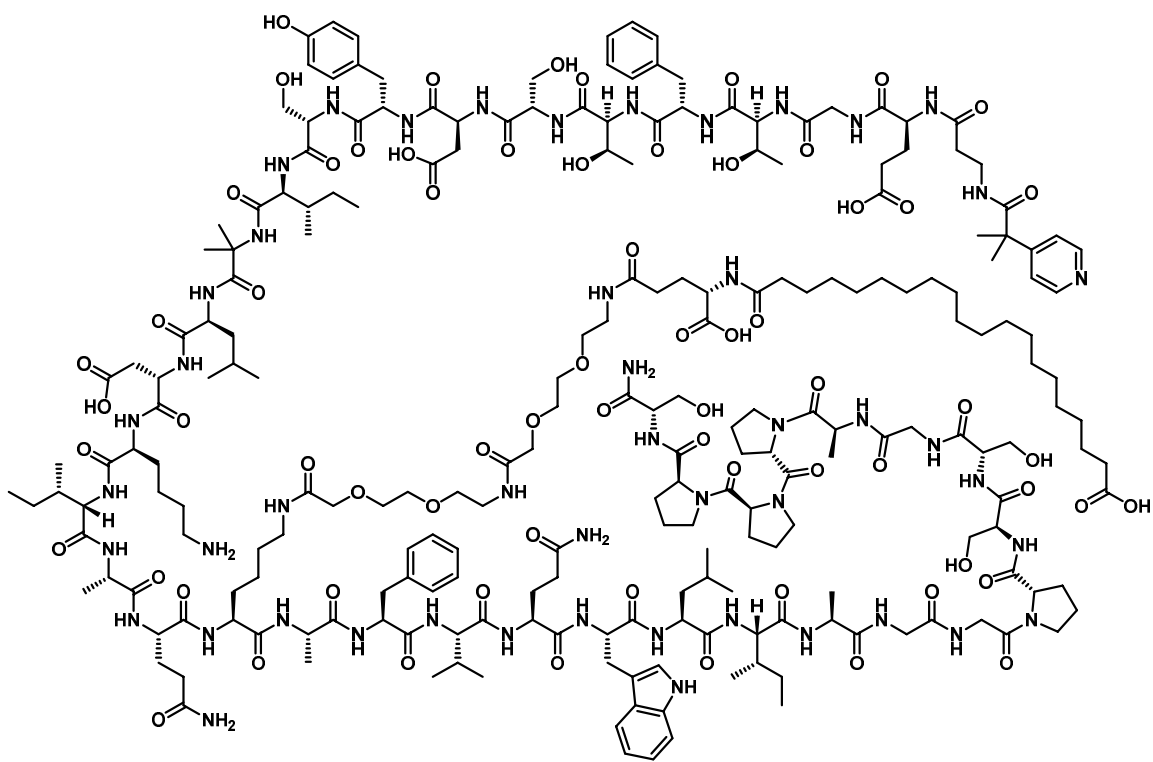
Compound 235,



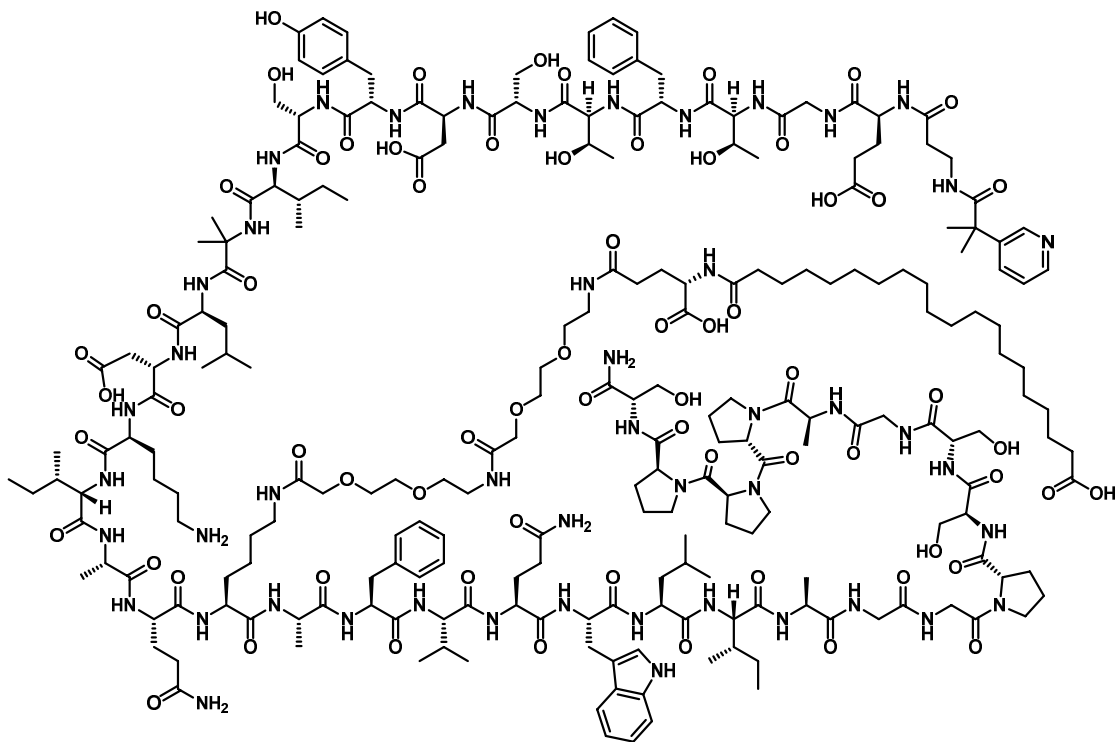
Compound 236,



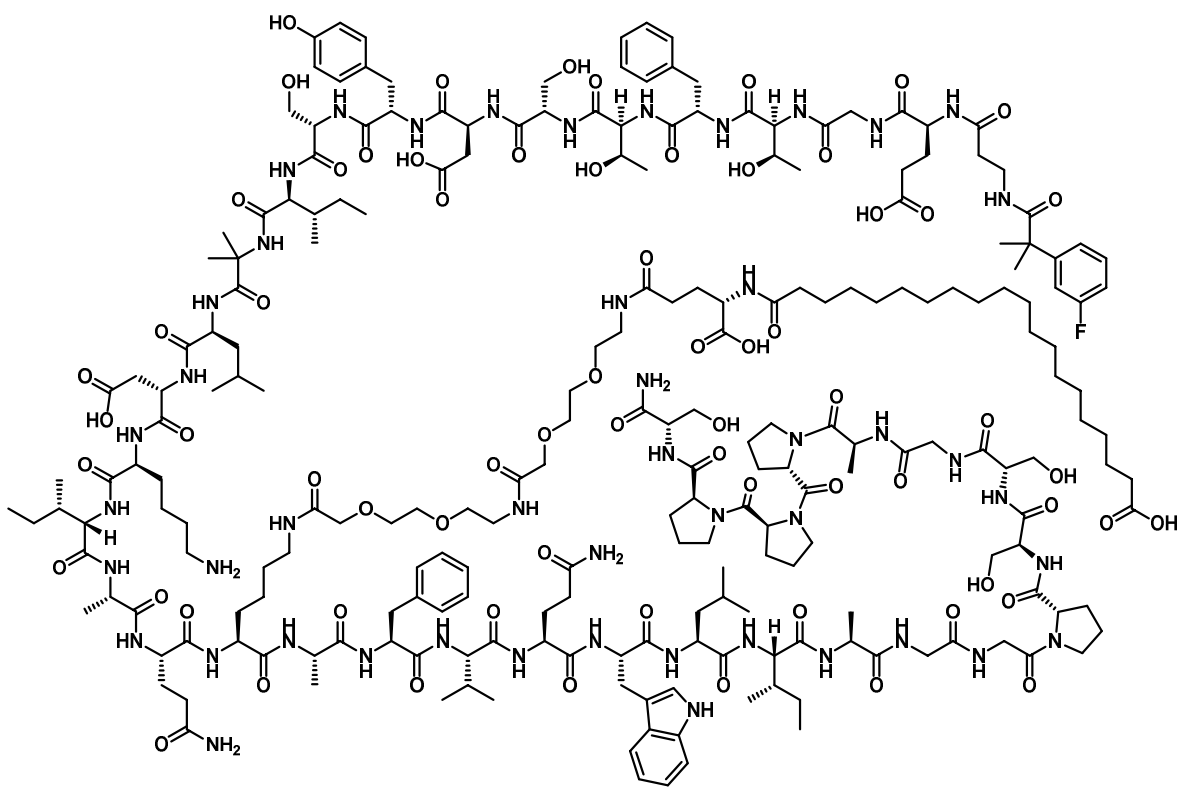
Compound 237,



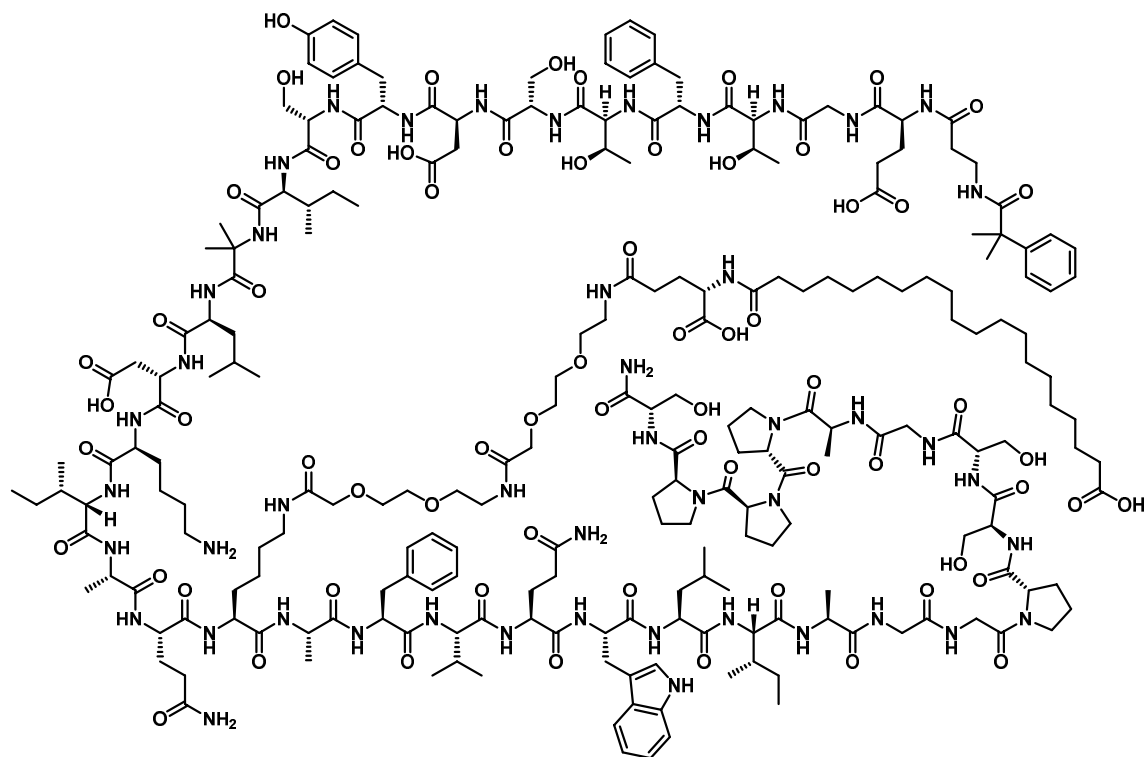
Compound 238,



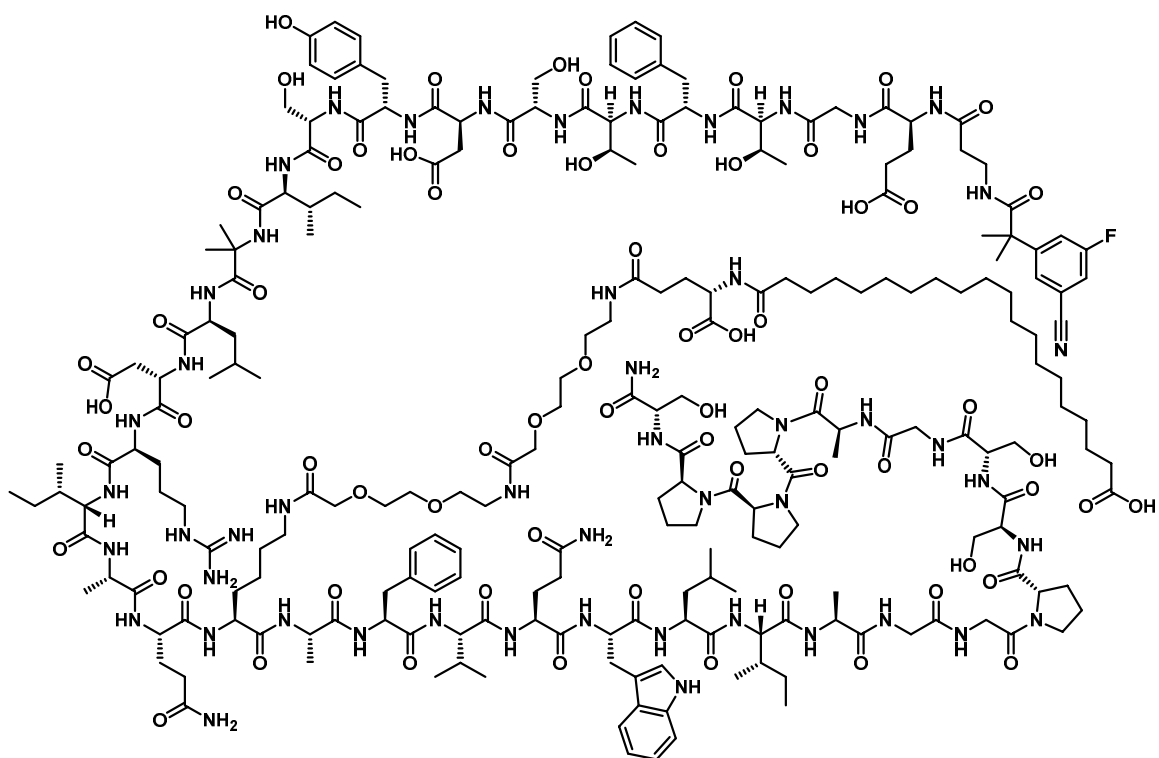
Compound 239,



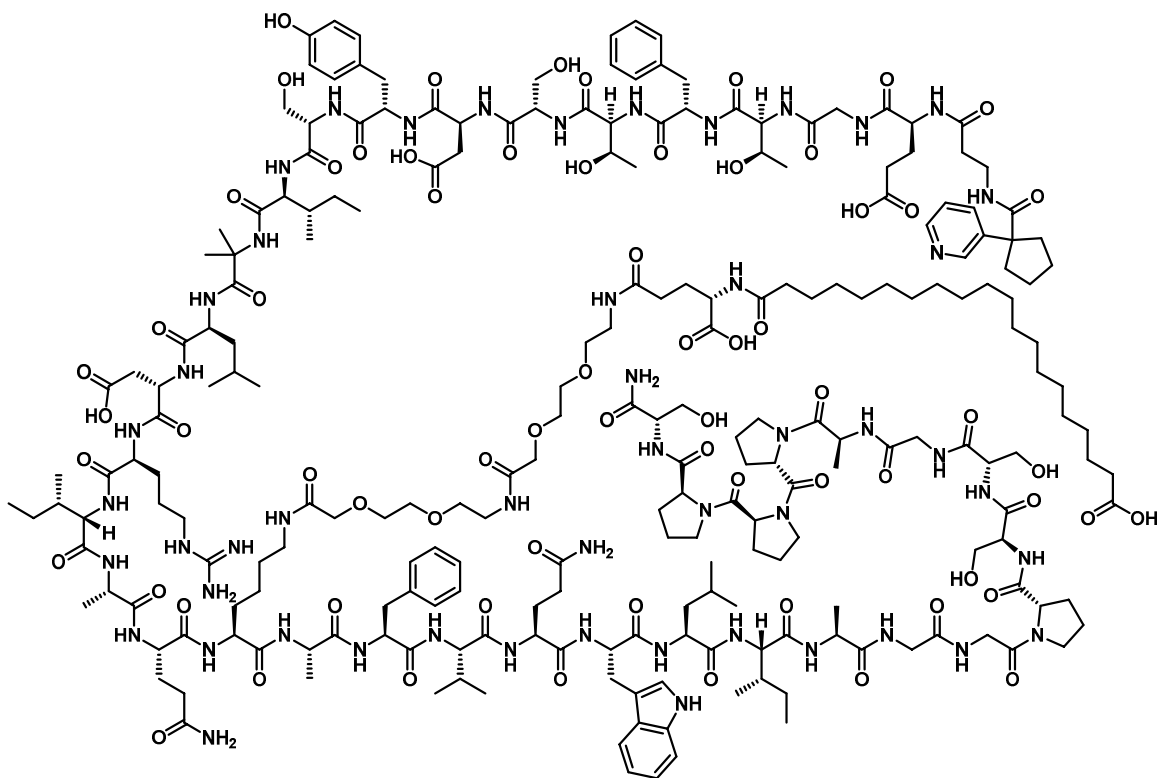
Compound 240,



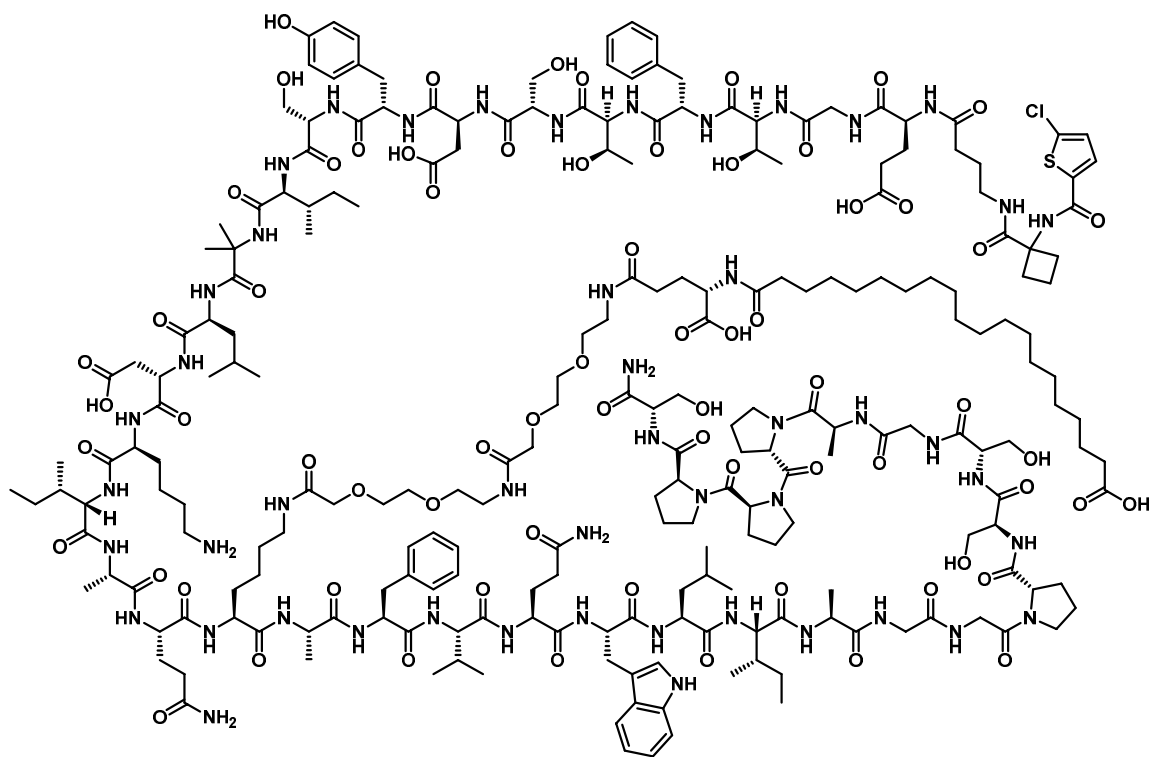
Compound 241,



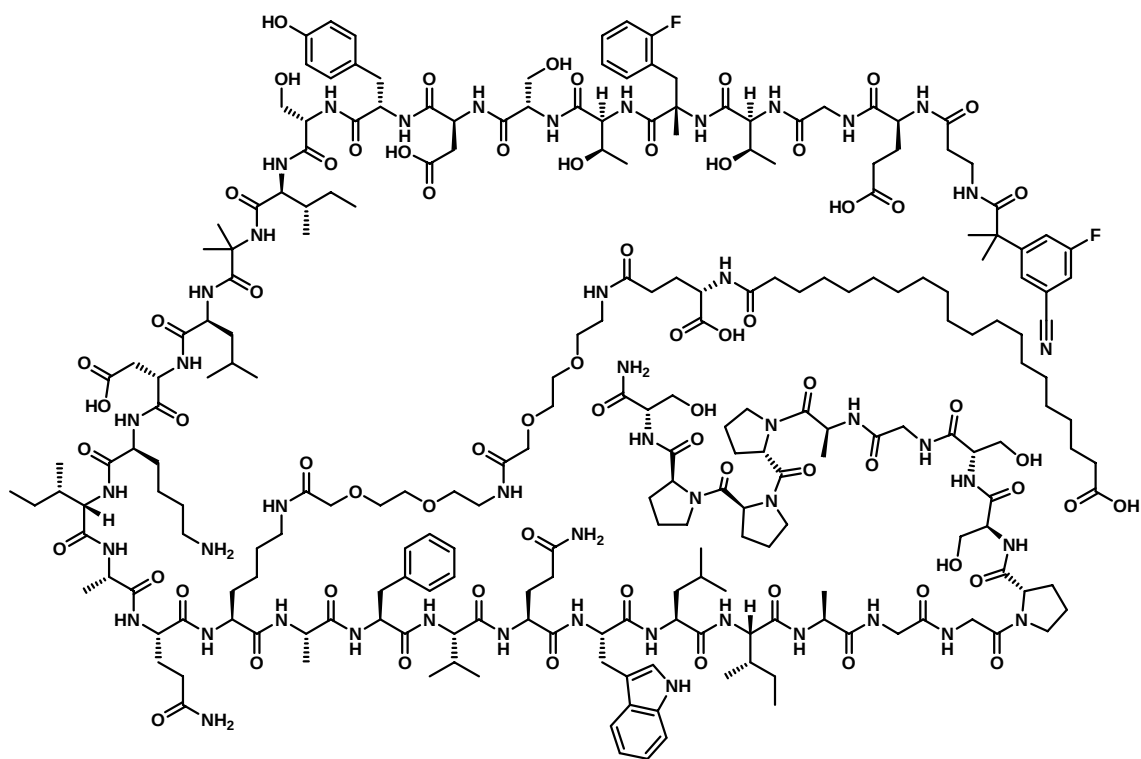
Compound 242,



Compound 243,

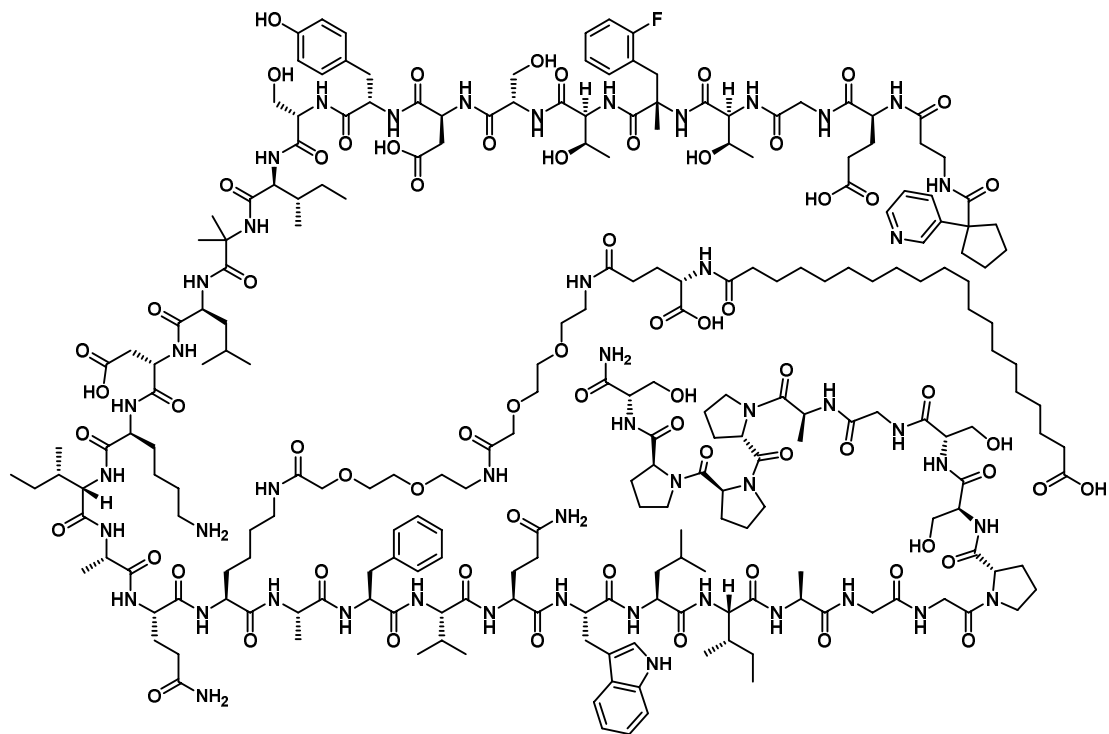


Compound 244,

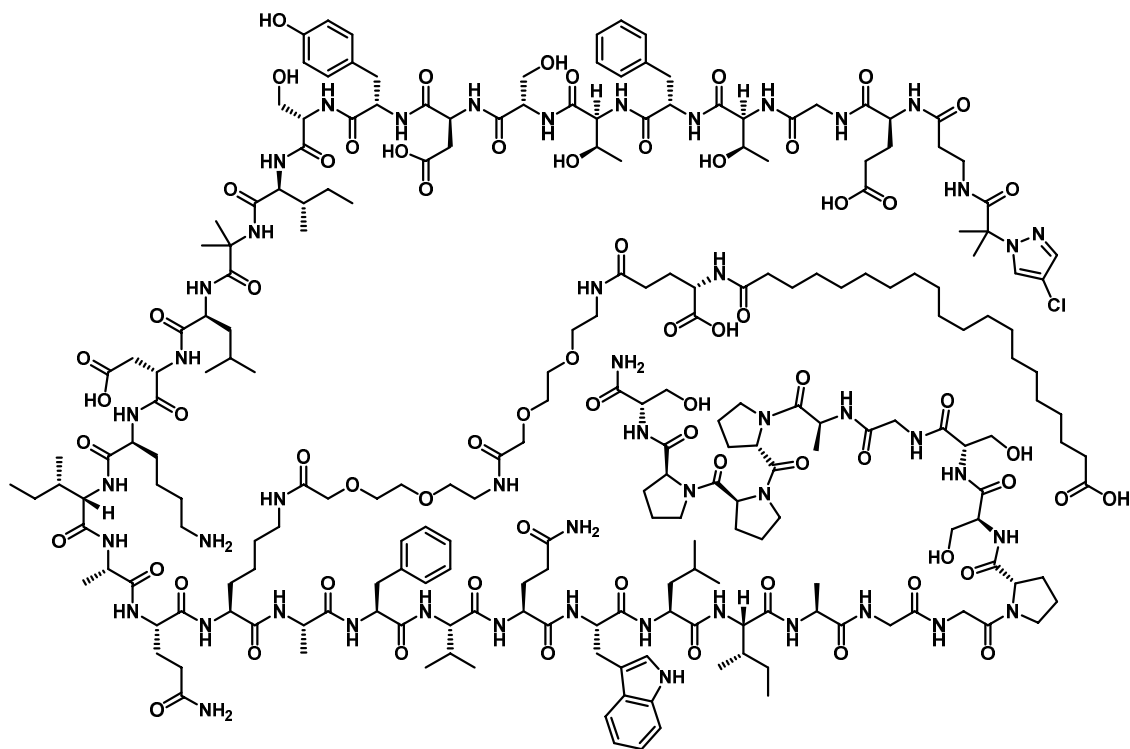


Compound 245,

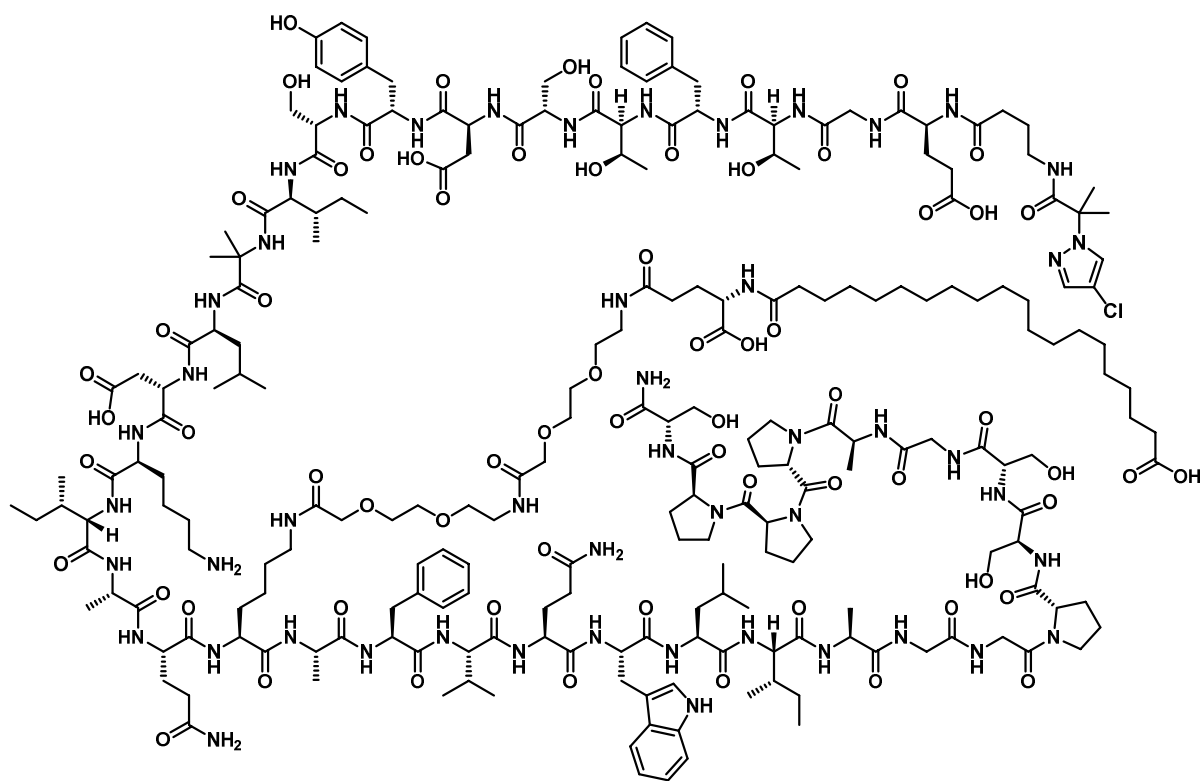
5



Compound 246,



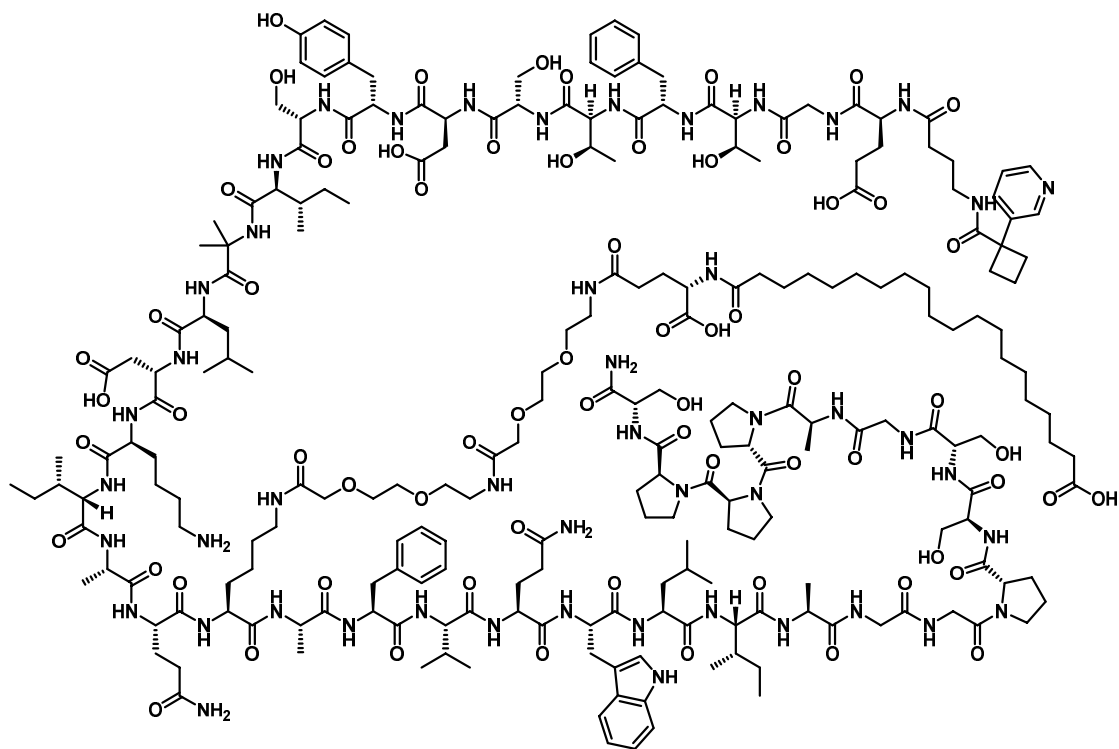
Compound 247,



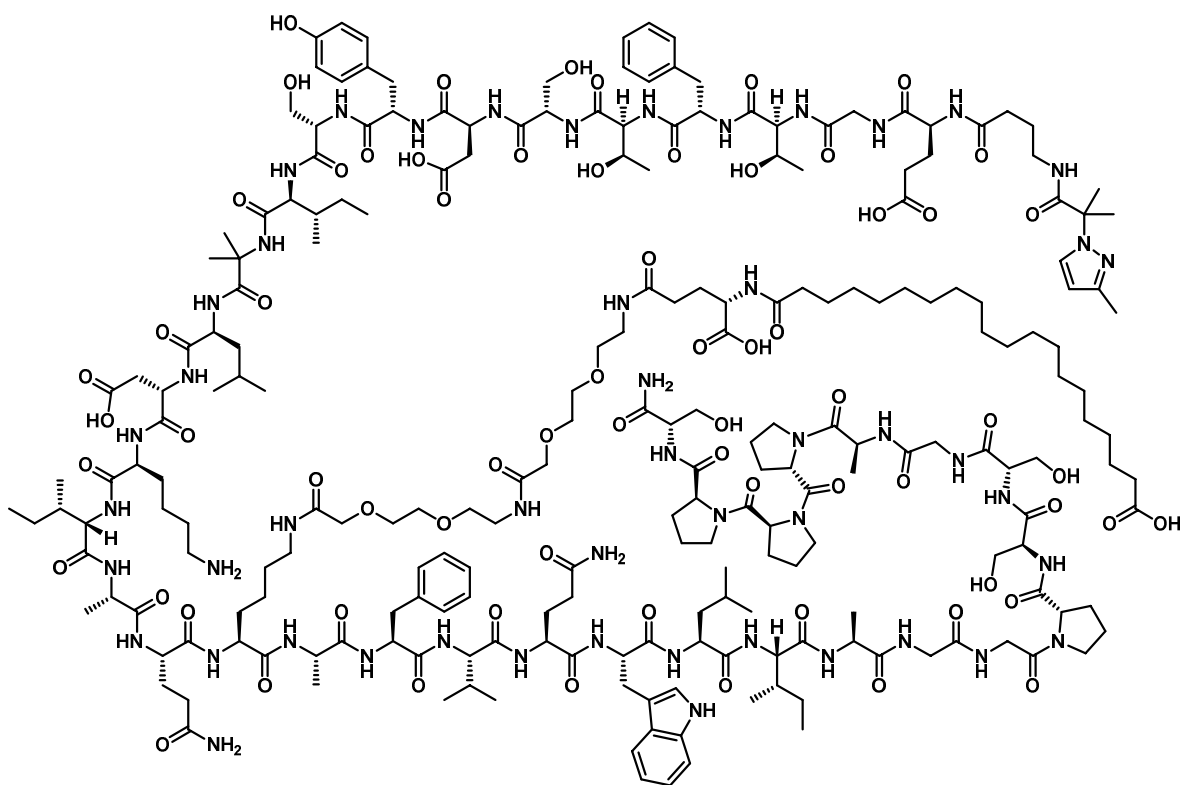
Compound 248,

[illegible]

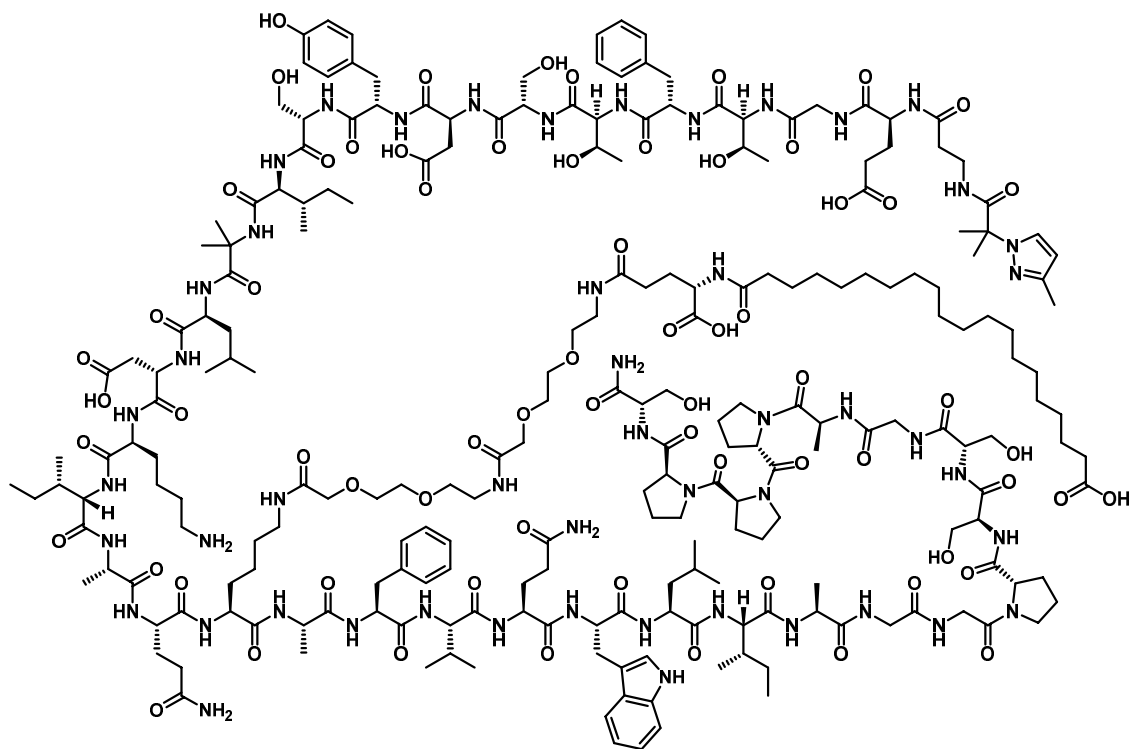
Compound 250,



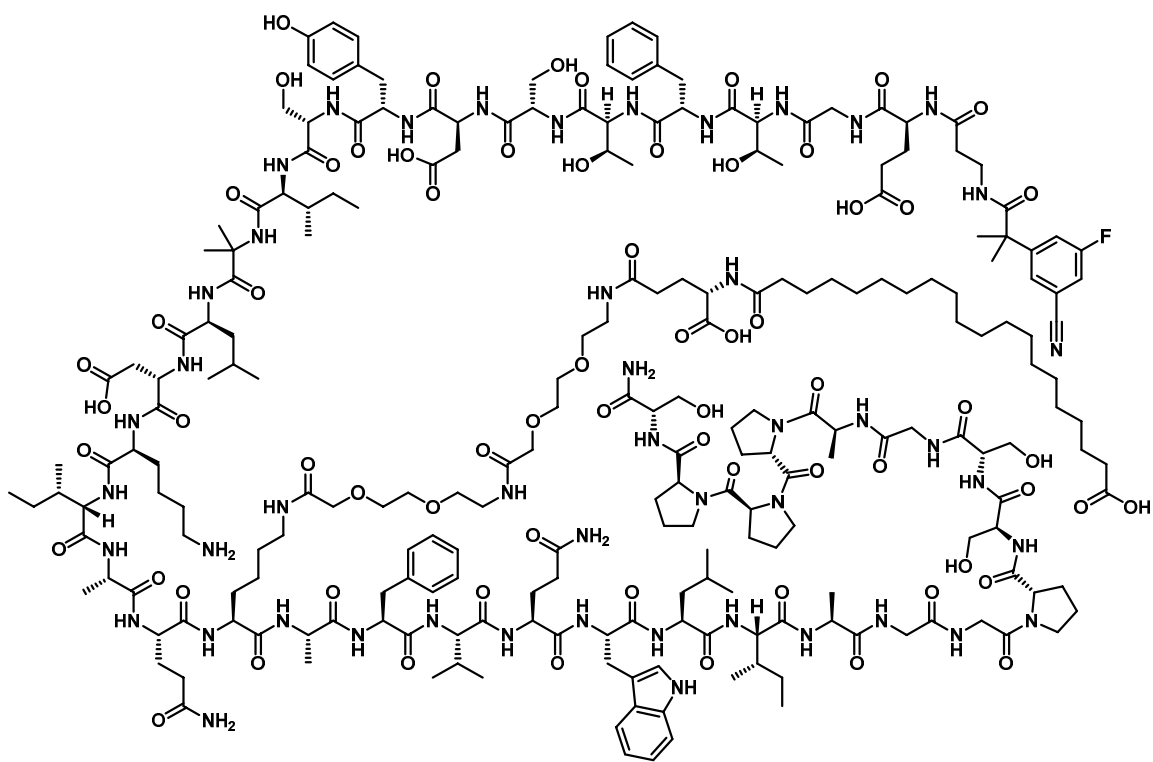
Compound 251,



Compound 252,



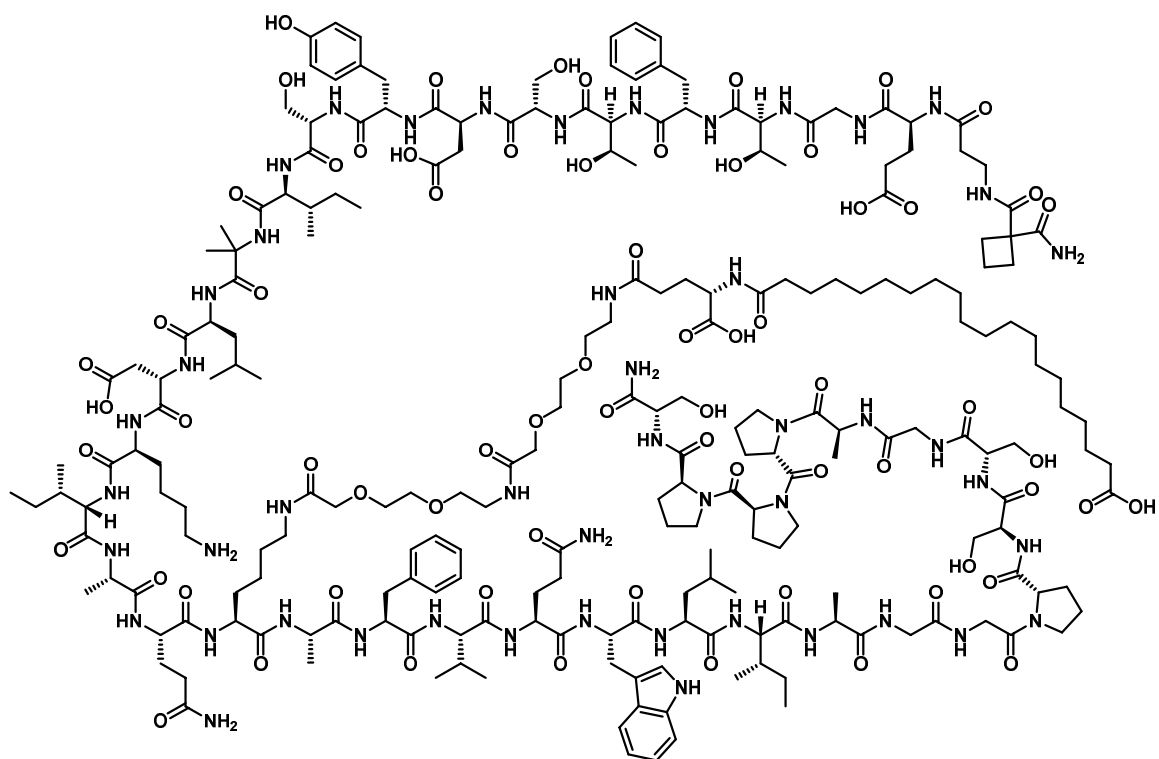
Compound 253,



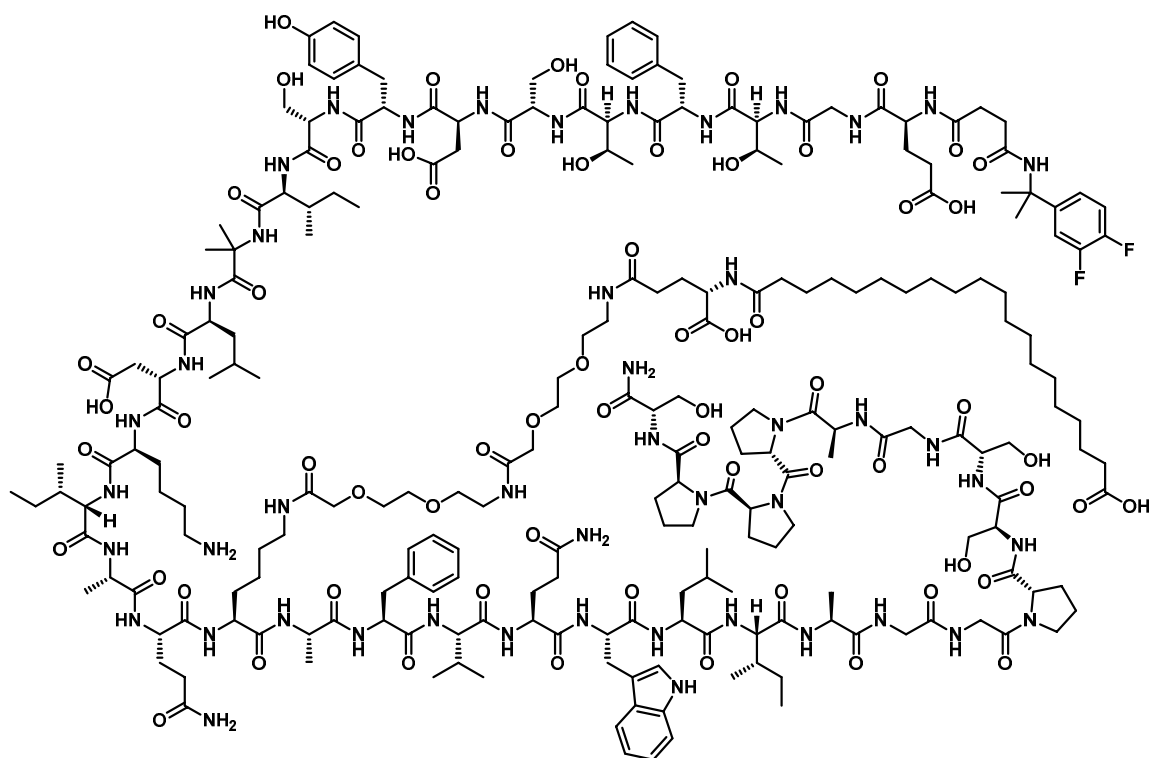
Compound 254,

[illegible]

Compound 256,

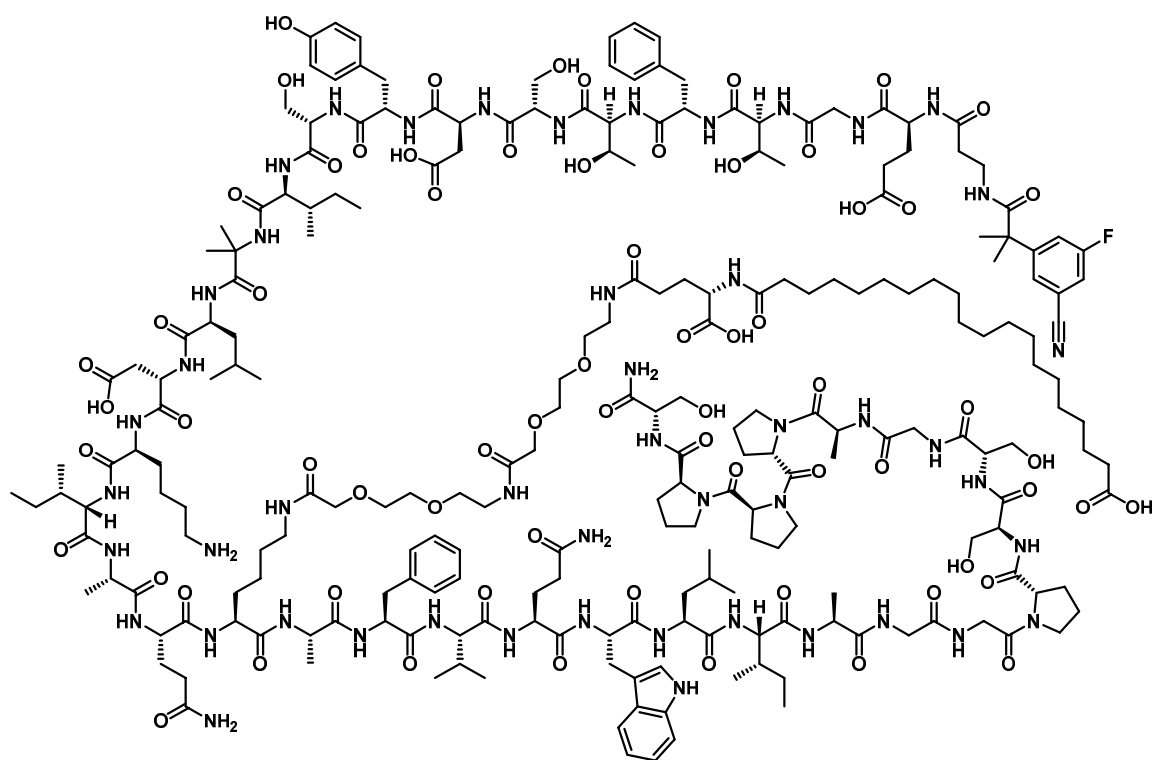


Compound 257, and



Compound 280.

4. The compound or pharmaceutically acceptable salt of claim 3, wherein the compound is:



5

Compound 254.

5. The compound of any one of claims 1-4.
- 10 6. The pharmaceutically acceptable salt of any one of claims 1-4.
7. A pharmaceutical composition comprising the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6 and one or more pharmaceutically acceptable excipients.
- 15 8. A method of modulating GLP-1R or GIPR activity, comprising contacting GLP-1R or GIPR with the compound or pharmaceutically acceptable salt thereof of any one of claims 1-6 or the pharmaceutical composition of claim 7, wherein the method is carried out *in vitro*.
9. The method of claim 8, wherein the method agonizes GLP-1R and/or GIPR.

10. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1-6 or the pharmaceutical composition of claim 7 in the manufacture of a medicament for improving glycemic control in a subject with type 2 diabetes mellitus, wherein the medicament is to be subcutaneously administered to the subject in need thereof.
11. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1-6 or the pharmaceutical composition of claim 7 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.
12. The use of claim 10 or 11, wherein the subject has one or more comorbidities, optionally pre-diabetes, hypertension, or dyslipidemia.
13. The use of claim 11 or 12, wherein the subject has type 2 diabetes mellitus.
14. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1-6 or the pharmaceutical composition of claim 7 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.
15. The use of claim 14, wherein the diabetes is type 2 diabetes mellitus.
16. The use of any one of claims 10-15, wherein the medicament is to be administered to the subject in combination with a diet therapy or an exercise therapy.
17. Use of the compound or pharmaceutically acceptable salt thereof of any one of claims 1-6 or the pharmaceutical composition of claim 7 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
5 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.

10

18. The use of any one of claims 10-17, wherein the subject is a human.