

(IAA)

wherein:

ring A is:

(i) a saturated or unsaturated monocyclic ring that includes 3-8 ring atoms (inclusive of G and the nitrogen atom labelled N*); or

(ii) a saturated or unsaturated bicyclic or tricyclic ring that includes 6-14 ring atoms (inclusive of G and the nitrogen atom labelled N*), wherein:

- G is C(O), S(O), or SO_2; and
- the dotted, circular line connecting G and N* is a divalent group that includes 1-6 ring atoms; wherein:

(a) 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(R^a), O, S, and SO_2; and

(b) 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(1) when ring A is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(2) when ring A is a bicyclic or tricyclic ring, then (A) or (B) applies:

(A) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, CR^b, and are fused to a second ring that is selected from the group consisting of:

(a) C_{6-10} aryl optionally substituted with 1-5 independently selected R^c;

(b) heteroaryl including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, $N(R^a)$, O, and S, wherein the heteroaryl is optionally substituted with 1-3 independently selected R^c;

(c) C_{3-10} cycloalkyl optionally substituted with 1-4 independently selected R^d;

(d) heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of $N(R^a)$, O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d; or

(B) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(a) C_{3-10} cycloalkyl optionally substituted with 1-4 independently selected R^d;

(b) heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of $N(R^a)$, O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d;

L is:

(i) $-(CH_2)_m-X^1-(CH_2)_n-X^2-(CH_2)_p-$, wherein m is 1-6; n is 0-2; and p is 0-8;

(ii) $-C(O)-(CH_2)_n-X^3-(CH_2)_p-$, wherein n is 0-2; and p is 0-8;

(iii) $-(CH_2)_q-$, wherein q is 1-10;

(iv) -C(O)-; or

(v) $-(CH_2)_m-X^1-(CH_2)_p-$, wherein m is 1-6; and p is 0-8;

X^1 is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of R' is independently selected from the group consisting of: H and C_{1-4} alkyl;

X^2 is:

(i) -O-;

(ii) -S-;

(iii) $-S(O)_t-$, wherein t is 1 or 2;

(iv) $-C(Q^1)(Q^2)-$, wherein each of Q^1 and Q^2 is independently selected from the group consisting of H and C_{1-4} alkyl; or Q^1 and Q^2, together with the carbon atom to

which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with 1-4 independently selected R^d and optionally fused to phenyl;

(v) C_{6-10} arylene optionally substituted with 1-5 independently selected R^c;

(vi) heteroarylene including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, N(R^a), O, and S; and which is optionally substituted with 1-5 independently selected R^c;

(vii) C_{3-10} cycloalkylene optionally substituted with 1-4 independently selected R^d;

(viii) heterocycloalkylene including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of N(R^a), O, and S; and which is optionally substituted with 1-5 independently selected R^d;

(ix) C_2-C_4 alkenylene optionally substituted with 1-2 R^e; or

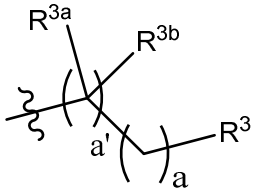
(x) C_2-C_4 alkynylene optionally substituted with 1-2 R^e;

X^3 is: -O-; -S-; or -$S(O)_t$-, wherein t is 1 or 2;

each of R^1, R^2, and R^4 is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$R^{2'}$ is as defined according to (AA) below:

(AA)

$R^{2'}$ is 

, wherein:

R^3 is -C(O)OH, -C(O)OR^{31}, -$CH(C(O)OH)_2$ or a carboxylic acid isostere;

a is 0-5;

a' is 0 or 1; and

each of R^{3a} and R^{3b} is independently H or C_{1-3} alkyl;

R^{31} is:

(i) C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e;

(ii) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with 1-4 independently selected R^d;

(iii) -(C_{0-3} alkylene)-heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of N(R^a), O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d;

(iv) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with 1-5 independently selected R^c; or

(v) -(C_{0-3} alkylene)-heteroaryl including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, N(R^a), O, and S, wherein the heteroaryl is optionally substituted with 1-3 independently selected R^c;

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

each occurrence of R^b is independently selected from the group consisting of: R^{31}; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of R^c is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; $-NO_2$; N_3; $-N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of R^d is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e; C_{1-4} haloalkyl; –OH; -F; Cl; $-N(R^a)(R'')$; oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of R^e is independently selected from the group consisting of: –OH; - $-N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

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

$-N(R^4)W$ is a peptide having formula (XIV):

GTF(Xaa4)SD(Xaa7)S(Xaa9)(Xaa10)(Xaa11)(Xaa12)(Xaa13)QA(Xaa16)(Xaa17)(Xaa18)F-(Xaa20)(Xaa21)WL(Xaa24)(Xaa25)GGPSSGAPPPS-R^5 (SEQ ID NO: 2);

wherein:

Xaa4 is T or I;

Xaa7 is Y, V, or L;

Xaa9 is I or S;

Xaa10 is Y, Q, or A;

Xaa11 is L, M, or L*;

Xaa12 is D or E;

Xaa13 is K, G, or E;

Xaa16 is A or V;

Xaa17 is (Aib) or K;

Xaa18 is E or L;

Xaa20 is V or I;

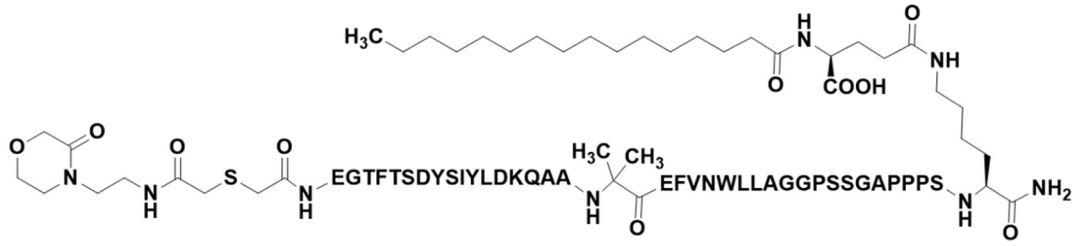
Xaa21 is N, A, or E;

Xaa24 is L or V; and

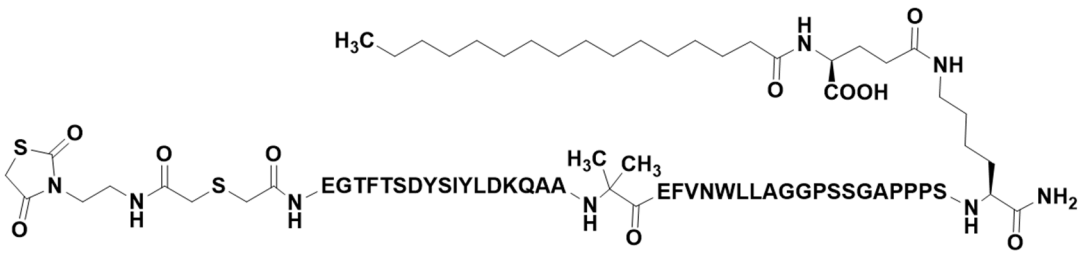
Xaa25 is A or K;

wherein R^5 is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with 1-2 modifying groups.

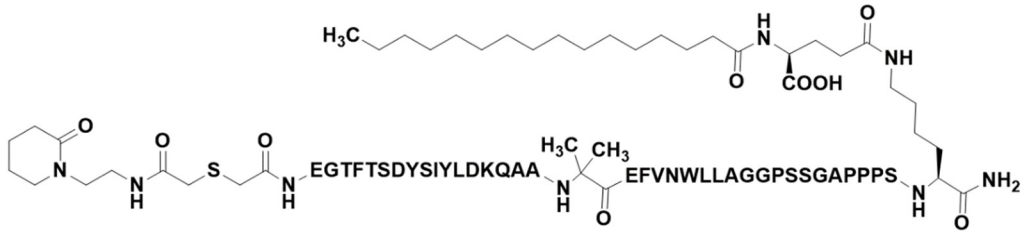
In one aspect, the present disclosure refers to a compound selected from the group consisting of:



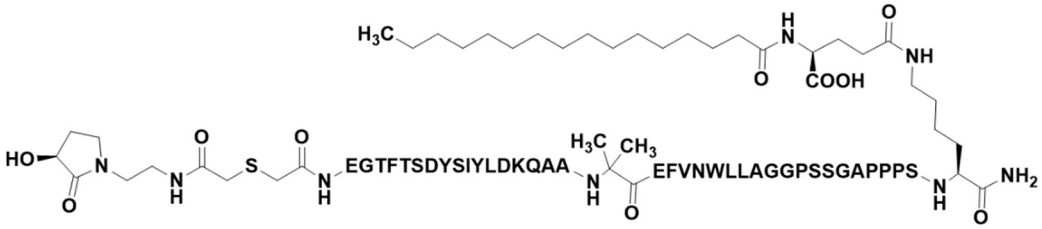
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H3C
COOH
NH
NH2
EGTFTSDYSIYLDKQAA
EFVNWLLAGGPSSGAPPPS

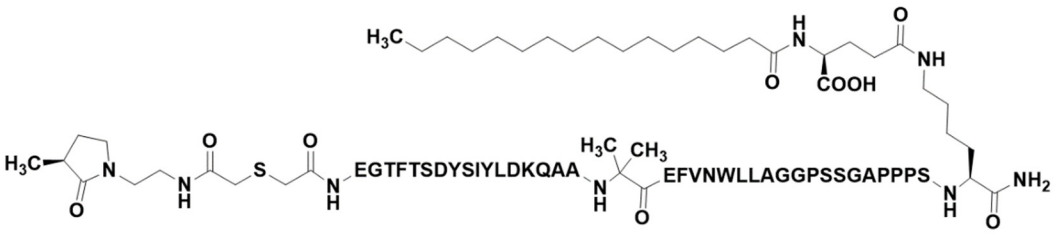
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H3C
COOH
NH
NH2
EGTFTSDYSIYLDKQAA
EFVNWLLAGGPSSGAPPPS

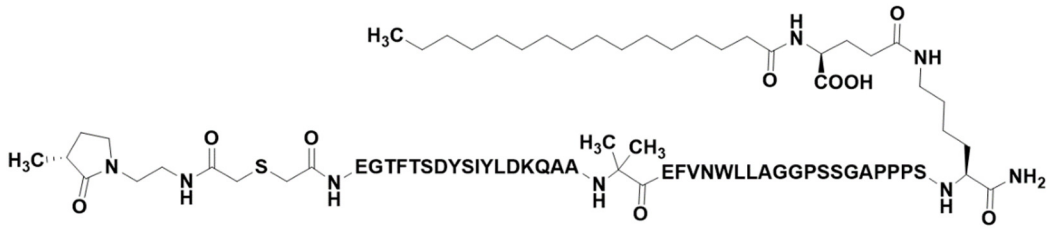
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NH2
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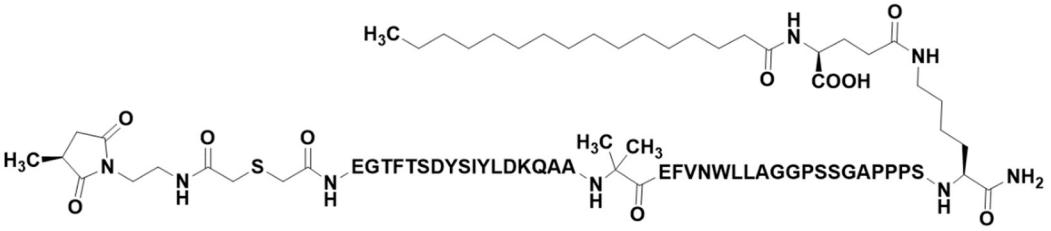
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H3C
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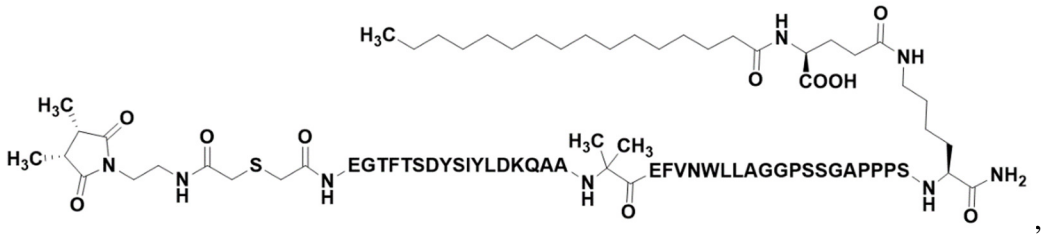
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or a pharmaceutically acceptable salt thereof.

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 as described 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). 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, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for modulating glucagon-like peptide-1 receptor (GLP-1R) and/or gastric inhibitory polypeptide receptor (GIPR) activity.

In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for increasing insulin levels in a human subject in need of such increasing.

In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for decreasing glucose levels in a human subject in need of such decreasing.

In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating diabetes, NASH, obesity, fatty liver disease, or steatohepatitis in a human subject in need thereof.

In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating type 2 diabetes mellitus in a human subject in need thereof.

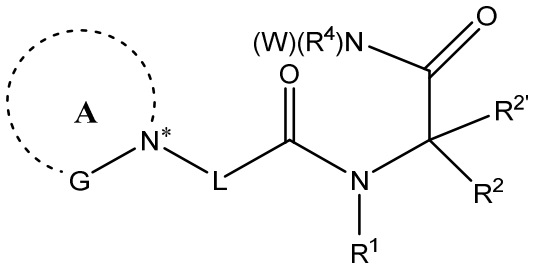
In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating obesity in a human subject in need thereof.

In one aspect, the present disclosure refers to use of the compound, or pharmaceutically acceptable salt thereof, as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating metabolic syndrome, diabetes, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, non-alcoholic steatohepatitis (NASH), fatty liver disease, steatohepatitis, brain insulin resistance, mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, dementia, 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, neuropathy, Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis (ALS), glaucoma, Creutzfeld-Jakob Disease, bovine spongiform encephalopathy, cognitive dysfunction, chronic wasting syndrome, osteoporosis, post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodistrophy in liver disease, coronary artery disease, peripheral artery disease, cerebrovascular disease, hypertension, retinopathy, nephropathy, bone fracture, or altered bone metabolism caused by renal failure, haemodialysis, bone fracture, bone surgery, aging, or pregnancy.

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).

WHAT IS CLAIMED IS:

1. A compound having formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA)

wherein:

ring A is:

(i) a saturated or unsaturated monocyclic ring that includes 3-8 ring atoms (inclusive of G and the nitrogen atom labelled N*); or

(ii) a saturated or unsaturated bicyclic or tricyclic ring that includes 6-14 ring atoms (inclusive of G and the nitrogen atom labelled N*), wherein:

- G is C(O), S(O), or SO_2; and
- the dotted, circular line connecting G and N* is a divalent group that includes 1-6 ring atoms; wherein:

(a) 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(R^a), O, S, and SO_2; and

(b) 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; wherein:

(1) when ring A is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(2) when ring A is a bicyclic or tricyclic ring, then (A) or (B) applies:

(A) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, CR^b, and are fused to a second ring that is selected from the group consisting of:

(a) C_{6-10} aryl optionally substituted with 1-5 independently selected R^c;

(b) heteroaryl including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, $N(R^a)$, O, and S, wherein the heteroaryl is optionally substituted with 1-3 independently selected R^c;

(c) C_{3-10} cycloalkyl optionally substituted with 1-4 independently selected R^d;

(d) heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of $N(R^a)$, O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d; or

(B) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(a) C_{3-10} cycloalkyl optionally substituted with 1-4 independently selected R^d;

(b) heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of $N(R^a)$, O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d;

L is:

(i) $-(CH_2)_m-X^1-(CH_2)_n-X^2-(CH_2)_p-$, wherein m is 1-6; n is 0-2; and p is 0-8;

(ii) $-C(O)-(CH_2)_n-X^3-(CH_2)_p-$, wherein n is 0-2; and p is 0-8;

(iii) -$(CH_2)_q$-, wherein q is 1-10;

(iv) -C(O)-; or

(v) -$(CH_2)_m$-X^1 -$(CH_2)_p$-, wherein m is 1-6; and p is 0-8;

X^1 is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of R' is independently selected from the group consisting of: H and C_{1-4} alkyl;

X^2 is:

(i) -O-;

(ii) -S-;

(iii) -$S(O)_t$-, wherein t is 1 or 2;

(iv) -$C(Q^1)(Q^2)$-, wherein each of Q^1 and Q^2 is independently selected from the group consisting of H and C_{1-4} alkyl; or Q^1 and Q^2, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with 1-4 independently selected R^d and optionally fused to phenyl;

(v) C_{6-10} arylene optionally substituted with 1-5 independently selected R^c;

(vi) heteroarylene including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, N(R^a), O, and S; and which is optionally substituted with 1-5 independently selected R^c;

(vii) C_{3-10} cycloalkylene optionally substituted with 1-4 independently selected R^d;

(viii) heterocycloalkylene including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of N(R^a), O, and S; and which is optionally substituted with 1-5 independently selected R^d;

(ix) C_2-C_4 alkenylene optionally substituted with 1-2 R^e; or

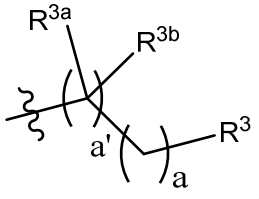
(x) C_2-C_4 alkynylene optionally substituted with 1-2 R^e;

X^3 is: -O-; -S-; or -$S(O)_t$-, wherein t is 1 or 2;

each of R^1, R^2, and R^4 is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$R^{2'}$ is as defined according to (AA) below:

(AA)

$R^{2'}$ is 

, wherein:

R^3 is -C(O)OH, -$C(O)OR^{31}$, -$CH(C(O)OH)_2$ or a carboxylic acid isostere;

a is 0-5;

a' is 0 or 1; and

each of R^{3a} and R^{3b} is independently H or C_{1-3} alkyl;

R^{31} is:

(i) C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e;

(ii) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with 1-4 independently selected R^d;

(iii) -(C_{0-3} alkylene)-heterocyclyl including 3-10 ring atoms, wherein 1-3 ring atoms are each independently selected from the group consisting of N(R^a), O, and S, wherein the heterocyclyl is optionally substituted with 1-4 independently selected R^d;

(iv) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with 1-5 independently selected R^c; or

(v) -(C_{0-3} alkylene)-heteroaryl including 5-10 ring atoms, wherein 1-4 ring atoms are each independently selected from the group consisting of N, N(R^a), O, and S, wherein the heteroaryl is optionally substituted with 1-3 independently selected R^c;

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

each occurrence of R^b is independently selected from the group consisting of: R^{31}; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of R^c is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of R^d is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-2 independently selected R^e; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of R^e is independently selected from the group consisting of: –OH; - -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

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

-N(R^4)W is a peptide having formula (XIV):

GTF(Xaa4)SD(Xaa7)S(Xaa9)(Xaa10)(Xaa11)(Xaa12)(Xaa13)QA(Xaa16)(Xaa17)(Xaa18)F-(Xaa20)(Xaa21)WL(Xaa24)(Xaa25)GGPSSGAPPPS-R^5 (SEQ ID NO: 2);

wherein:

Xaa4 is T or I;

Xaa7 is Y, V, or L;

Xaa9 is I or S;

Xaa10 is Y, Q, or A;

Xaa11 is L, M, or L*;

Xaa12 is D or E;

Xaa13 is K, G, or E;

Xaa16 is A or V;

Xaa17 is (Aib) or K;

Xaa18 is E or L;

Xaa20 is V or I;

Xaa21 is N, A, or E;

Xaa24 is L or V; and

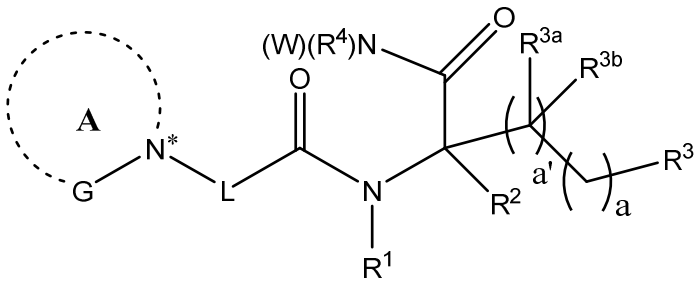
Xaa25 is A or K;

wherein R^5 is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with 1-2 modifying groups.

2. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein Xaa17 is Aib.

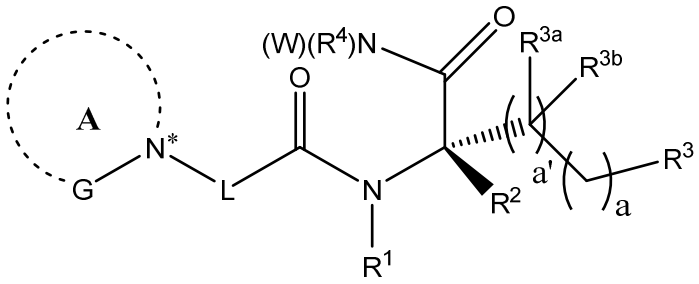
3. The compound, or pharmaceutically acceptable salt thereof, of claim 1 or 2, wherein —N(R^4)W has formula (XIV-B): GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPS-R^5 (SEQ ID NO: 4).

4. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-3, wherein the compound has formula (IA), or a pharmaceutically acceptable salt thereof:



(IA).

5. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-3, wherein the compound has formula (IIA):



(IIA), and wherein

R^1, R^2, R^{3a} and R^{3b} are H,

a' and a are each 1, and

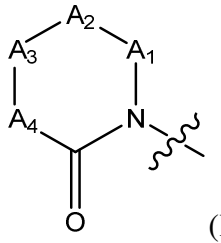
R^3 is -C(O)OH.

6. The compound of any one of claims 1-5, wherein G is C(O).

7. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-5, wherein G is S(O) or SO_2.

8. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-7, wherein ring A is a saturated or unsaturated monocyclic ring that includes 3-8 ring atoms.

9. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein ring A has the following formula (III):



(III) wherein:

A_1 is a bond, A^{1A}-A^{1B}, C(O), CH_2, CHR^b, or $C(R^b)_2$;

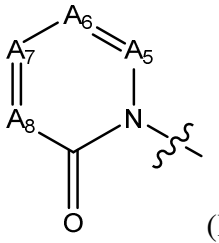
each of A^{1A} and A^{1B} is independently C(O), CH_2, CHR^b, or $C(R^b)_2$;

A_2 is C(O), CH_2, CHR^b, or $C(R^b)_2$;

A_3 is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; SO_2, or $N(R^a)$;

A_4 is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; or $N(R^a)$; provided that A_3 and A_4 cannot both be O; S; or $N(R^a)$; or a combination thereof.

10. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein ring A has formula (IV):



(IV), wherein:

each of A_6, and A_7 is independently selected from CH and CR^b; and

each of A_5 and A_8 is independently N, CH, or CR^b.

11. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-7, wherein ring A is a saturated or unsaturated bicyclic or tricyclic ring that includes 6-14 ring atoms.

12. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-11, wherein L has the formula $-(CH_2)_m-X^1-(CH_2)_n-X^2-(CH_2)_p-$.

13. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-12, wherein:

m is 2-6;

$n + p > 2$; and

X^2 is: -O-; -S-; $-S(O)_t-$, or CH_2.

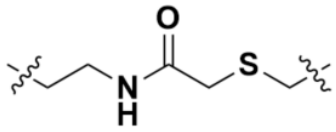
14. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-12, wherein:

m is 1;

$n + p \leq 2$; and

X^2 is: -O-; -S-; -$S(O)_t$-, or $C(Q^1)(Q^2)$.

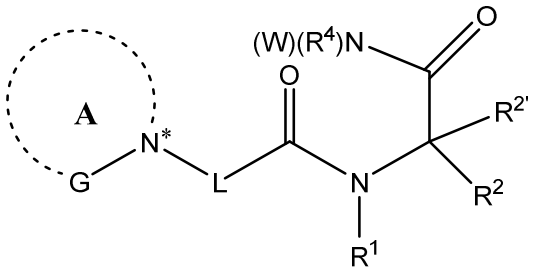
15. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-11, wherein L has the following structure:



.

16. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-11, wherein L has the formula -$C(O)$-$(CH_2)_n$-X^3-$(CH_2)_p$-.

17. A compound having formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA), wherein:

ring A is:

a saturated or unsaturated monocyclic ring that includes 3-8 ring atoms (inclusive of G and the nitrogen atom labelled N*), wherein:

- G is C(O); and
- the dotted, circular line connecting G and N* is a divalent group that includes 1-6 ring atoms; wherein:

(a) 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, O, and S; and

(b) 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

L is:

(i) $-(CH_2)_m-X^1-(CH_2)_n-X^2-(CH_2)_p-$, wherein m is 1-6; n is 0-2; and p is 0-8; or

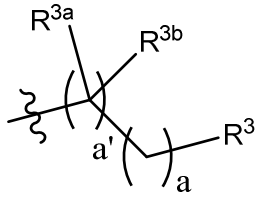
(ii) $-(CH_2)_m-X^1-(CH_2)_p-$, wherein m is 1-6; and p is 0-8;

X^1 is -N(R')C(O)- or -C(O)N(R')-; wherein each occurrence of R' is H;

X^2 is: -S-;

each of R^1, R^2, and R^4 is H;

$R^{2'}$ is



, wherein:

R^3 is -C(O)OH;

a is 0-5;

a' is 0 or 1; and

each of R^{3a} and R^{3b} is H;

each occurrence of R^b is independently selected from the group consisting of: C_{1-6} alkyl; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

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

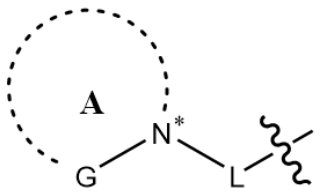
each occurrence of $R^{''}$, $R^{'''}$, and $R^{''''}$ is independently selected from the group consisting of: H and C_{1-6} alkyl; and

-N(R^4)W is a peptide having formula:

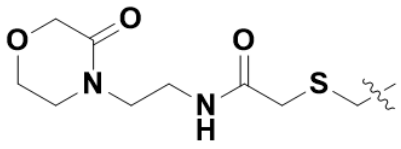
GTFTSDYSIYLDKQAA(Aib)EFVNWLLAGGPSSGAPPPS-R^5;

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

18. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

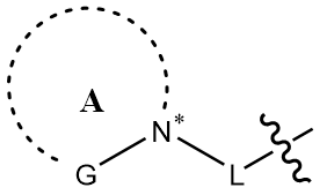


is represented by the structure

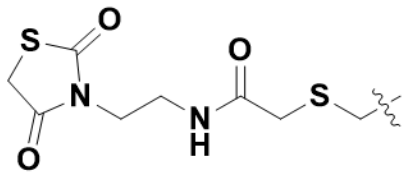


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19. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

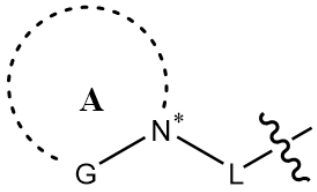


is represented by the structure

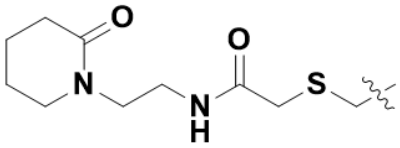


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20. The compound or pharmaceutically acceptable salt thereof, of claim 17, wherein

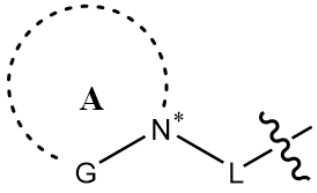


is represented by the structure

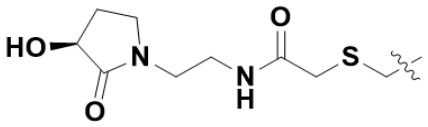


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21. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

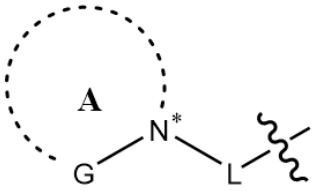


is represented by the structure

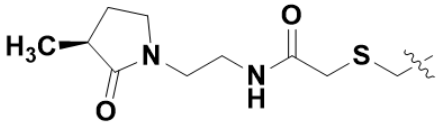


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22. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

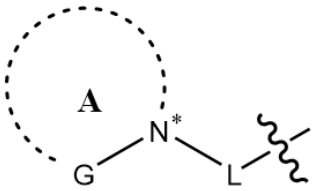


is represented by the structure

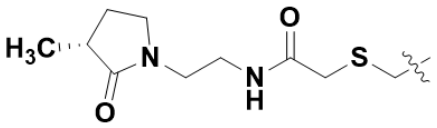


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23. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

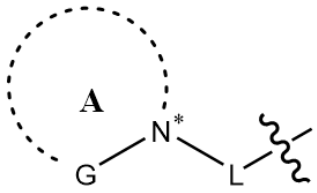


is represented by the structure

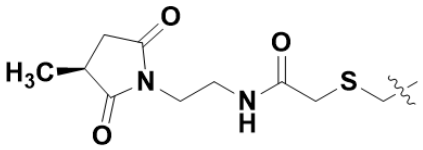


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24. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

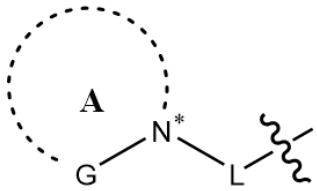


is represented by the structure

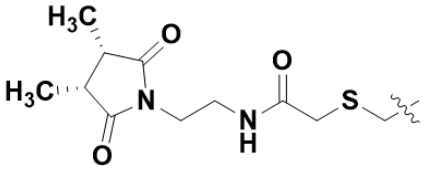


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25. The compound, or pharmaceutically acceptable salt thereof, of claim 17, wherein

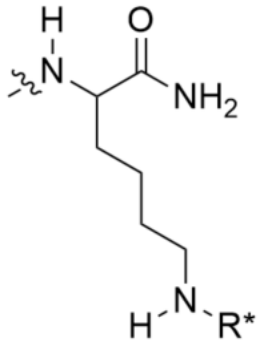


is represented by the structure



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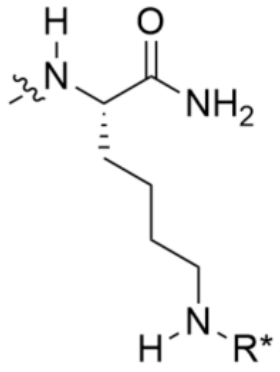
26. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-25, wherein R^5 has formula (XI):



(XI),

wherein R* is H or a modifying group.

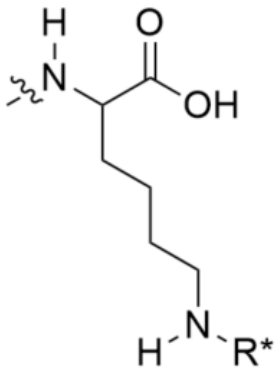
27. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-25, wherein R^5 has the formula:



, wherein R* is H or a modifying group.

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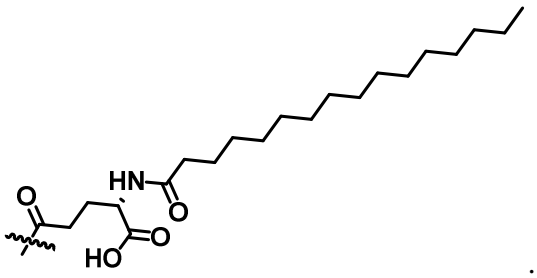
28. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-25, wherein R^5 has formula (XI-OH):



(XI-OH),

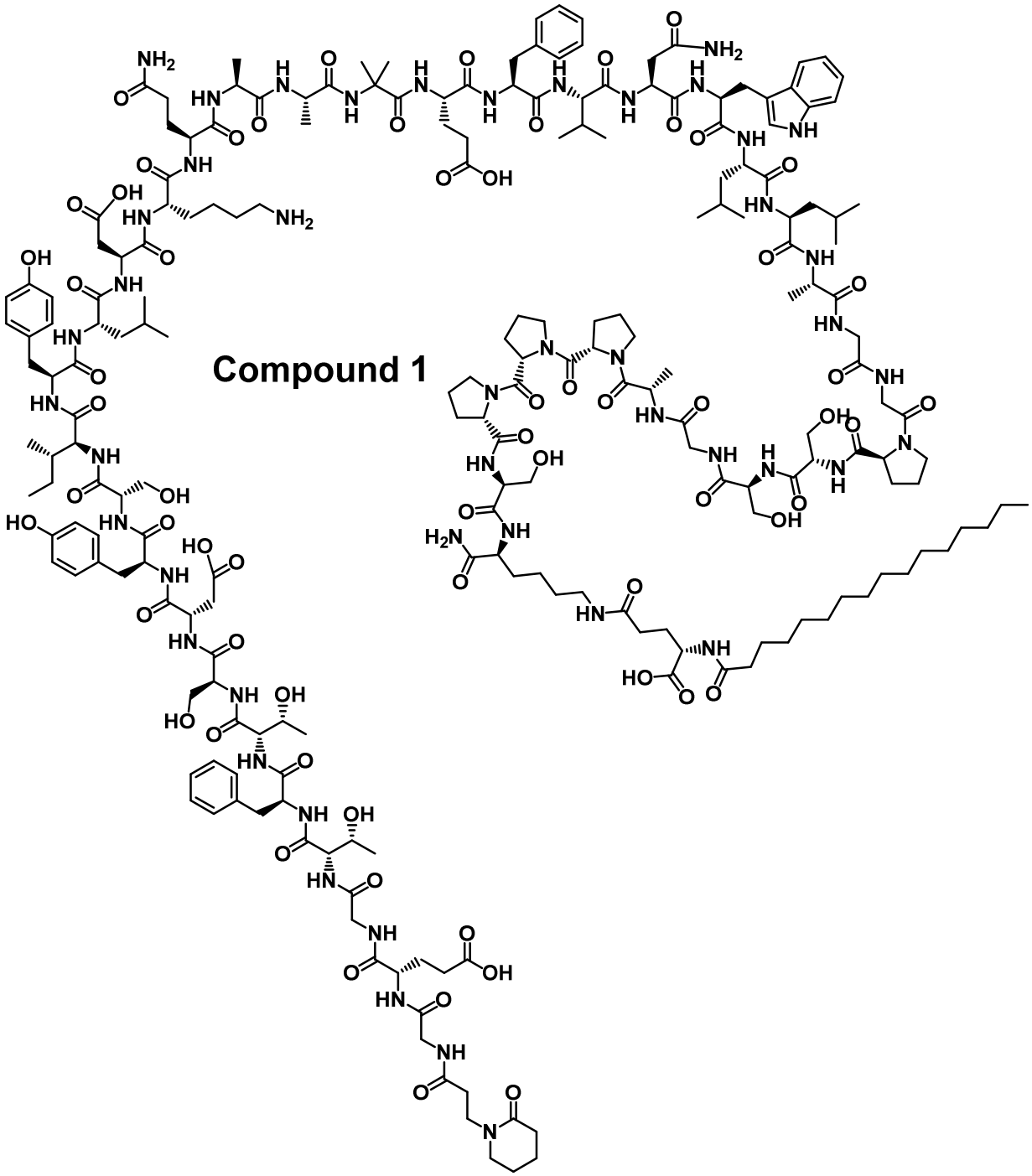
wherein R* is H or a modifying group.

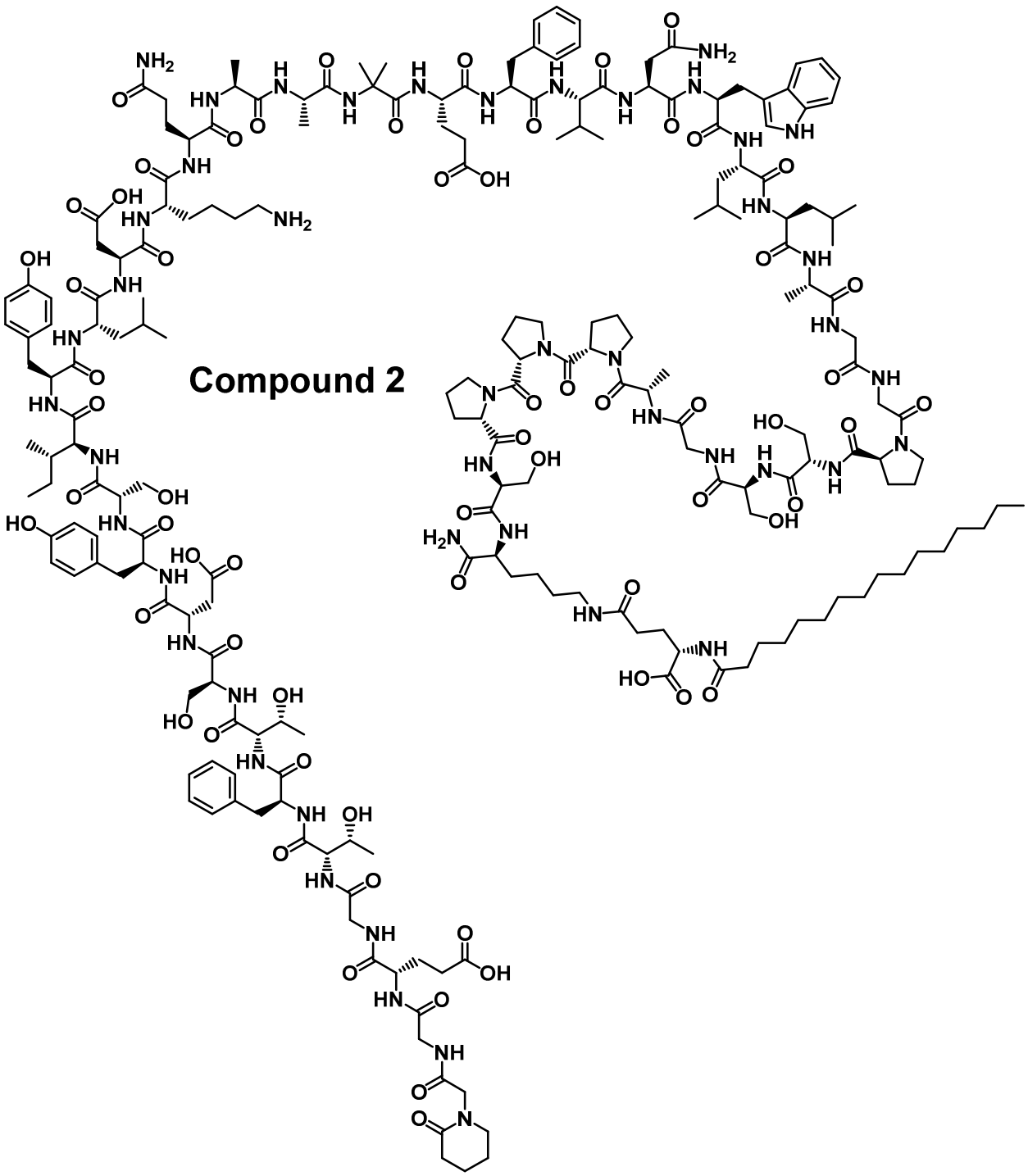
29. The compound, or pharmaceutically acceptable salt thereof, of any one of claims 26-28, wherein R* is

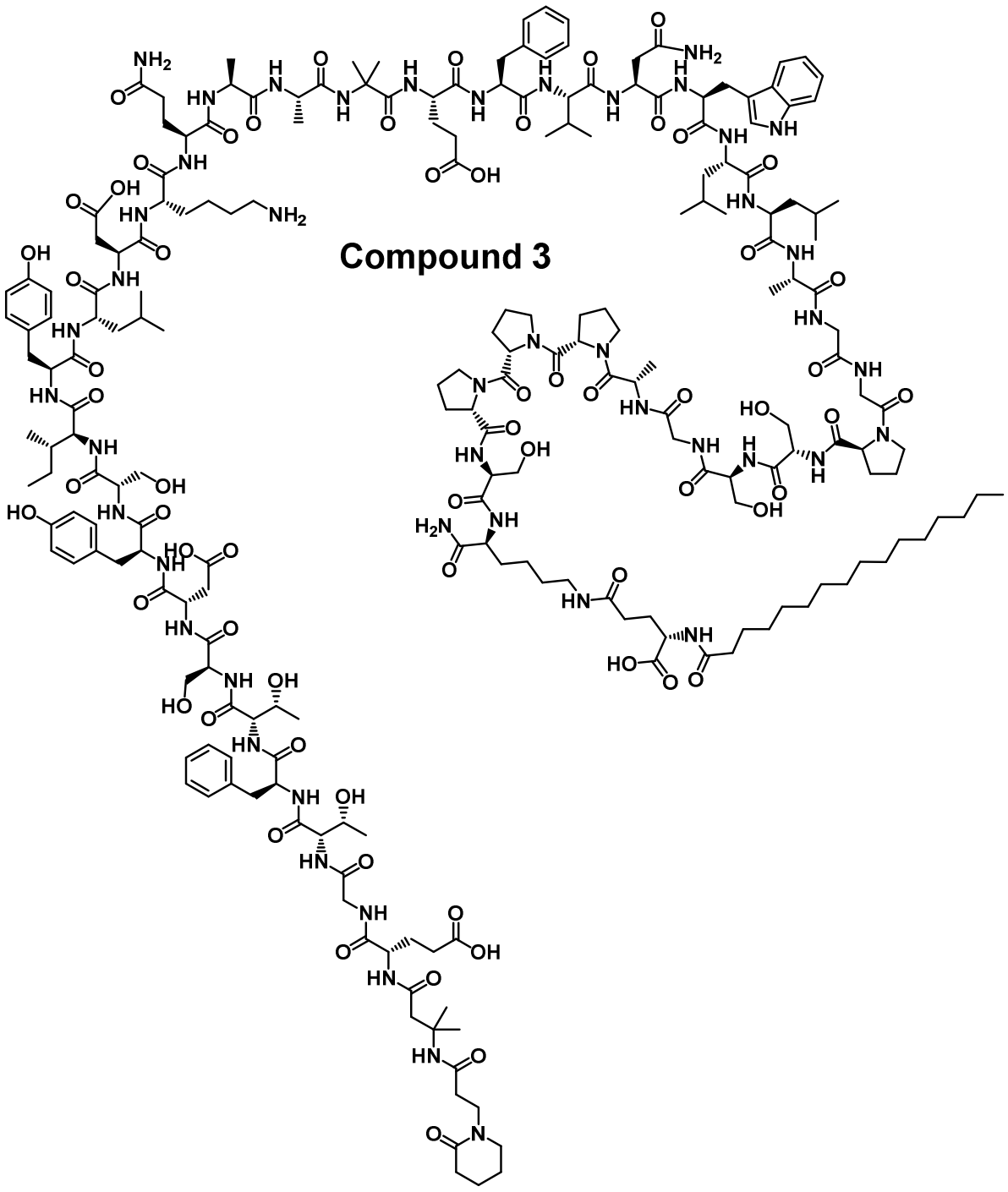


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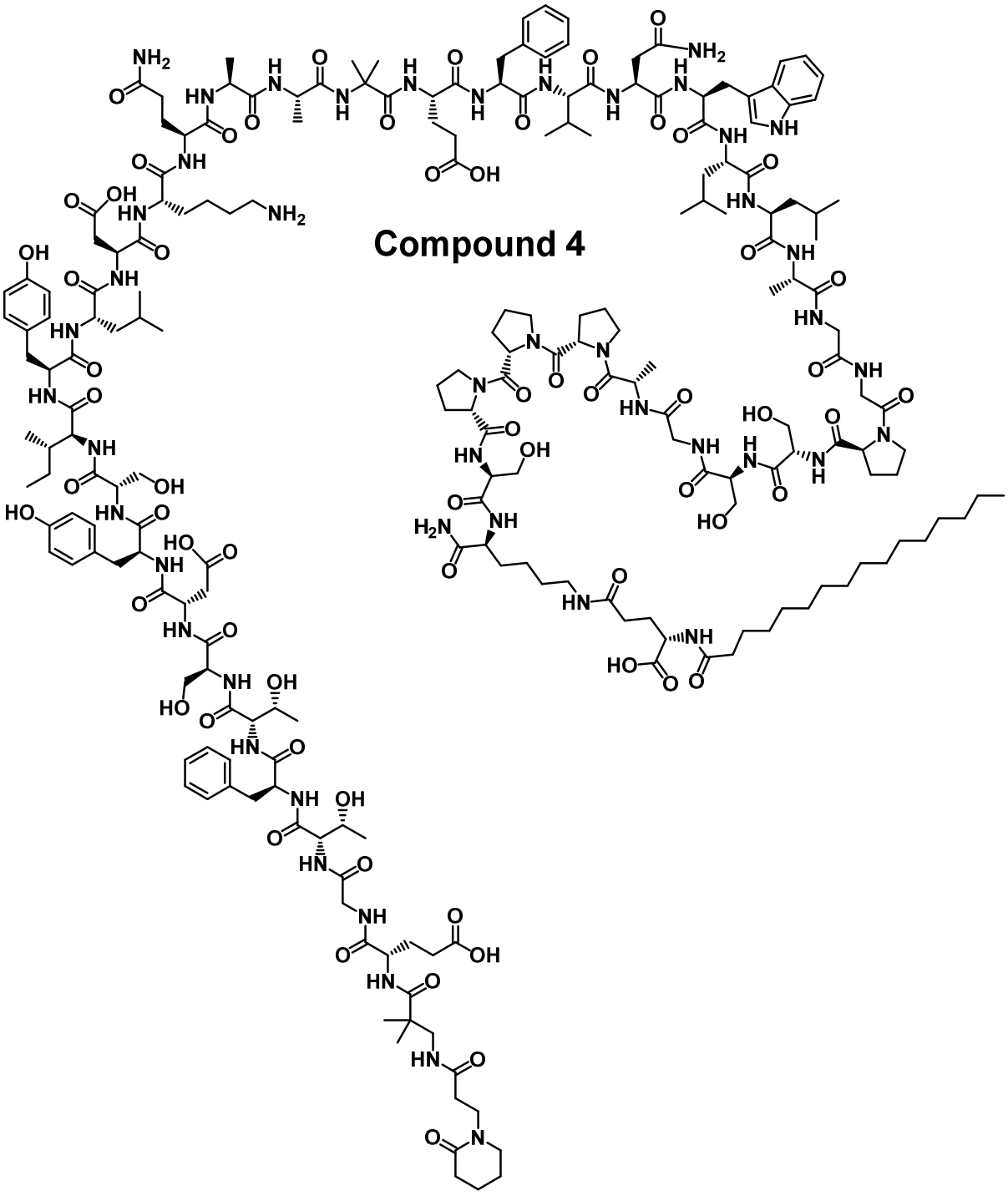
30. The compound, or pharmaceutically acceptable salt thereof, of claim 1, wherein the compound is selected from the group consisting of:

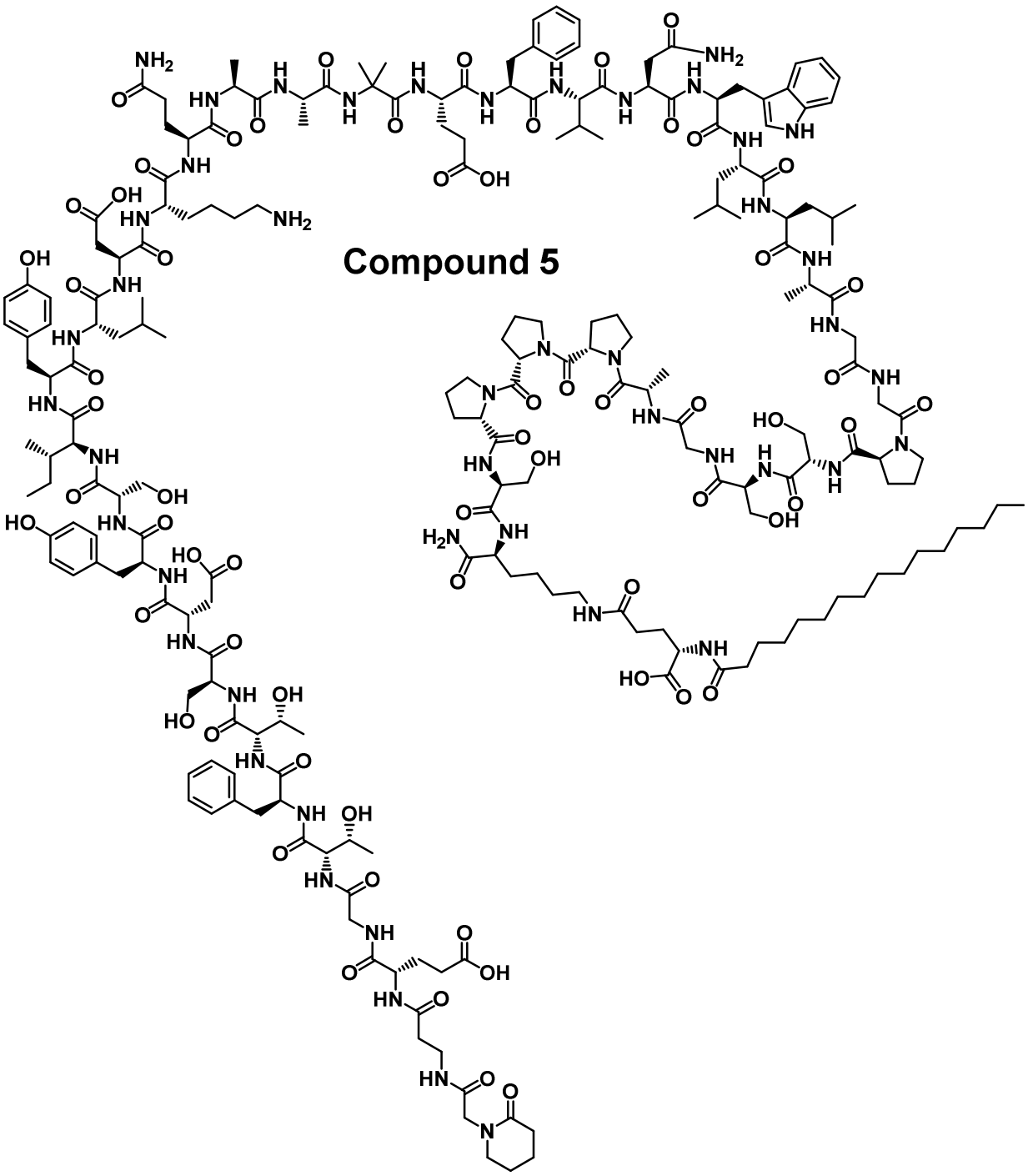

Compound 1

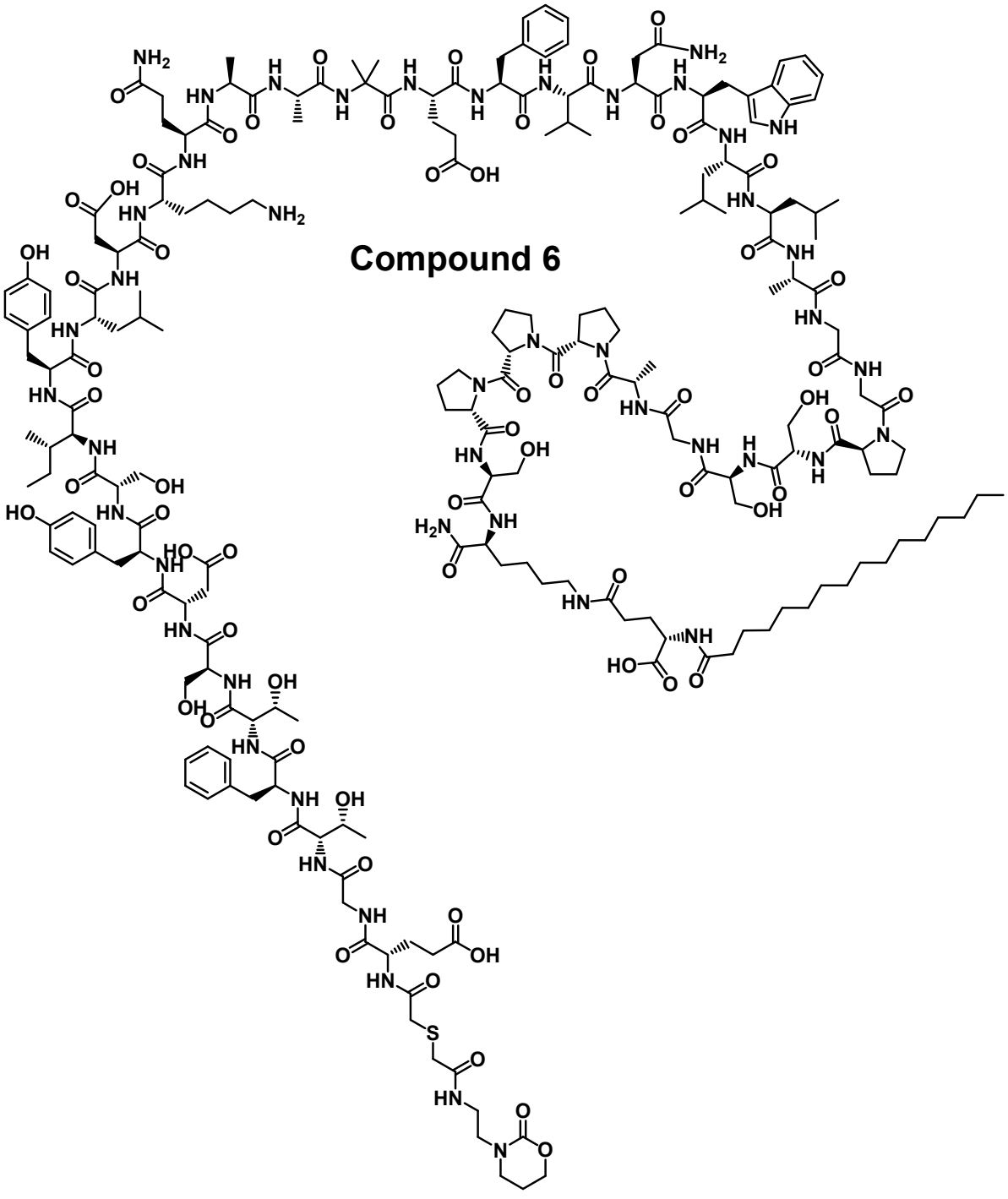

Compound 2



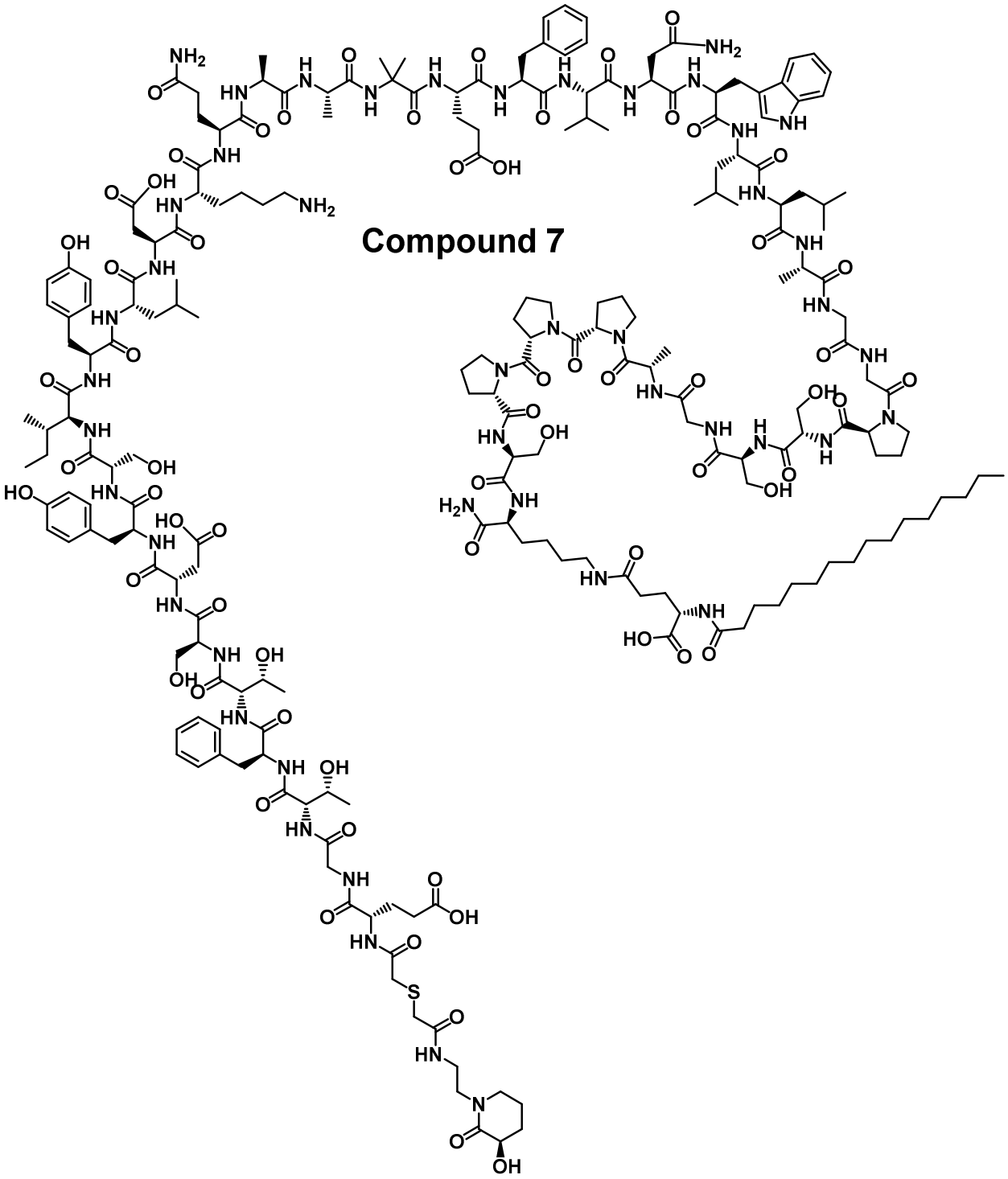
Compound 3

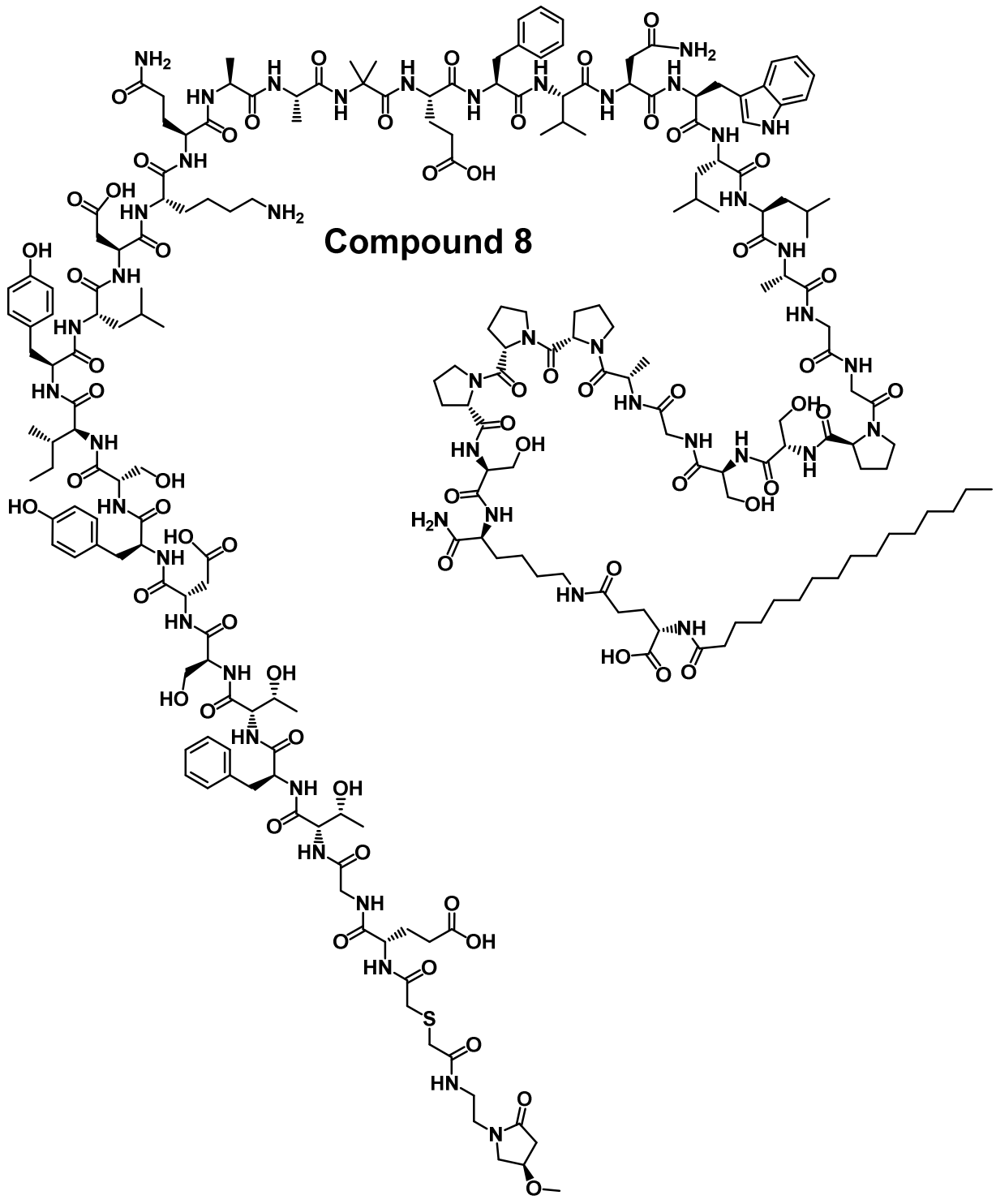

Compound 4

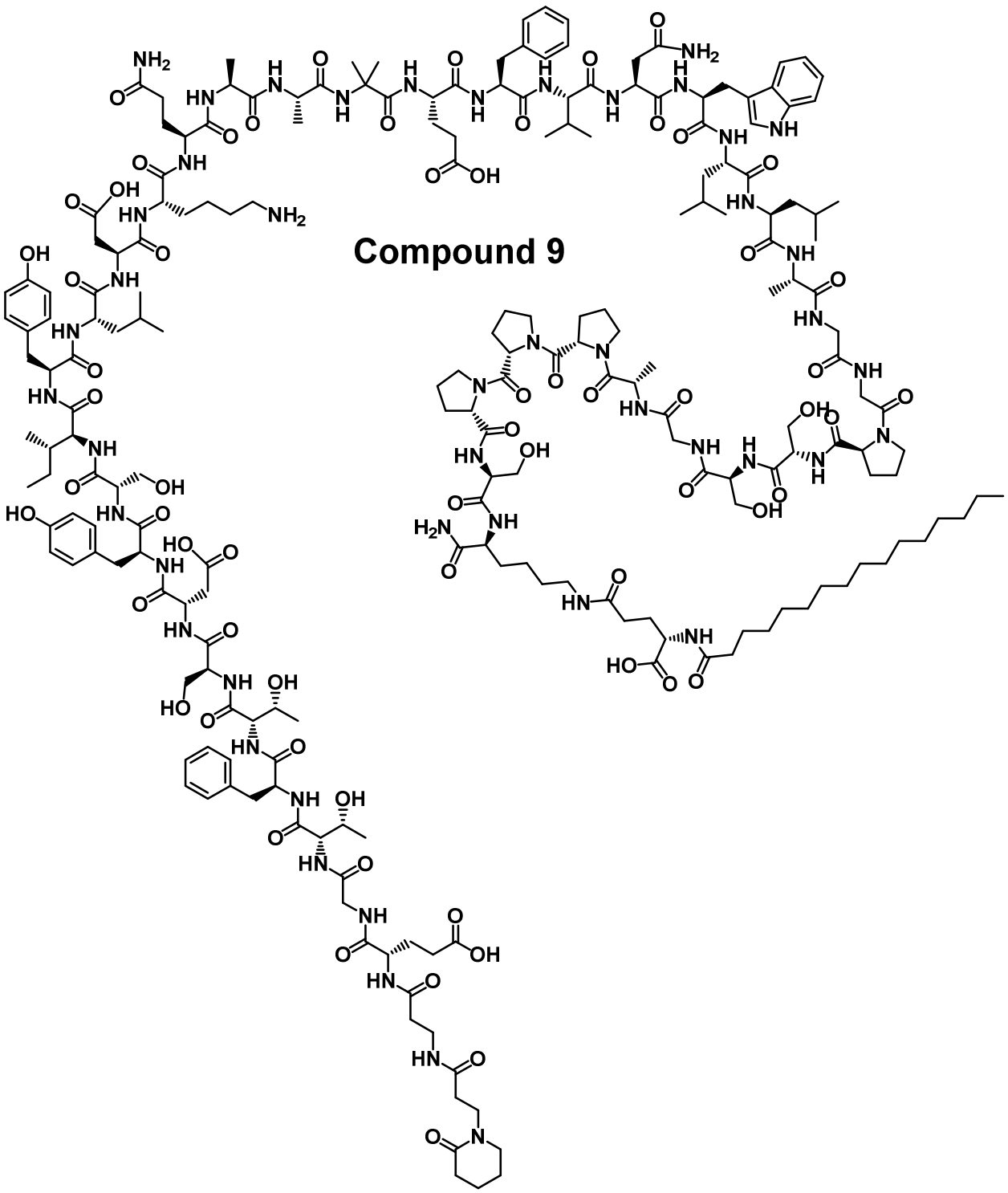

Compound 5

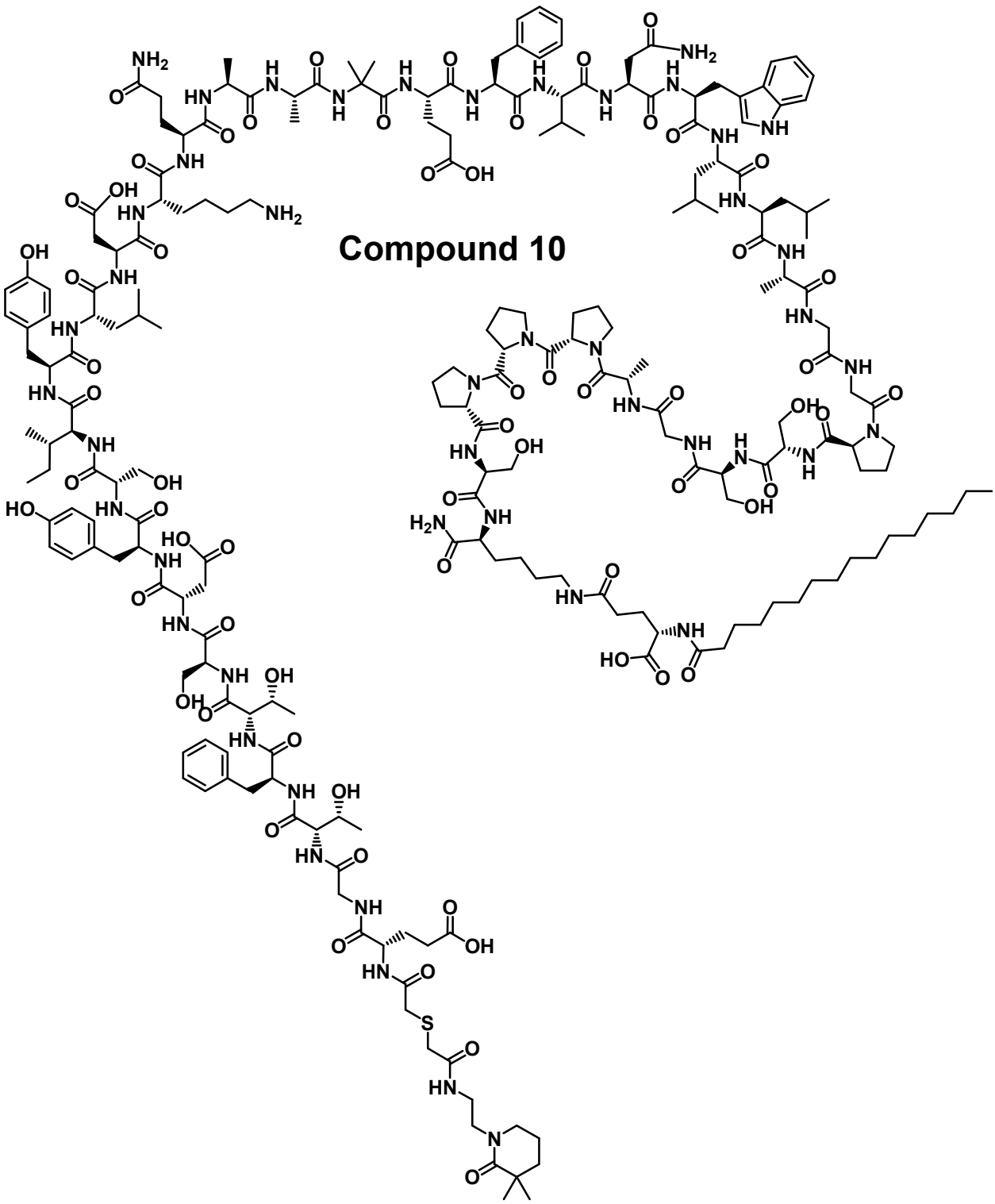


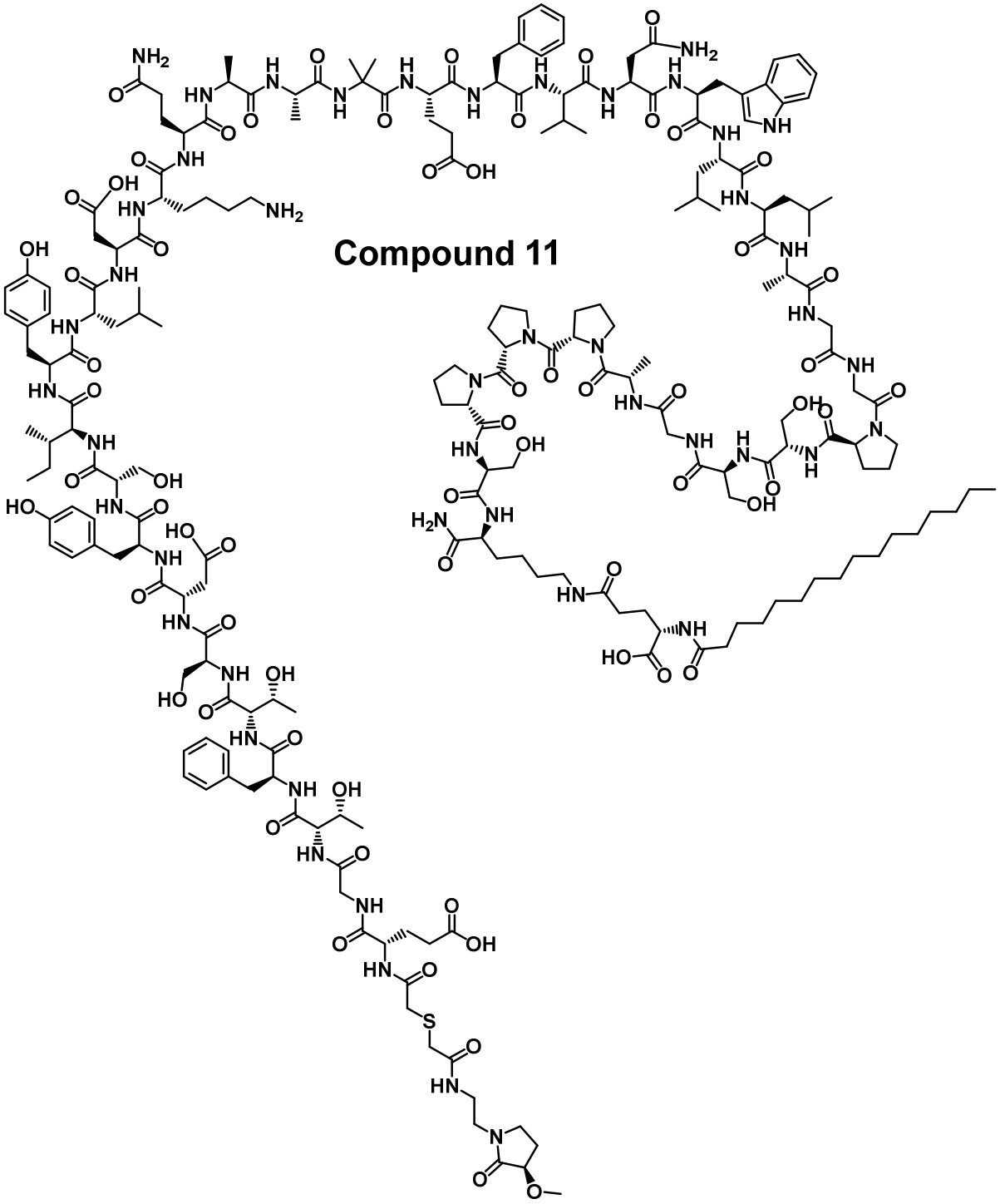
Compound 6


Compound 7

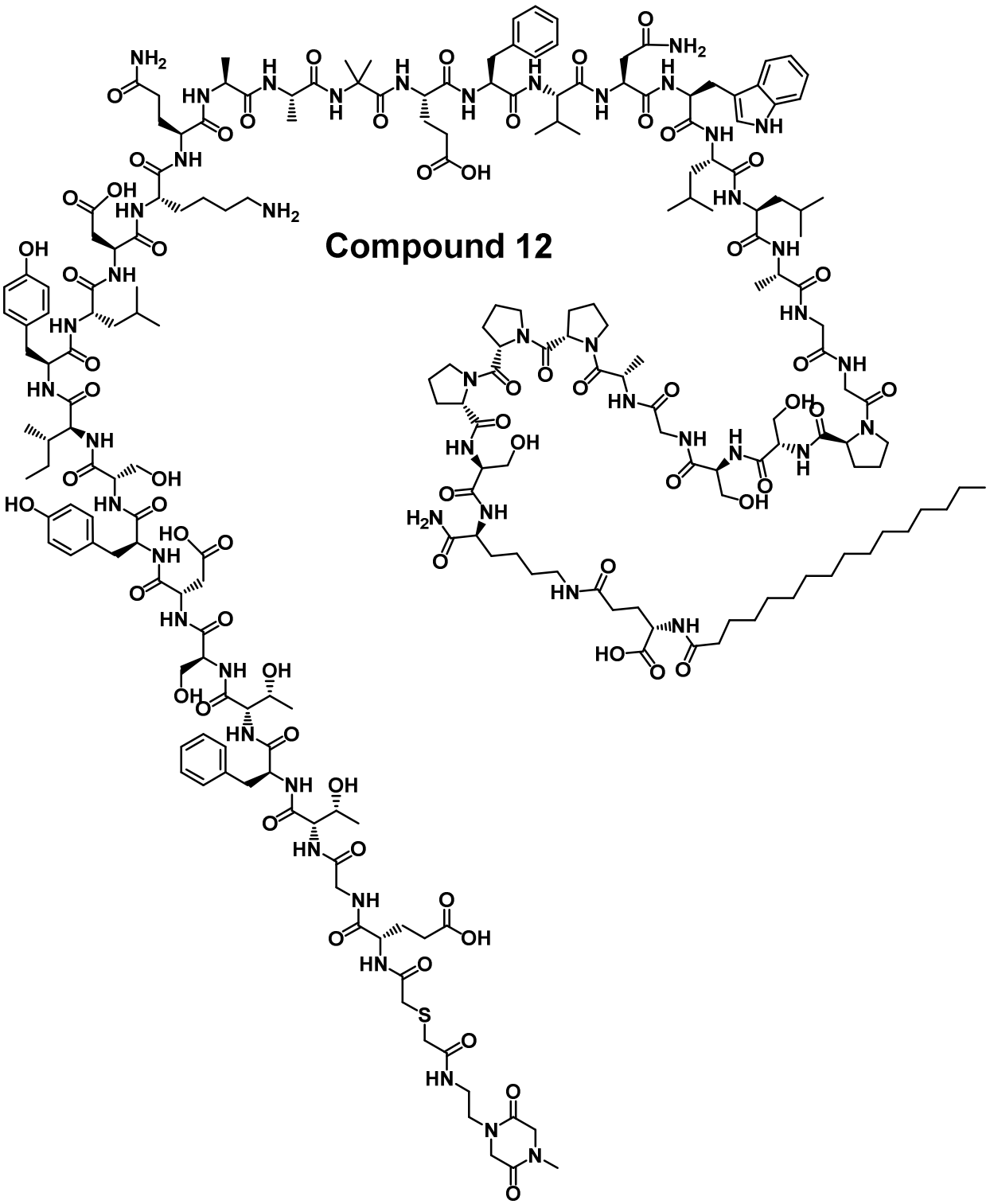

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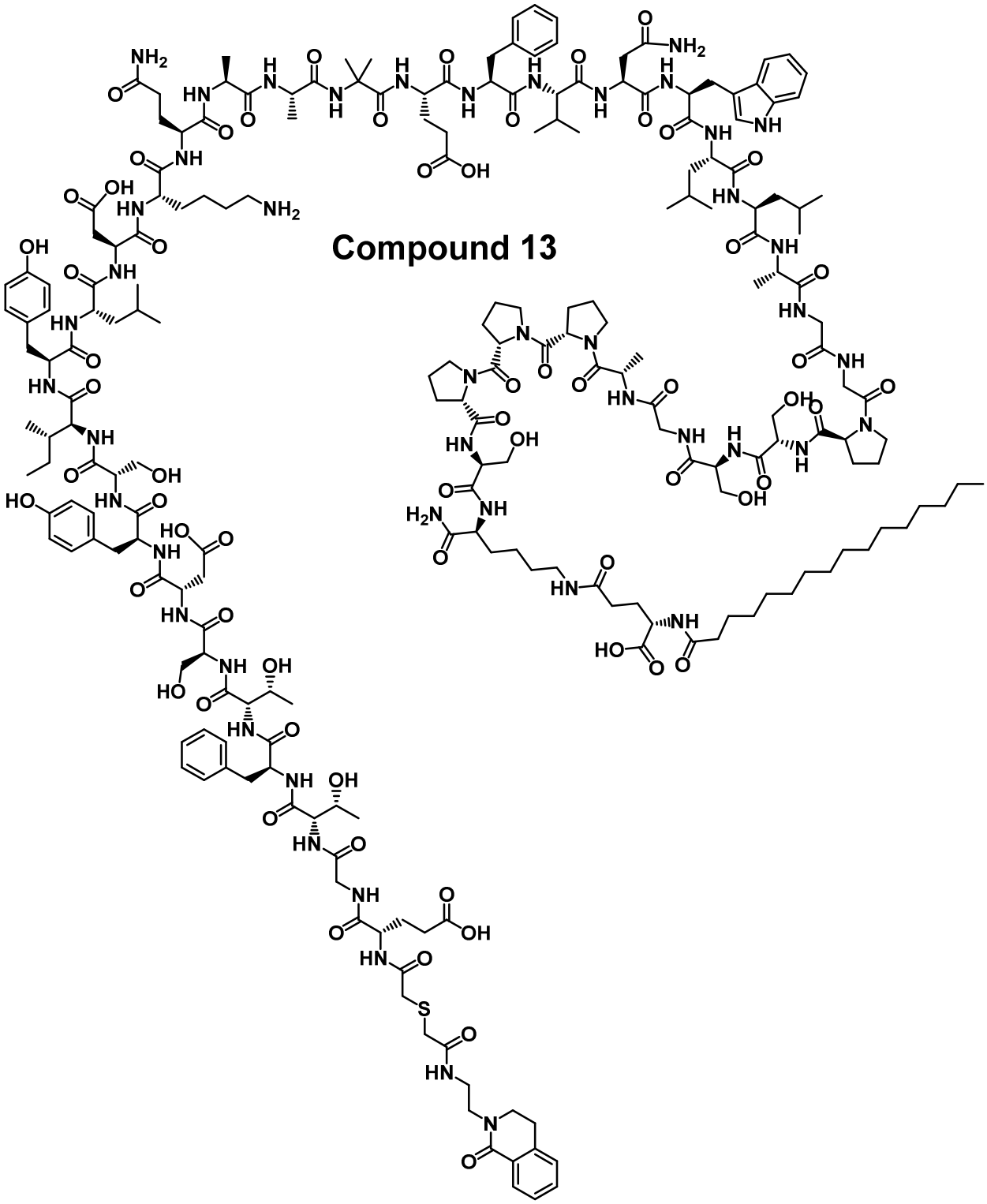

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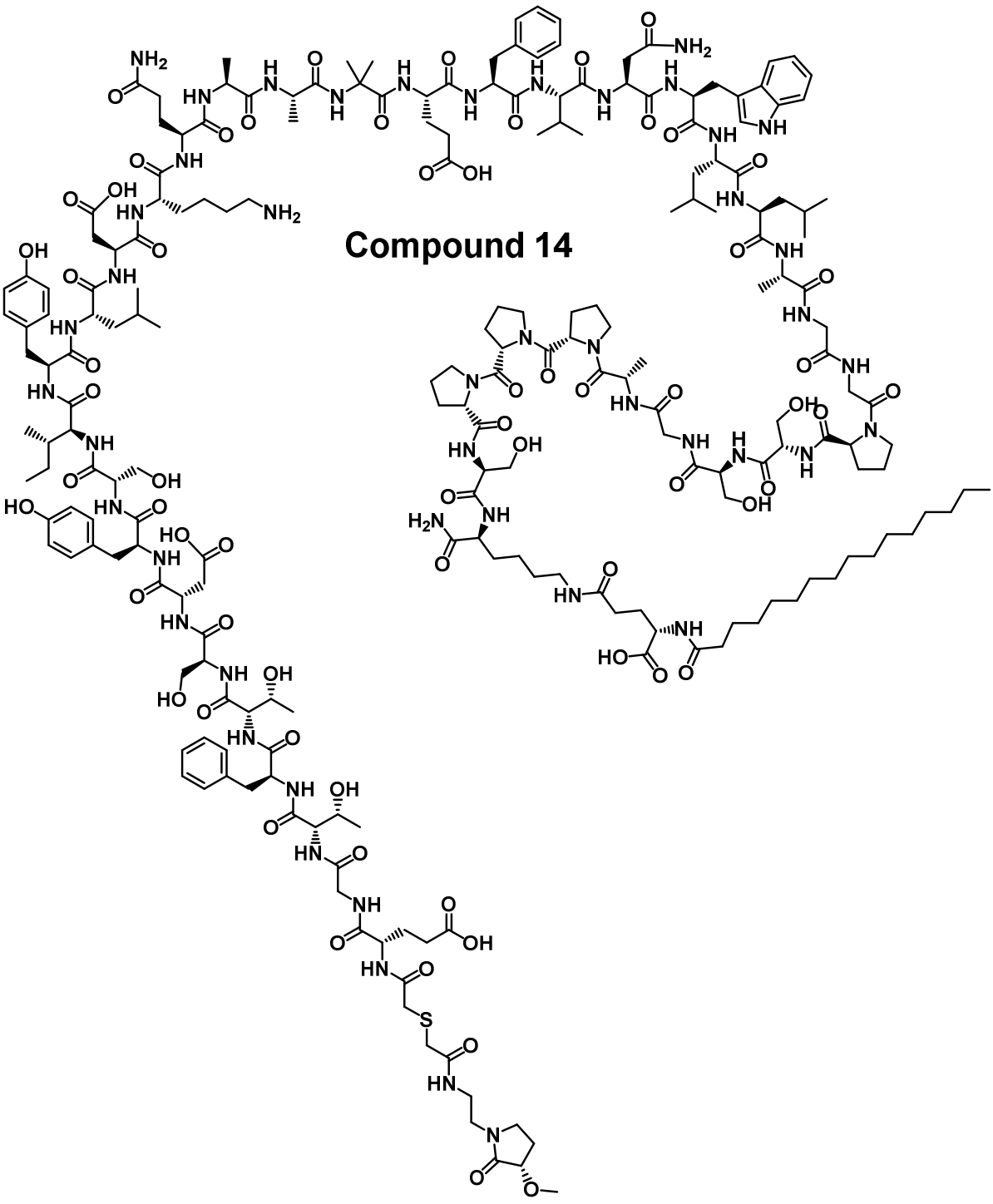

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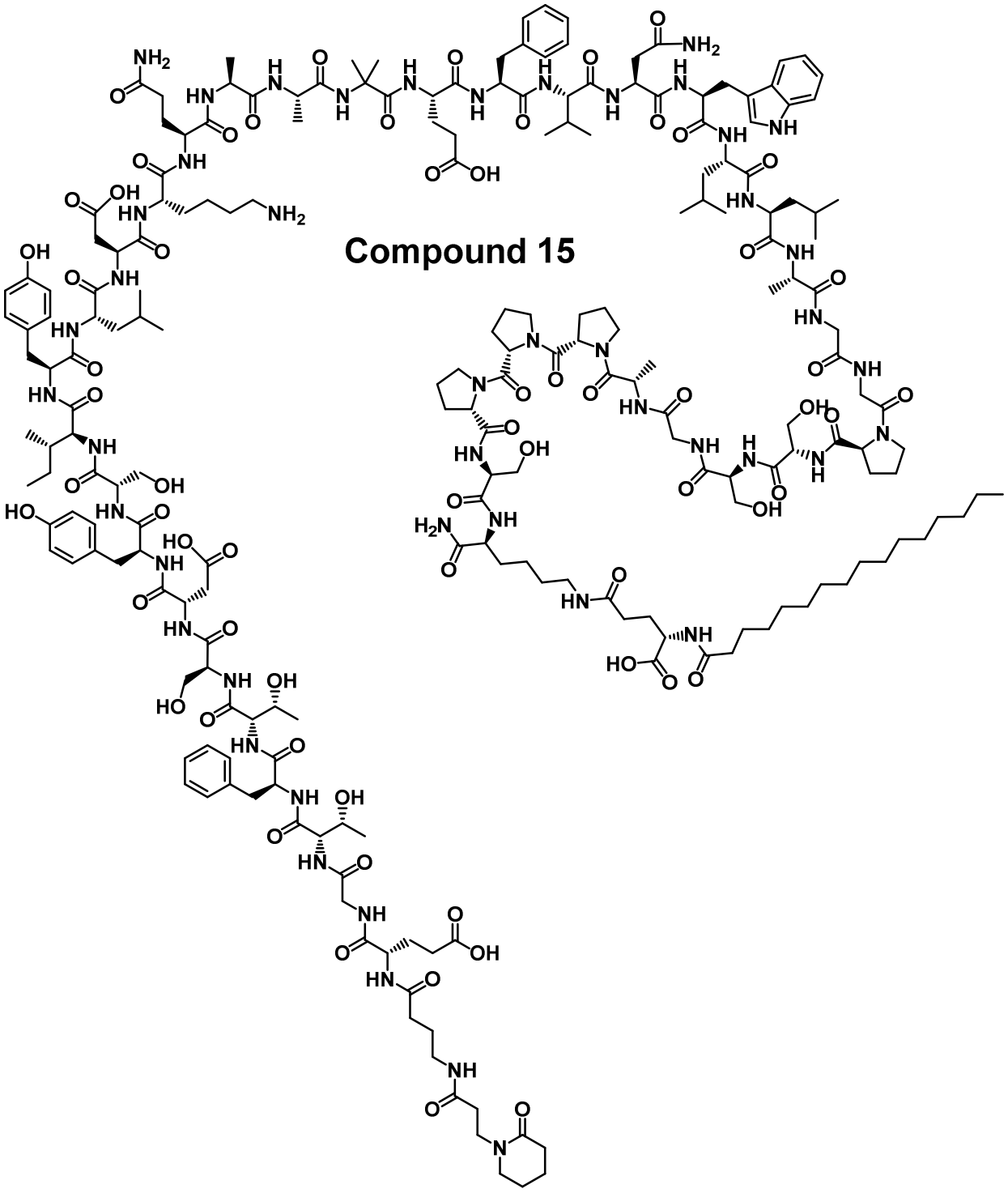


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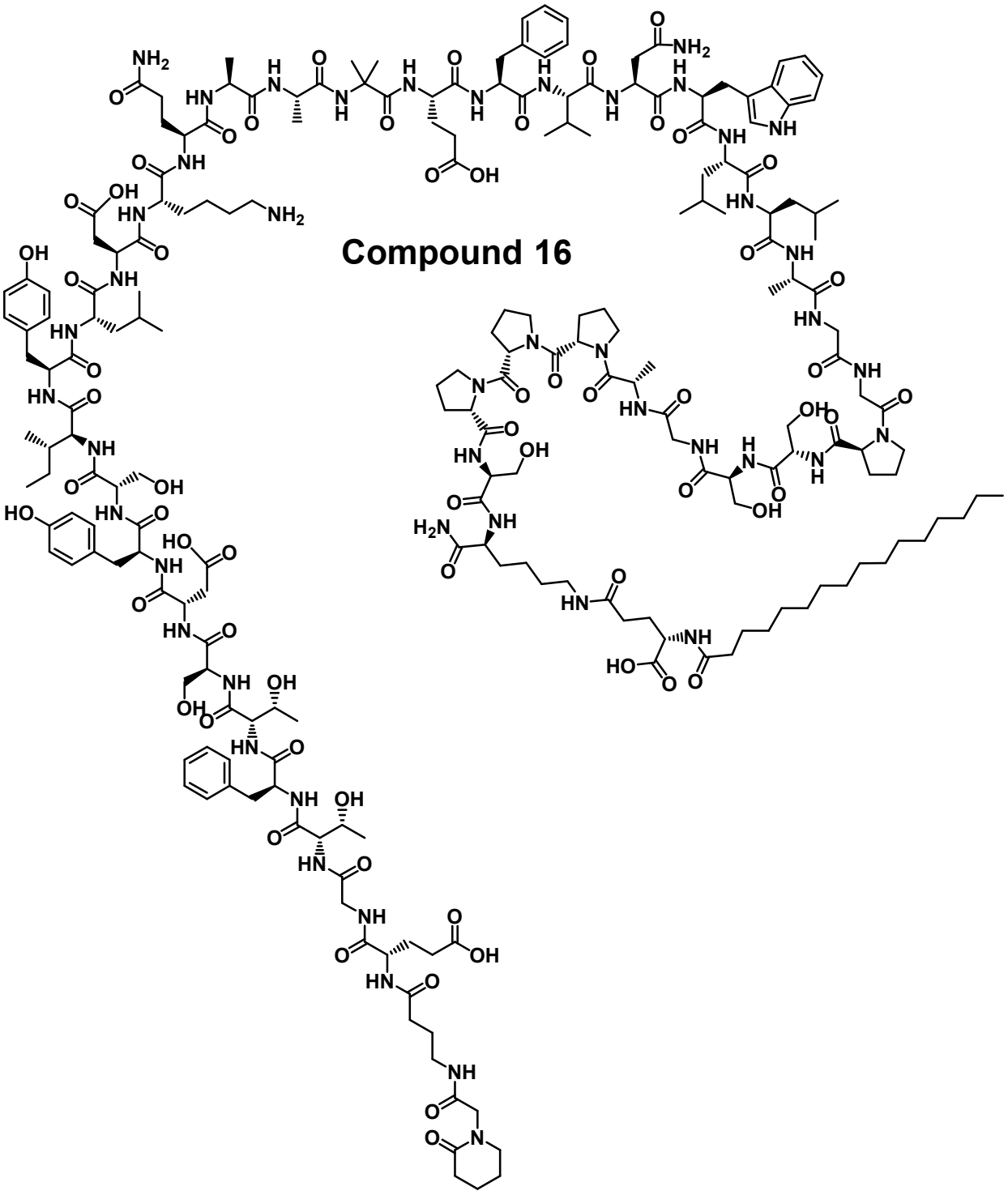

Compound 12


Compound 13

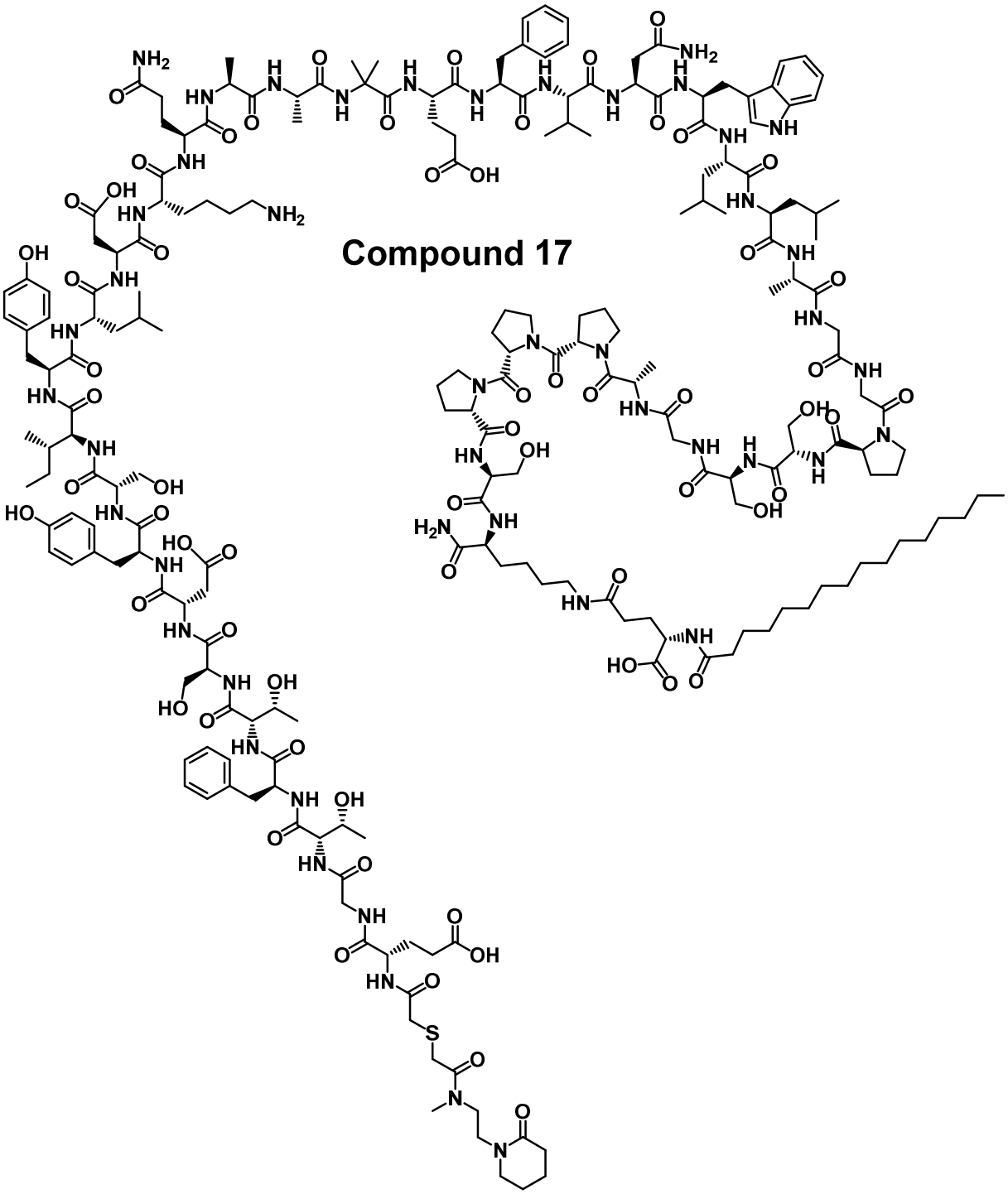

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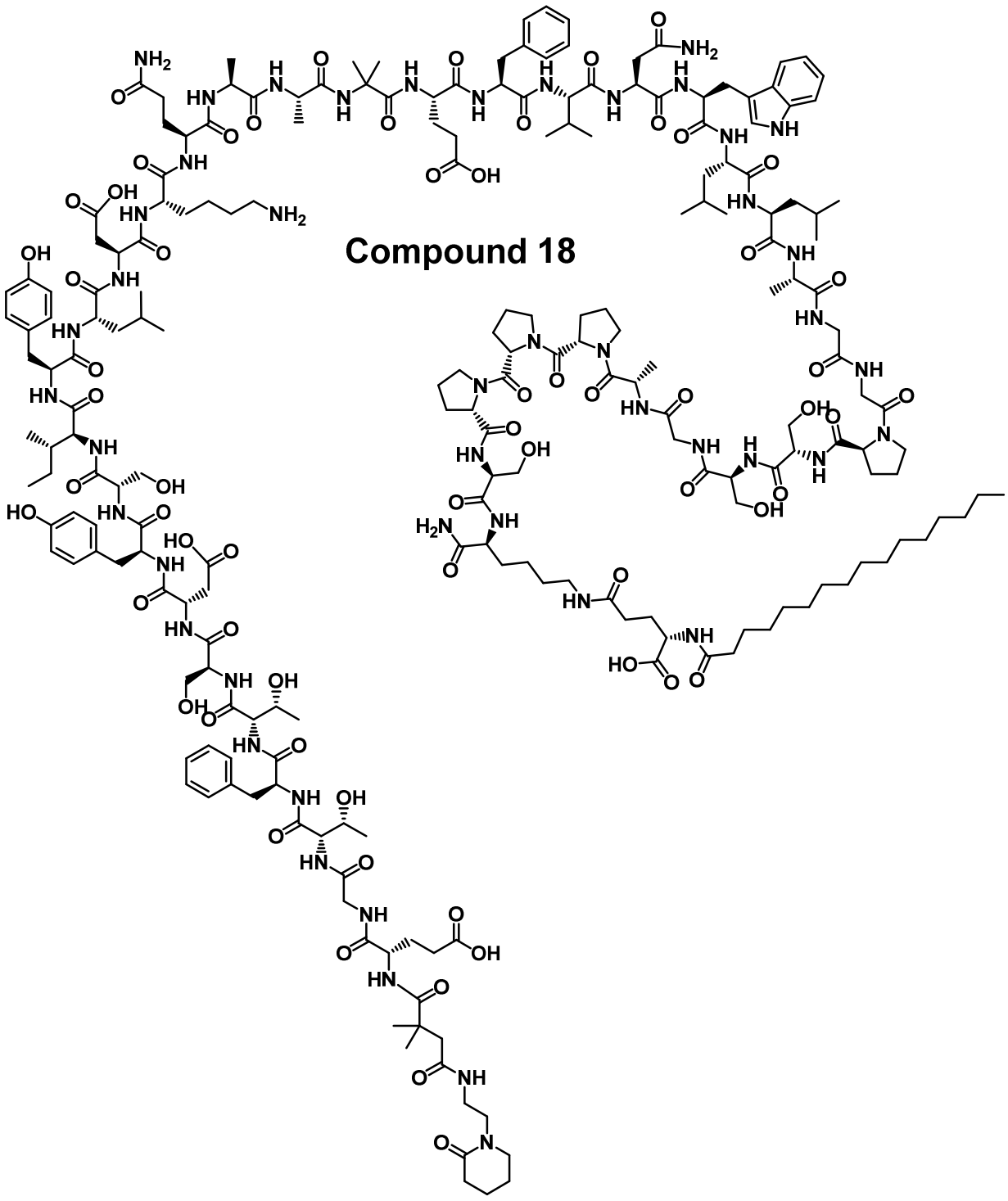


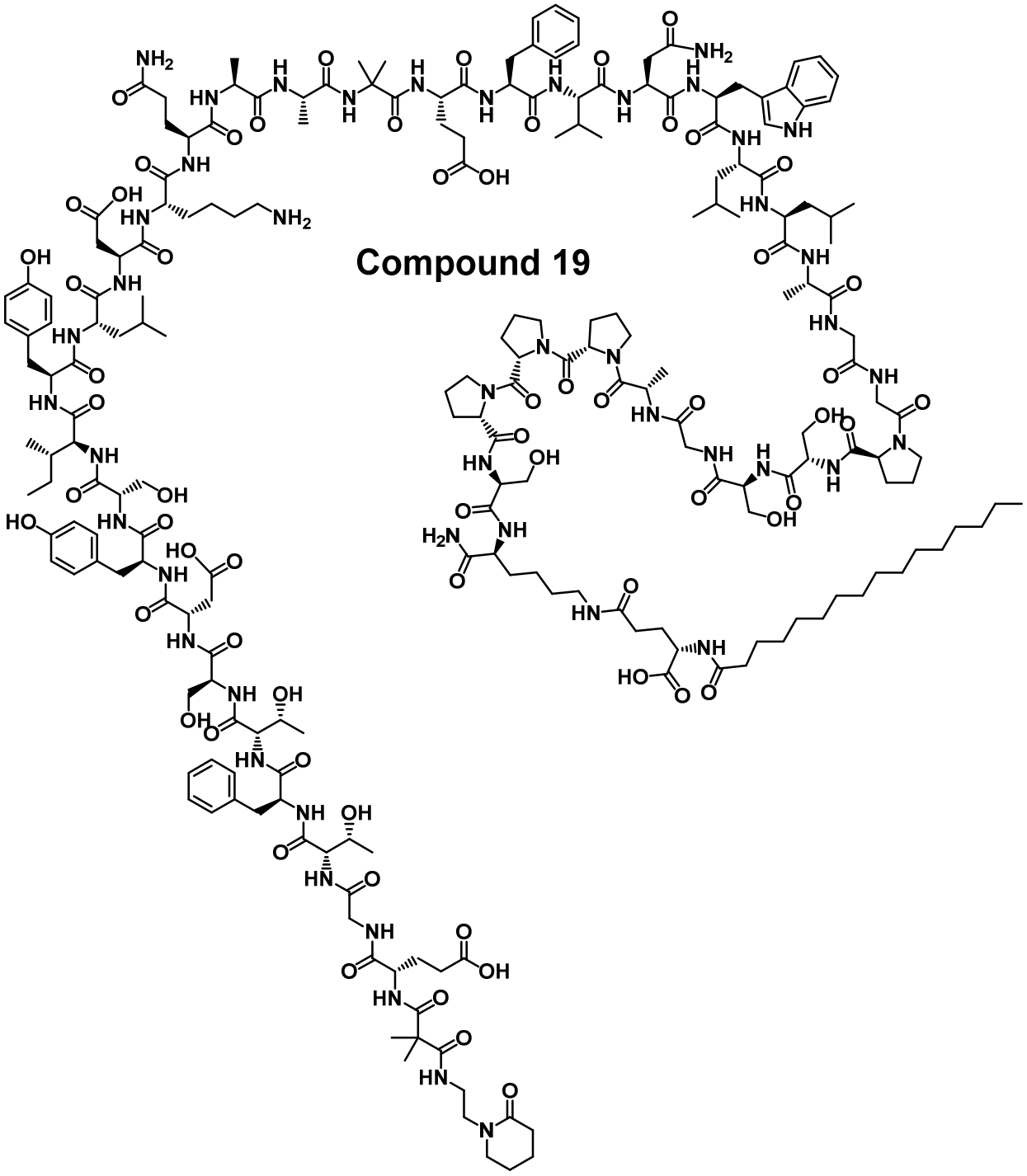
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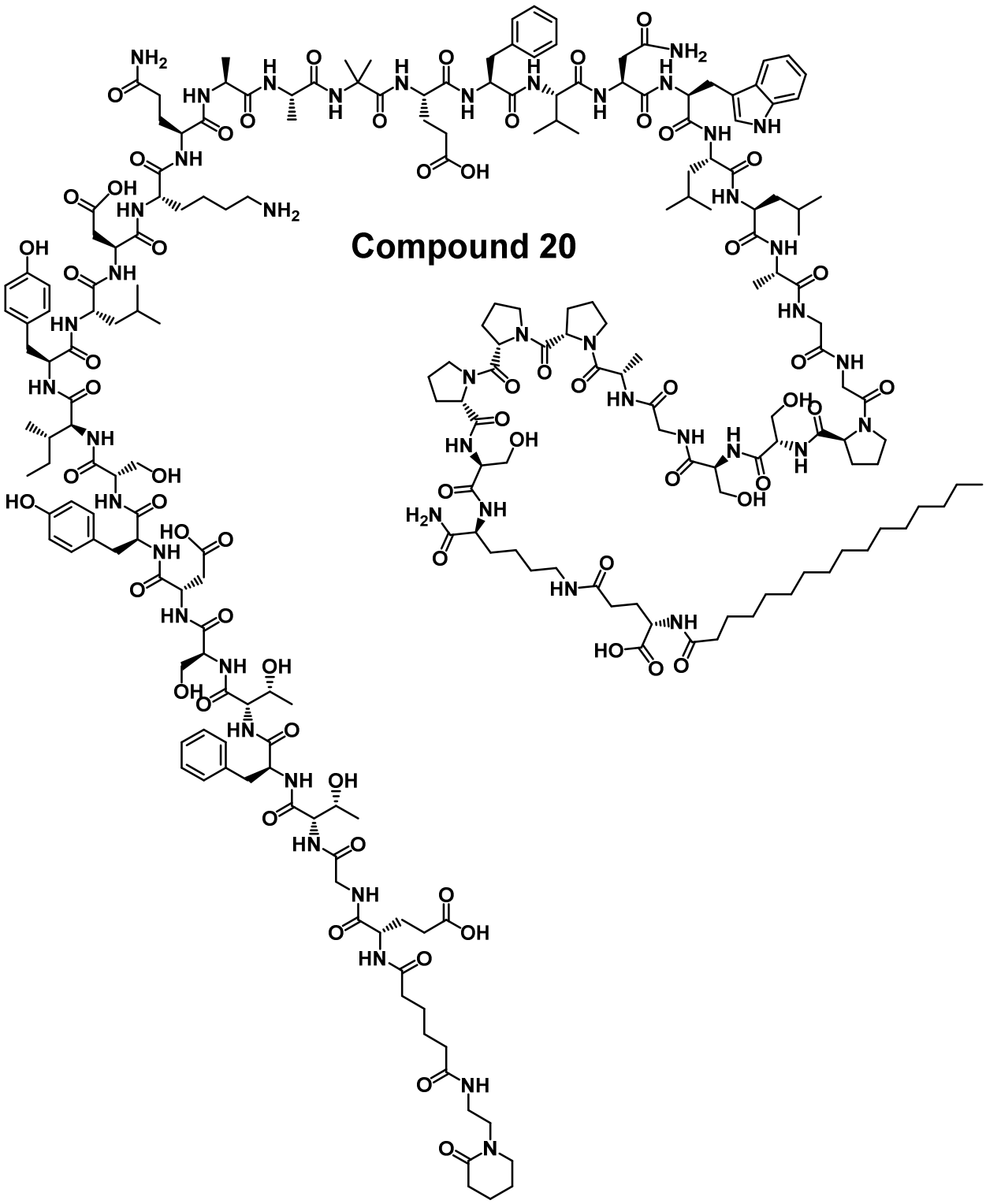


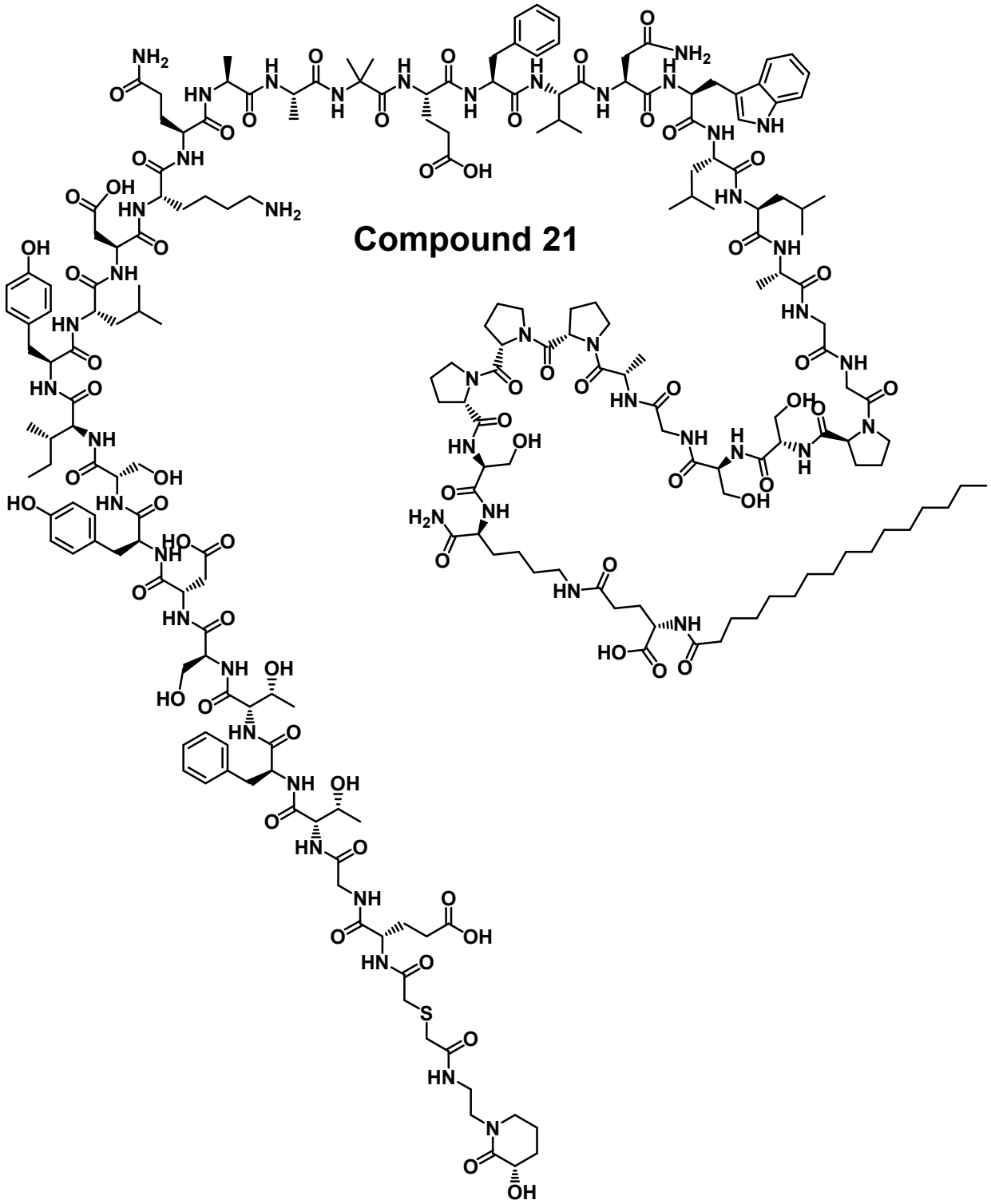
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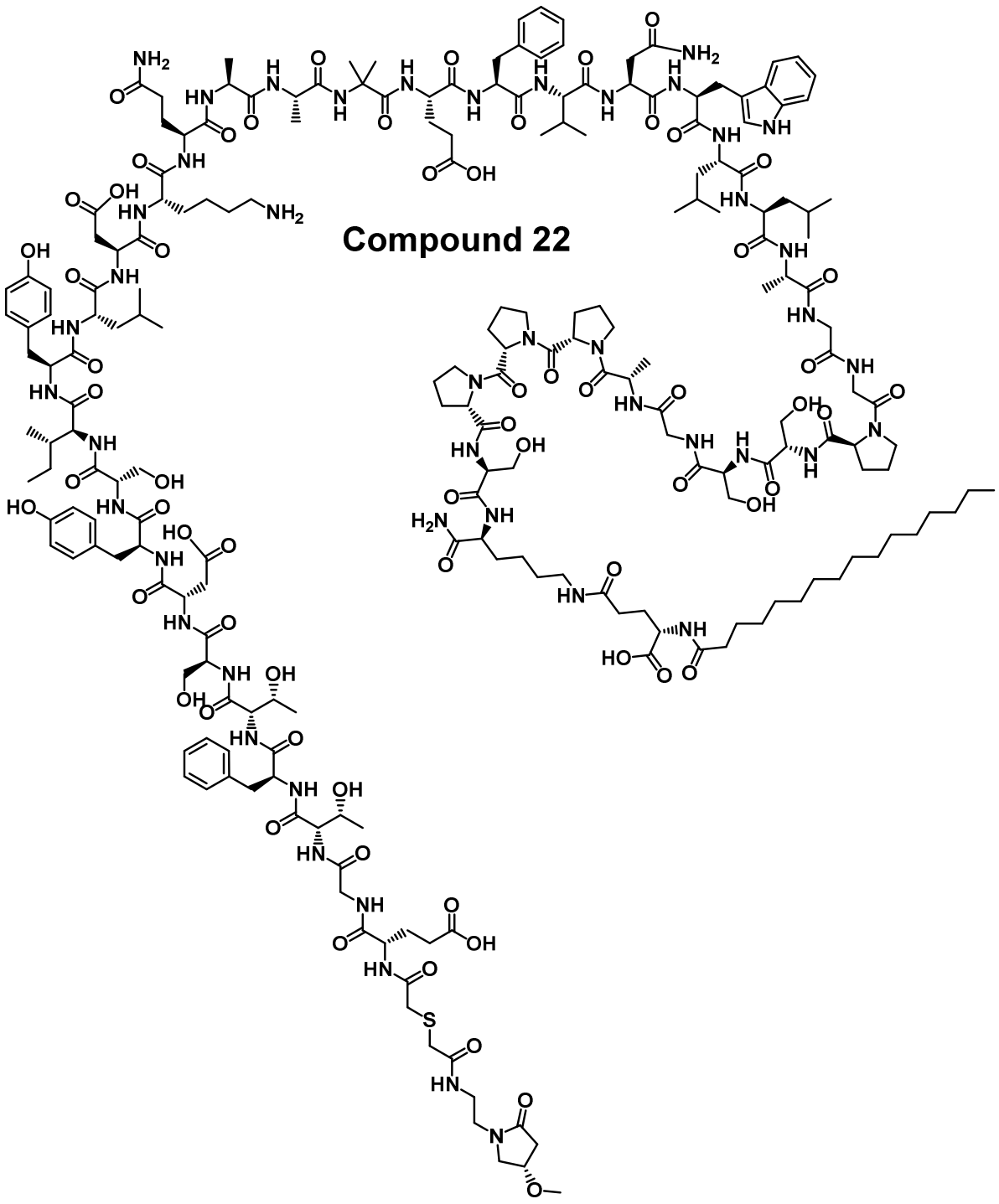

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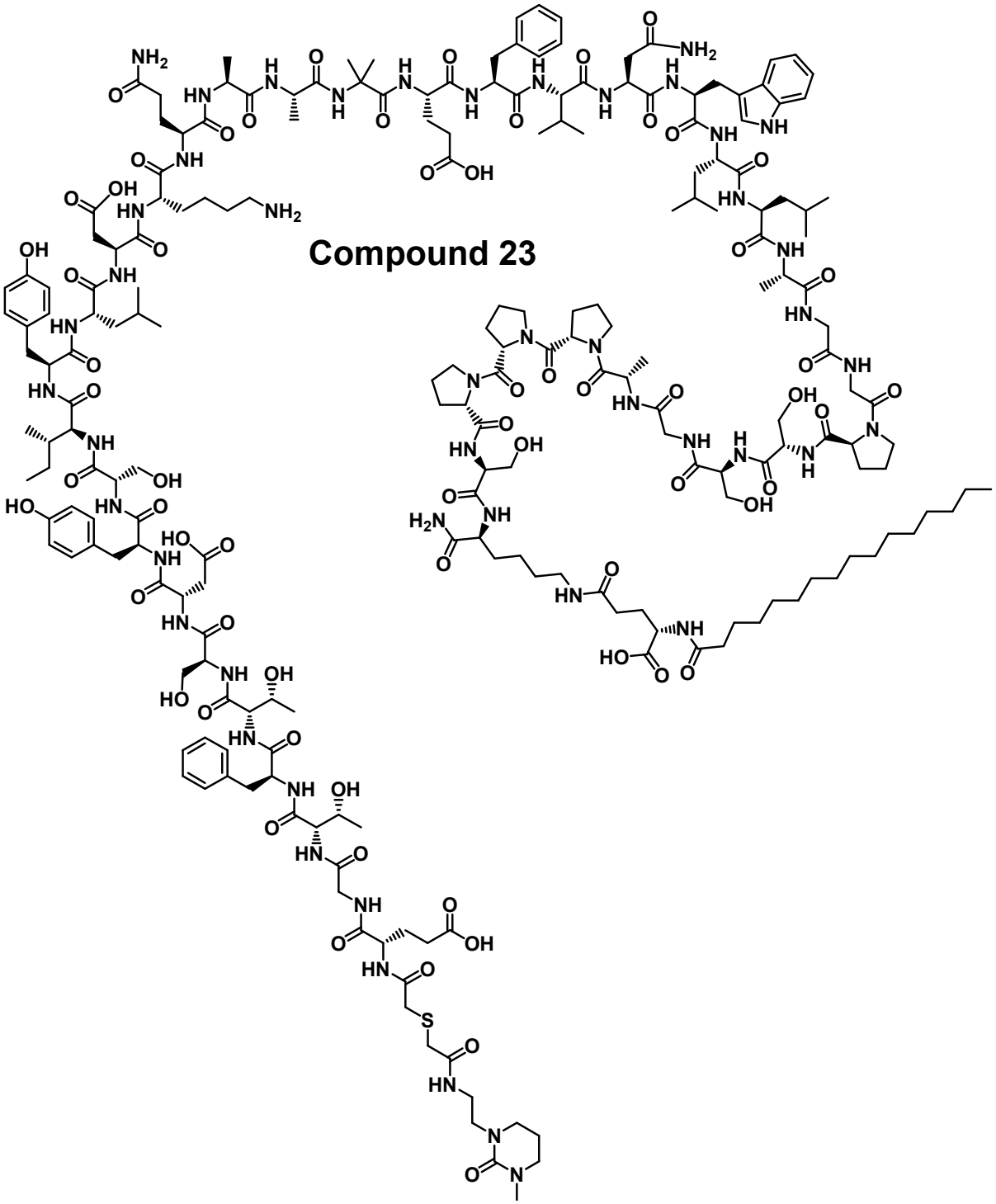

Compound 19


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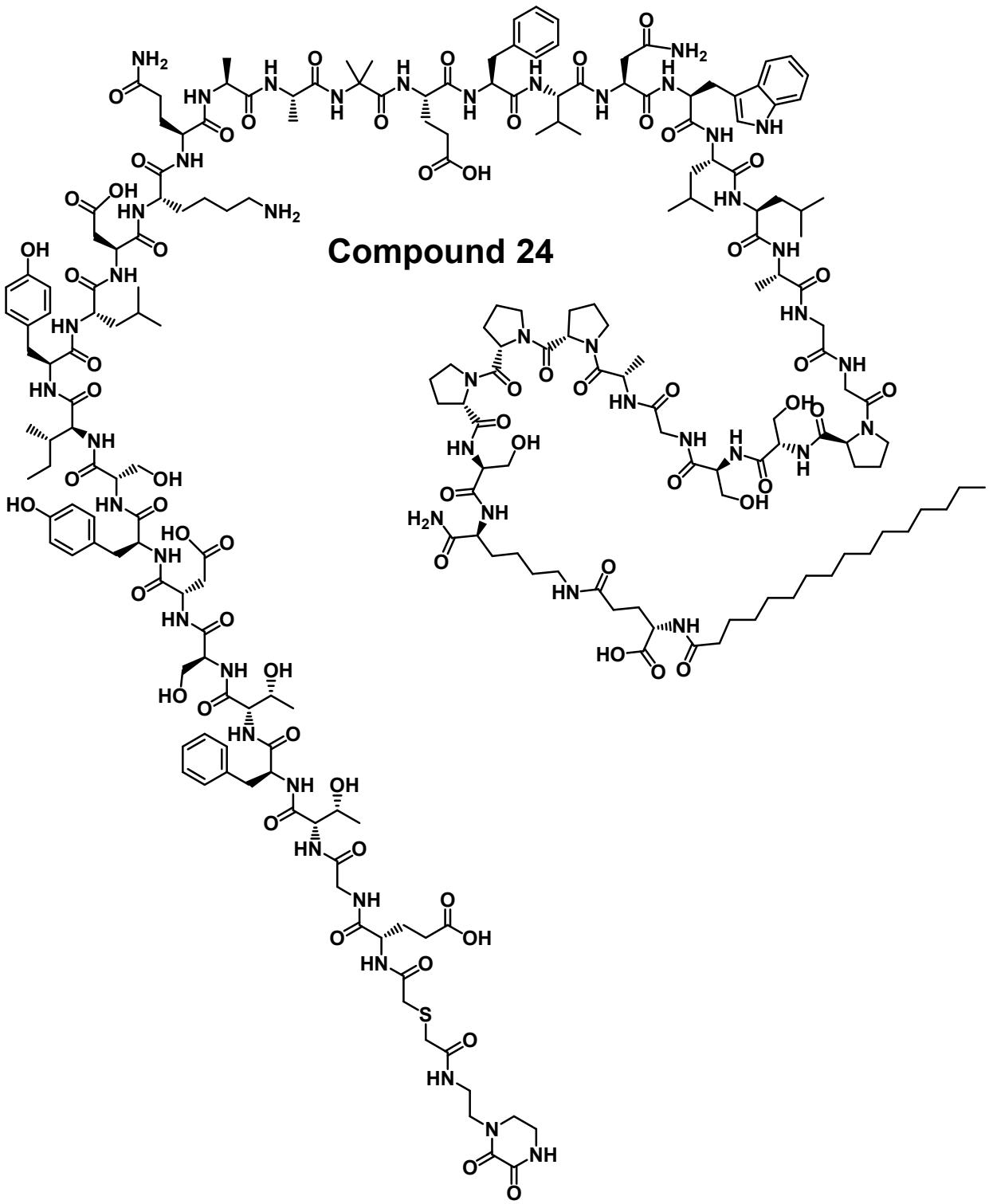


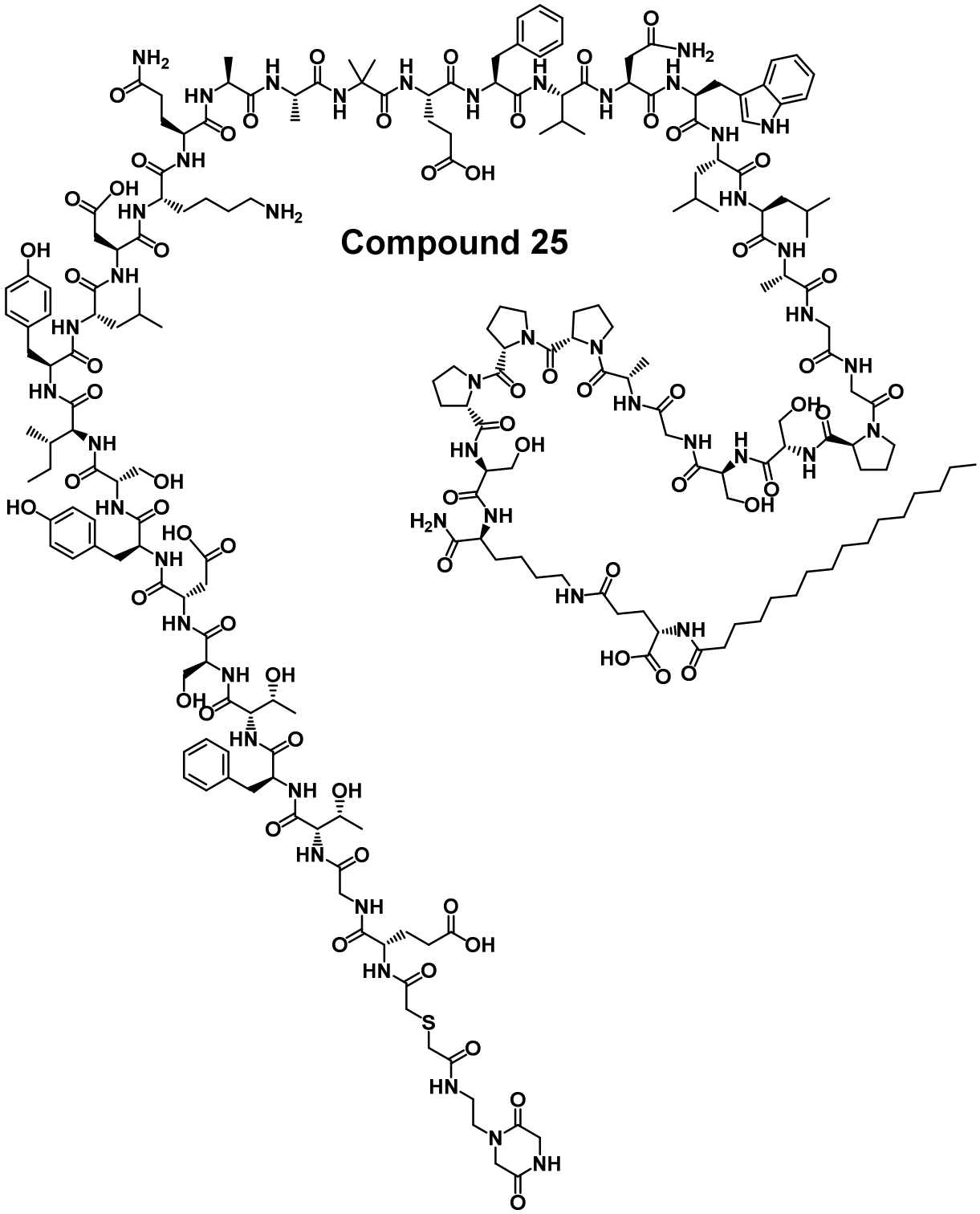
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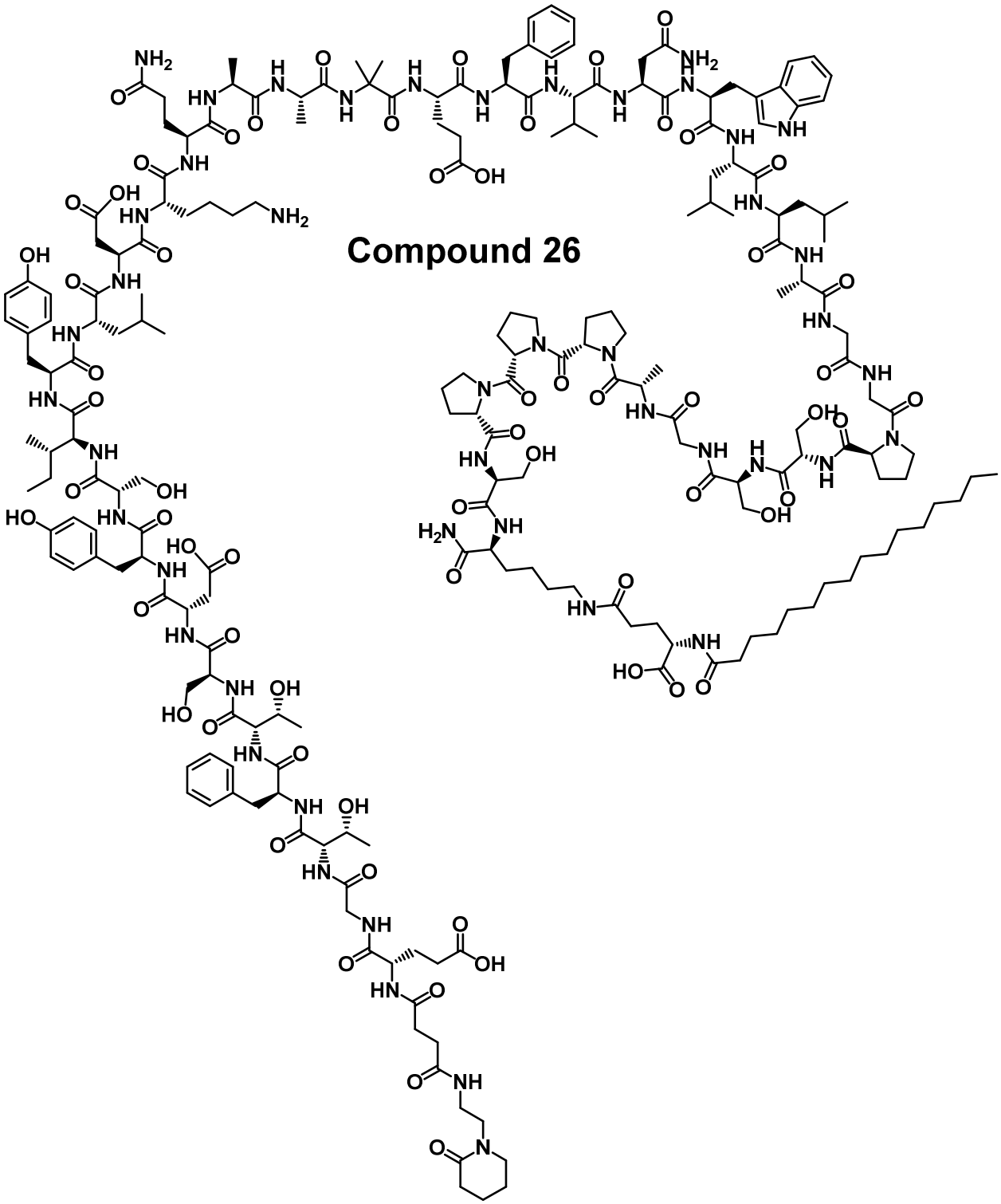

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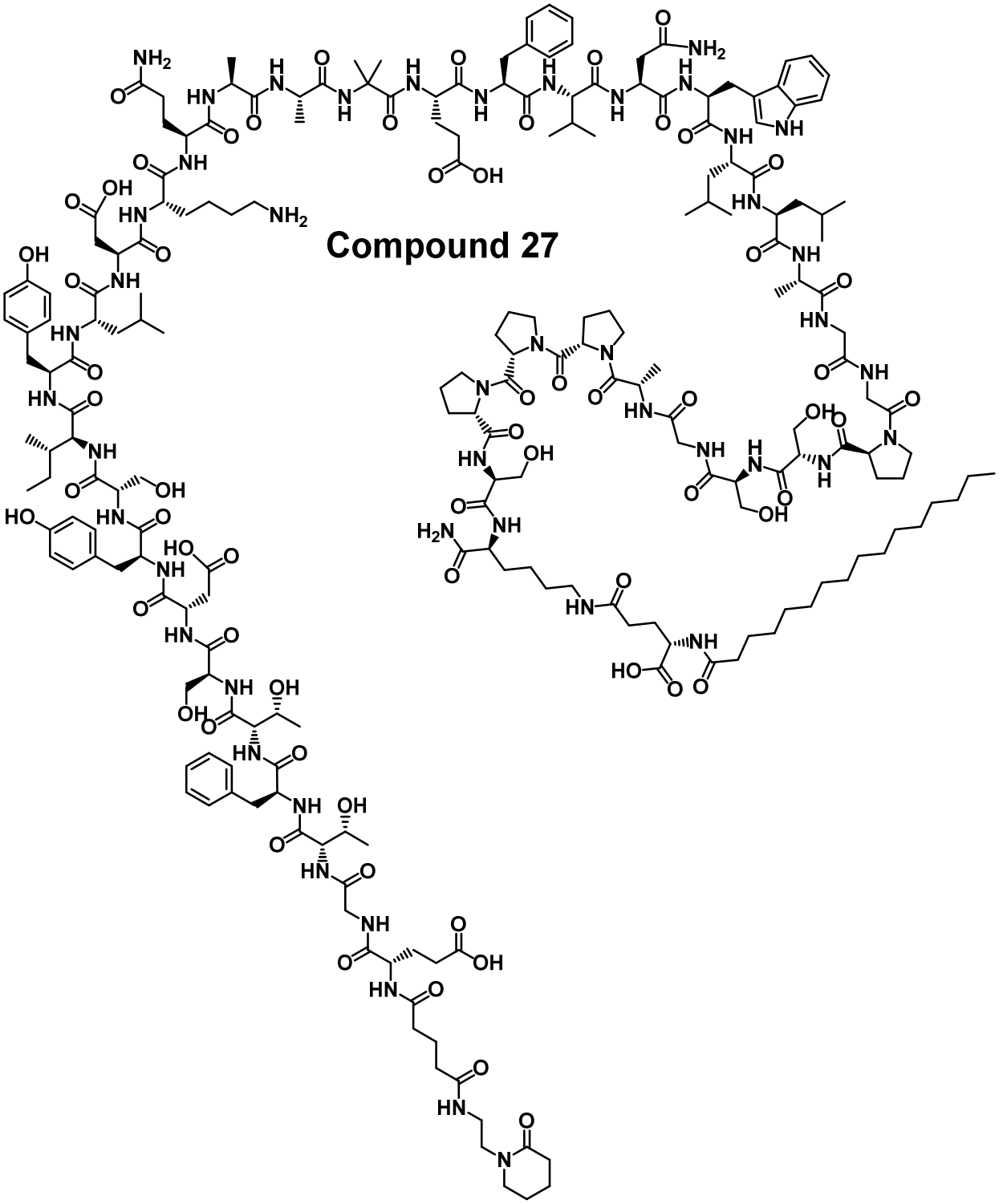


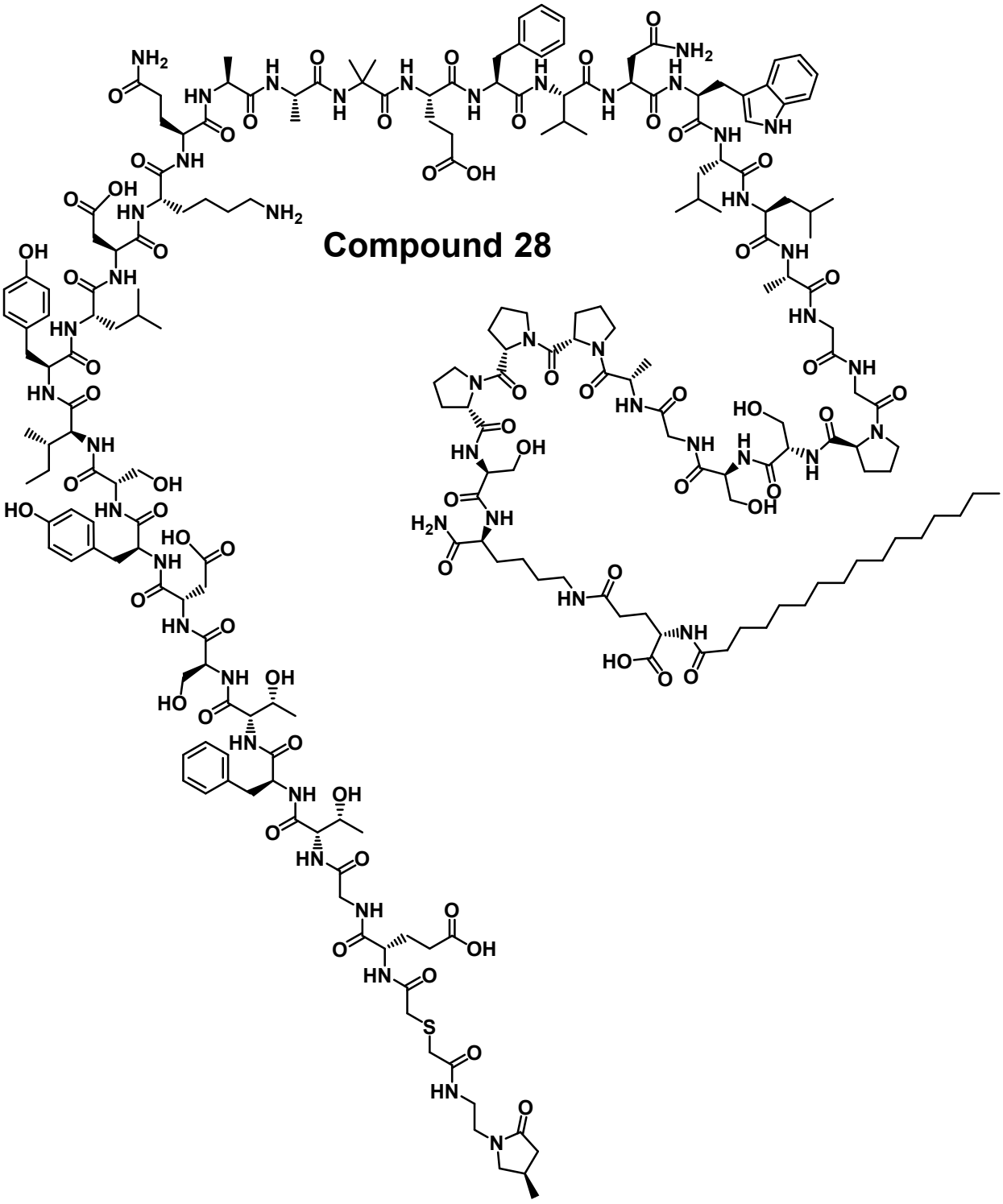
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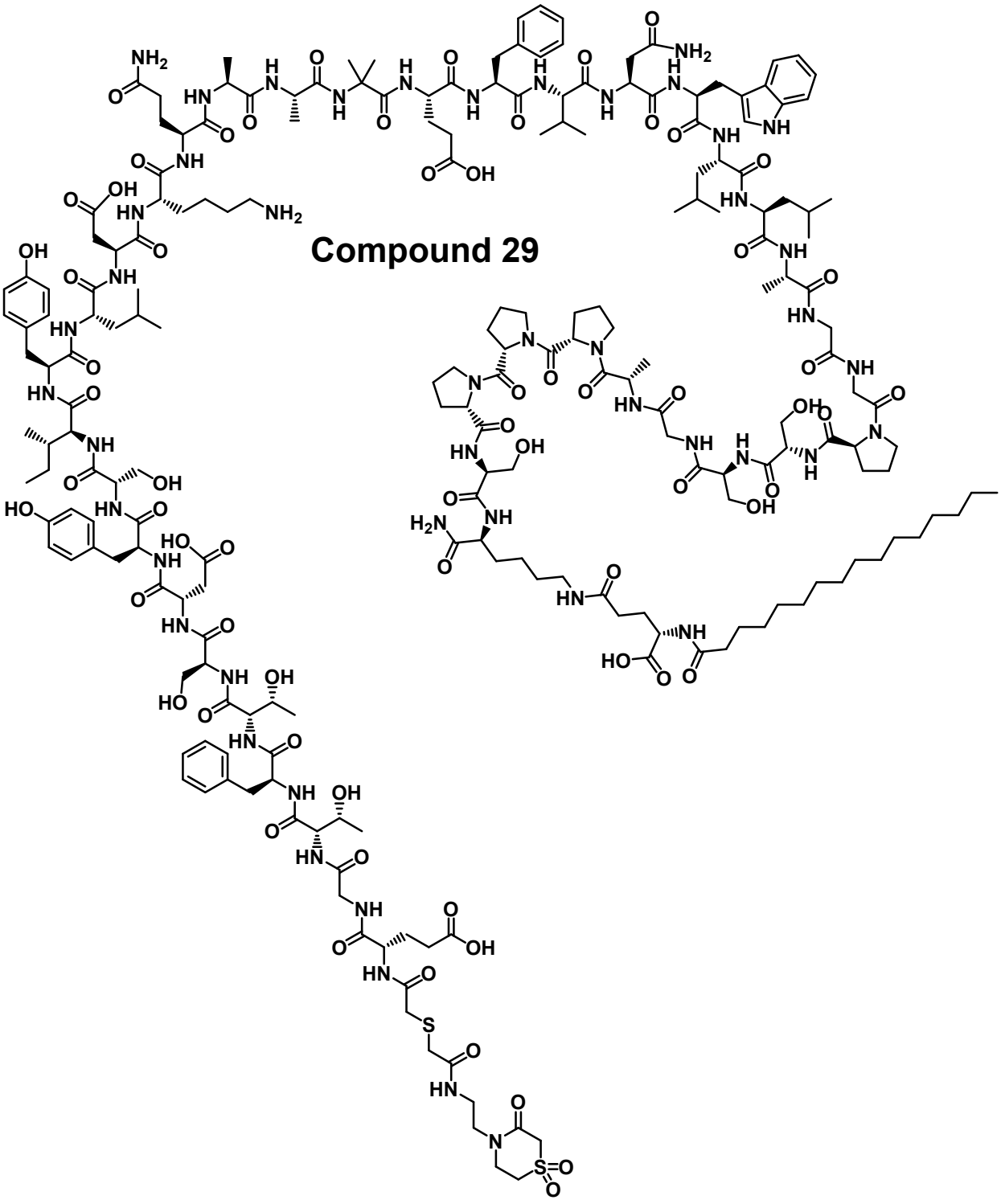

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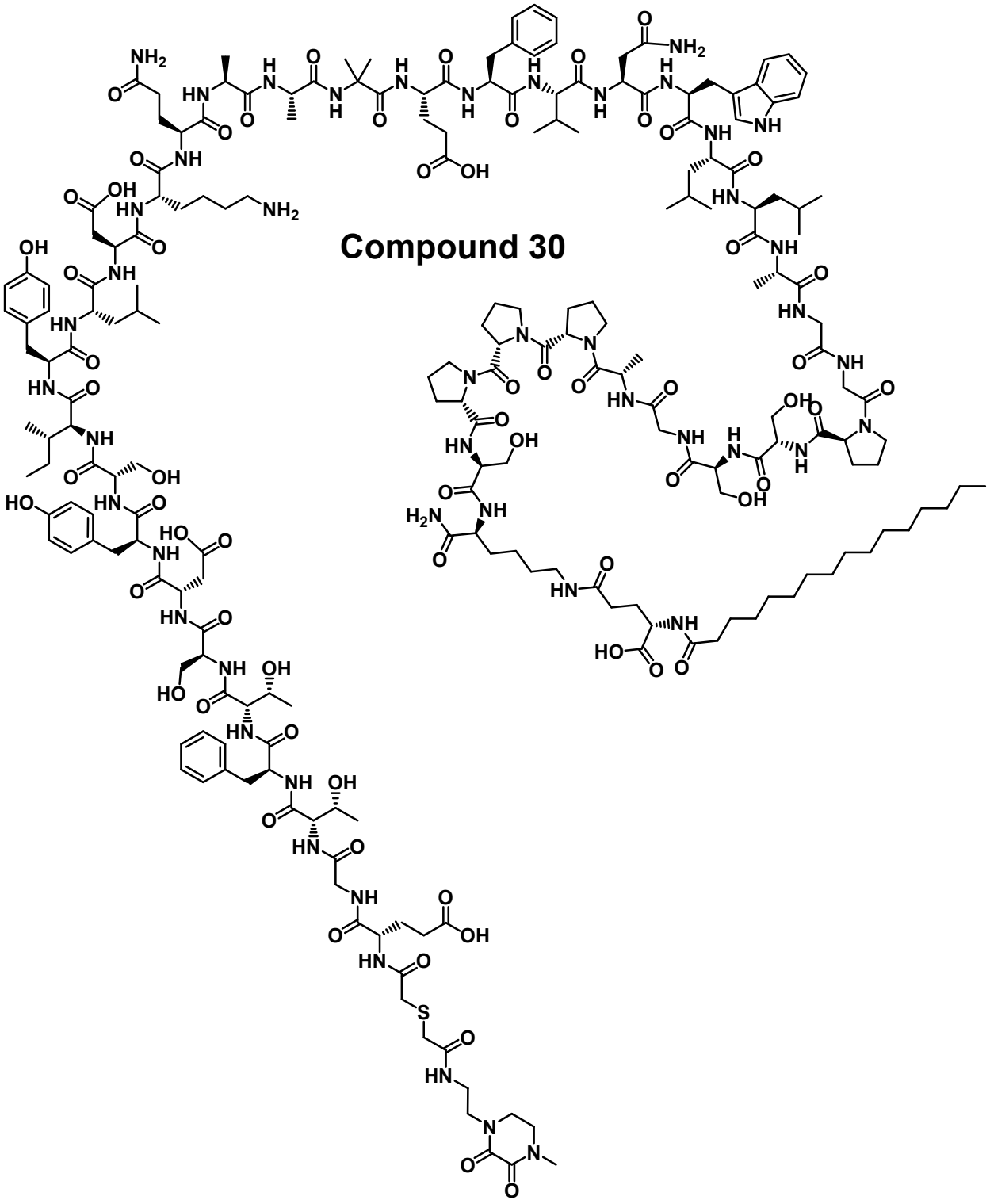

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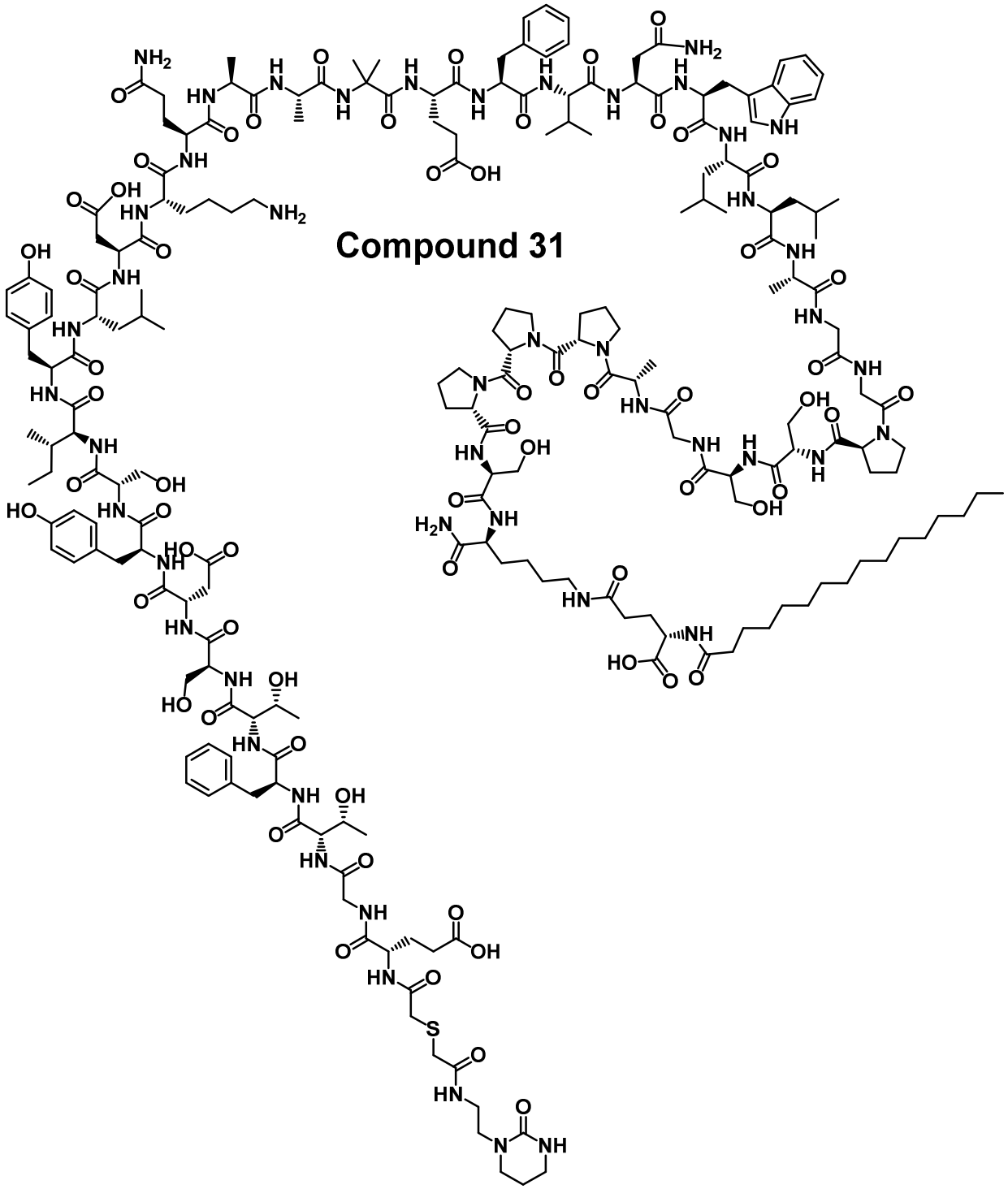

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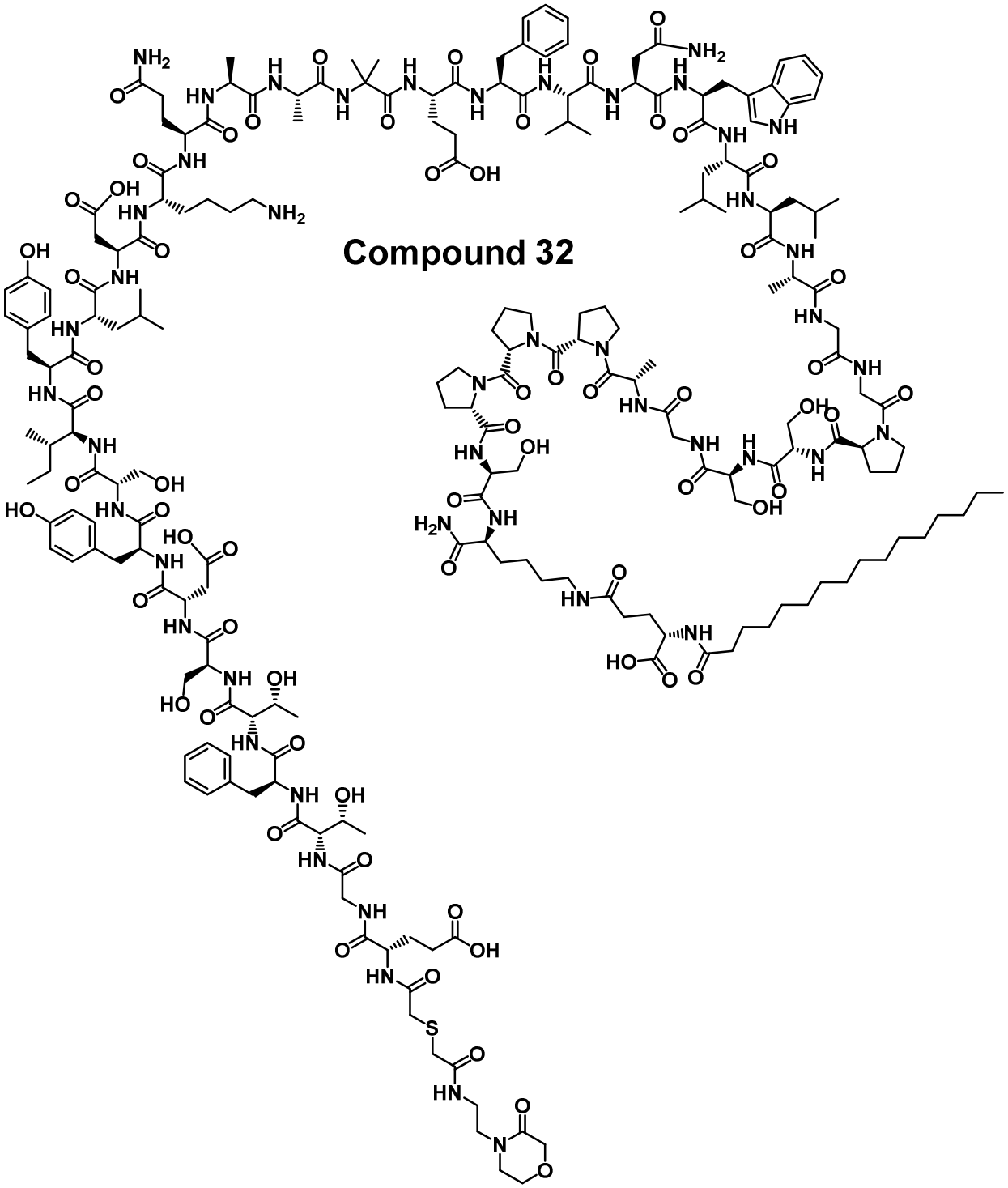


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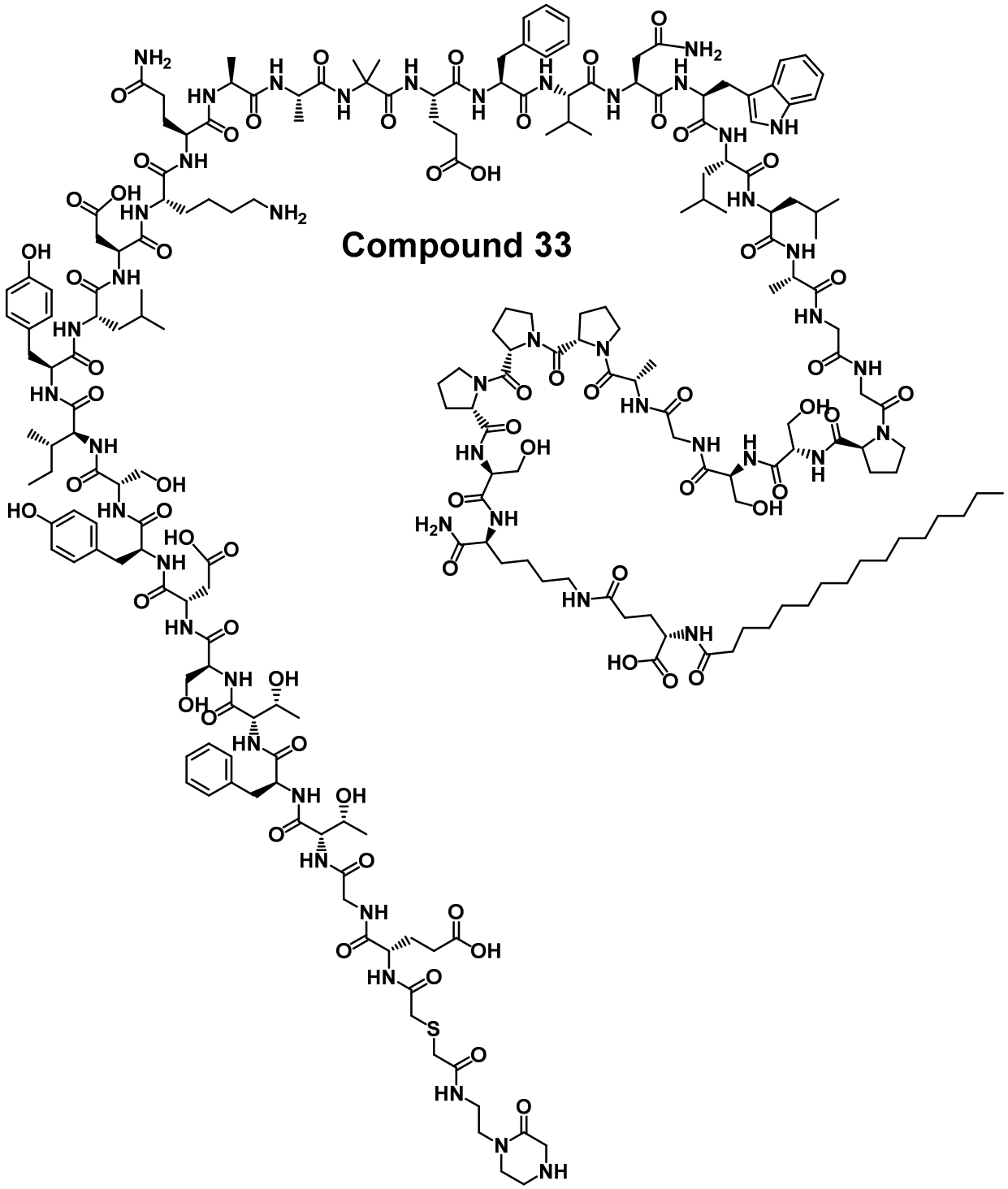

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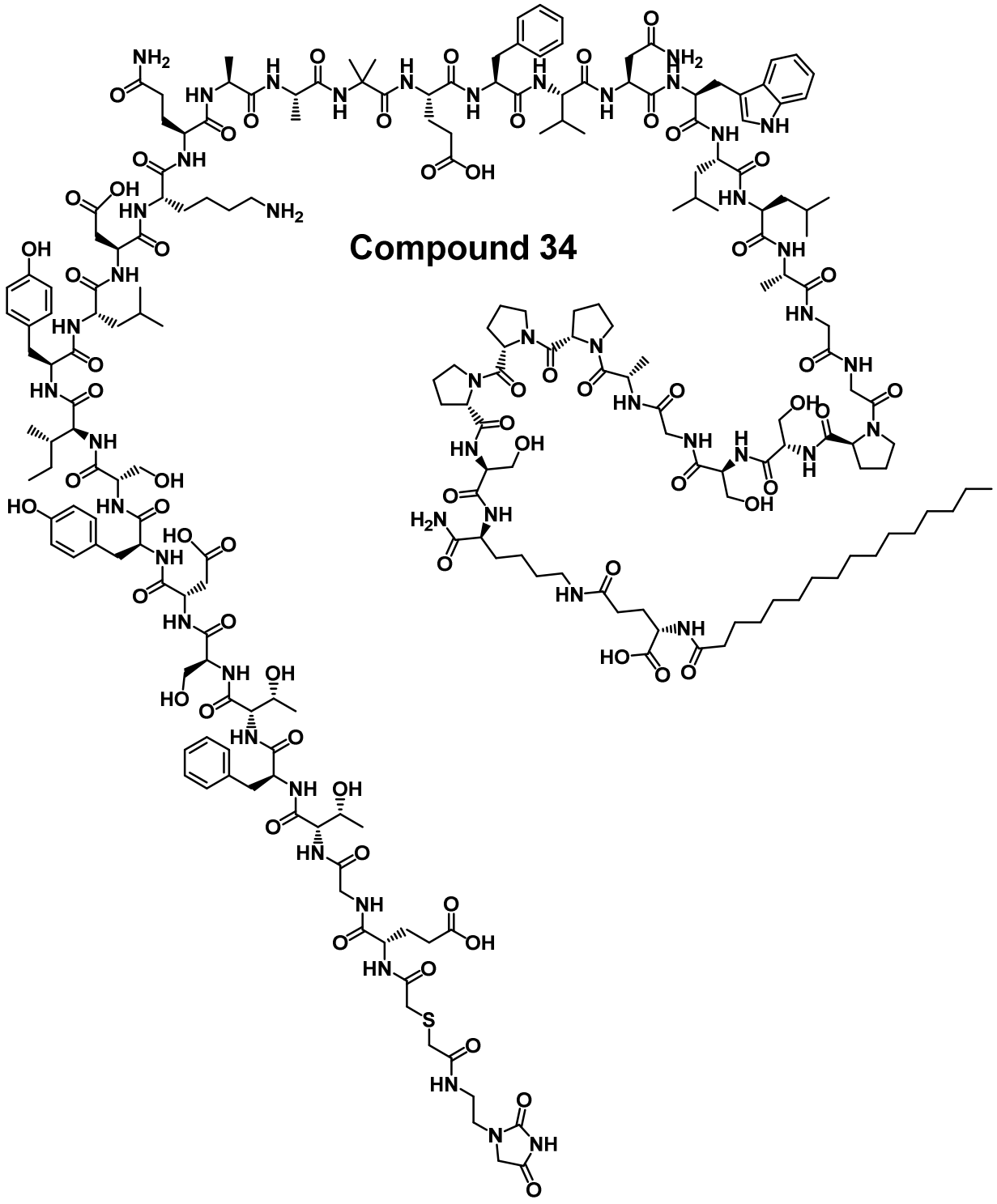

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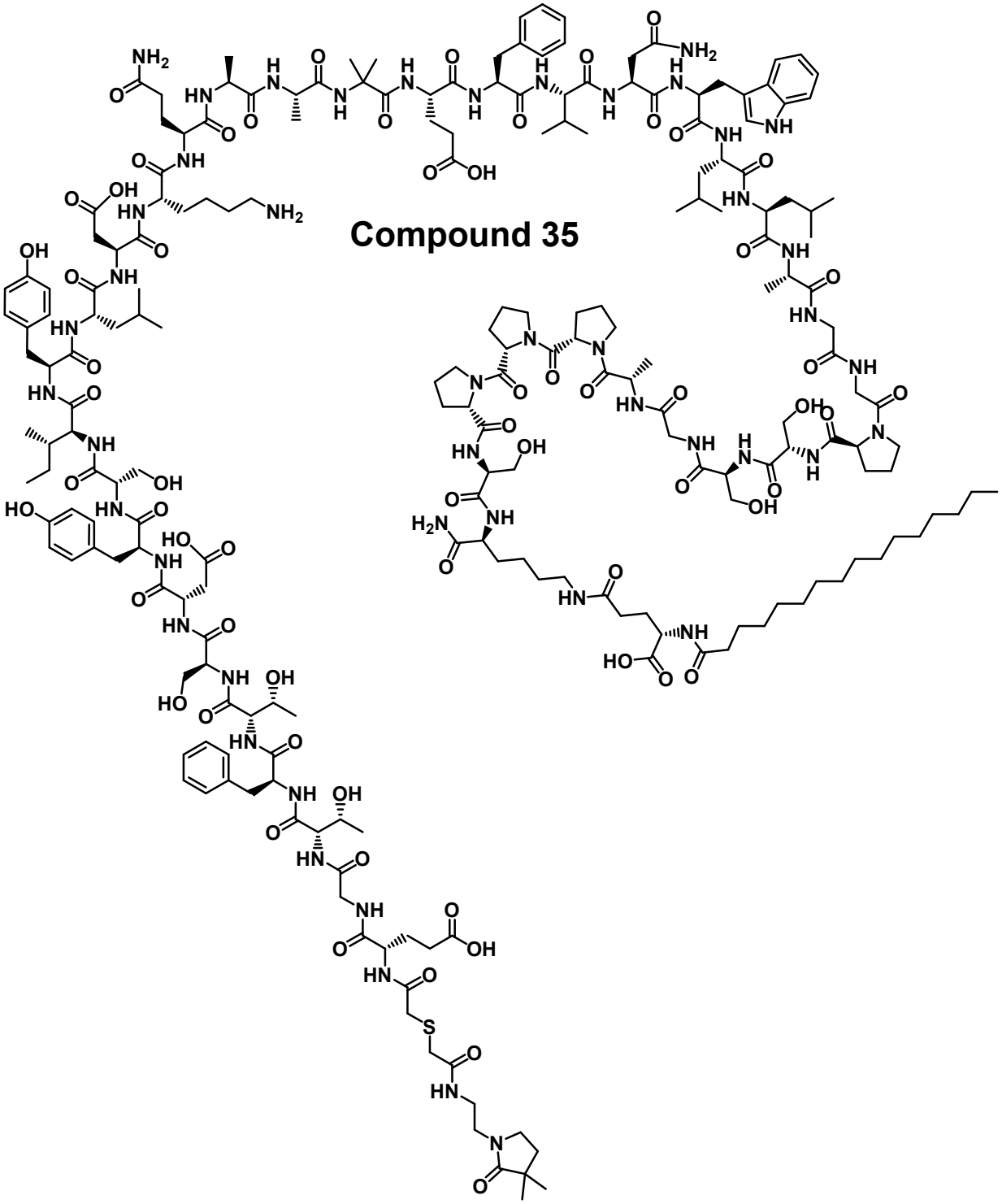


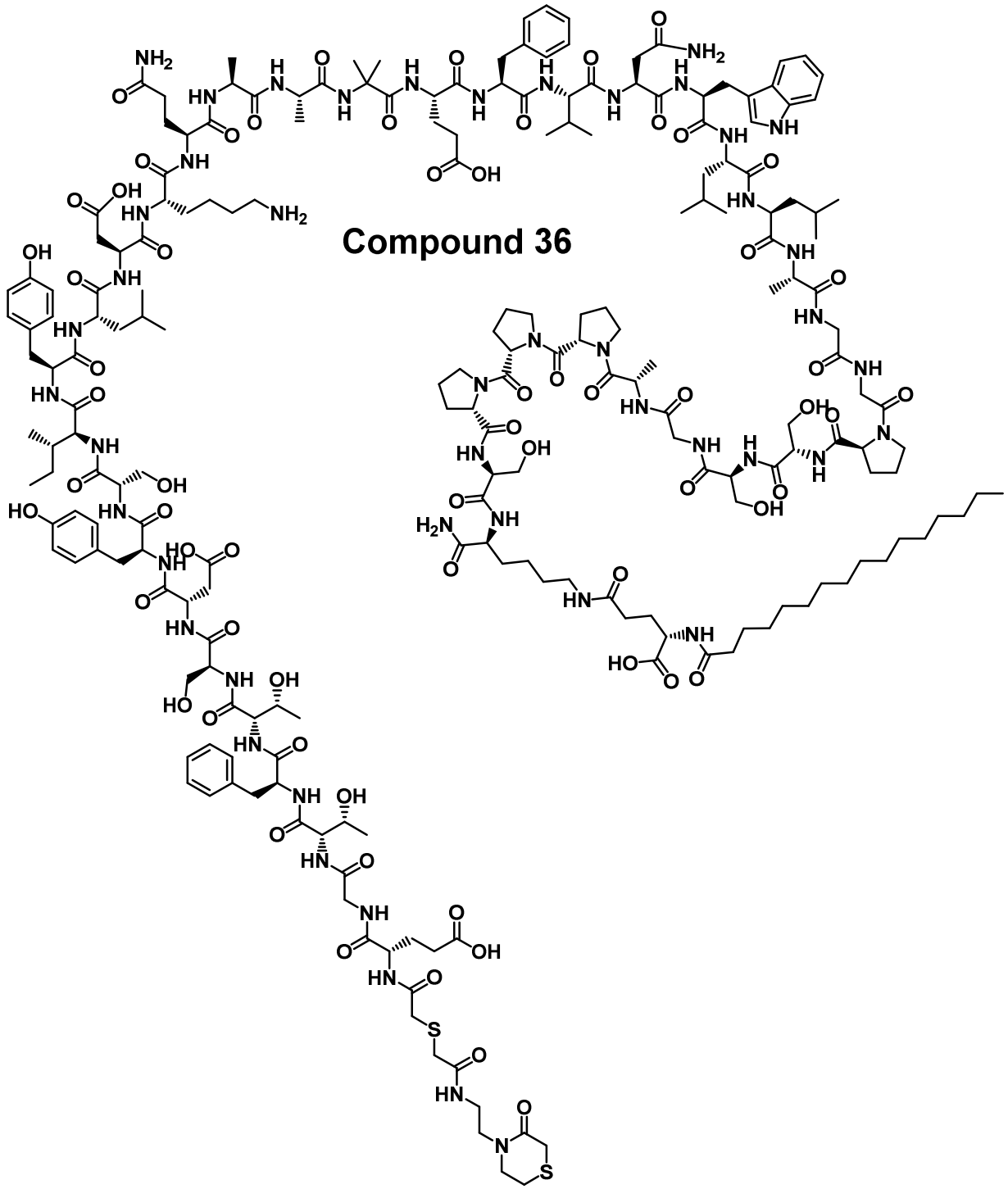
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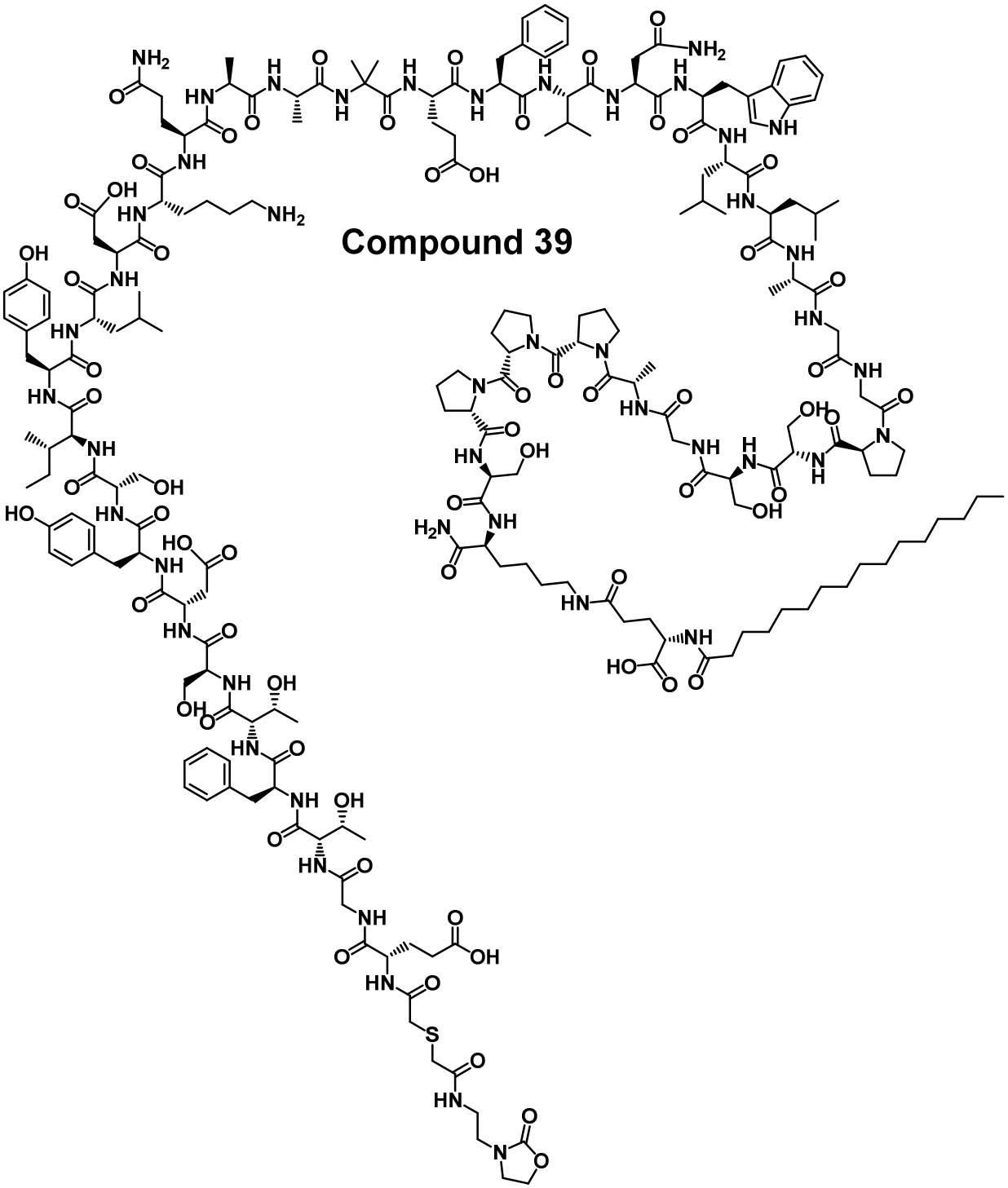
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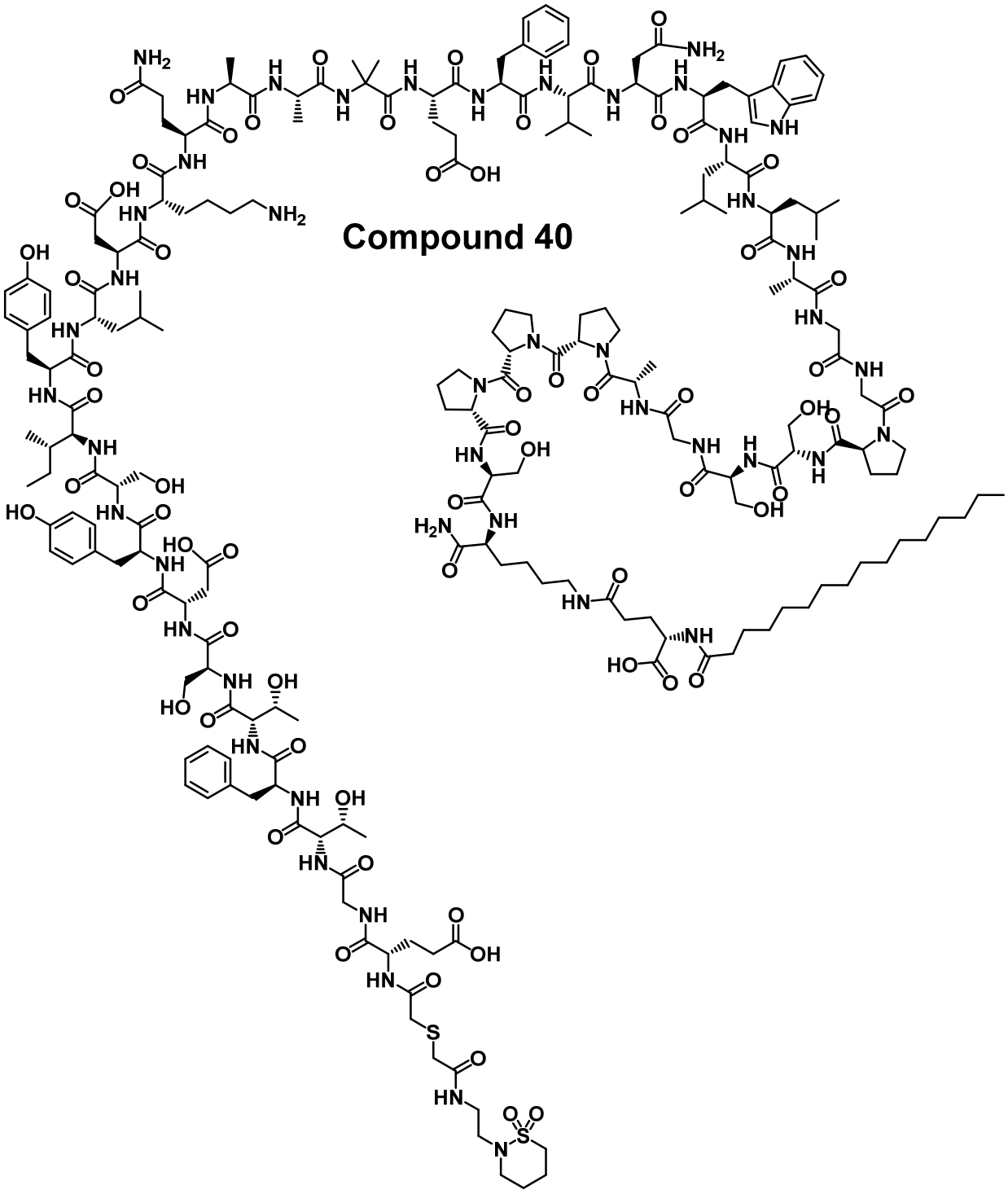

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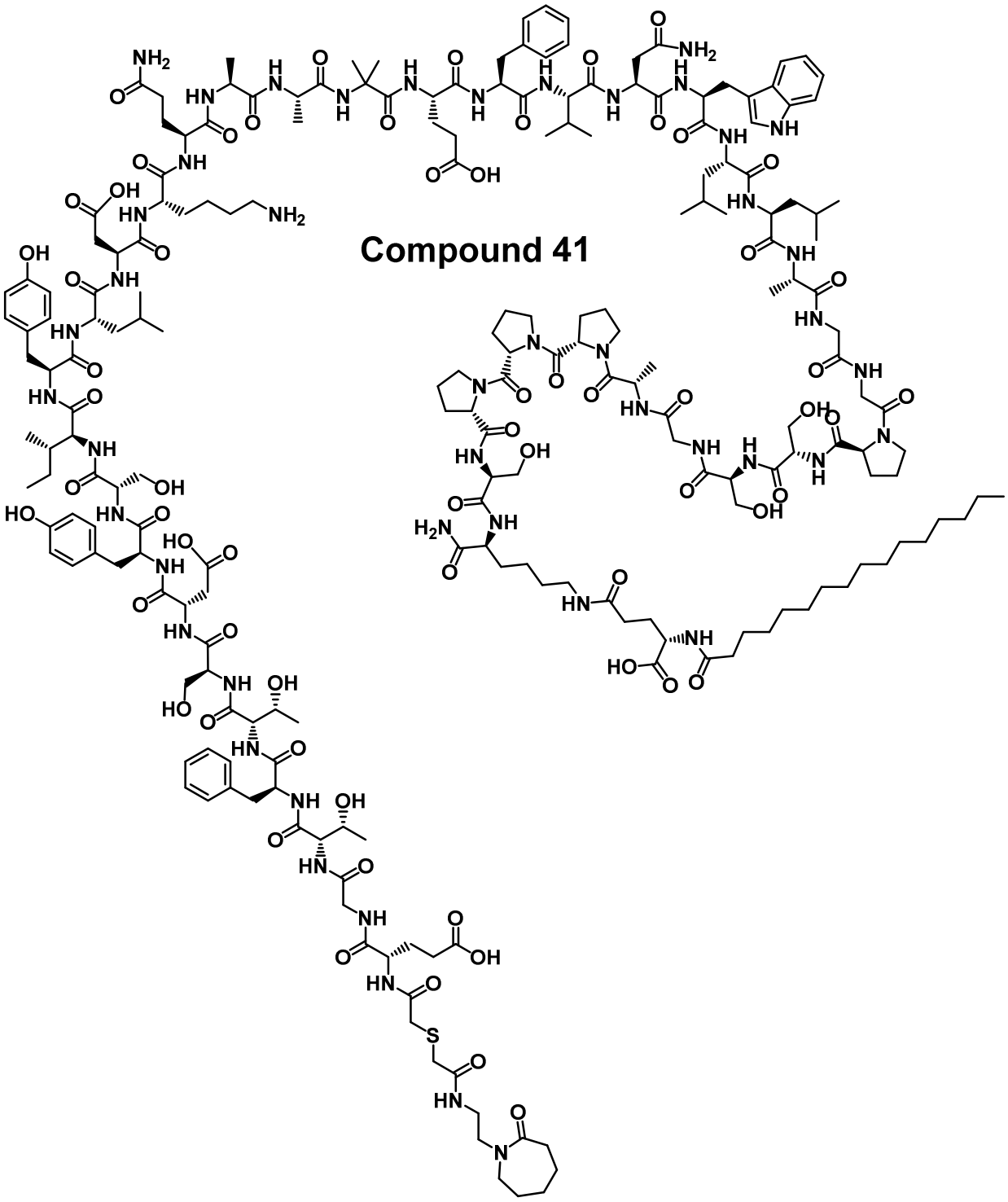


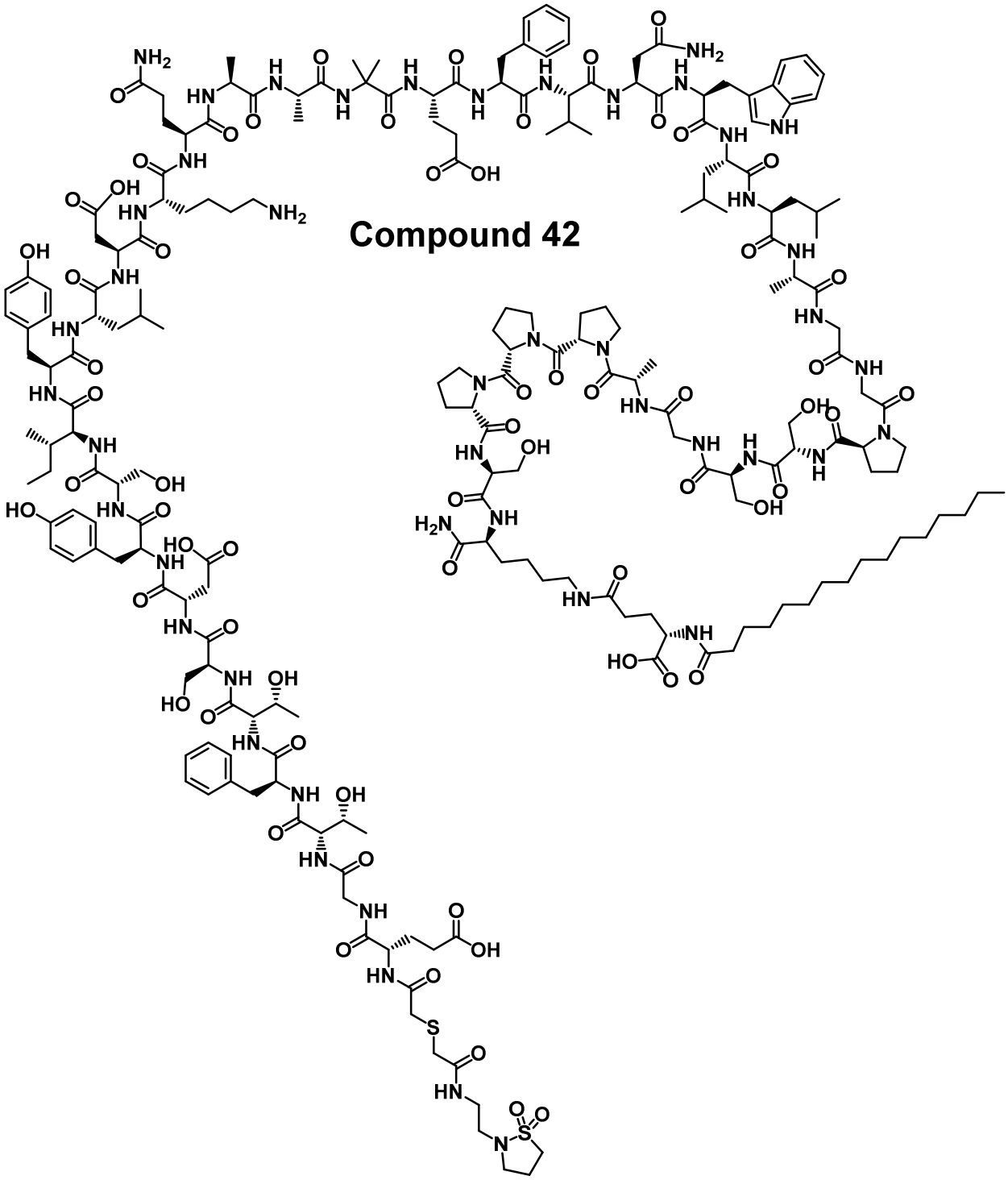
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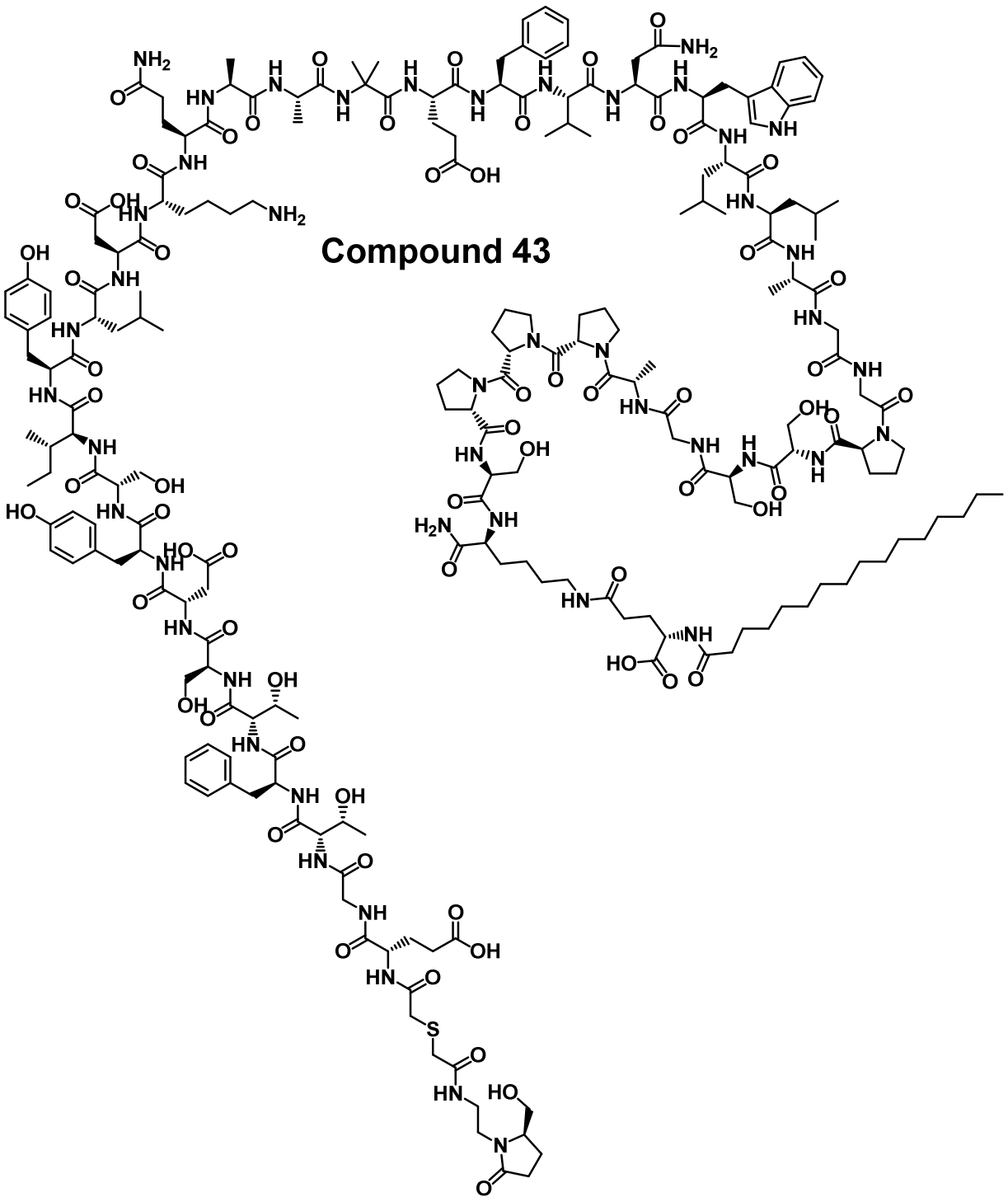


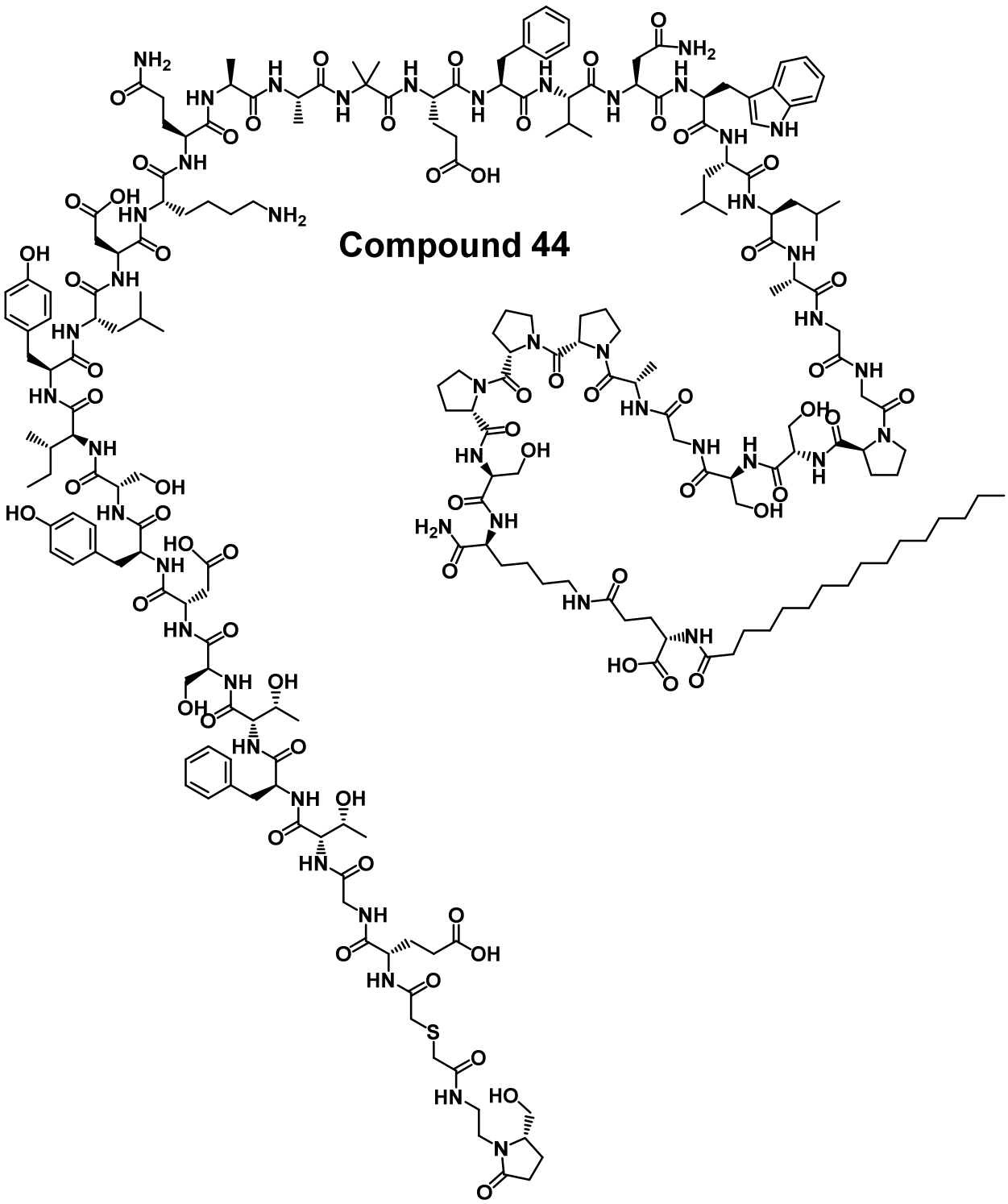
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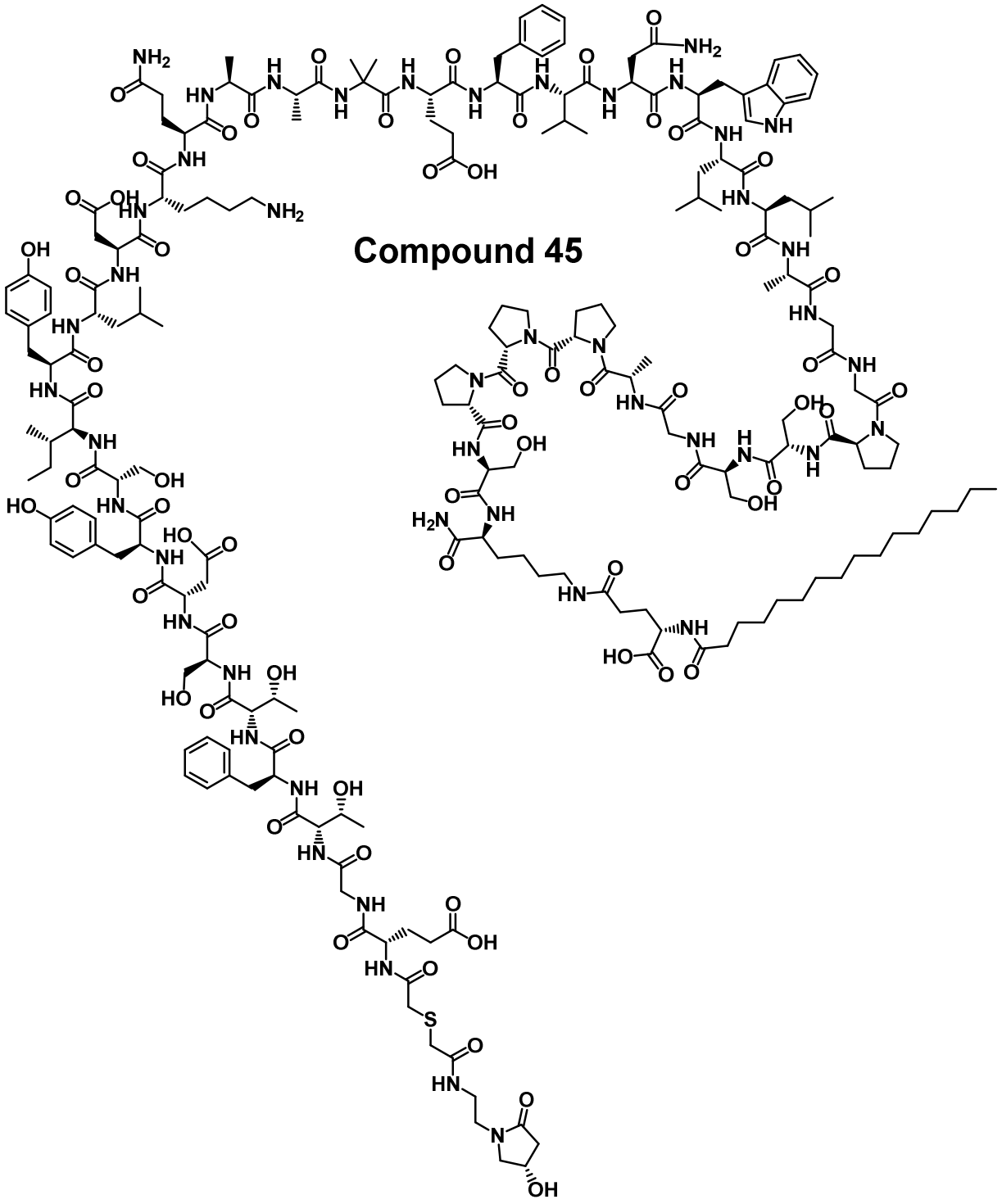

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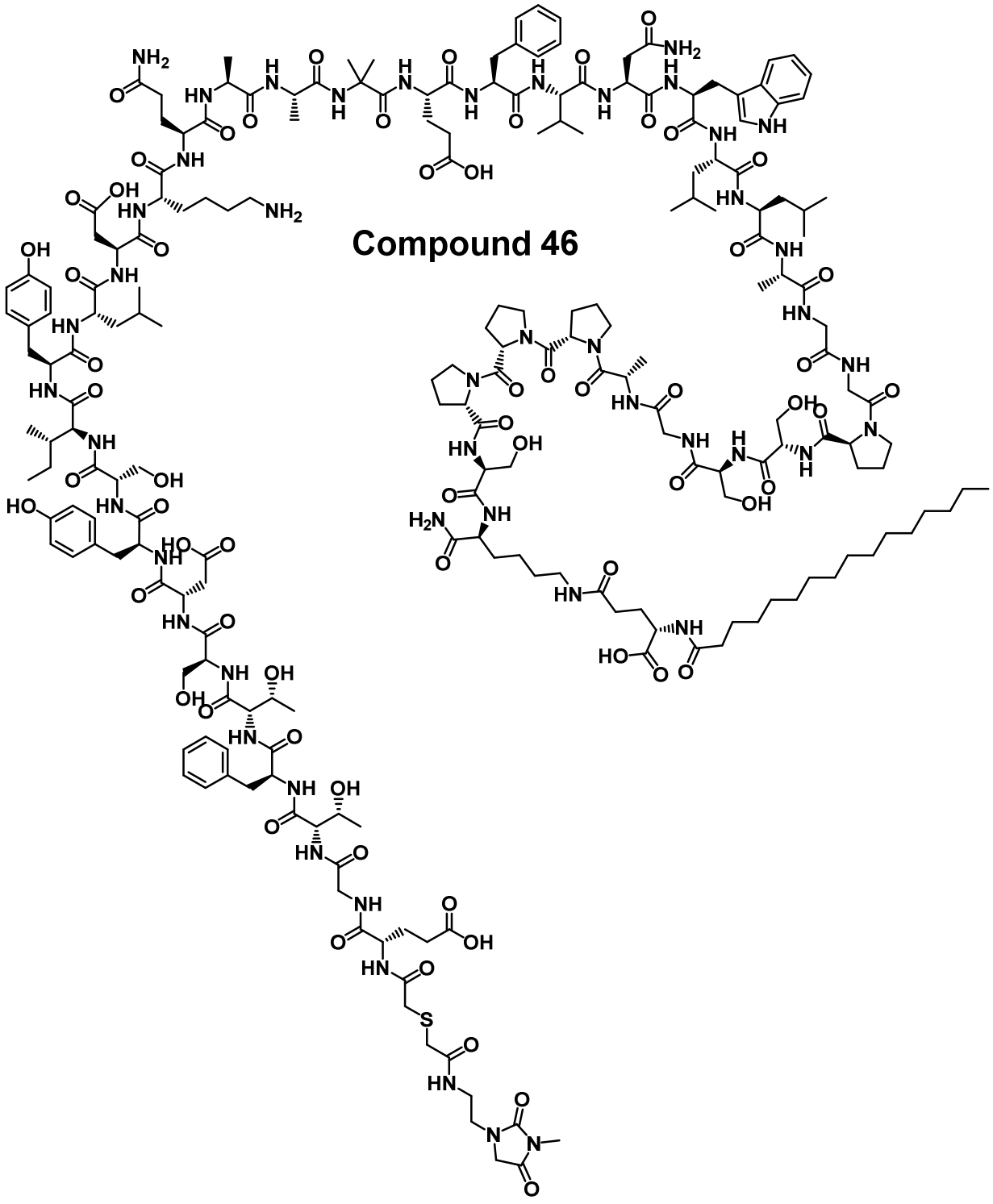

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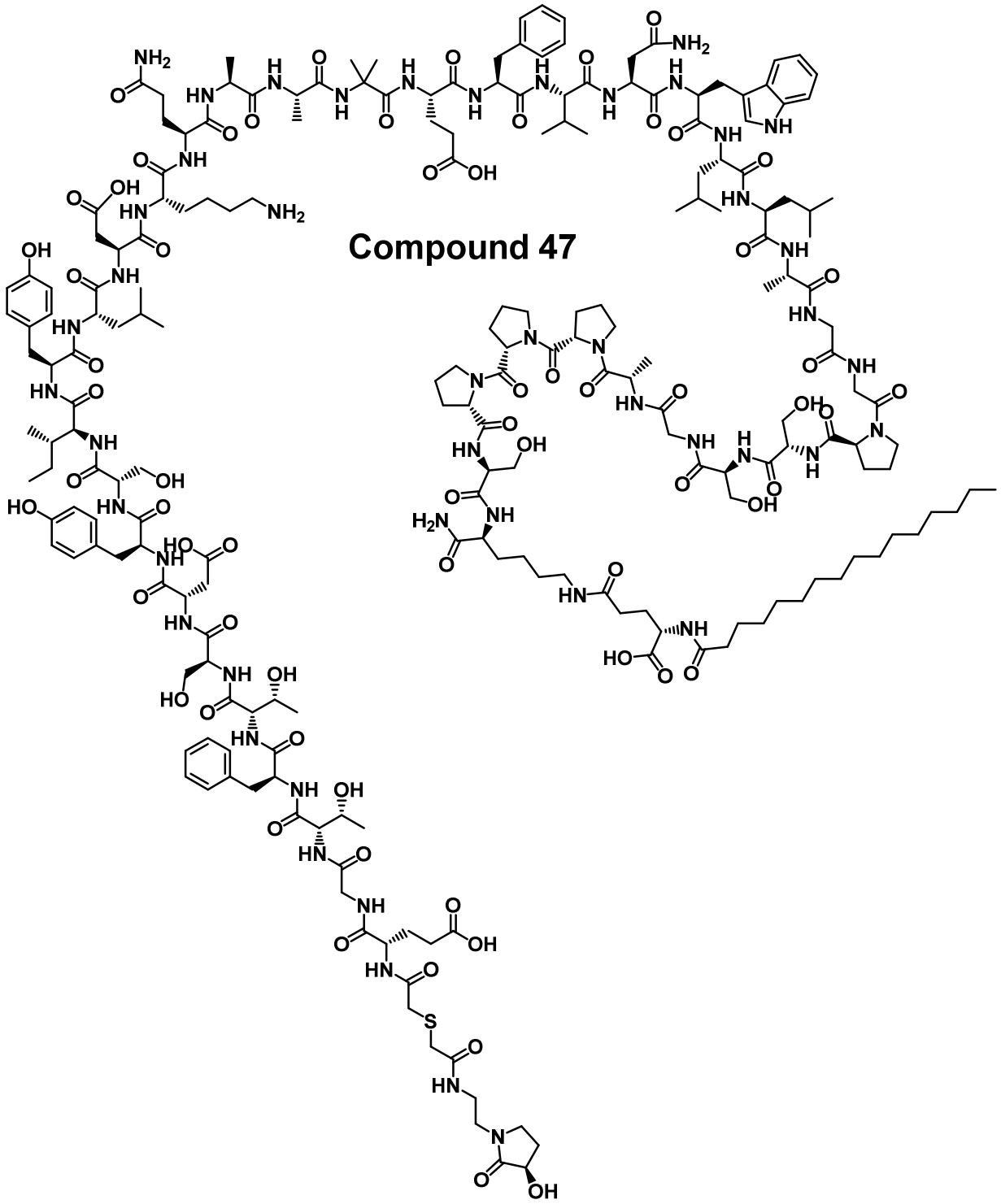

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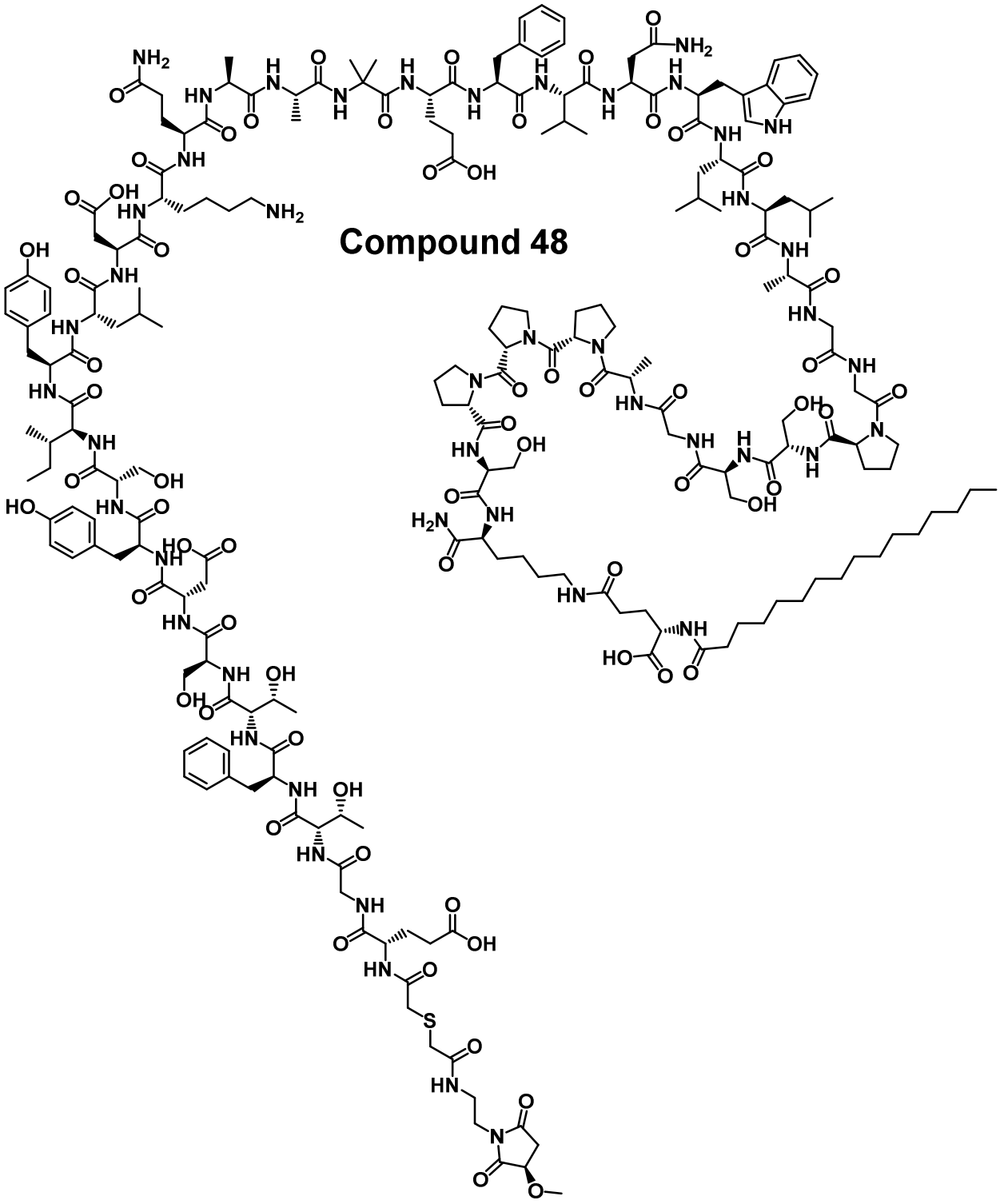

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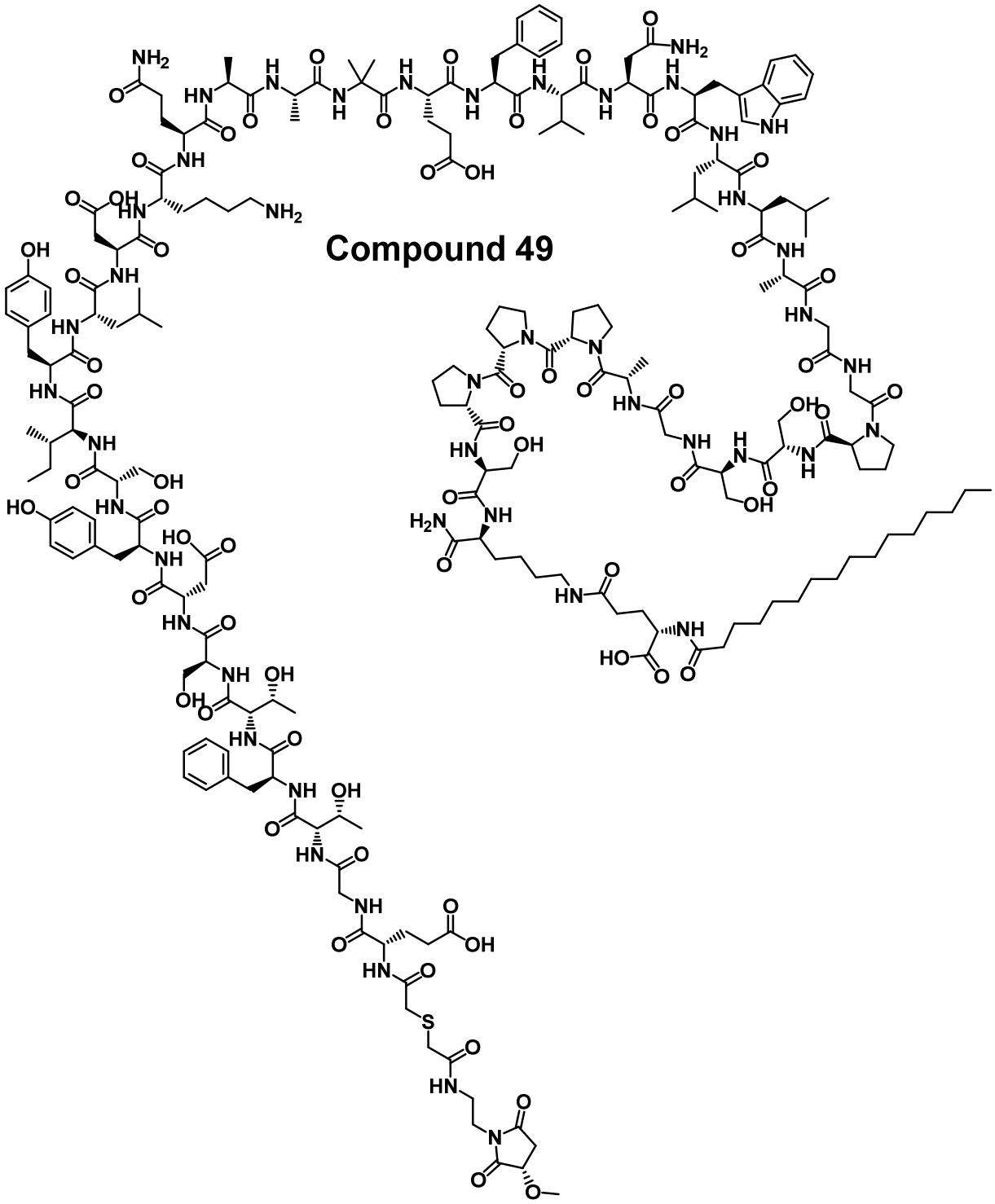


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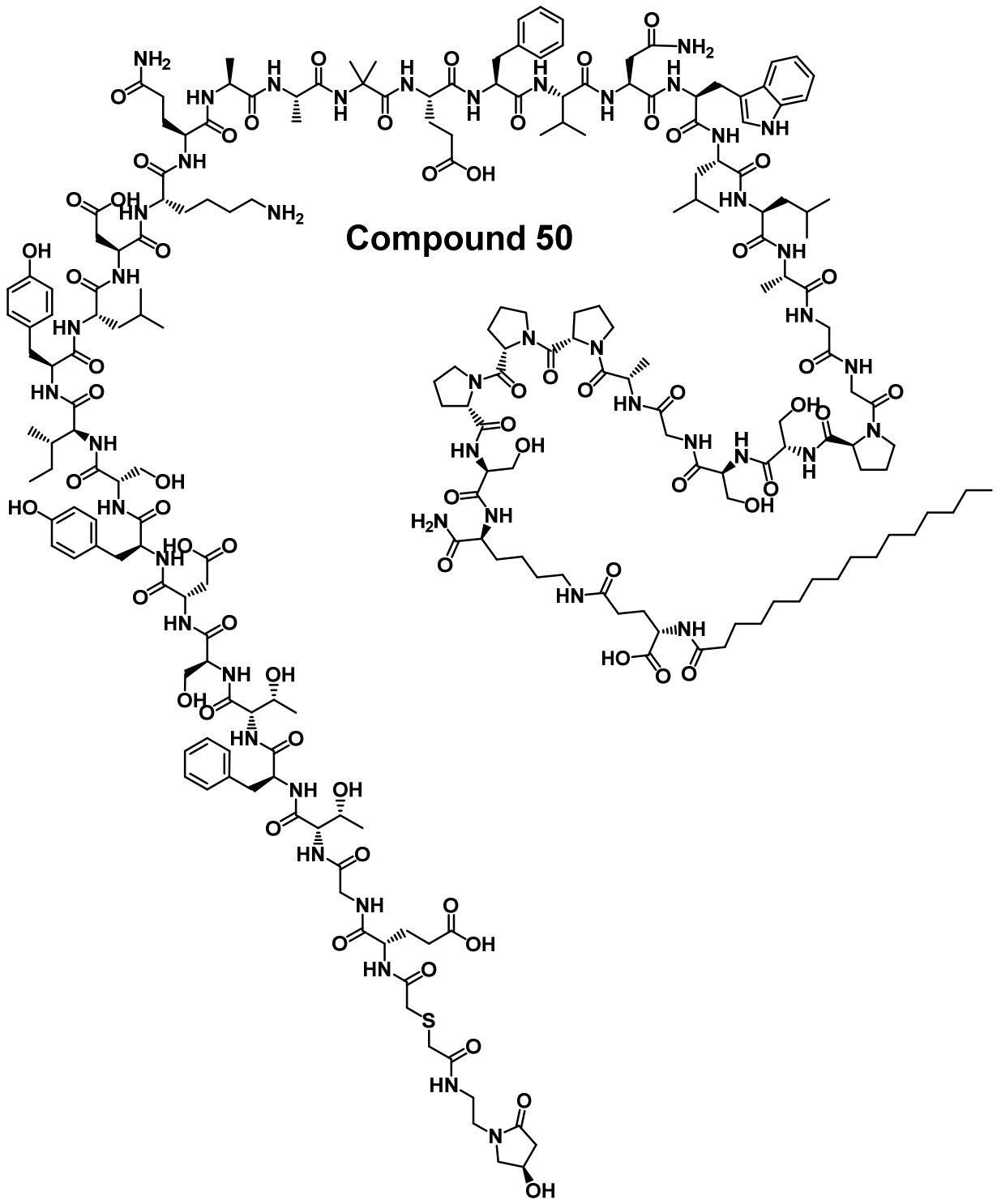

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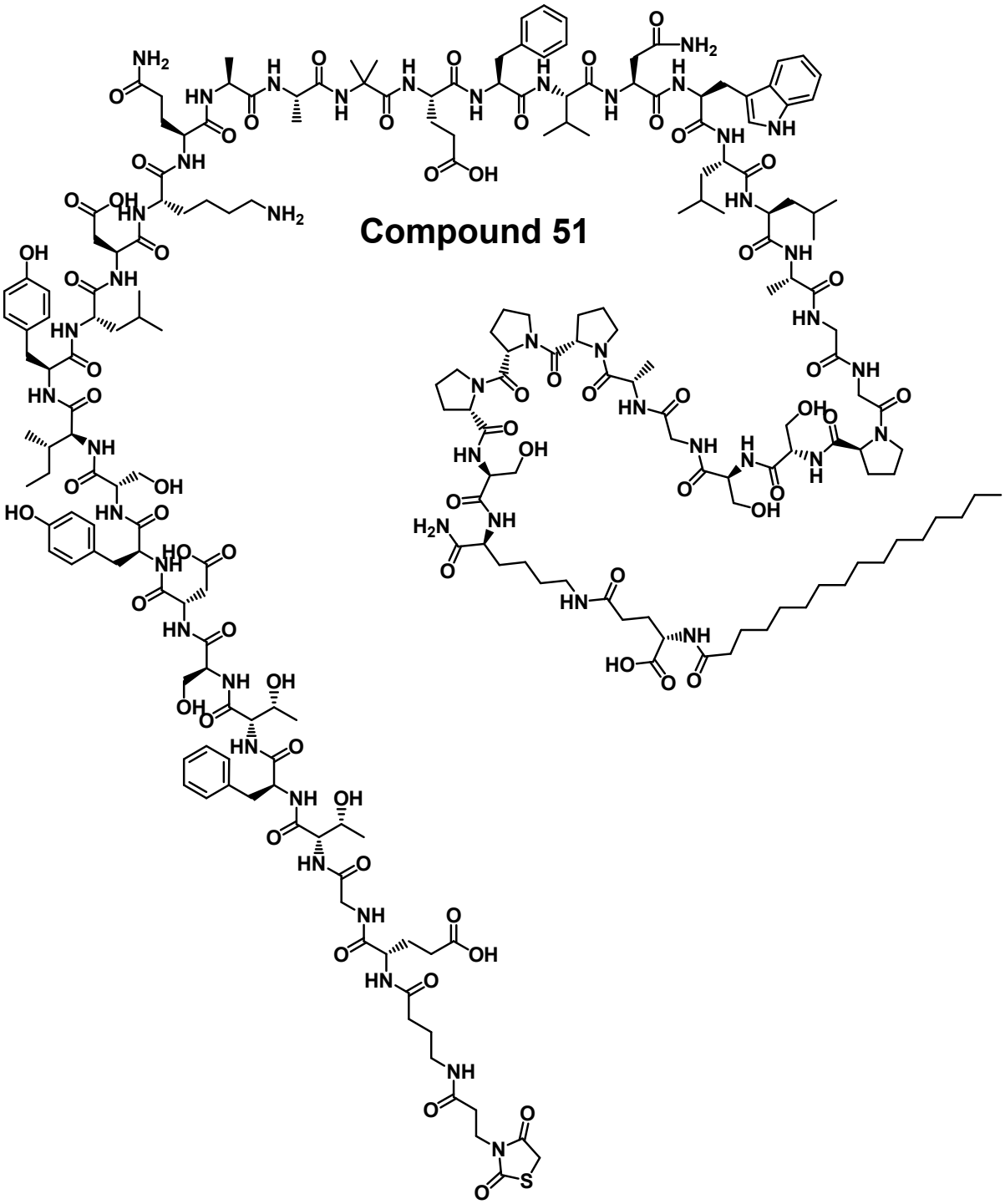


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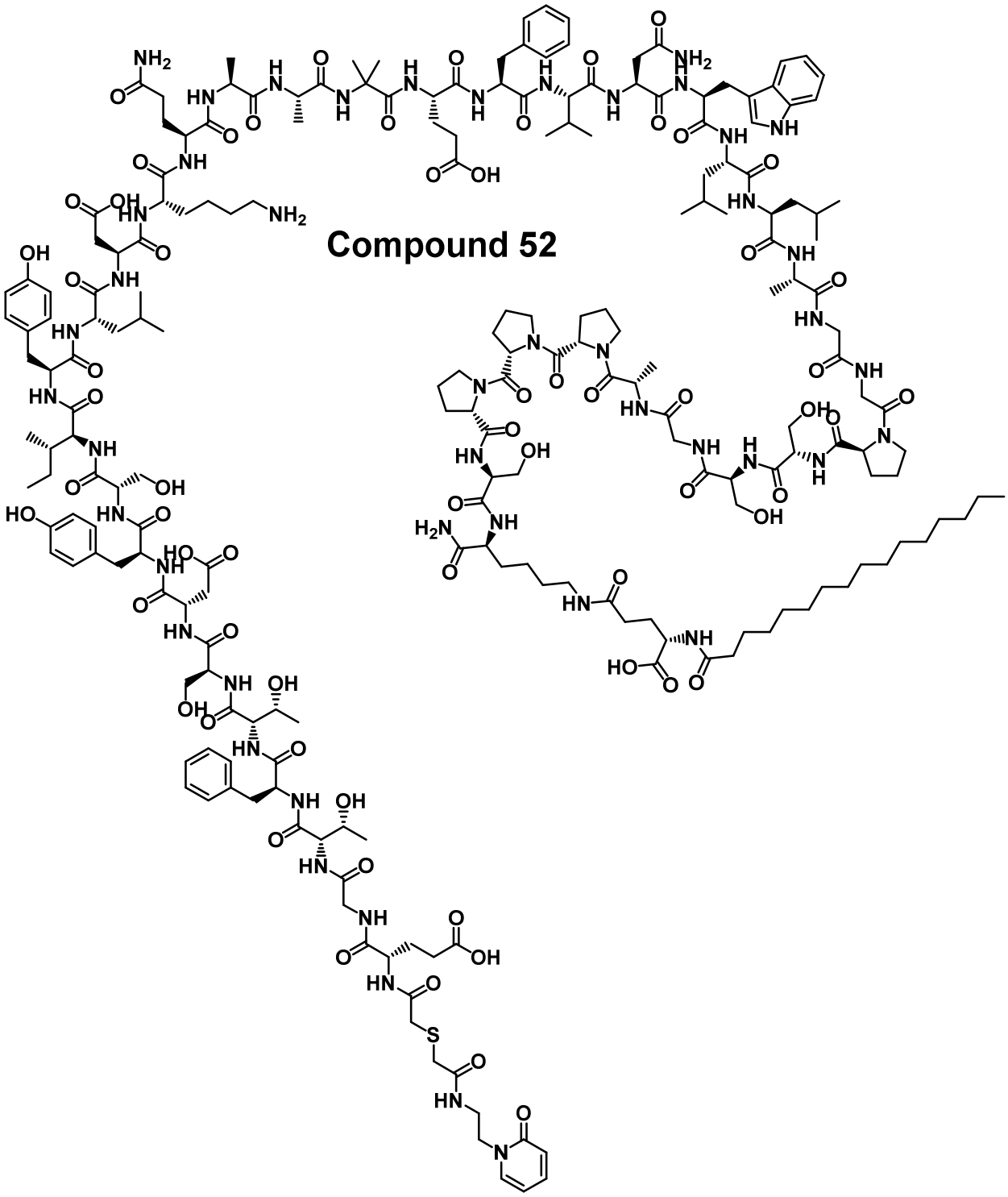


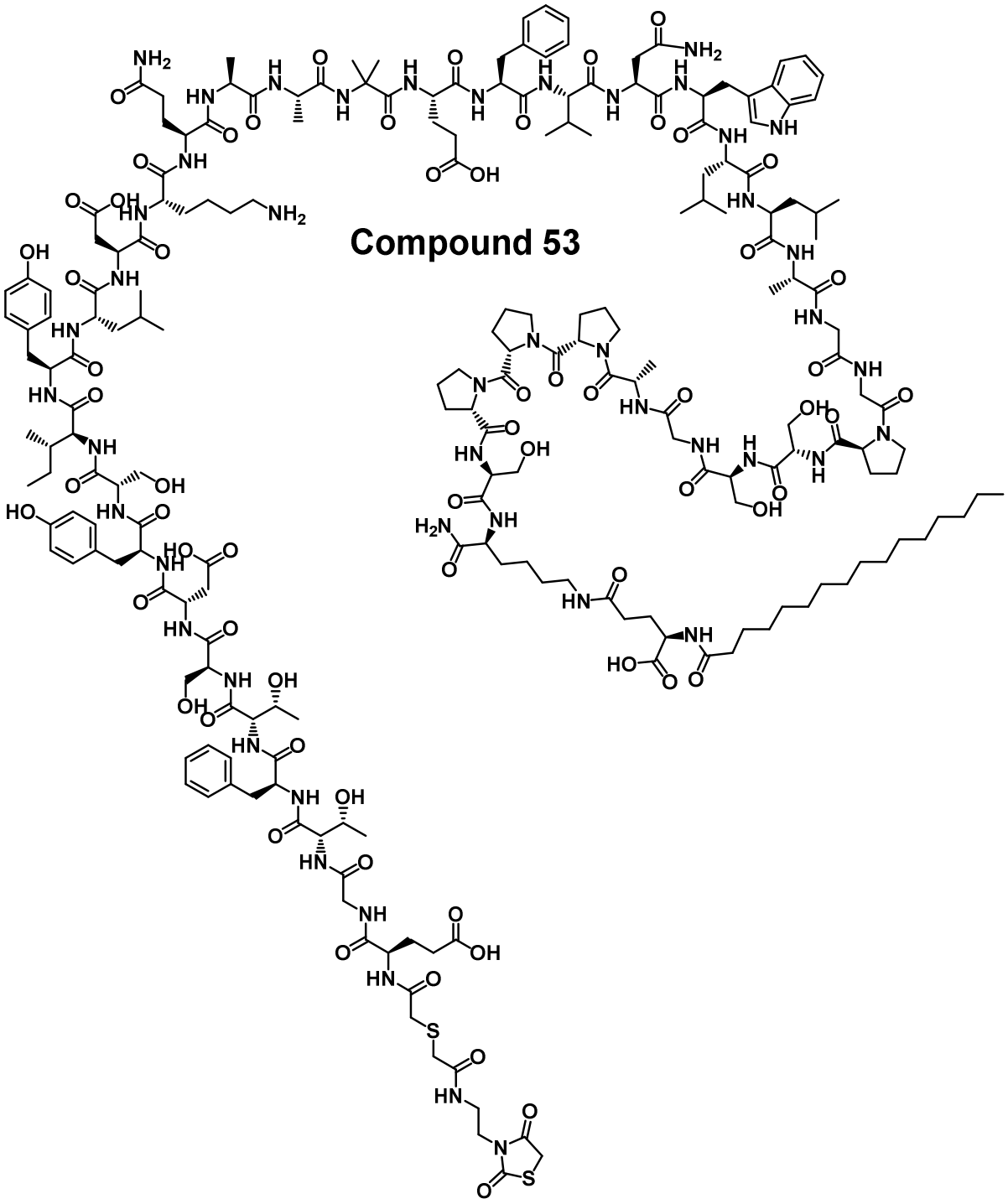
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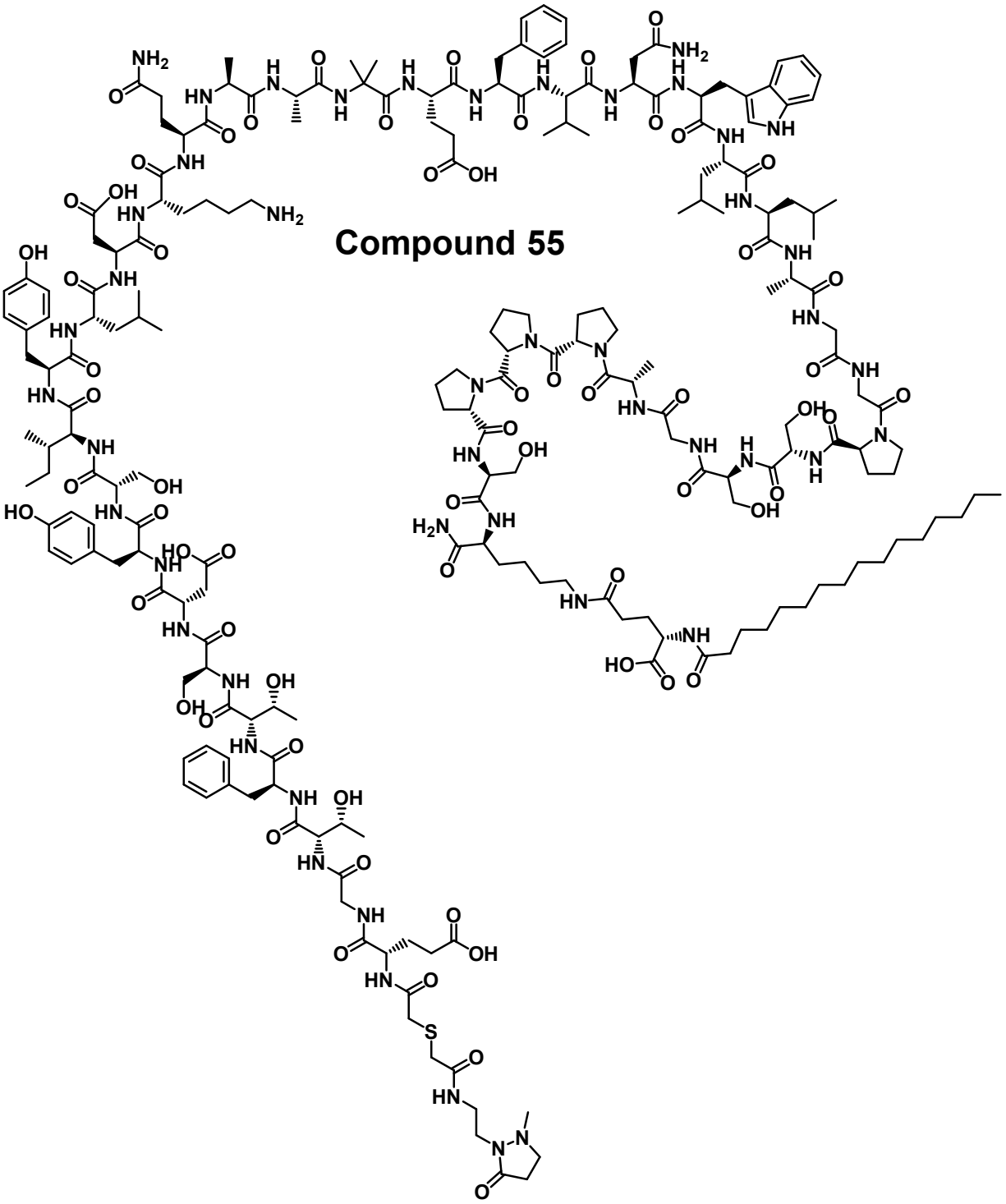

Compound 50



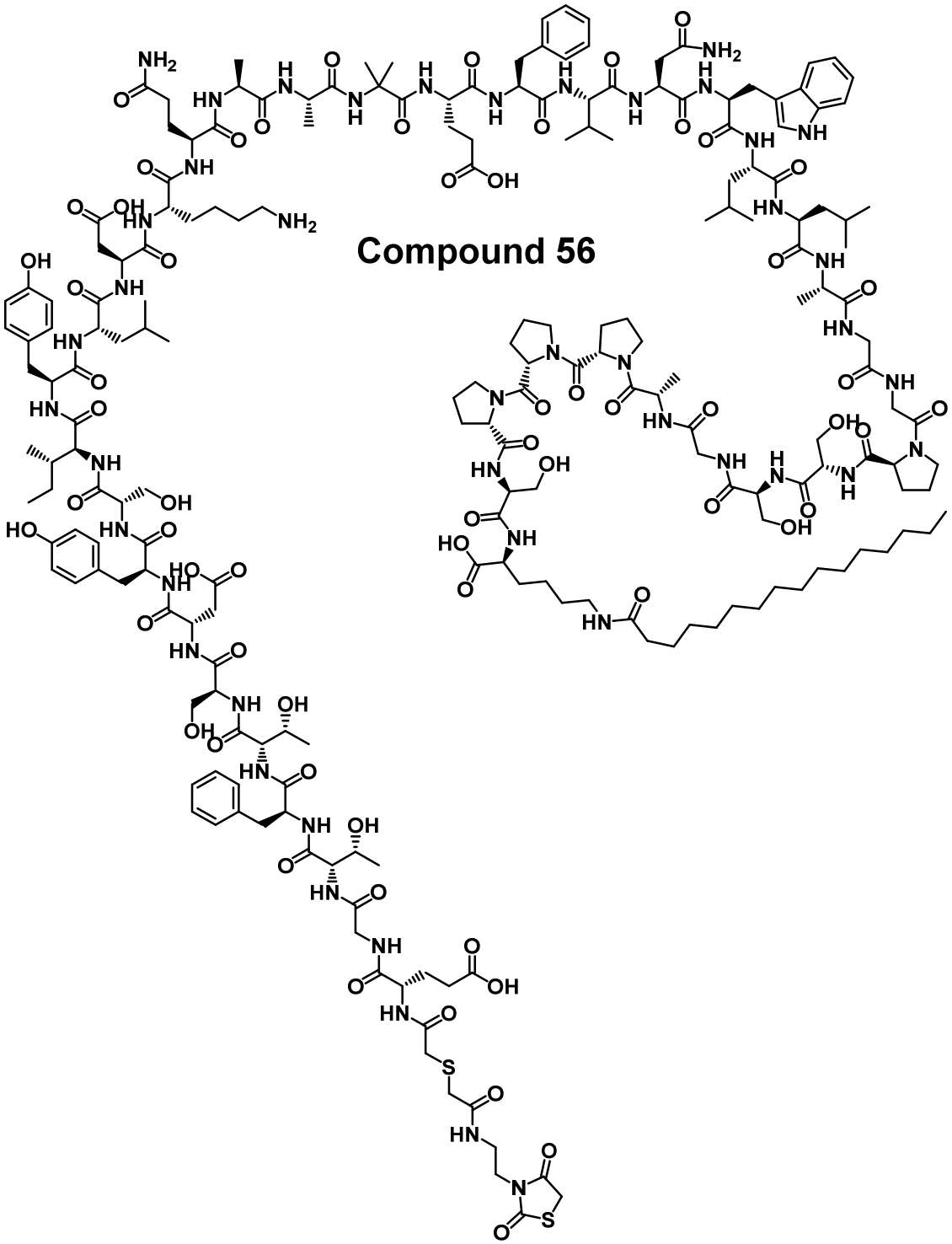
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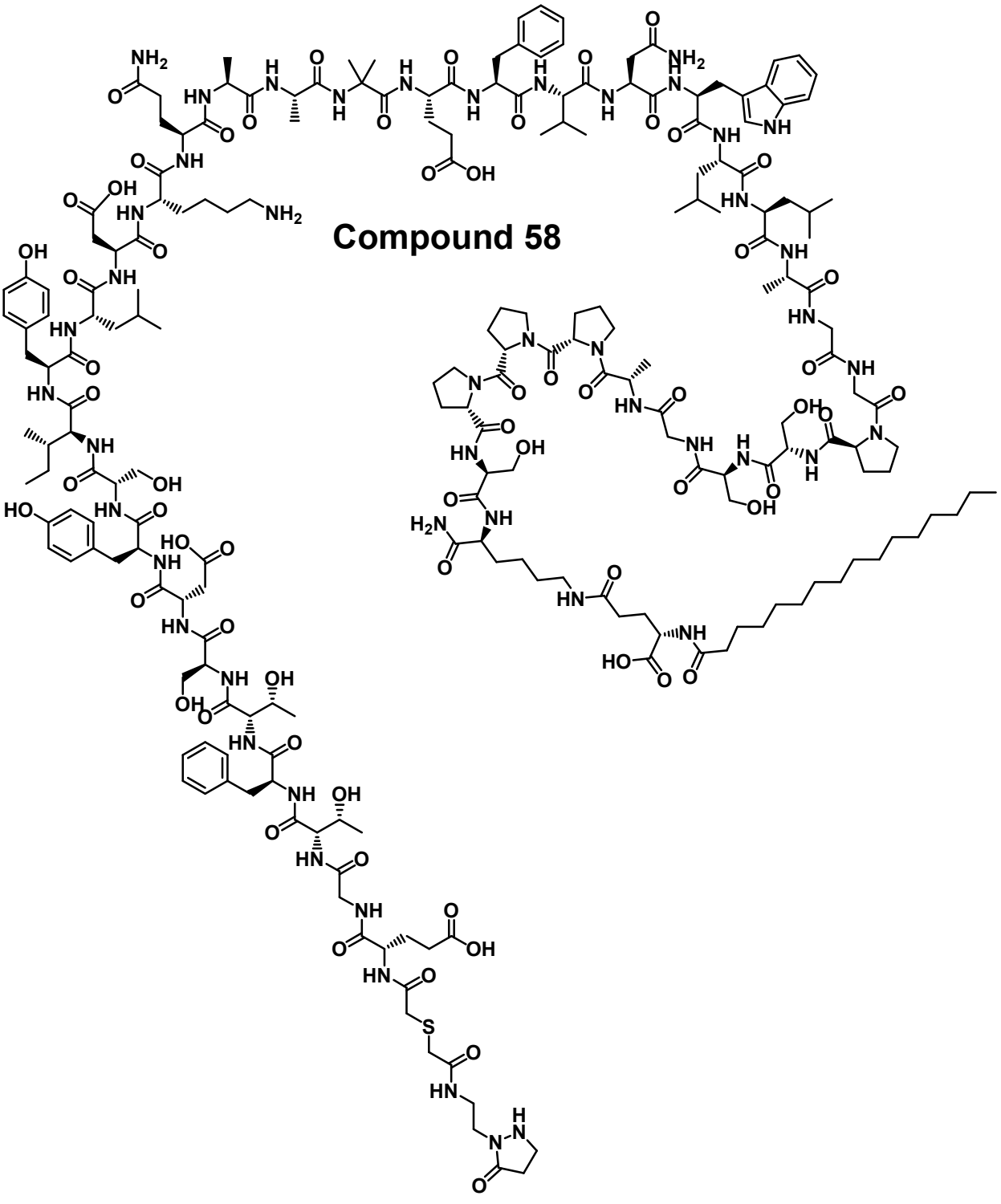

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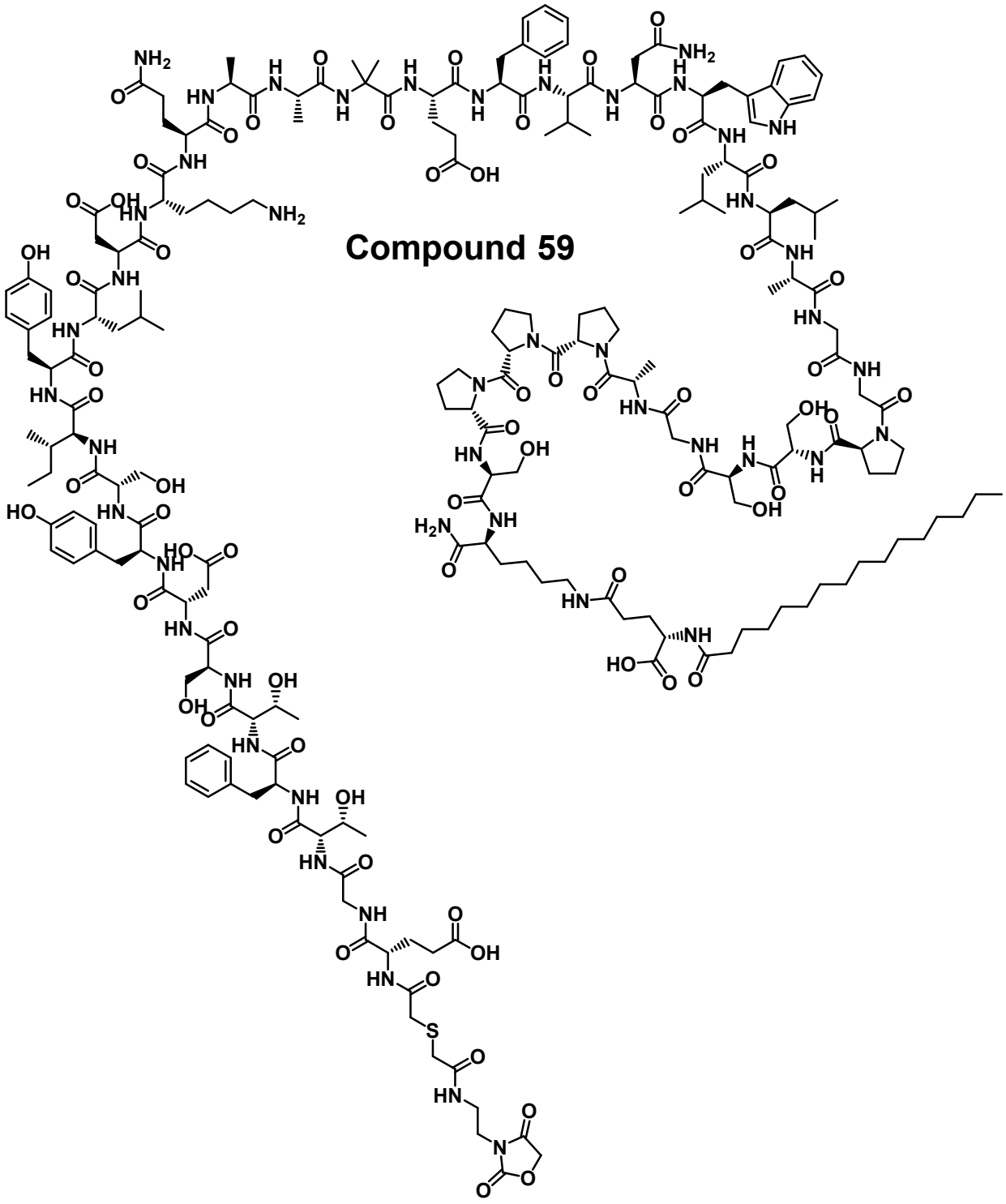

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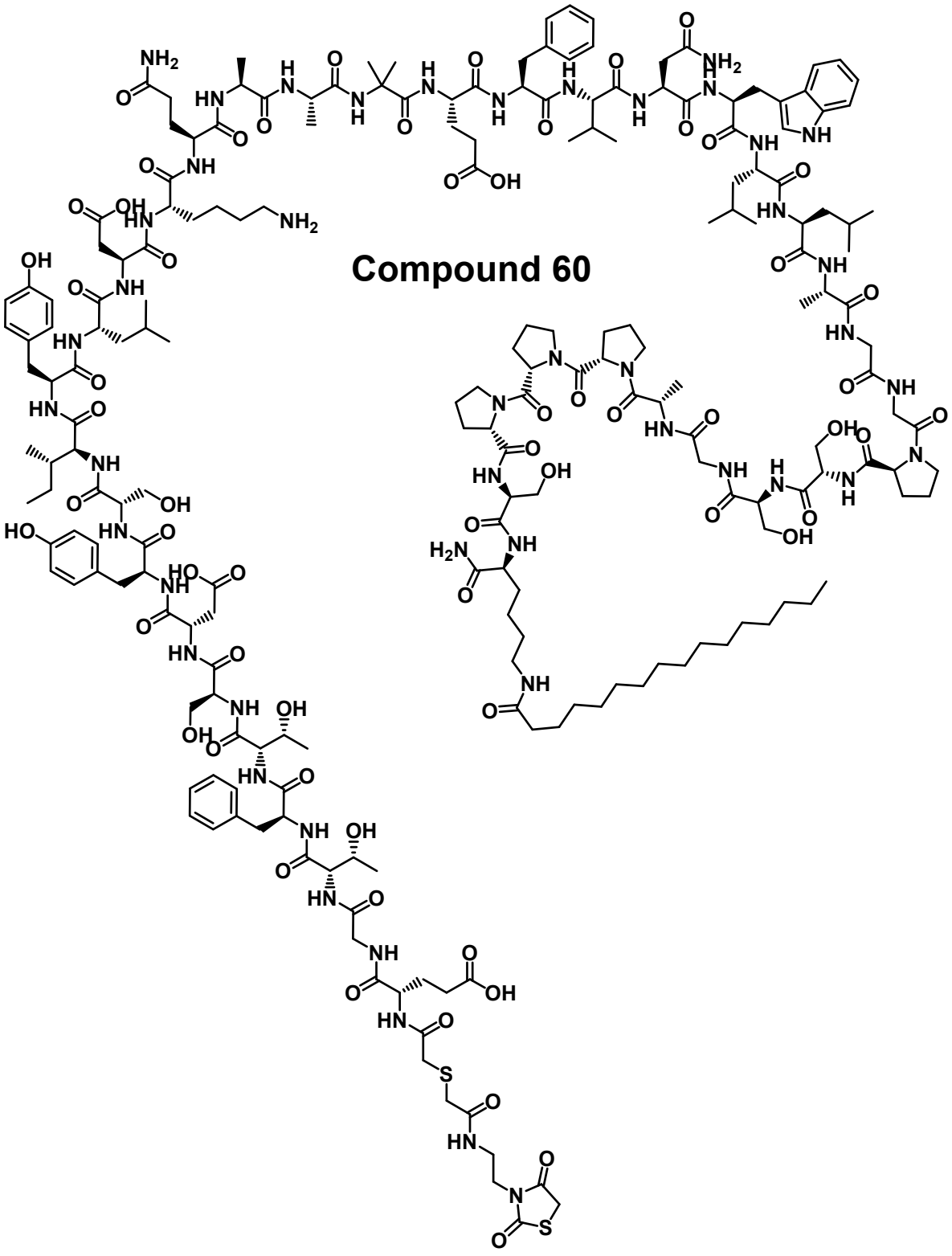
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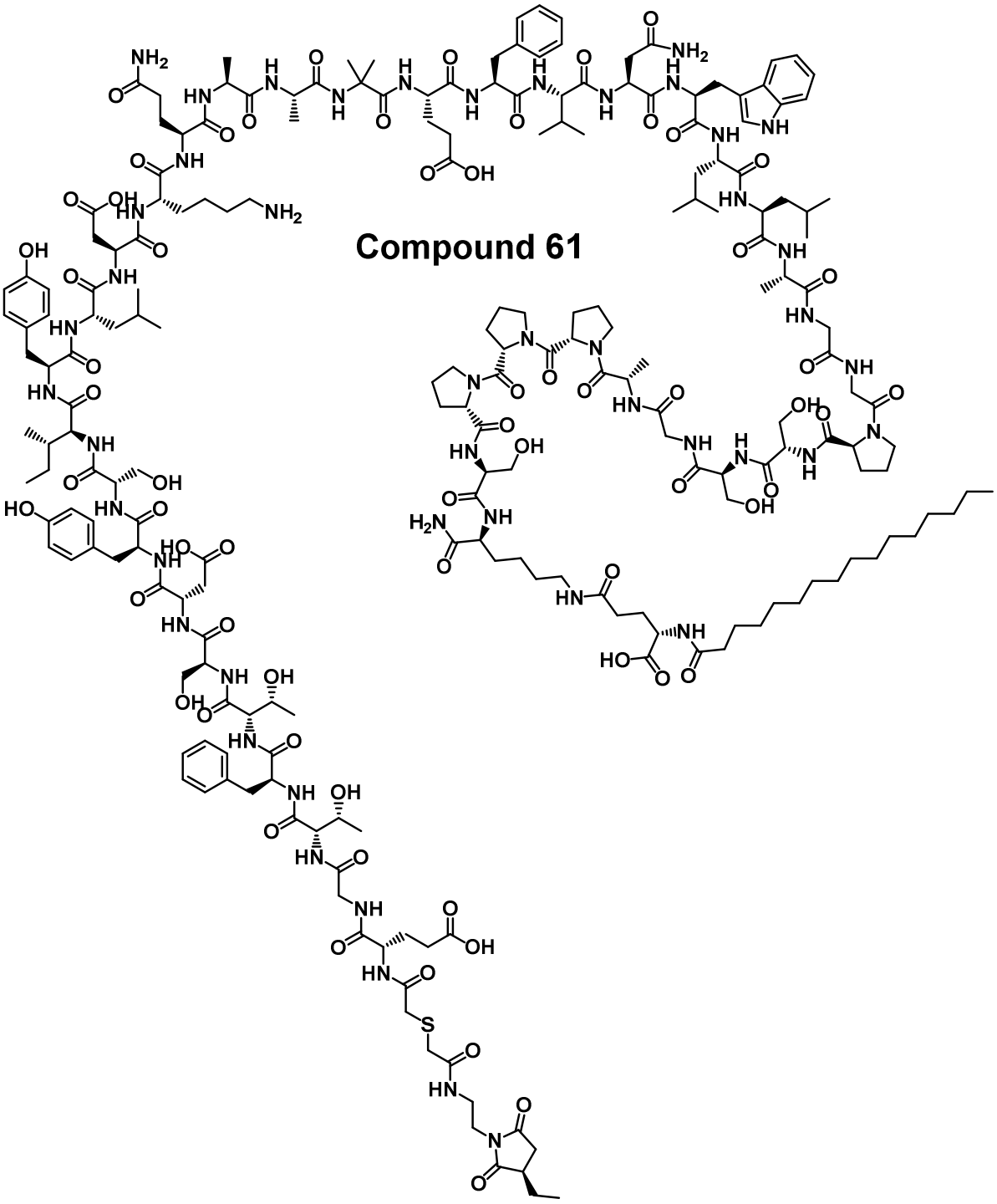

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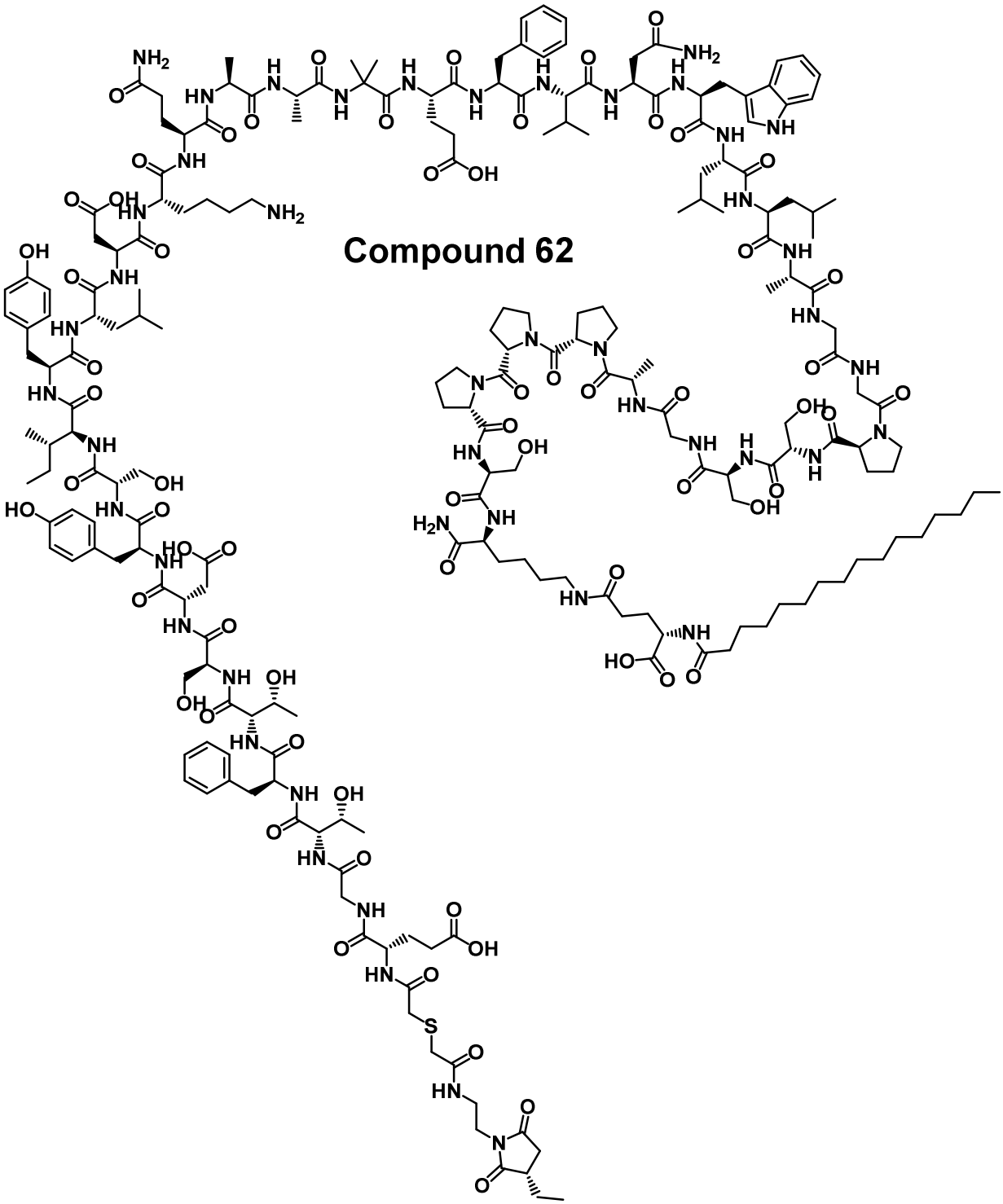

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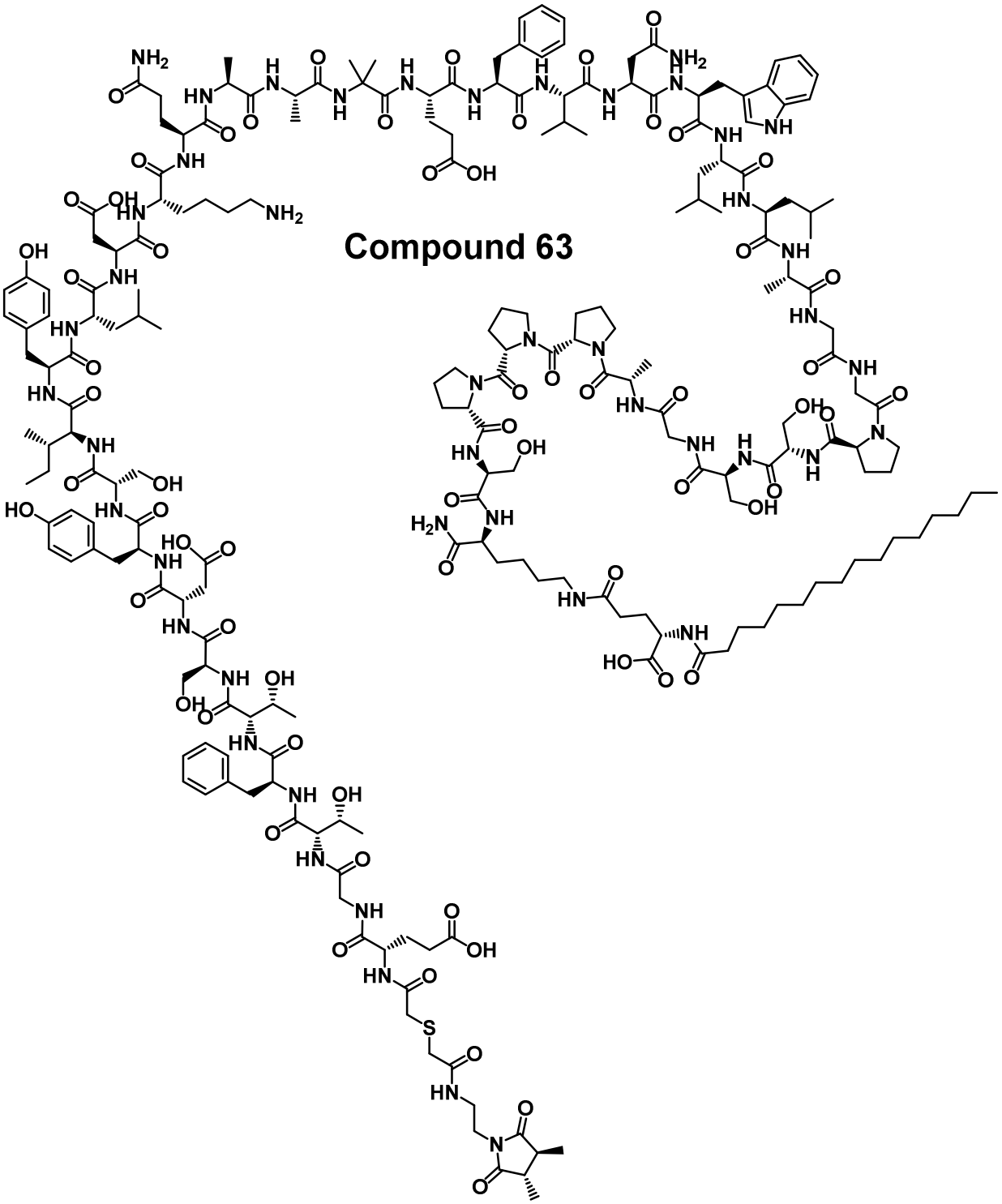


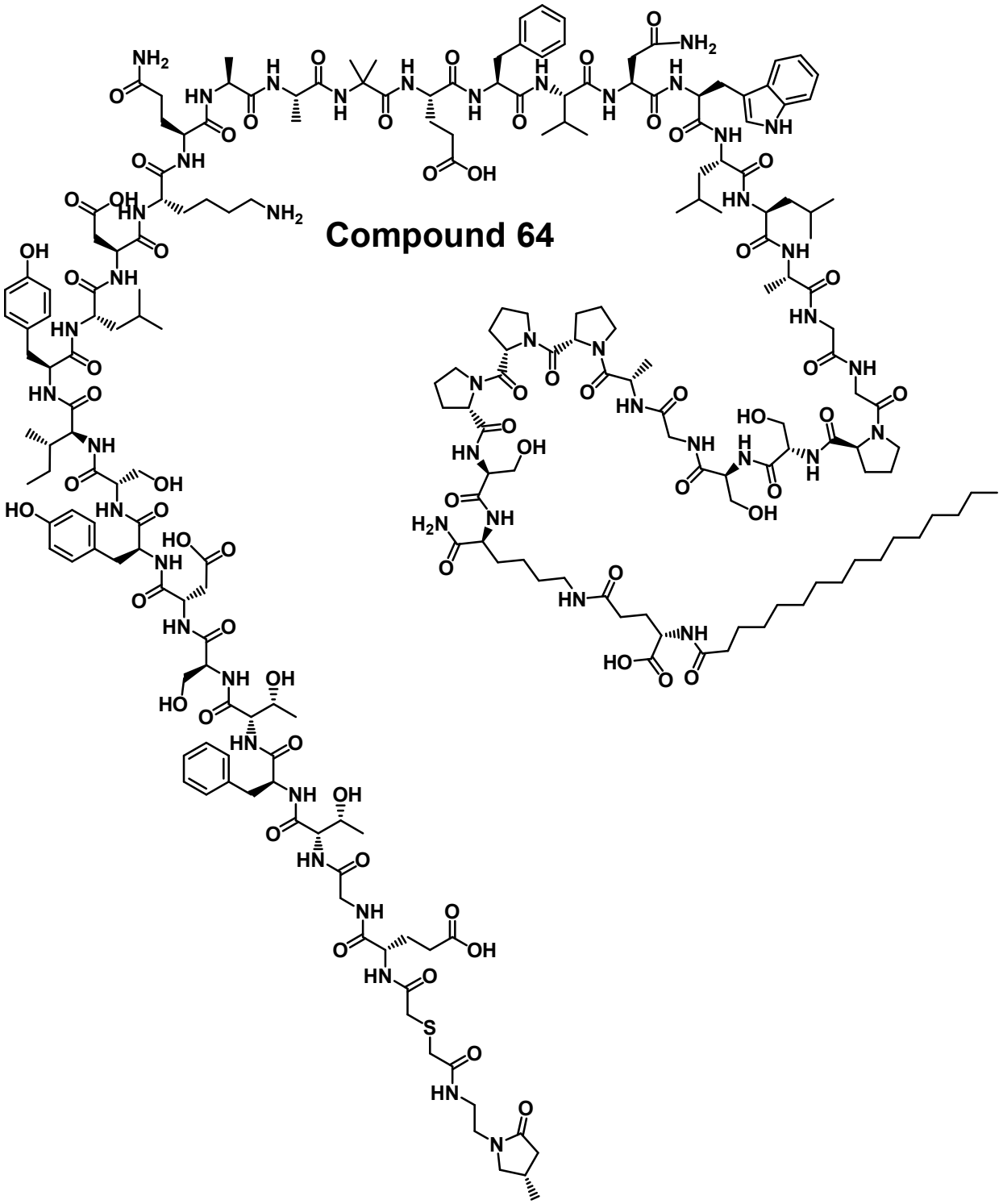
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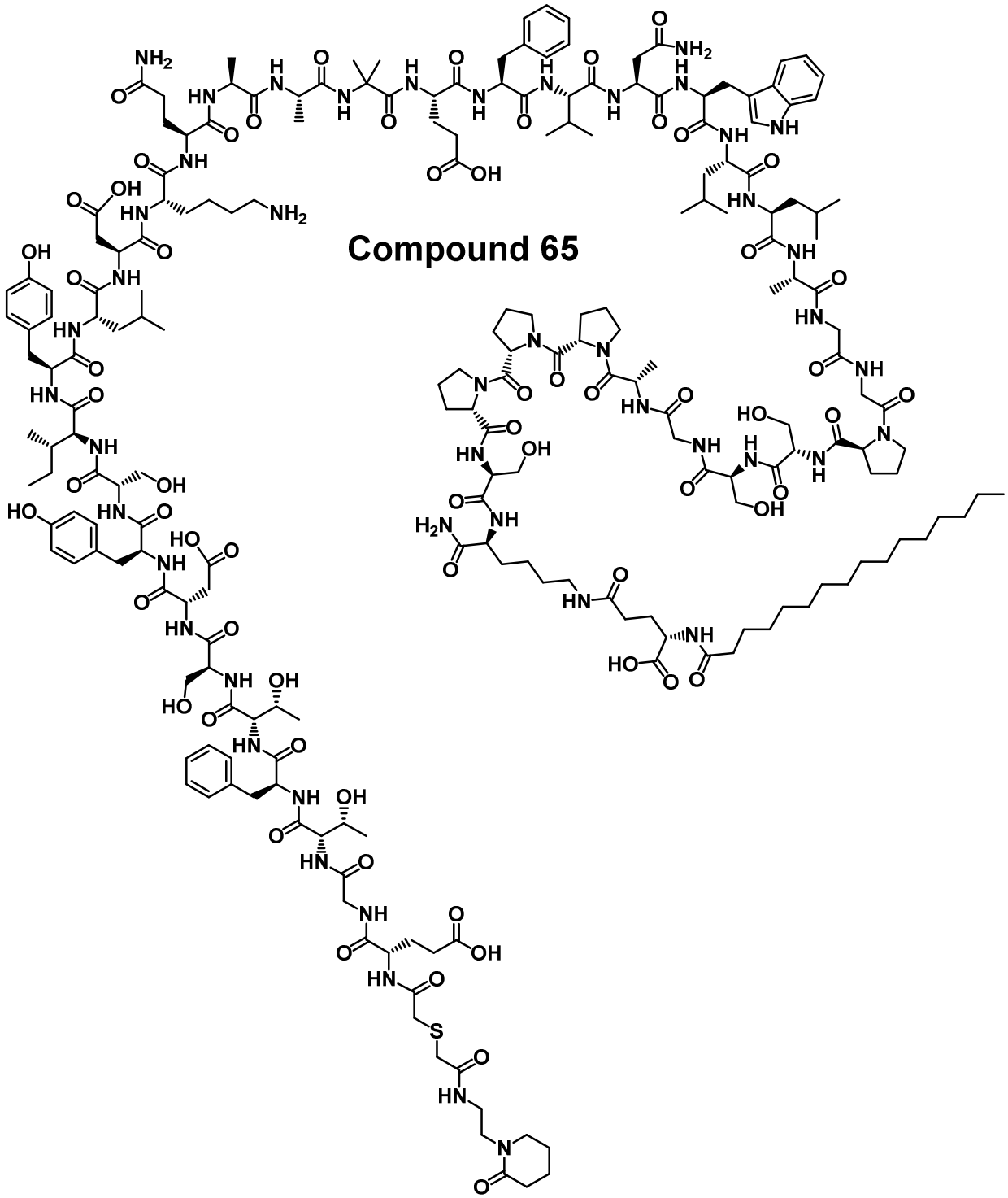

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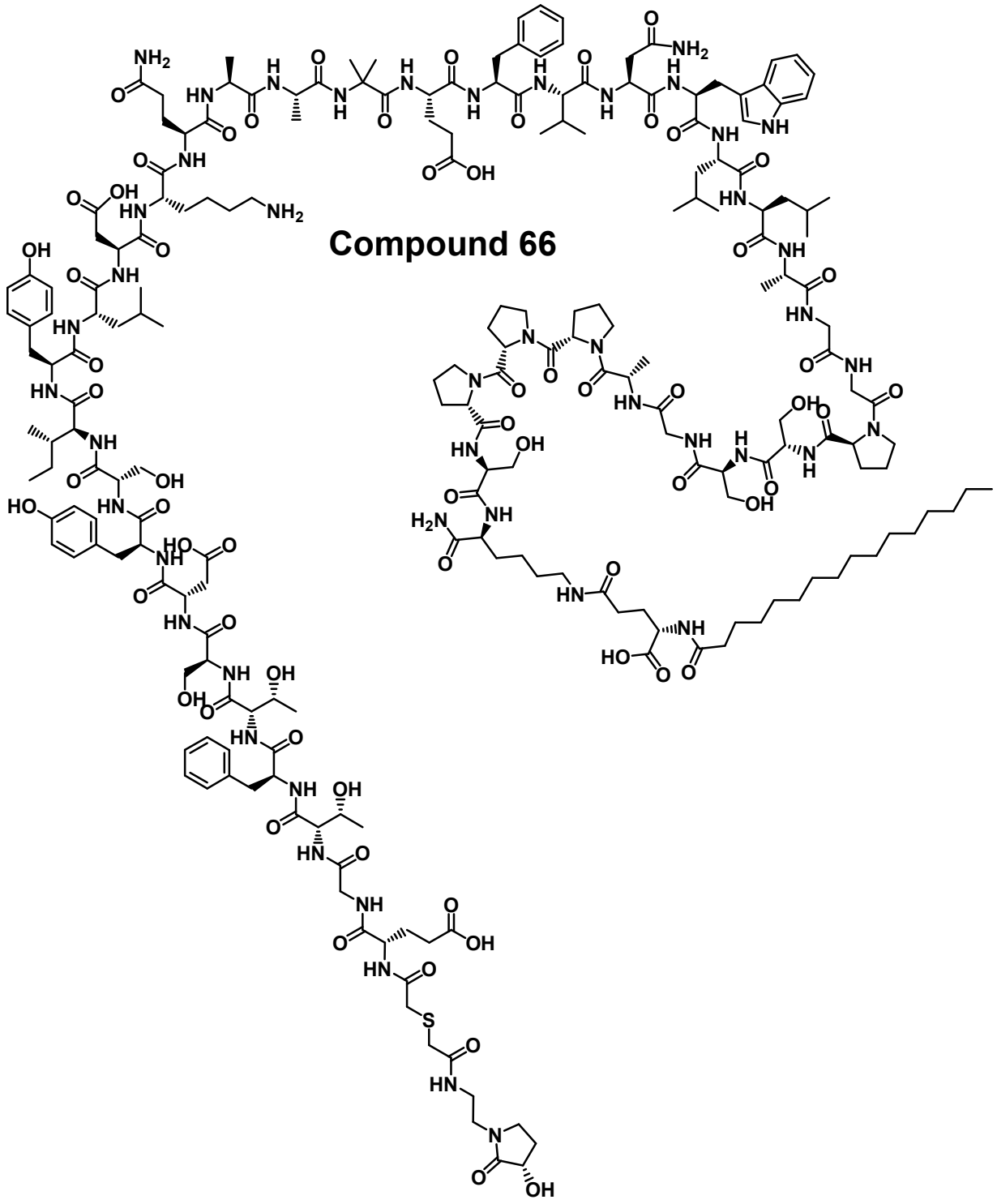

Compound 61


Compound 62

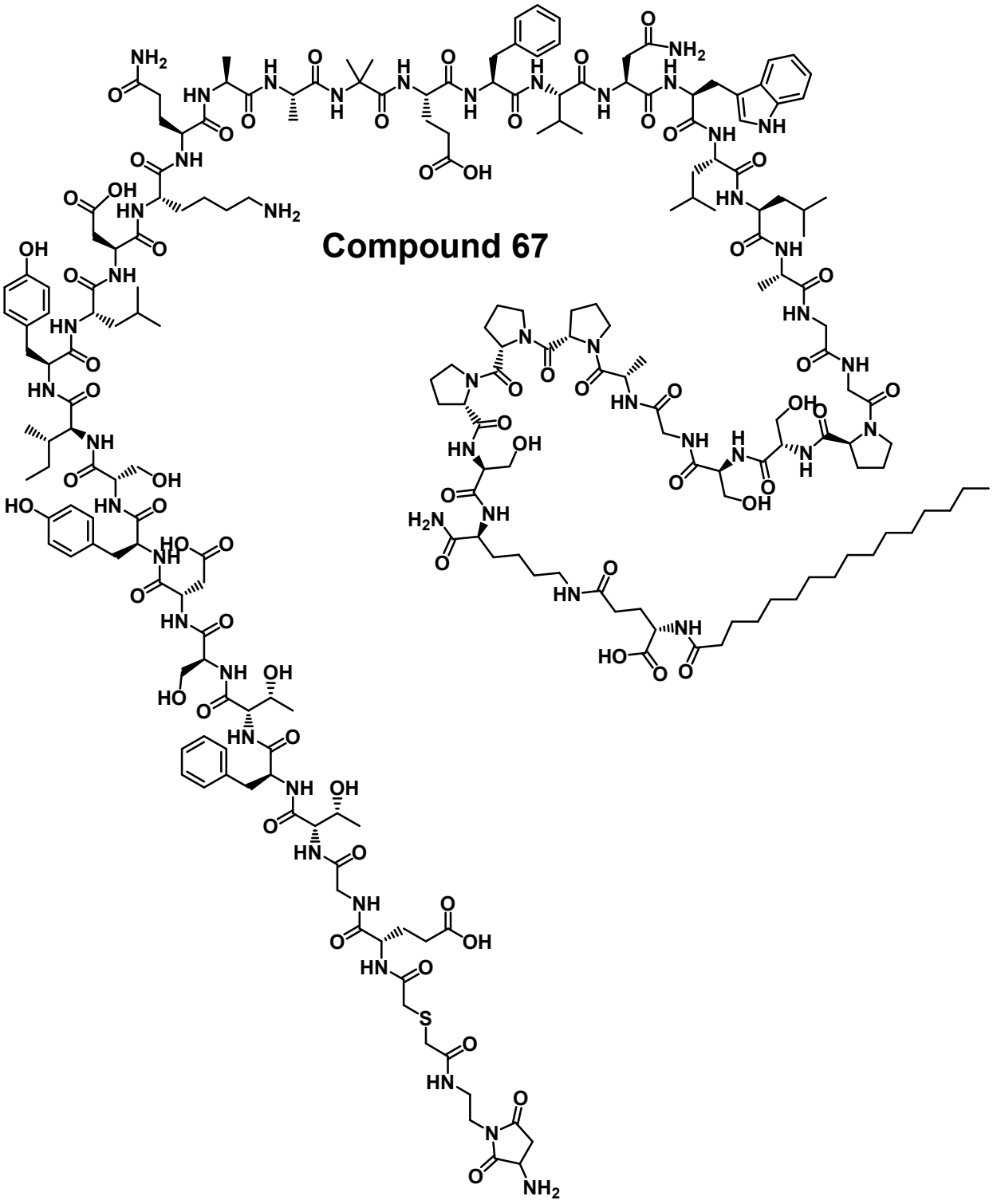

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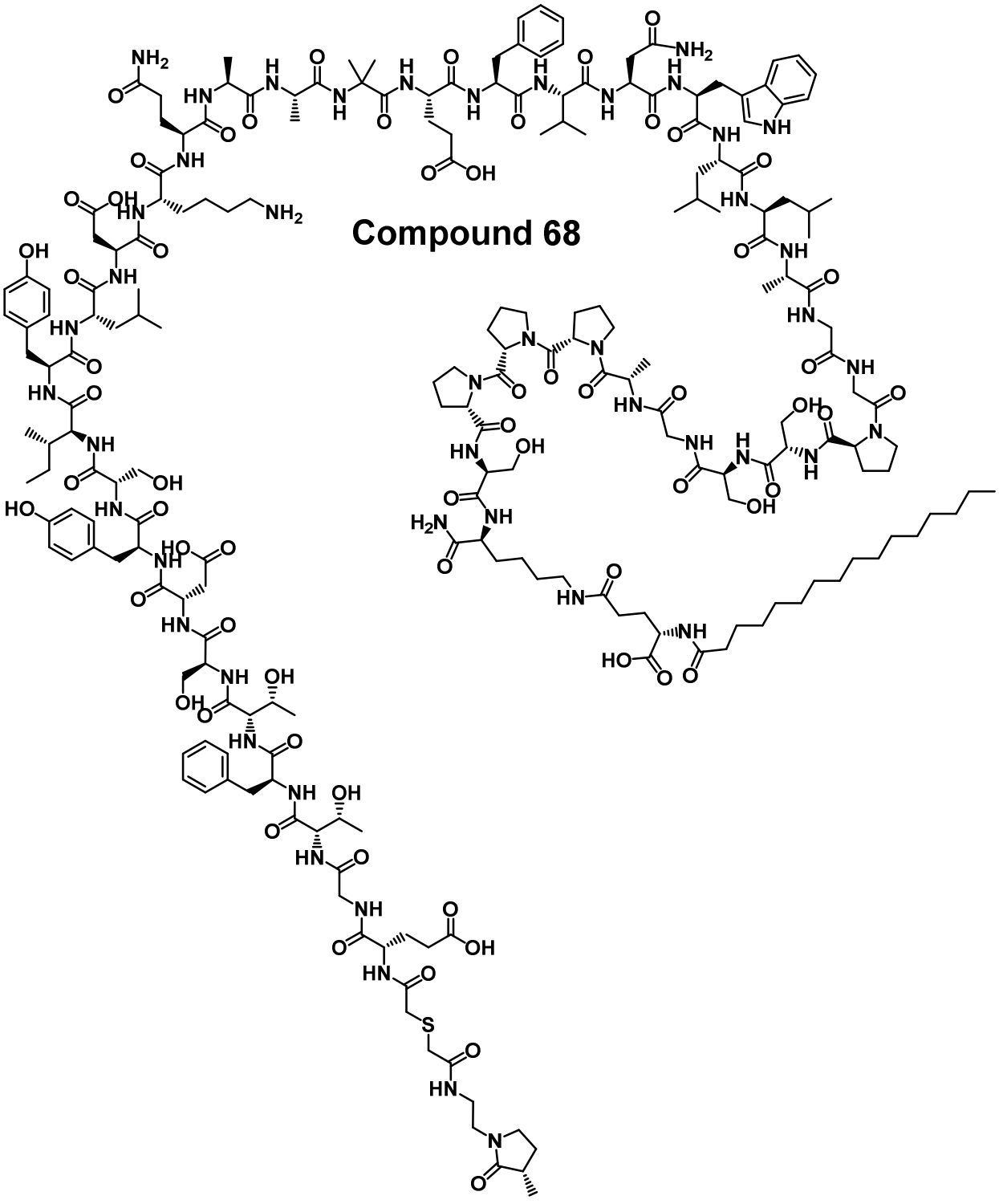

Compound 64


Compound 65

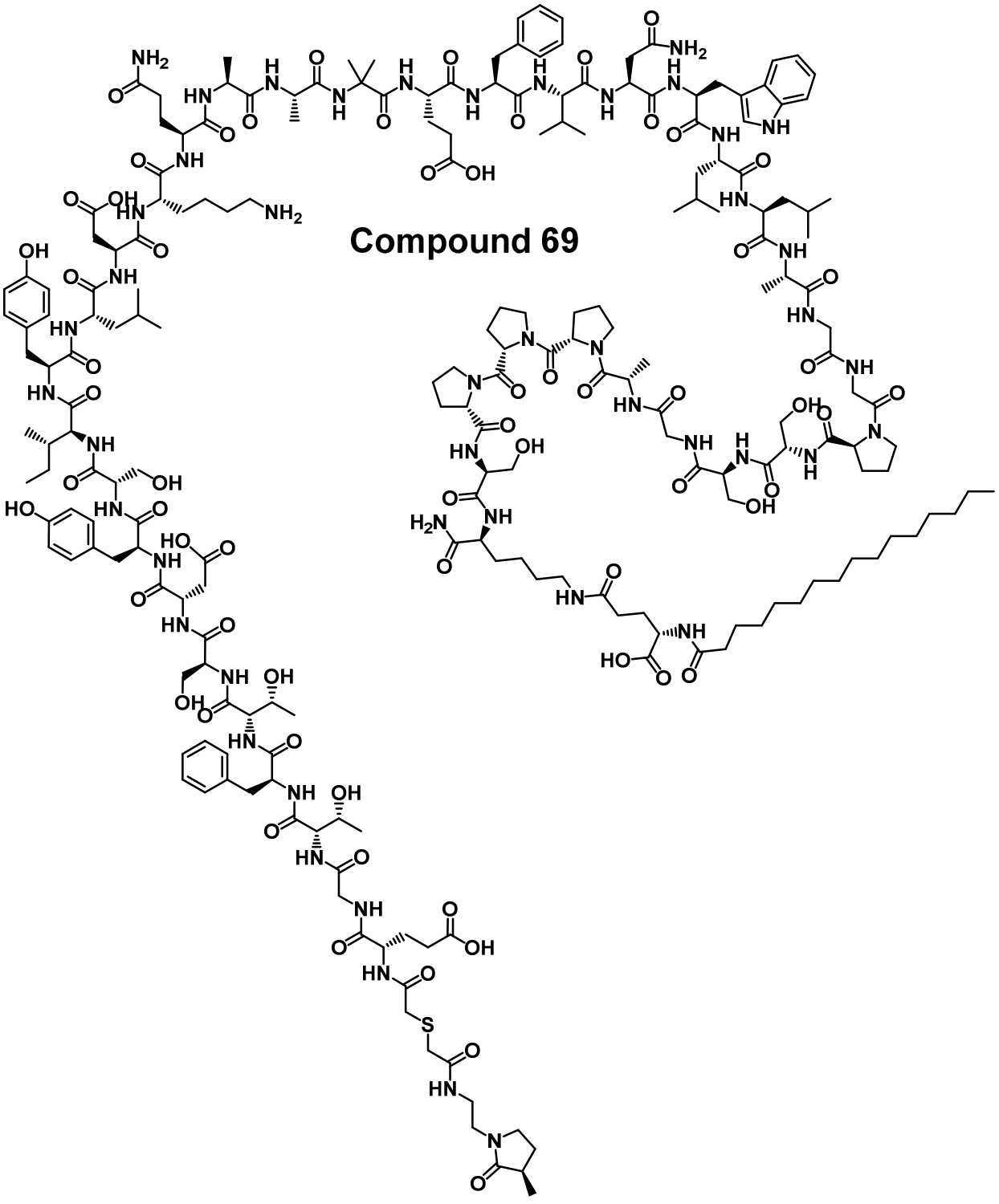


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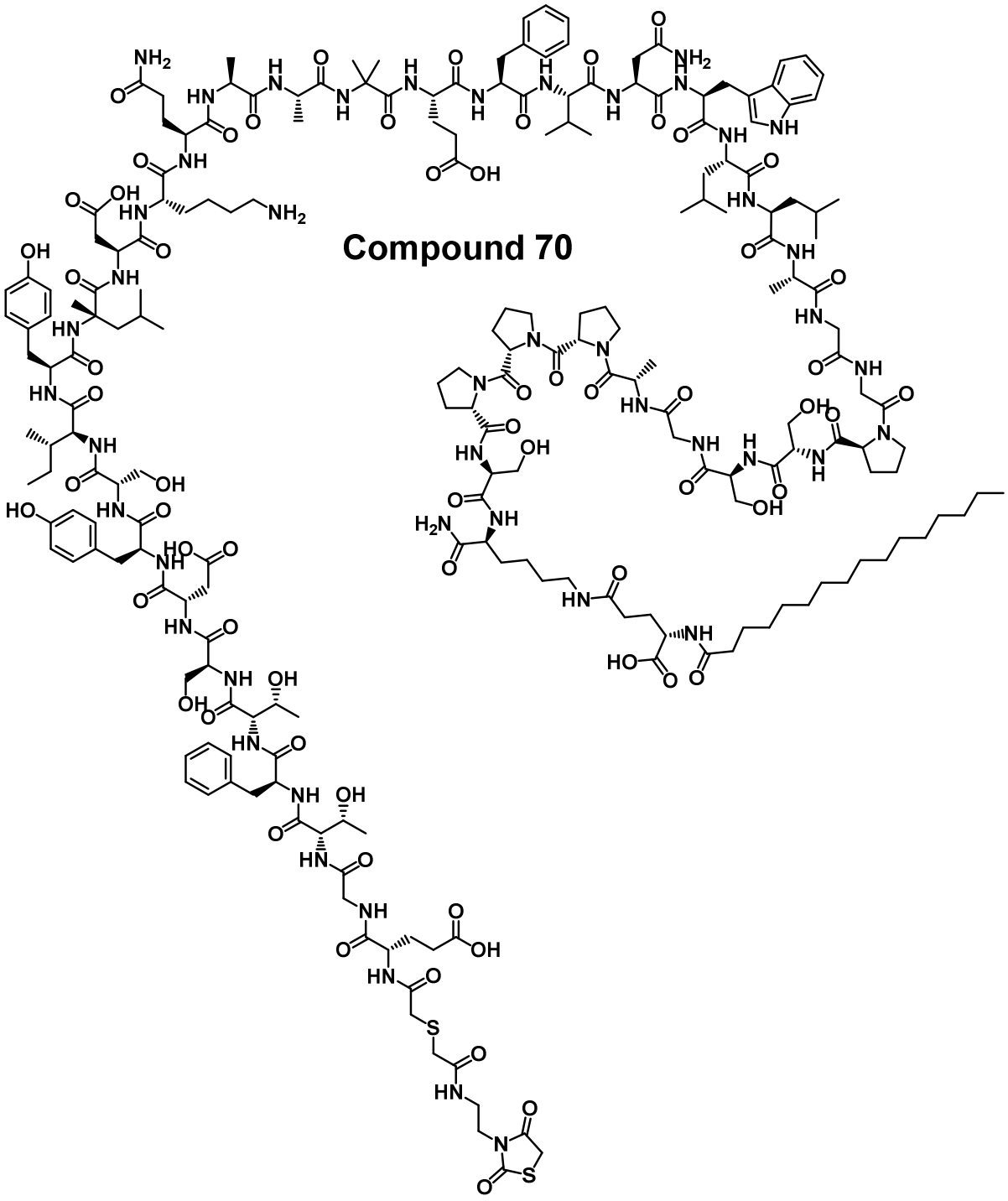

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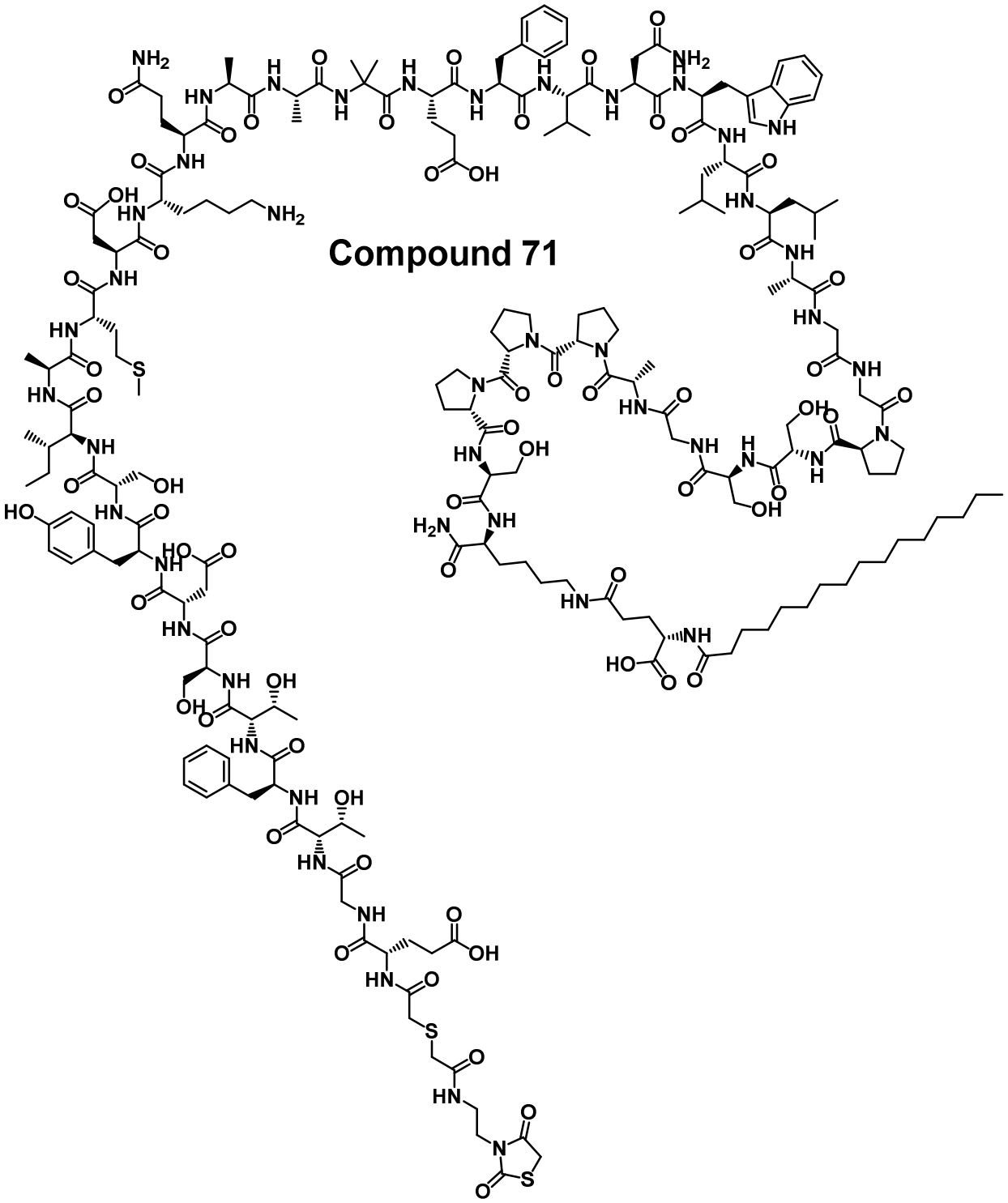


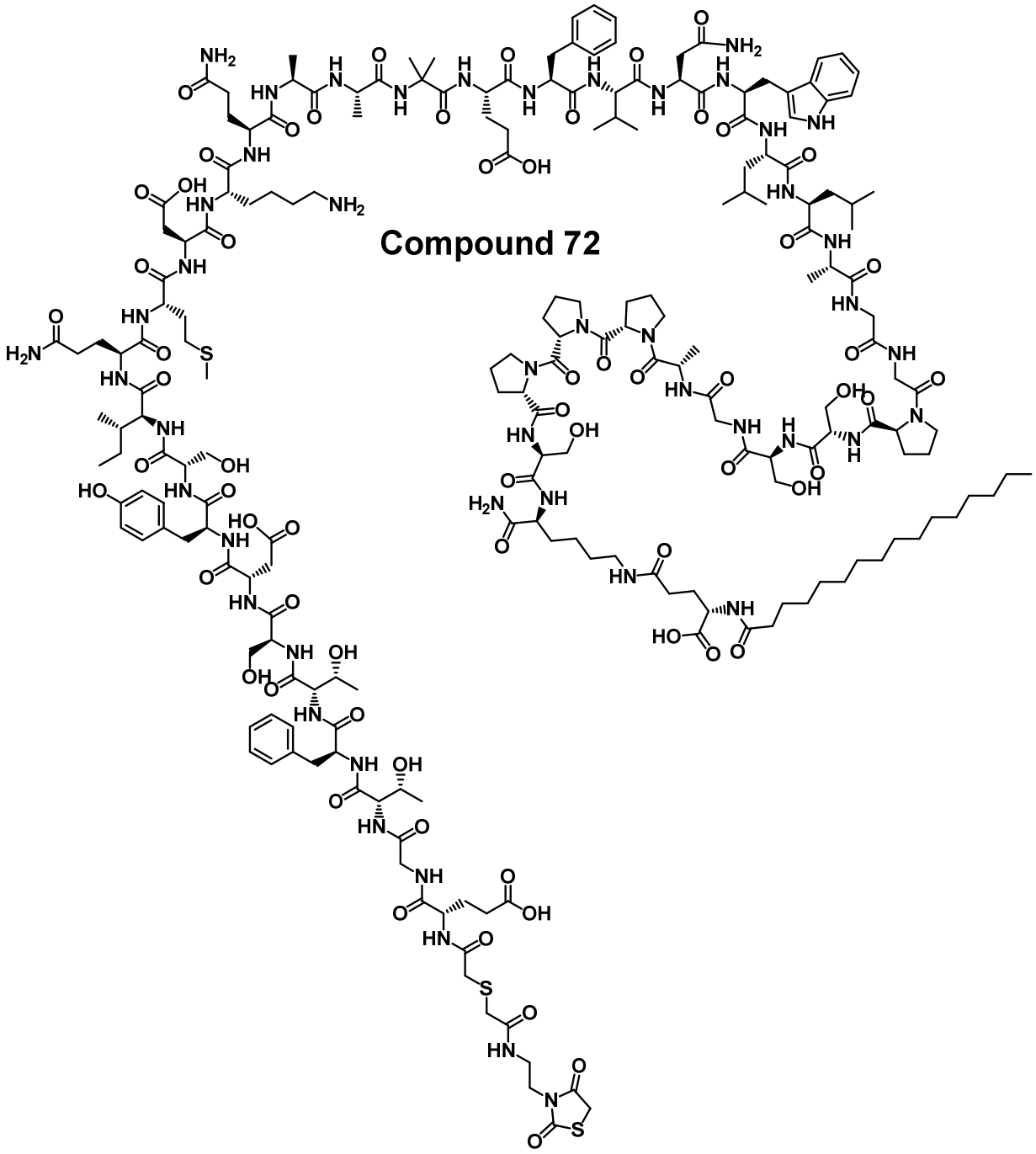
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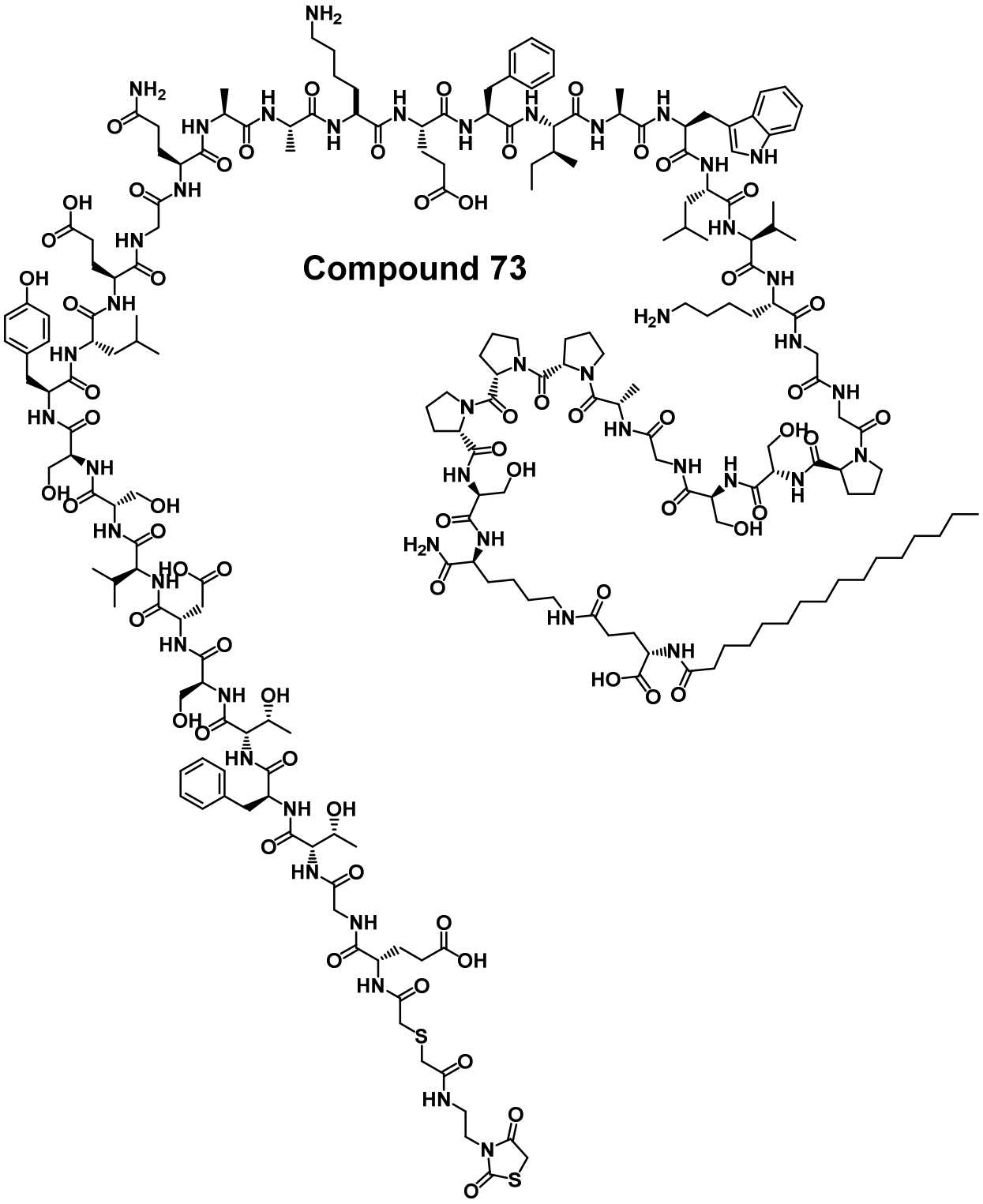


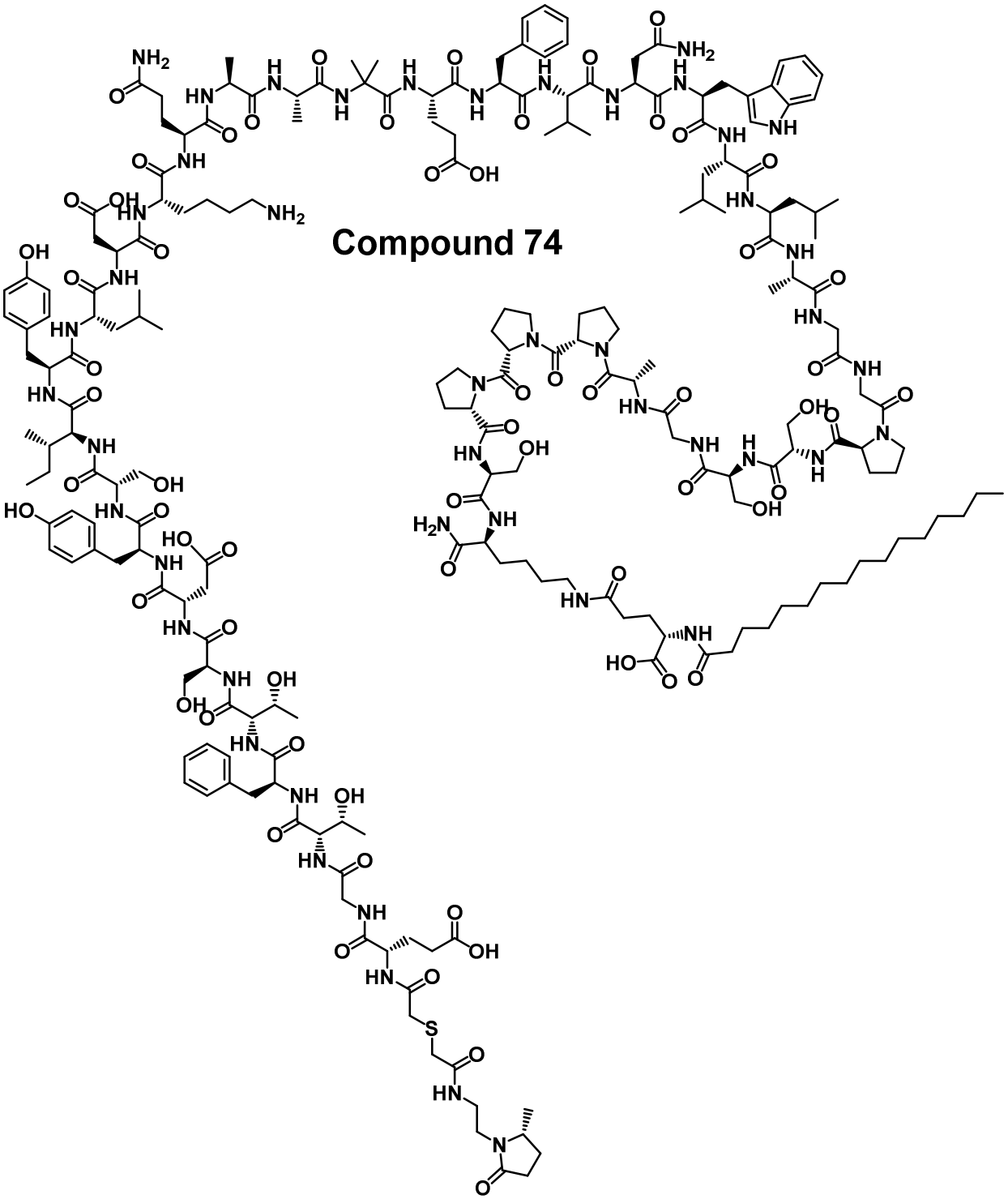
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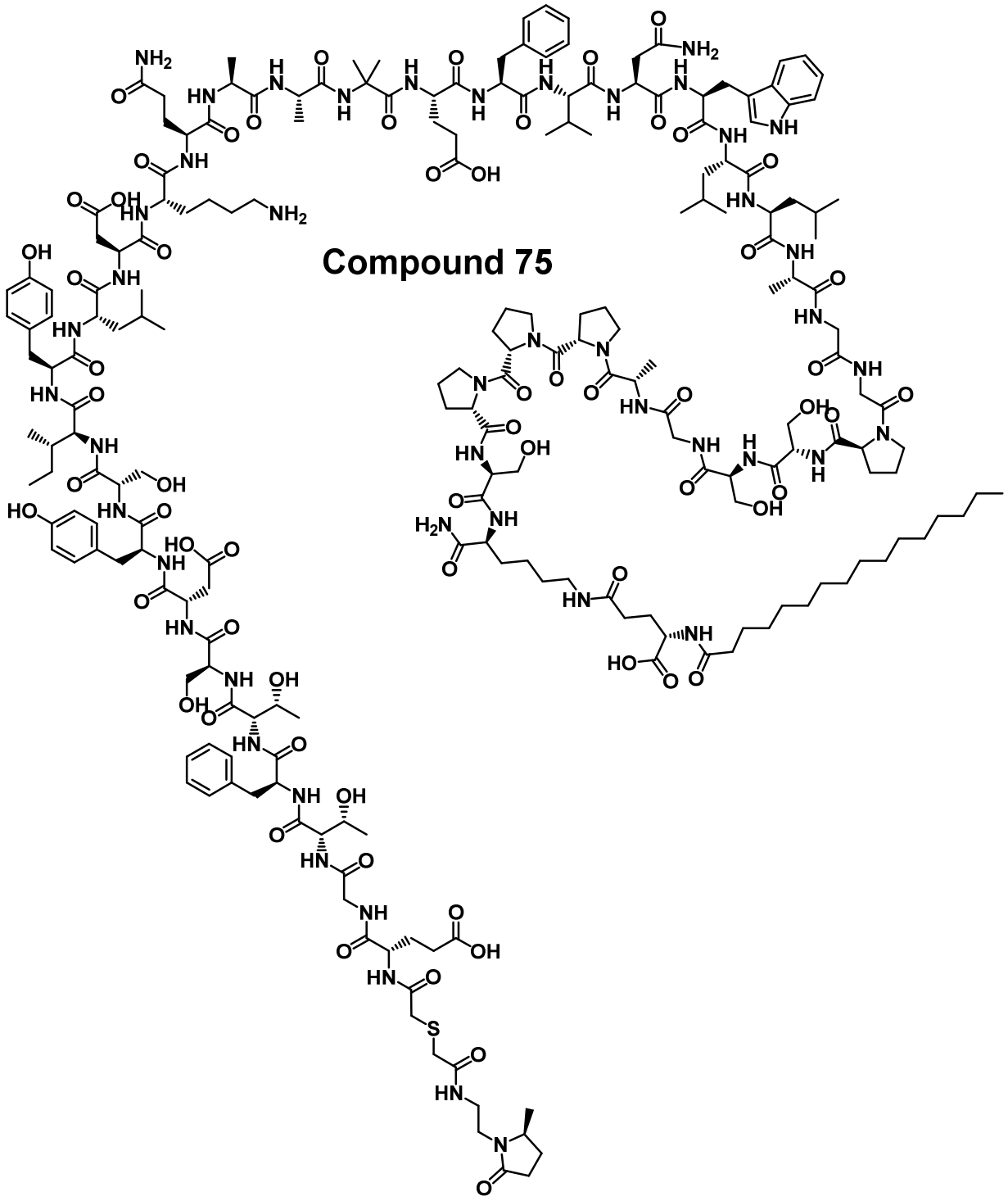

Compound 70

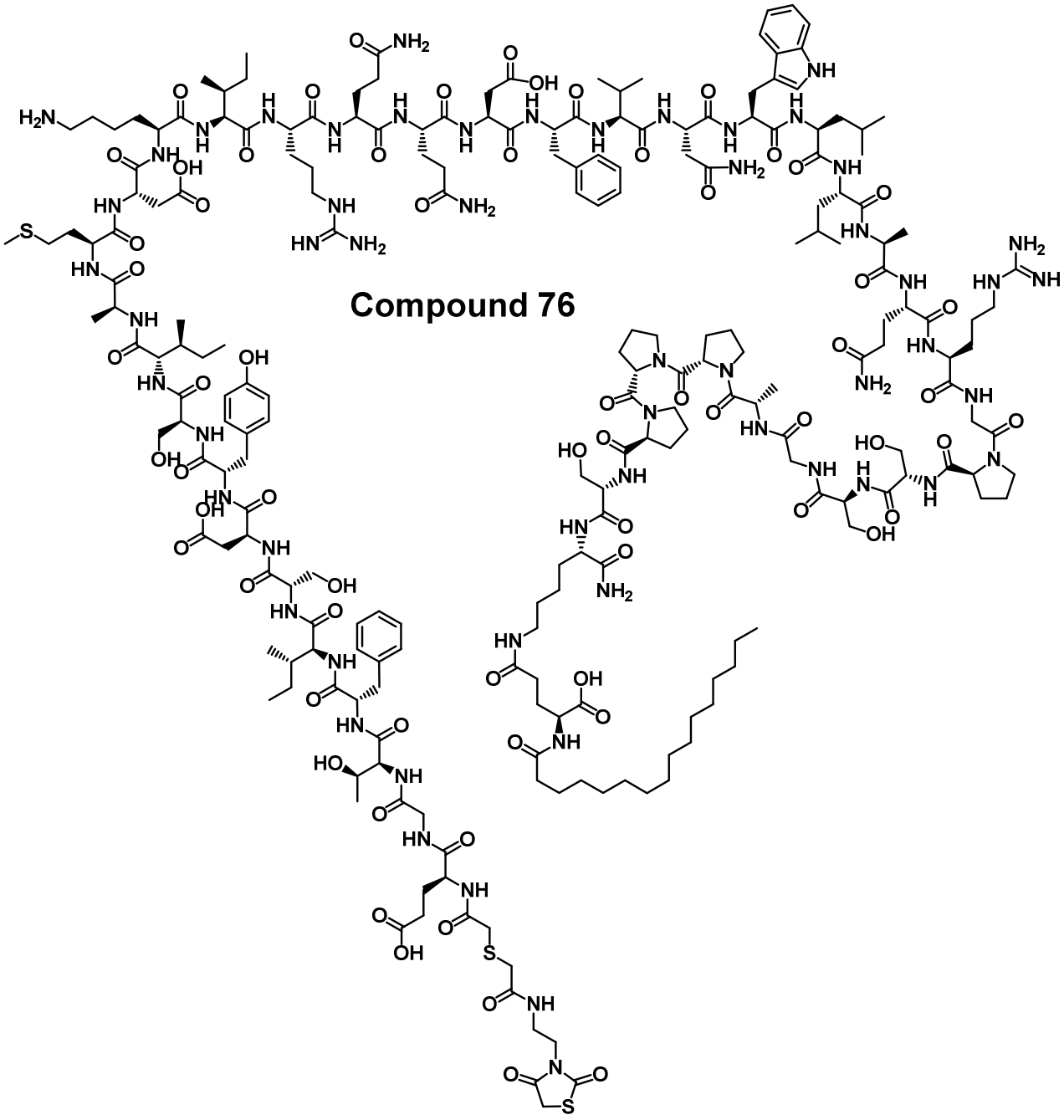

Compound 71


Compound 72

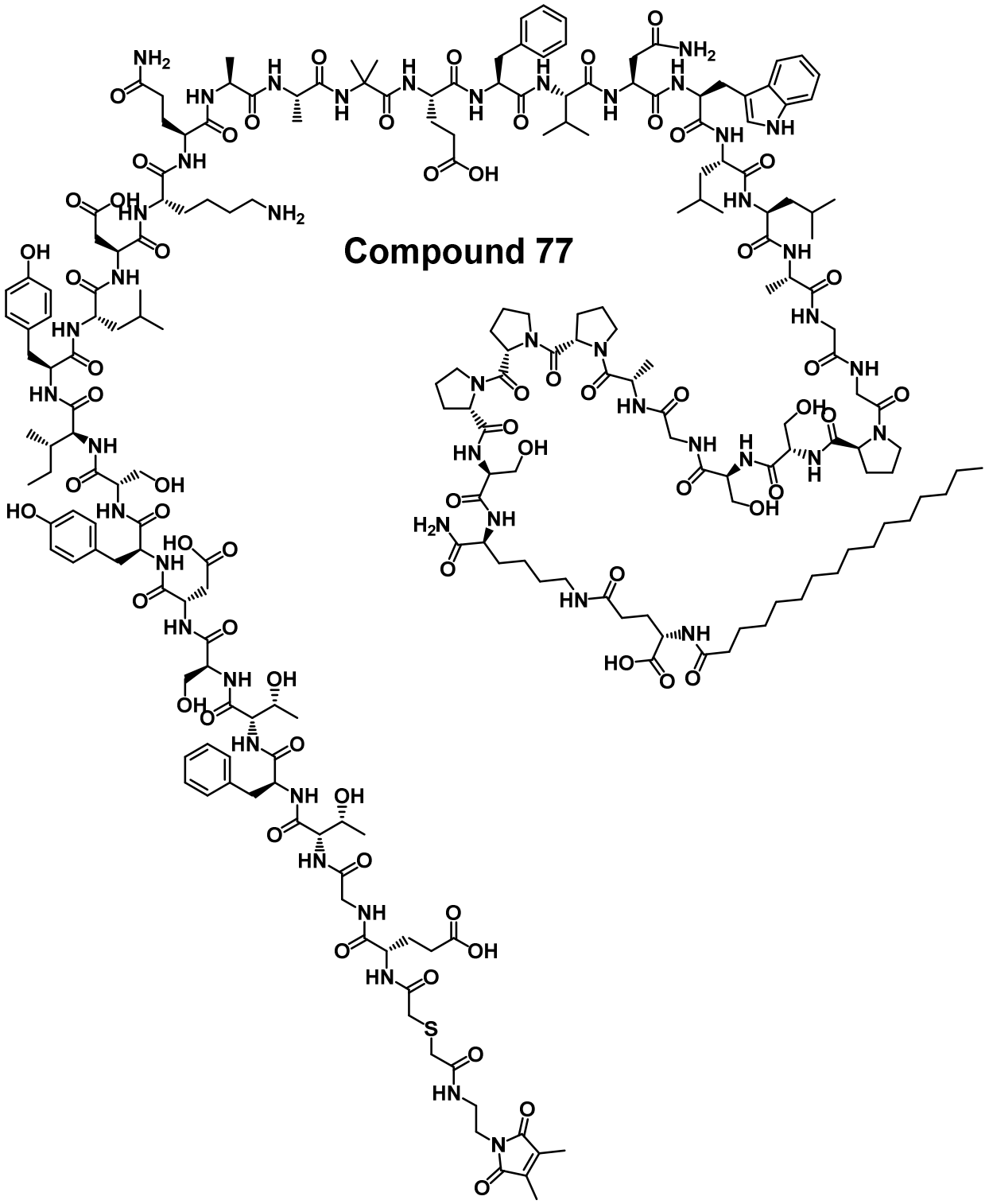

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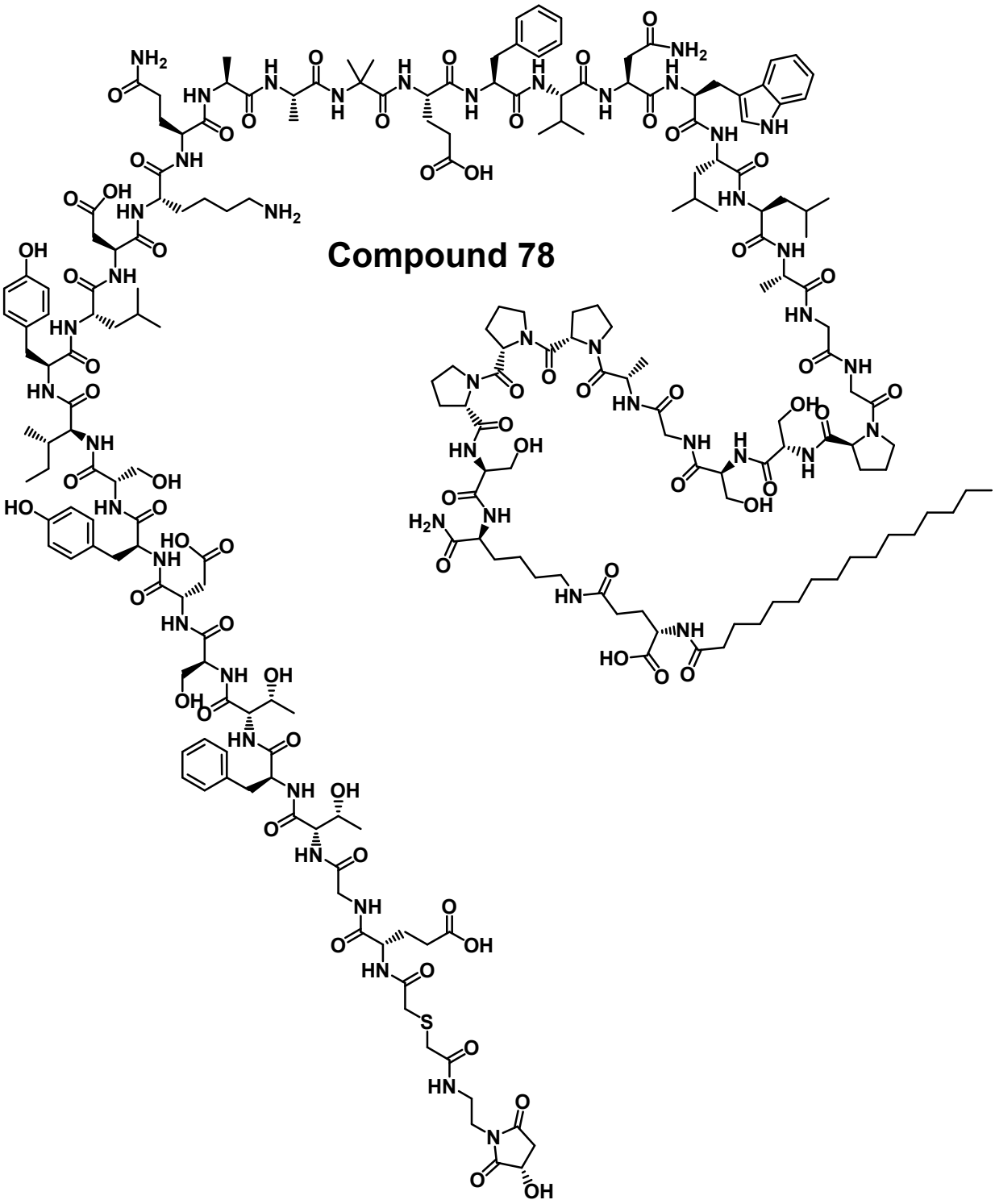

Compound 74


Compound 75

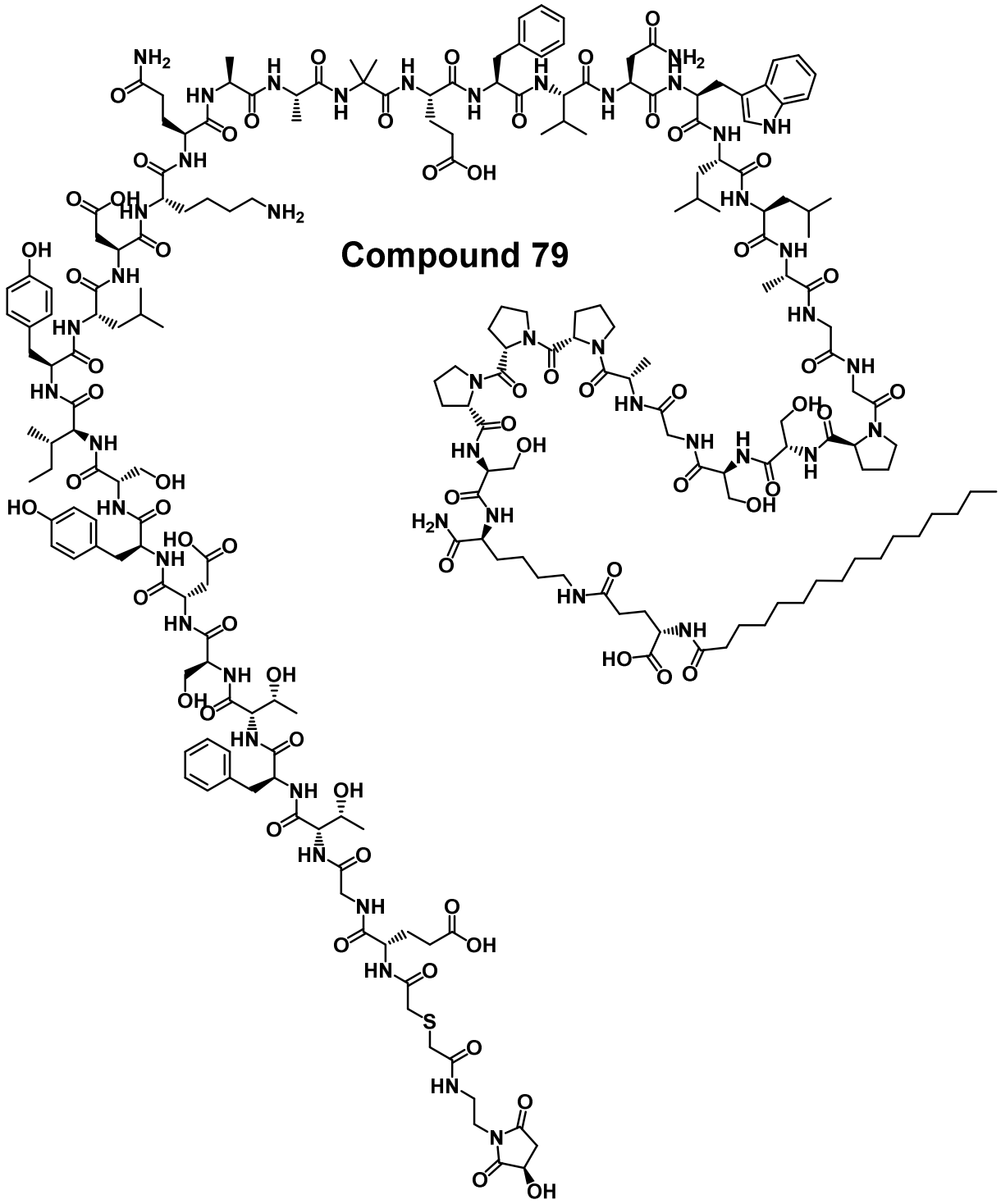


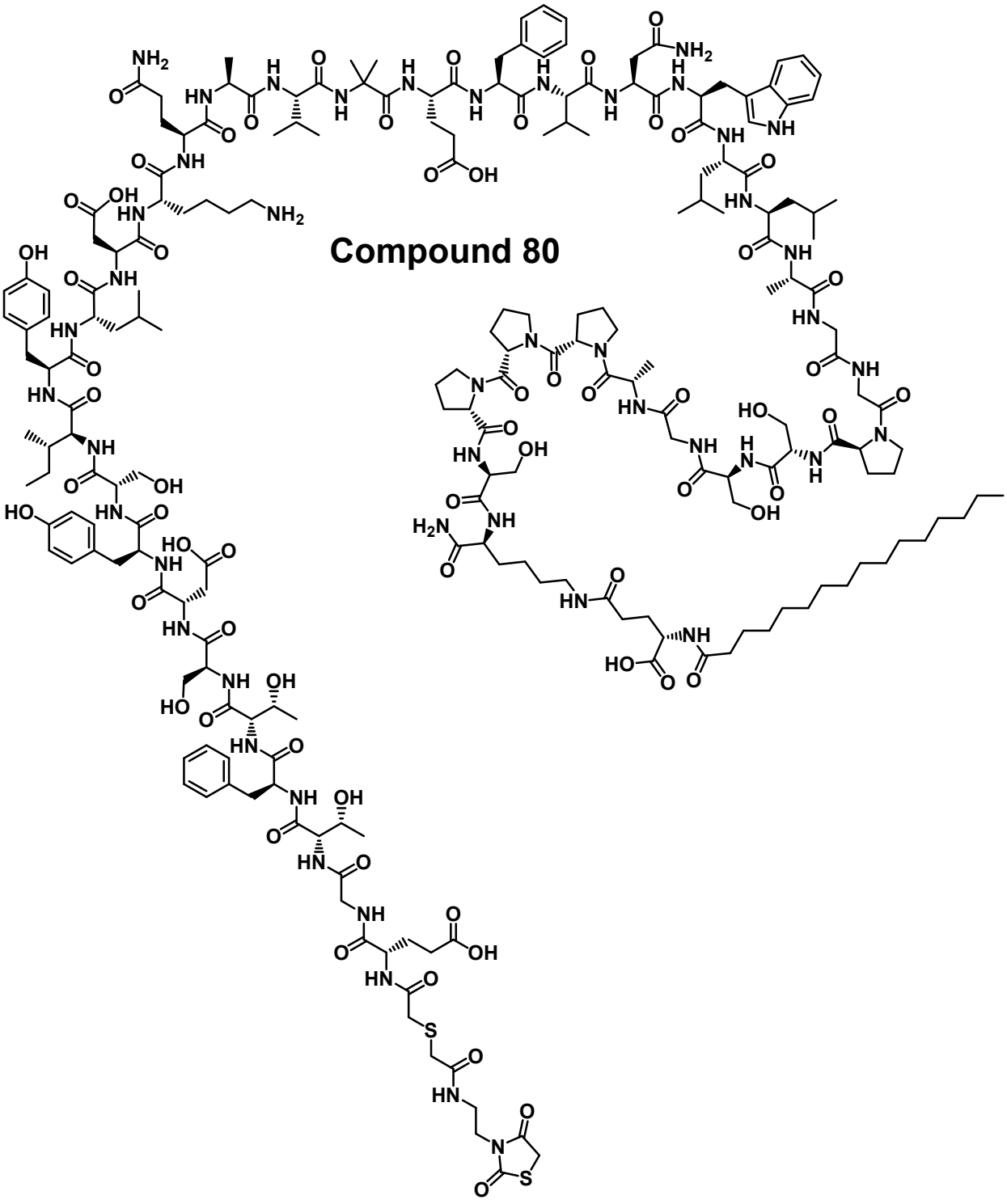
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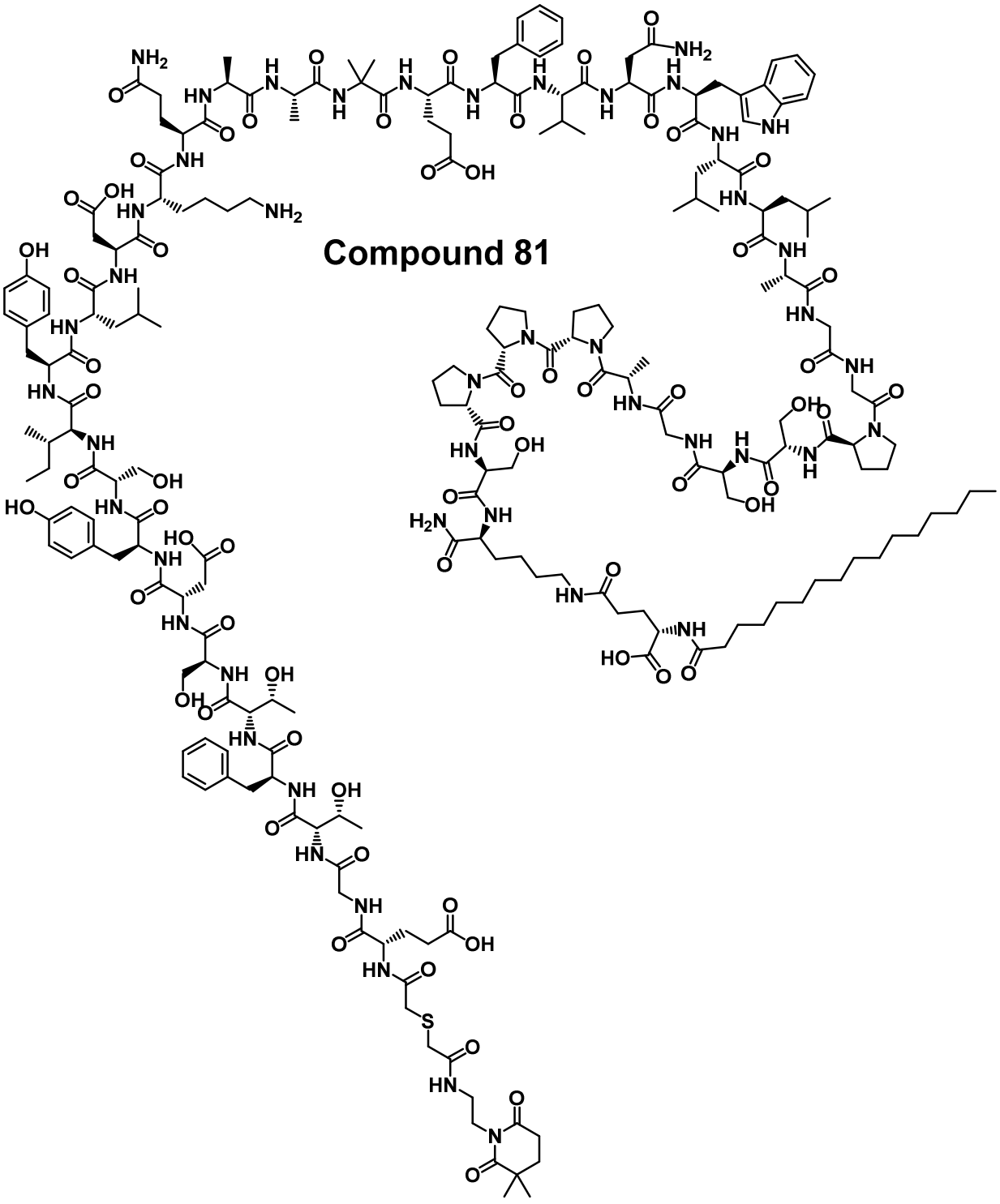

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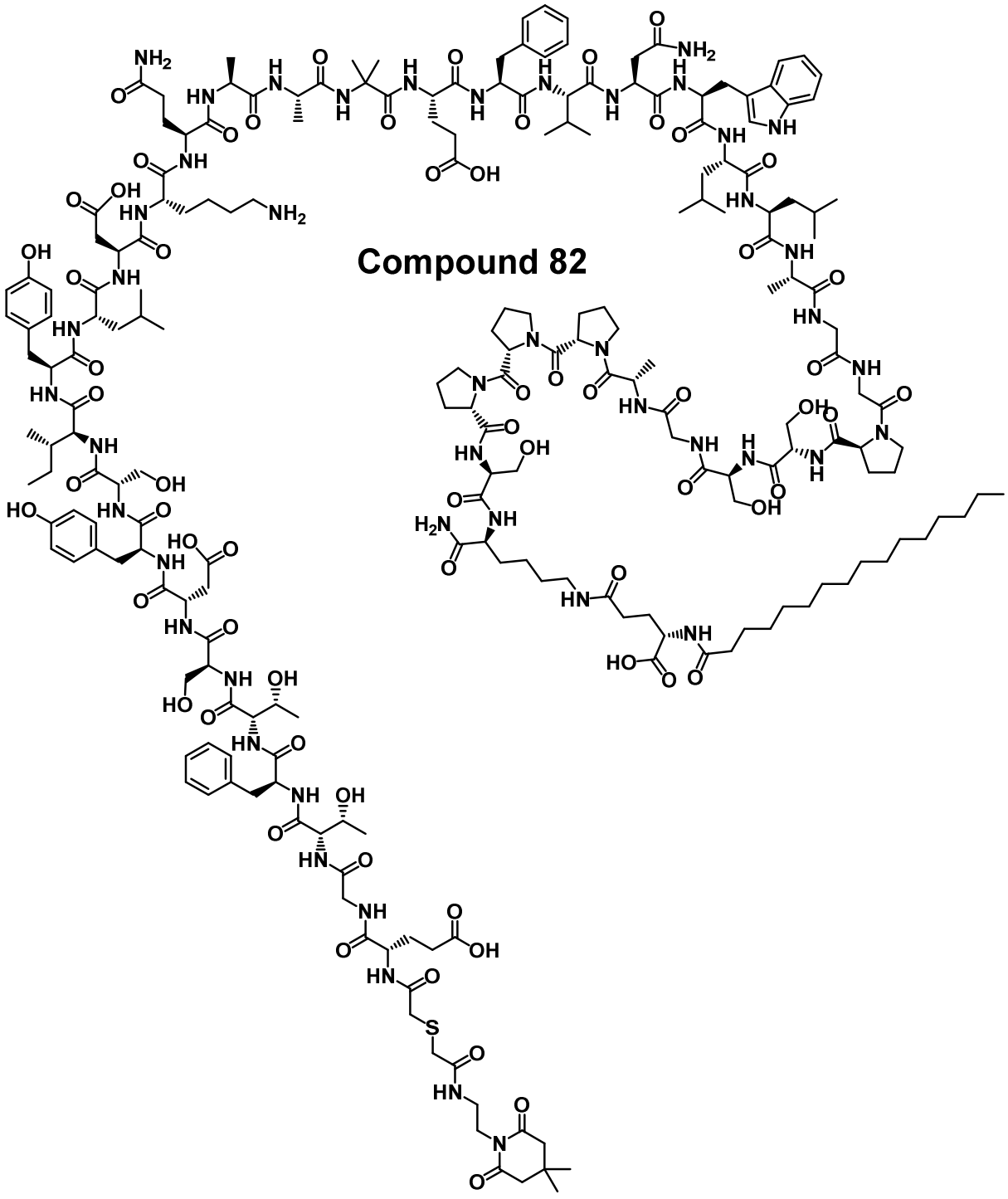


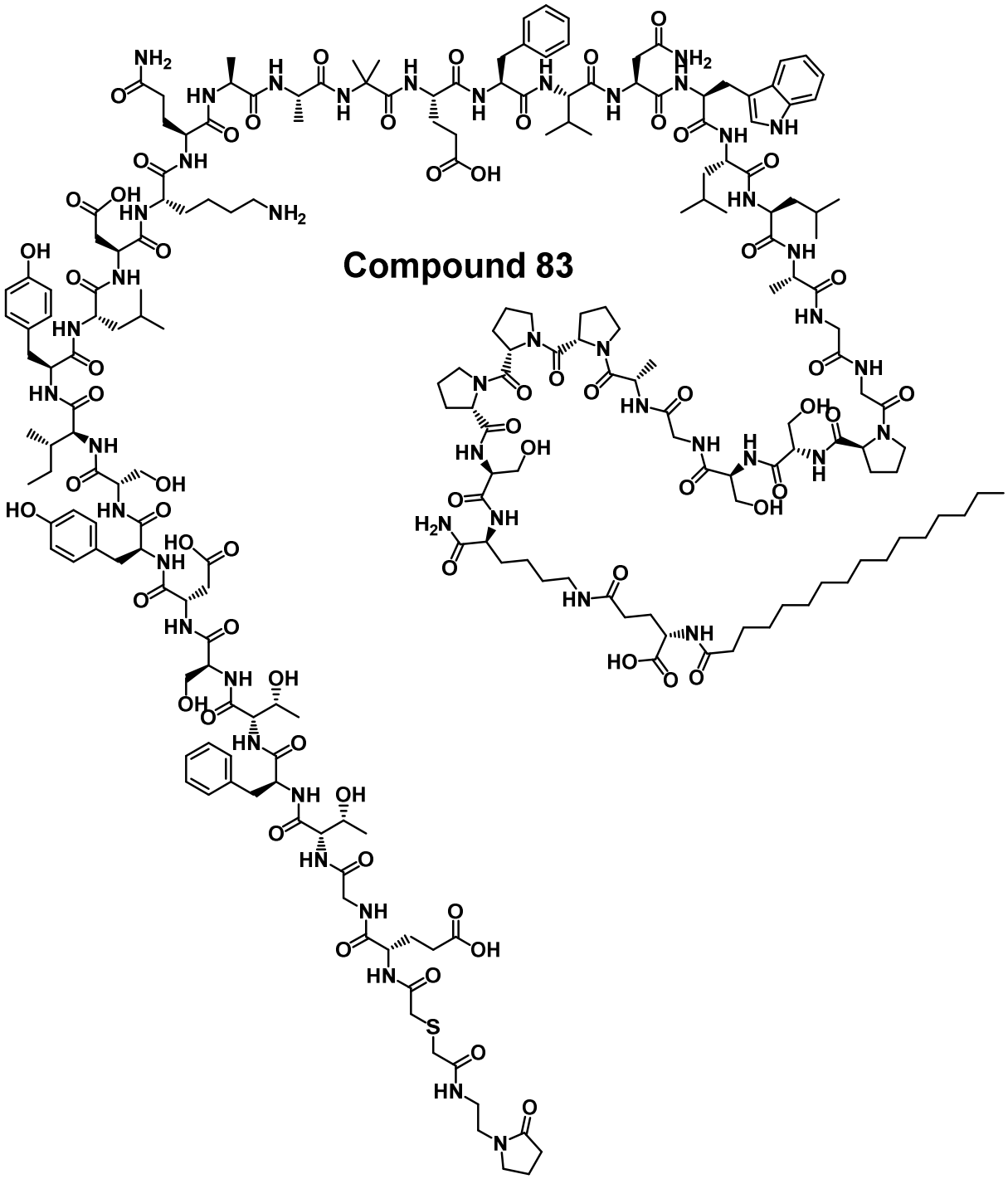
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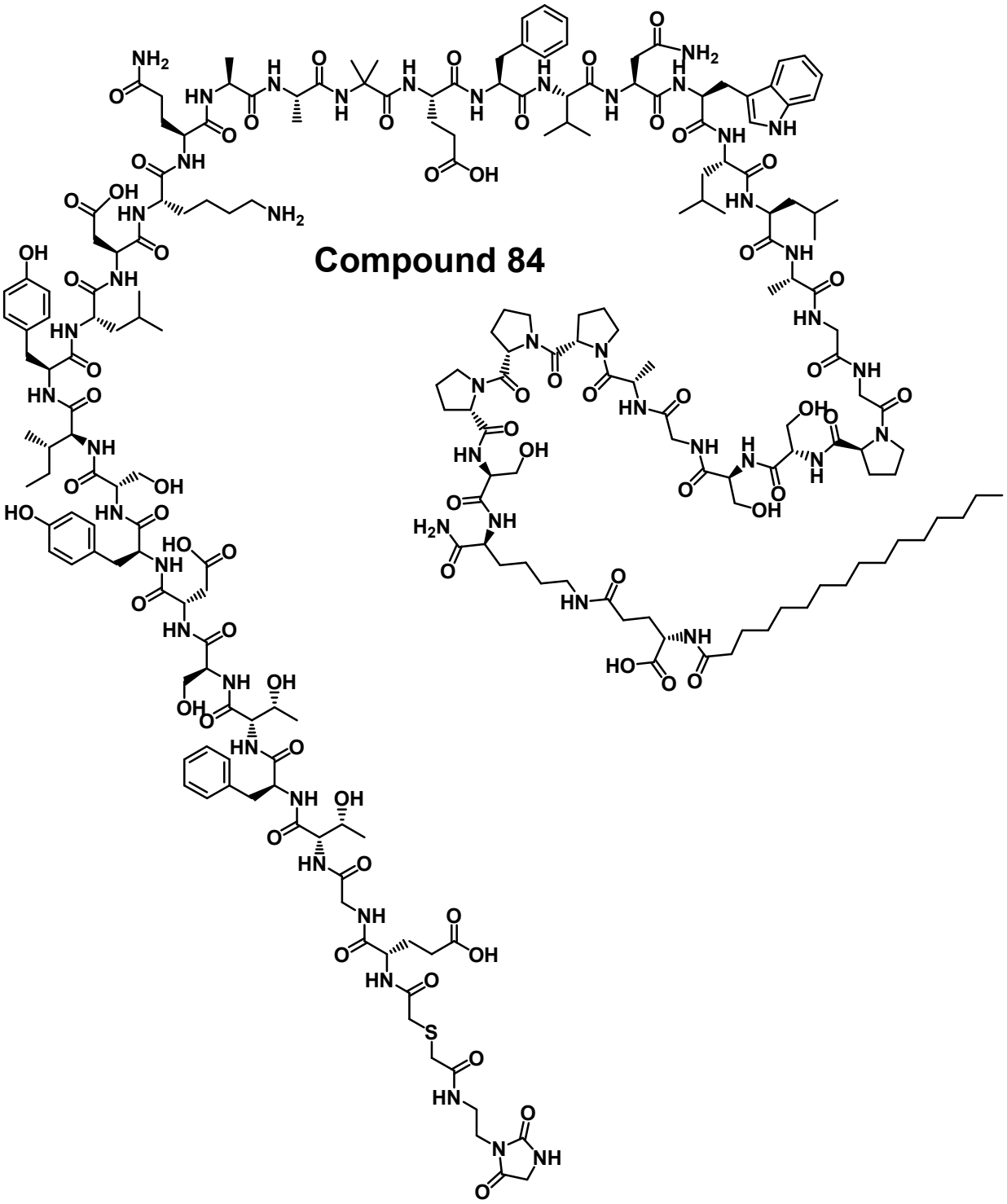

Compound 79


Compound 80

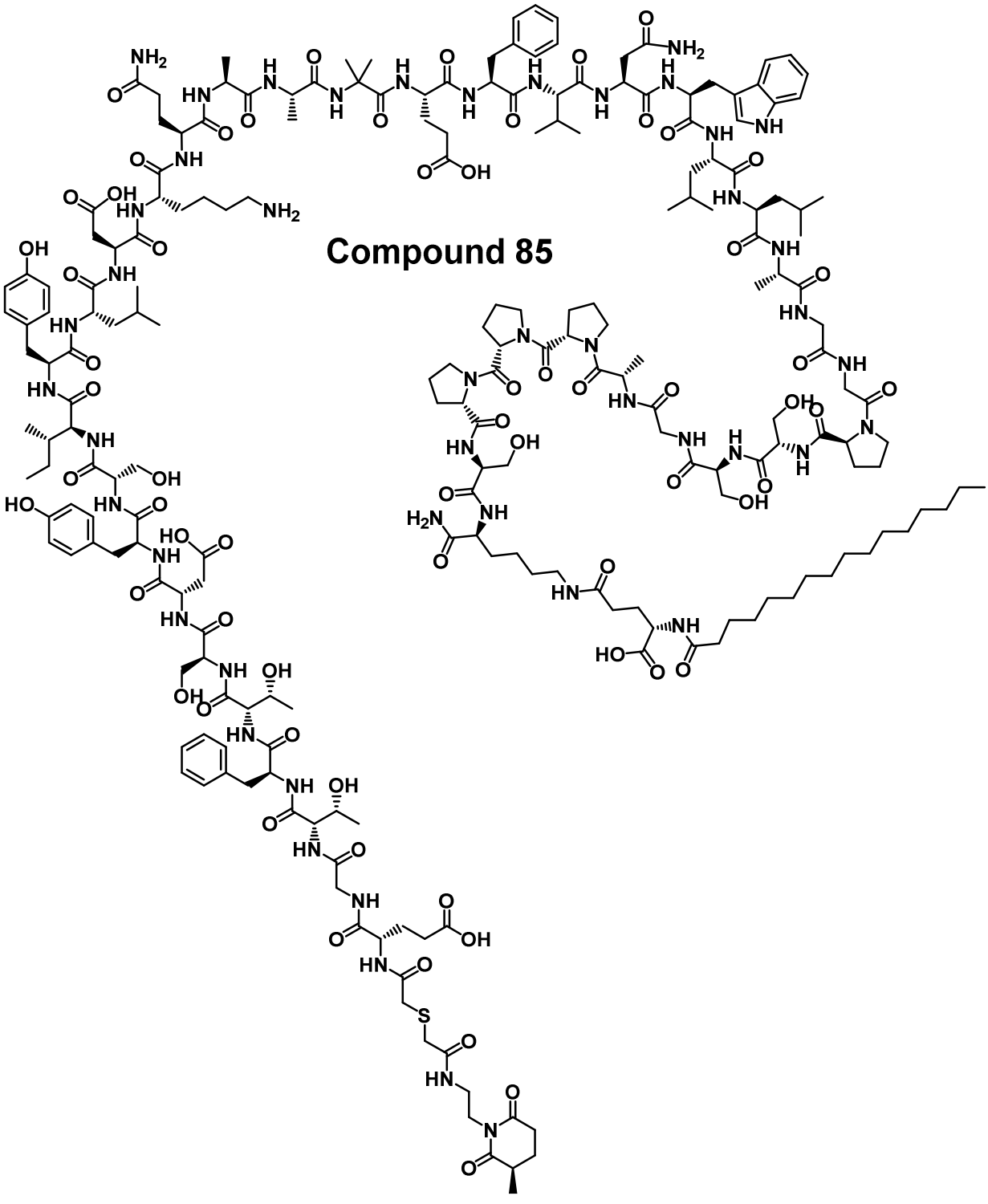

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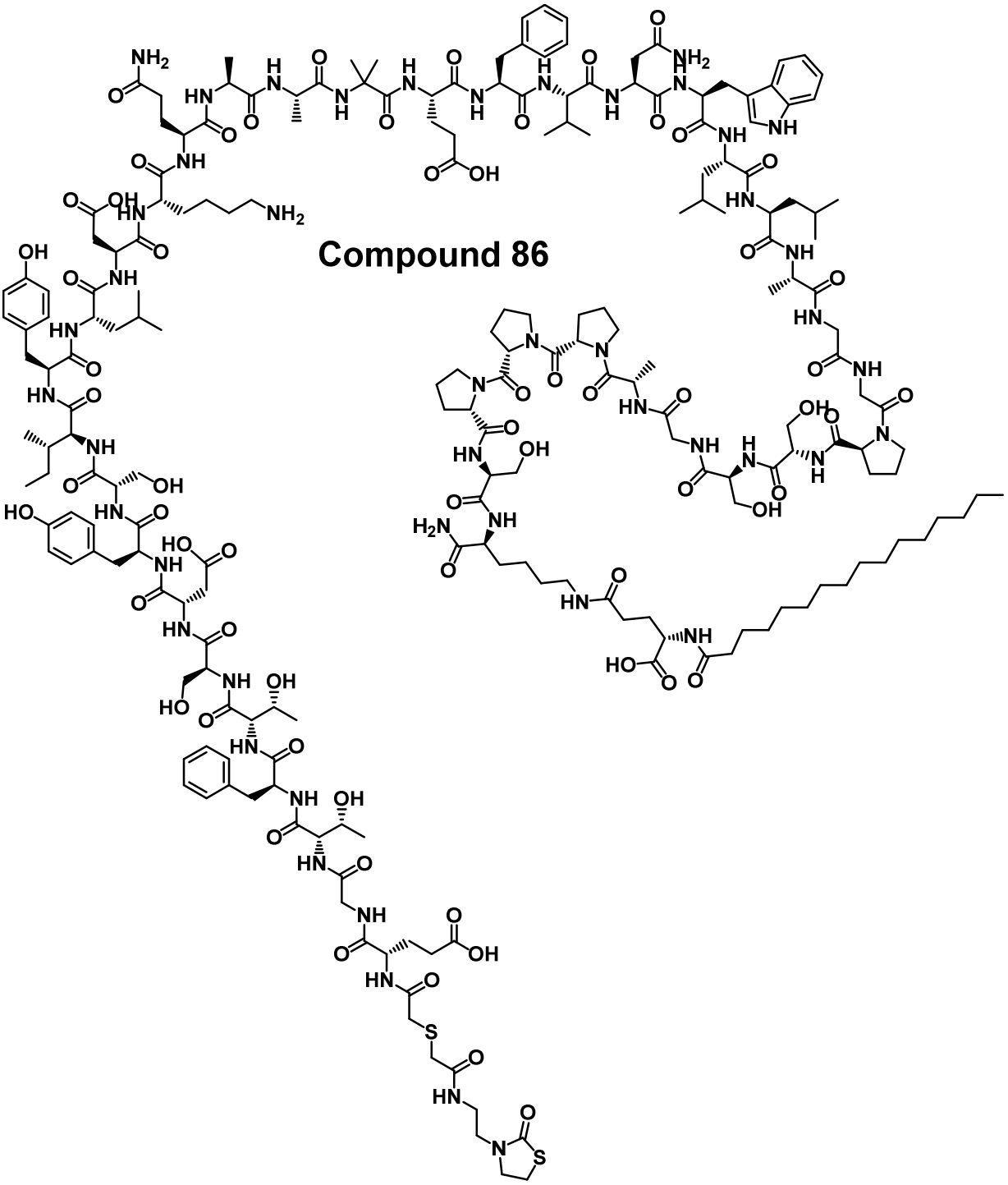

Compound 82


Compound 83

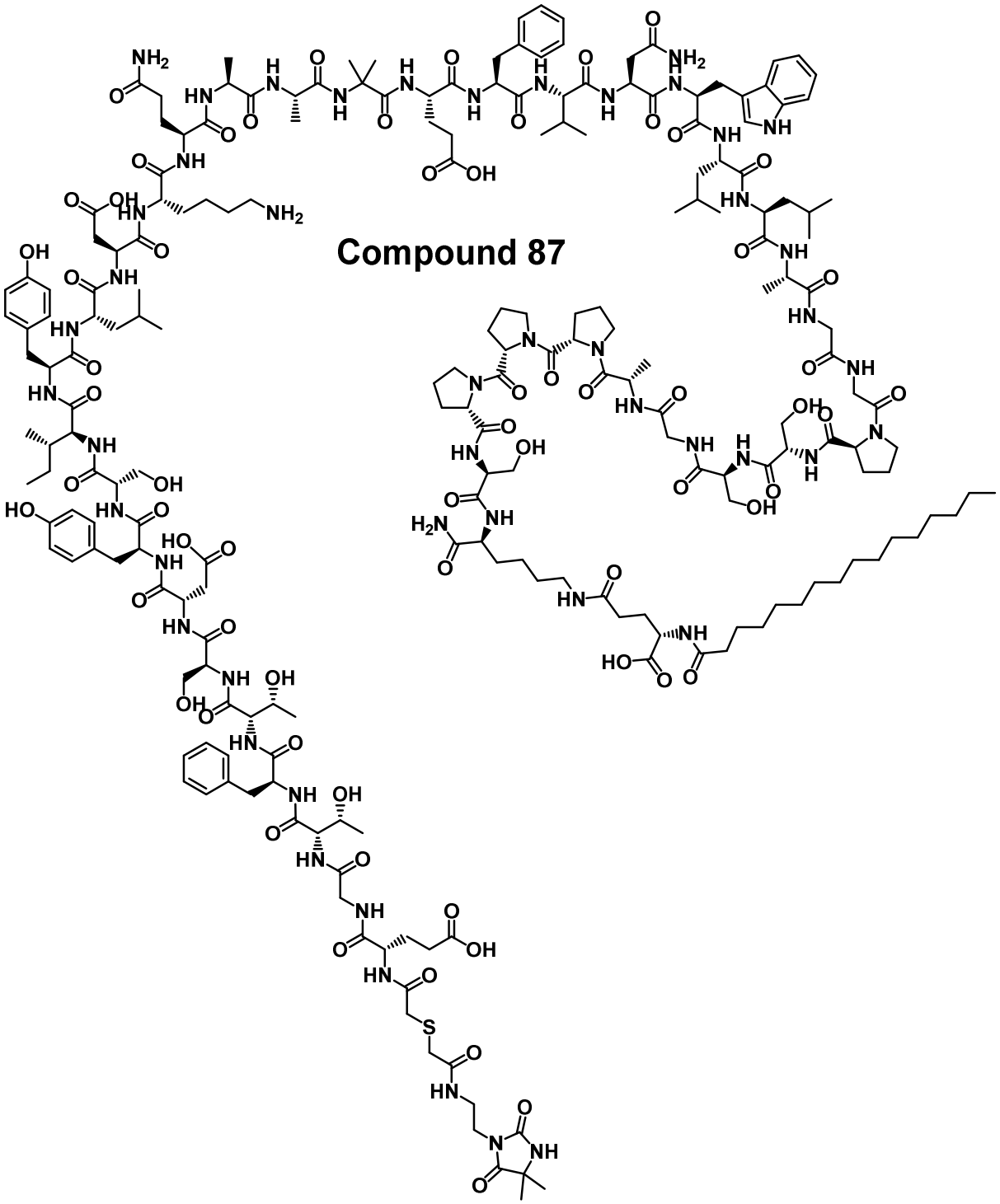


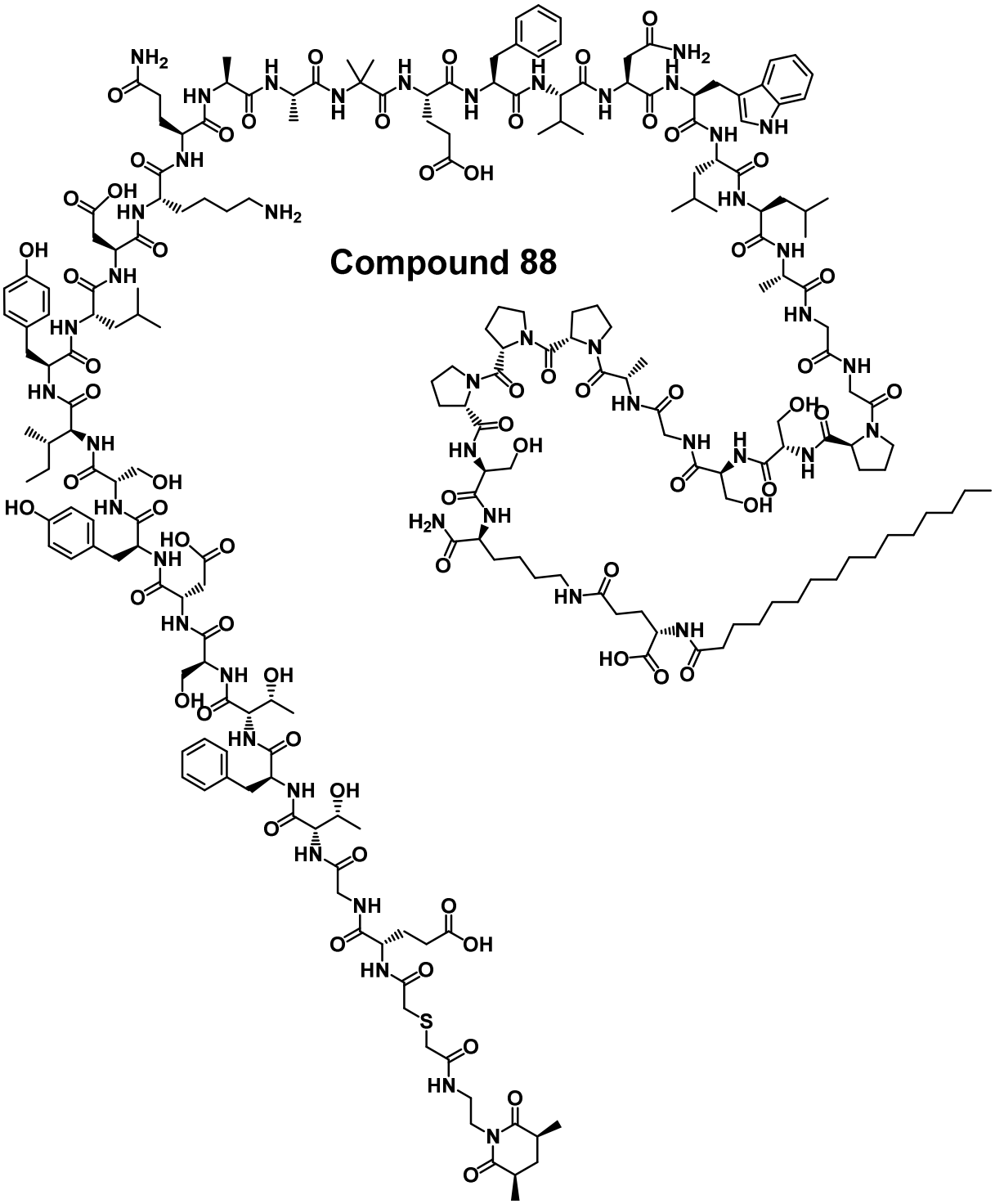
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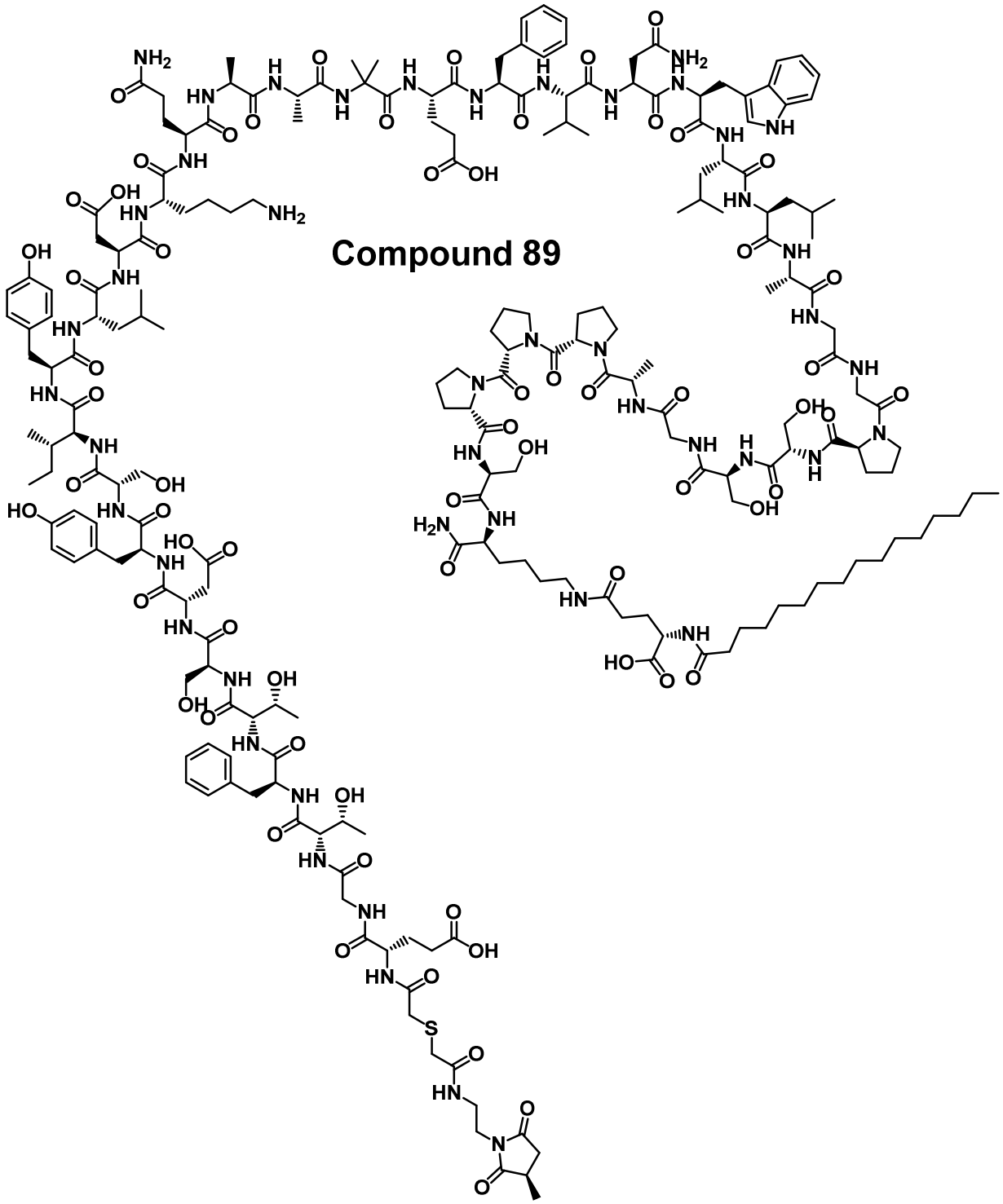

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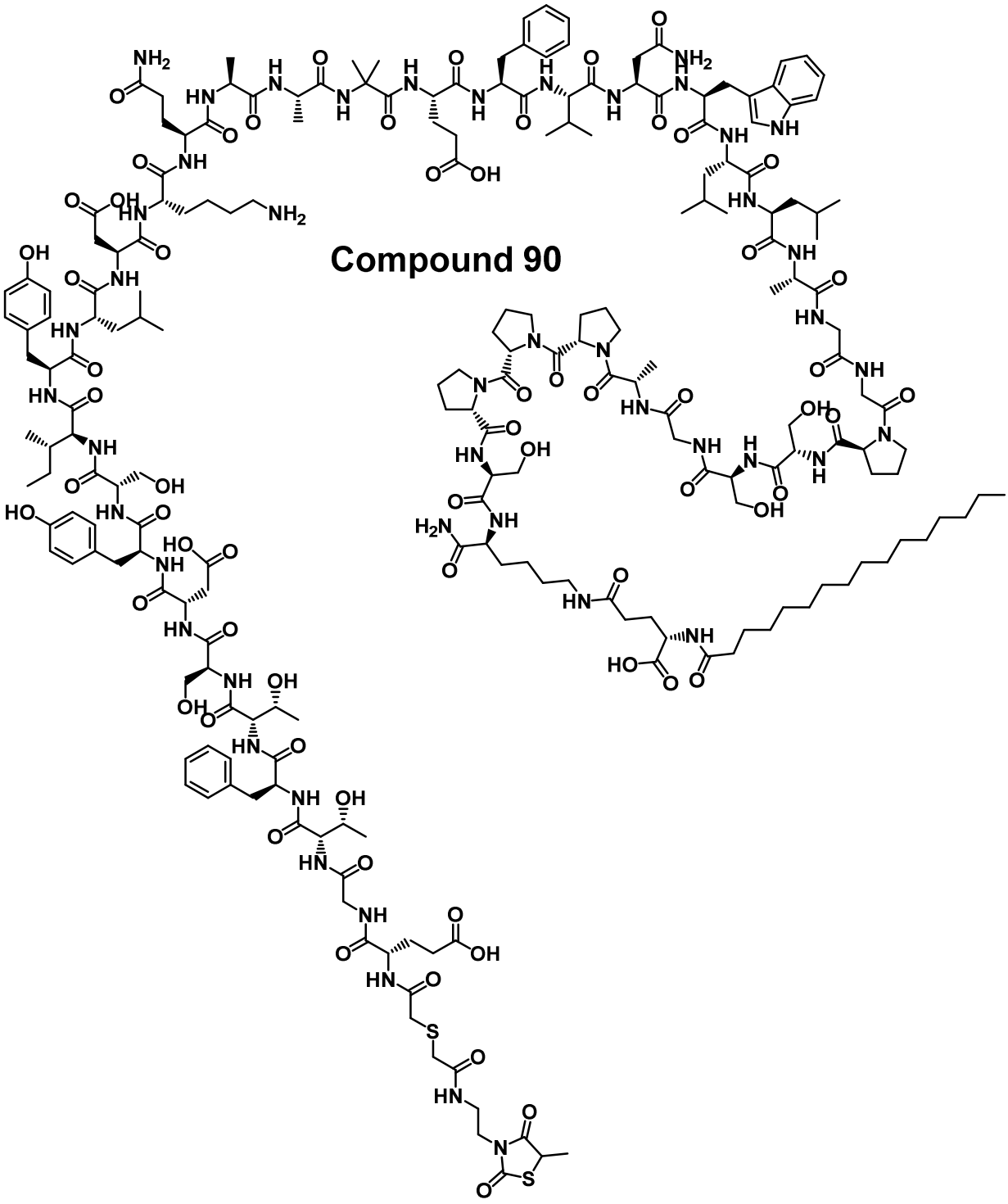


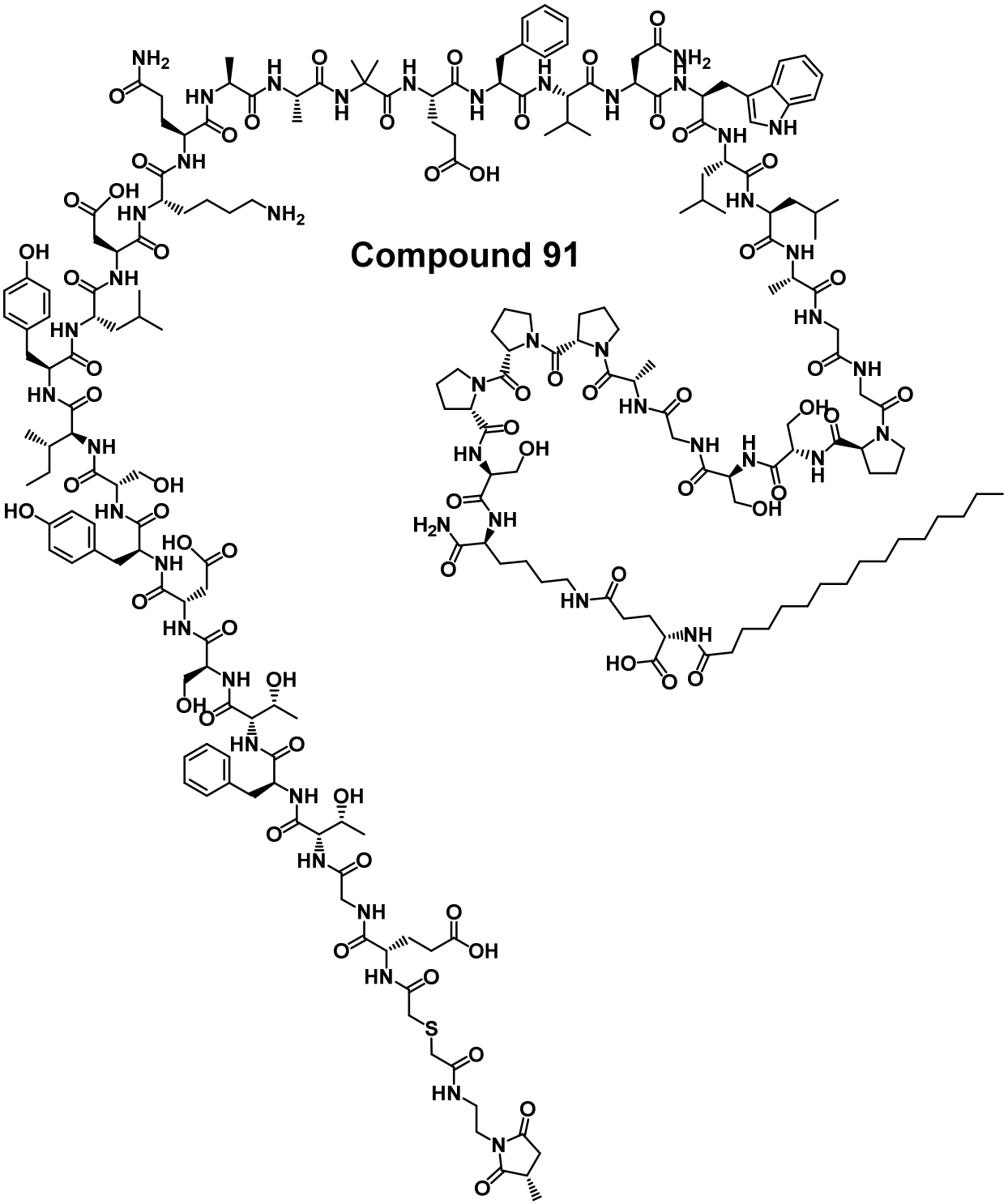
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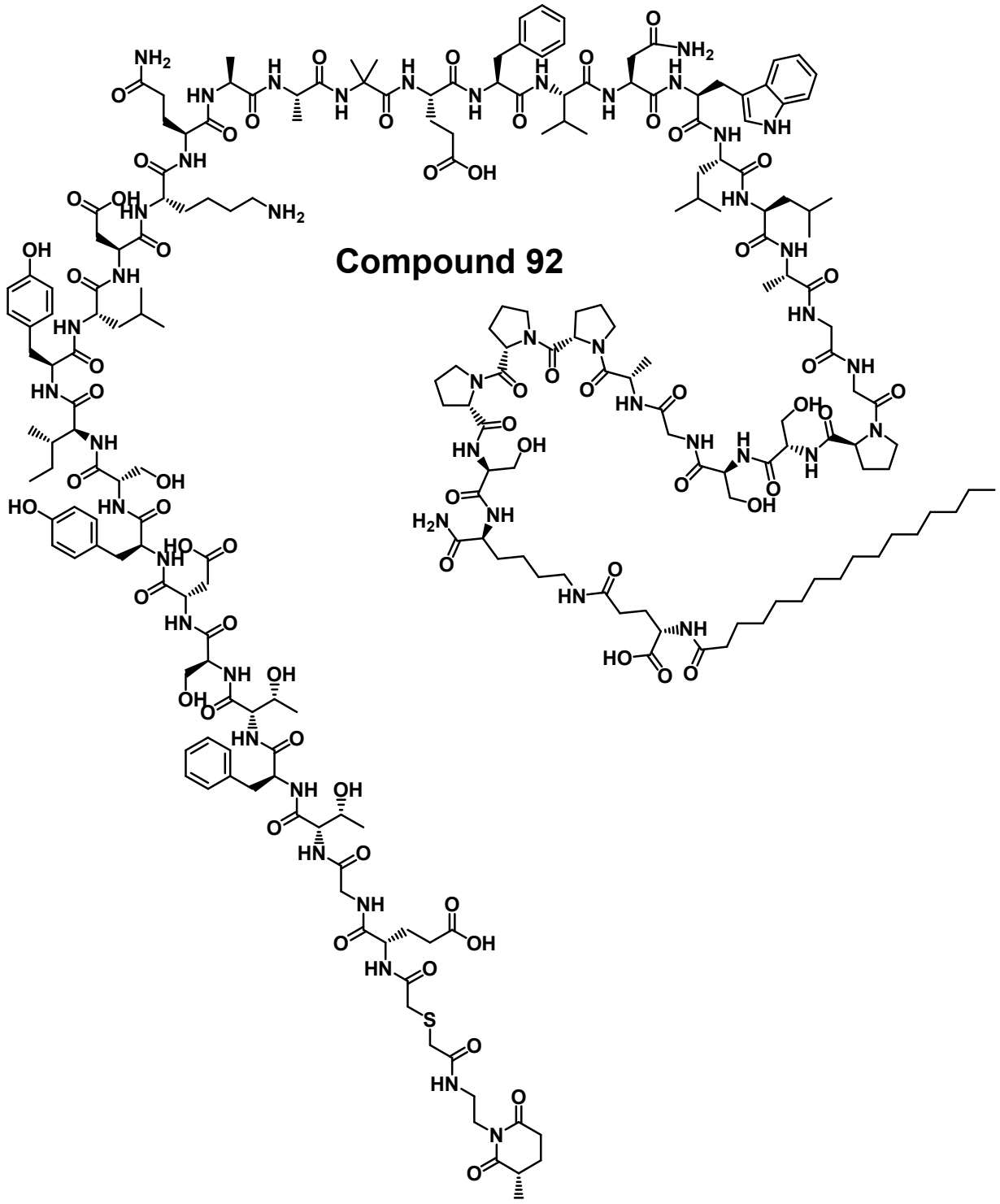

Compound 87


Compound 88

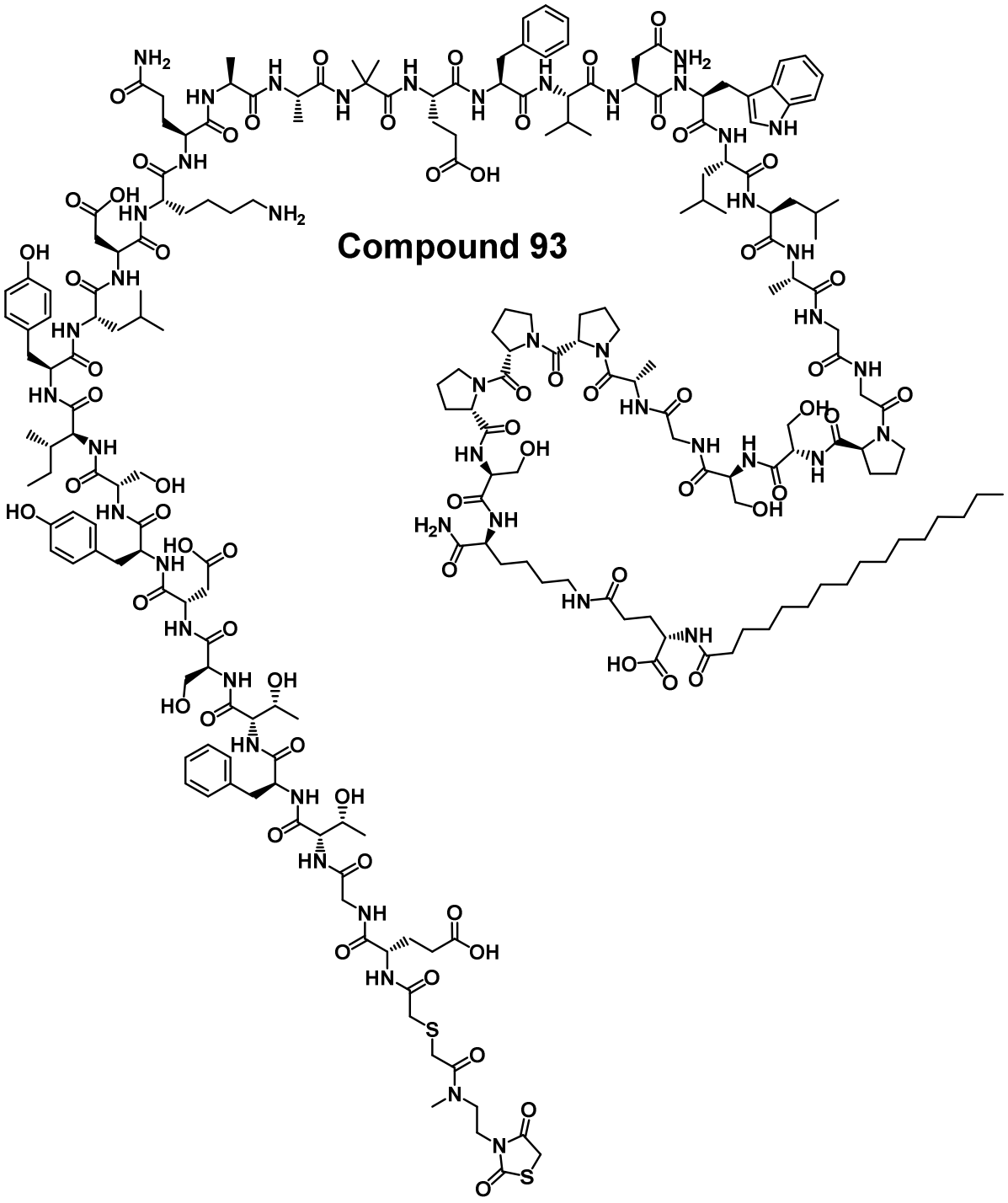

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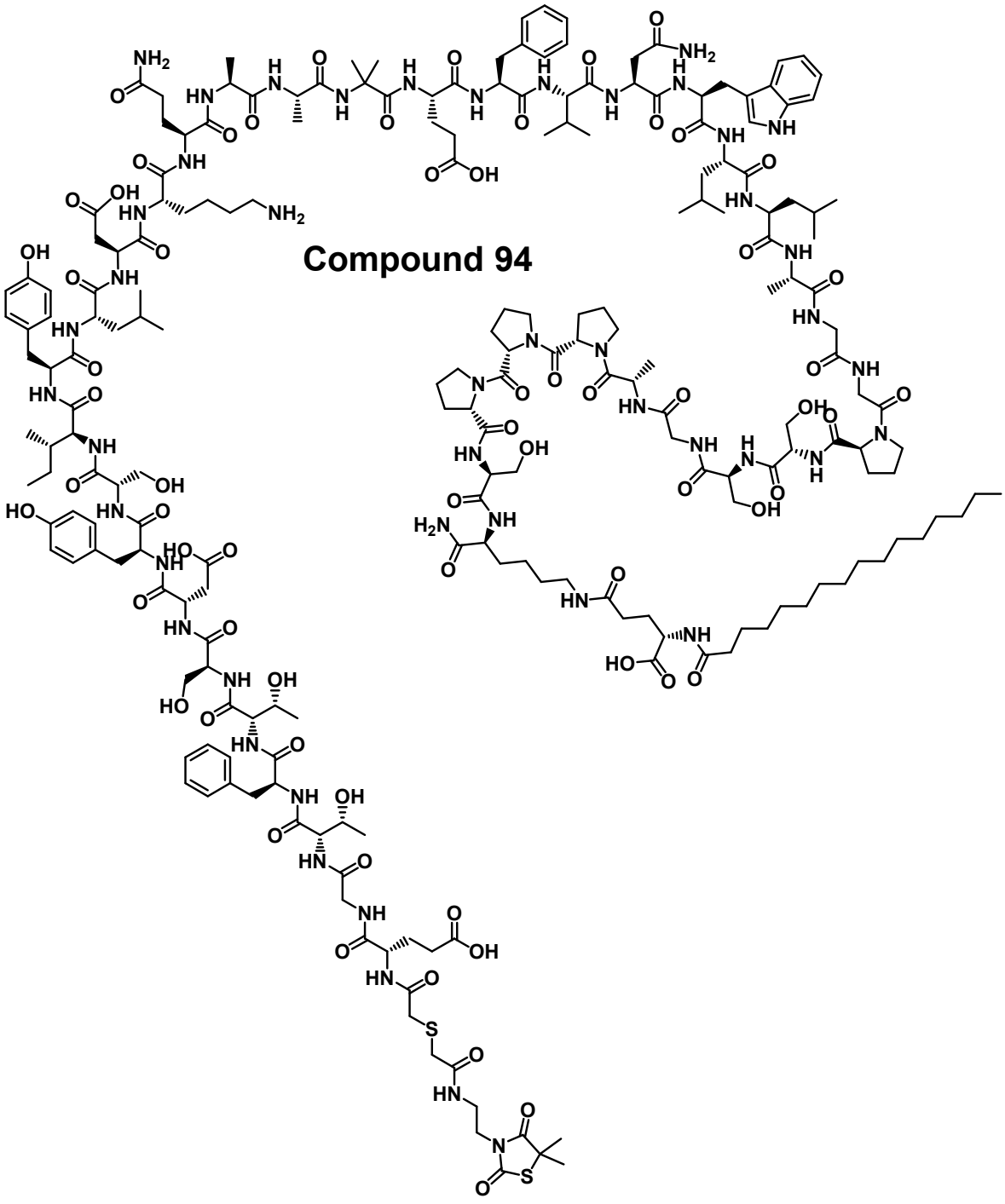

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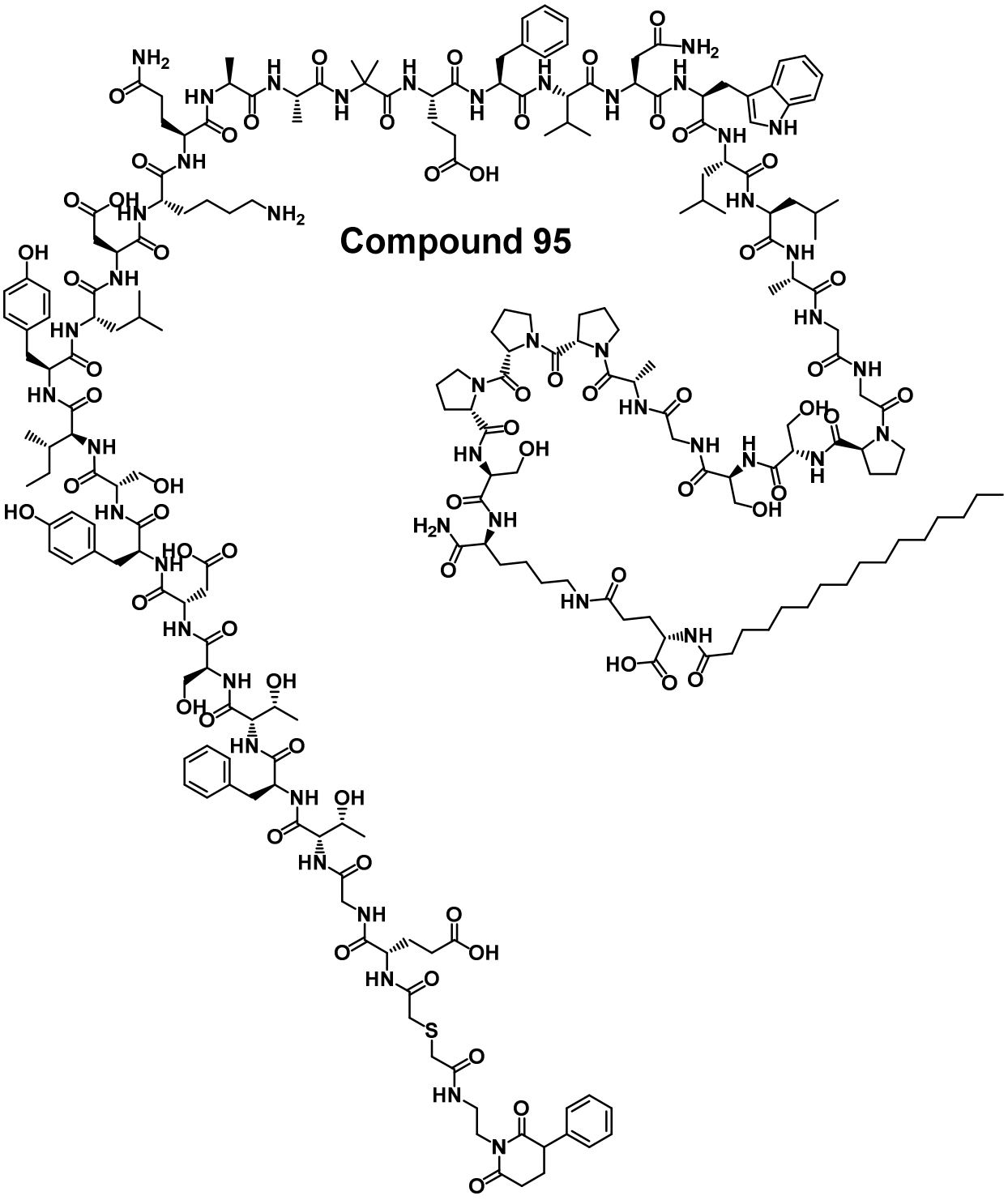


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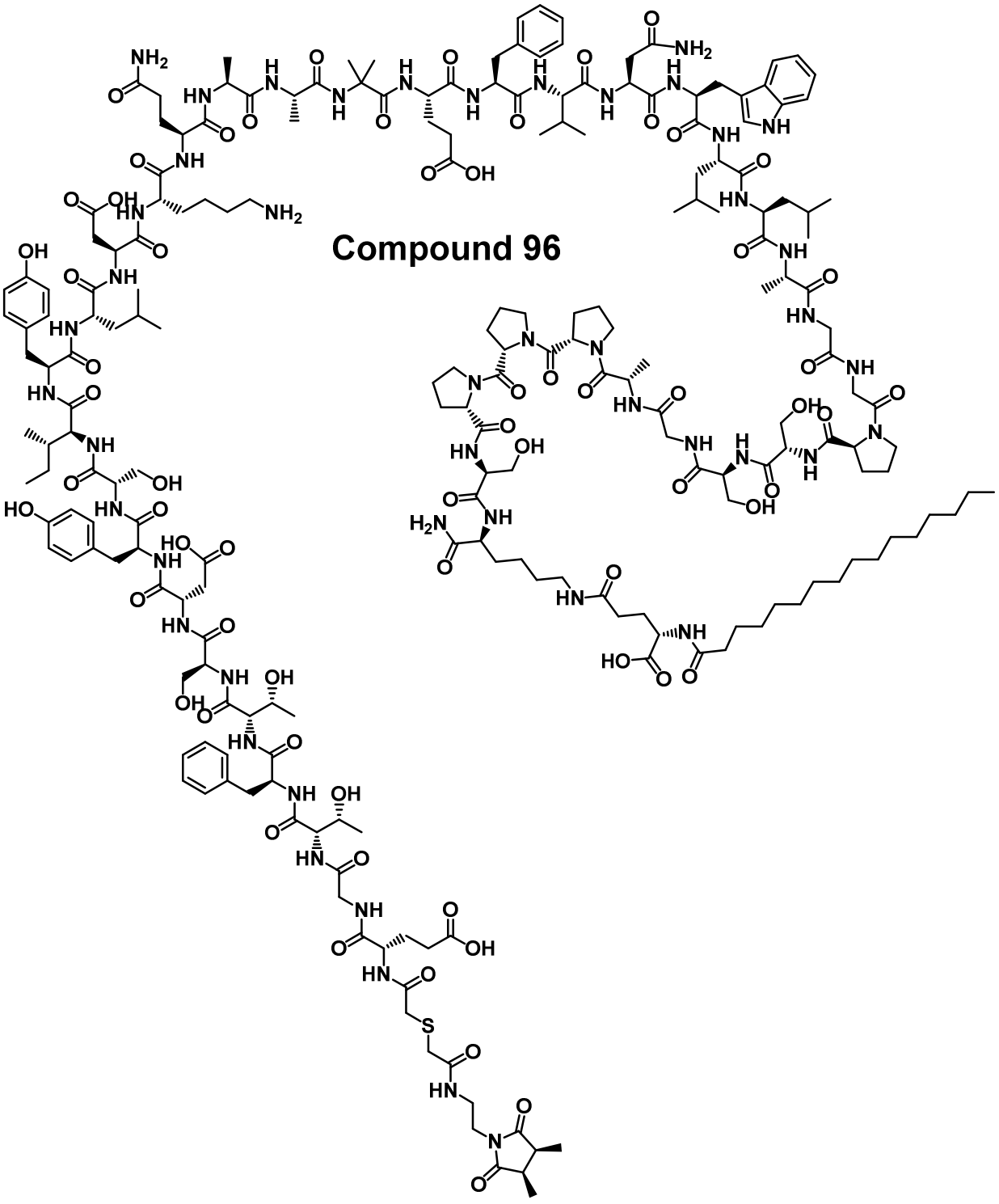

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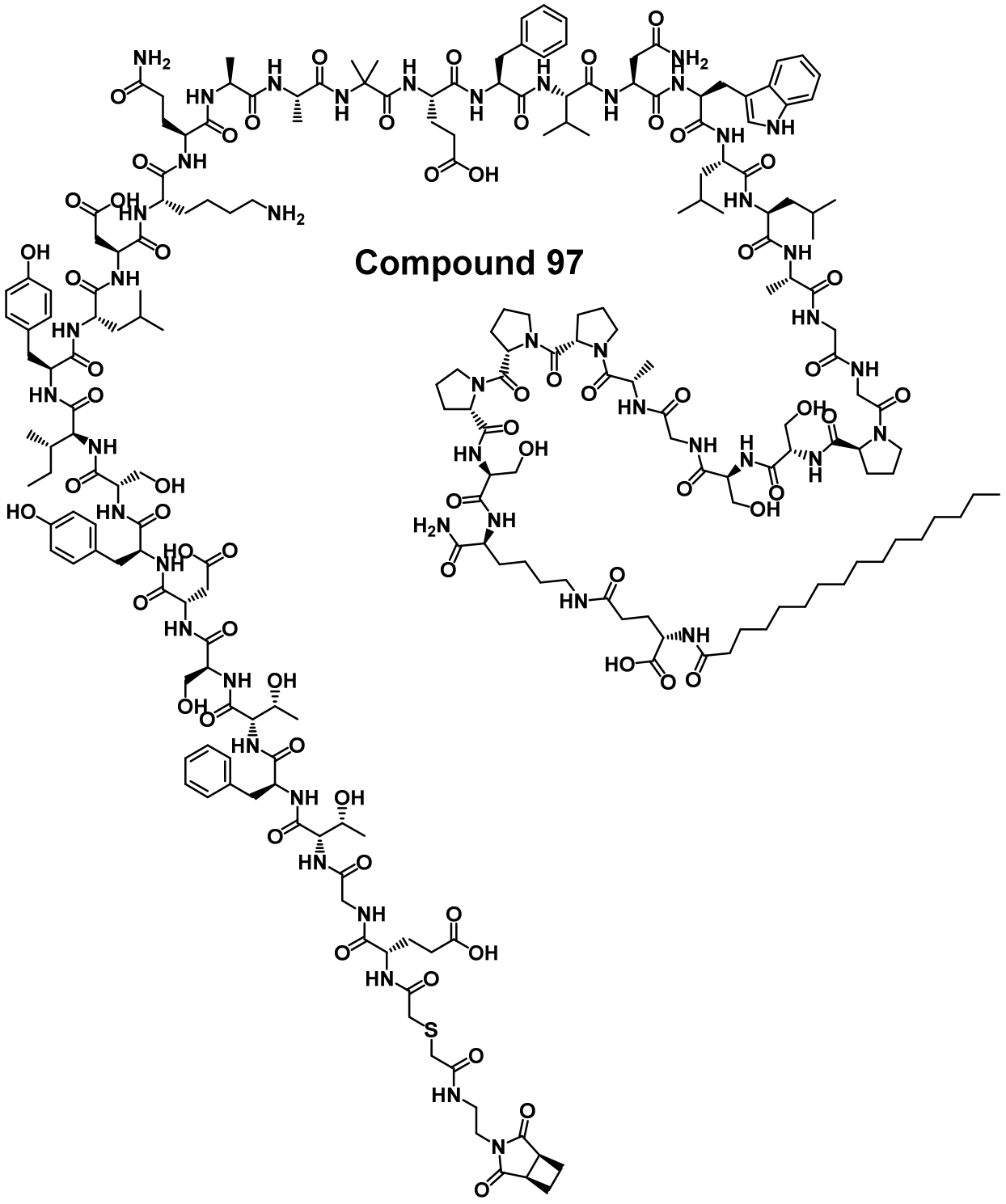


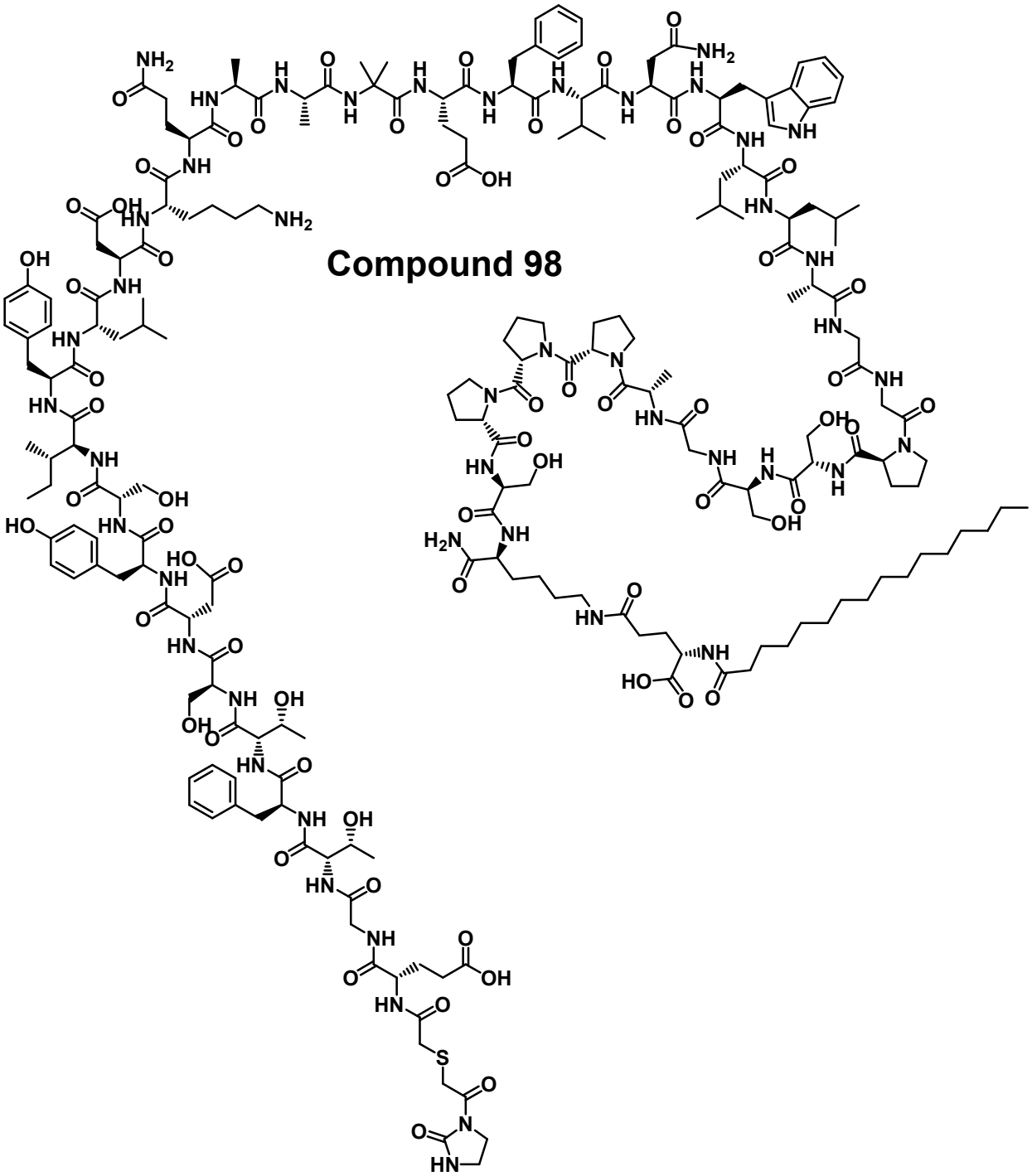
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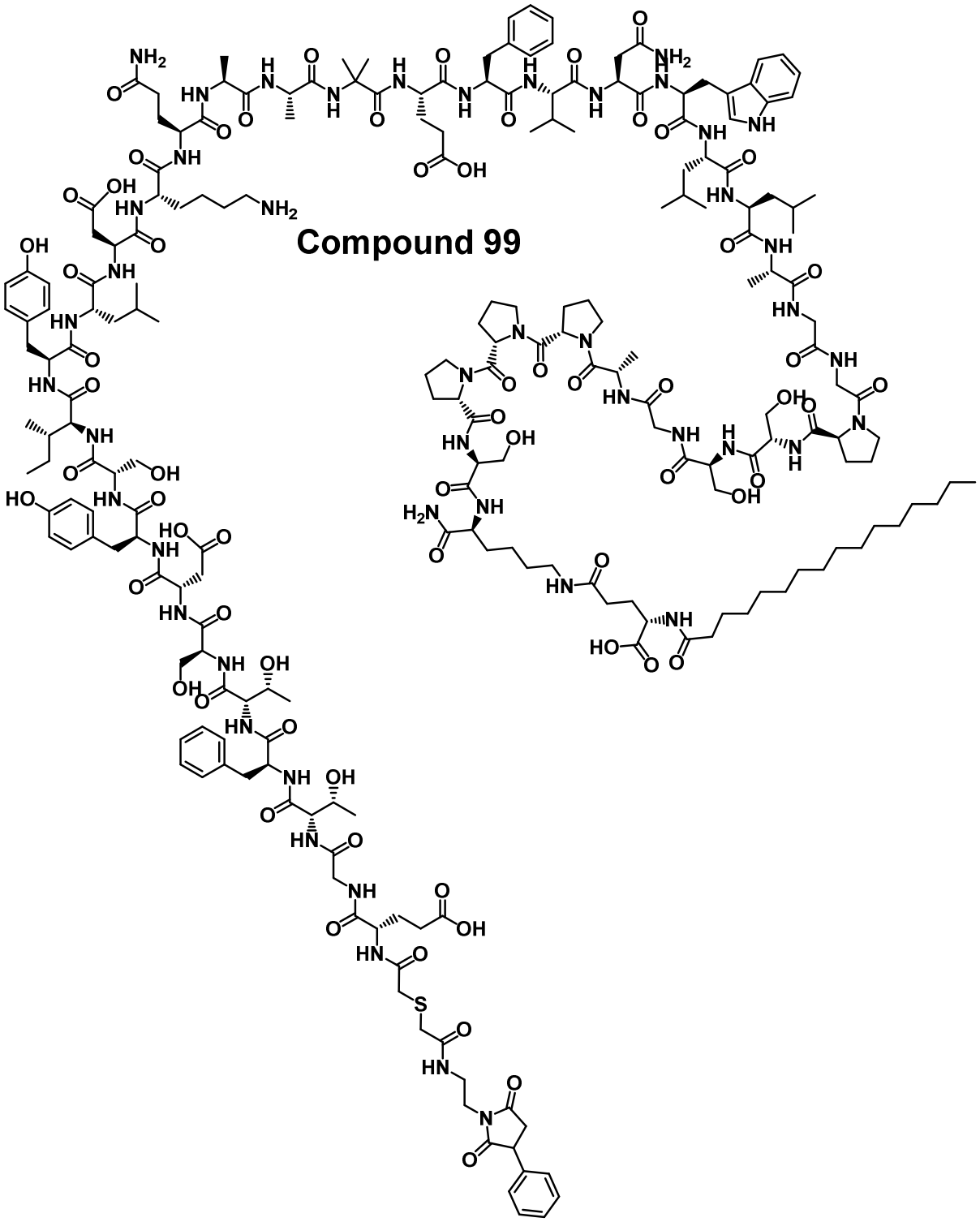
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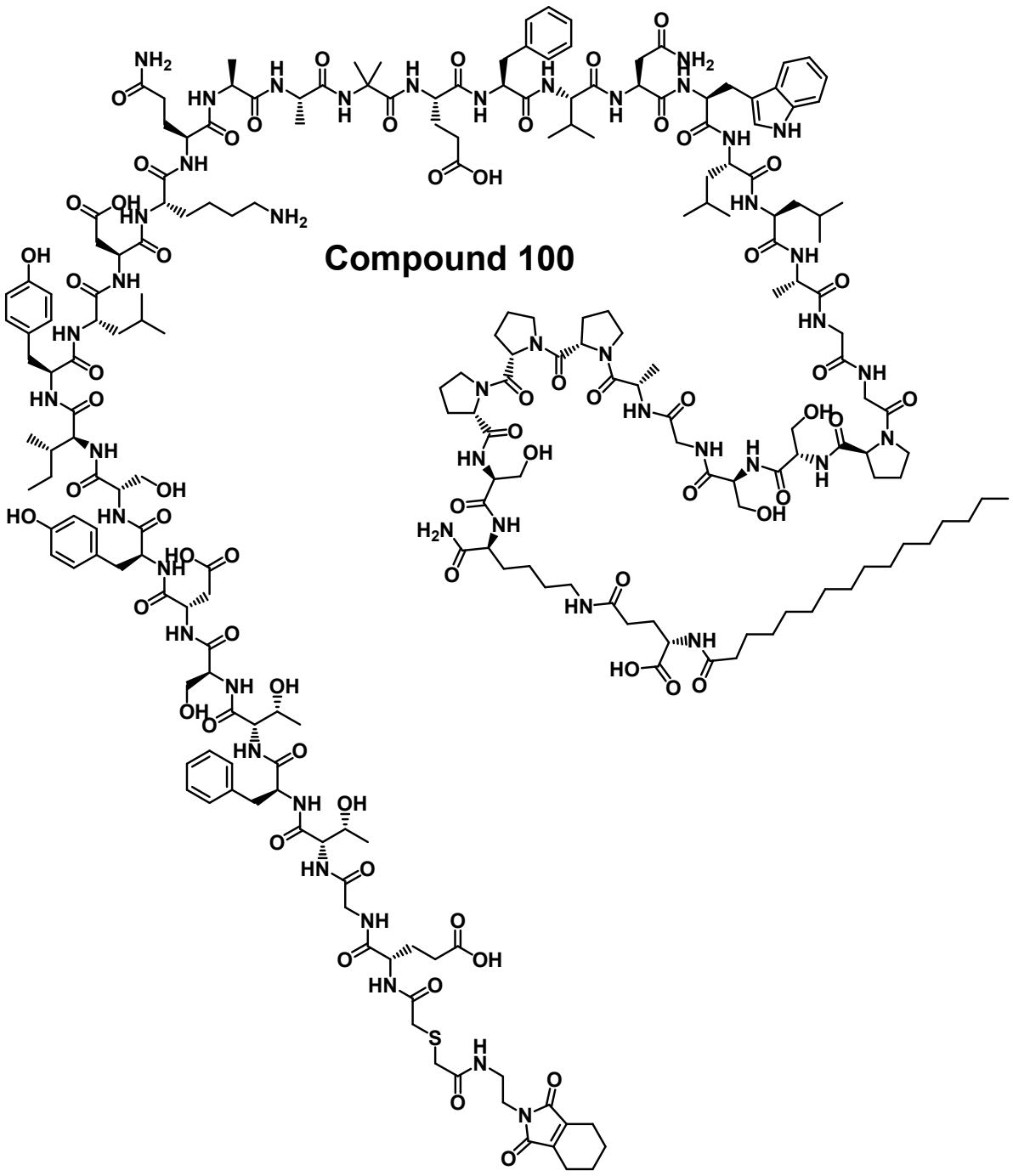

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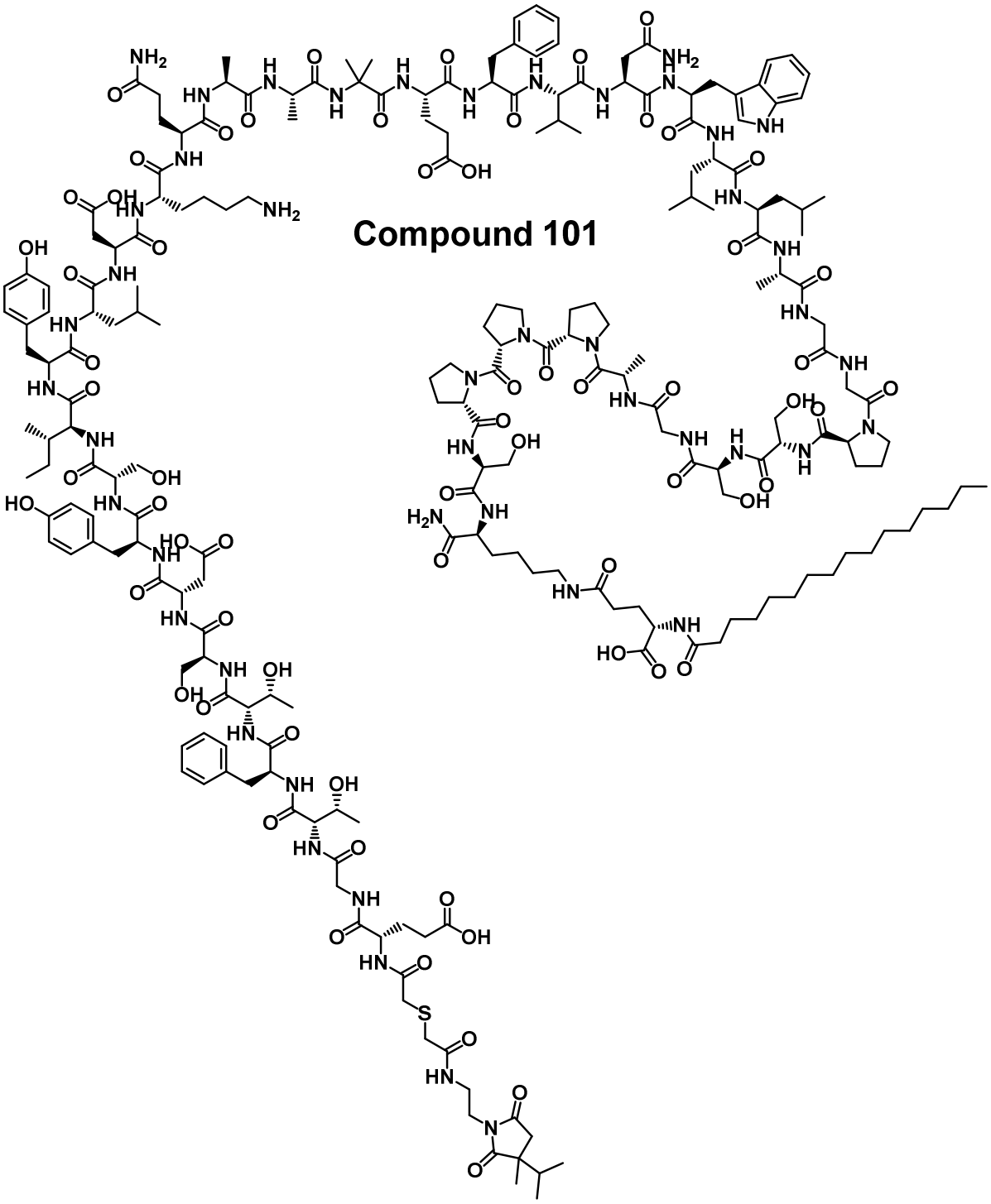
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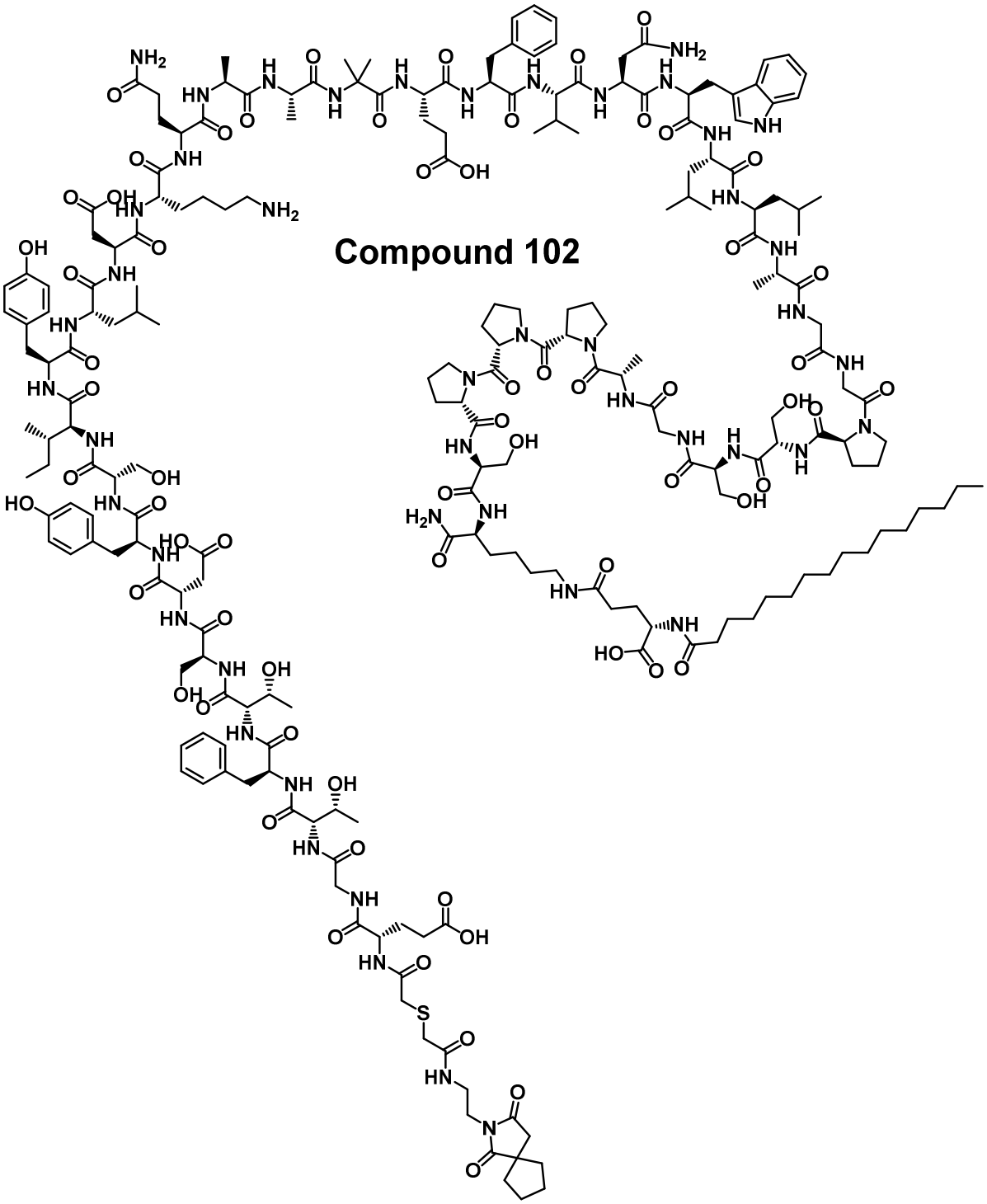


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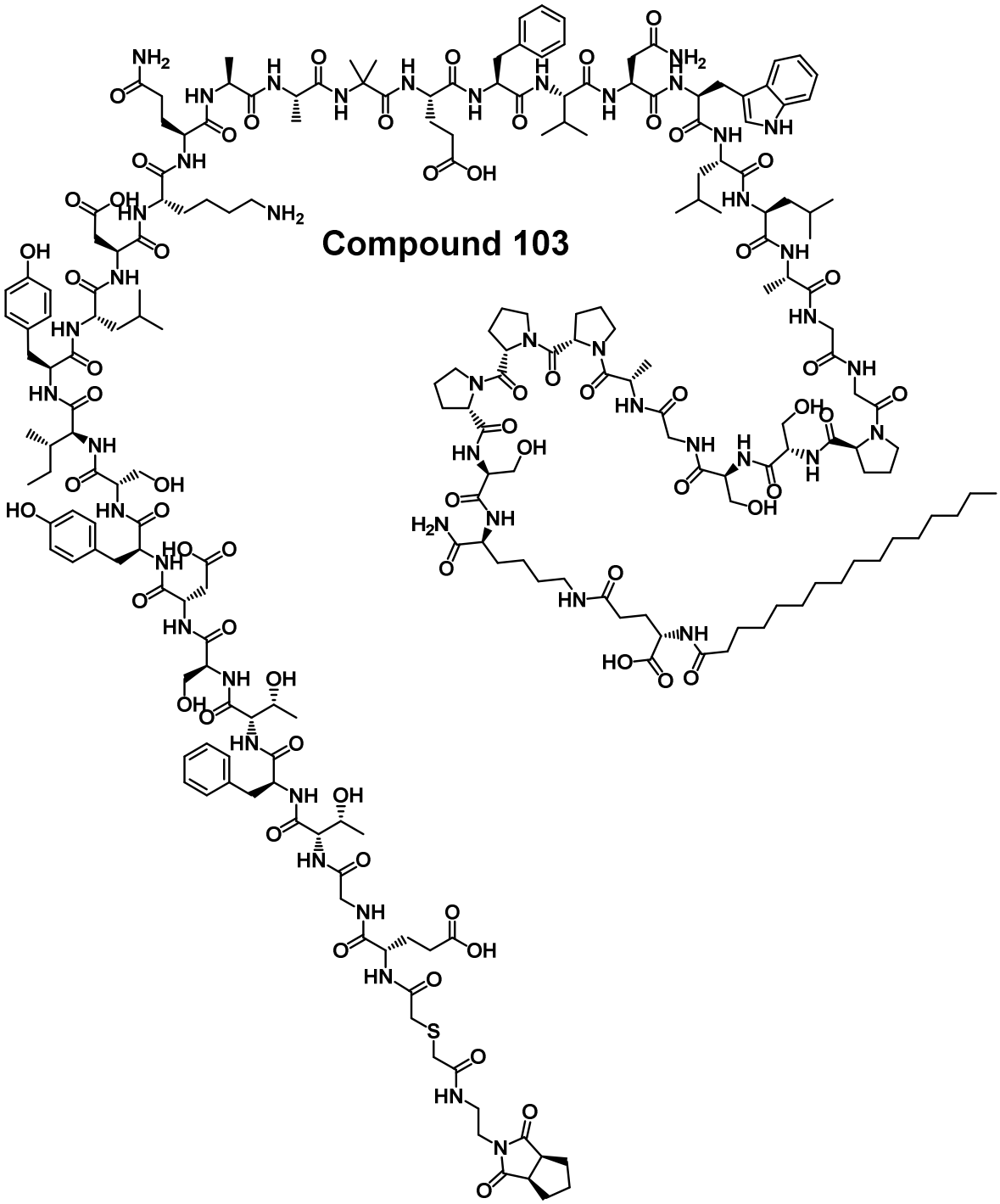


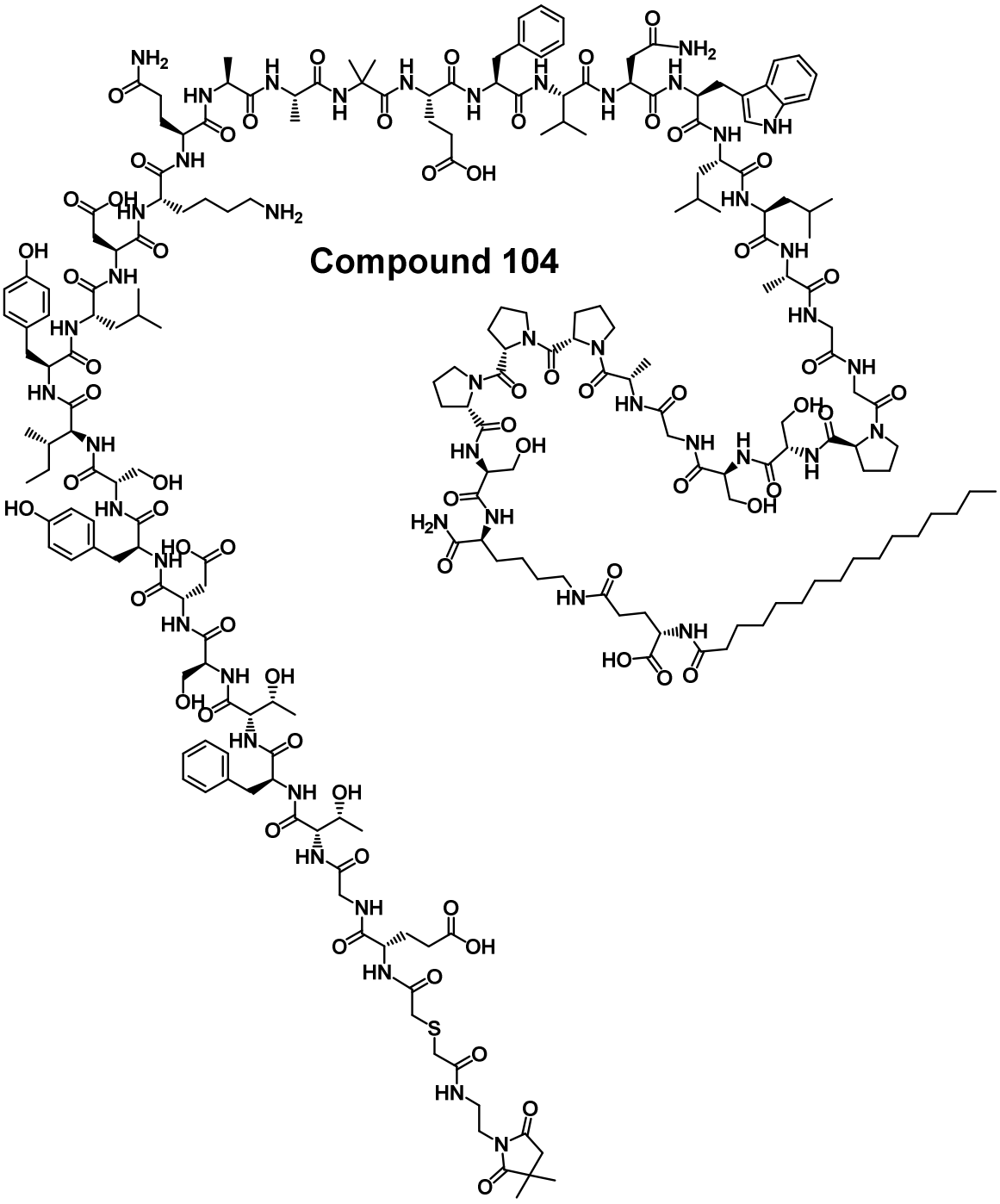
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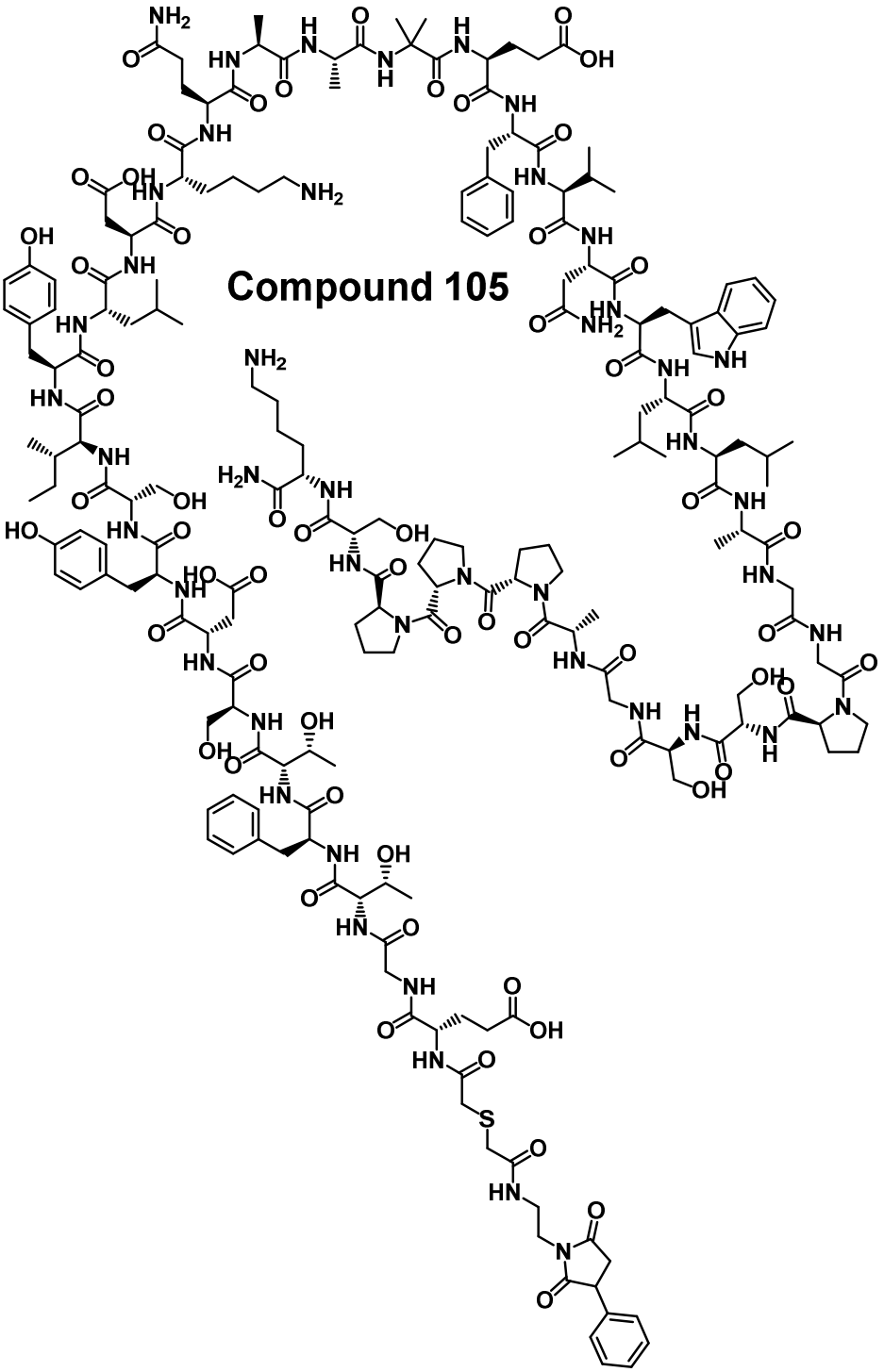

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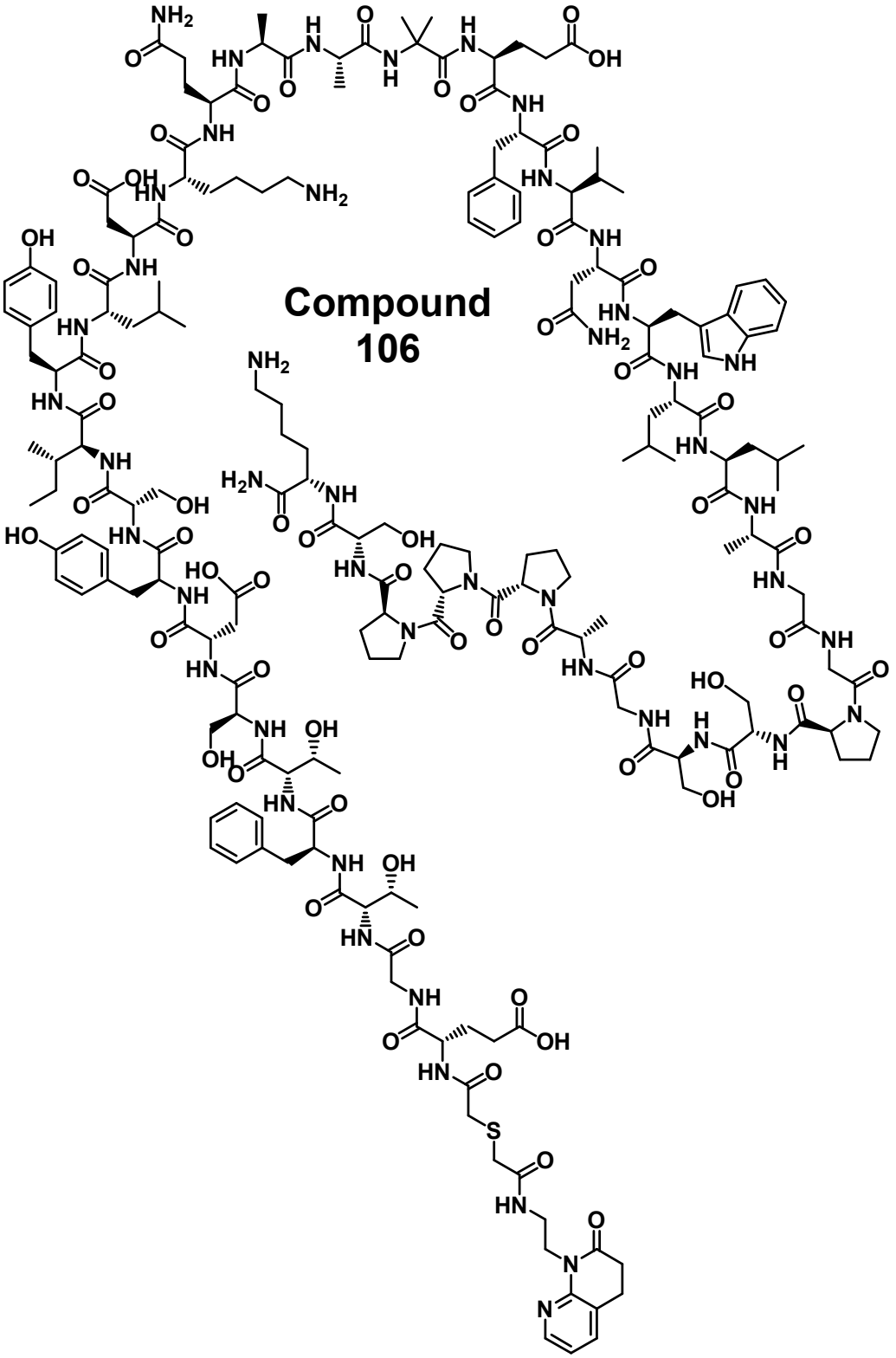


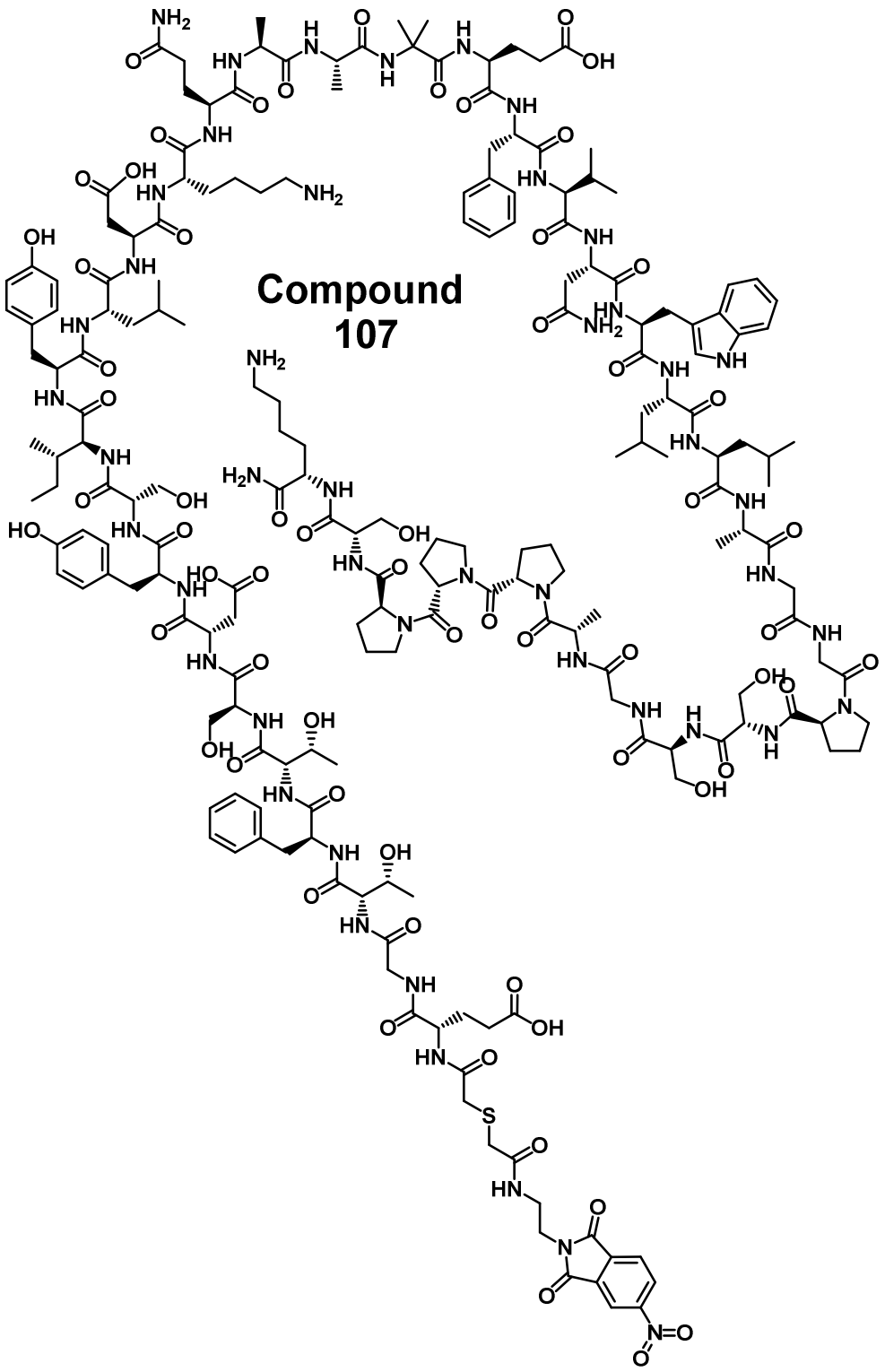
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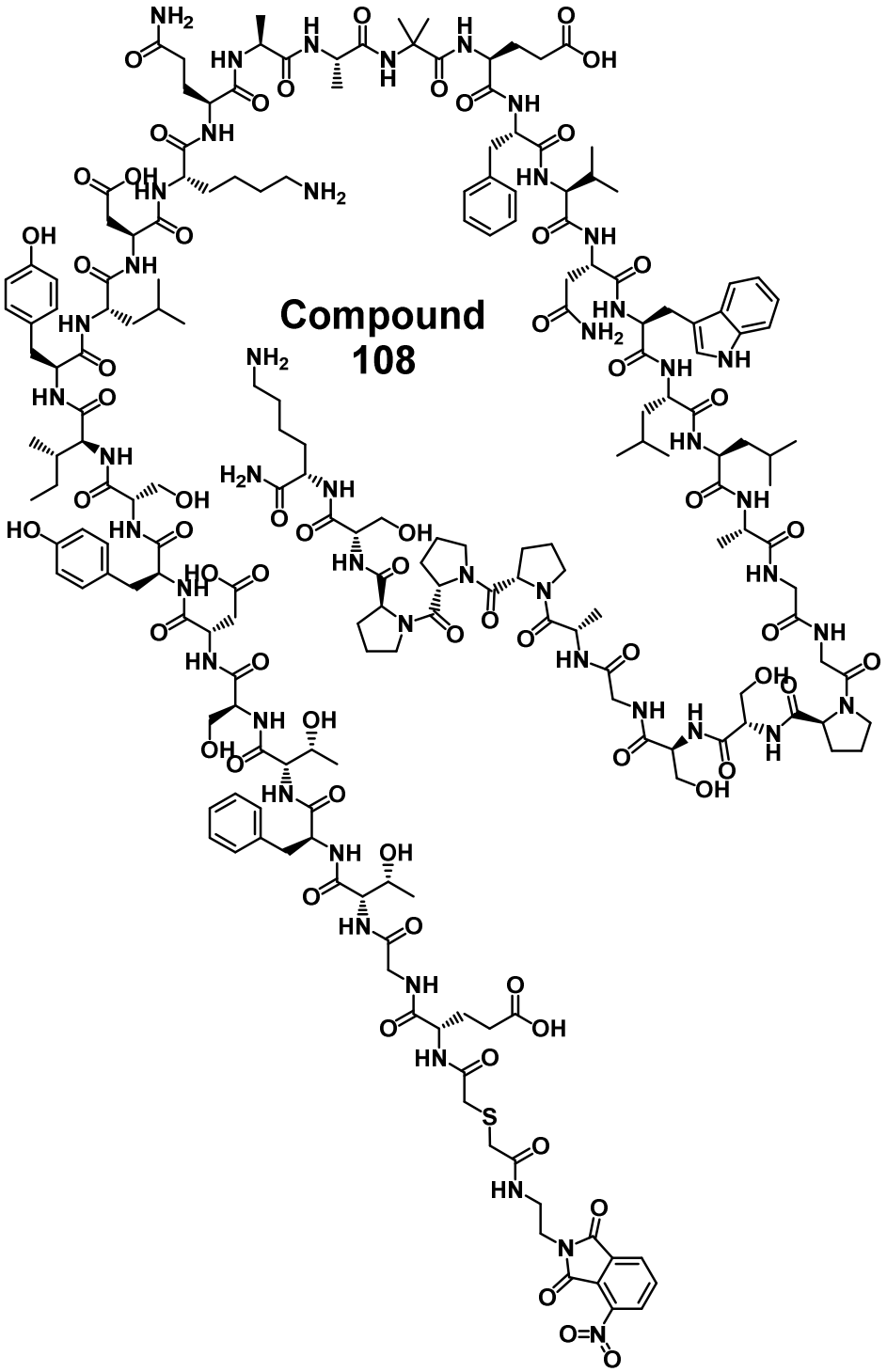

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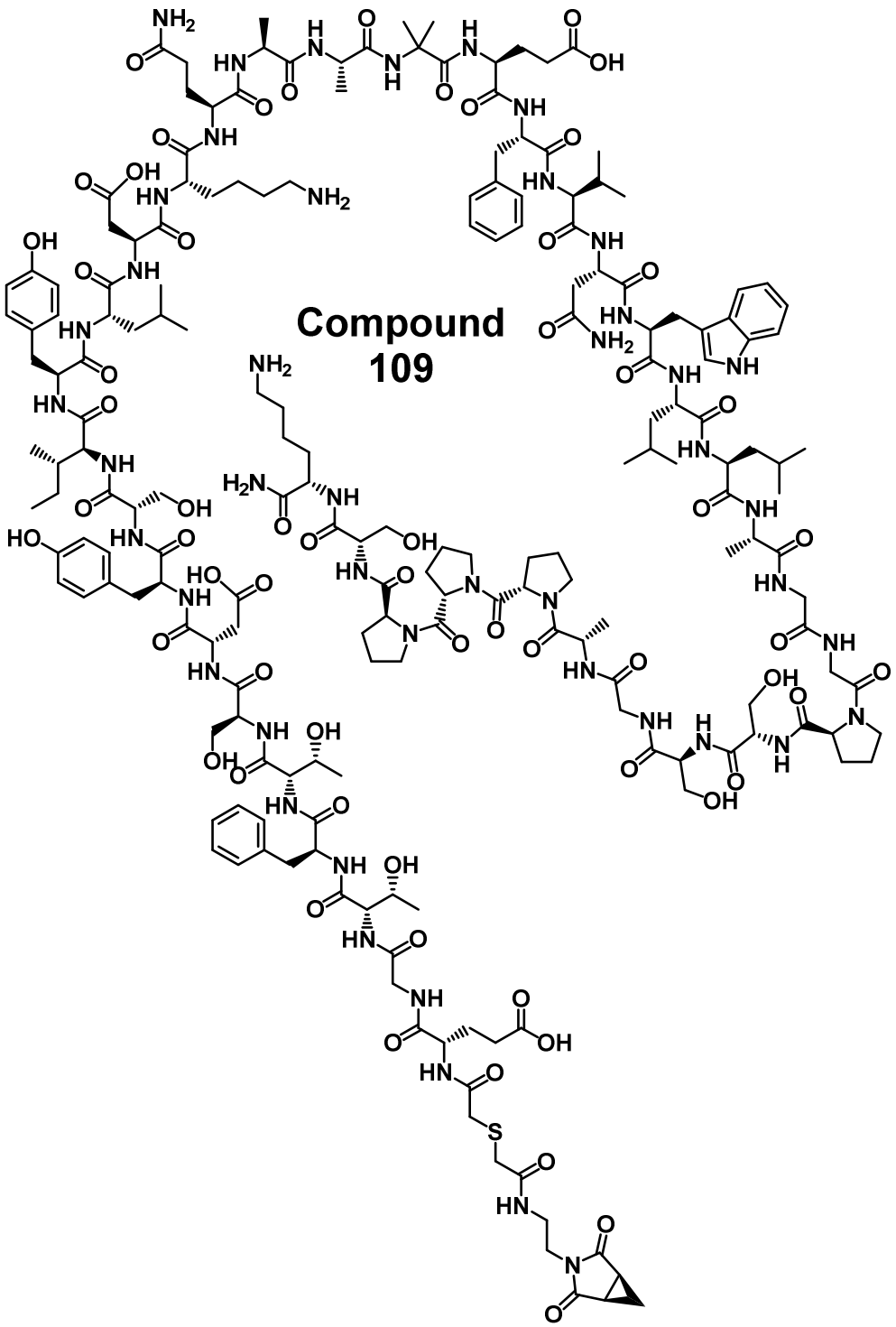

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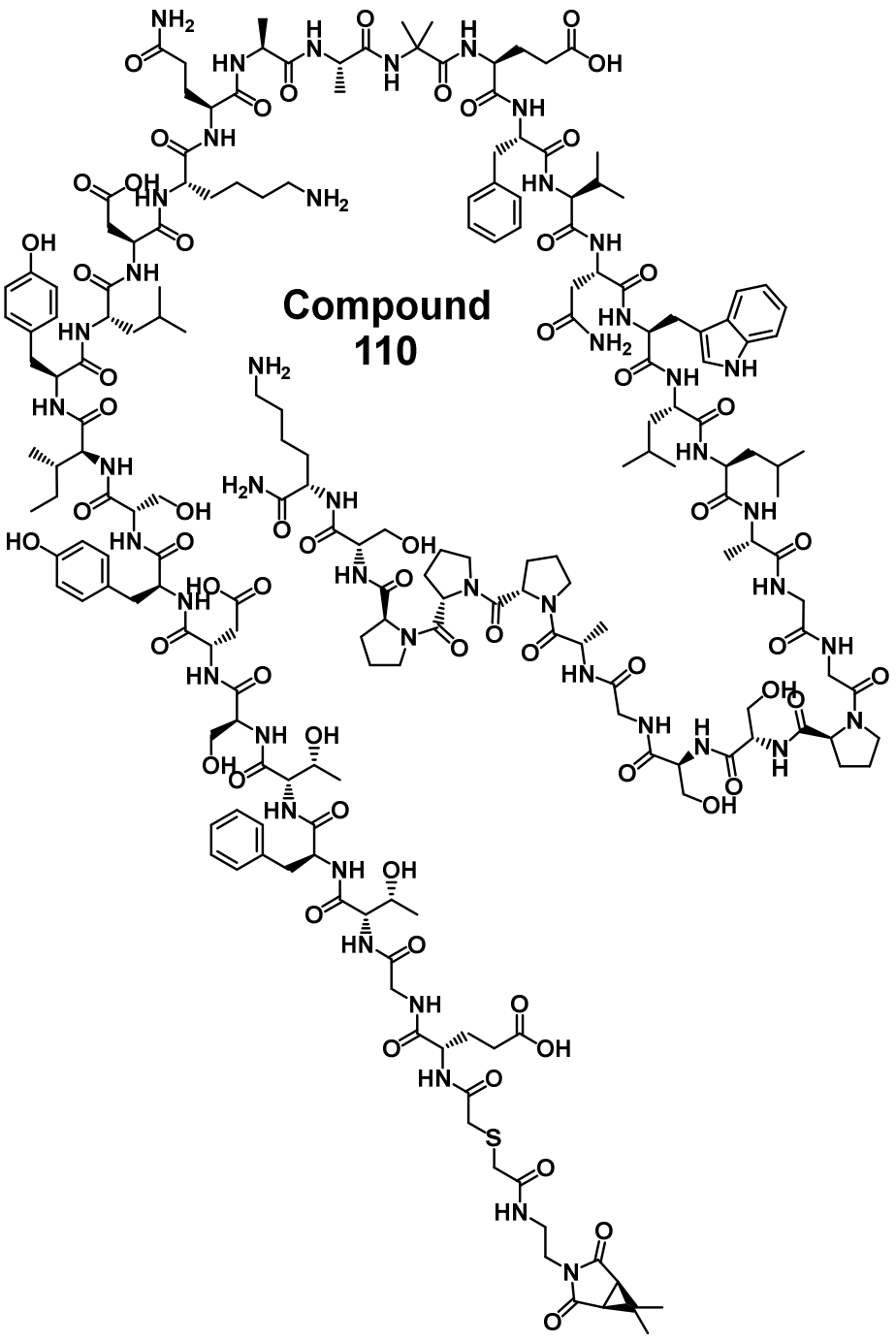

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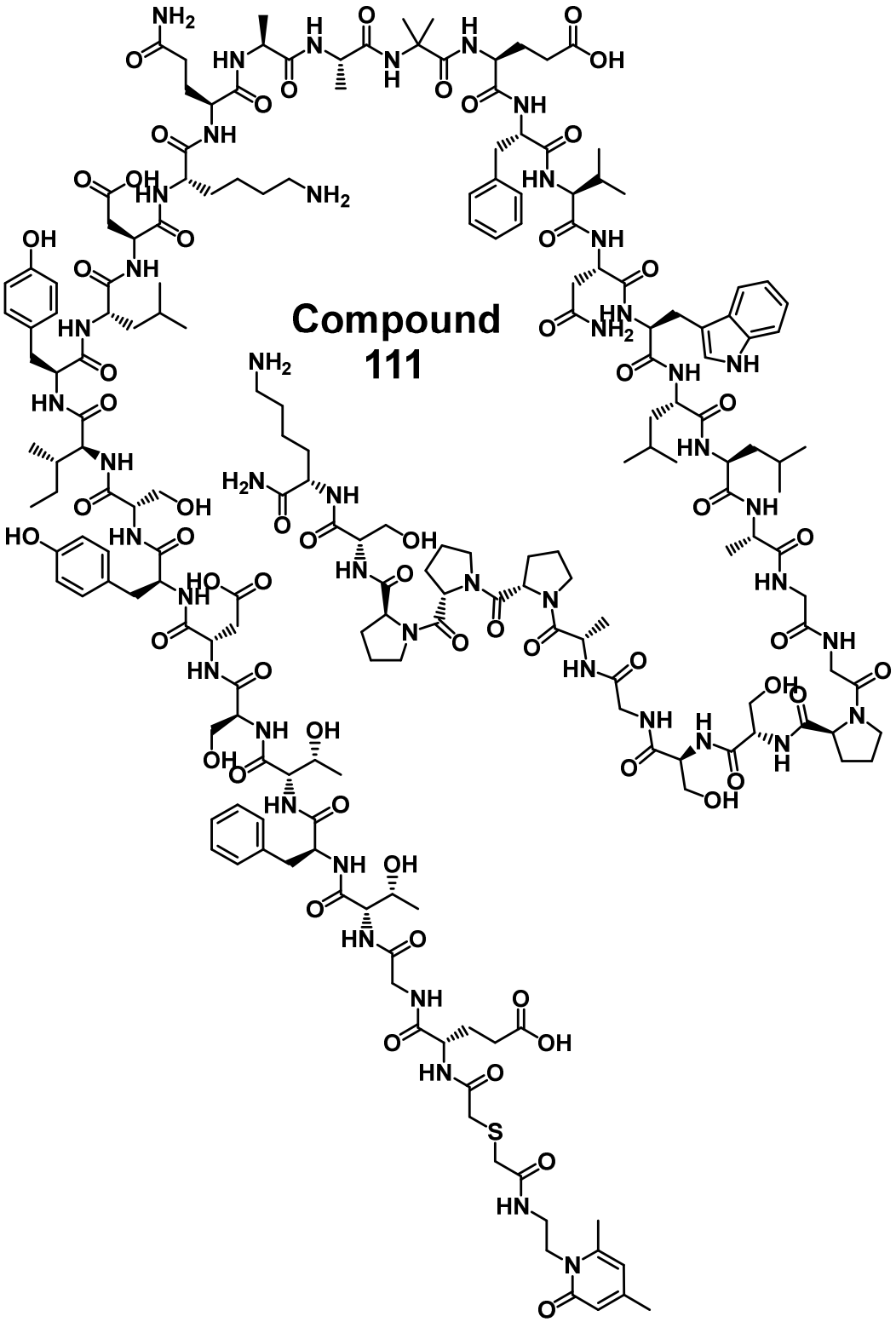

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106

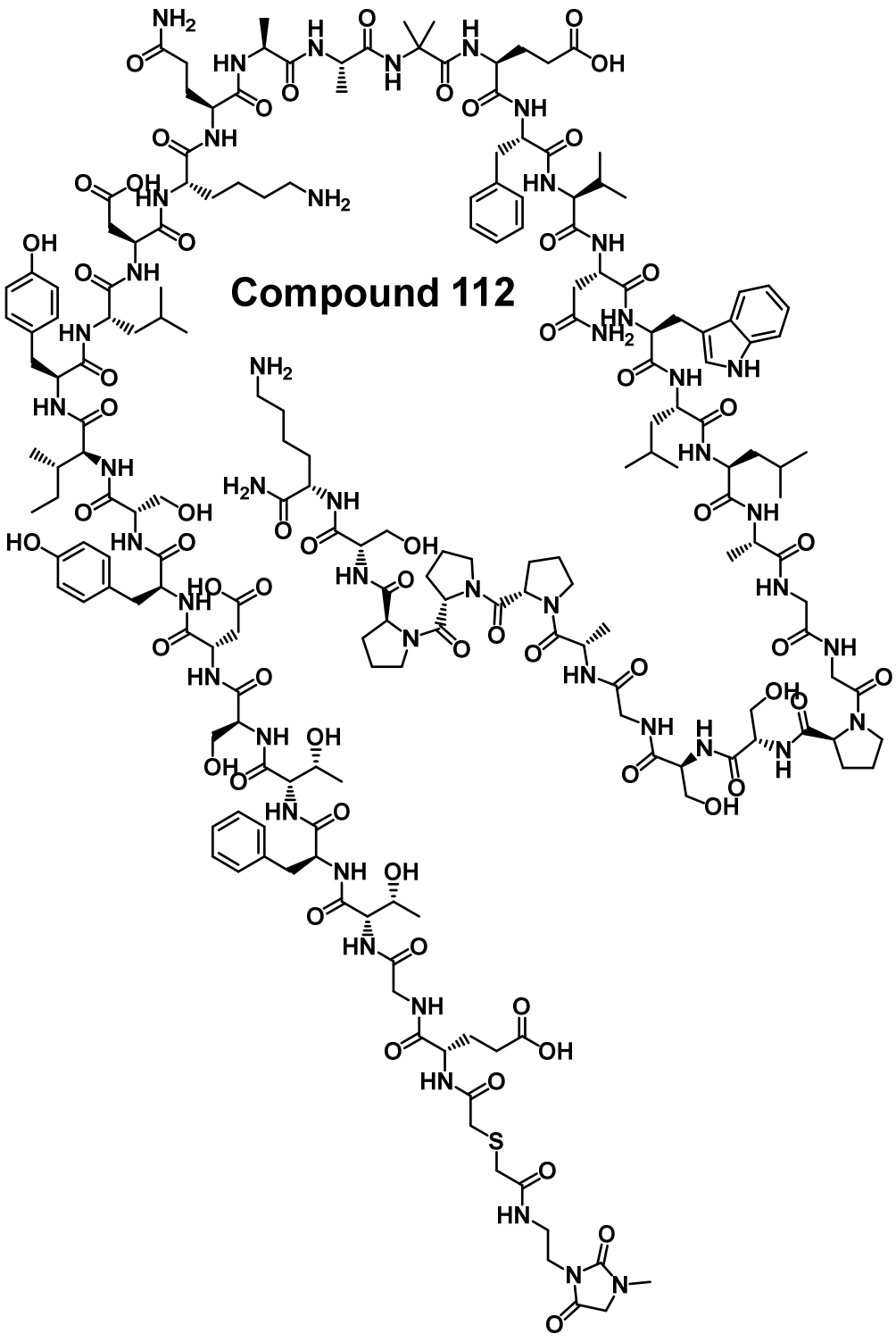

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107

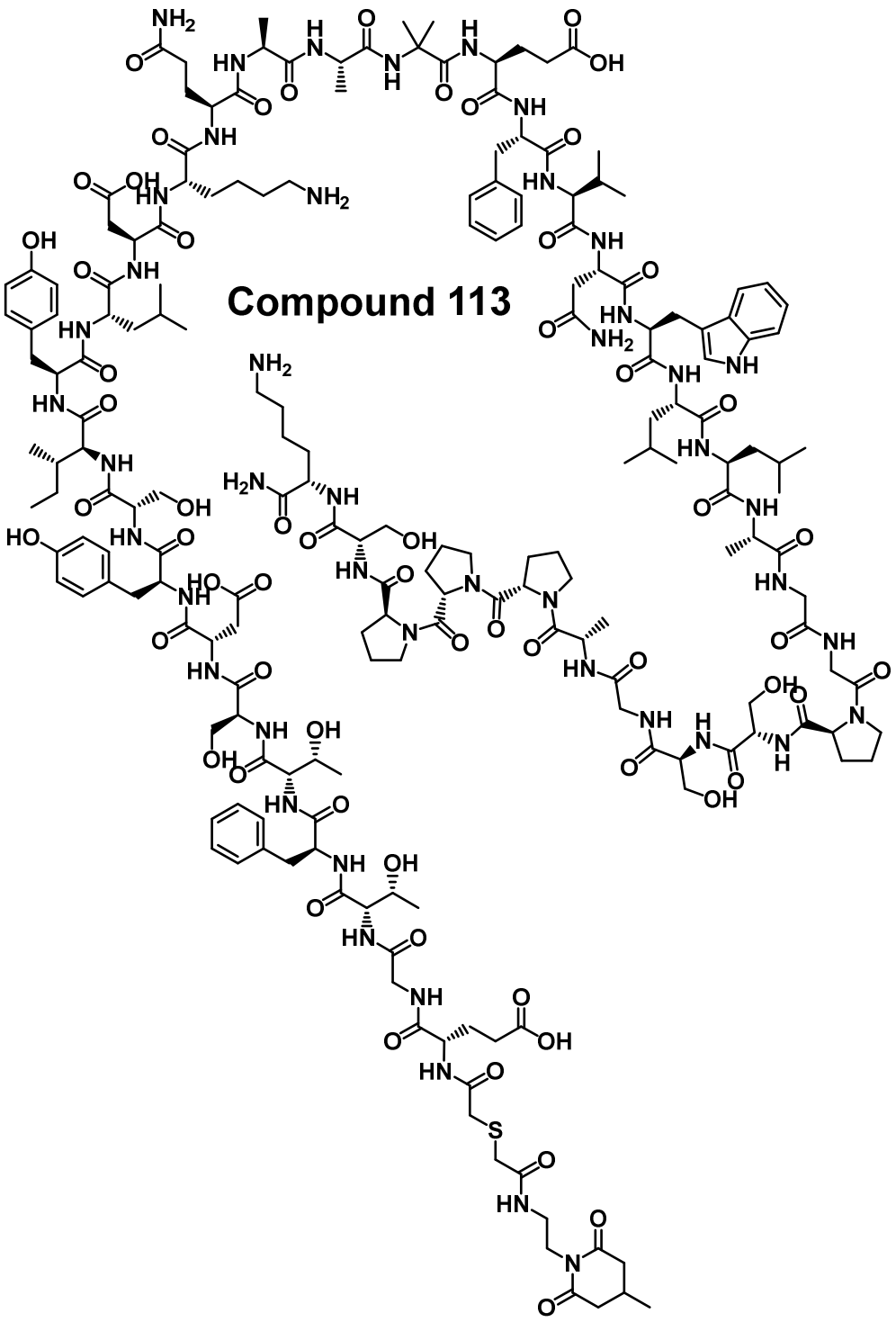

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108

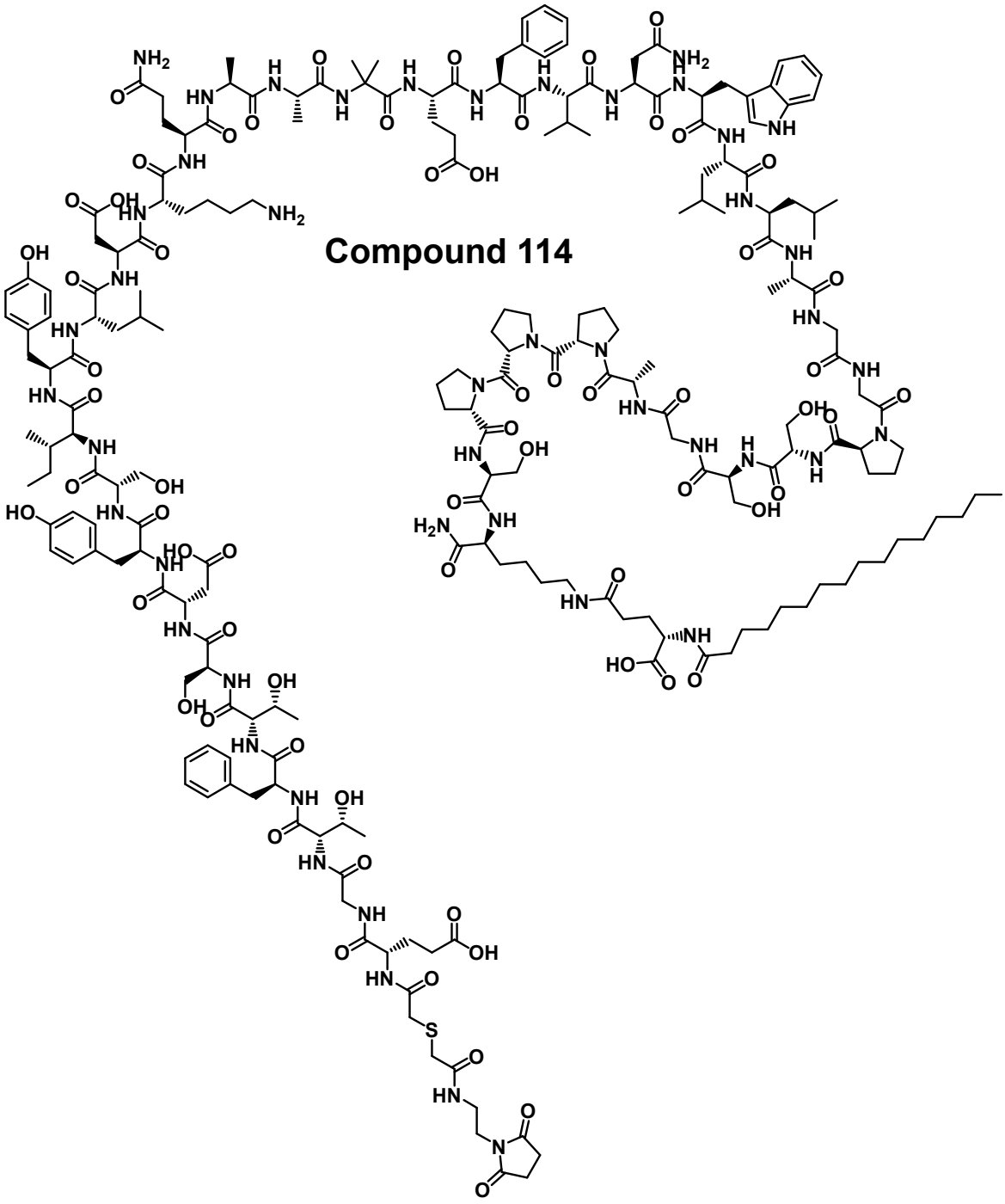

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109

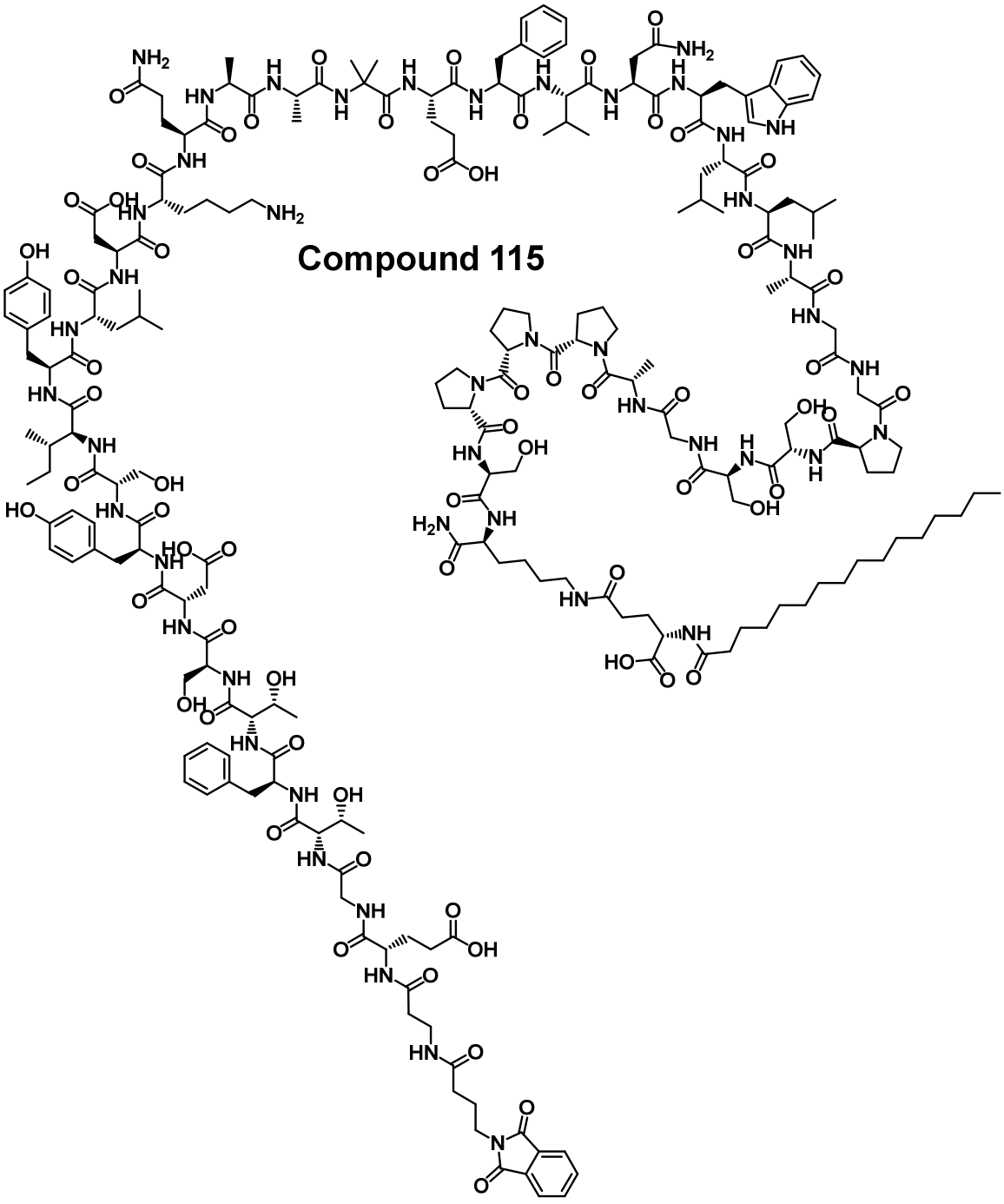

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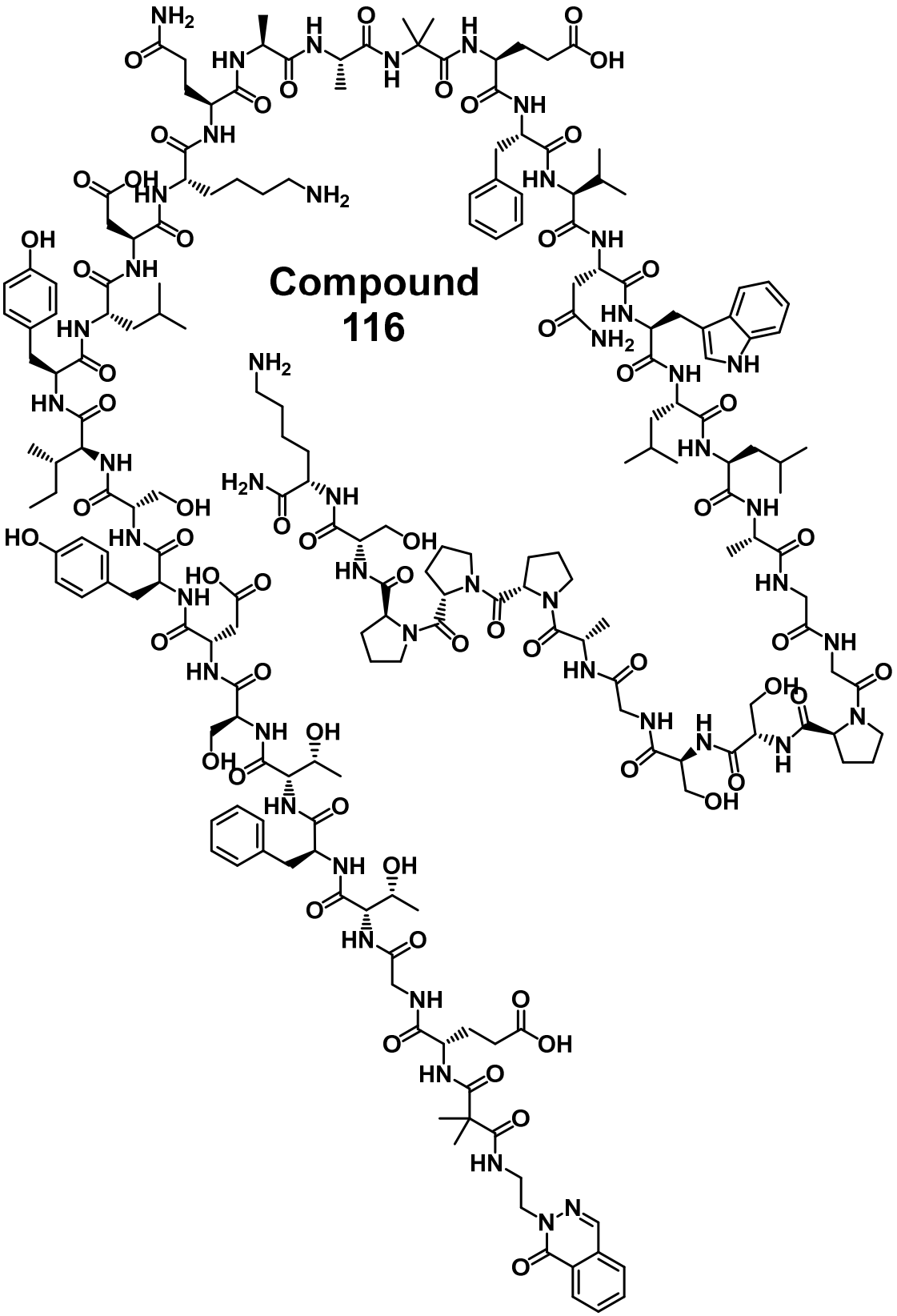

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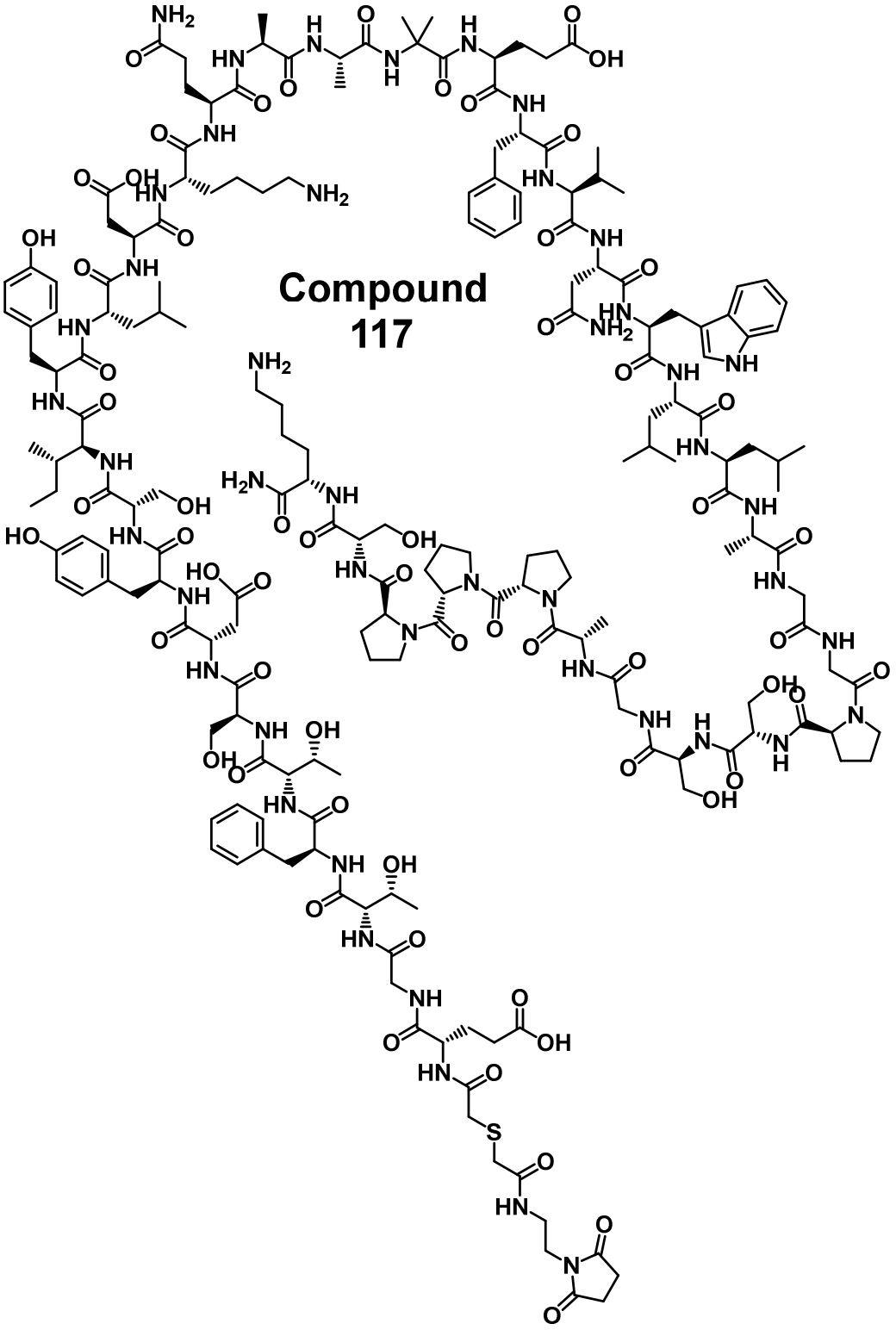

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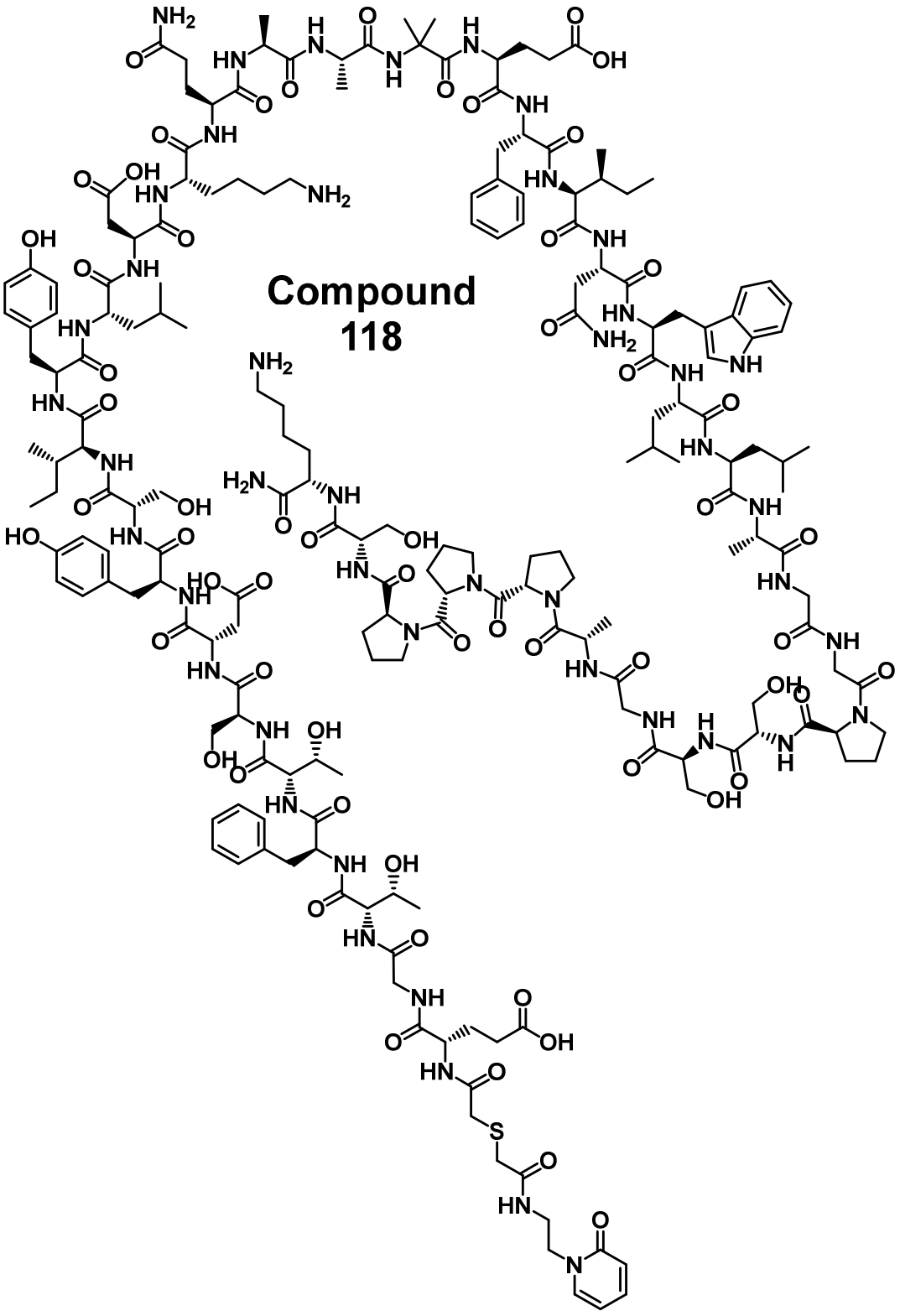

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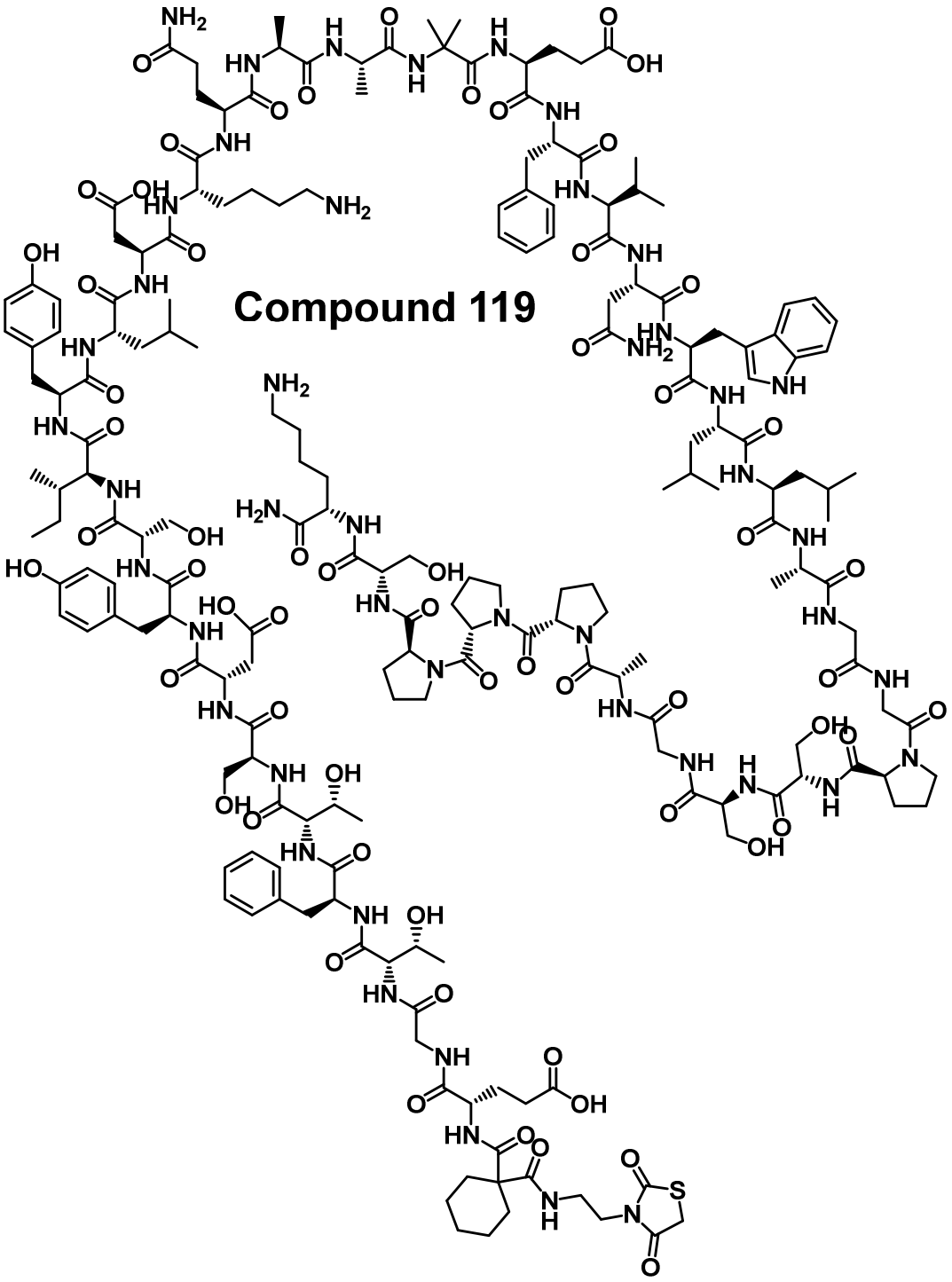

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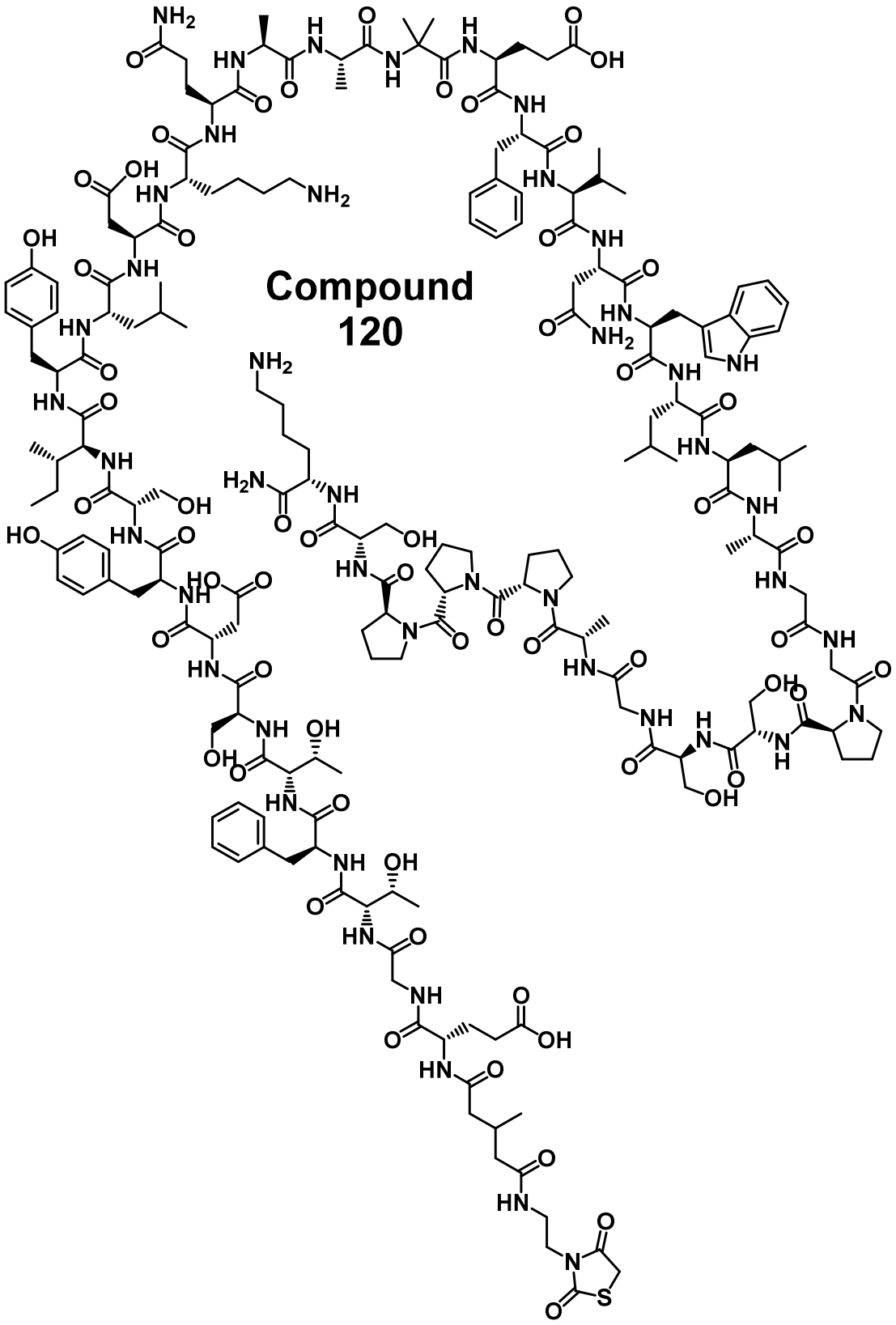

Compound 115

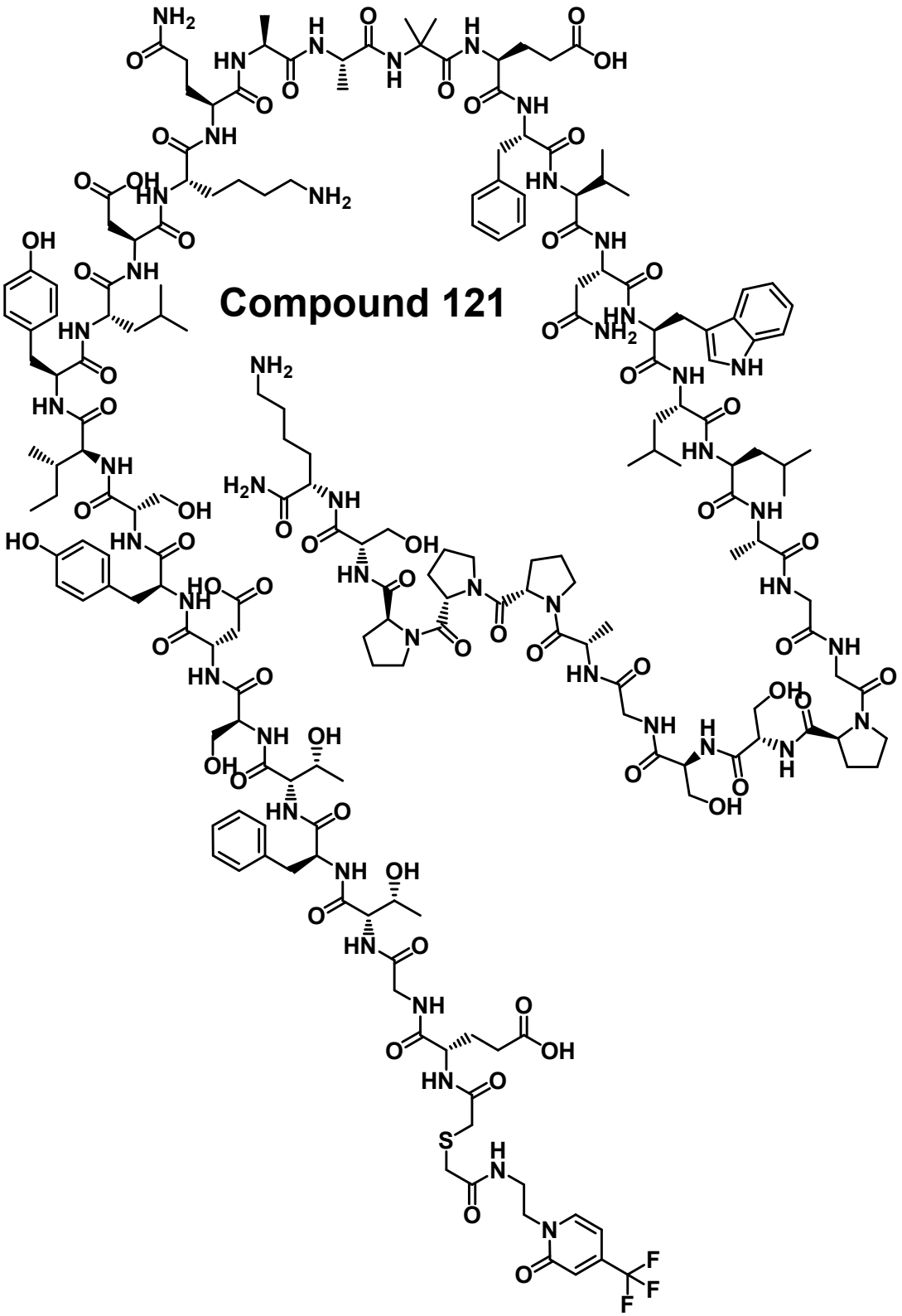

Compound
116

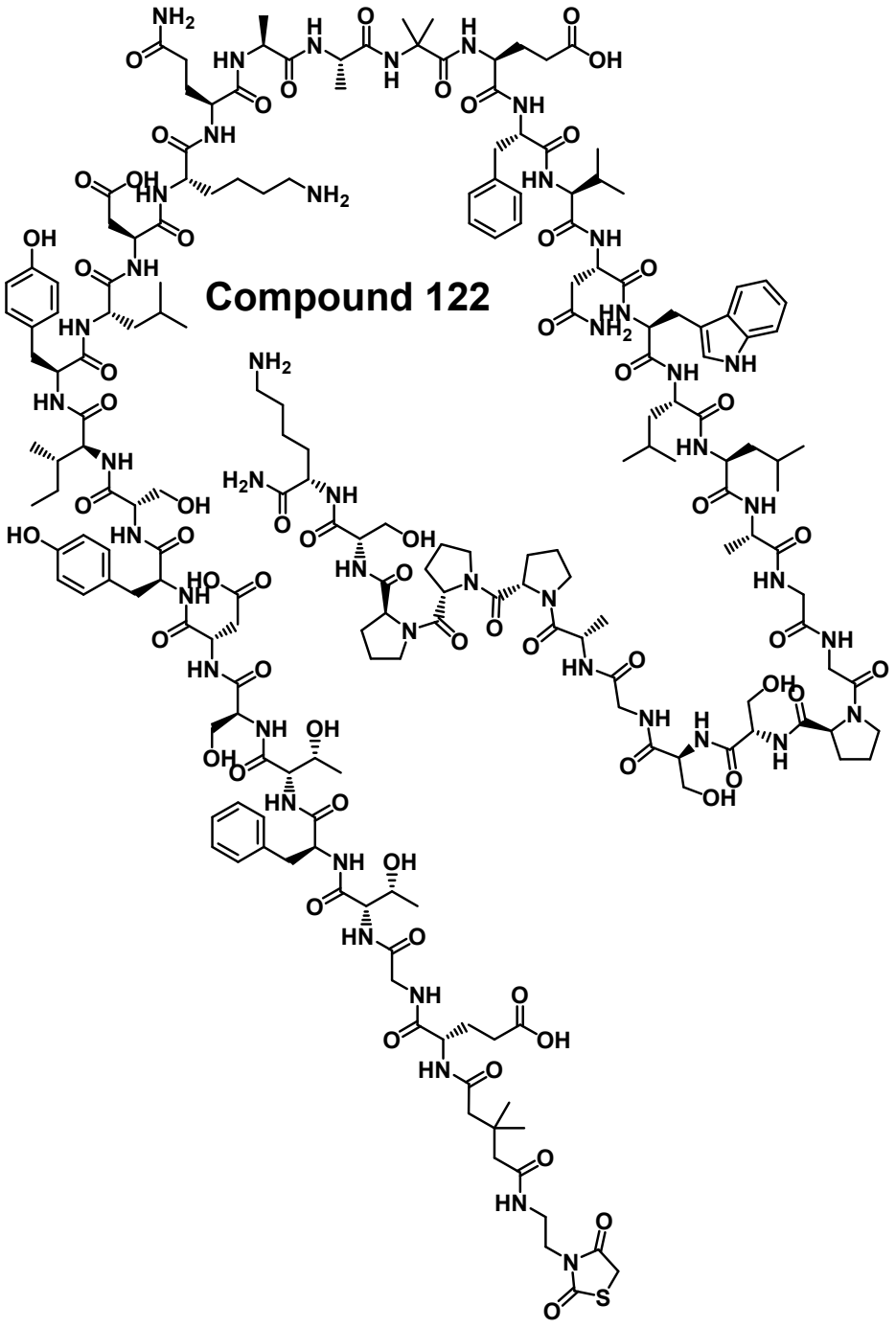

Compound
117

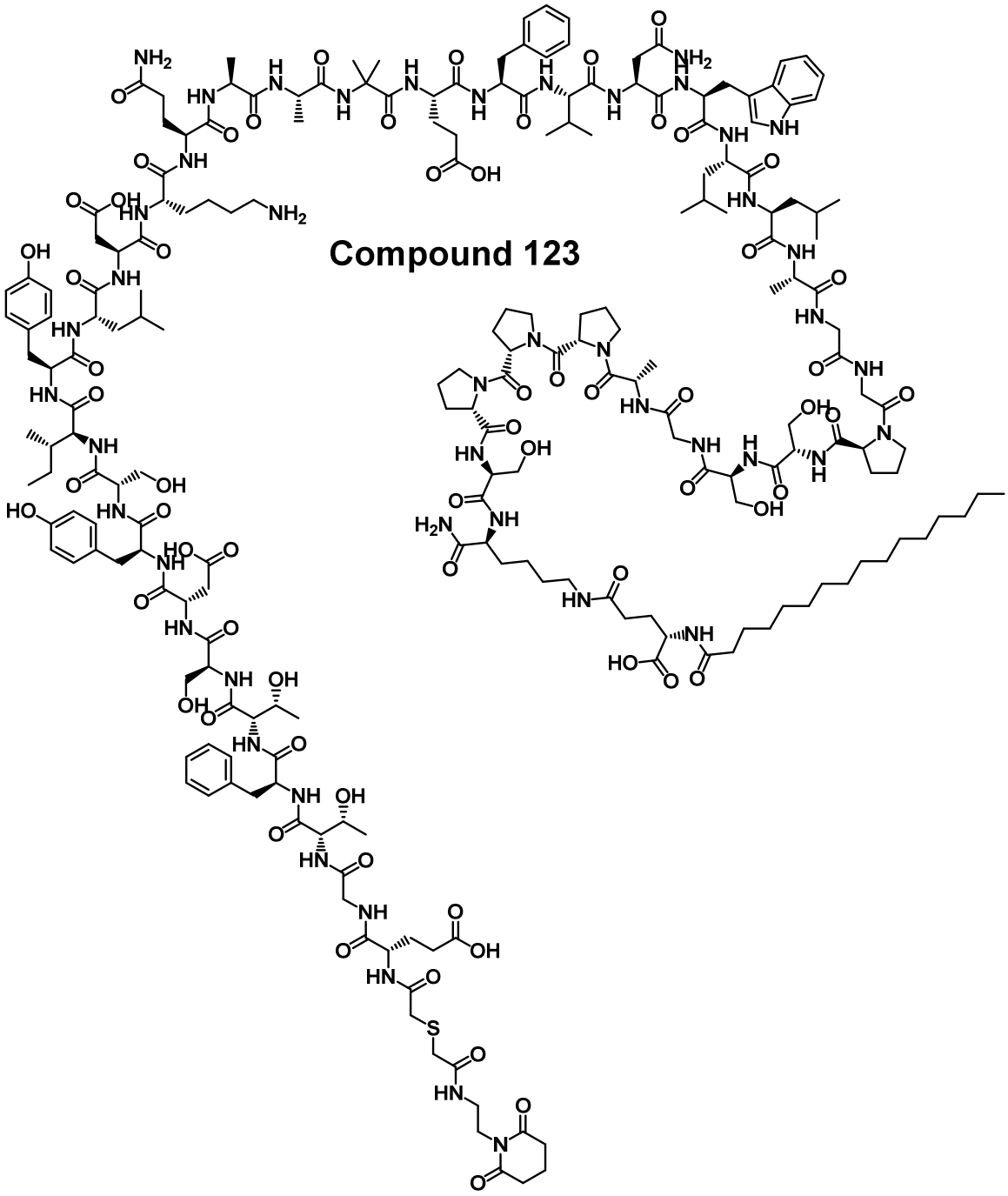

Compound
118

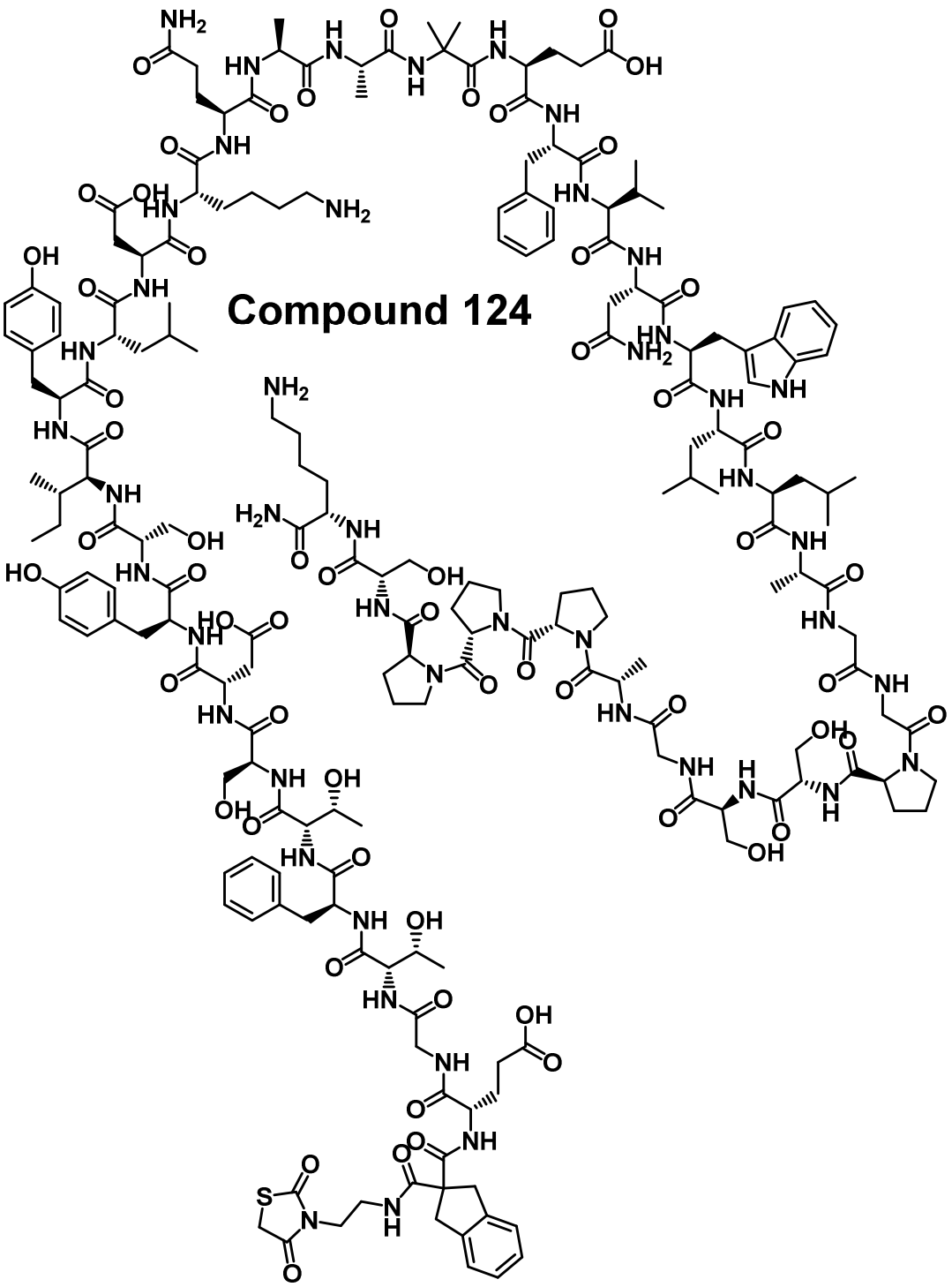

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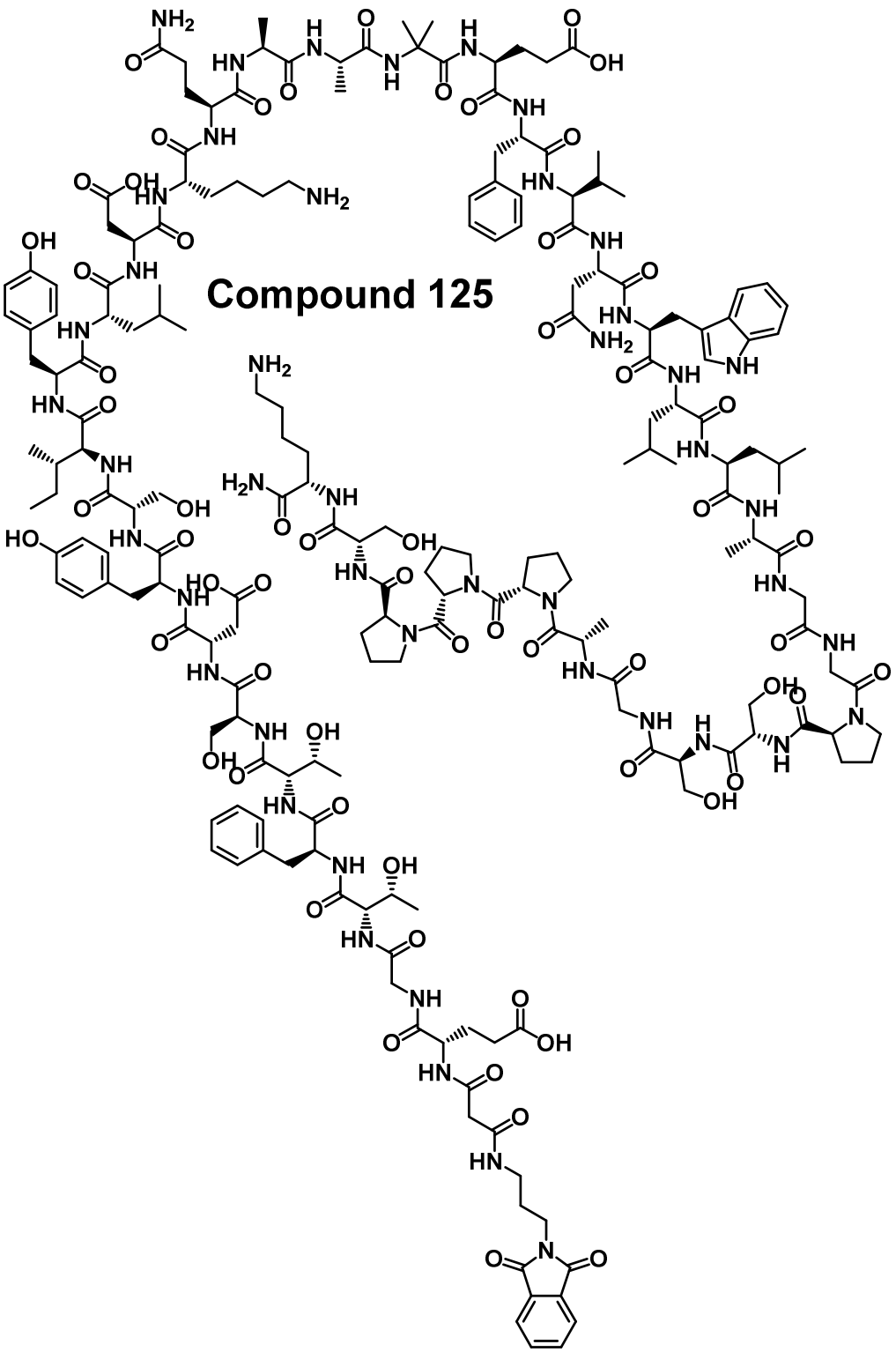

Compound
120

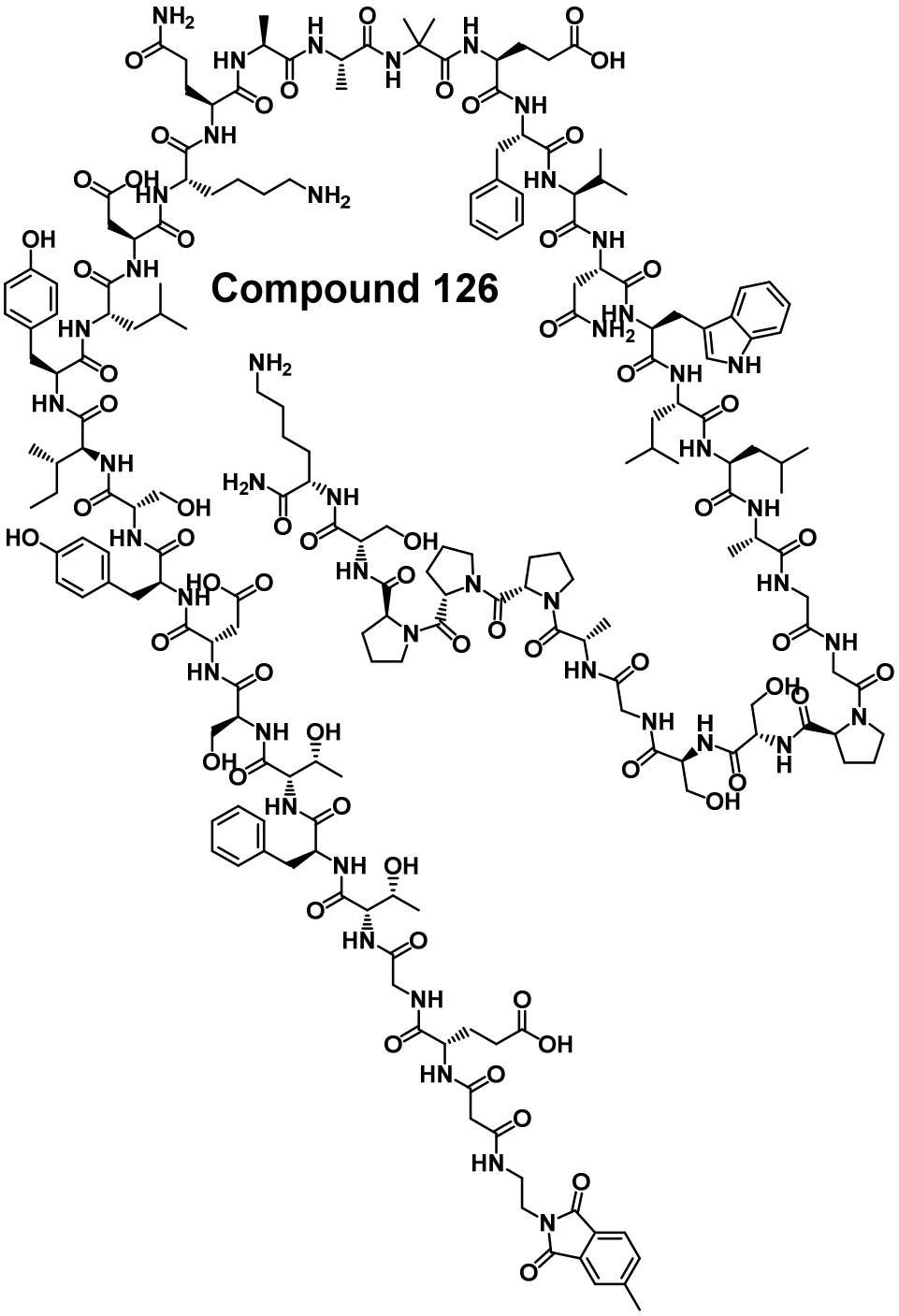

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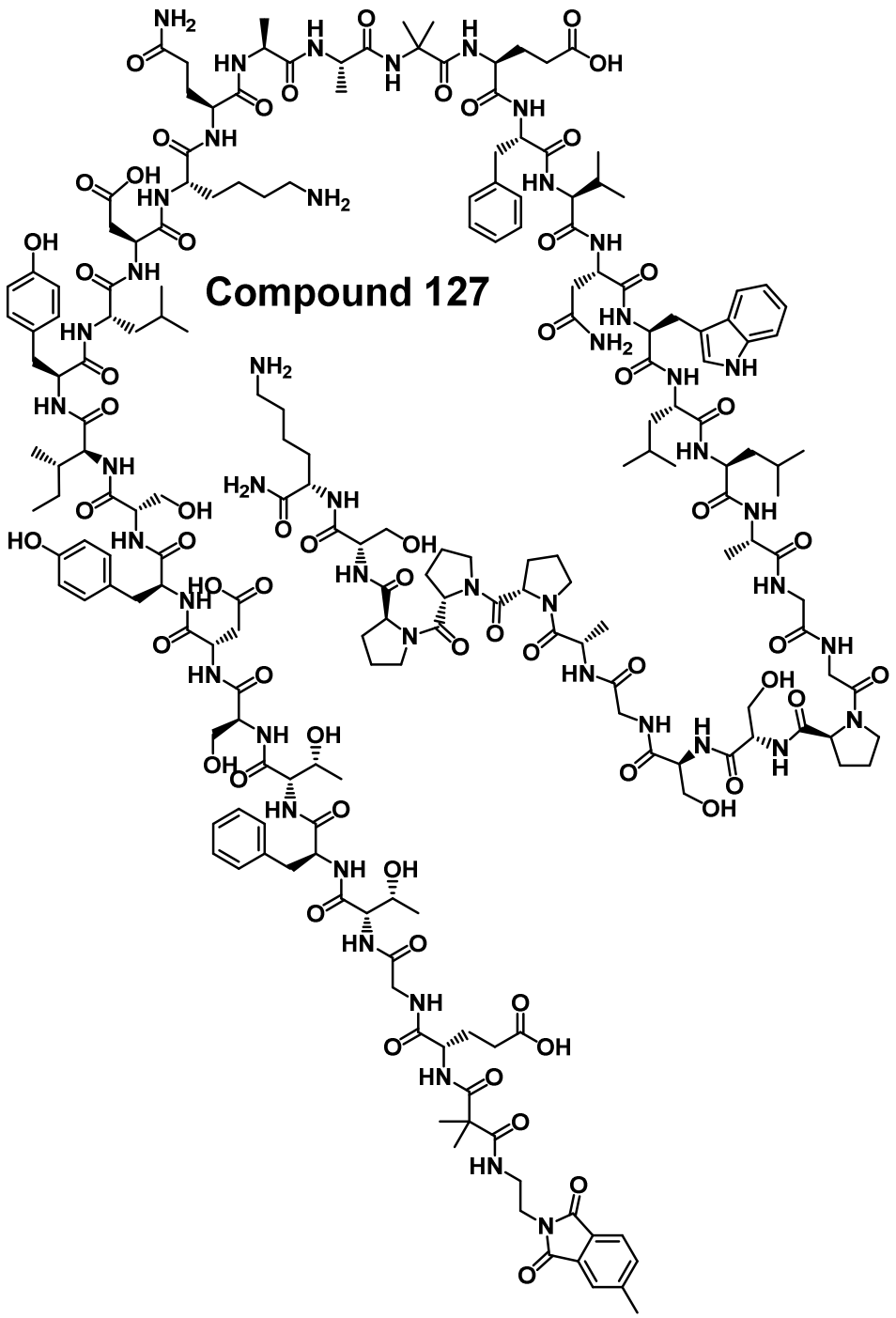

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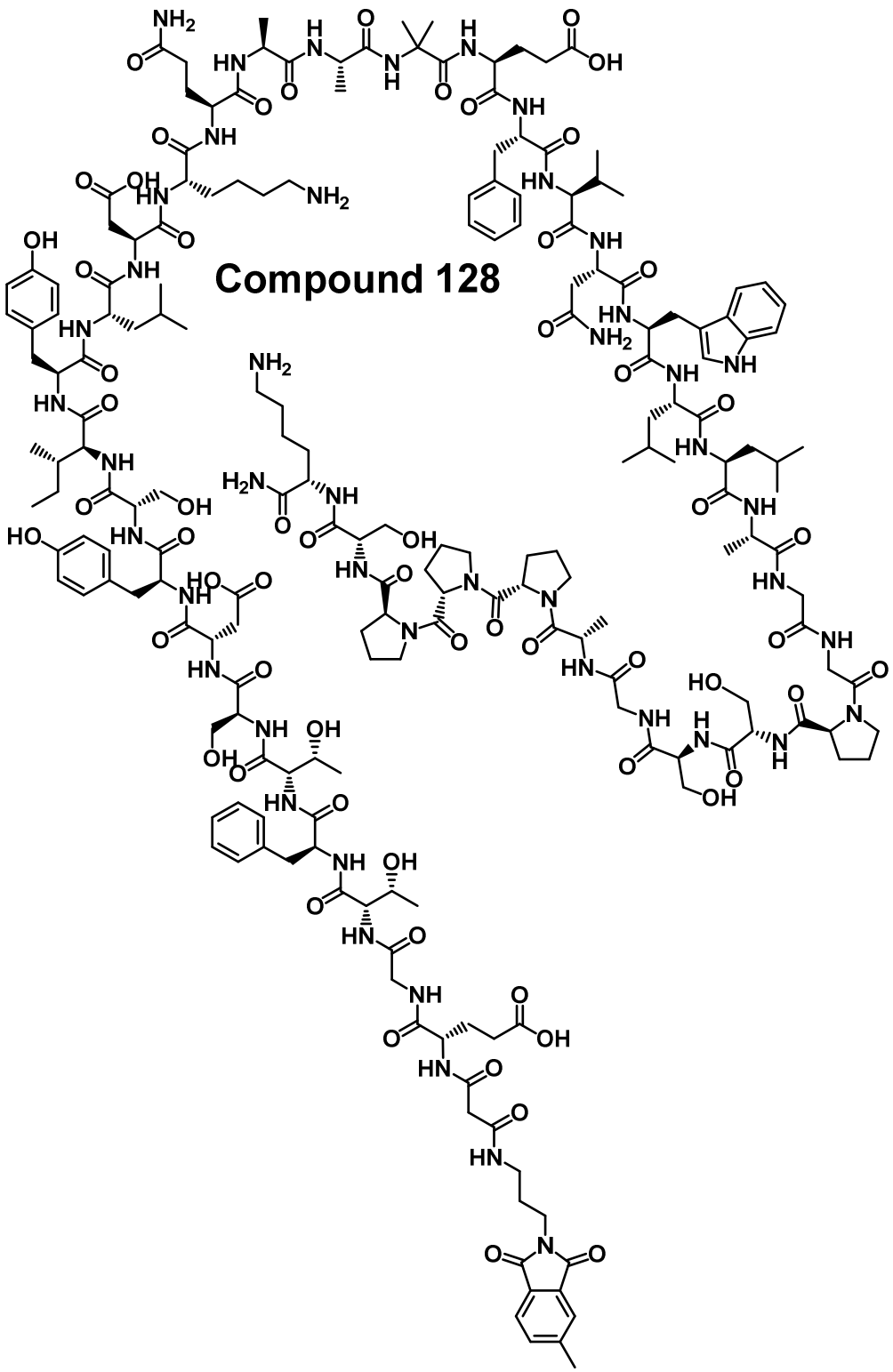

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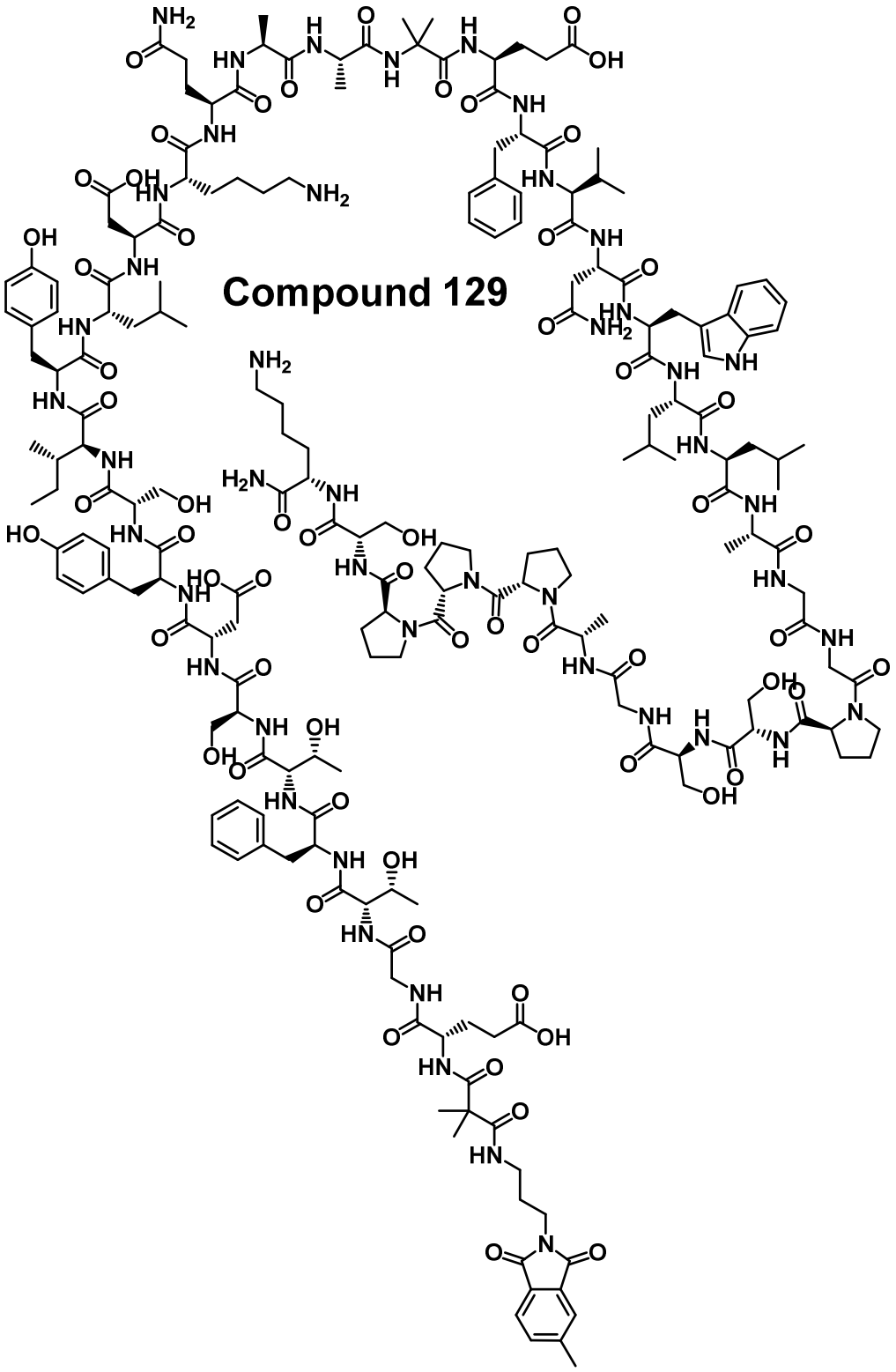

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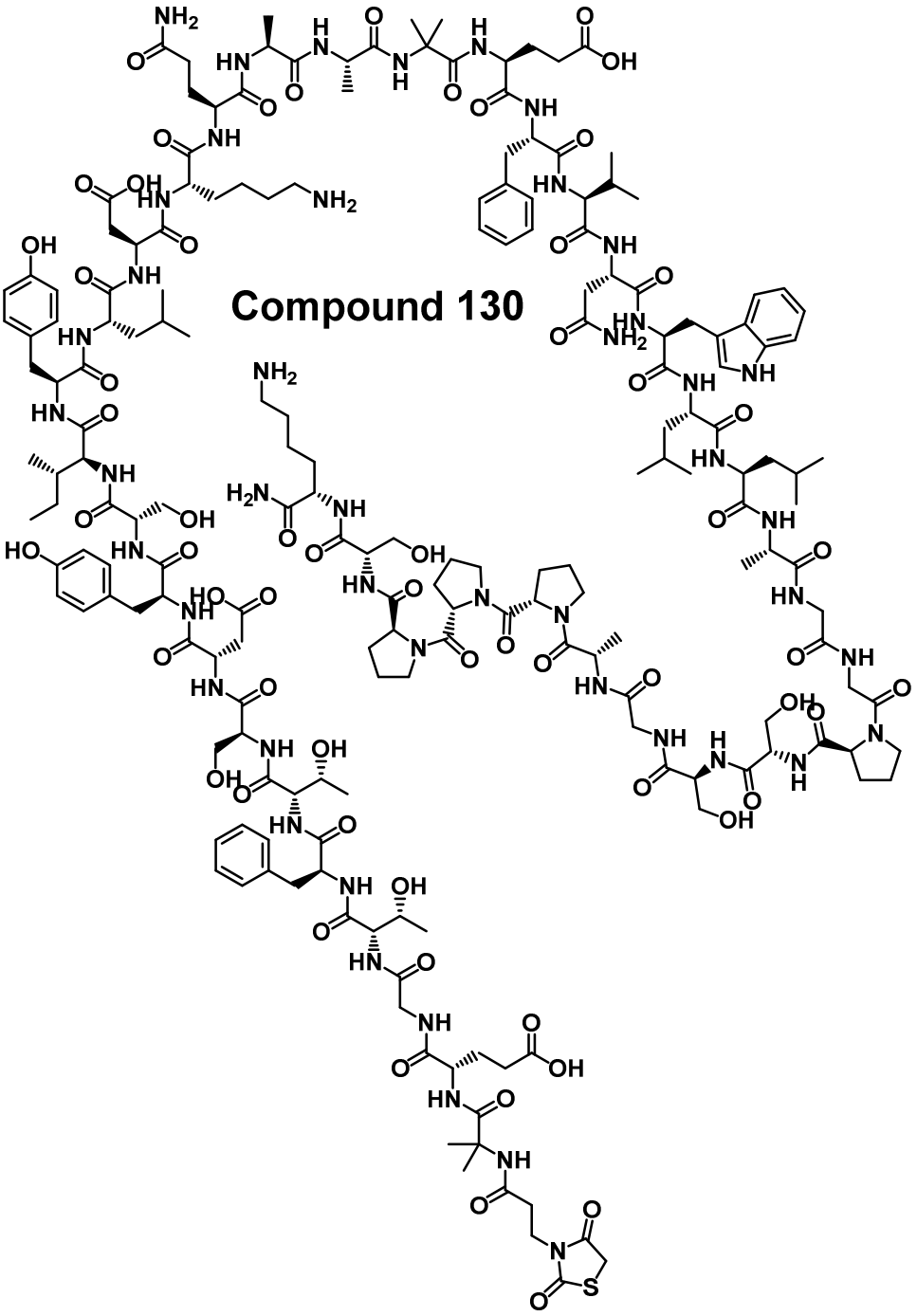

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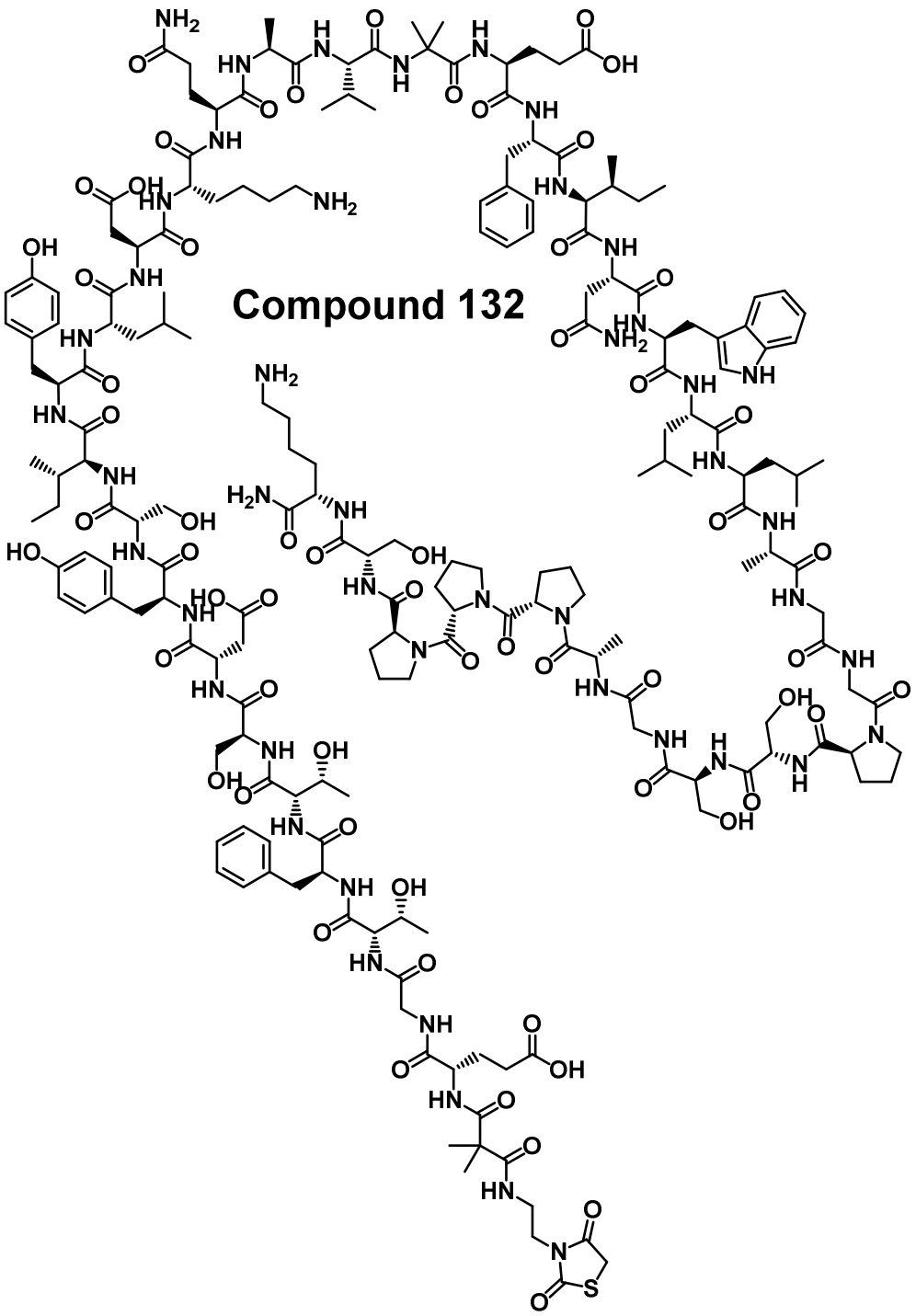

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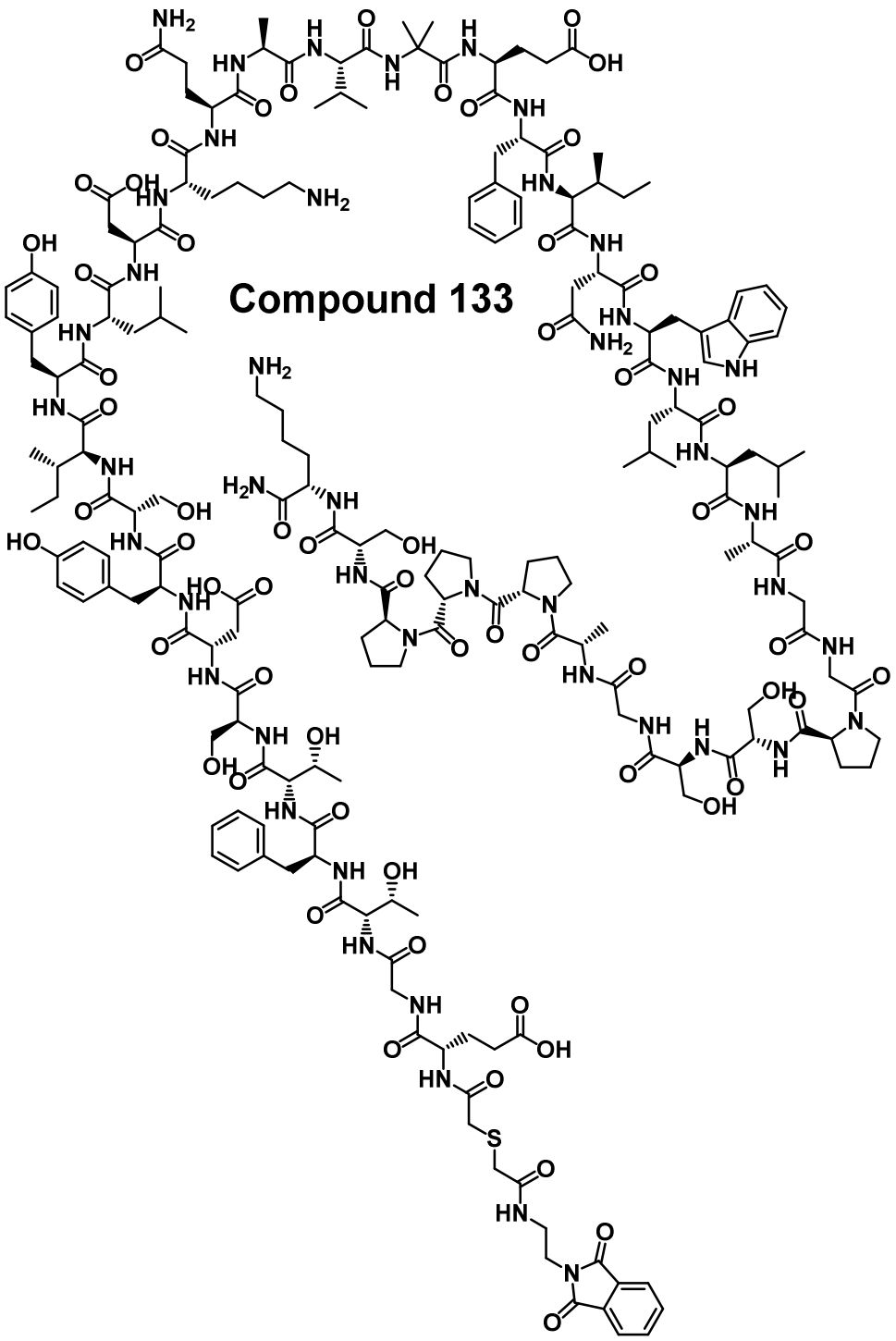

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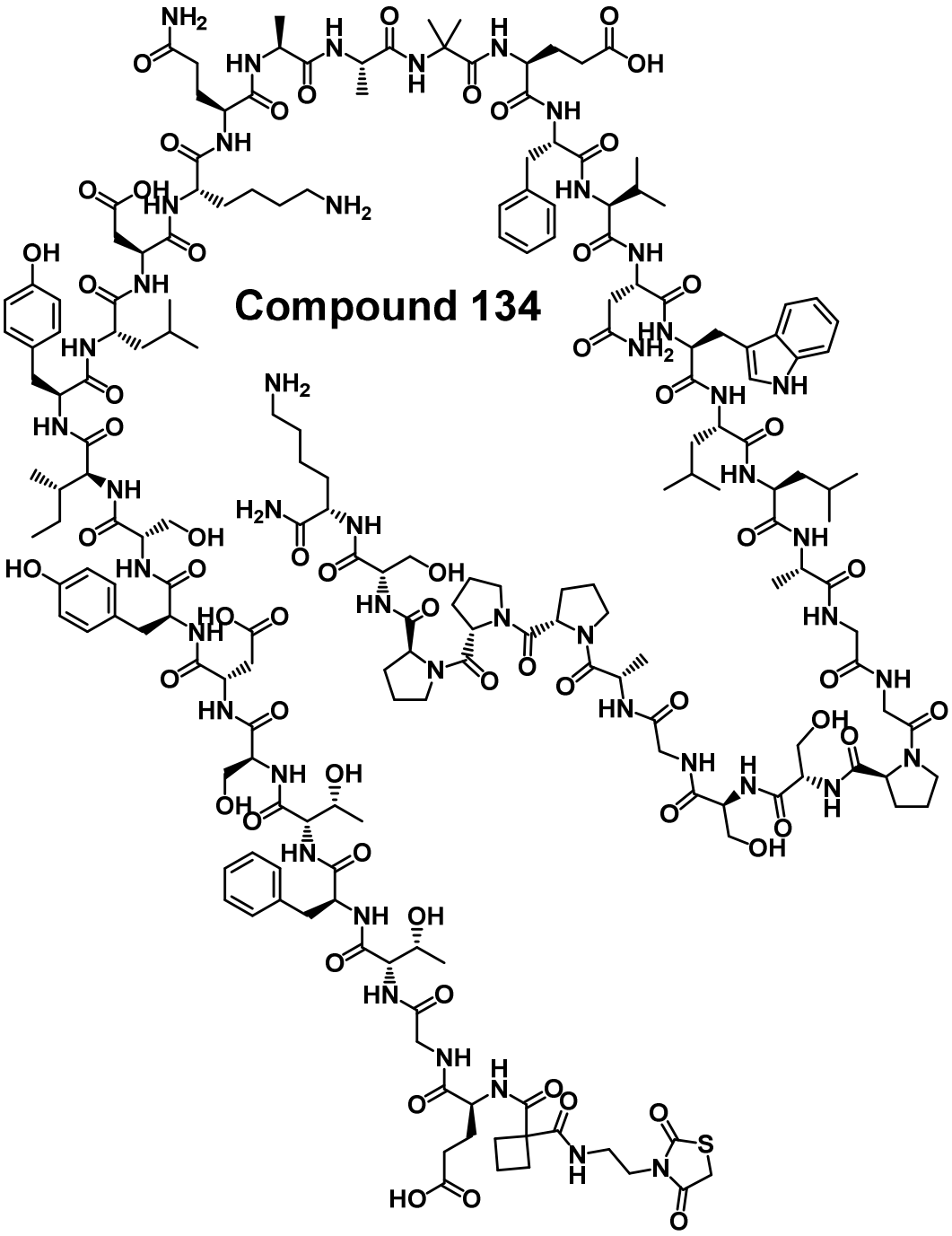

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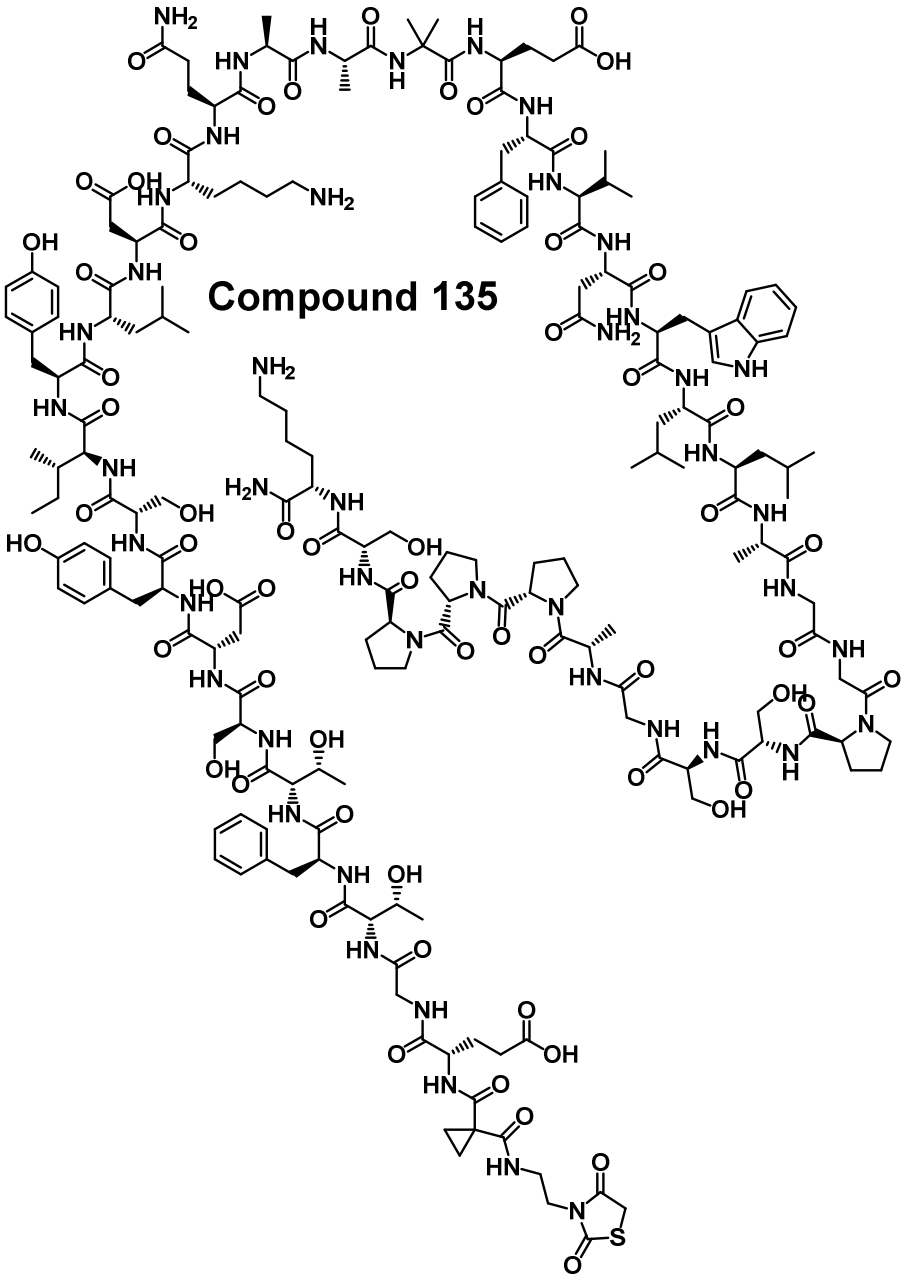

Compound 129

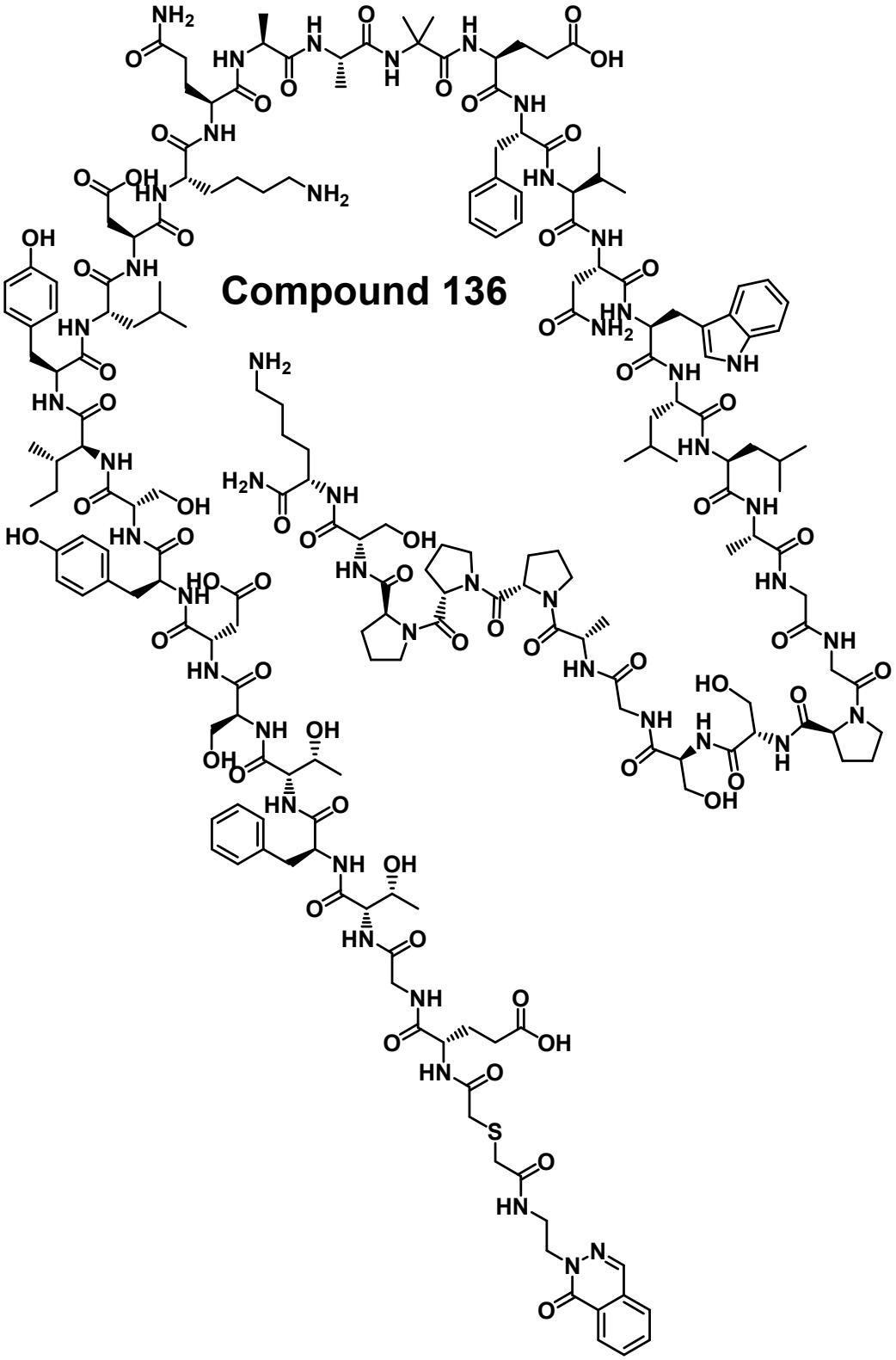

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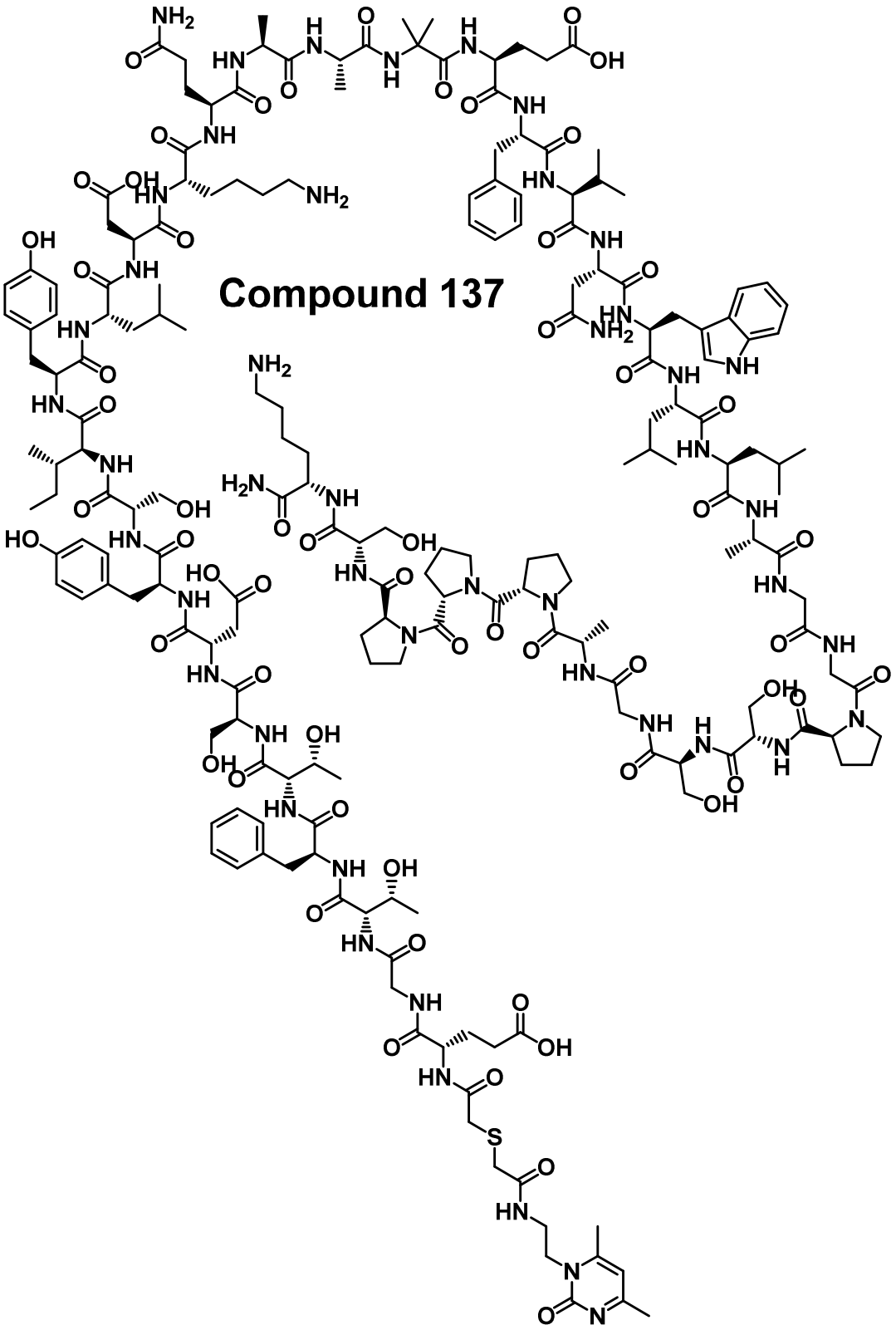

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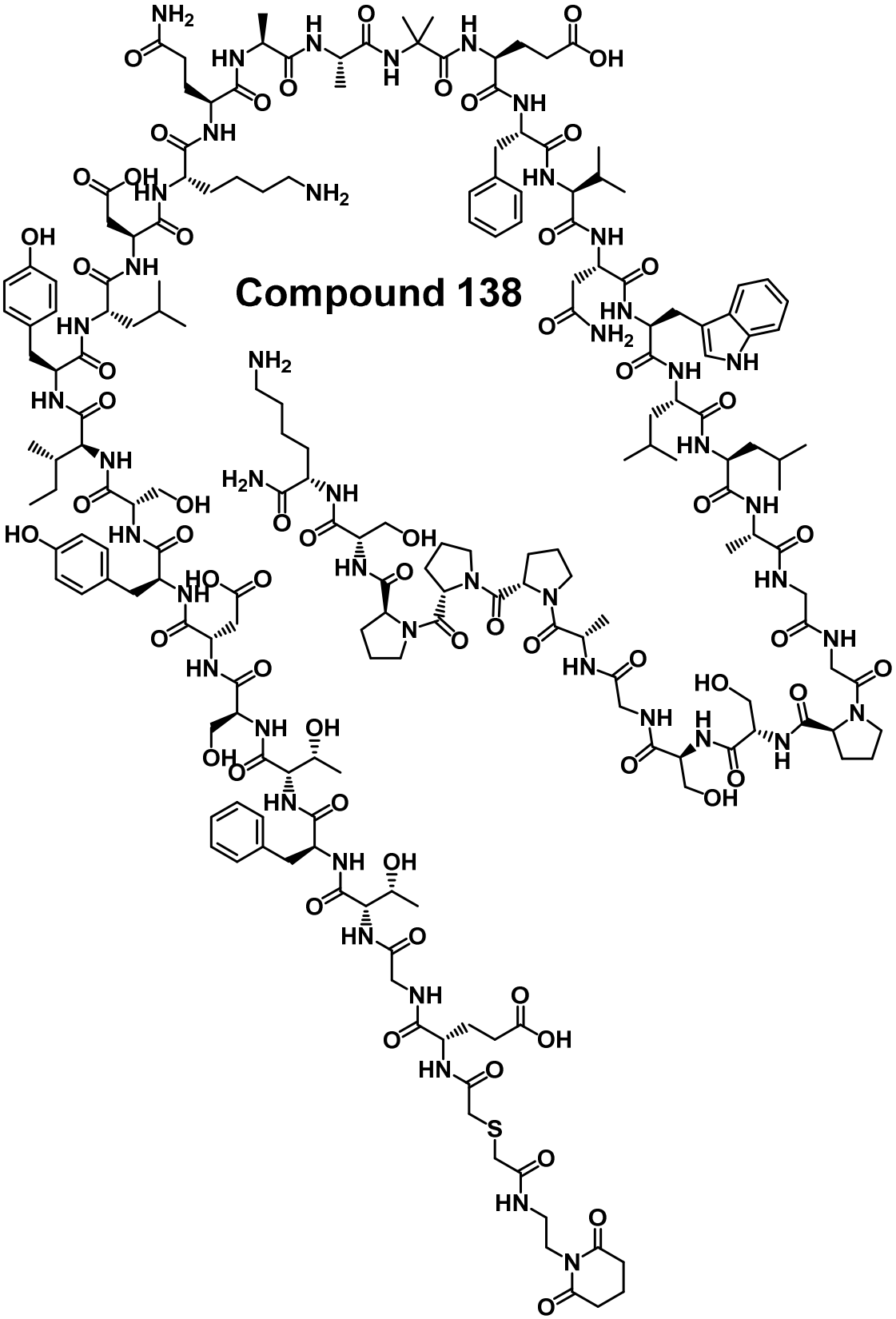

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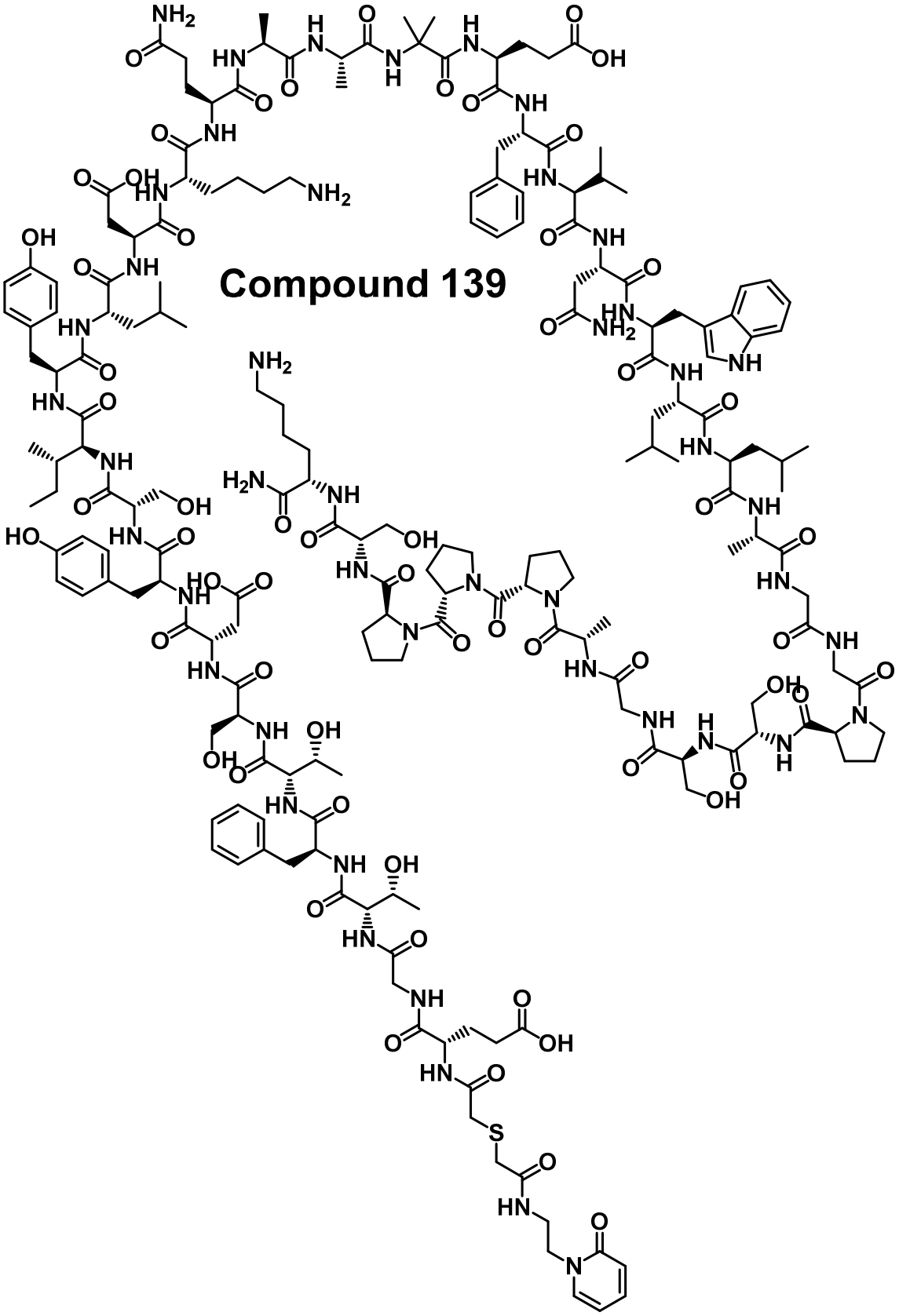

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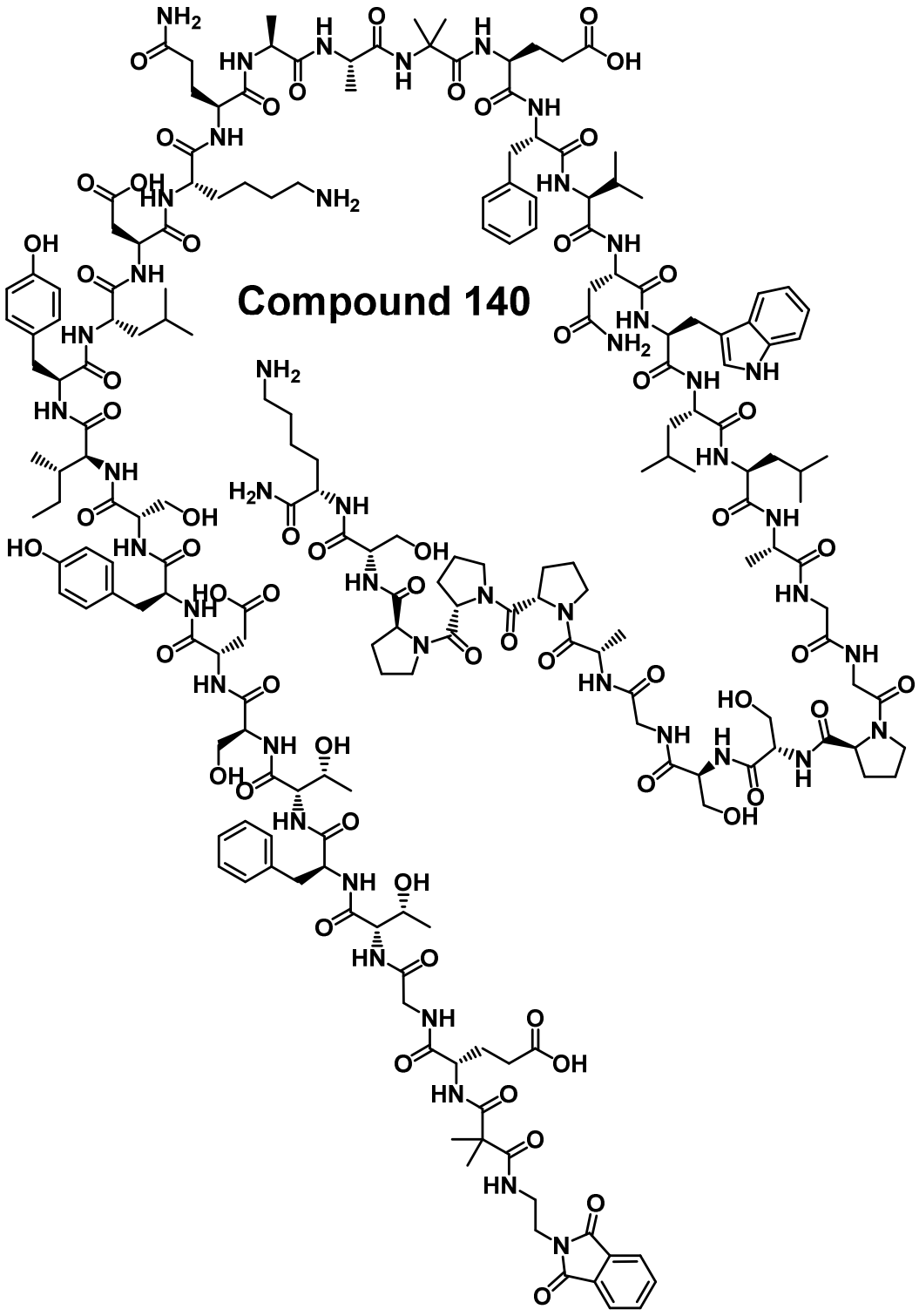

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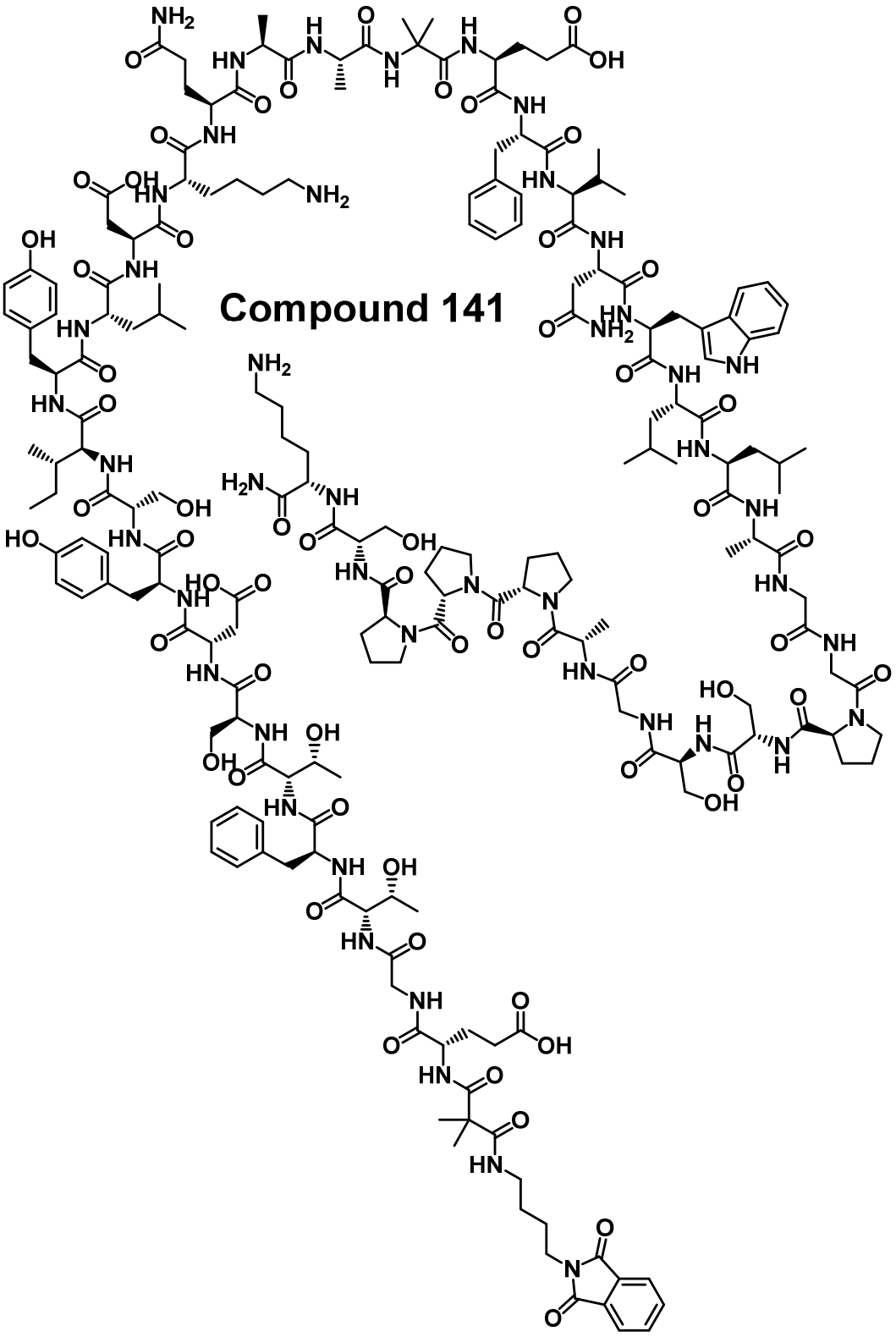

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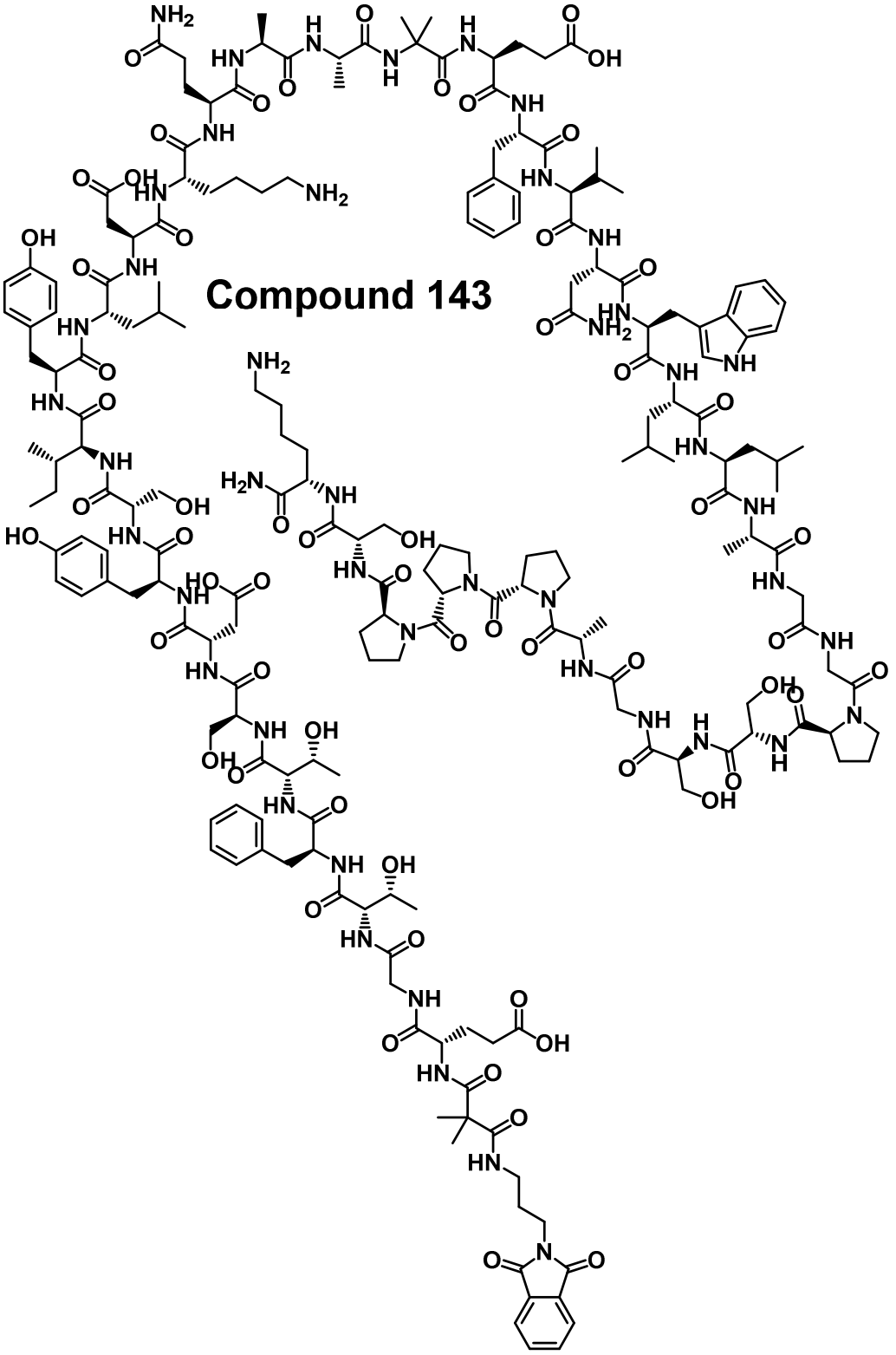

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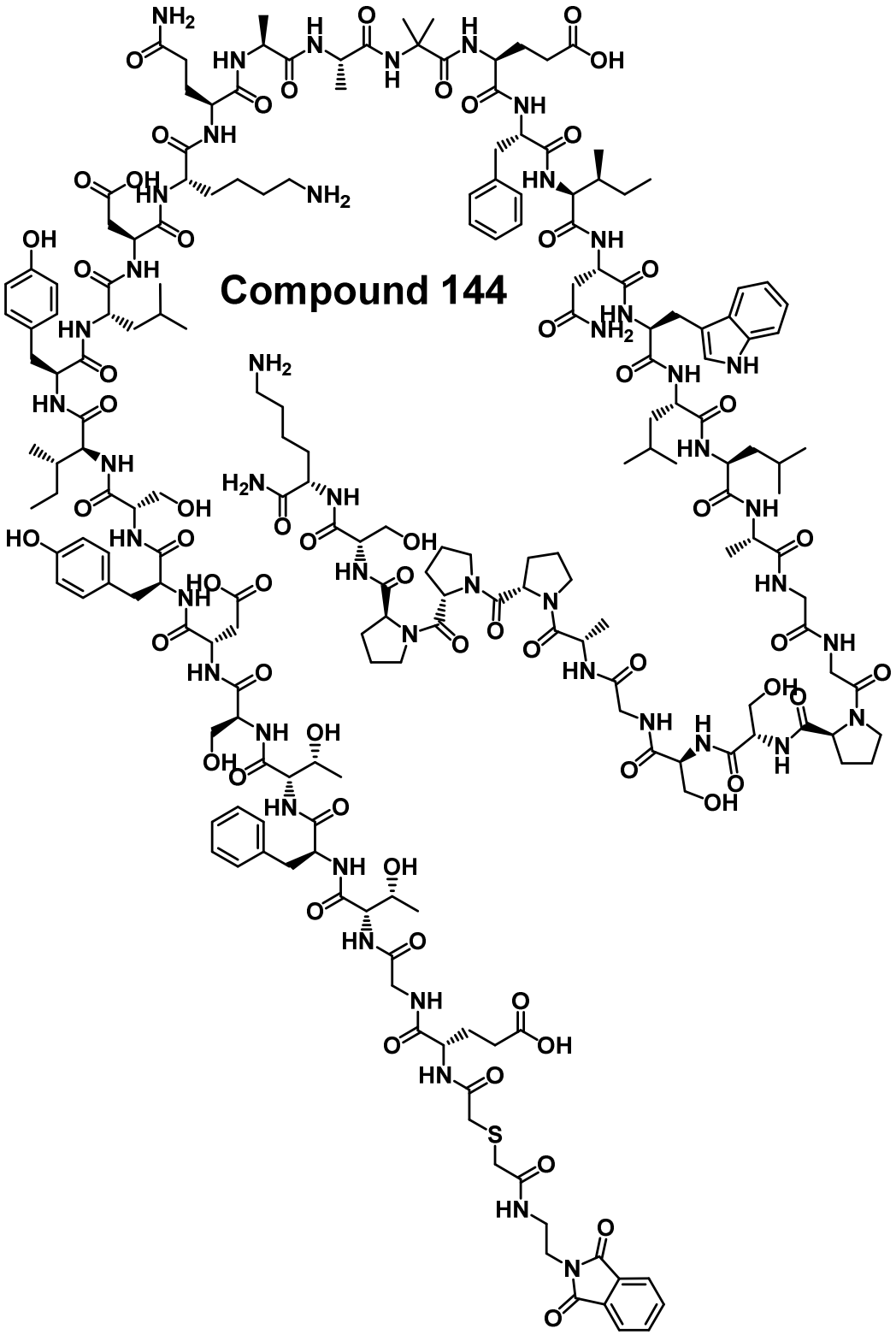

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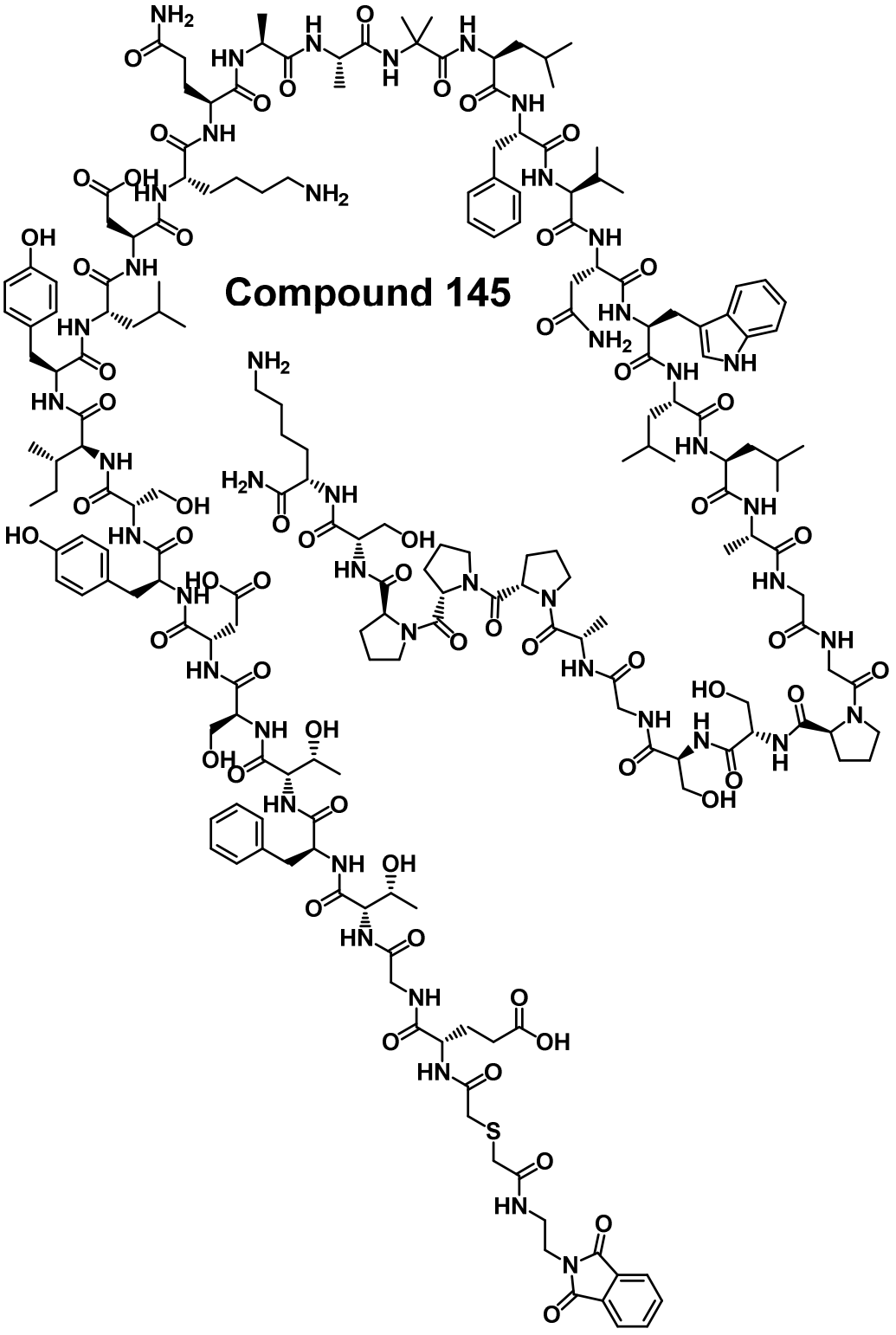

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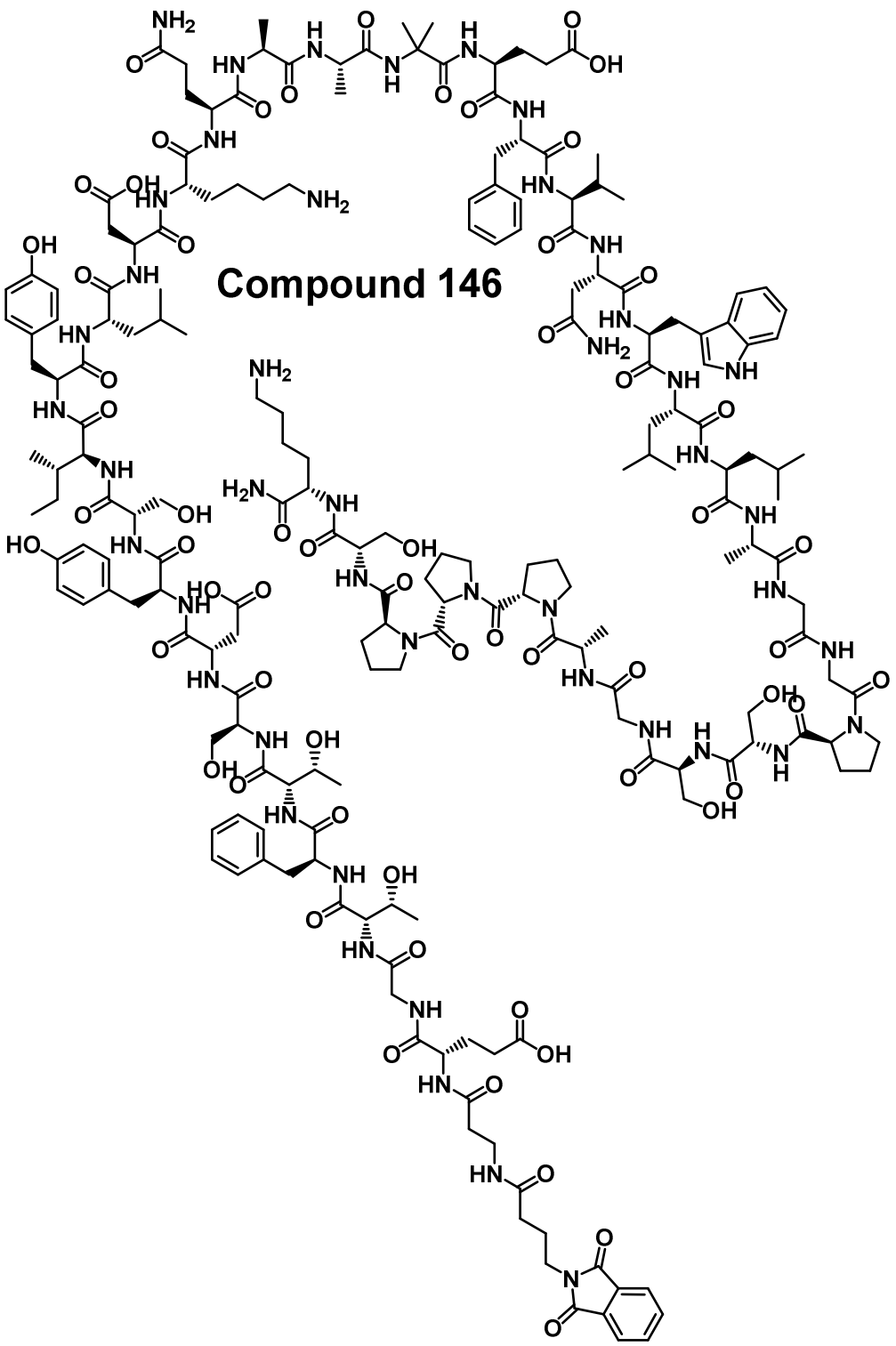

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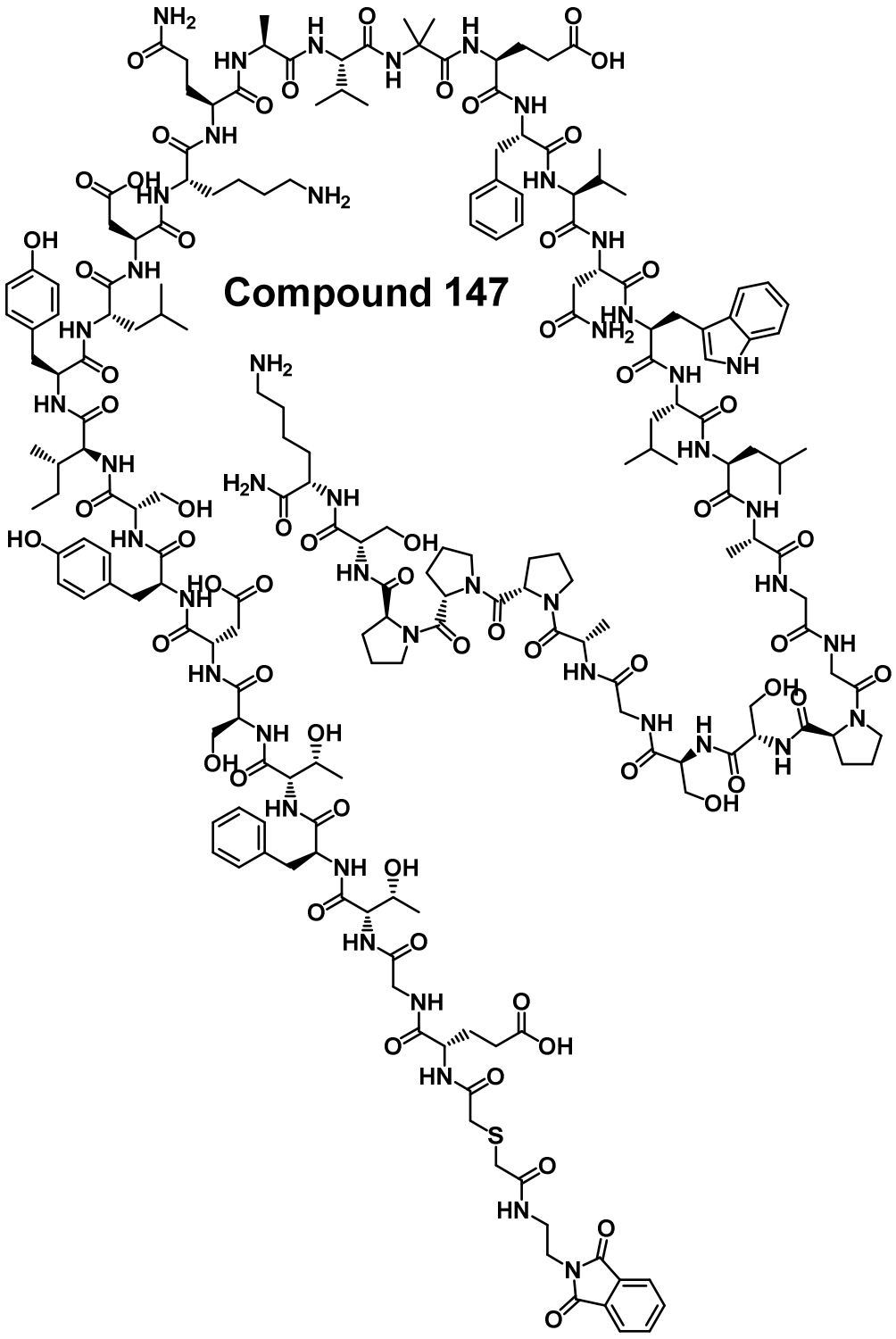

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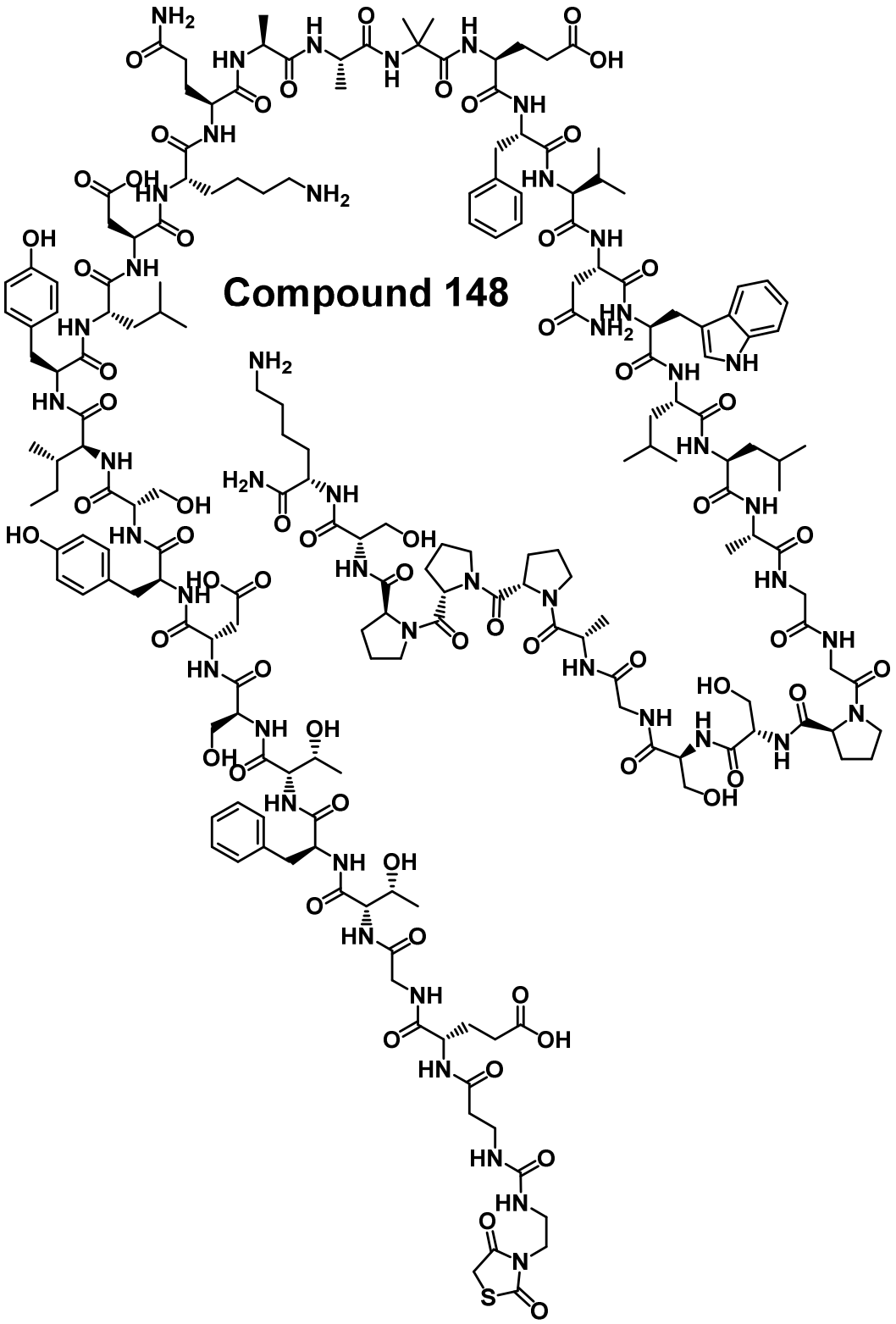

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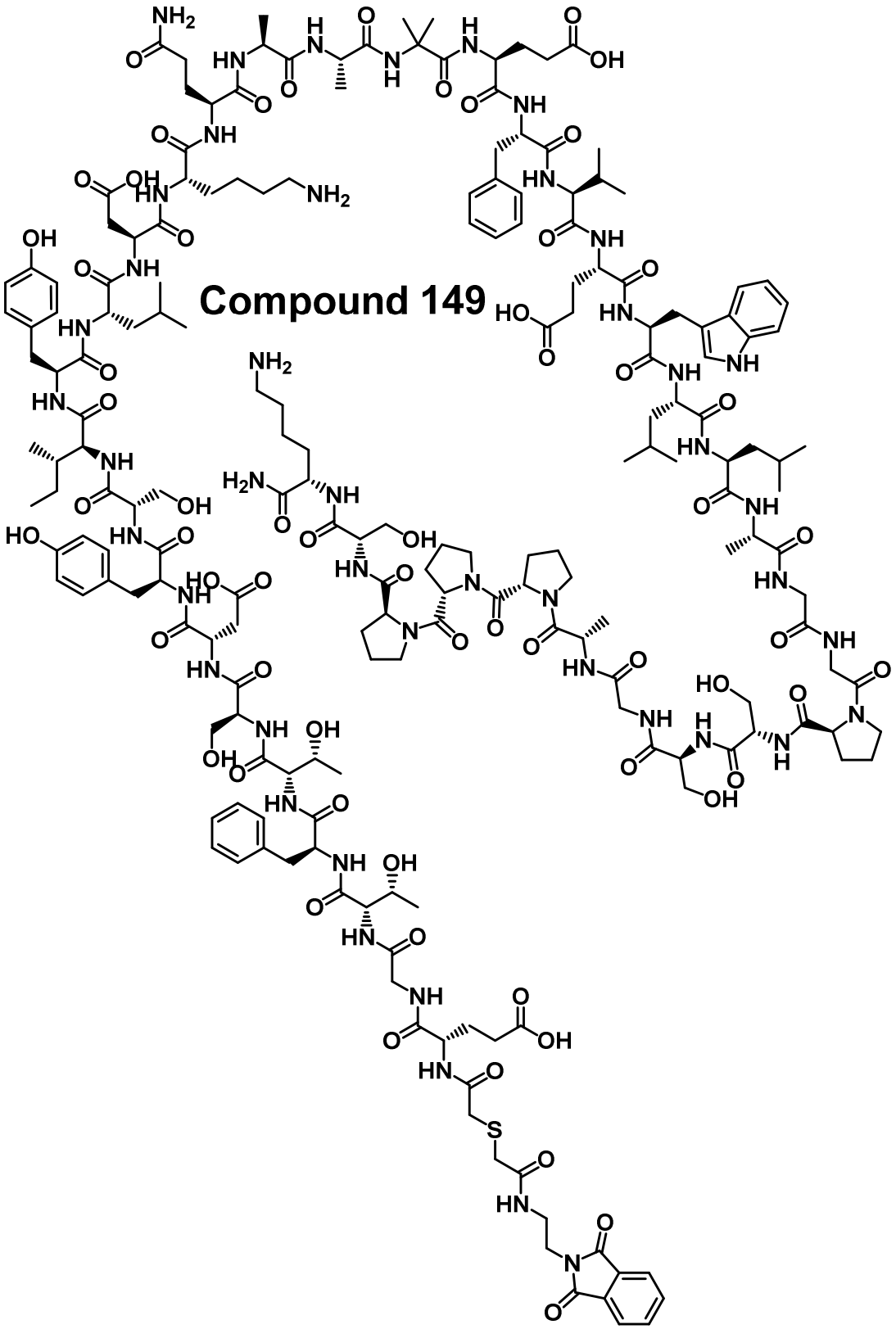

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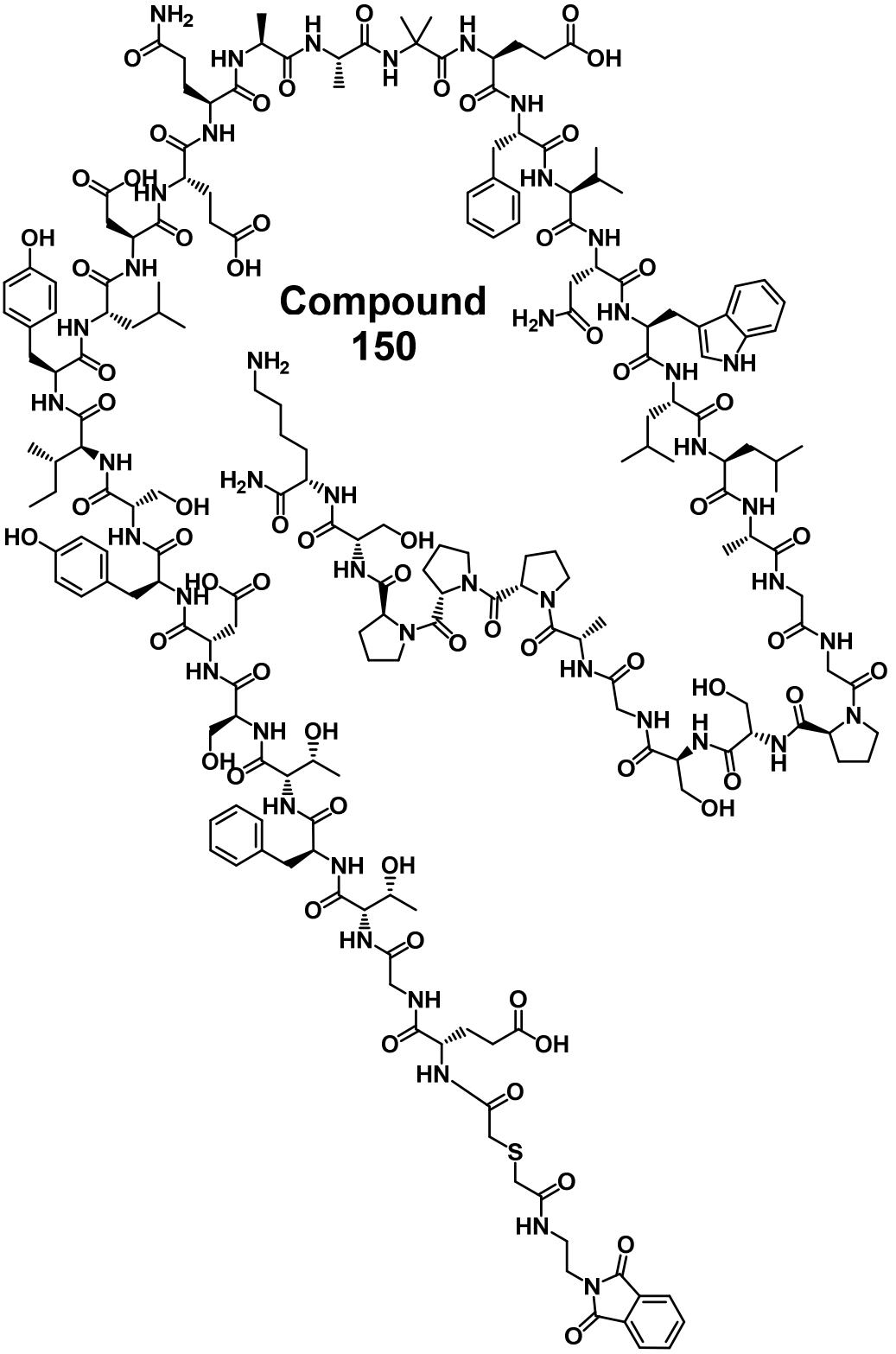

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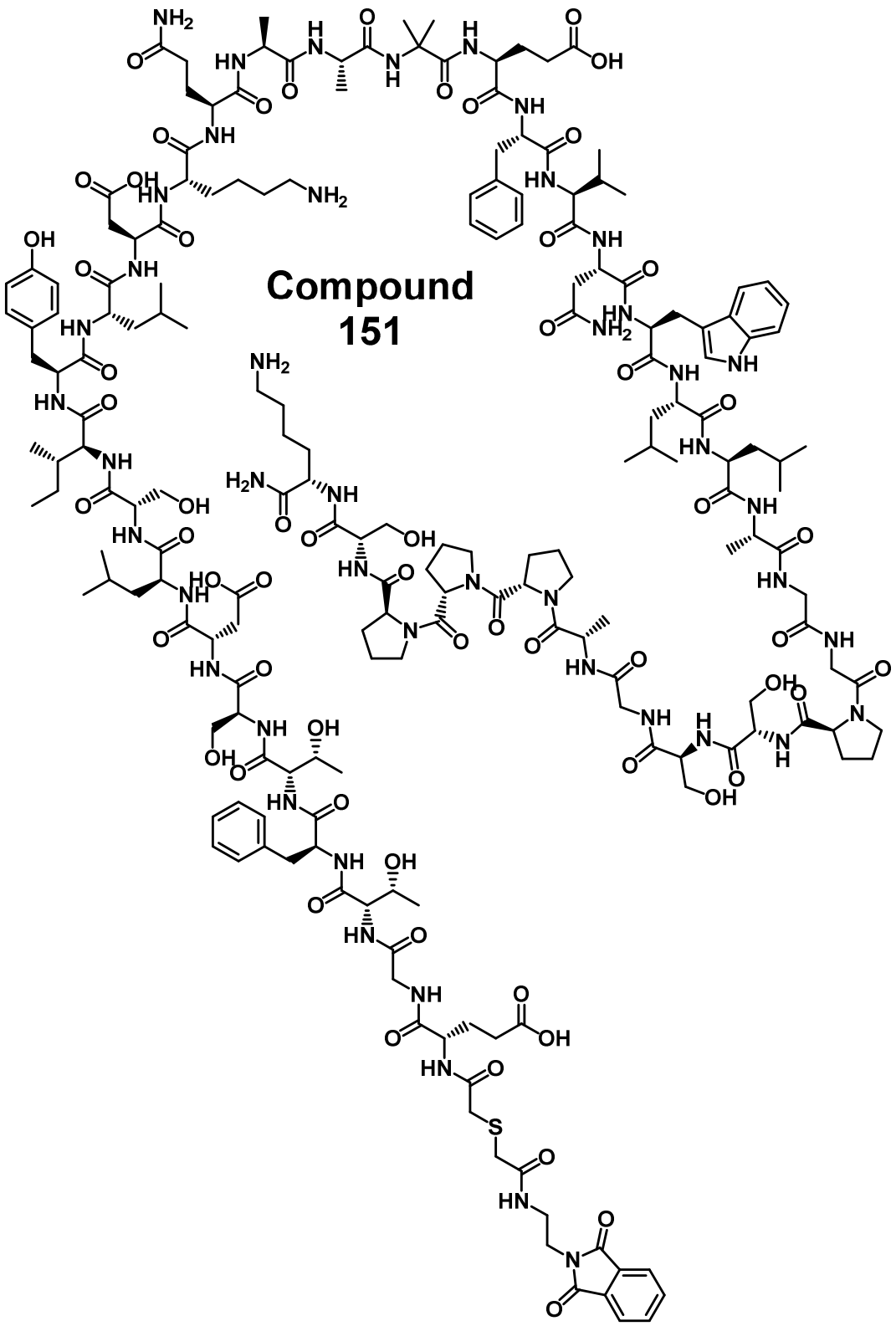

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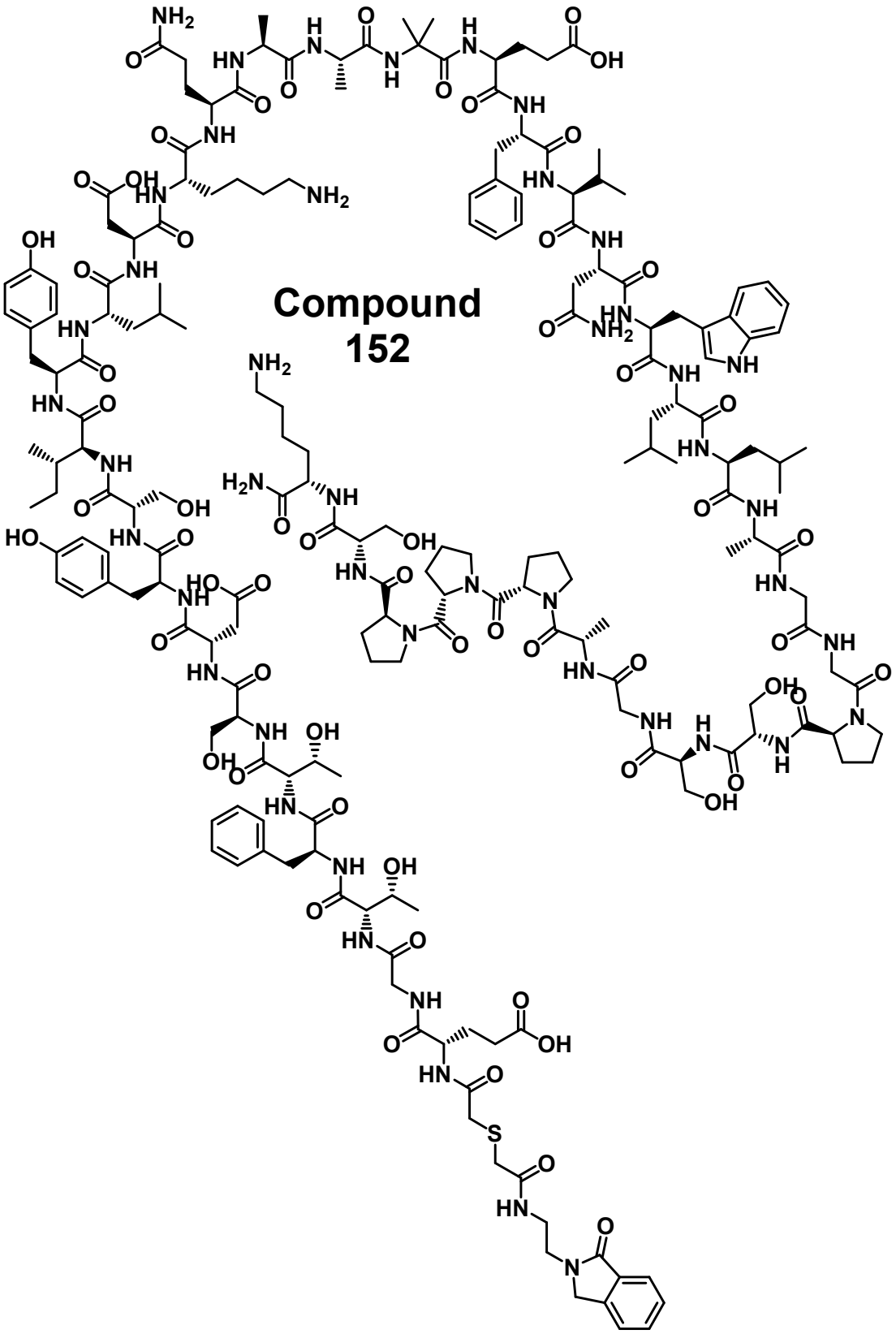

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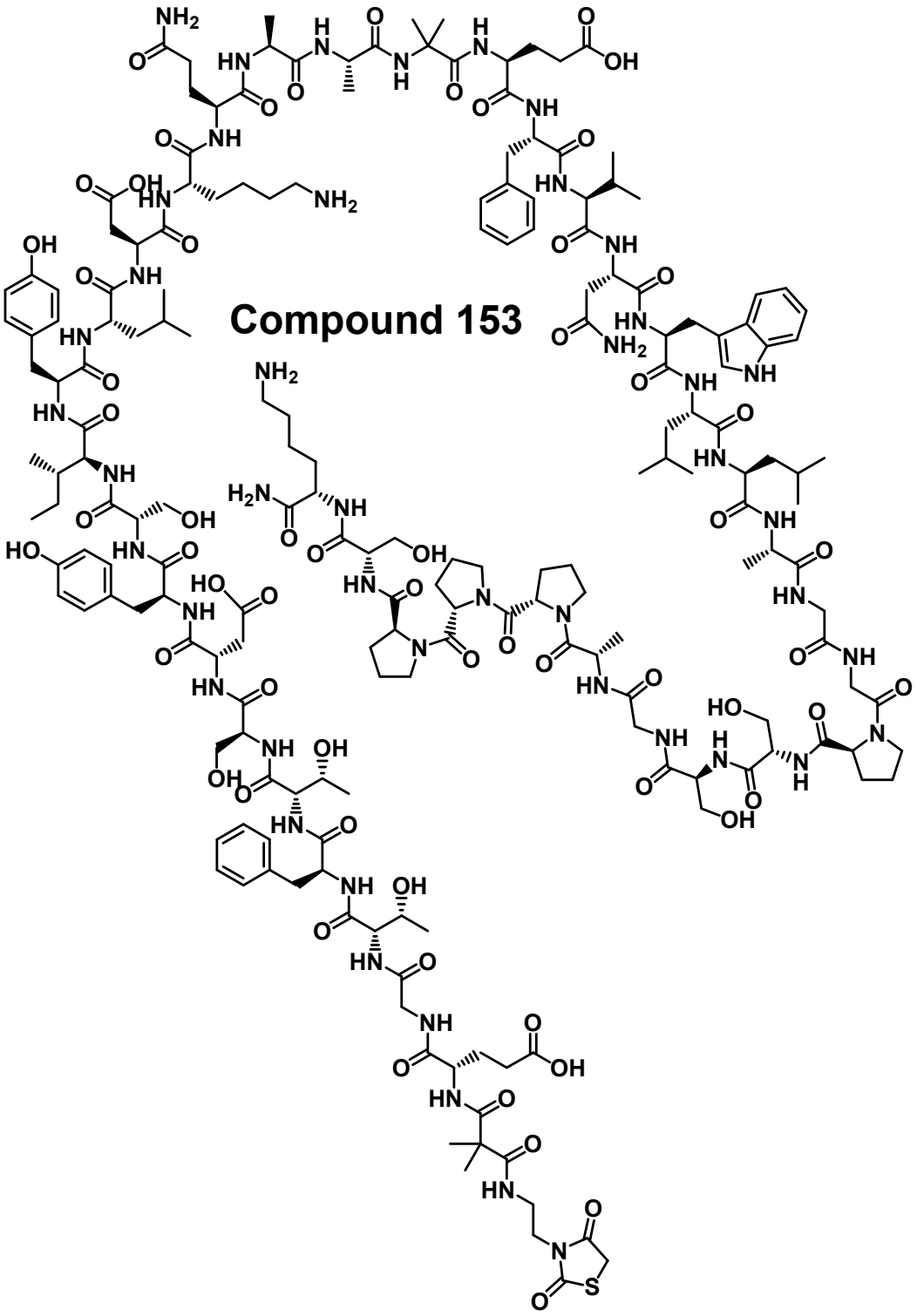

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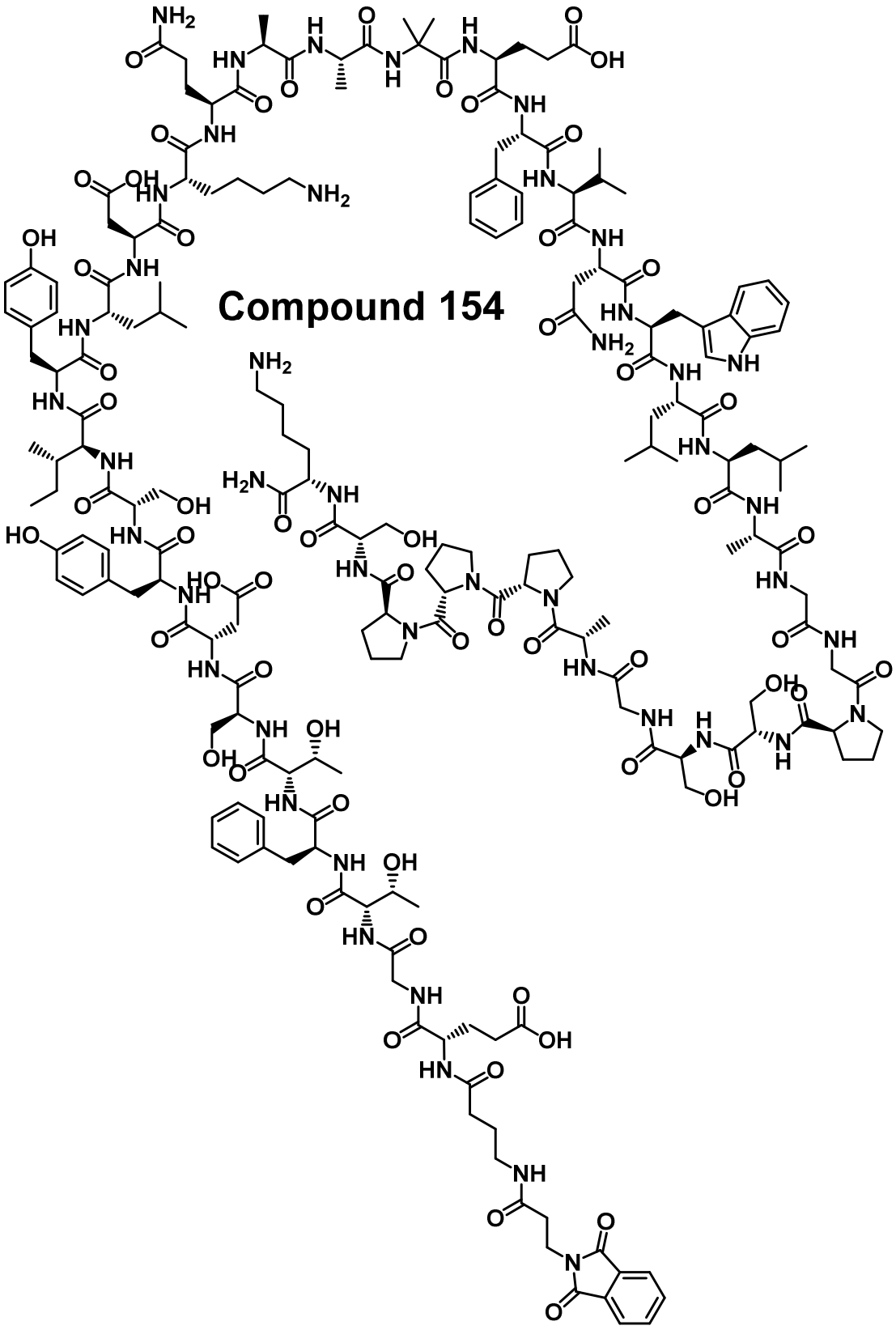

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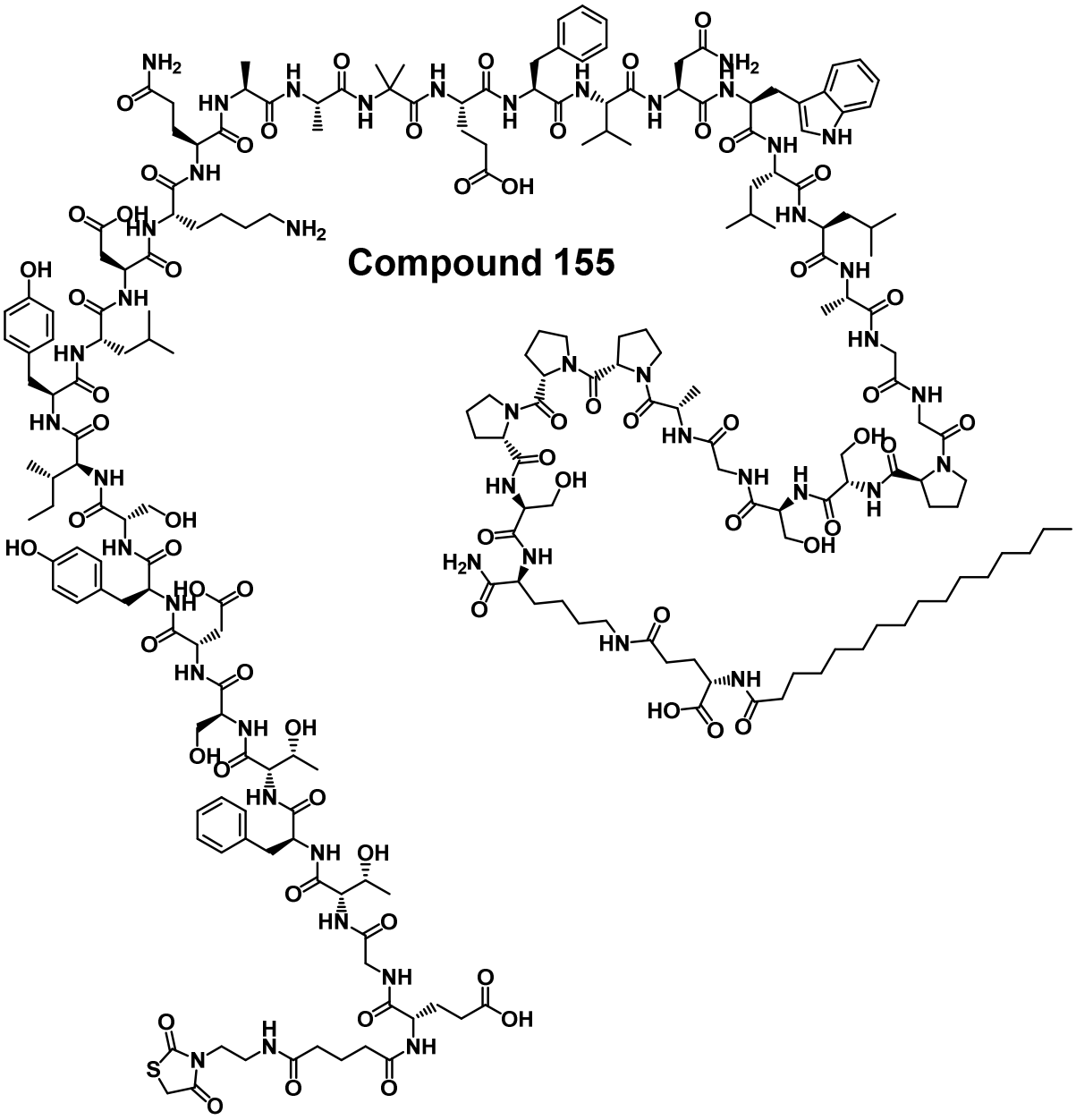

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150

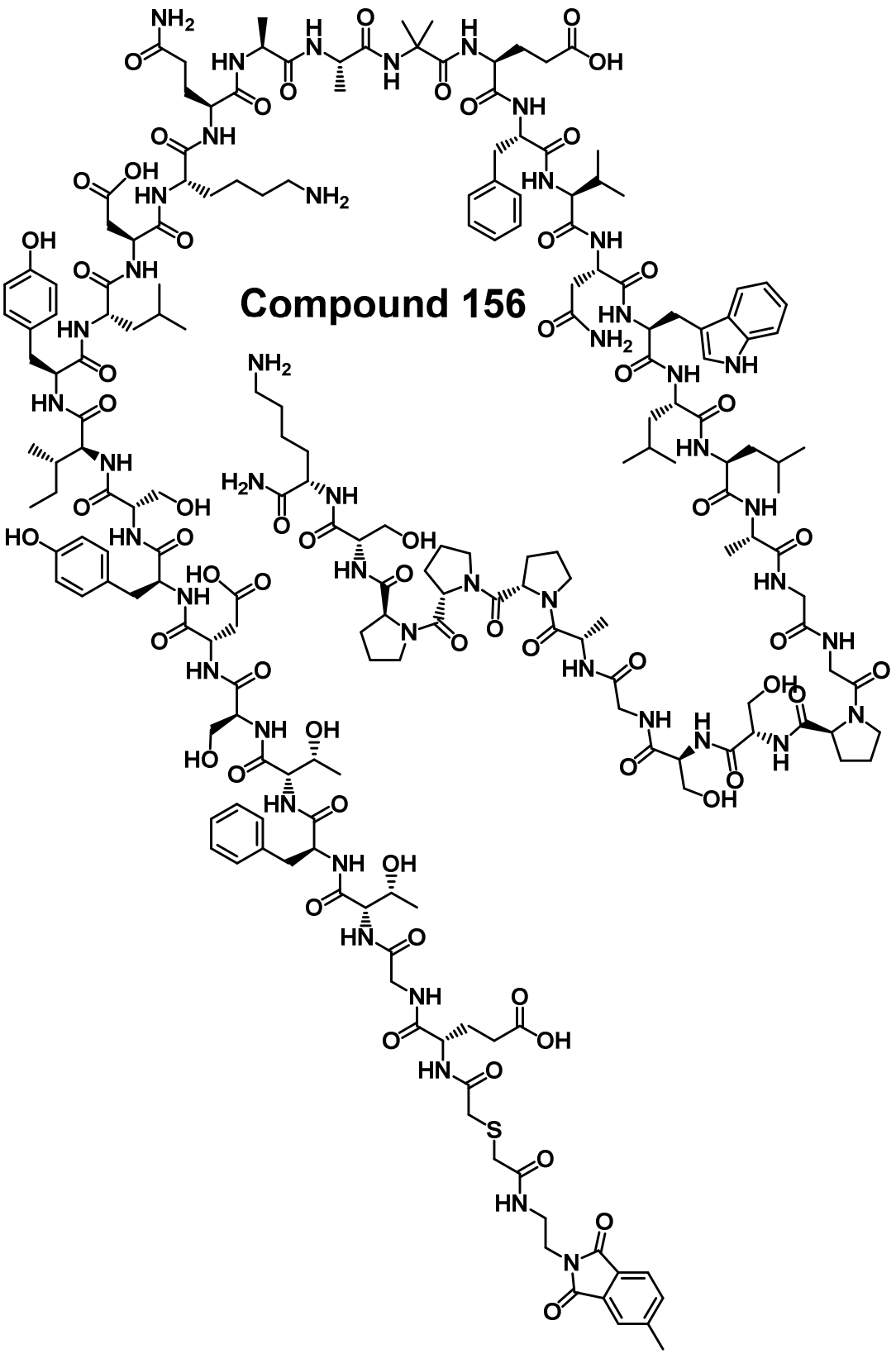

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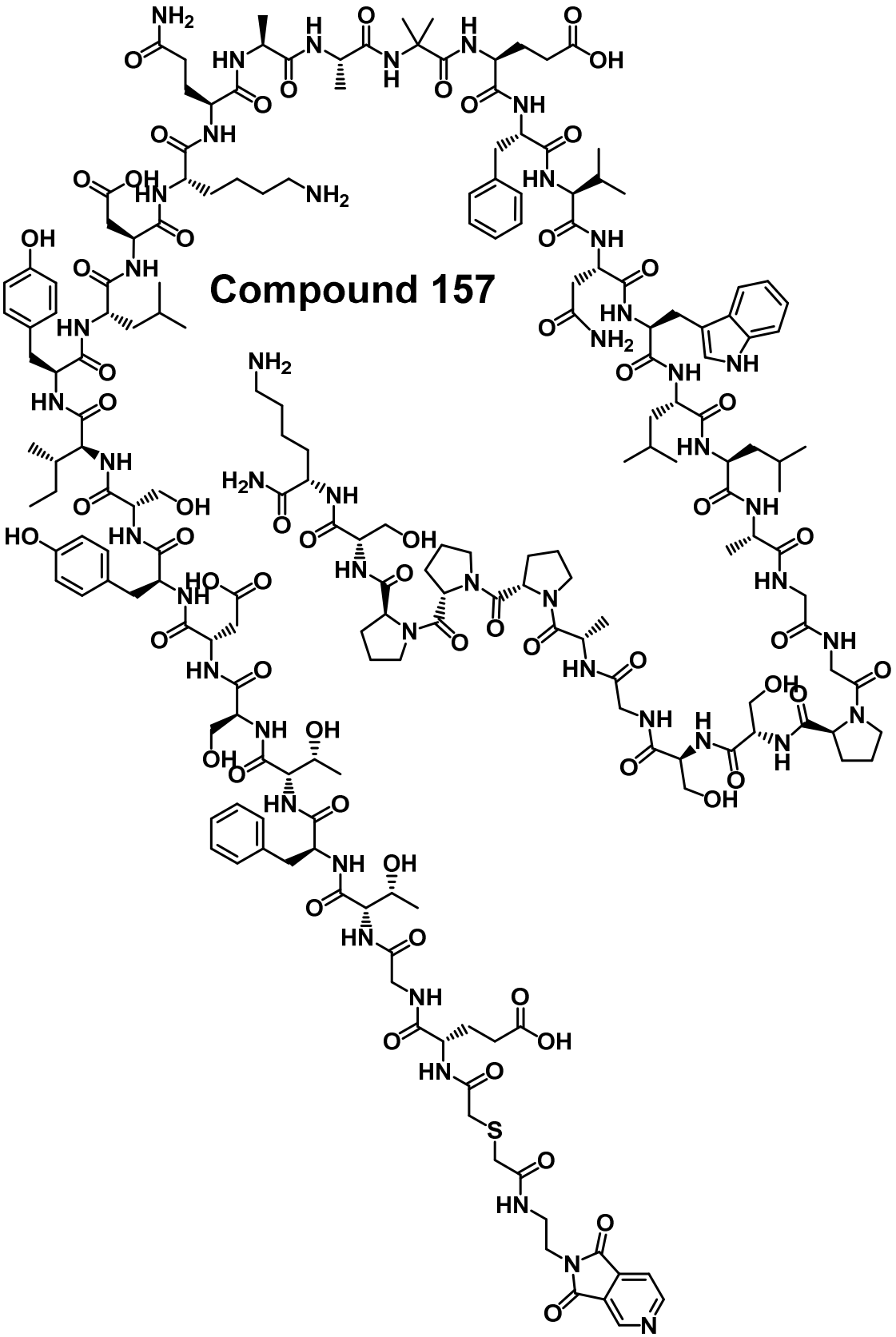

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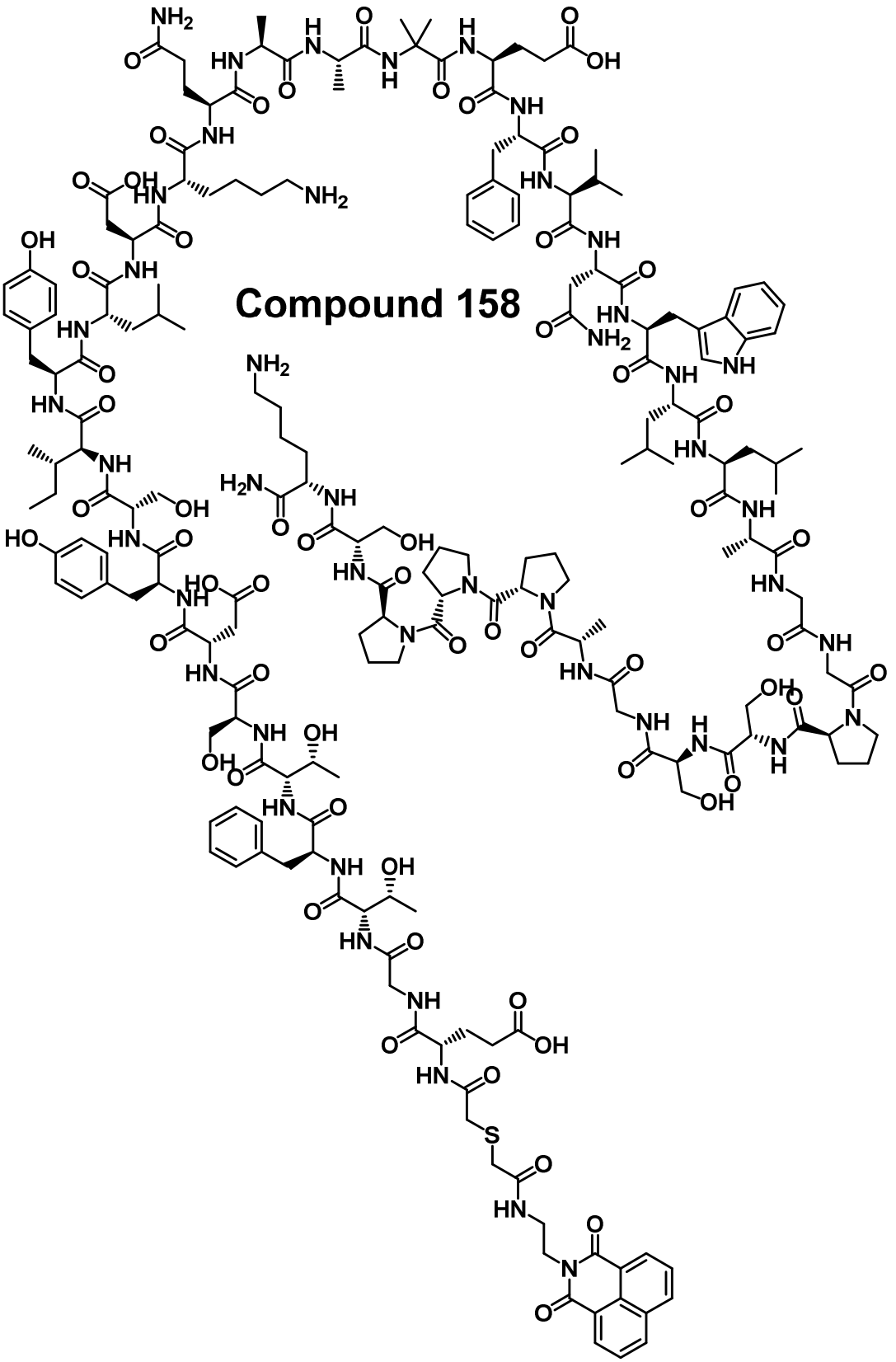

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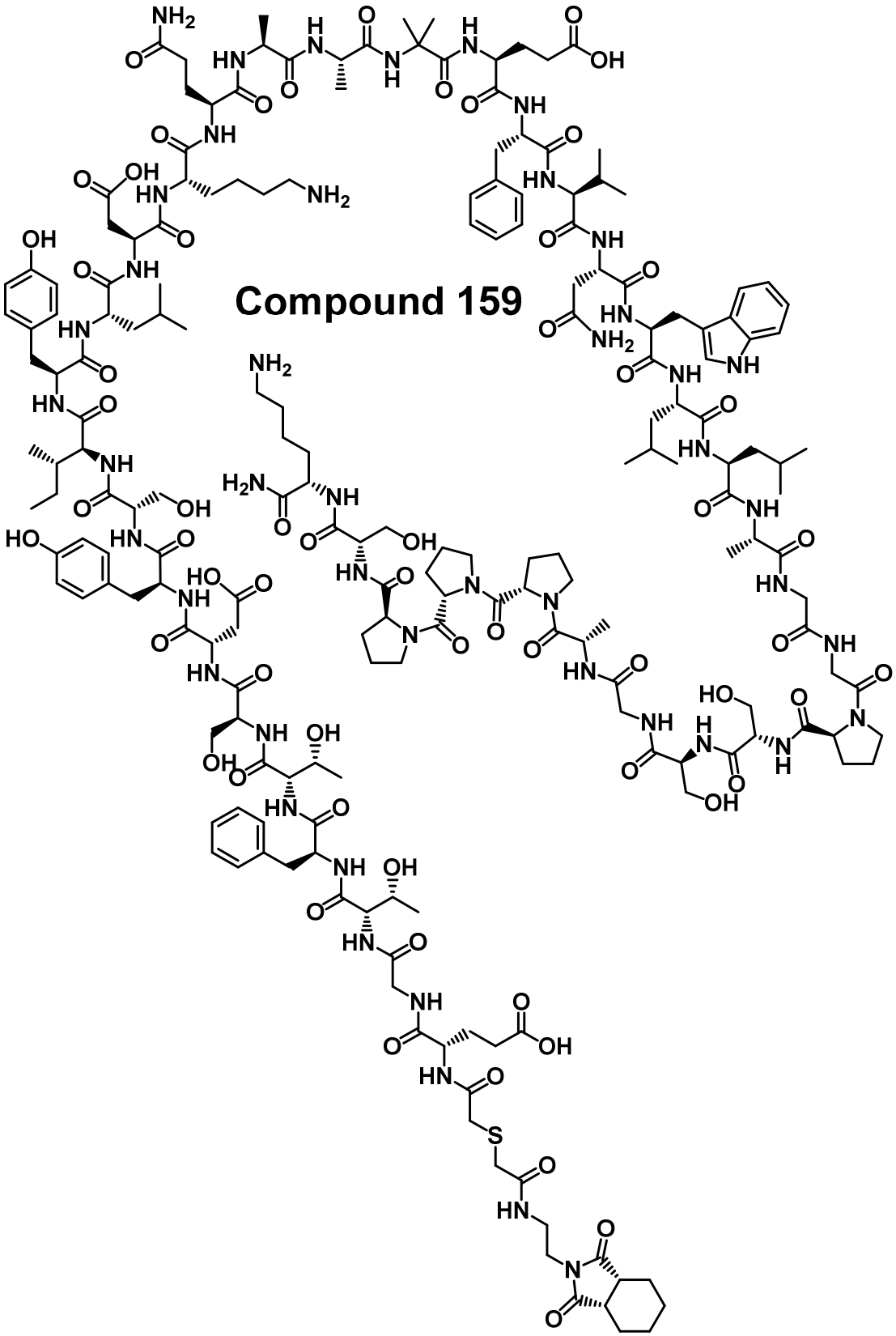

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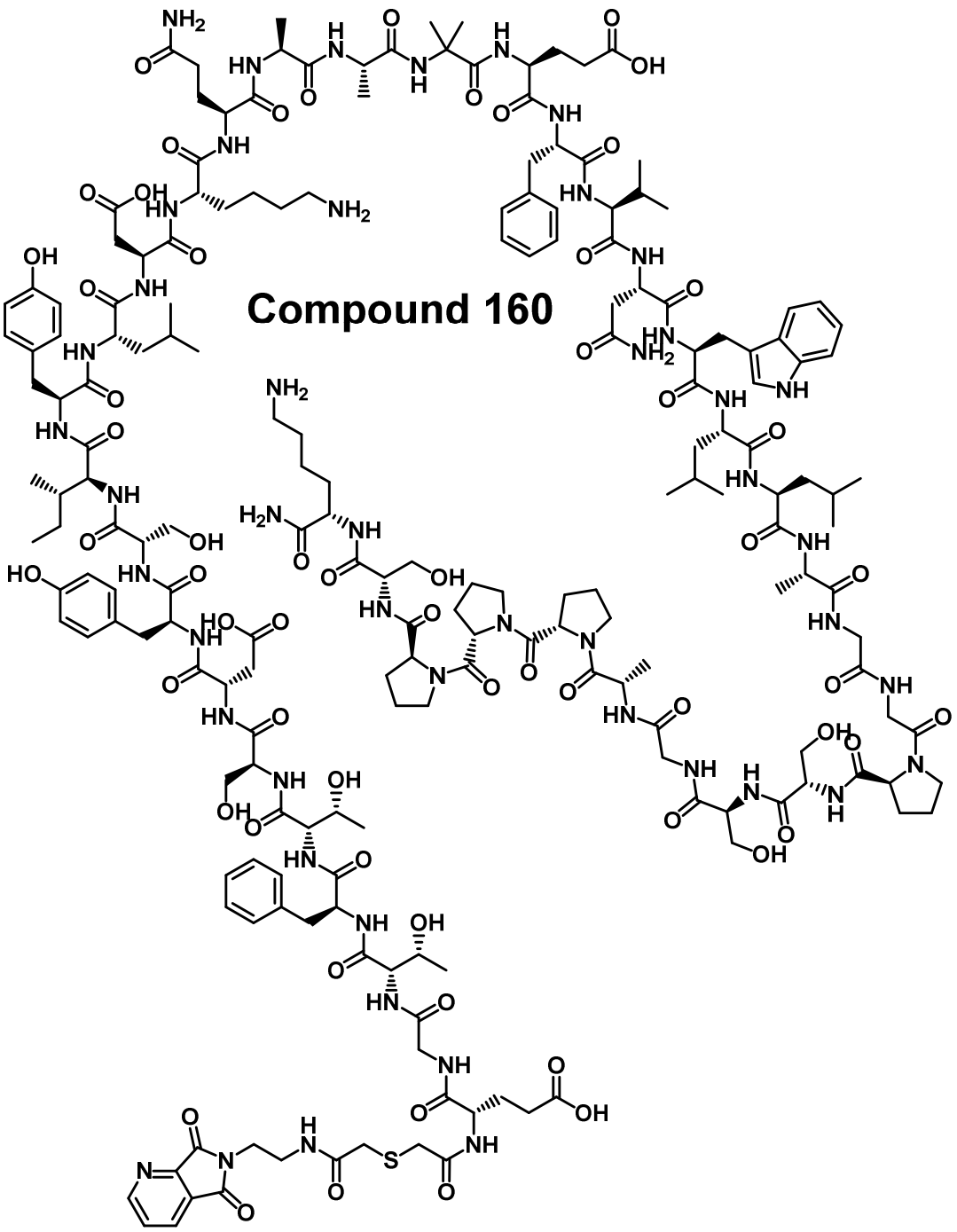

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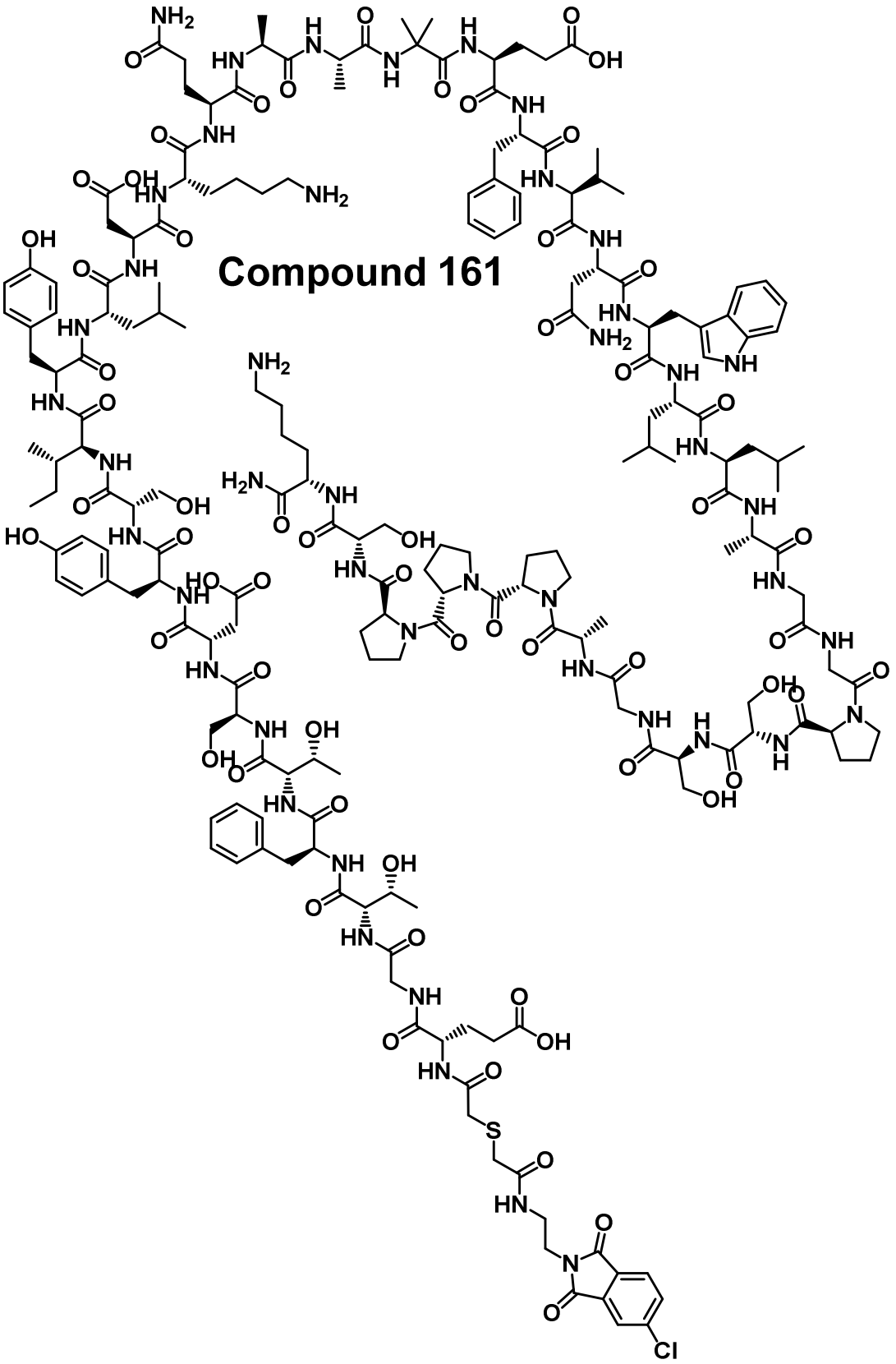

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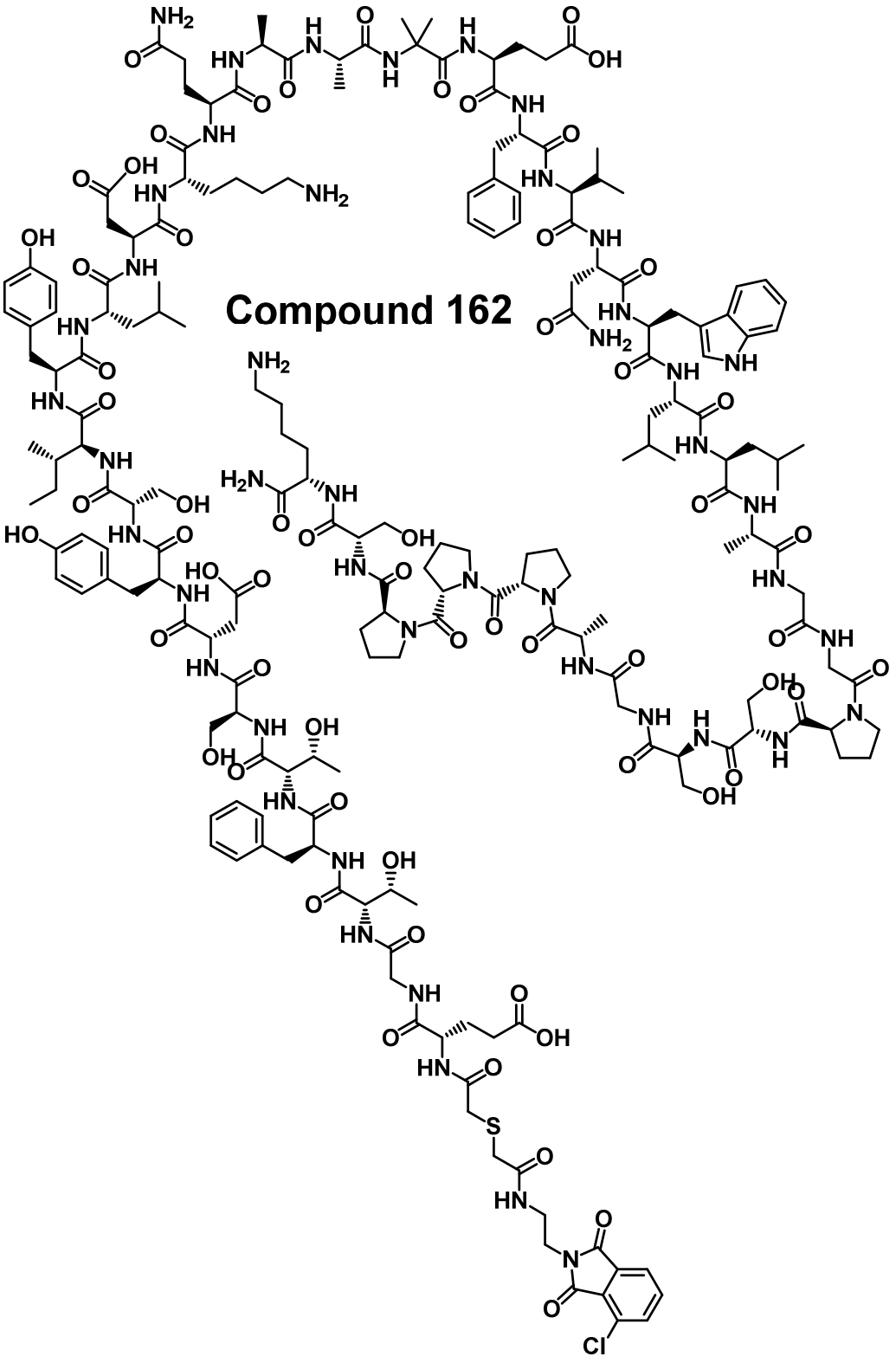

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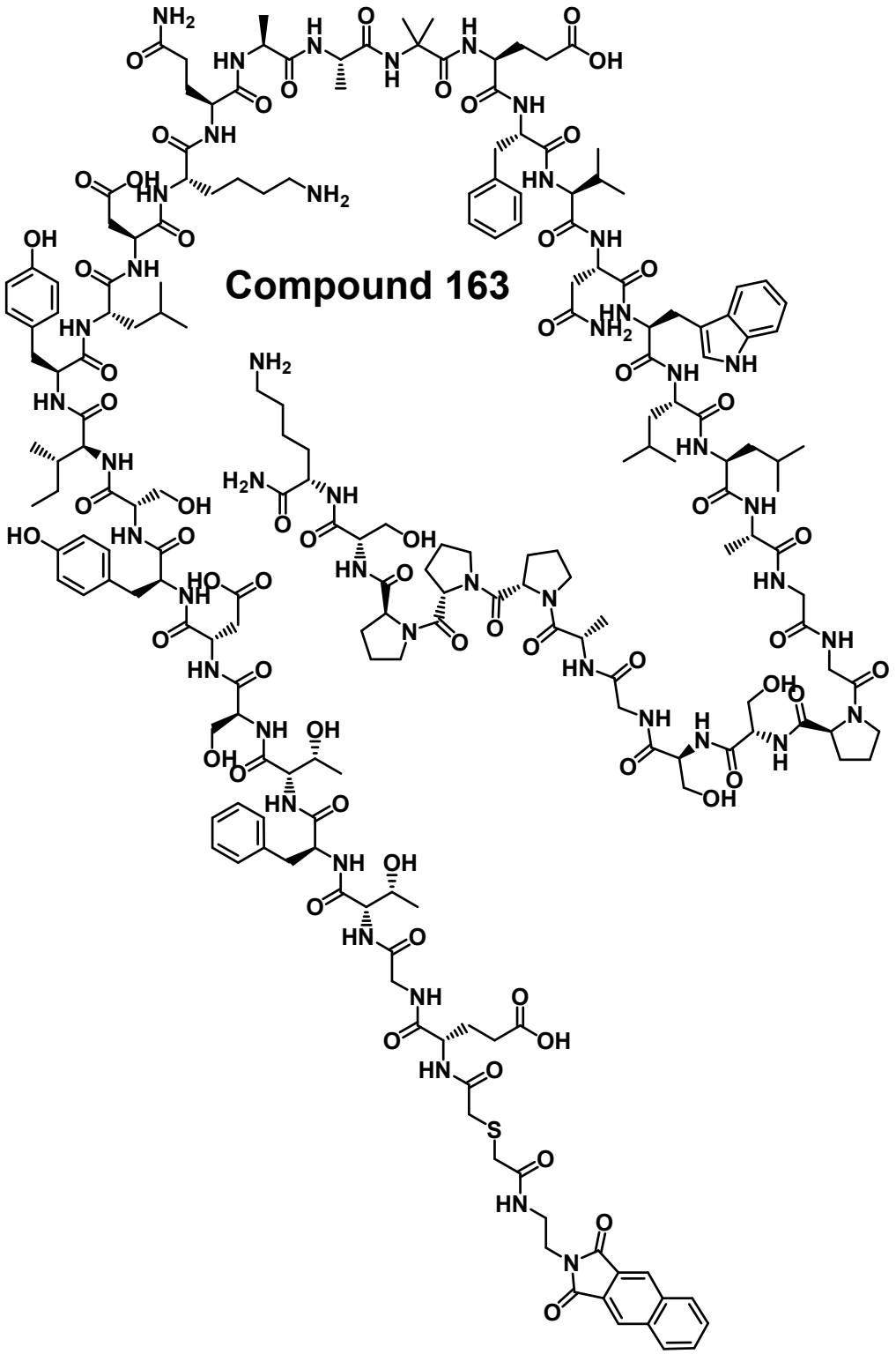

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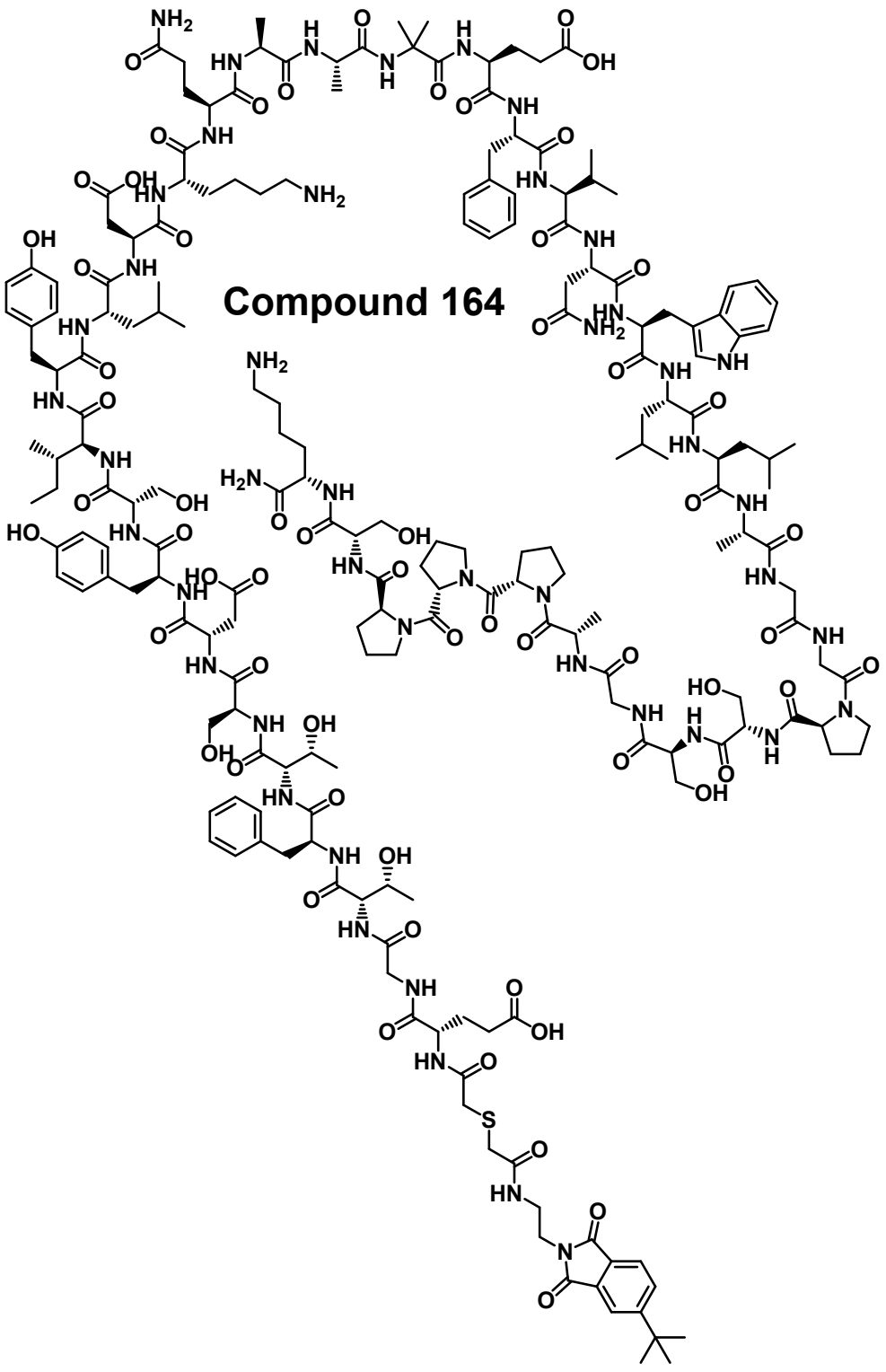


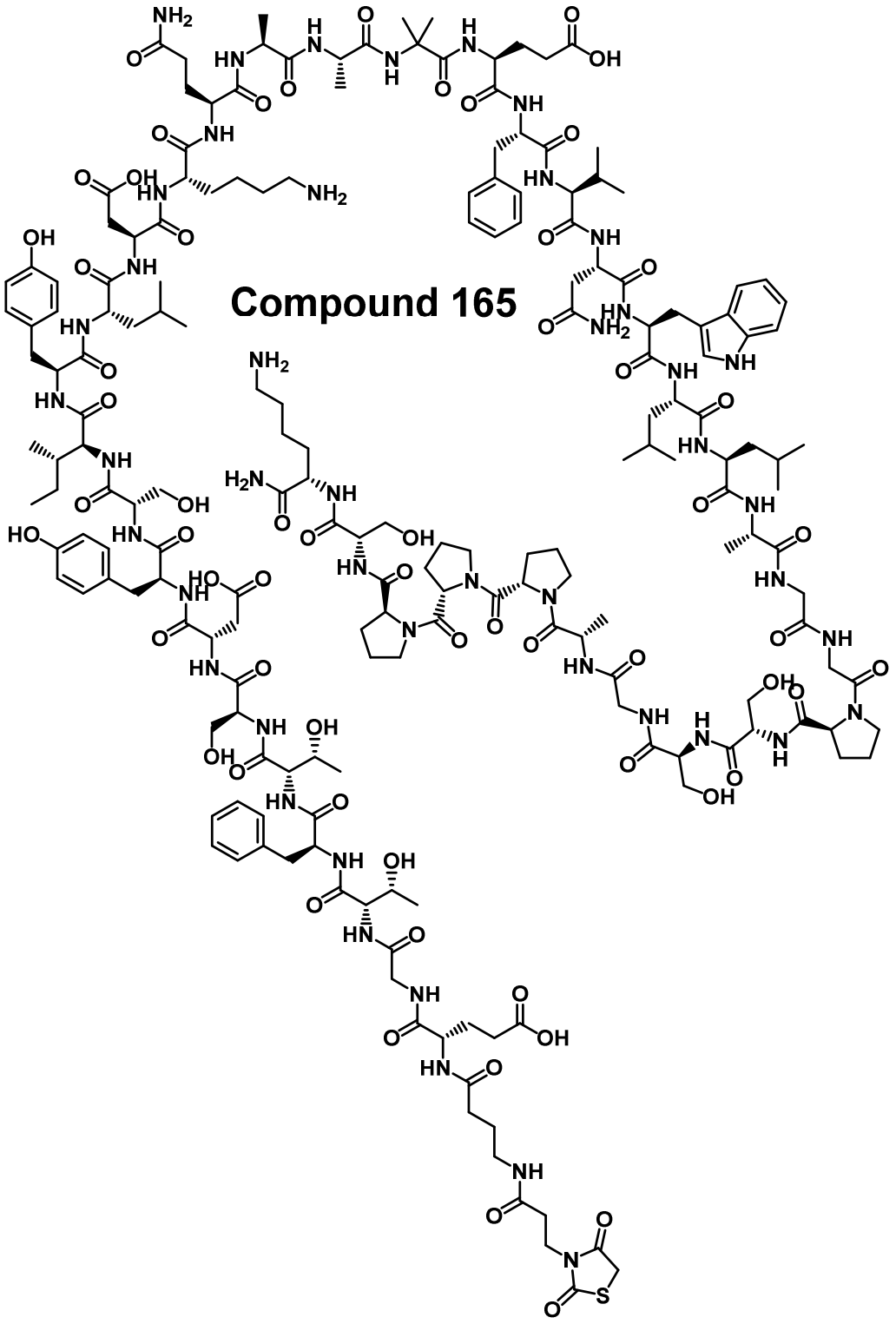
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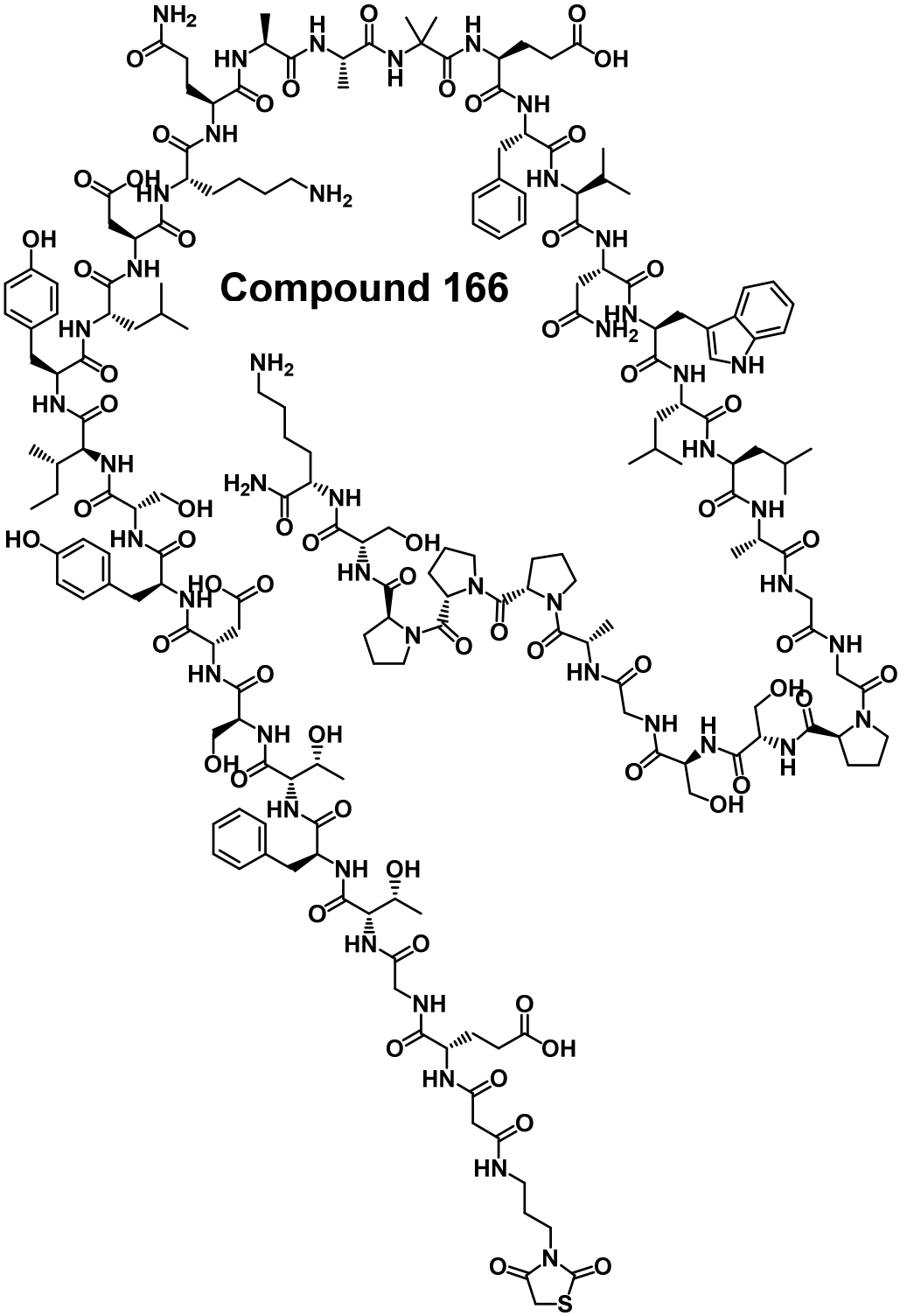

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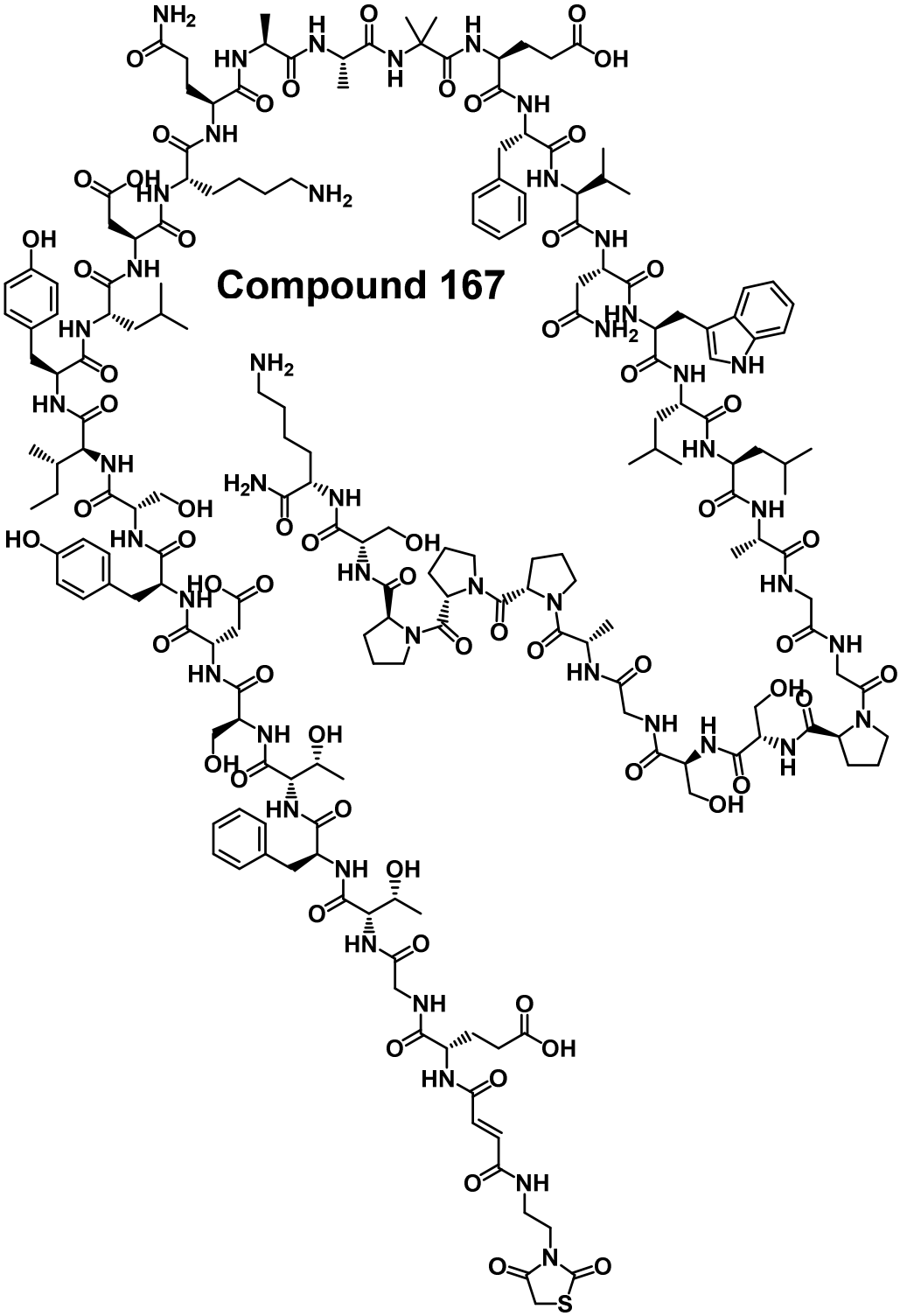

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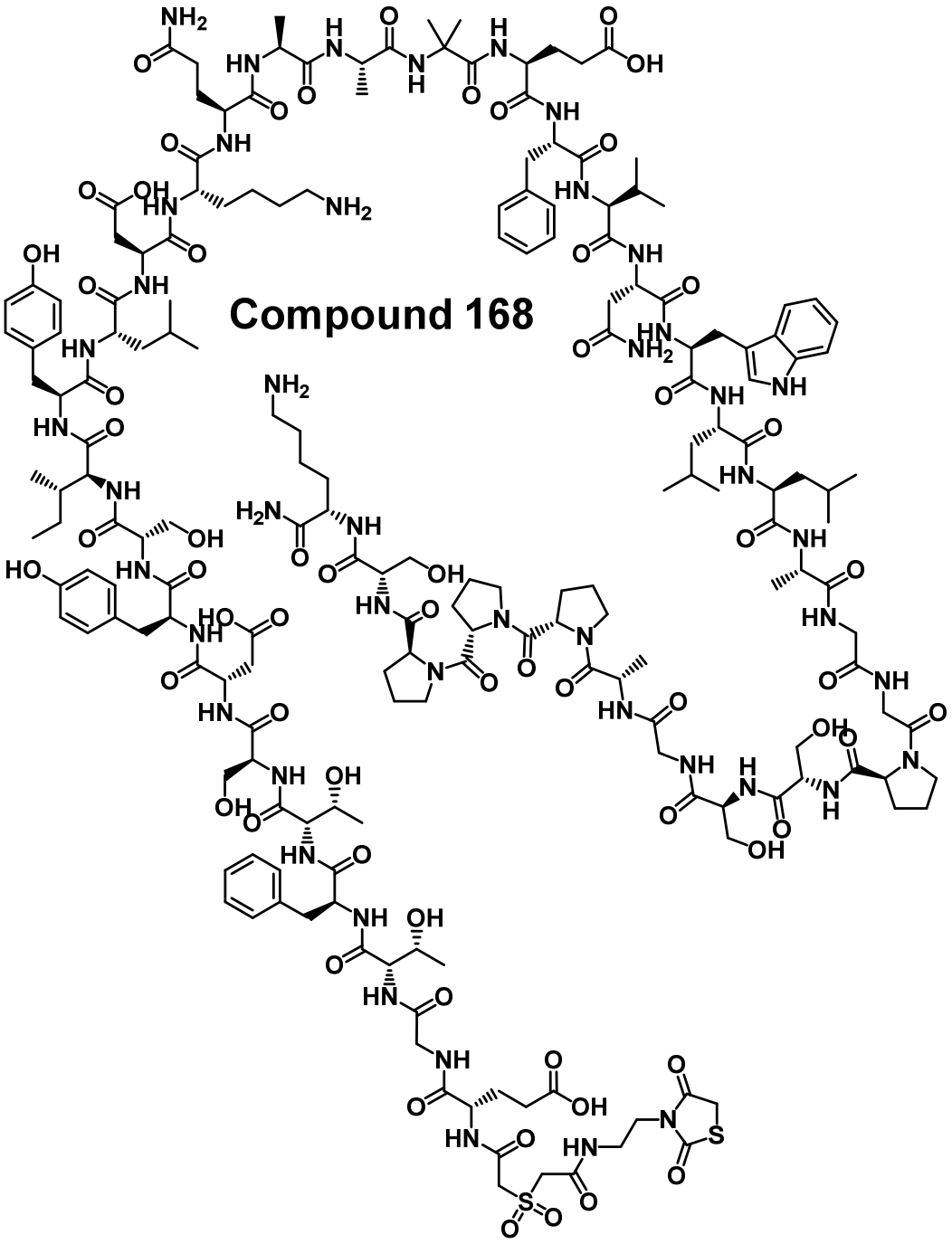

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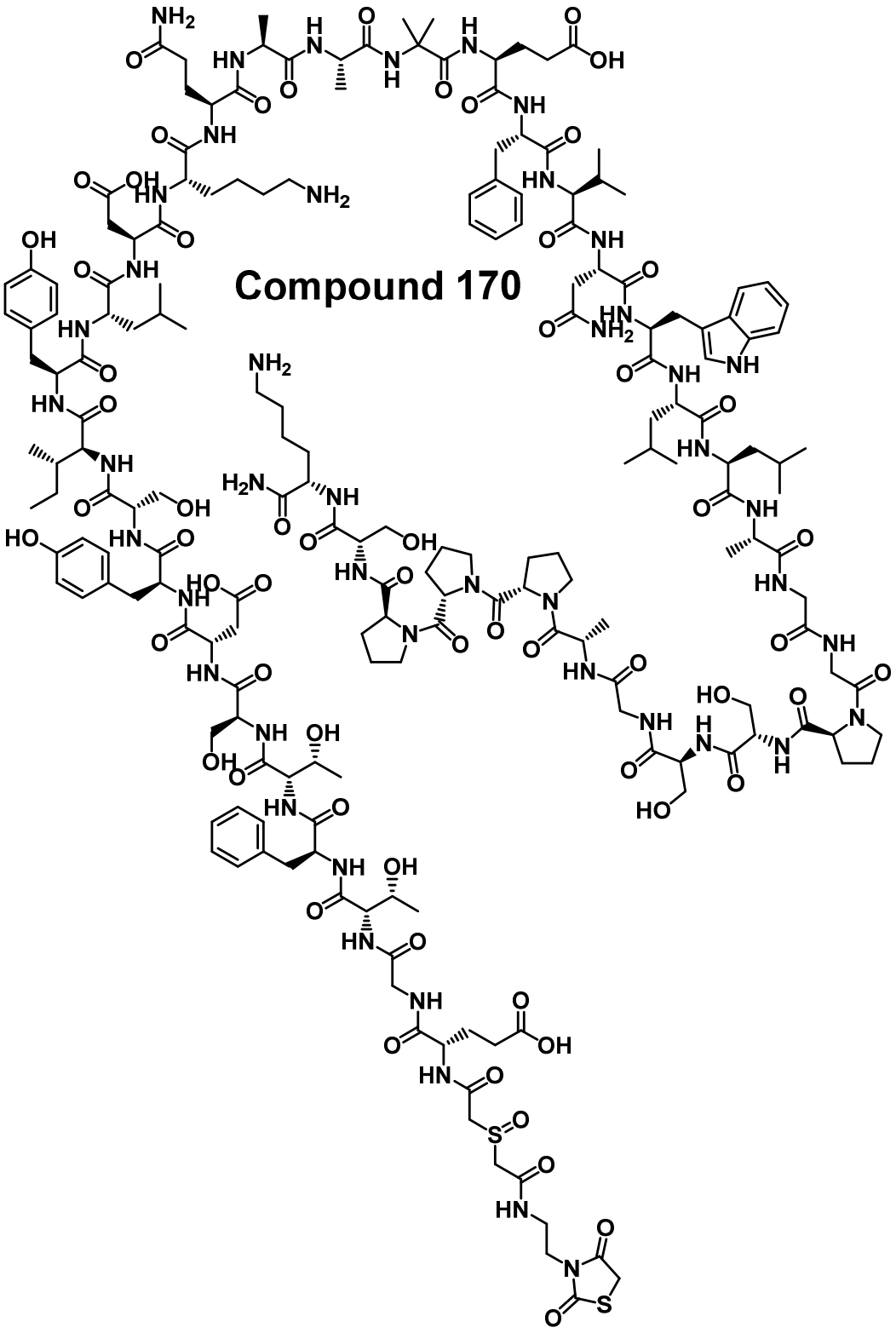

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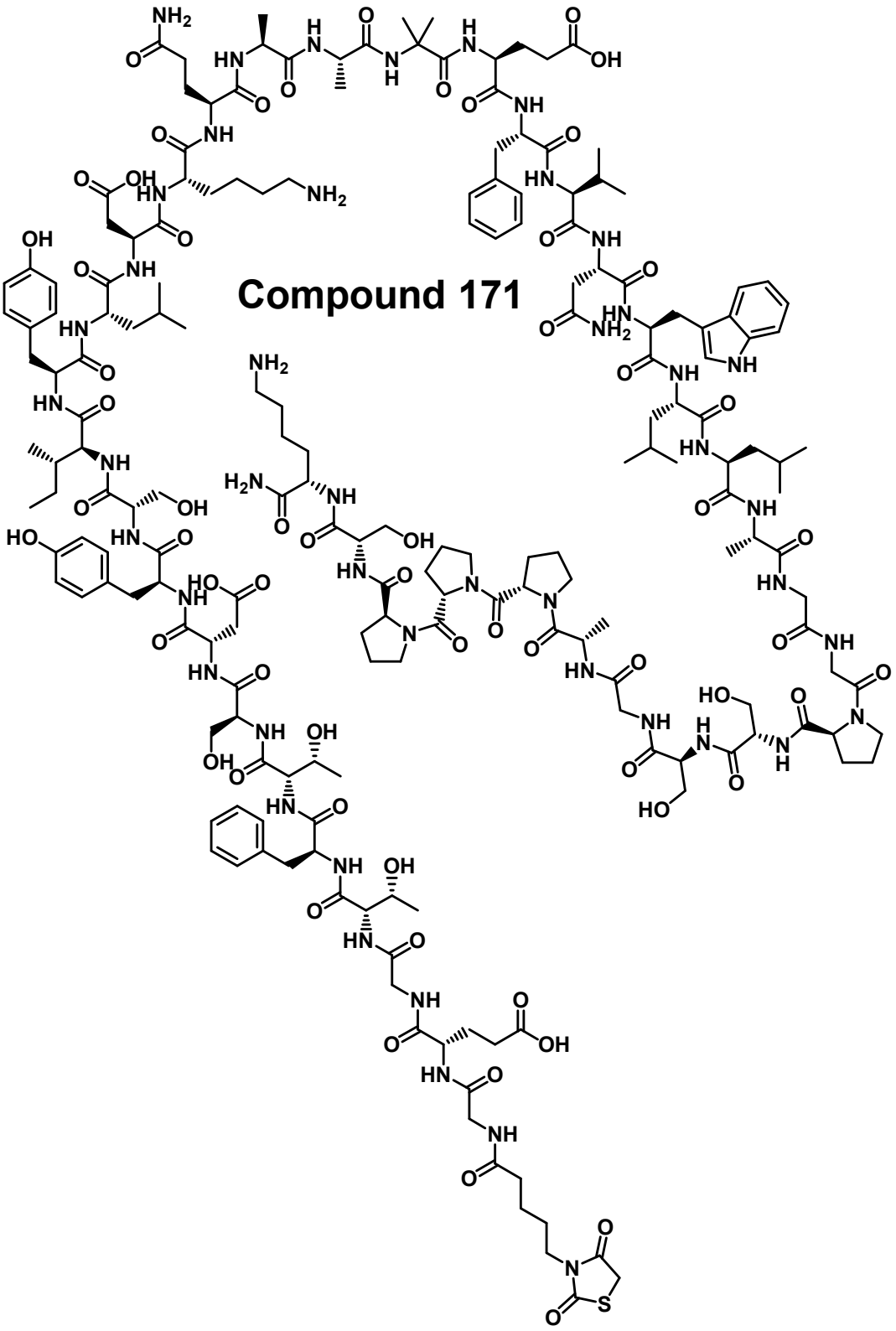

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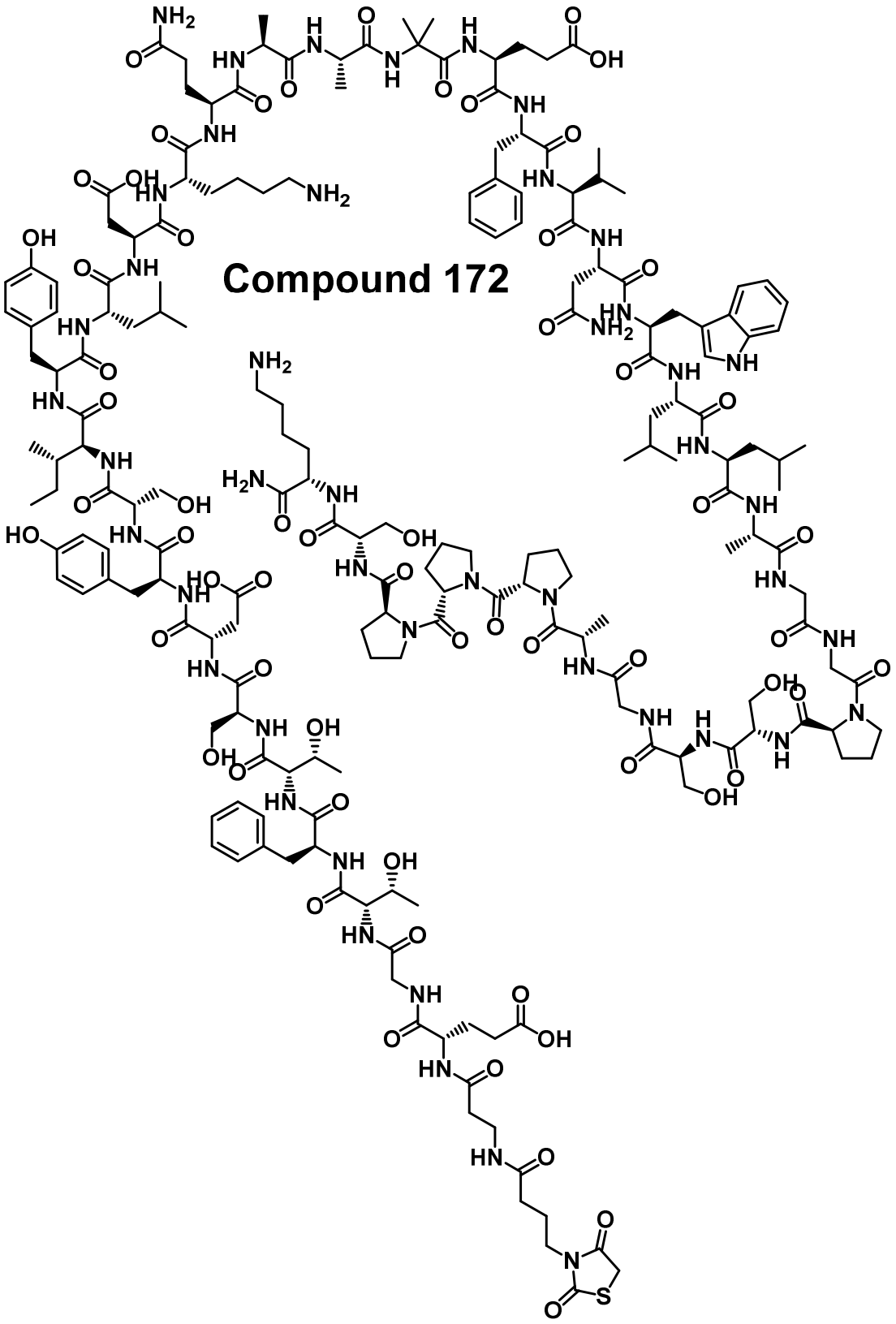

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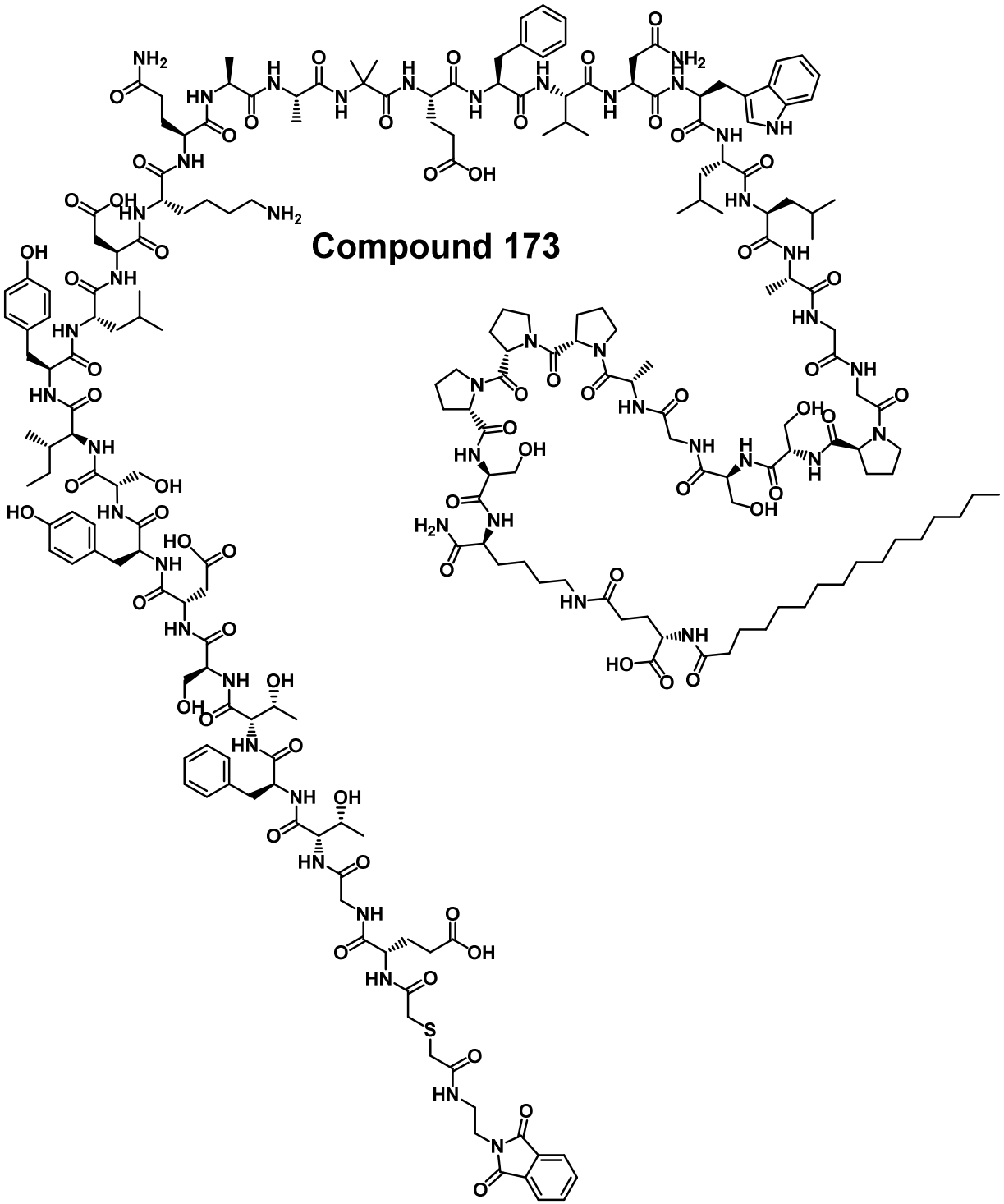

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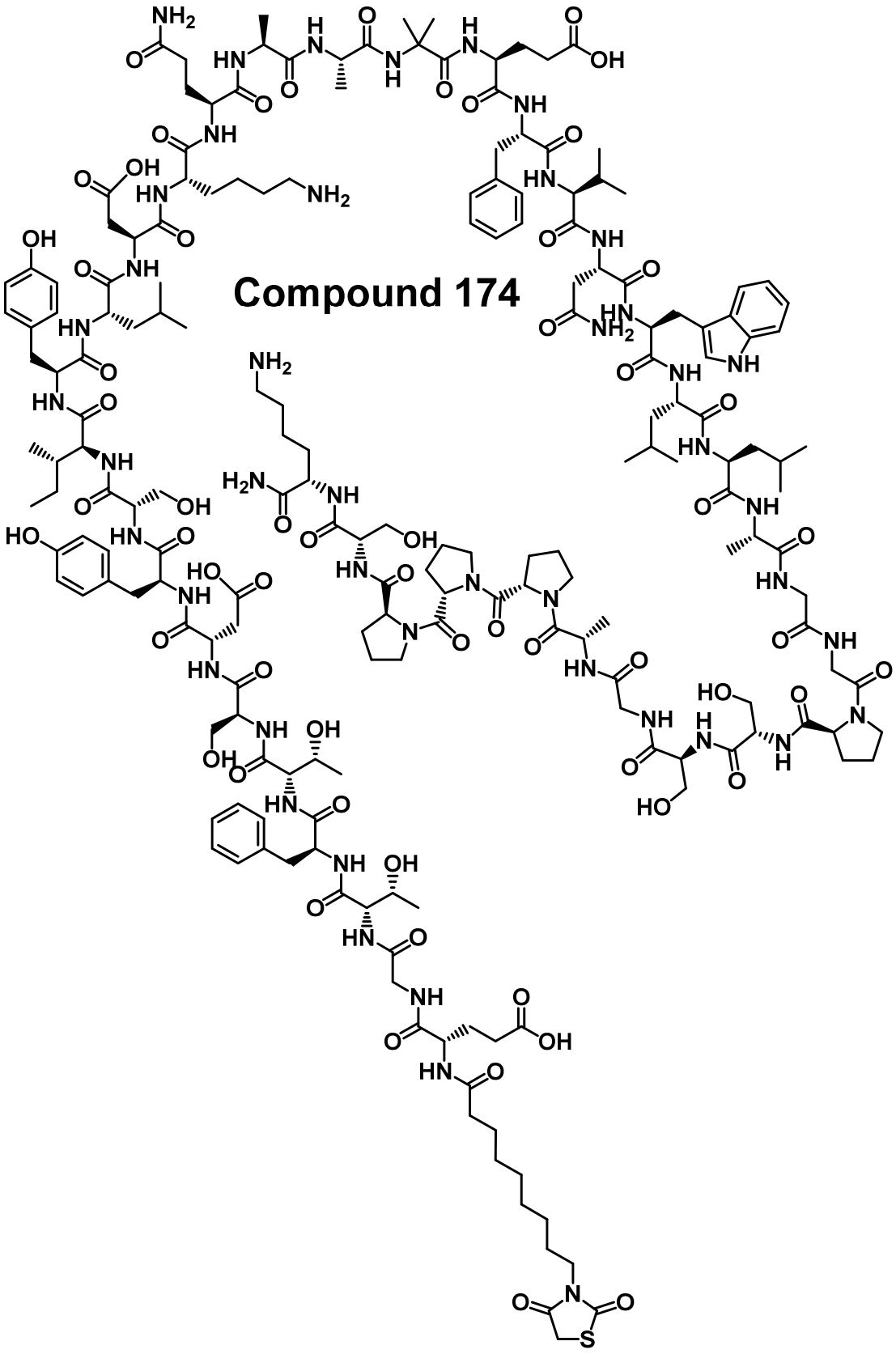

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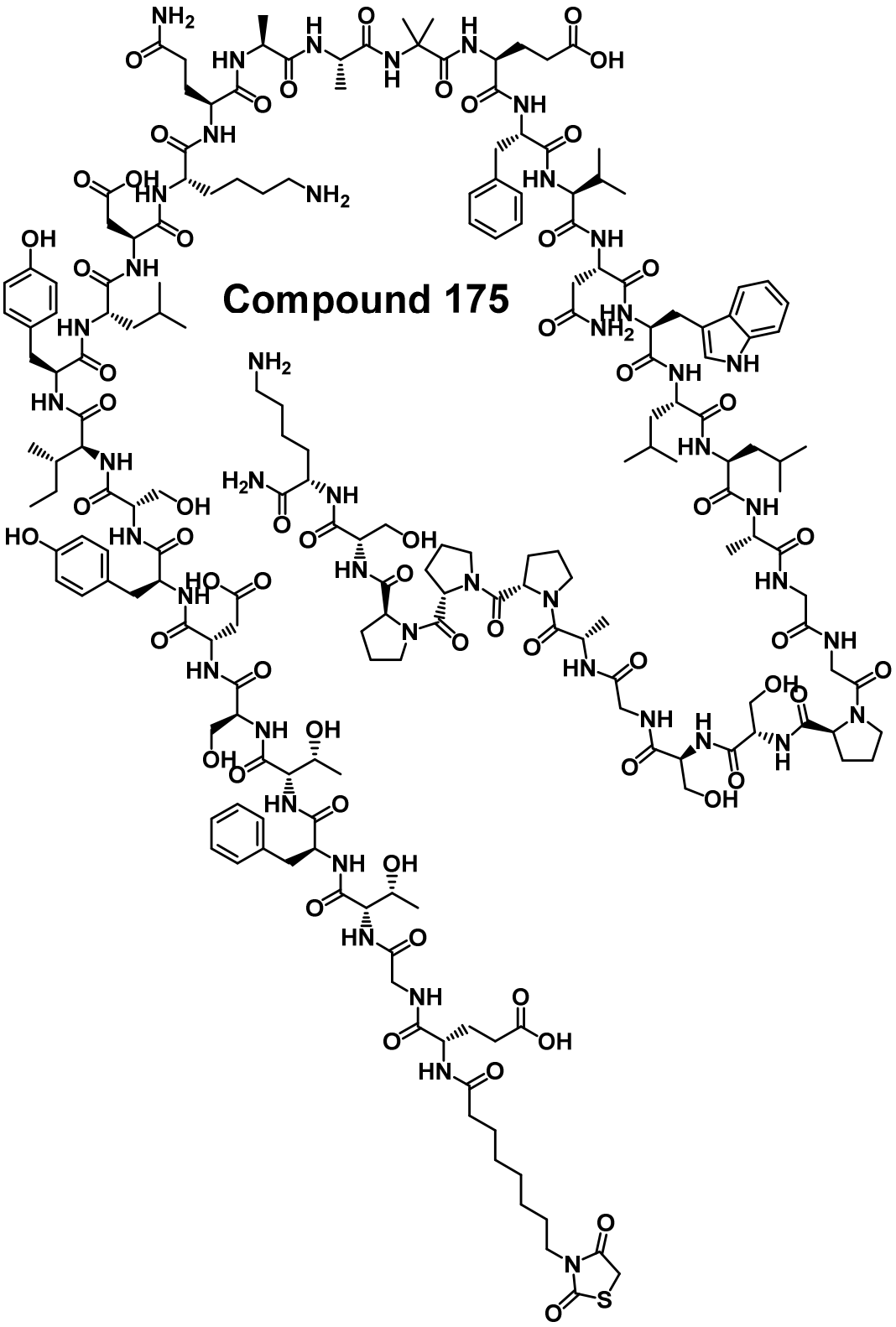

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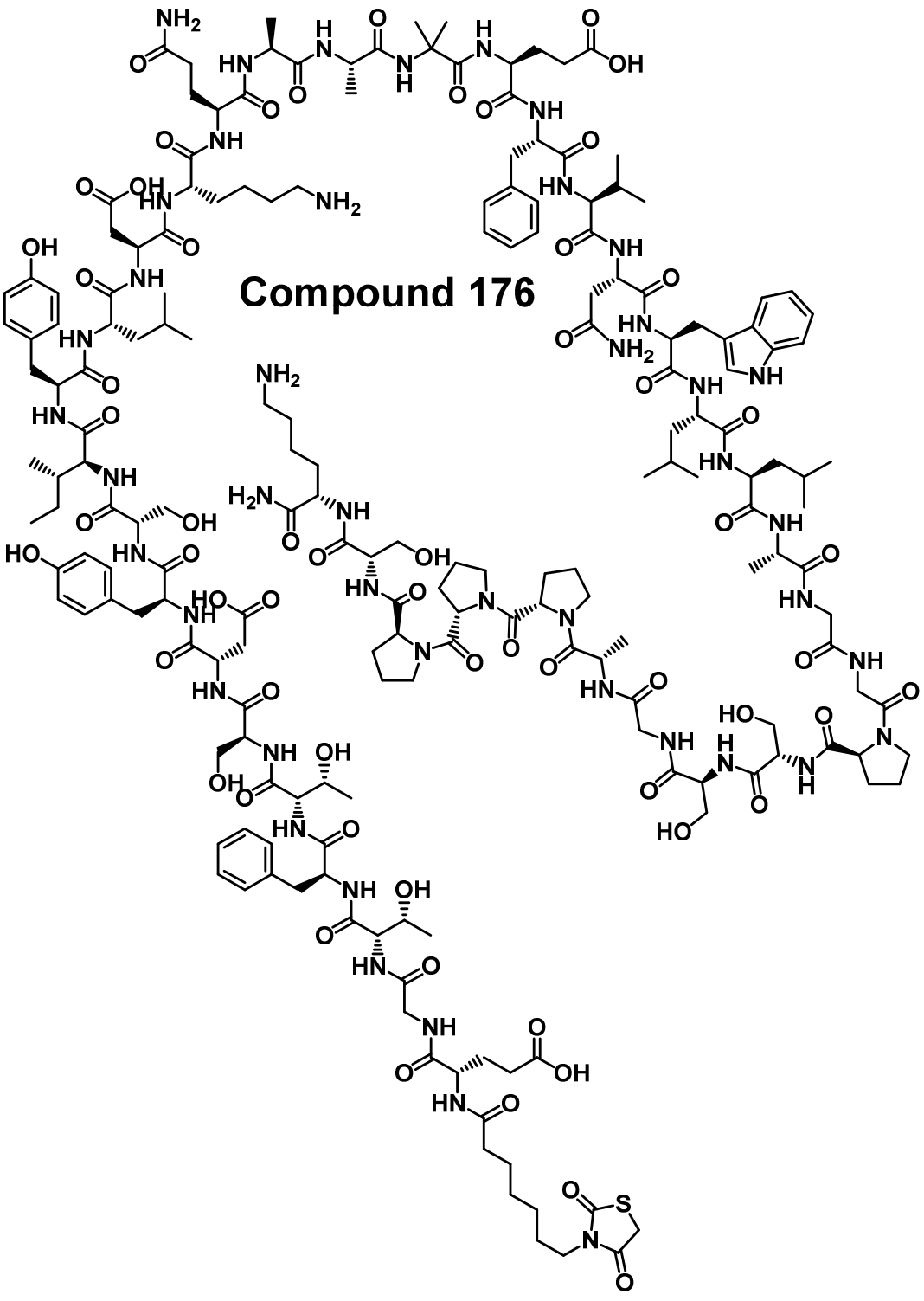

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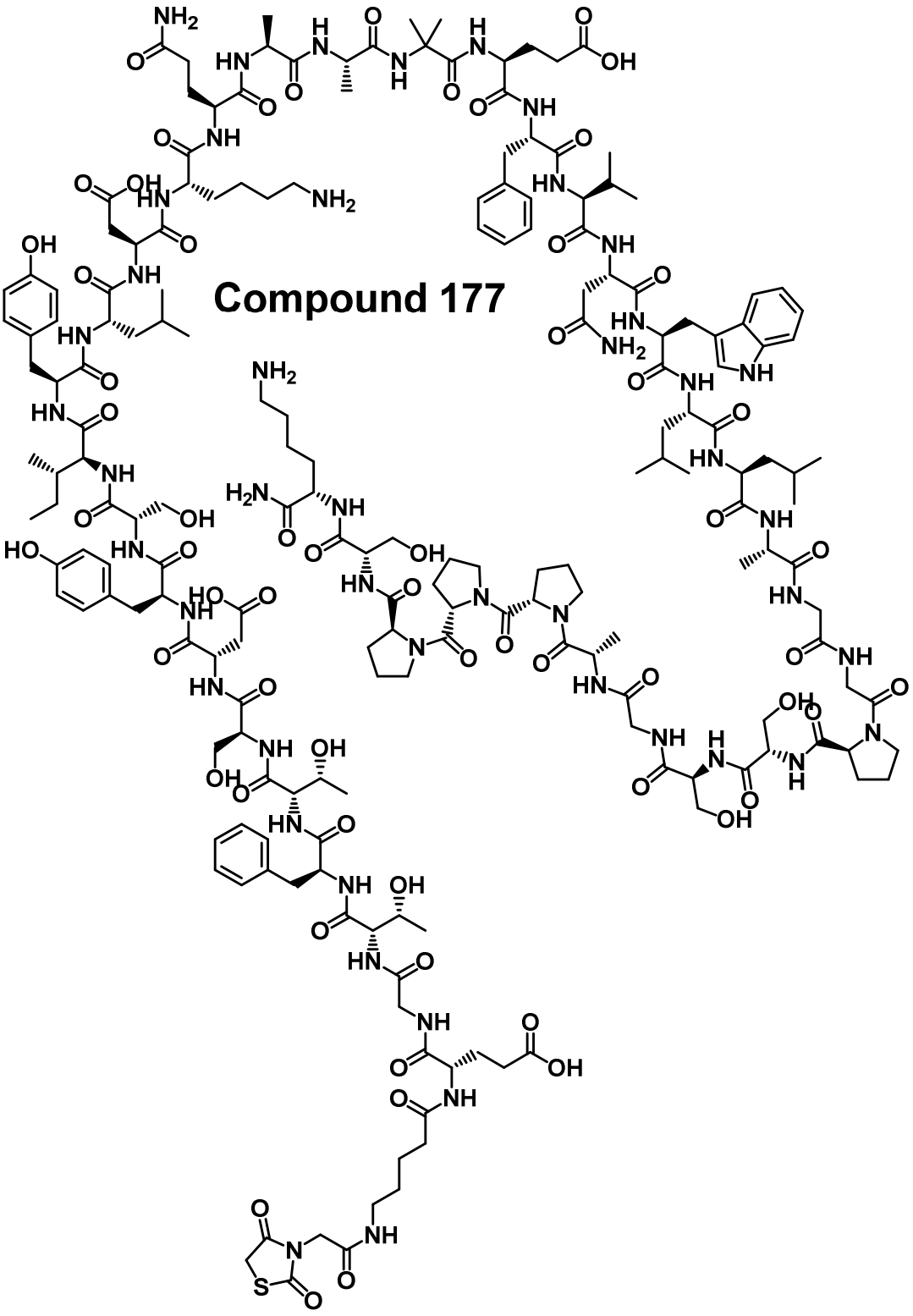

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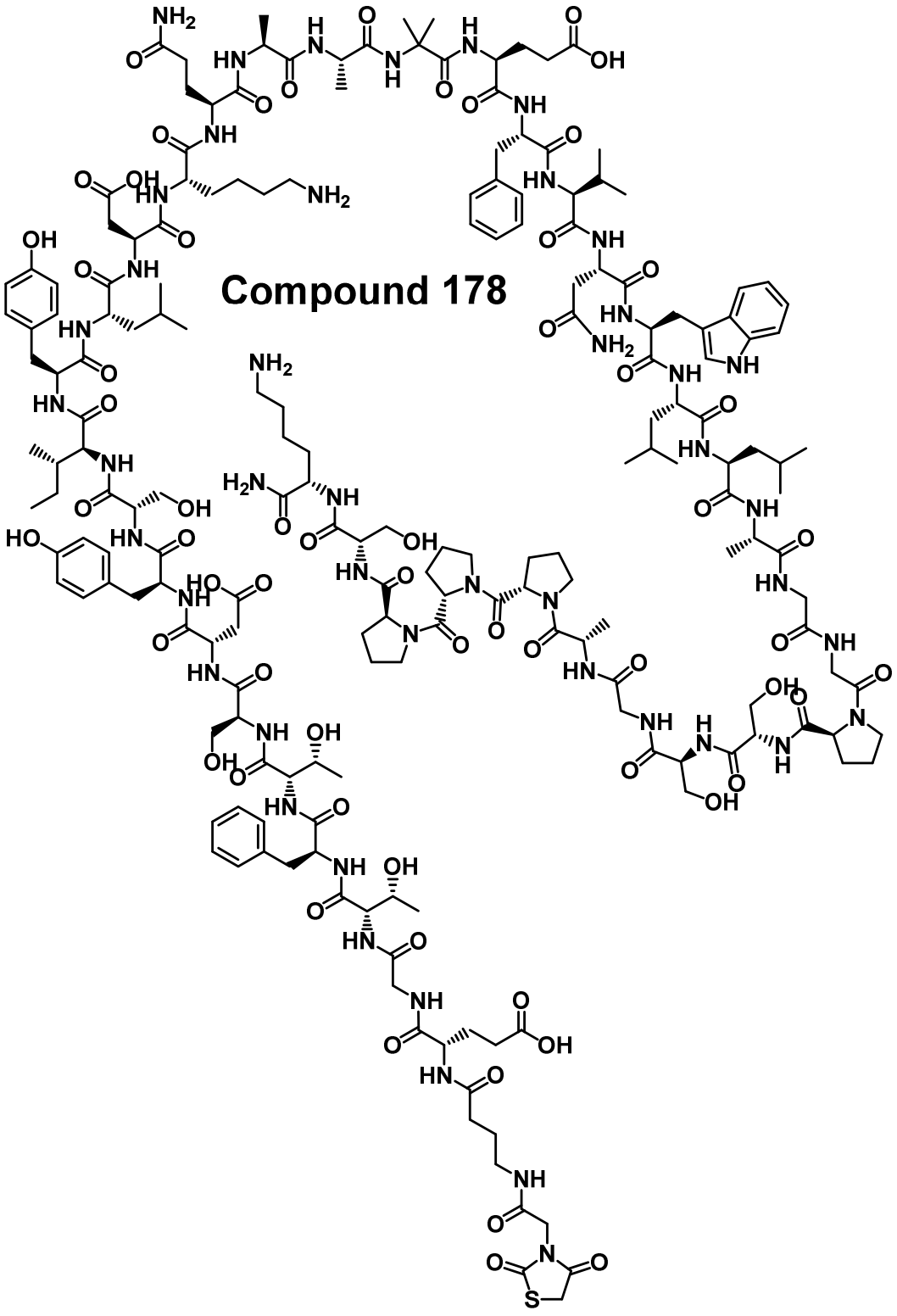

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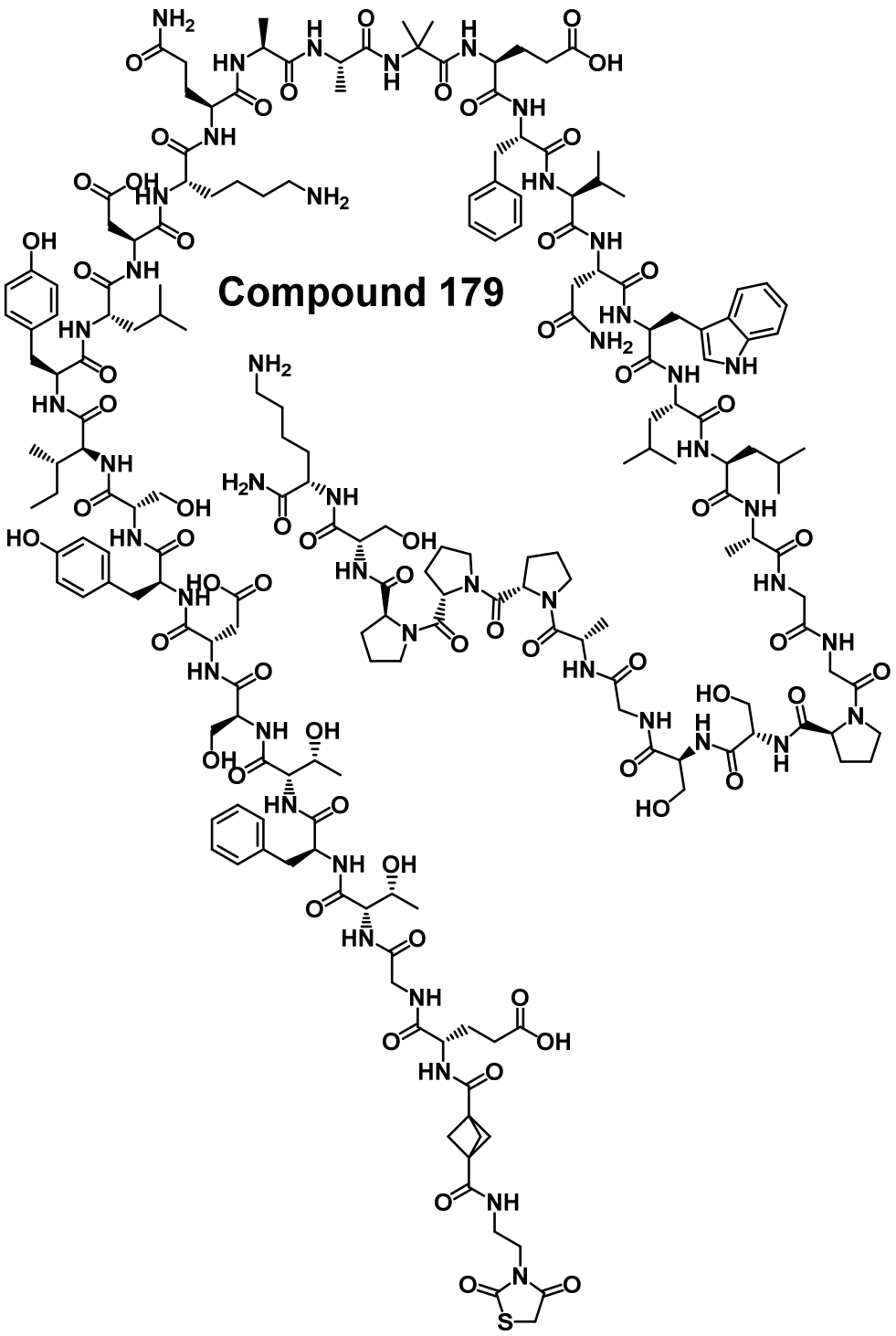

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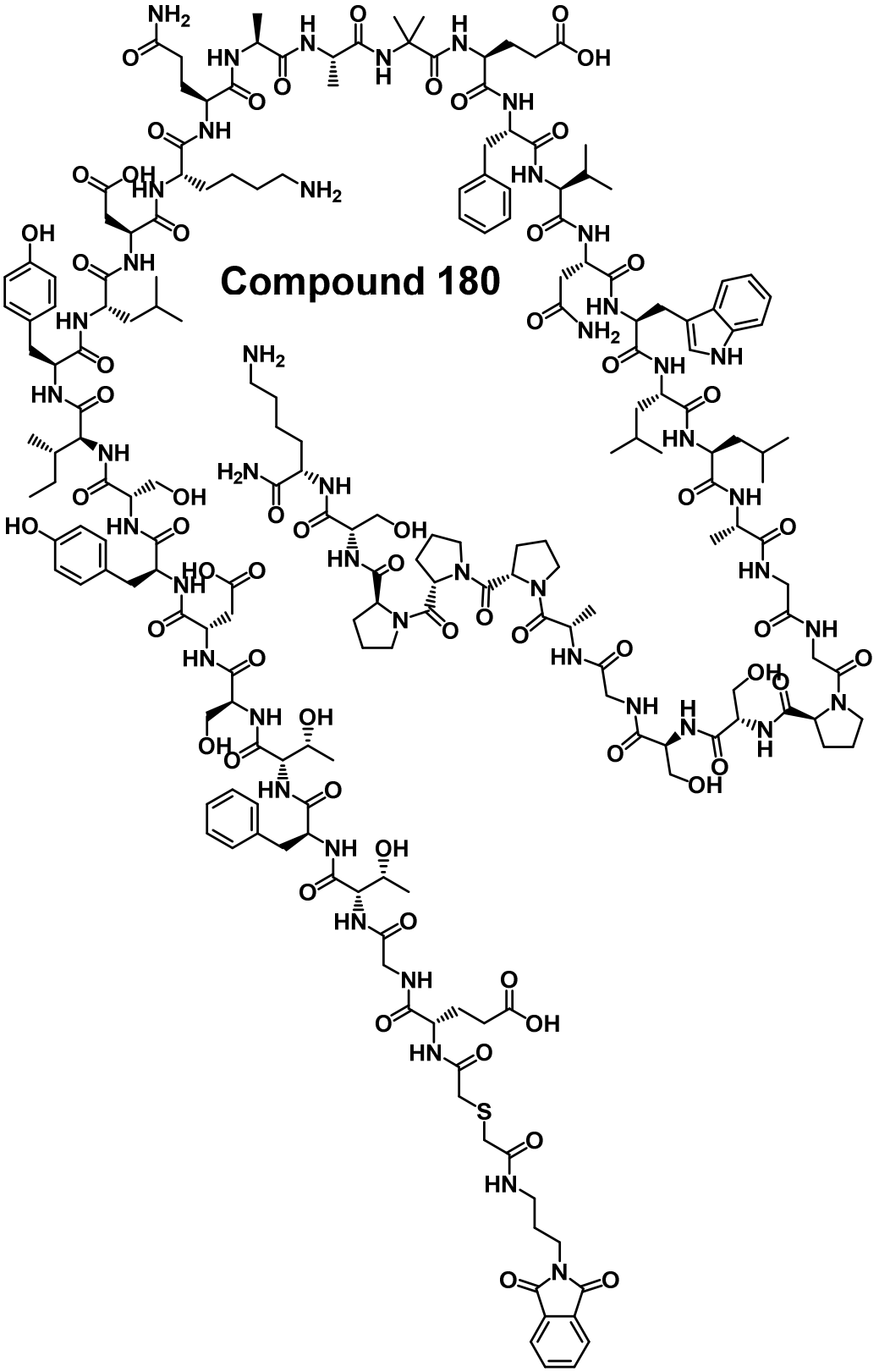

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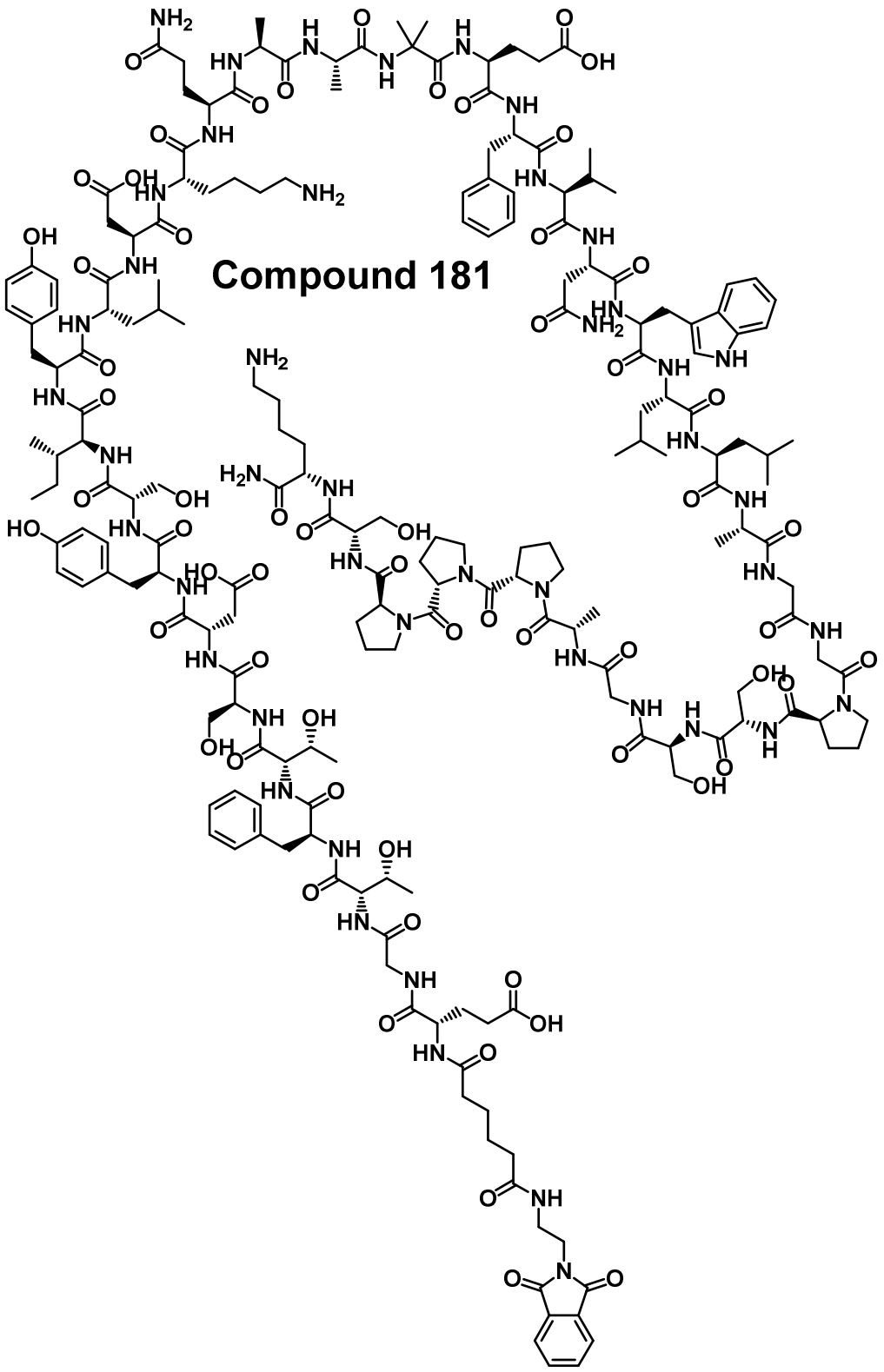

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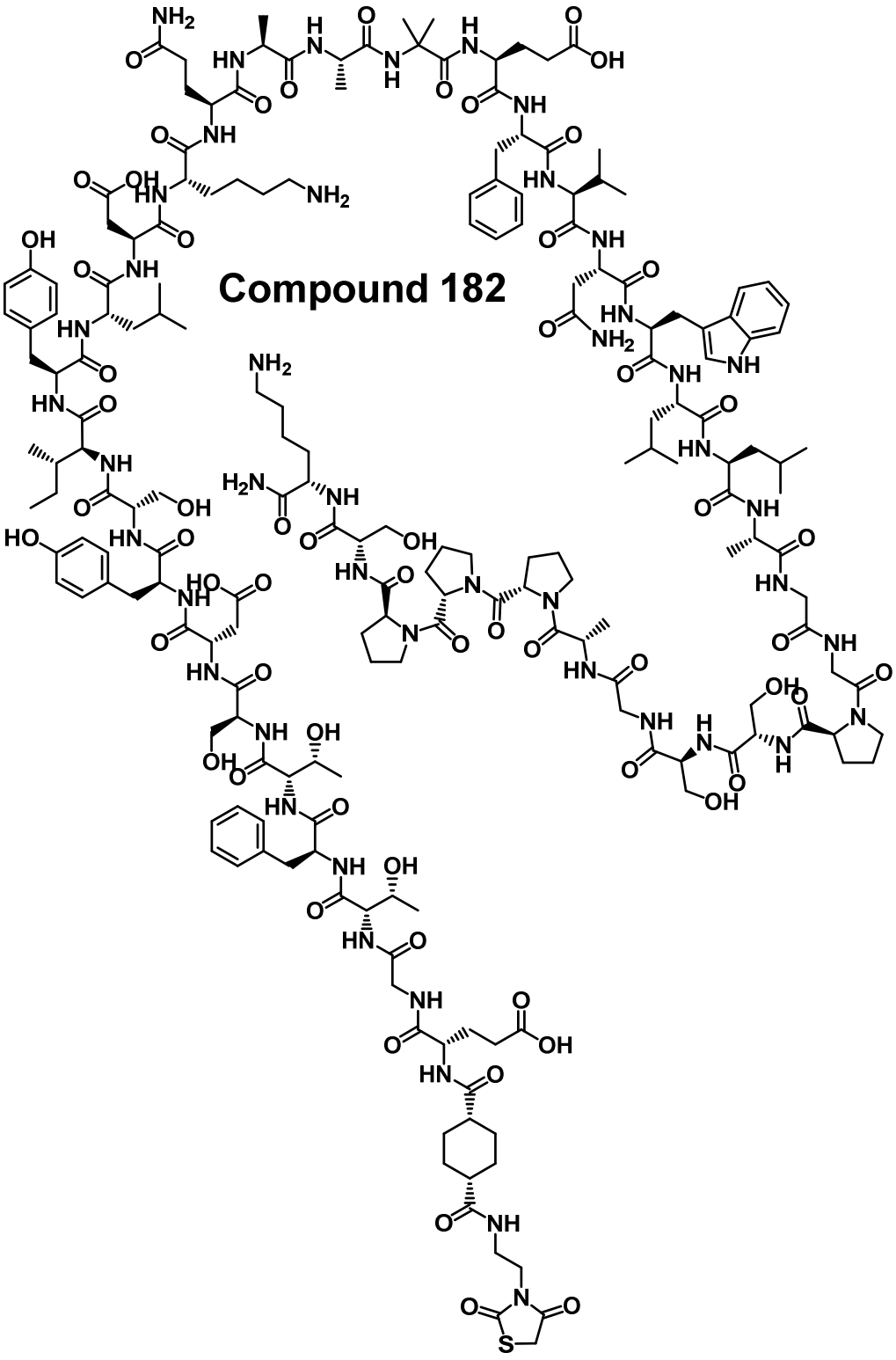

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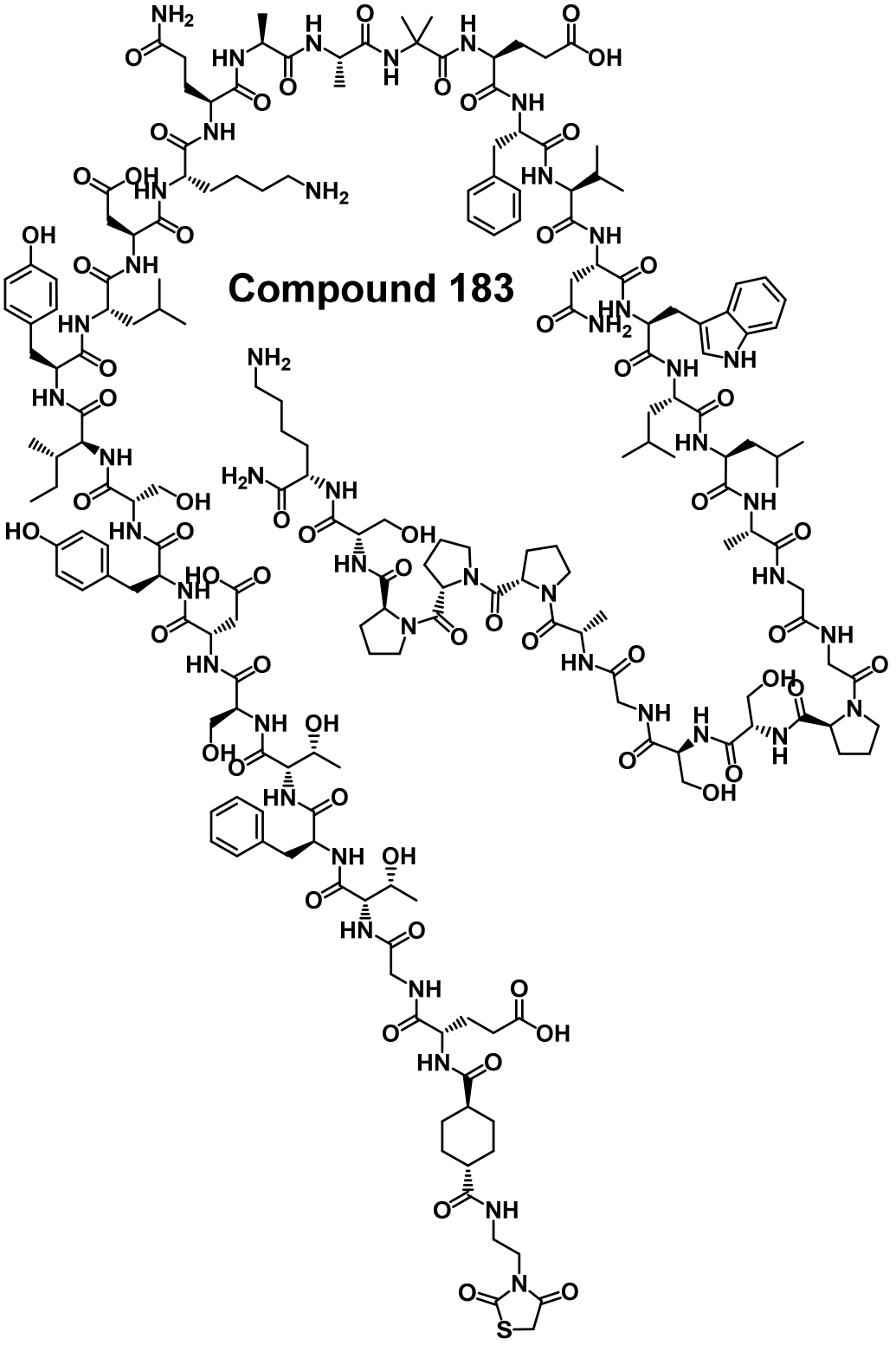

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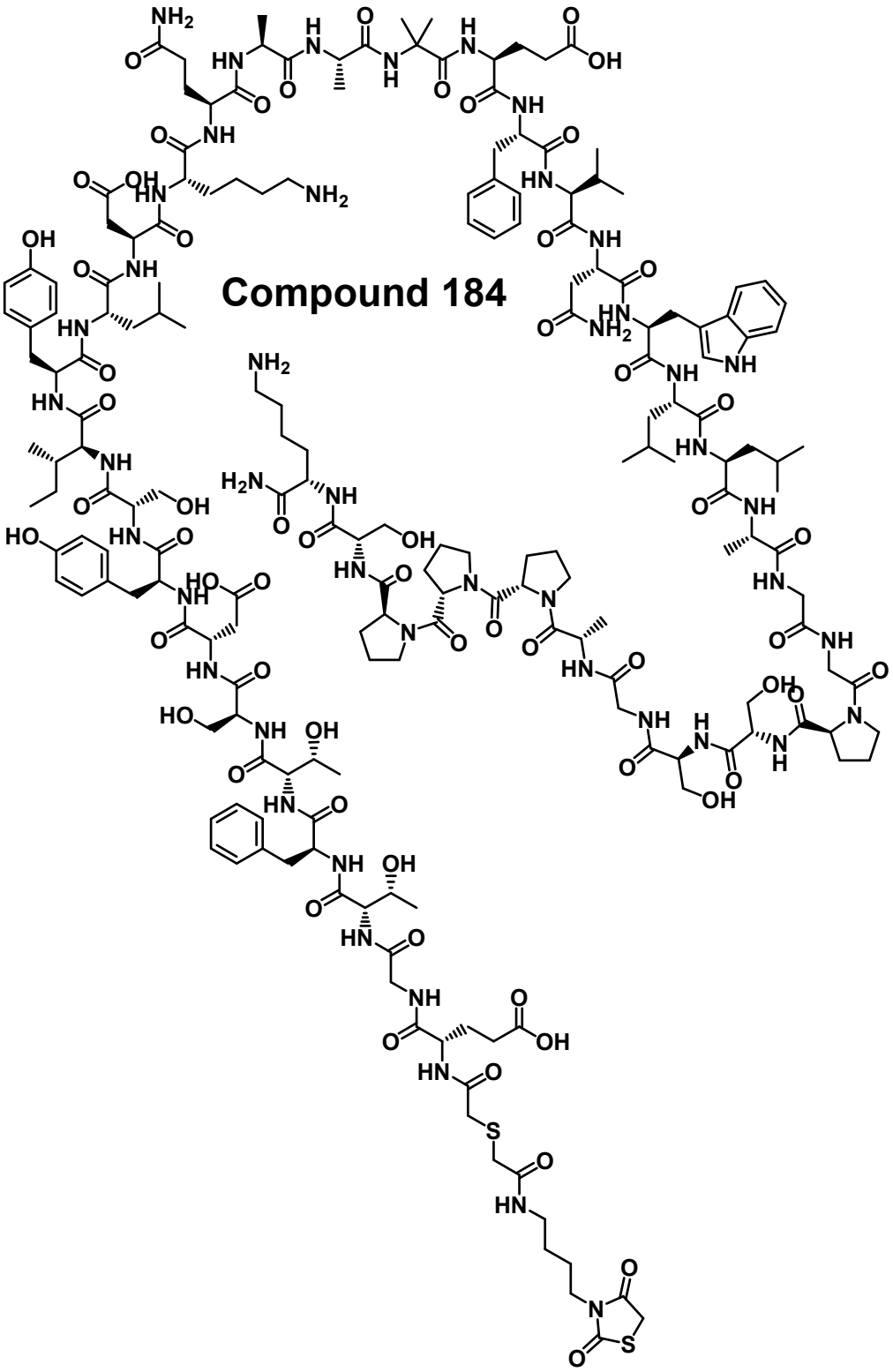

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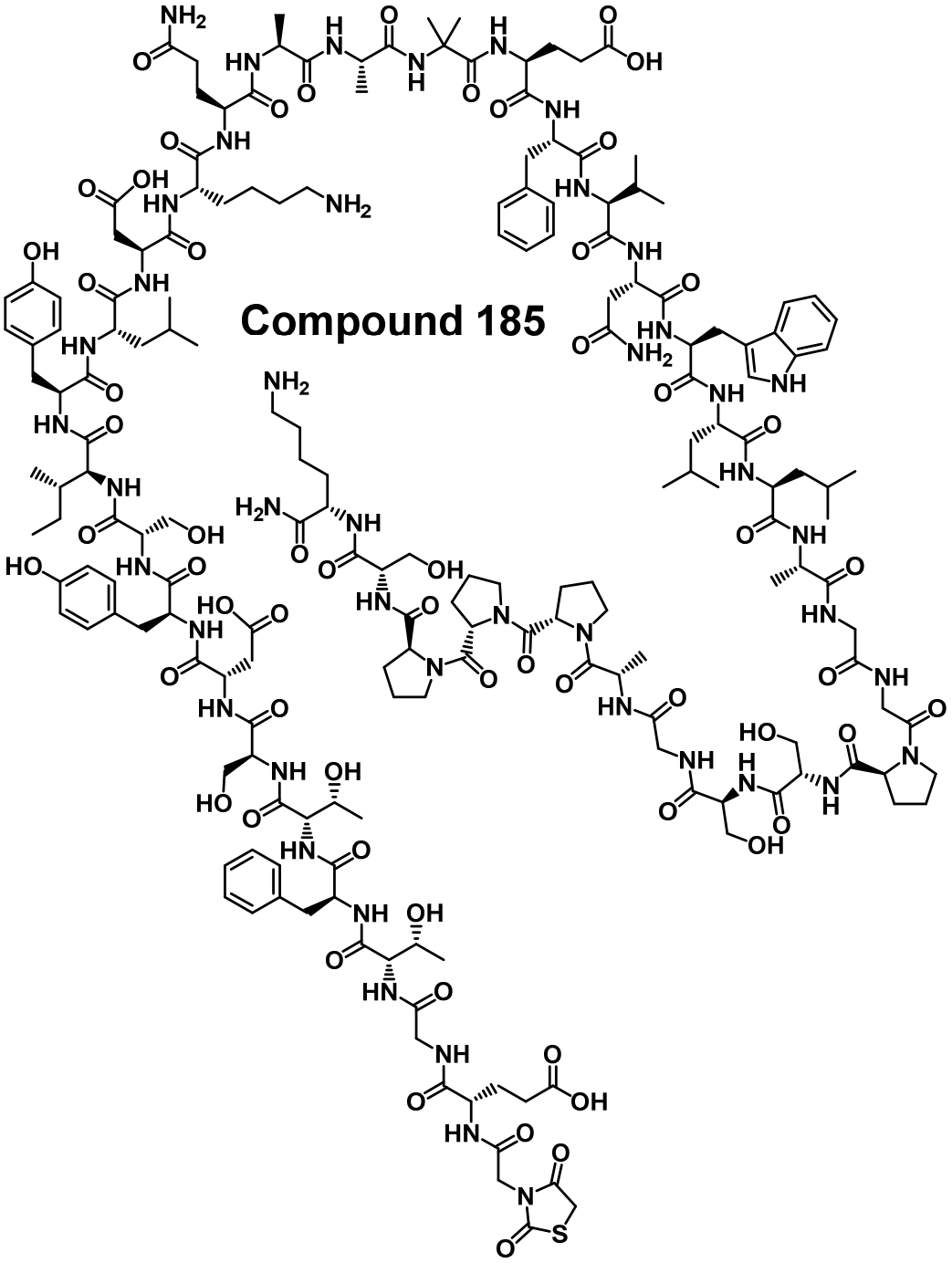

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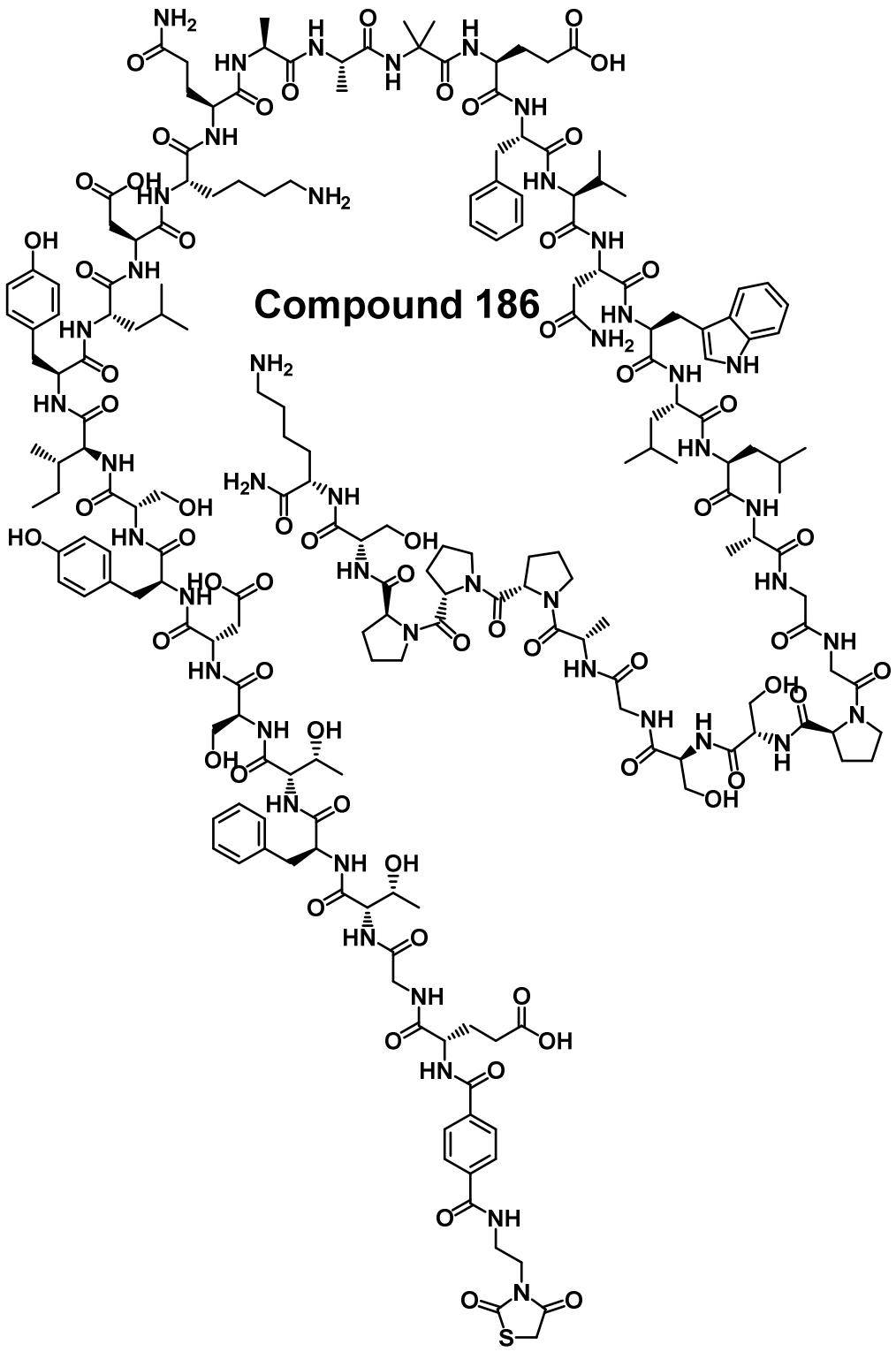

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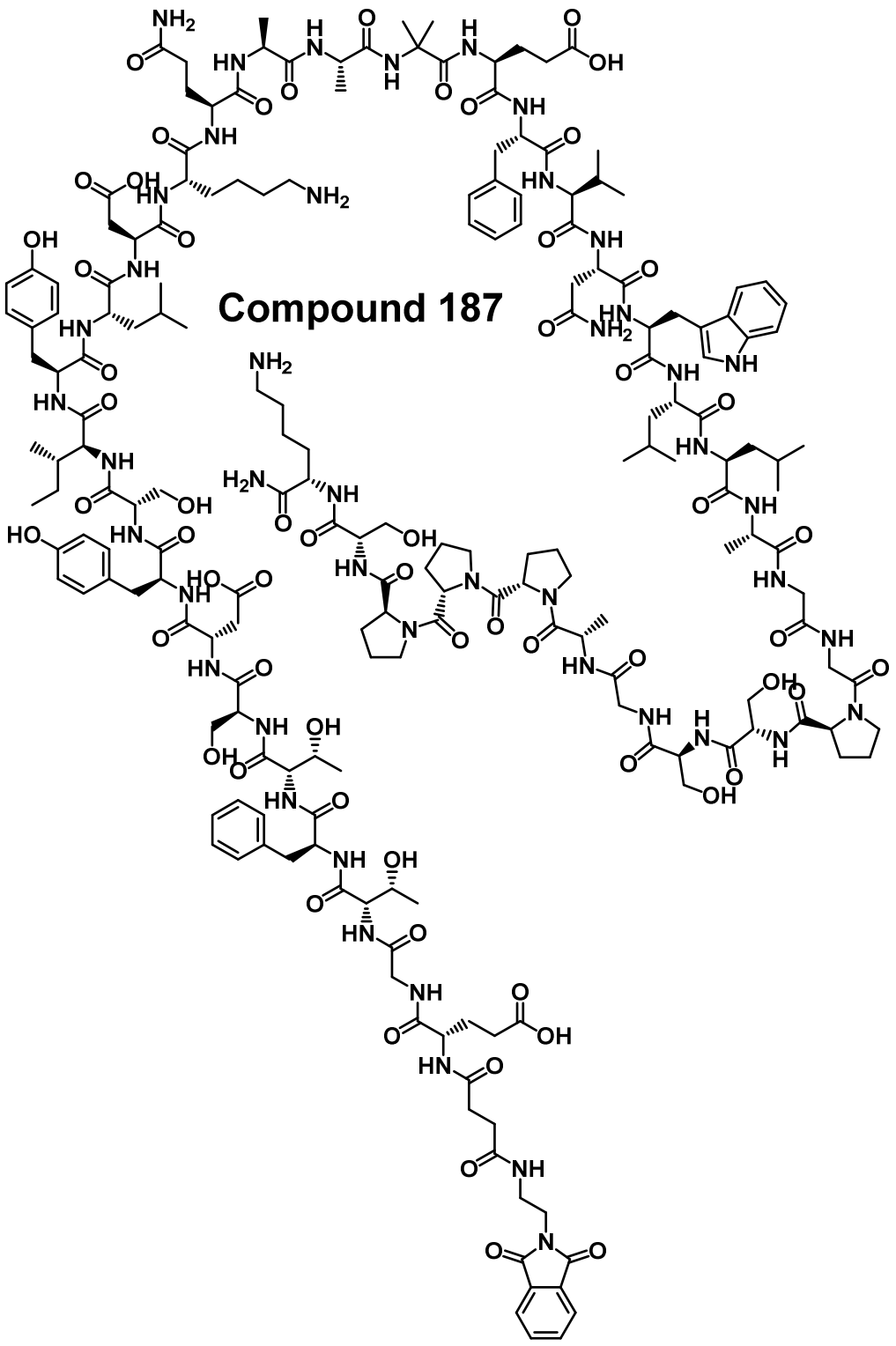

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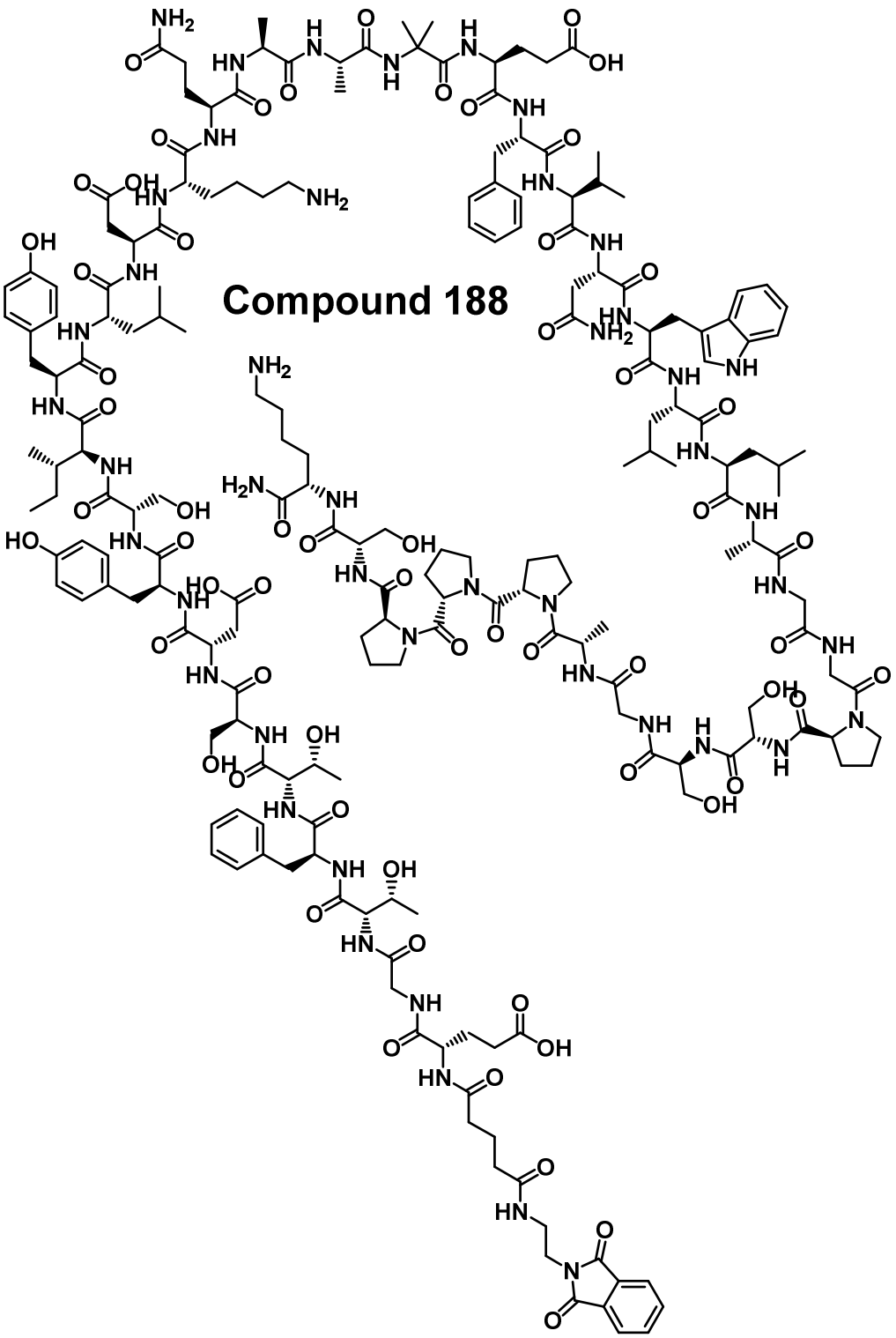

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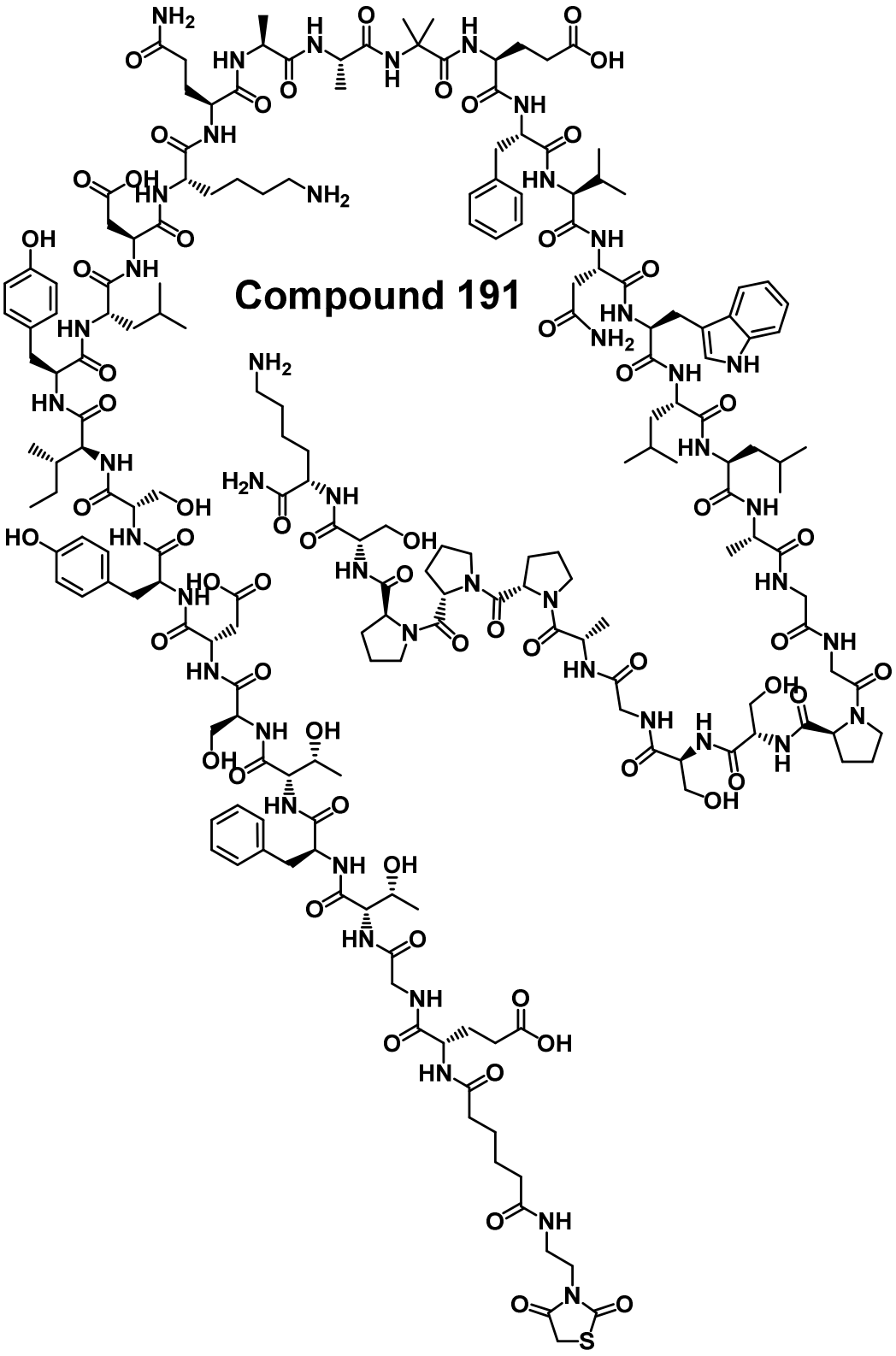

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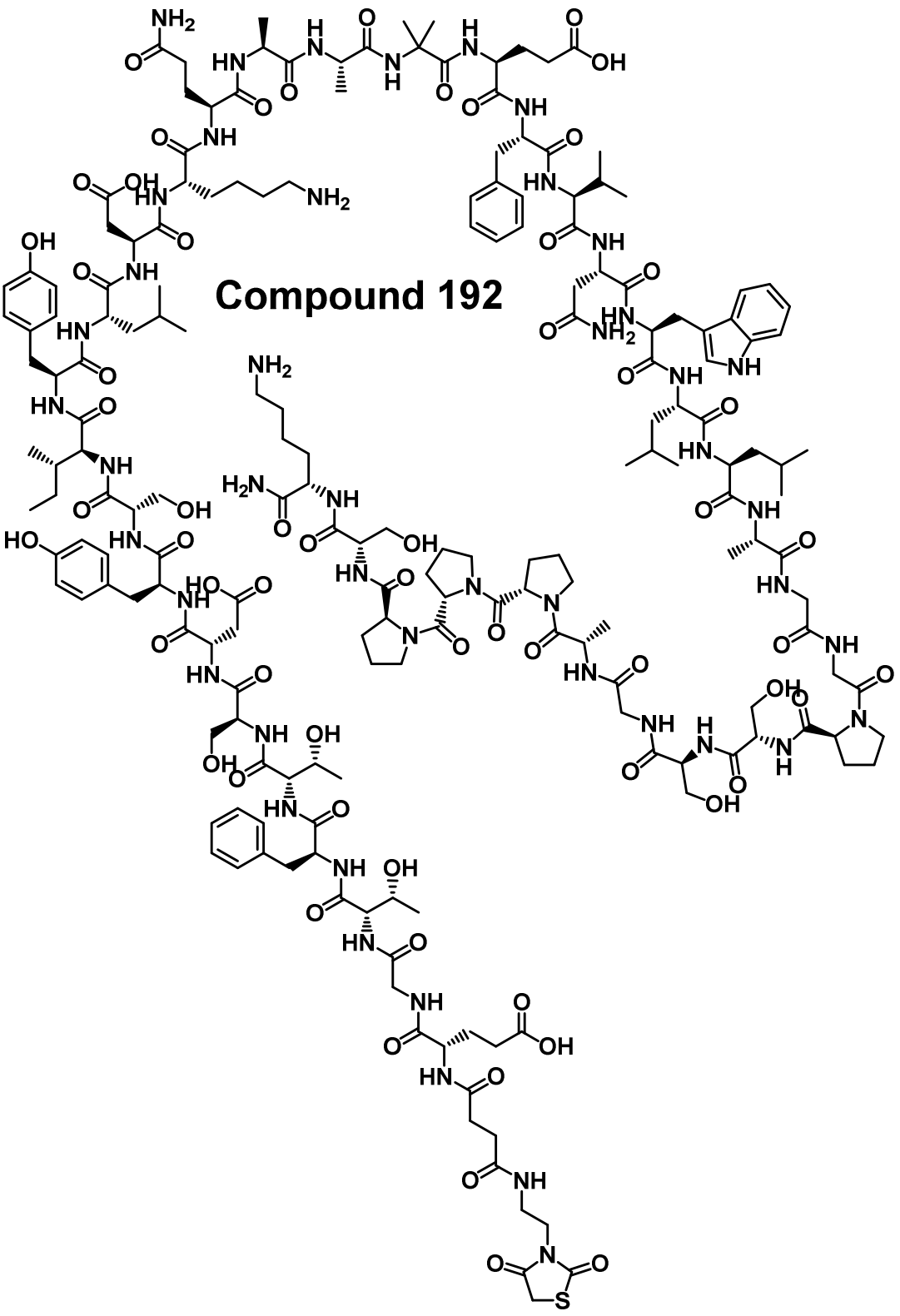

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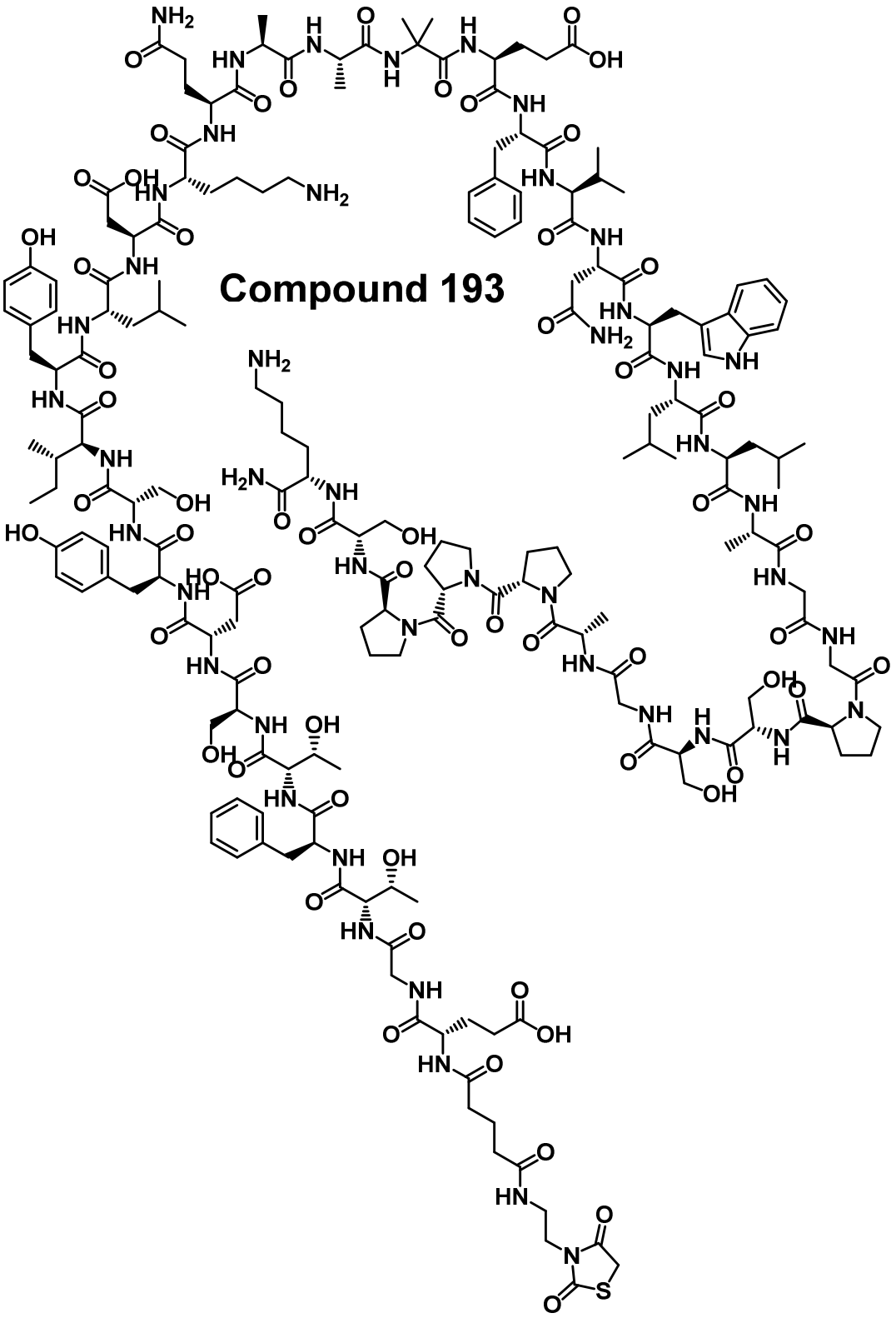

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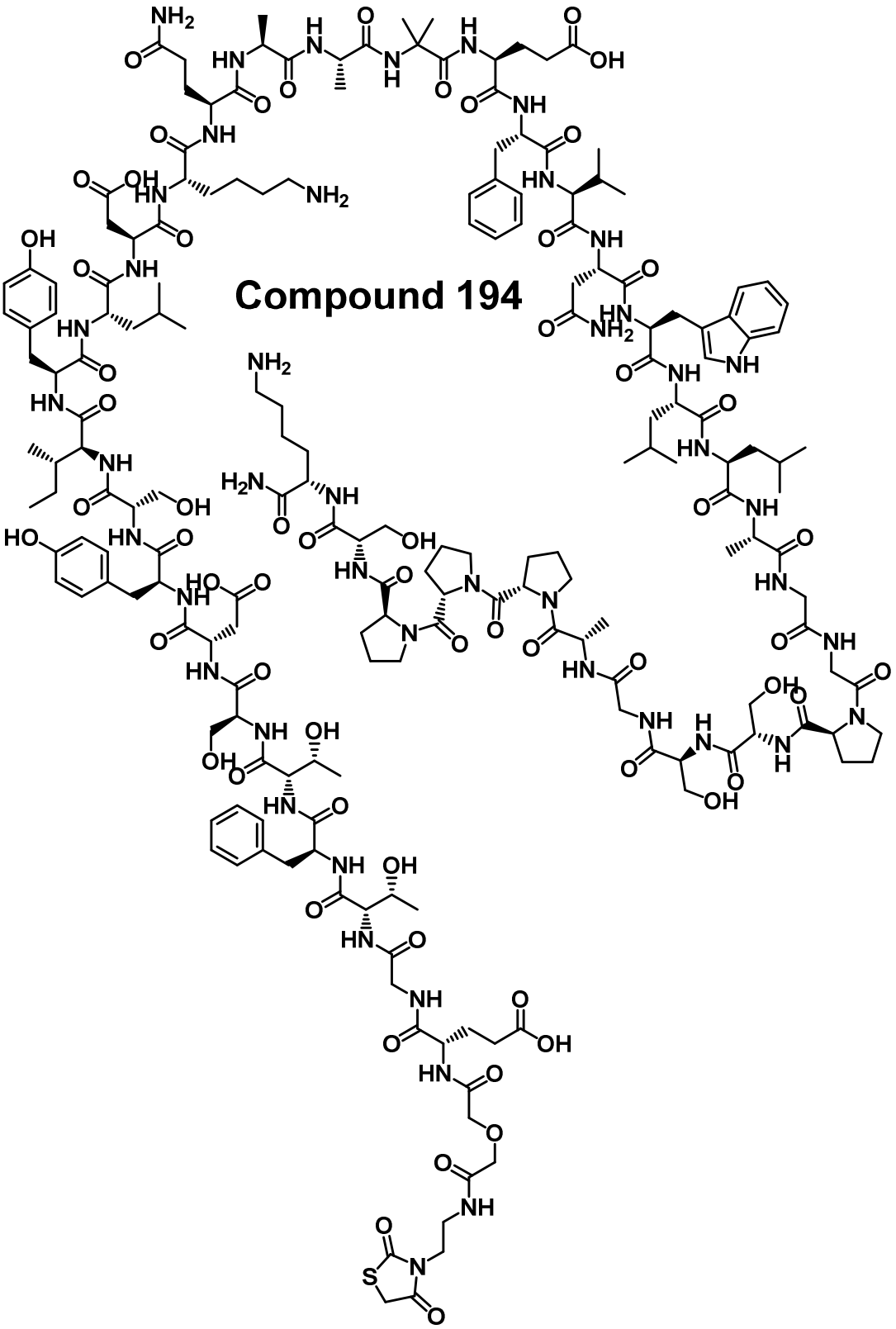

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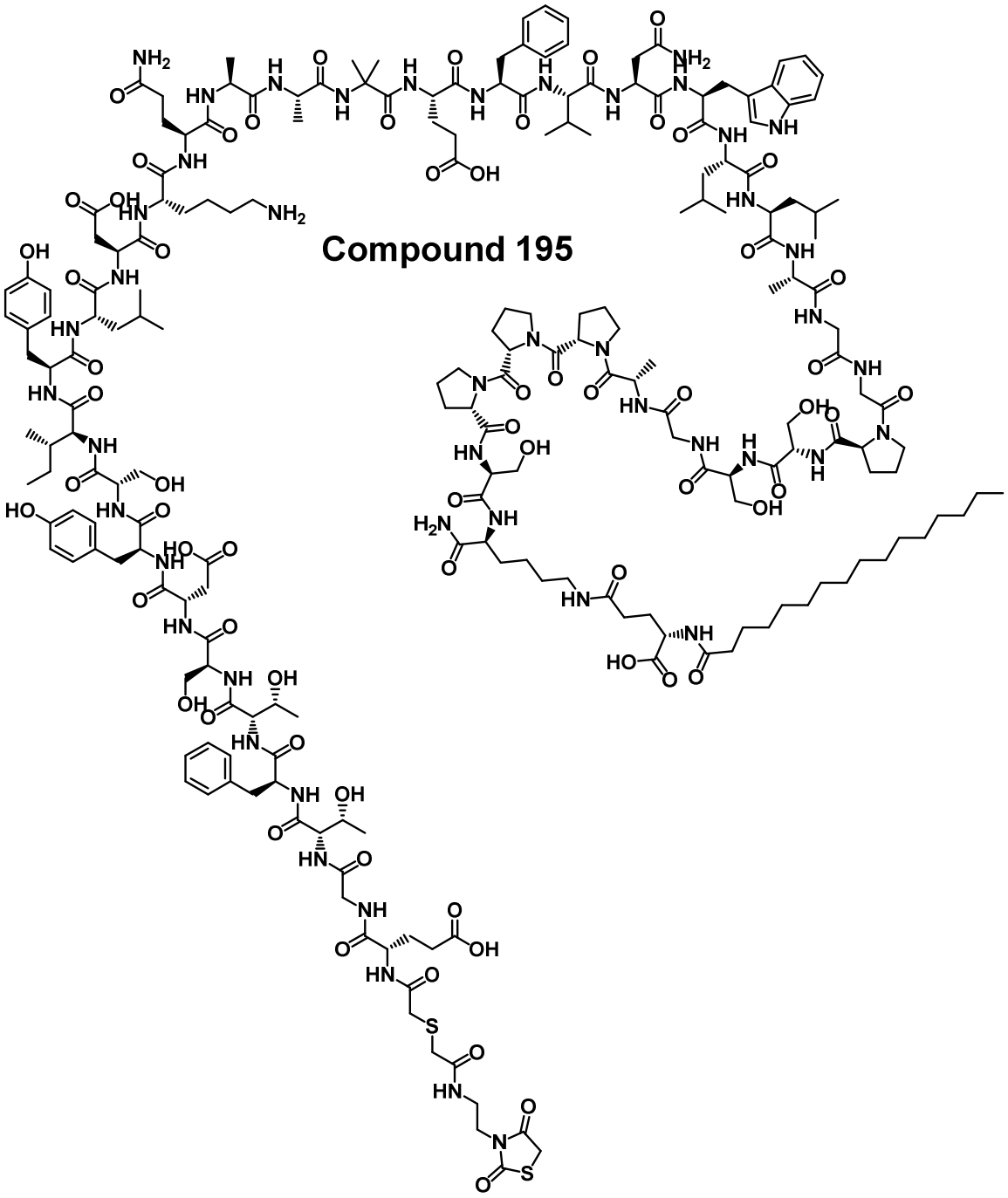

Compound 188


Compound 191

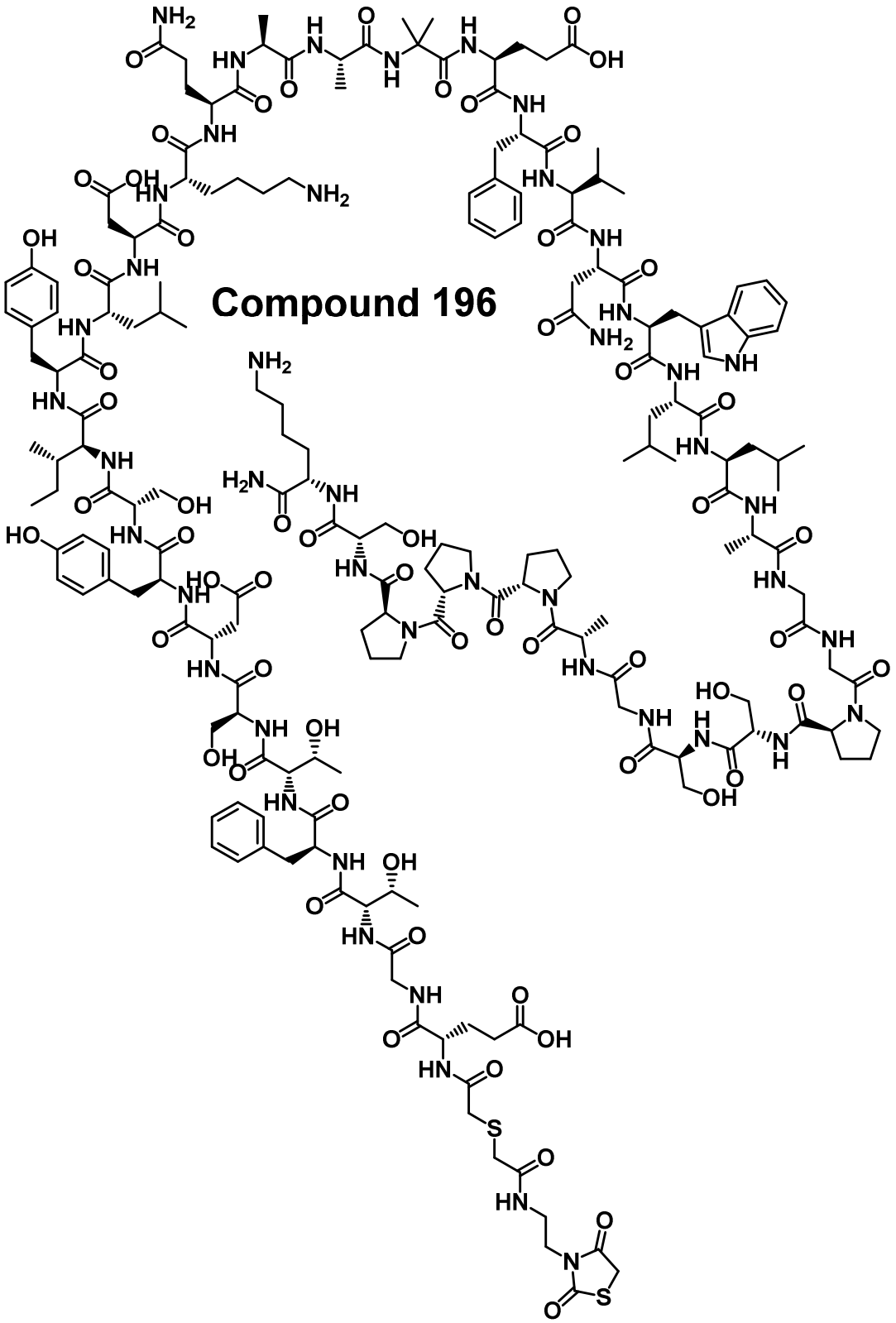

Compound 192

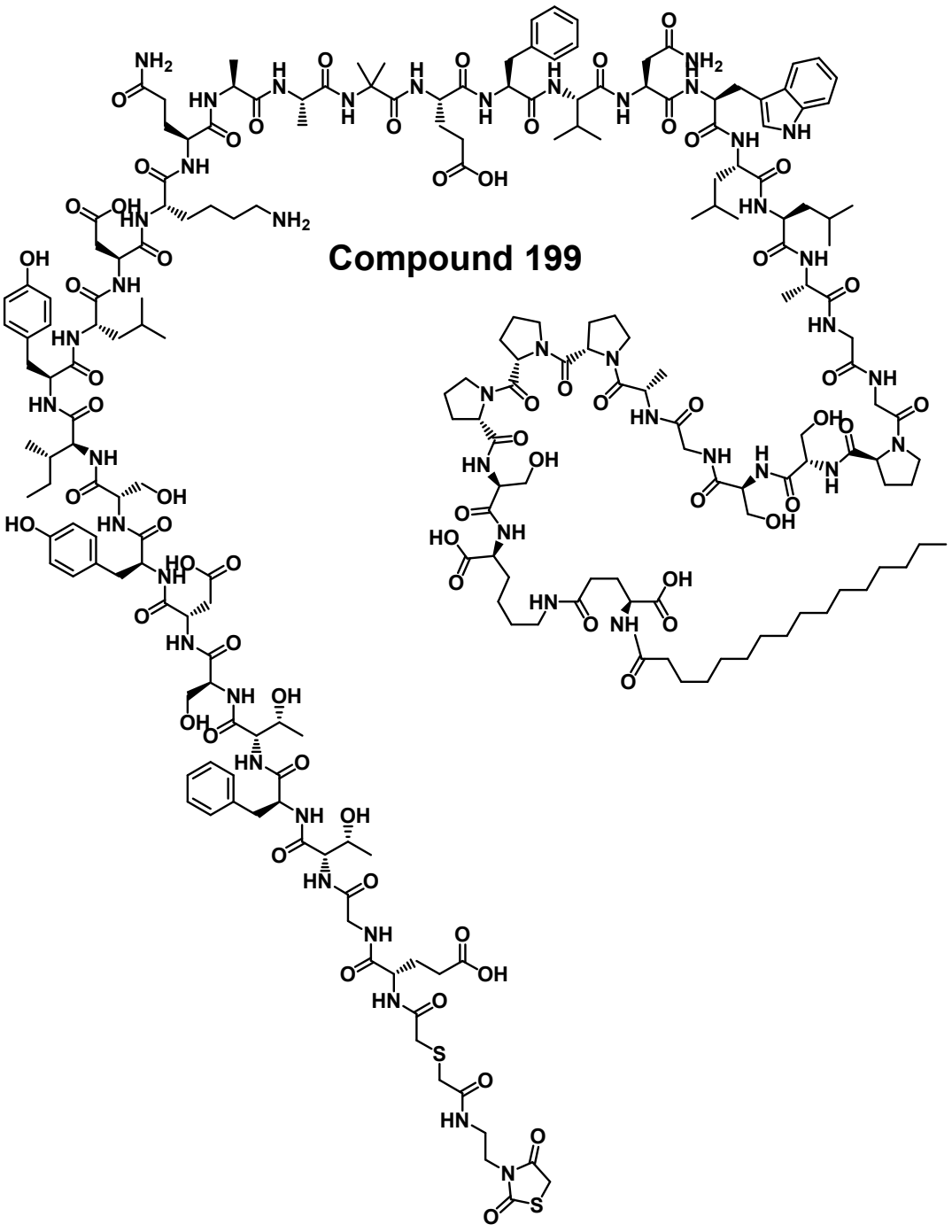

Compound 193


Compound 194

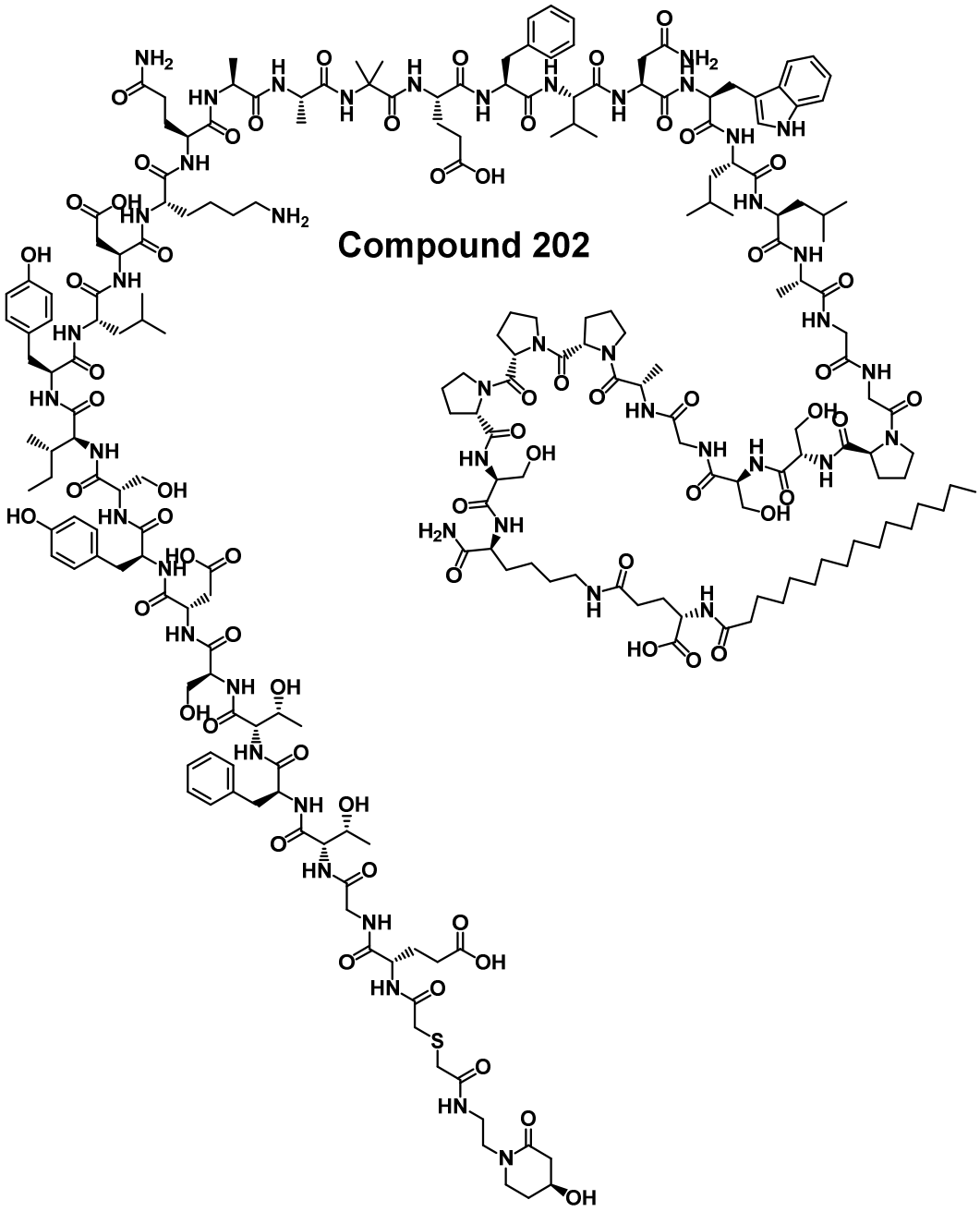


Compound 195

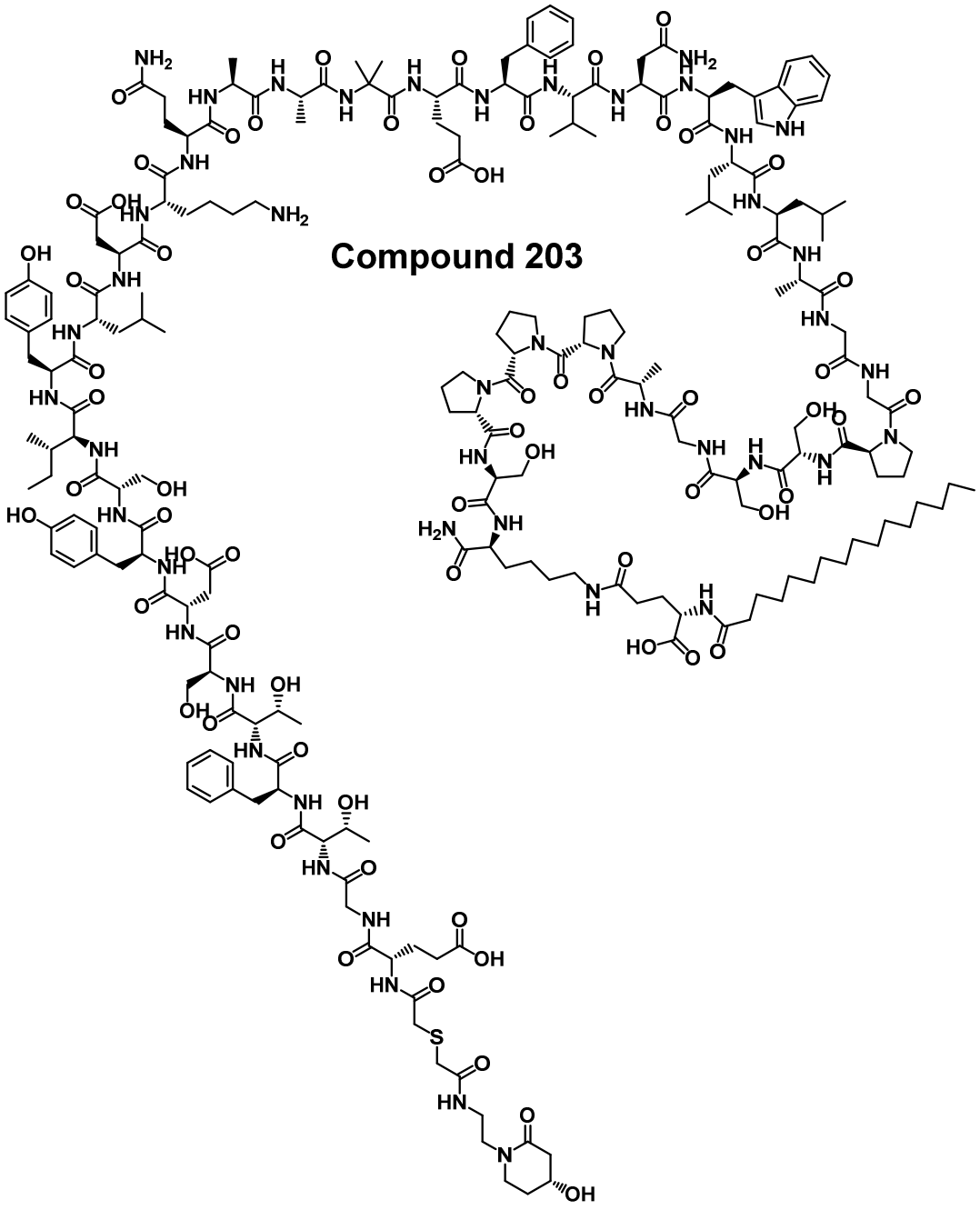

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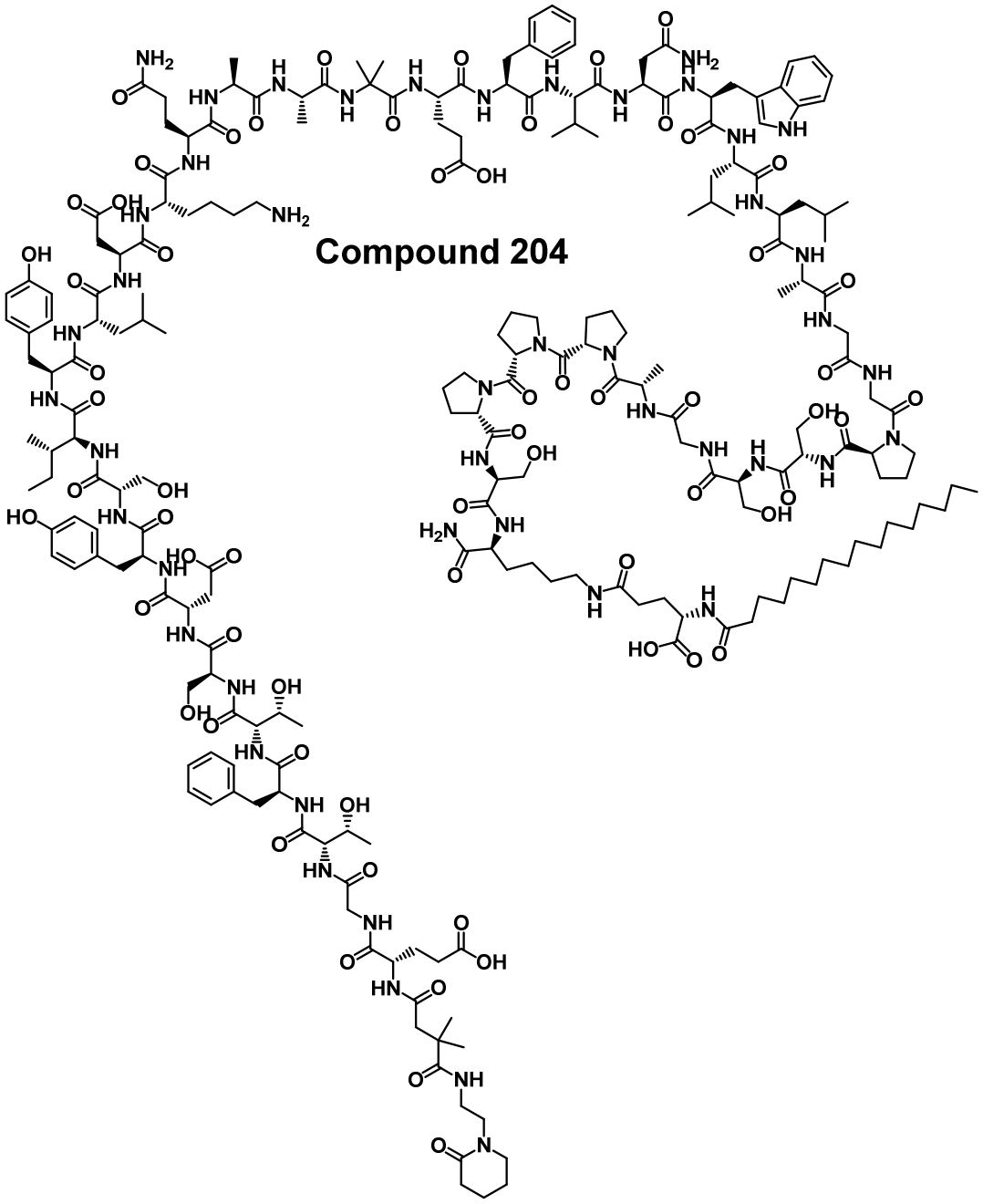
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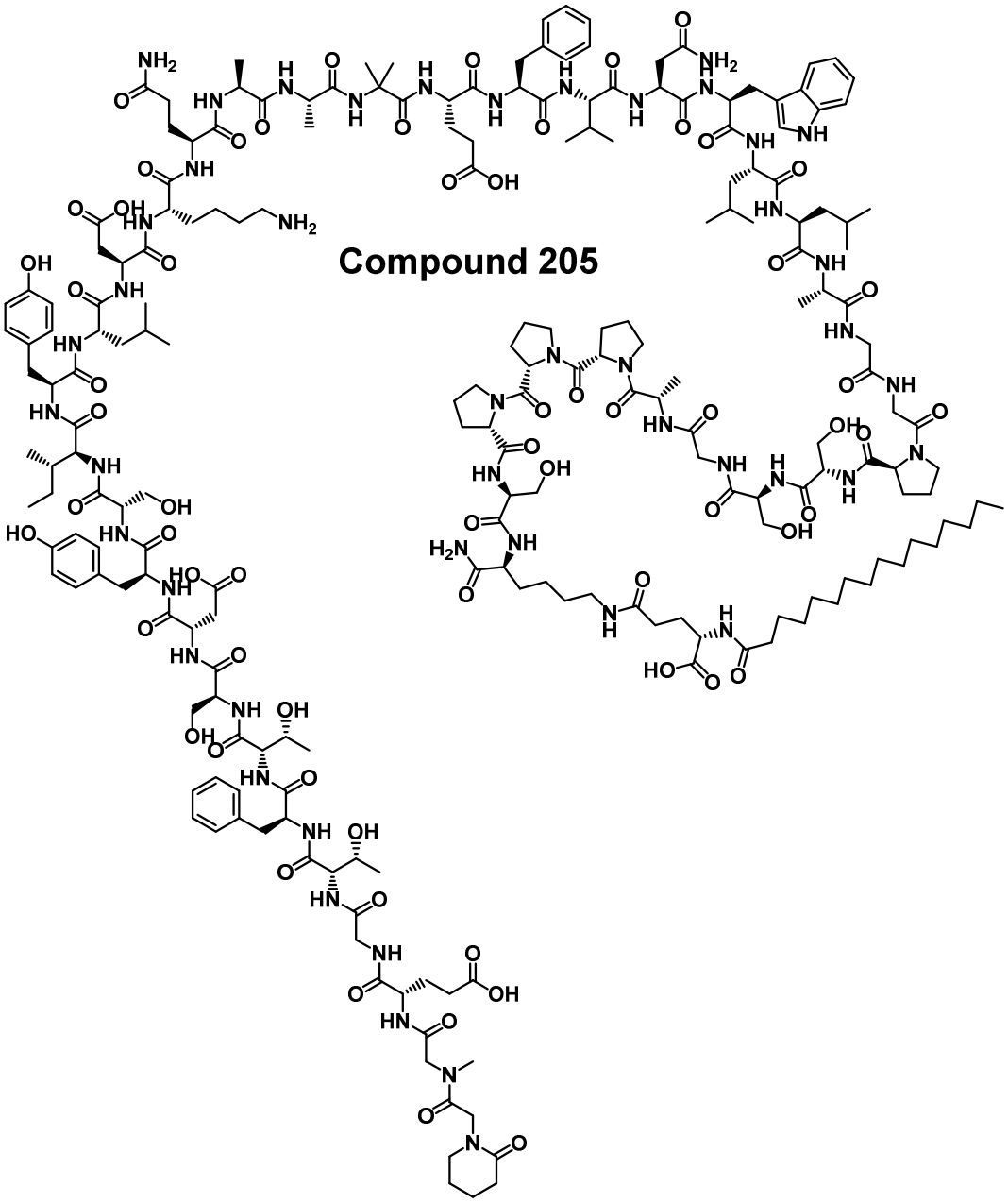


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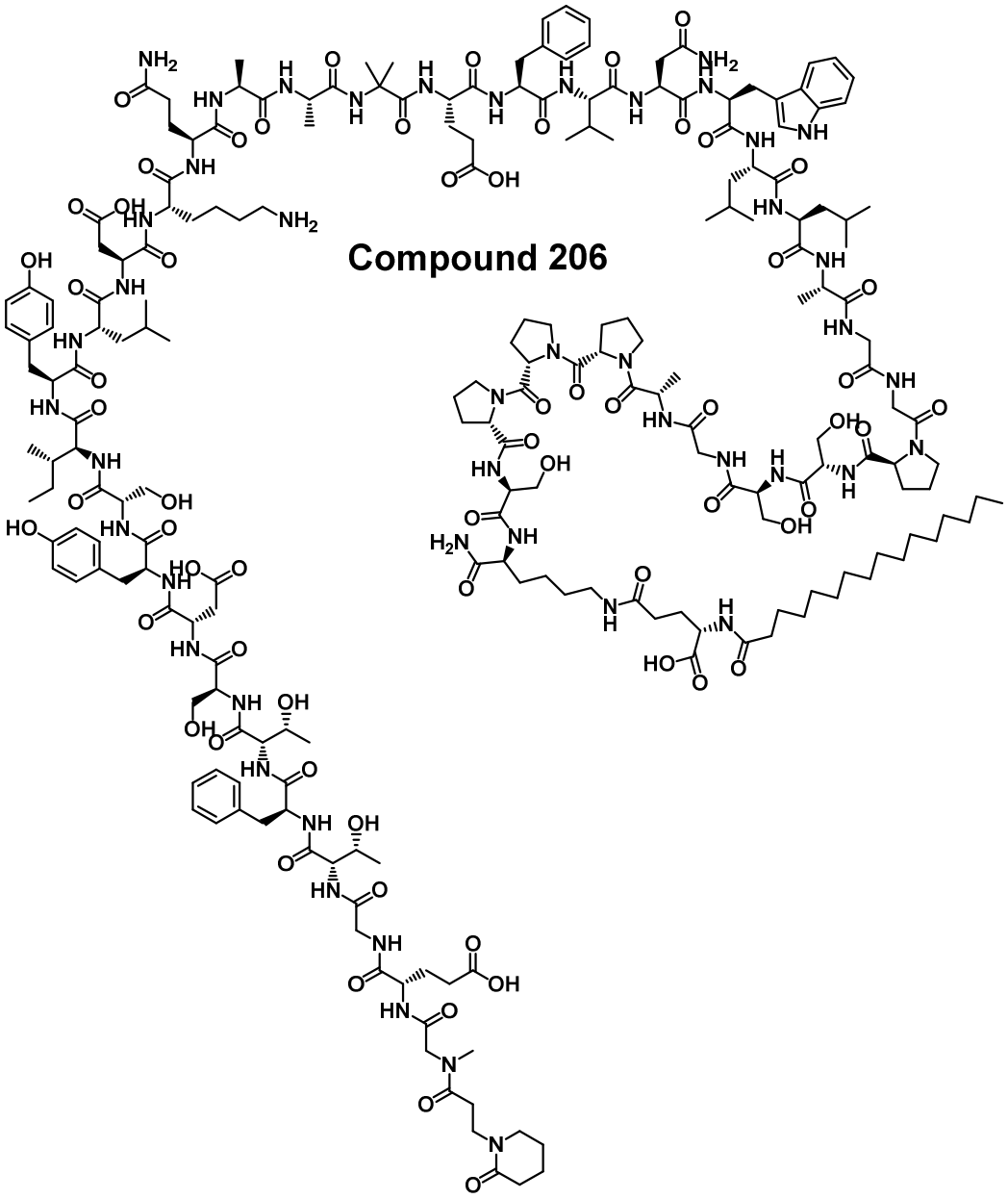


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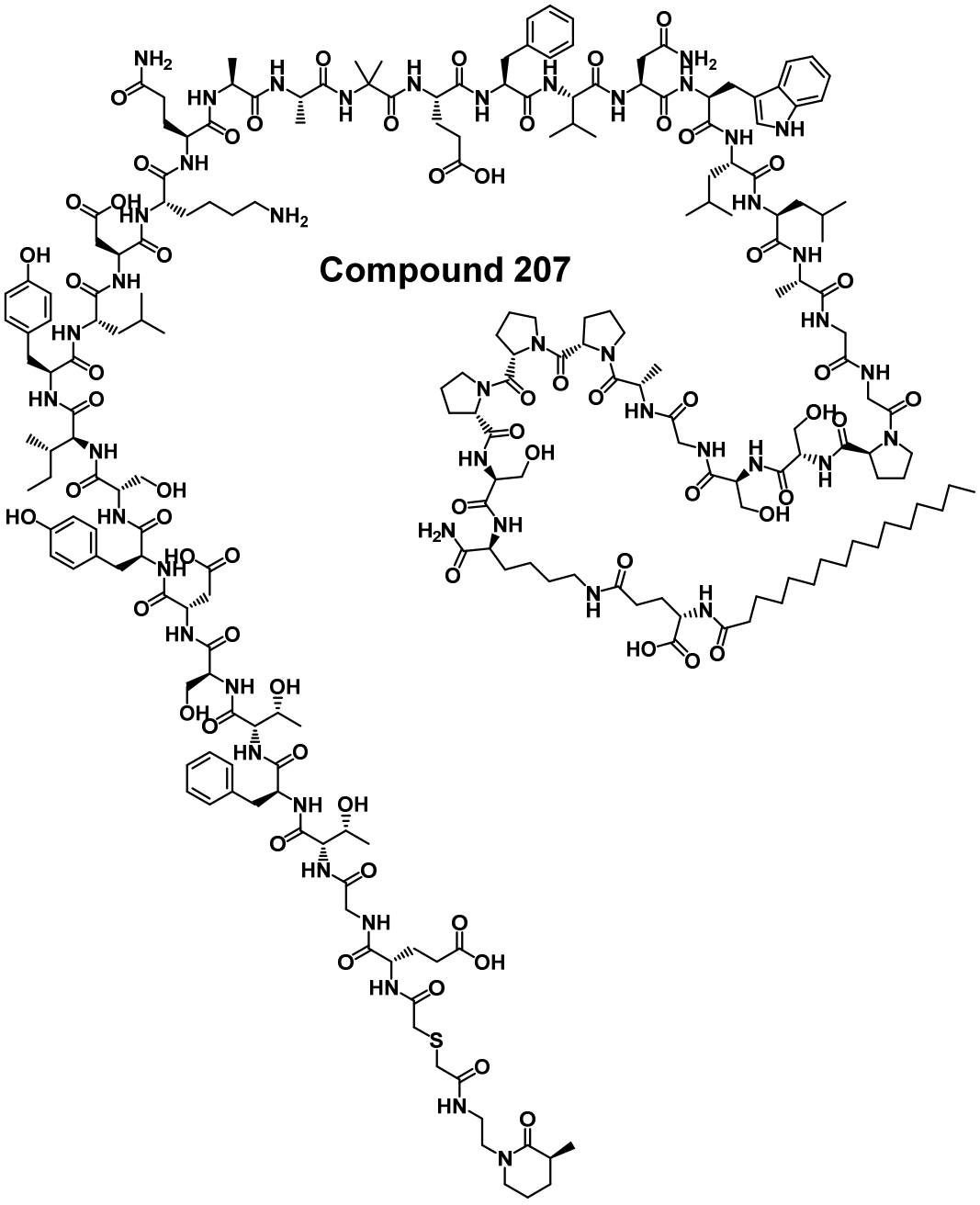

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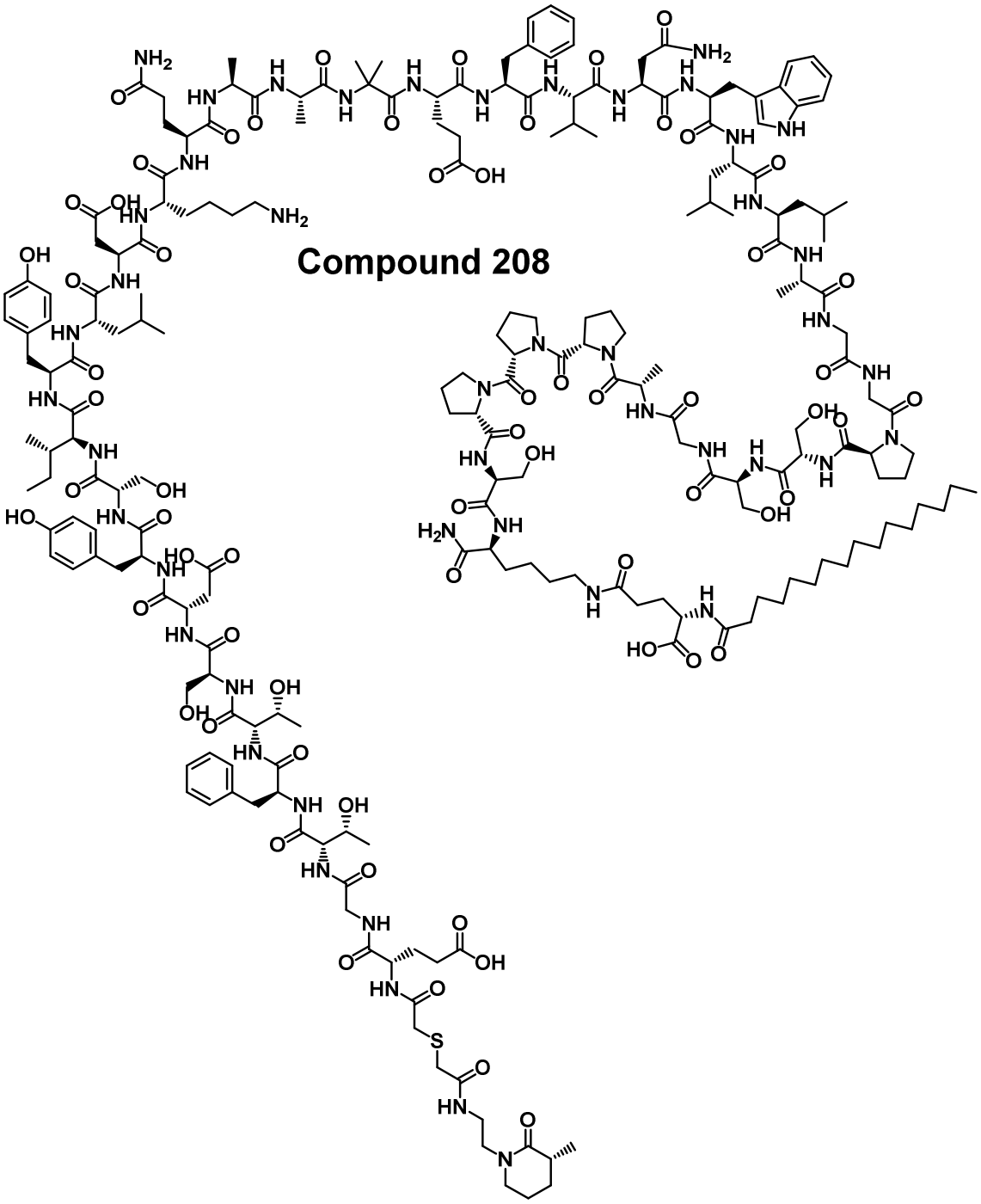
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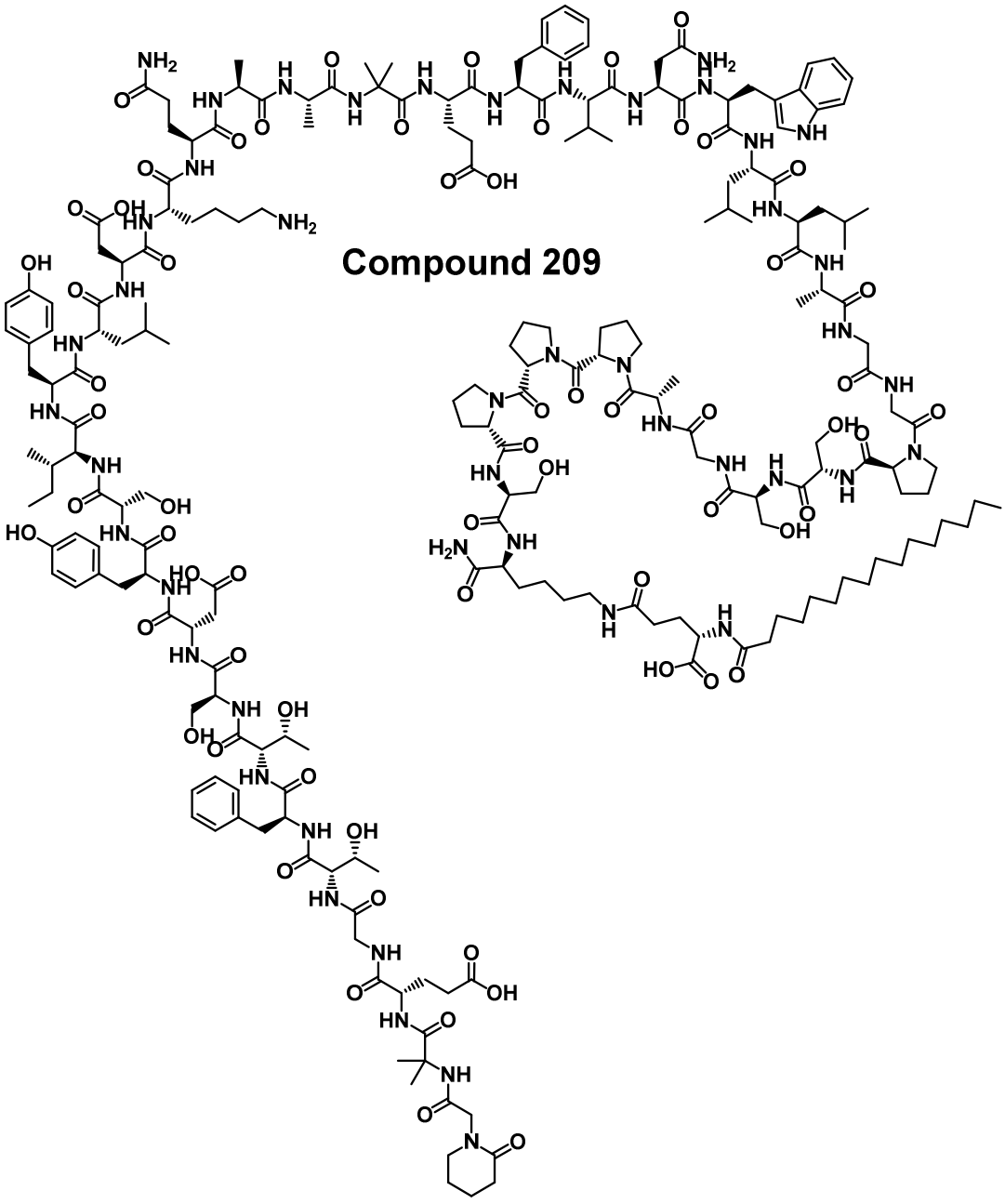
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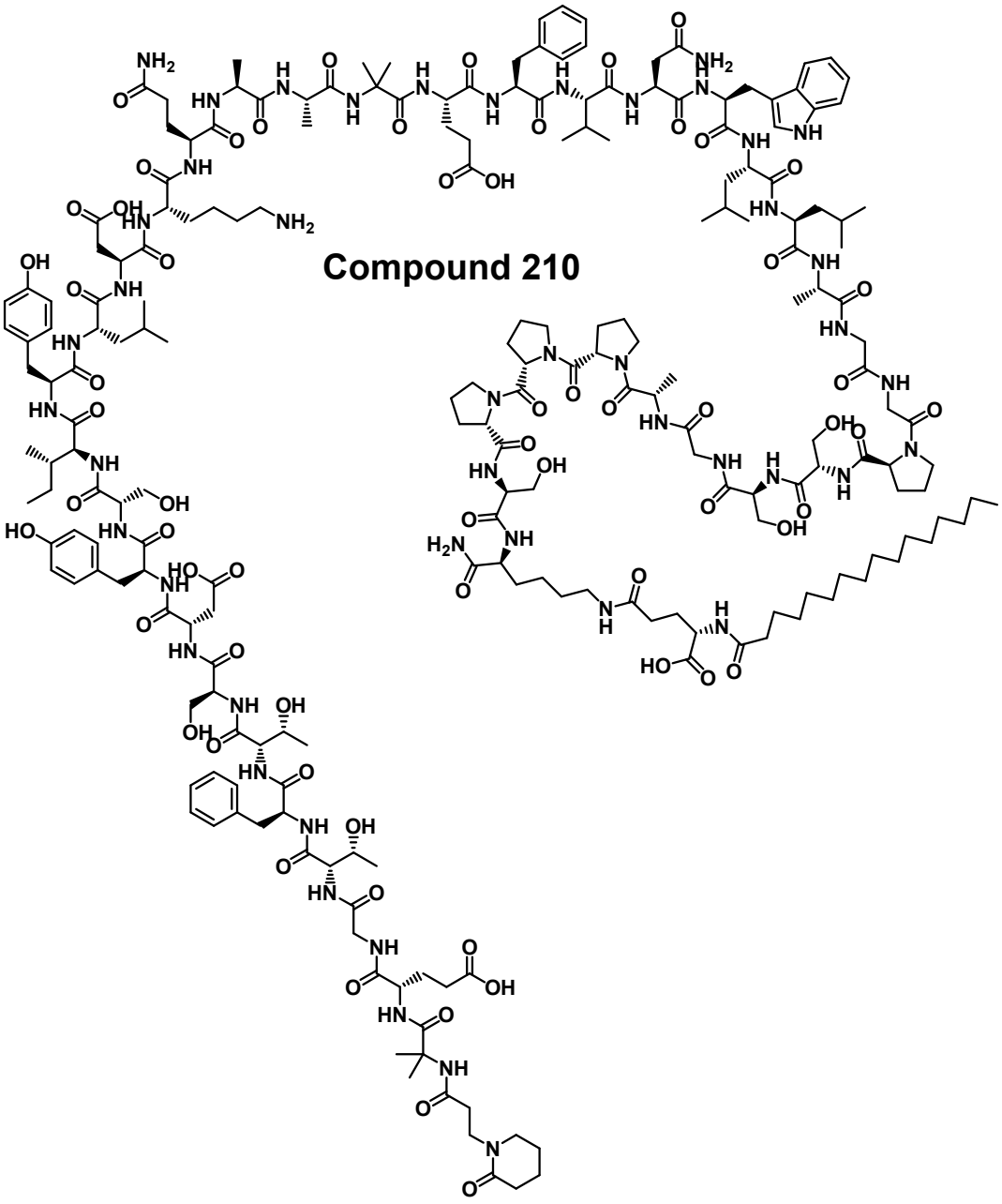


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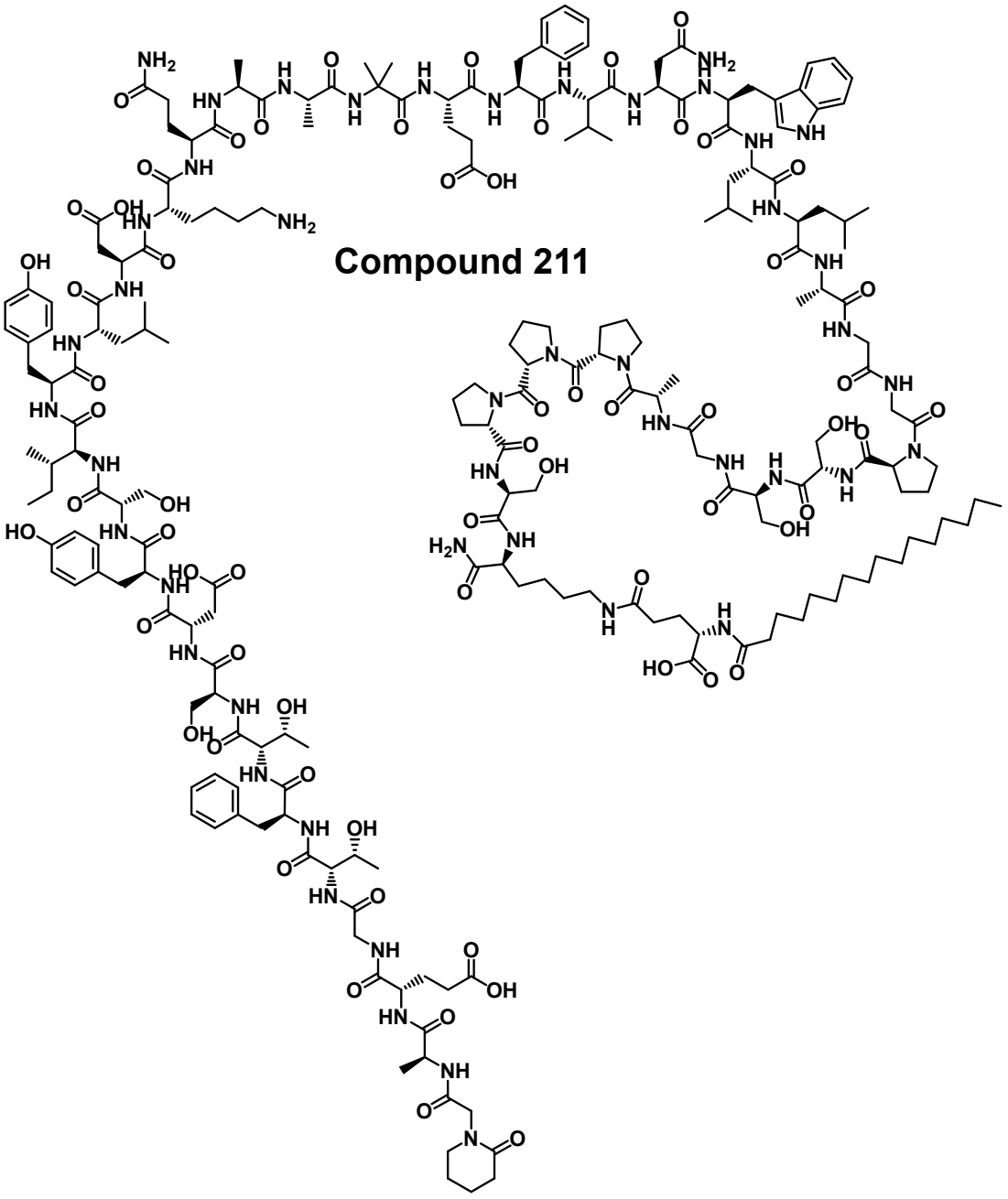


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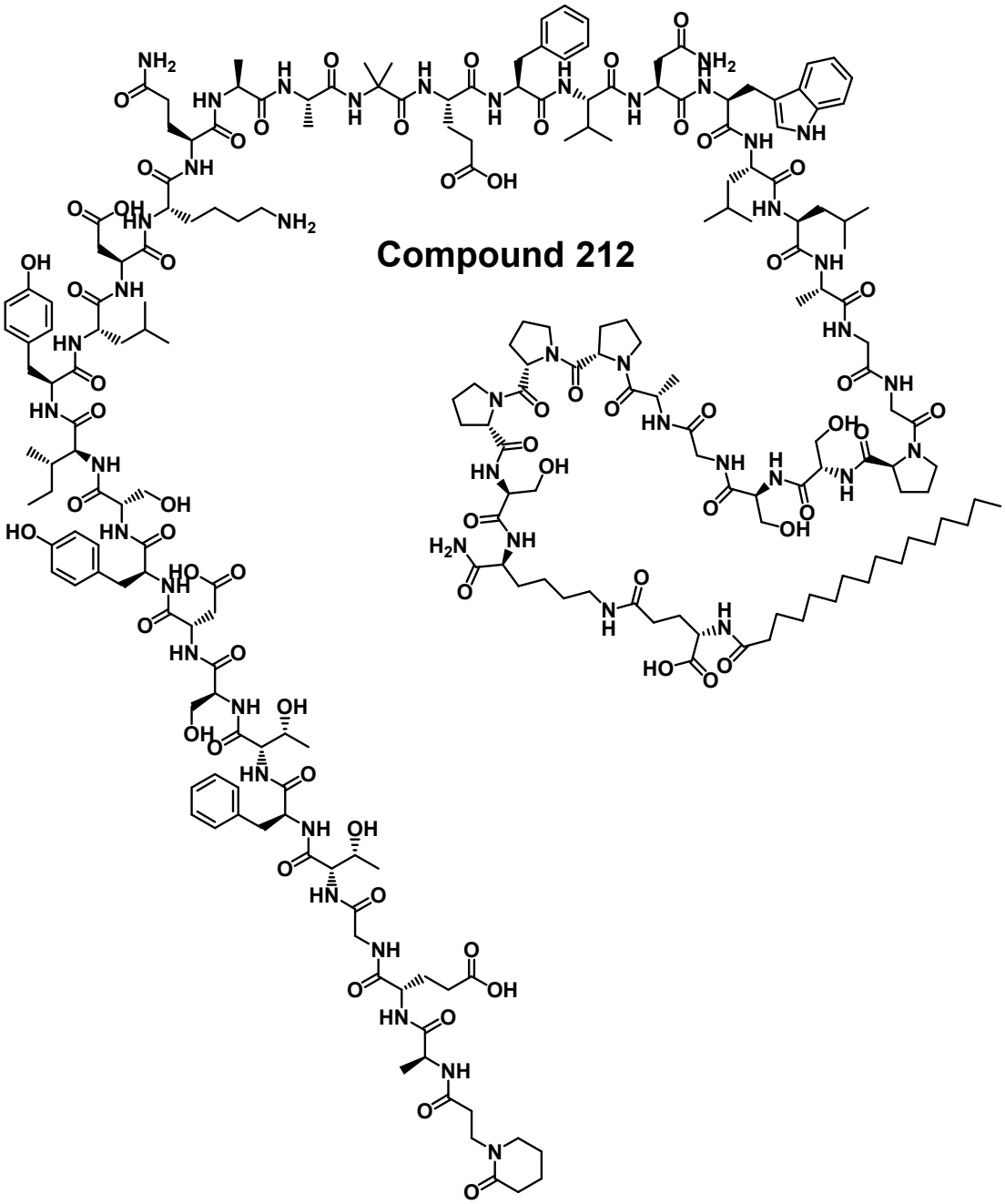

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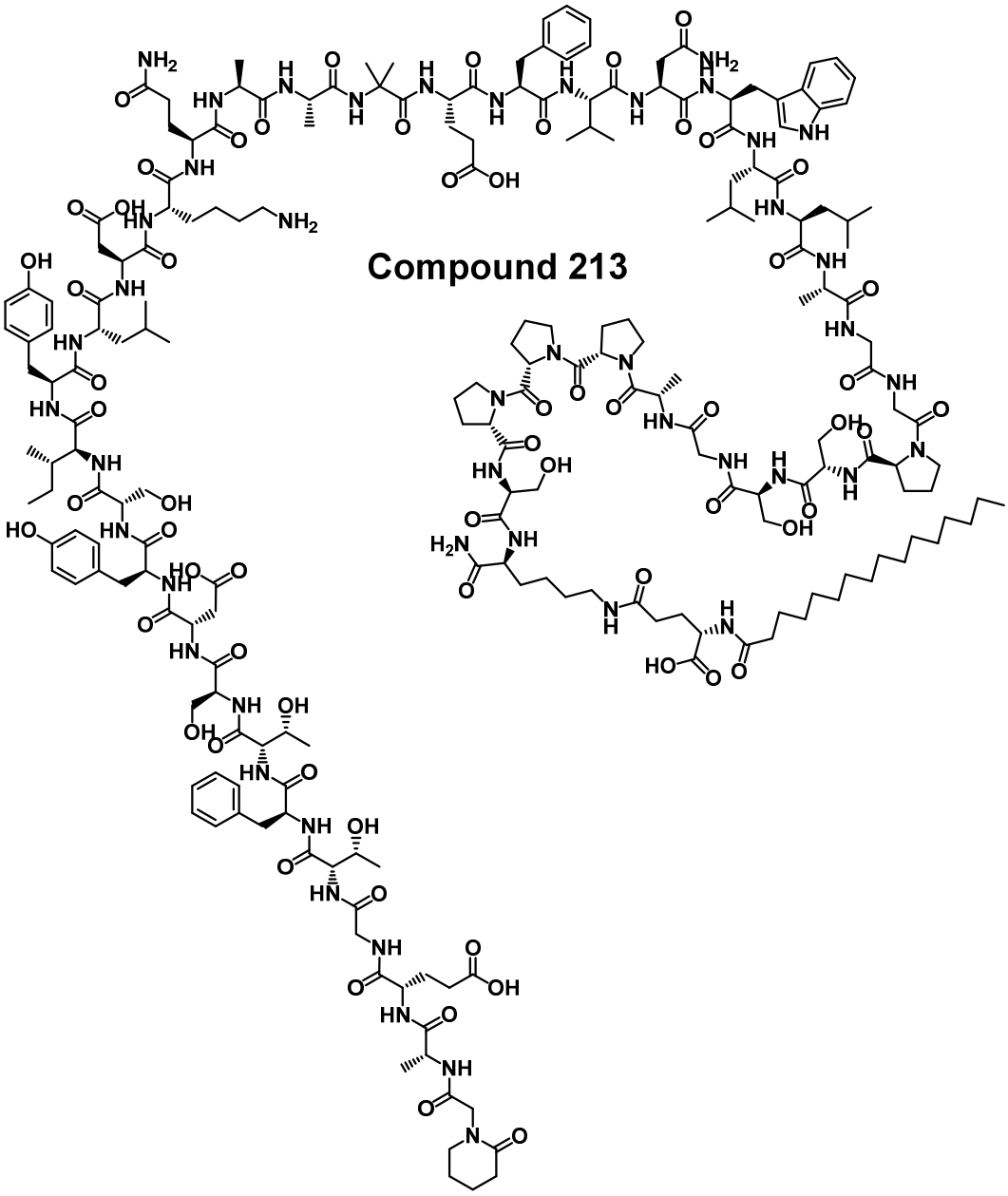
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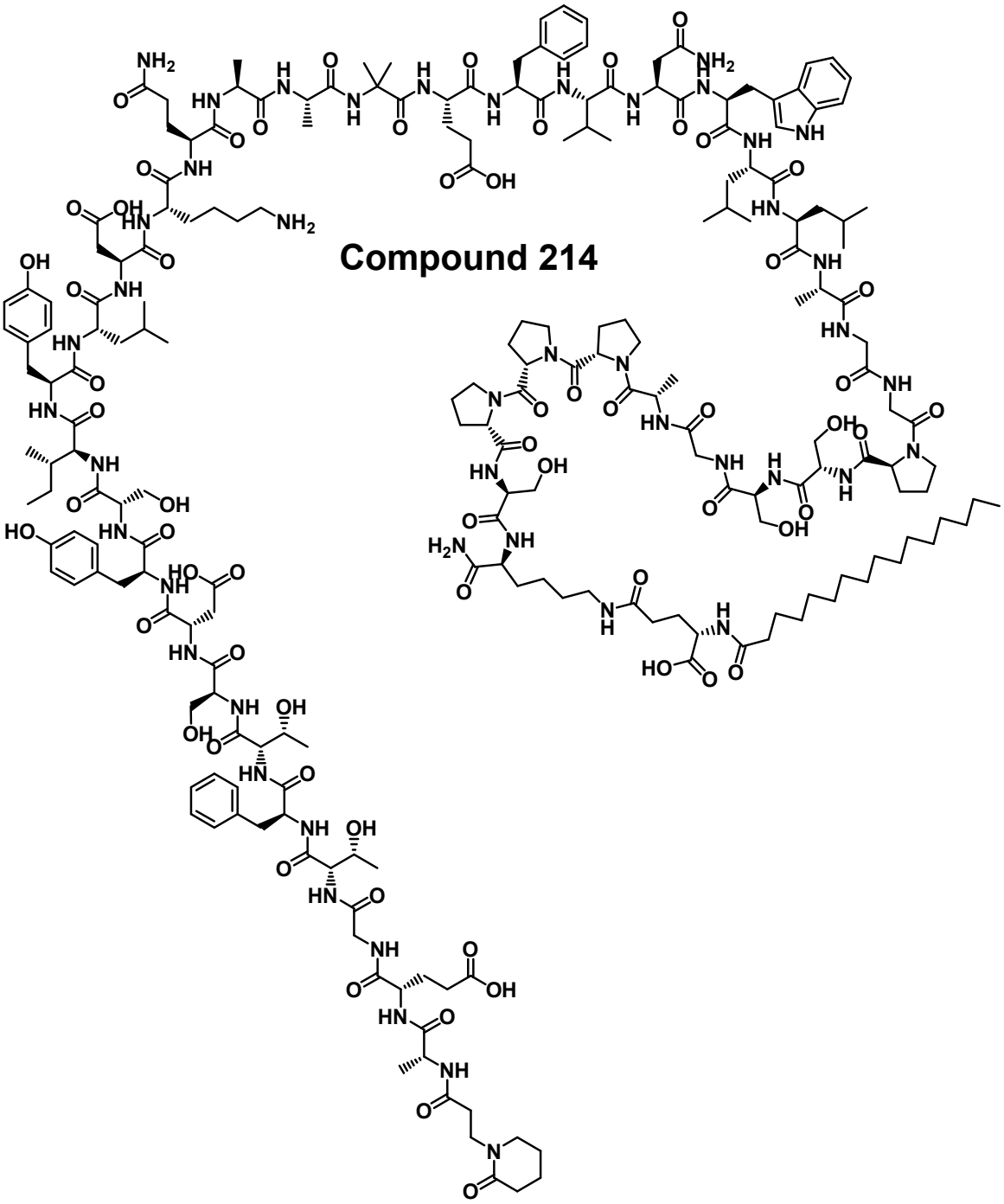


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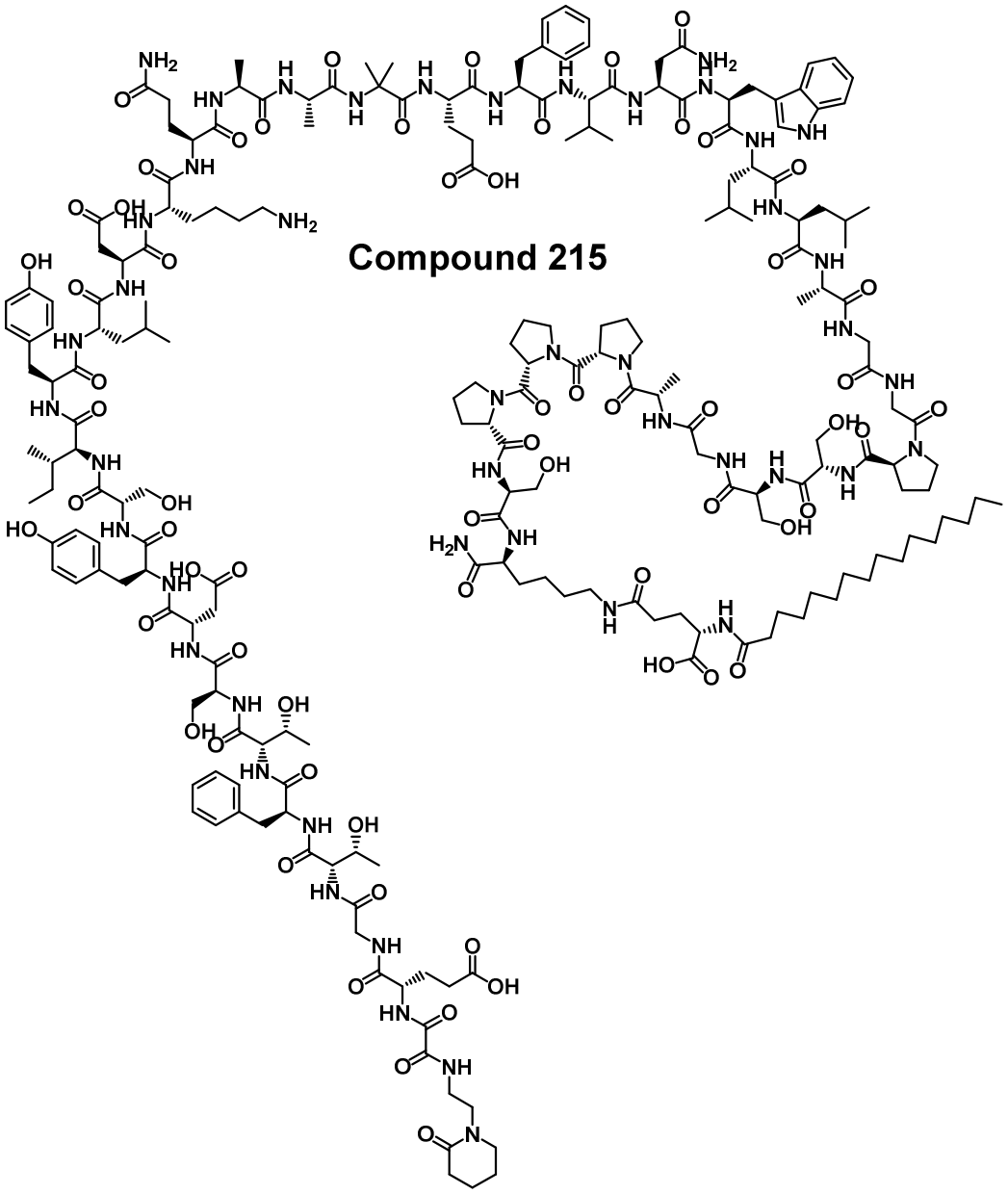


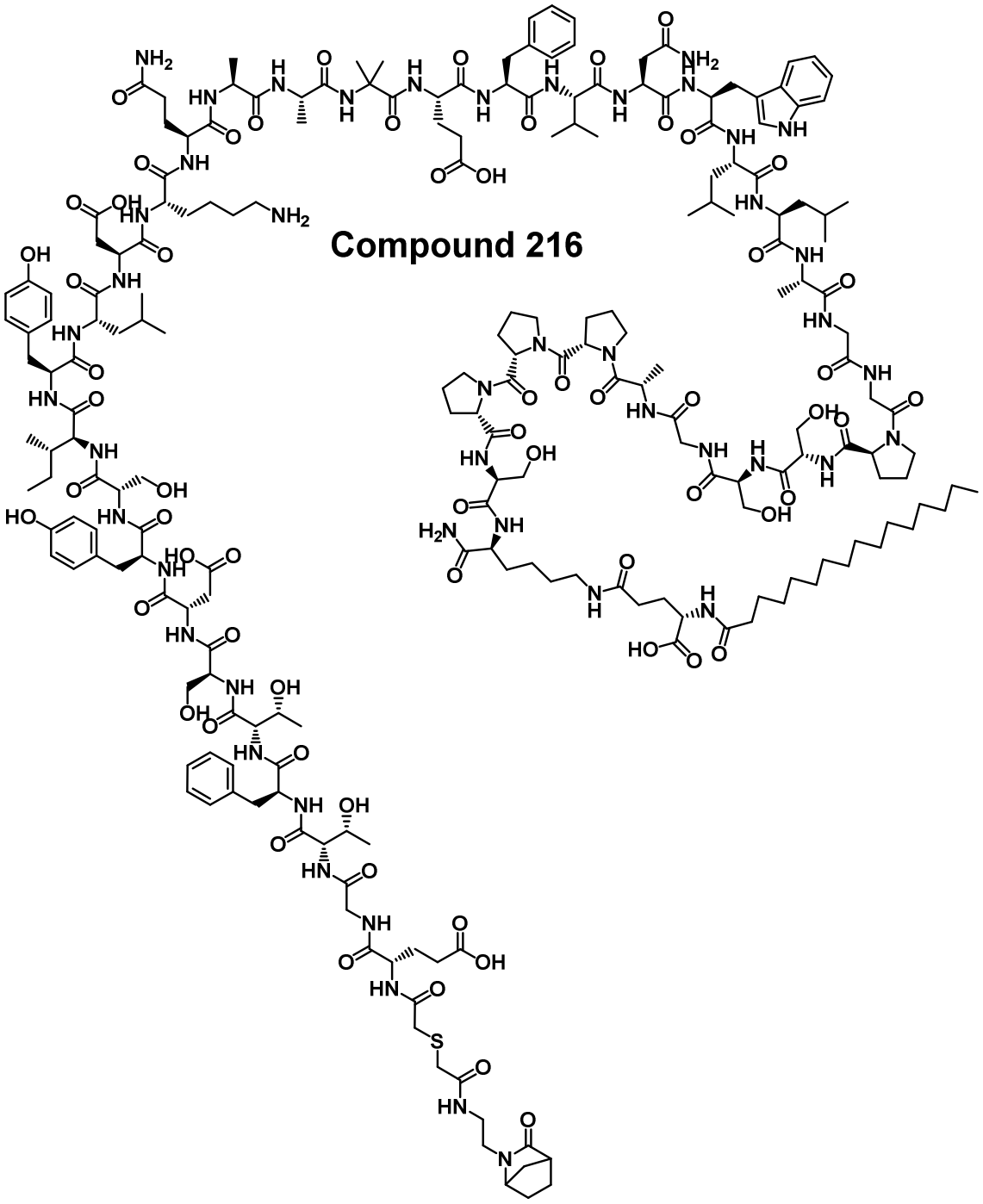
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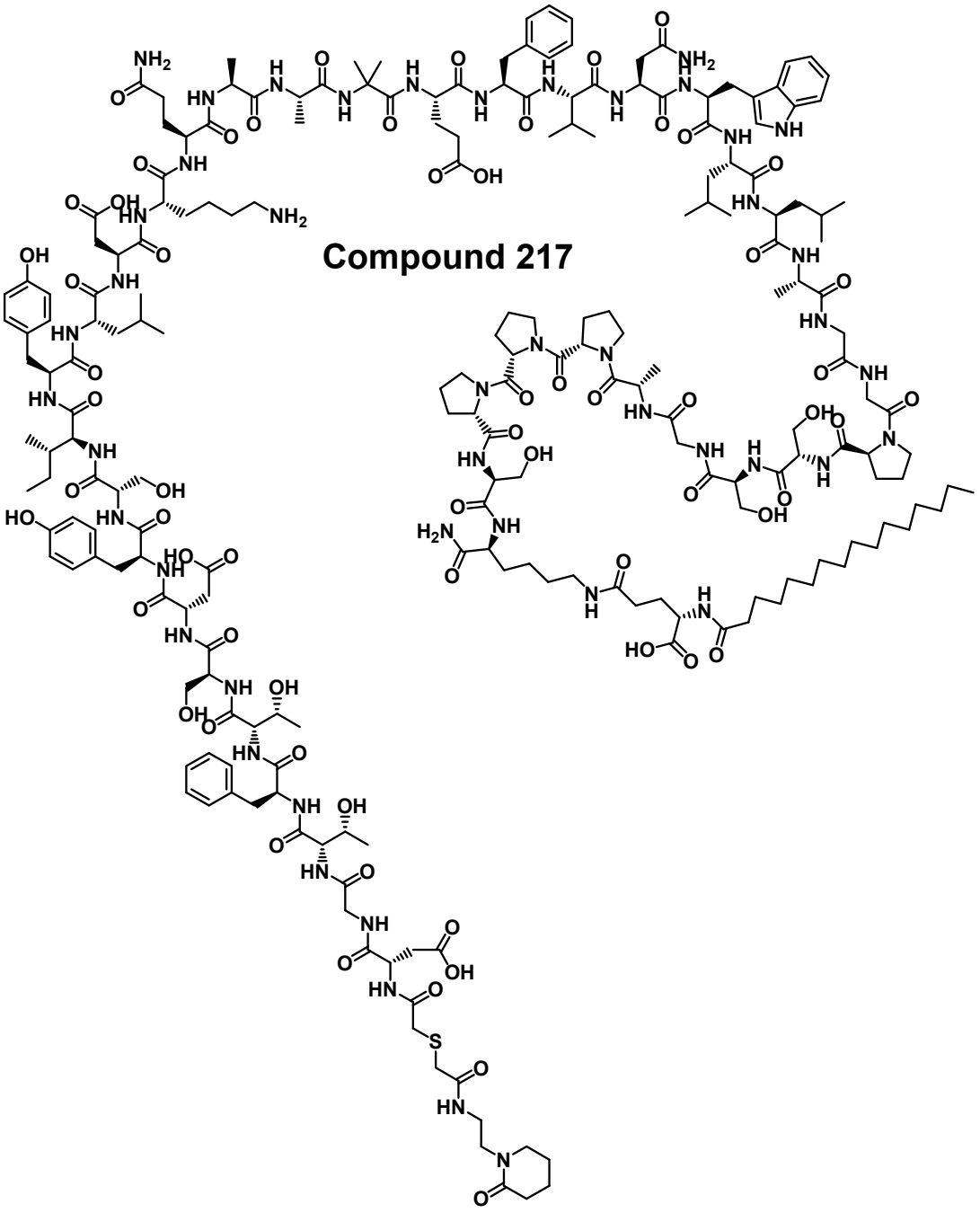

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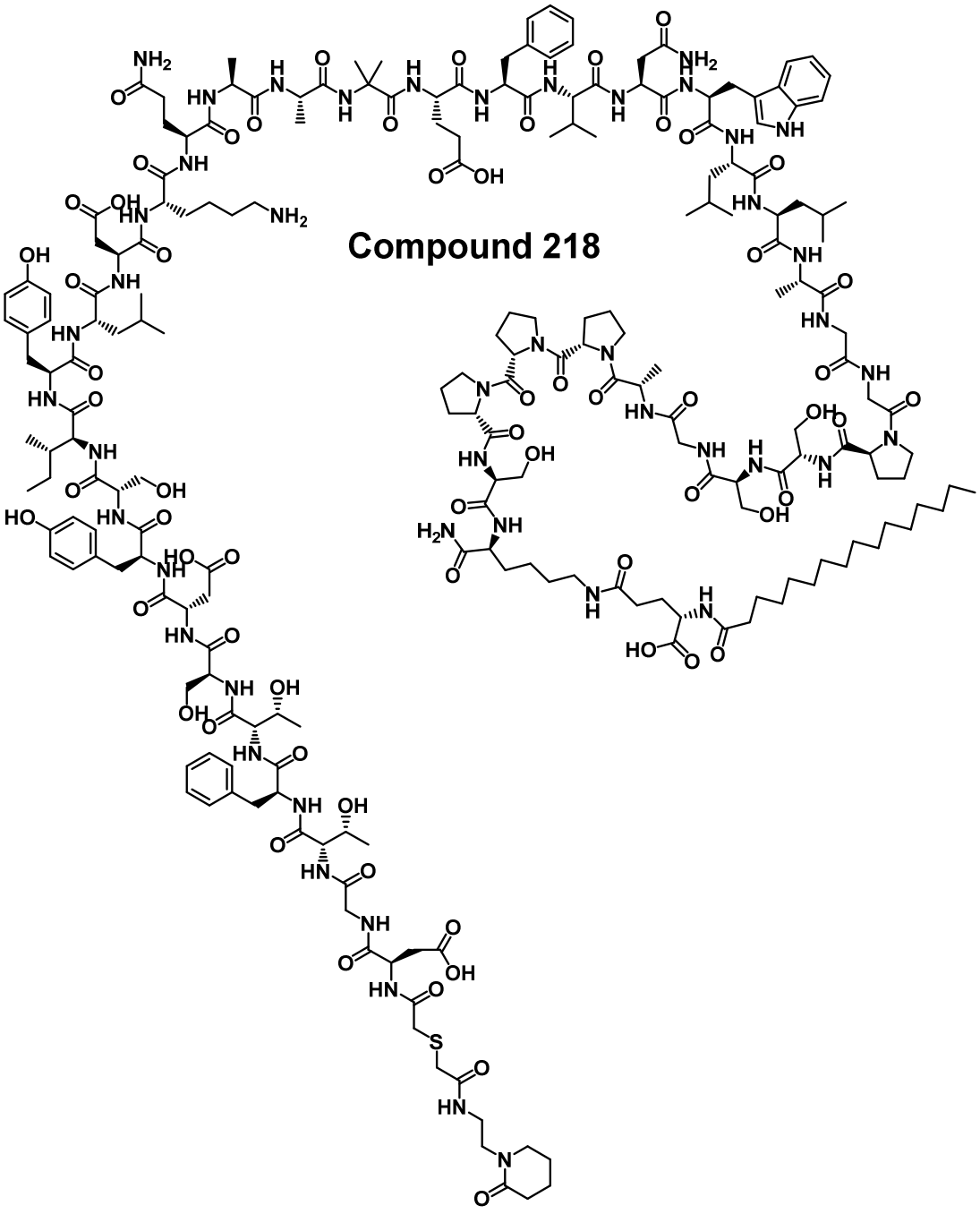
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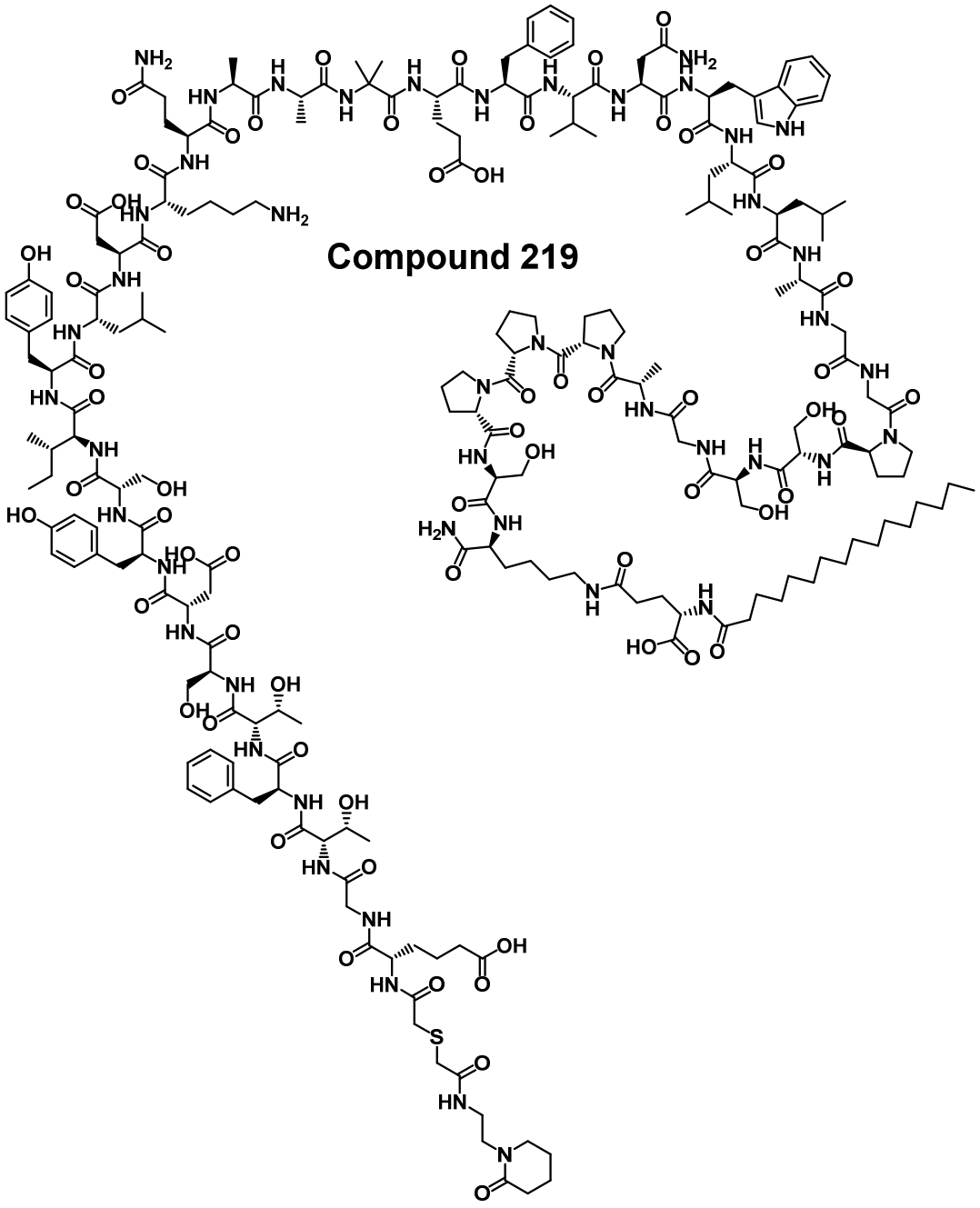

Compound 215


Compound 216

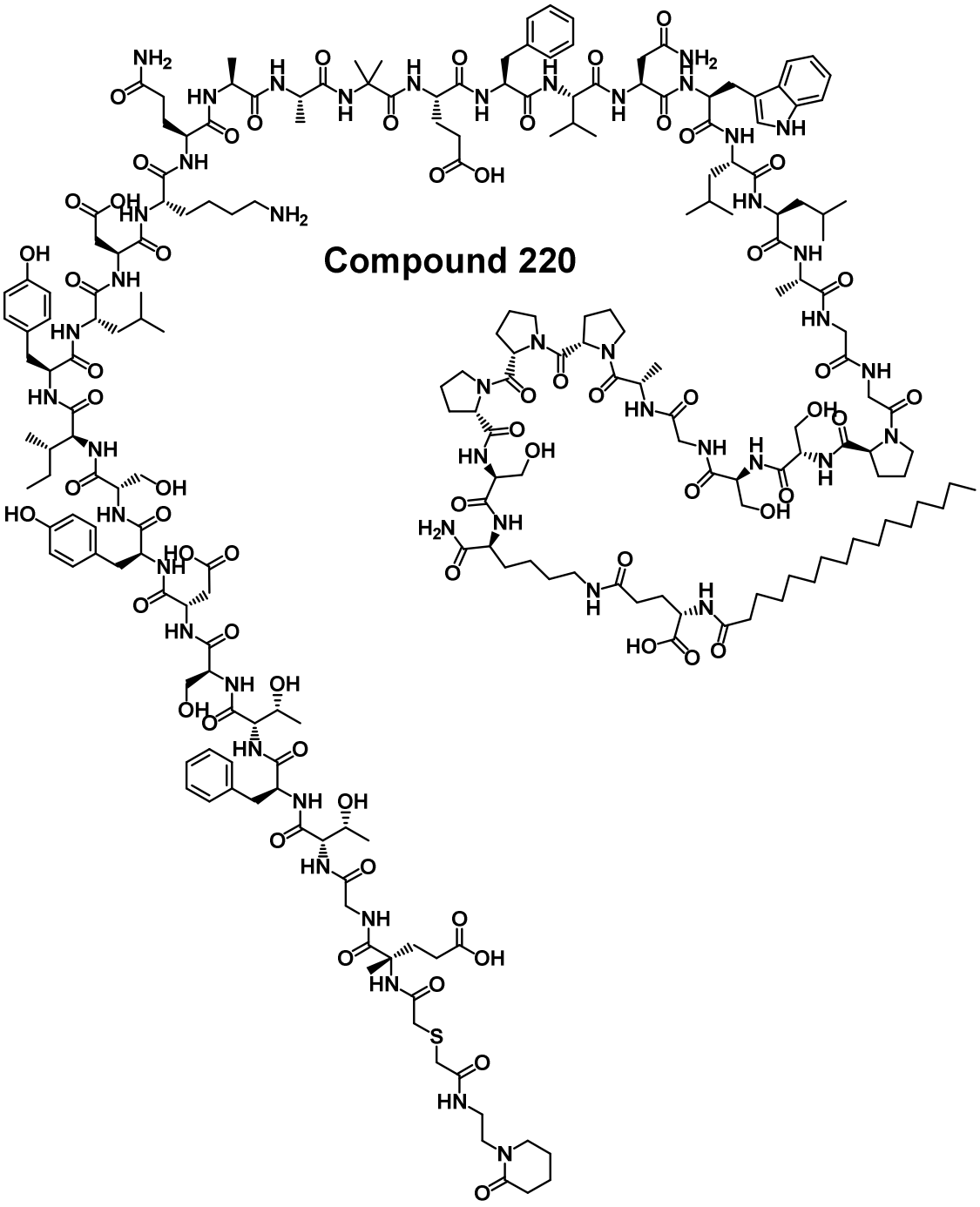


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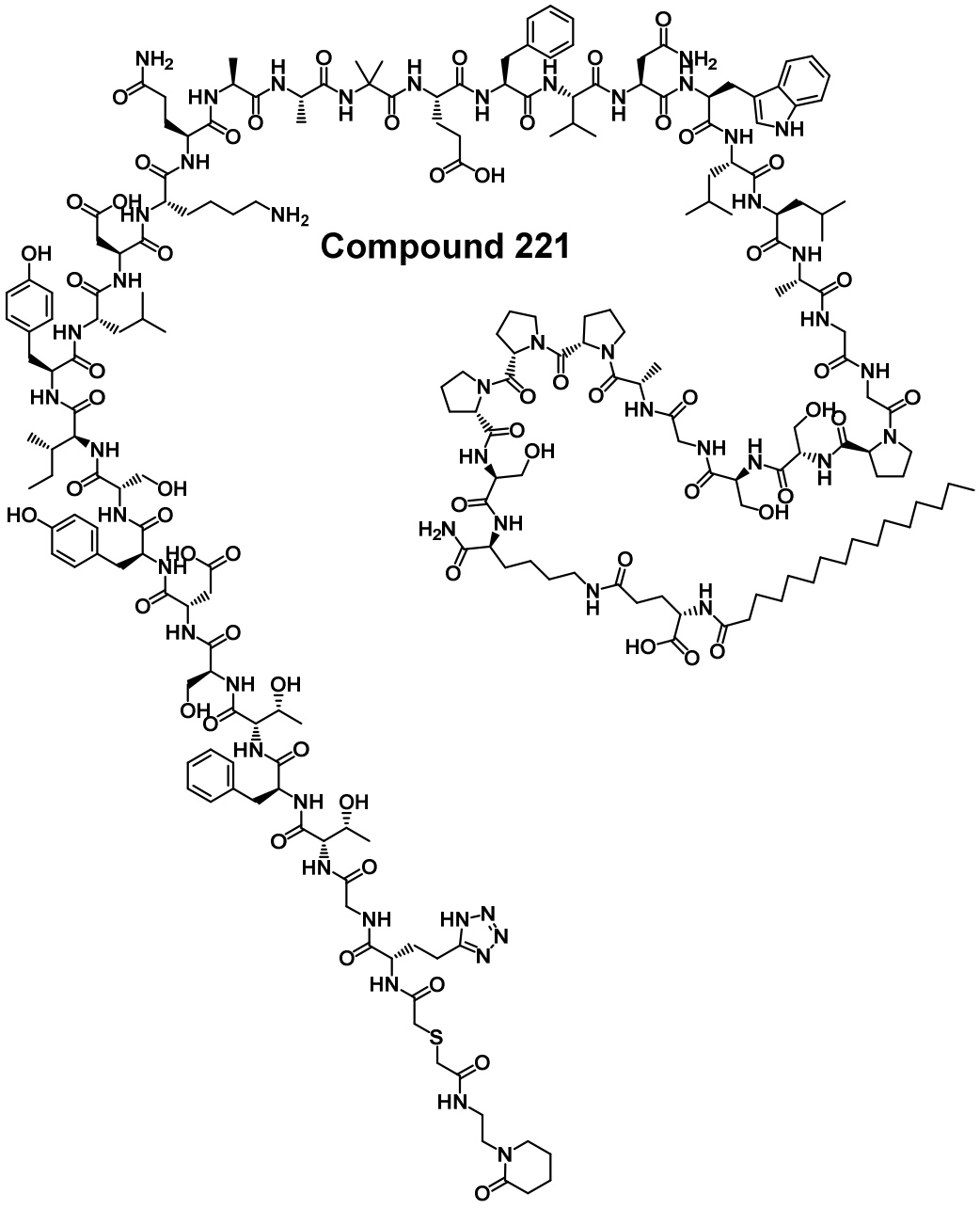

Compound 218



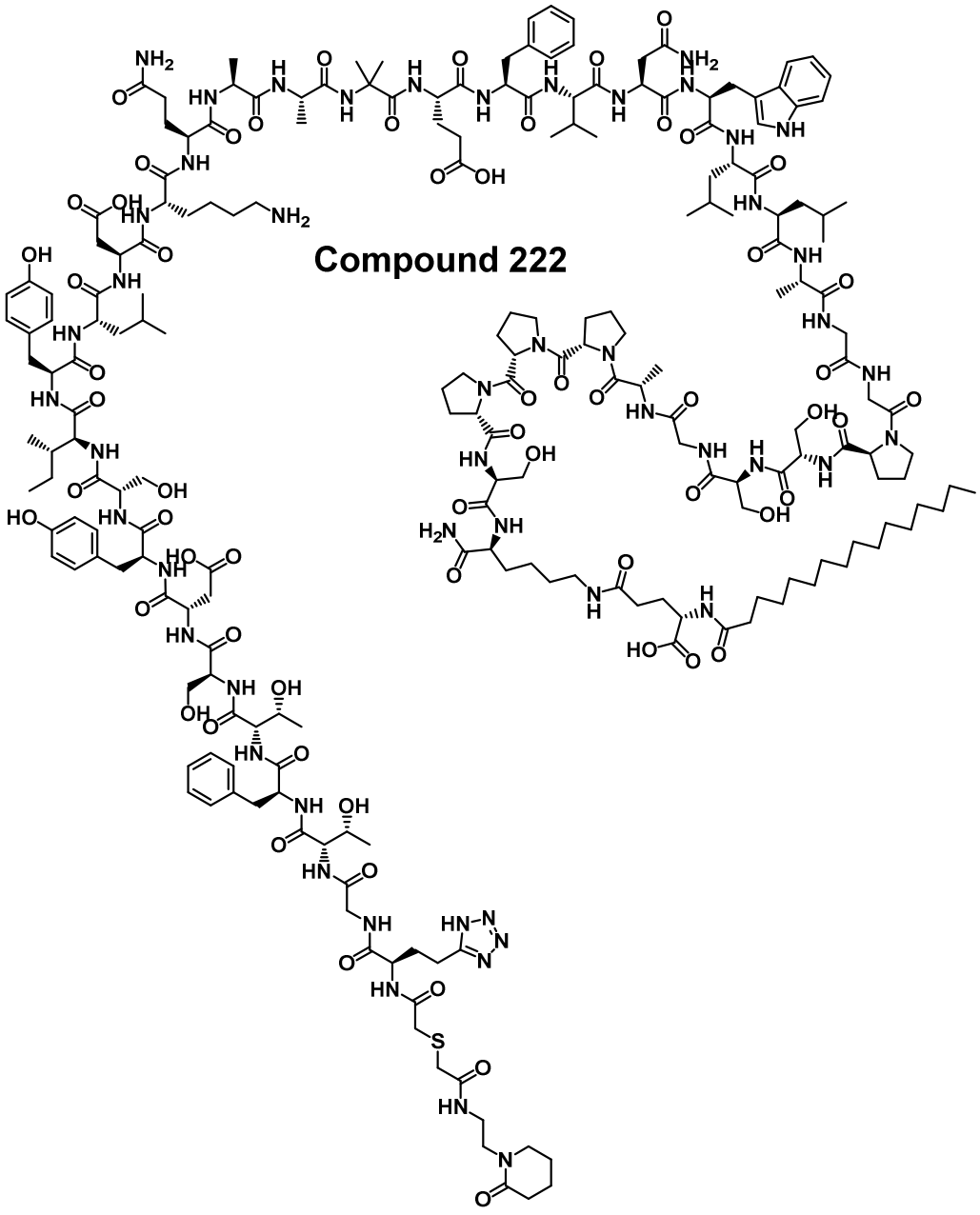
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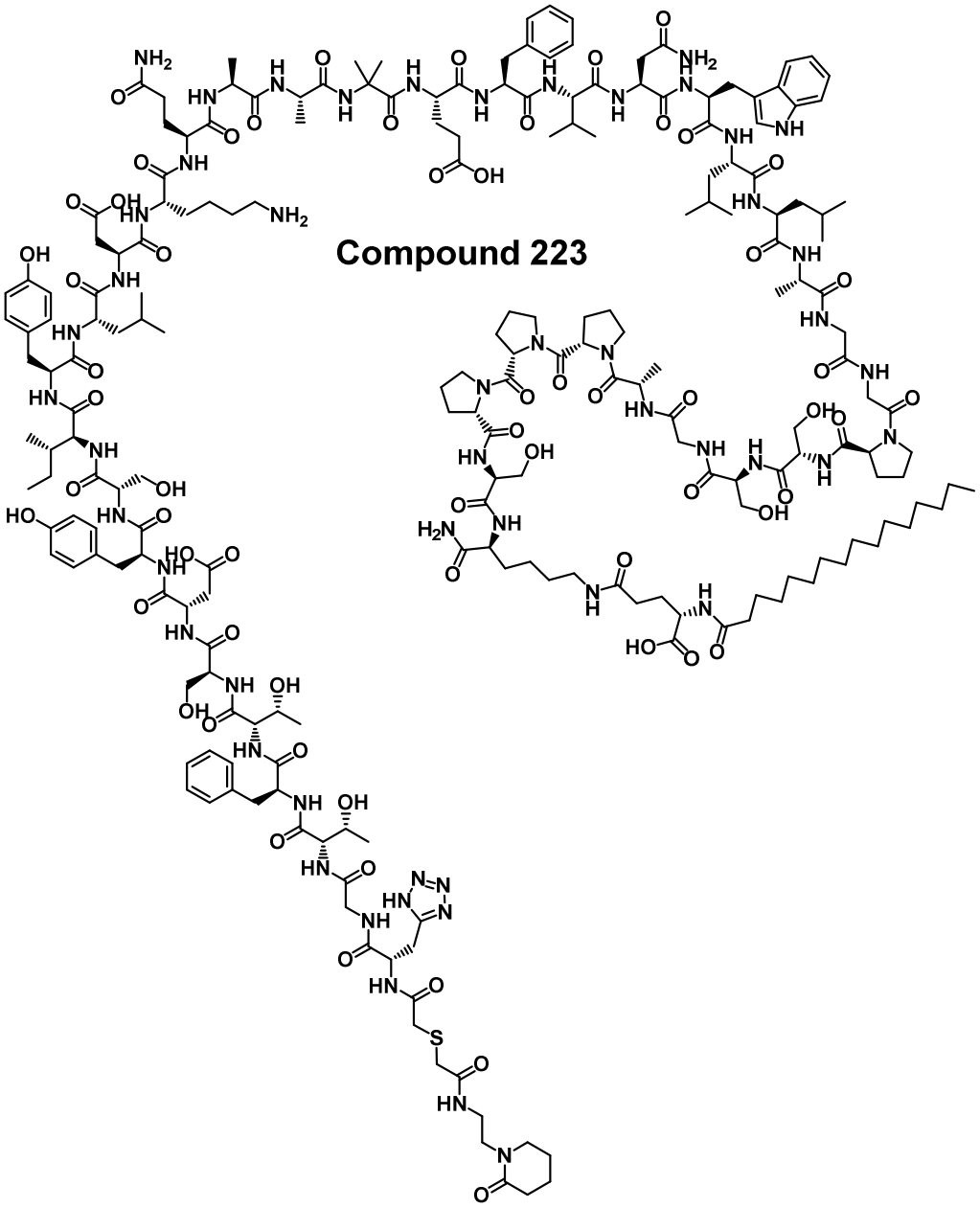
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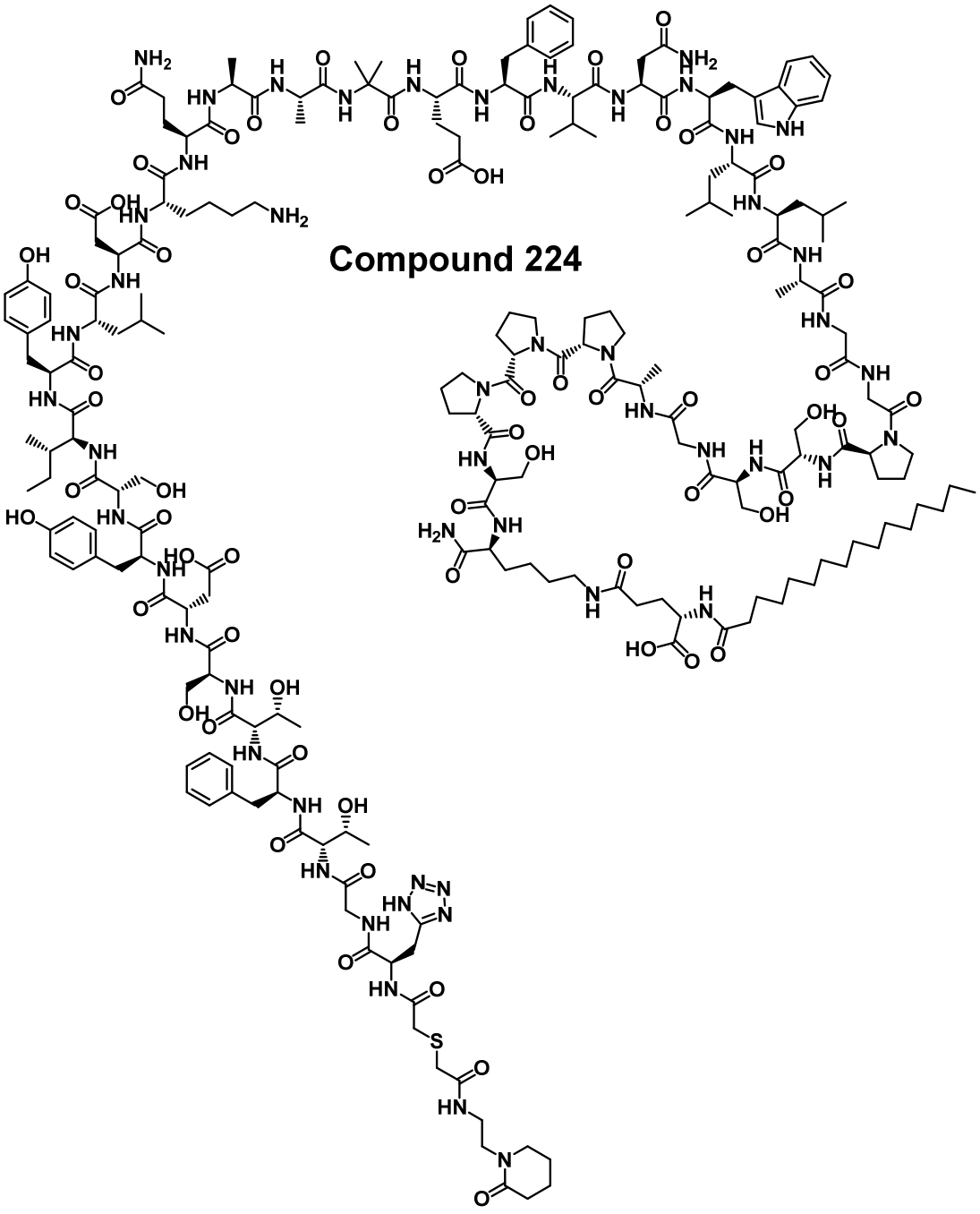


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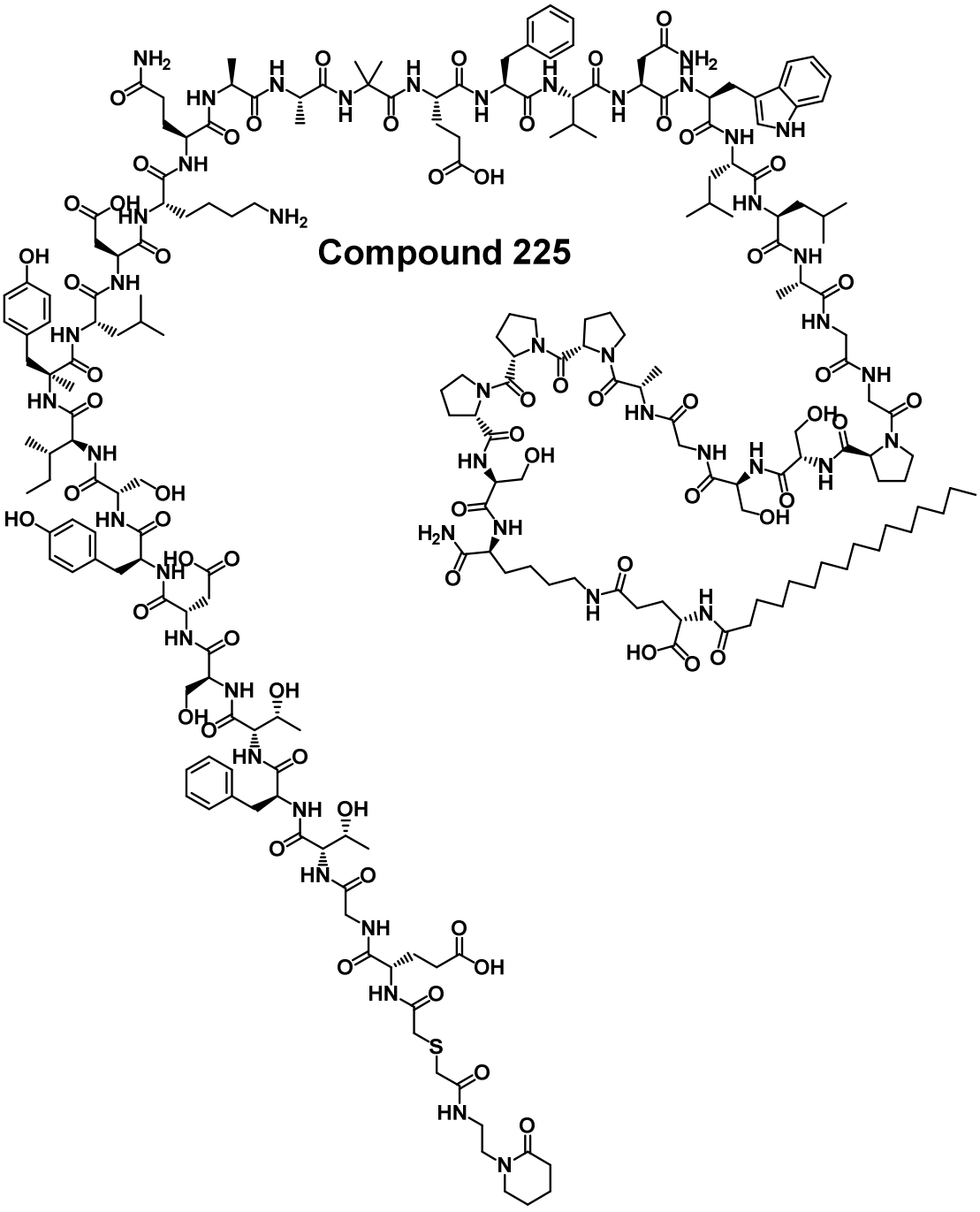


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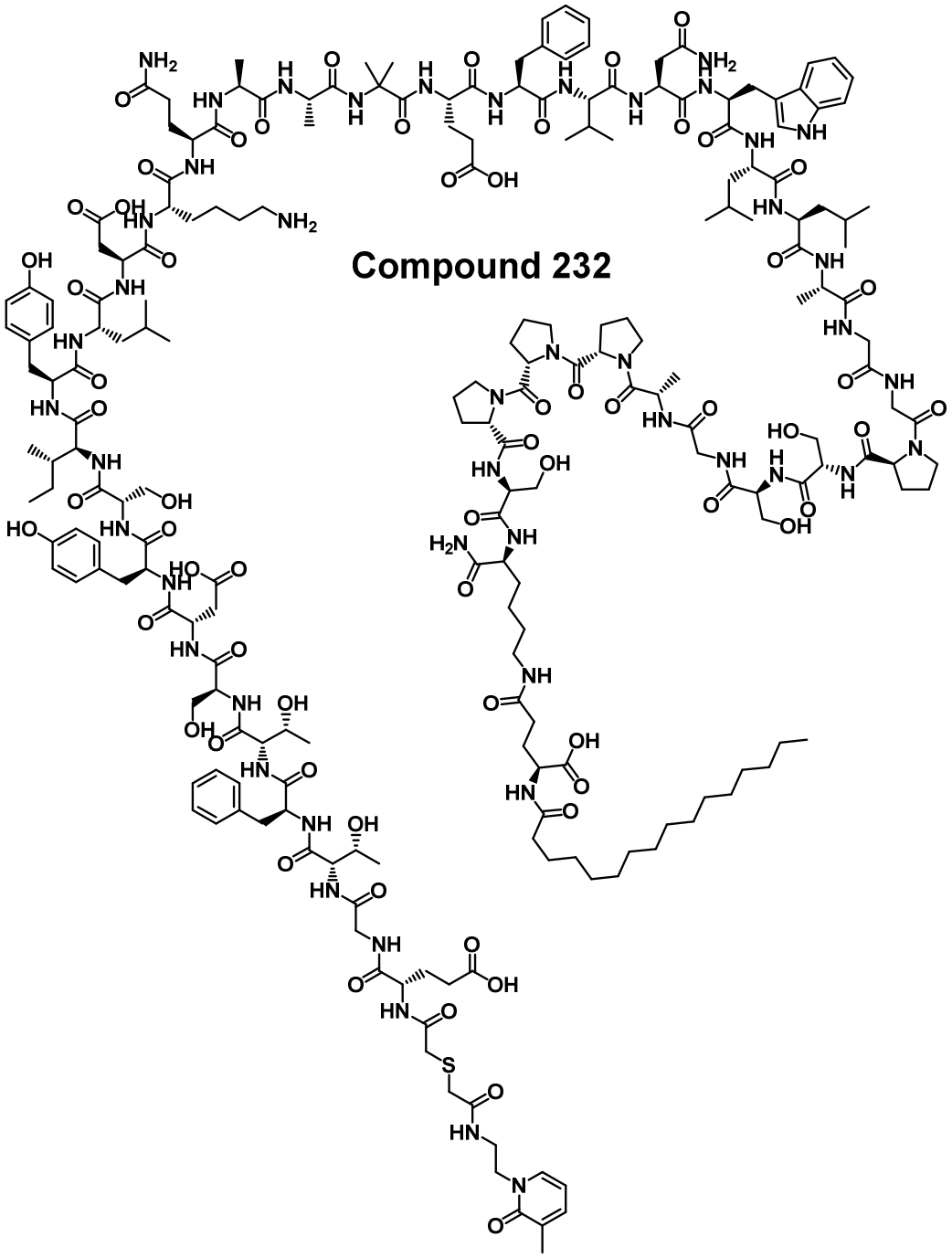

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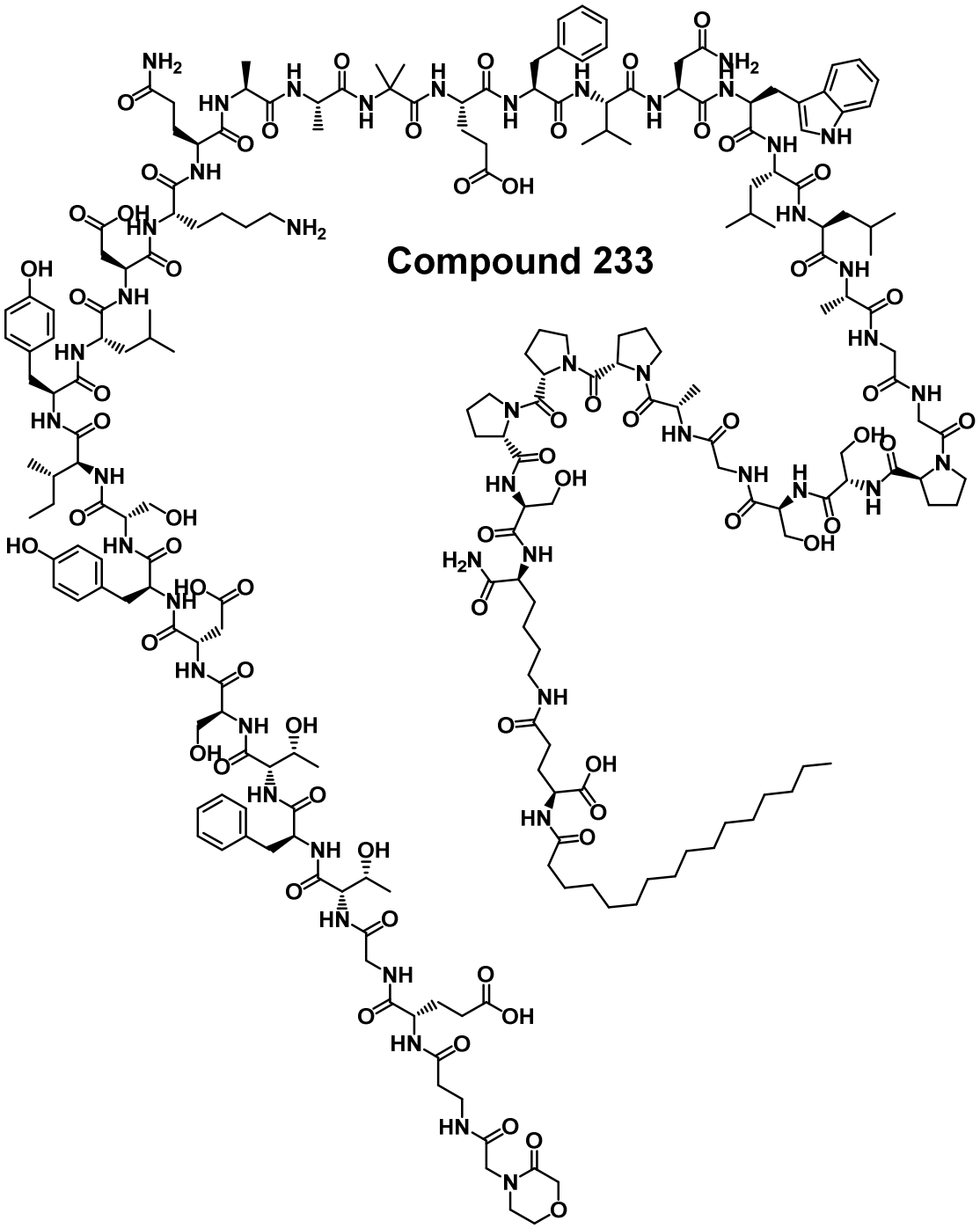


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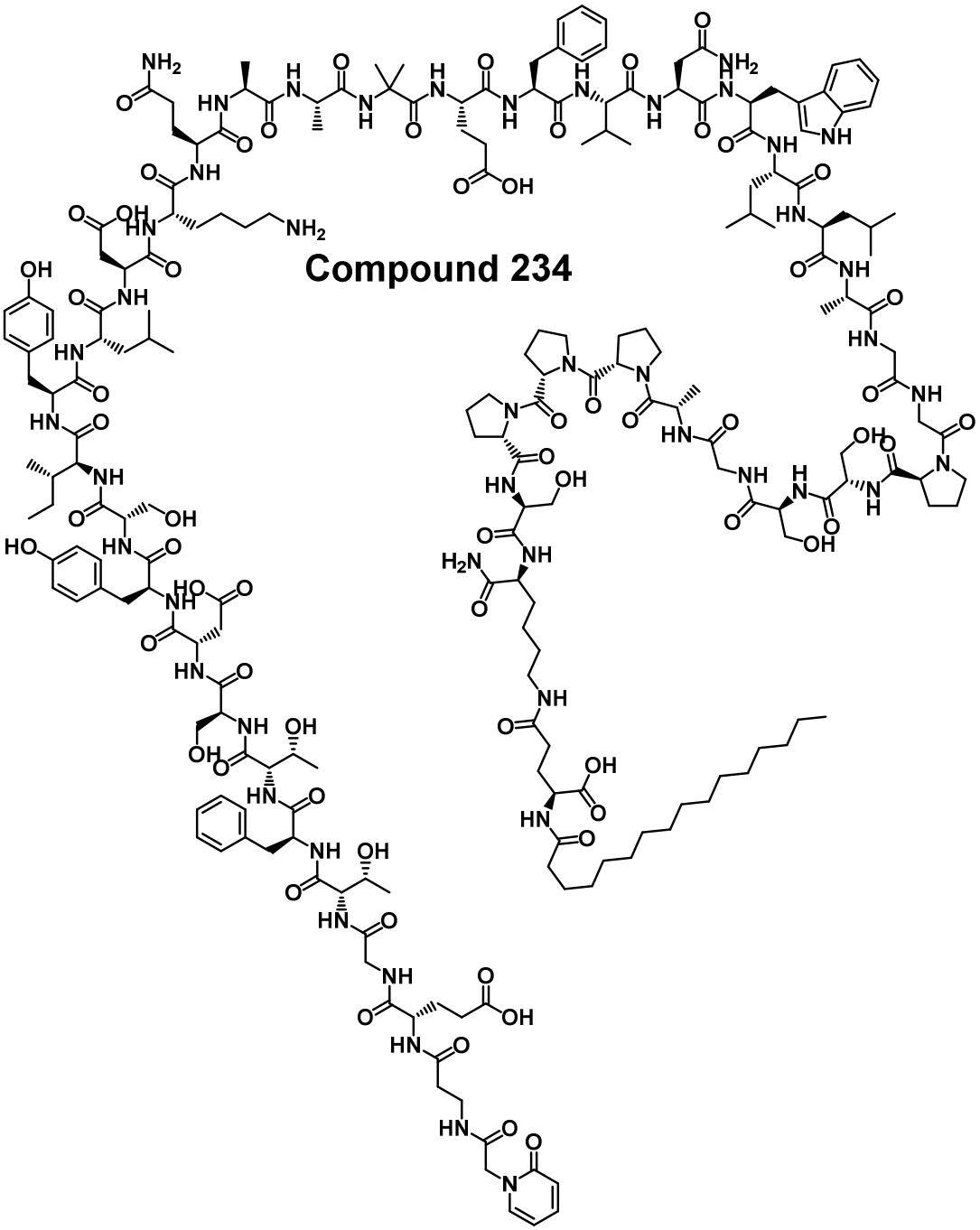


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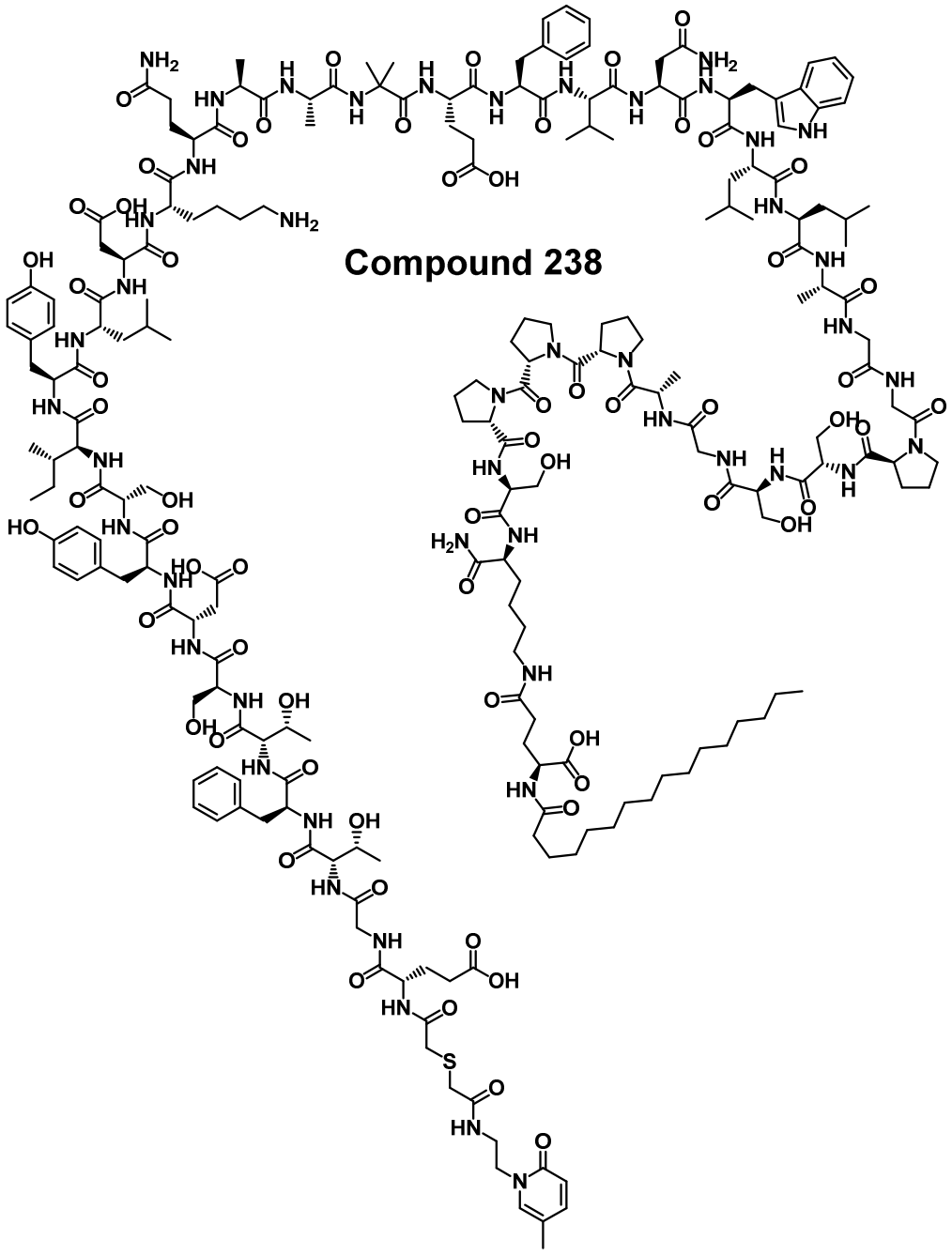

Compound 232



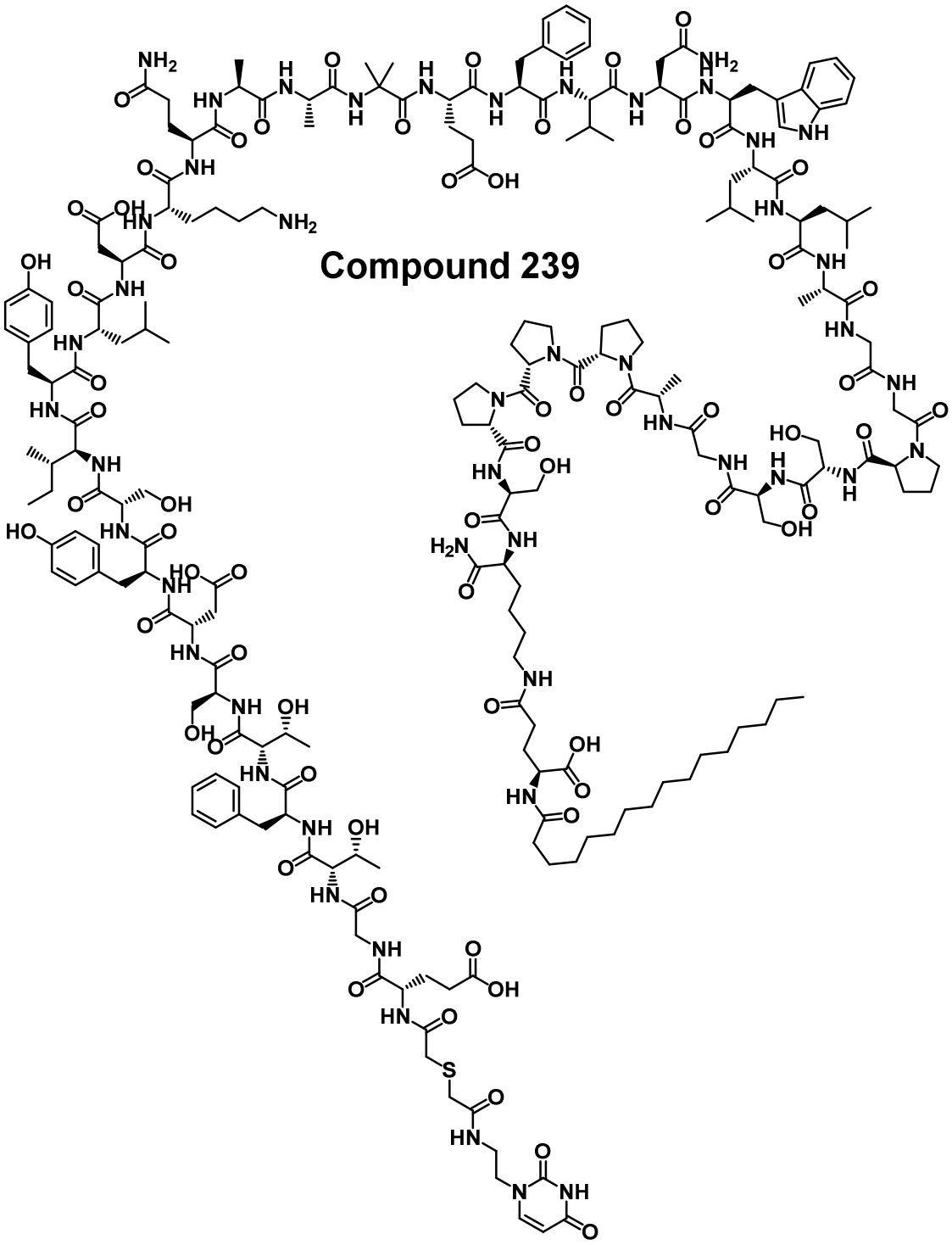
Compound 233



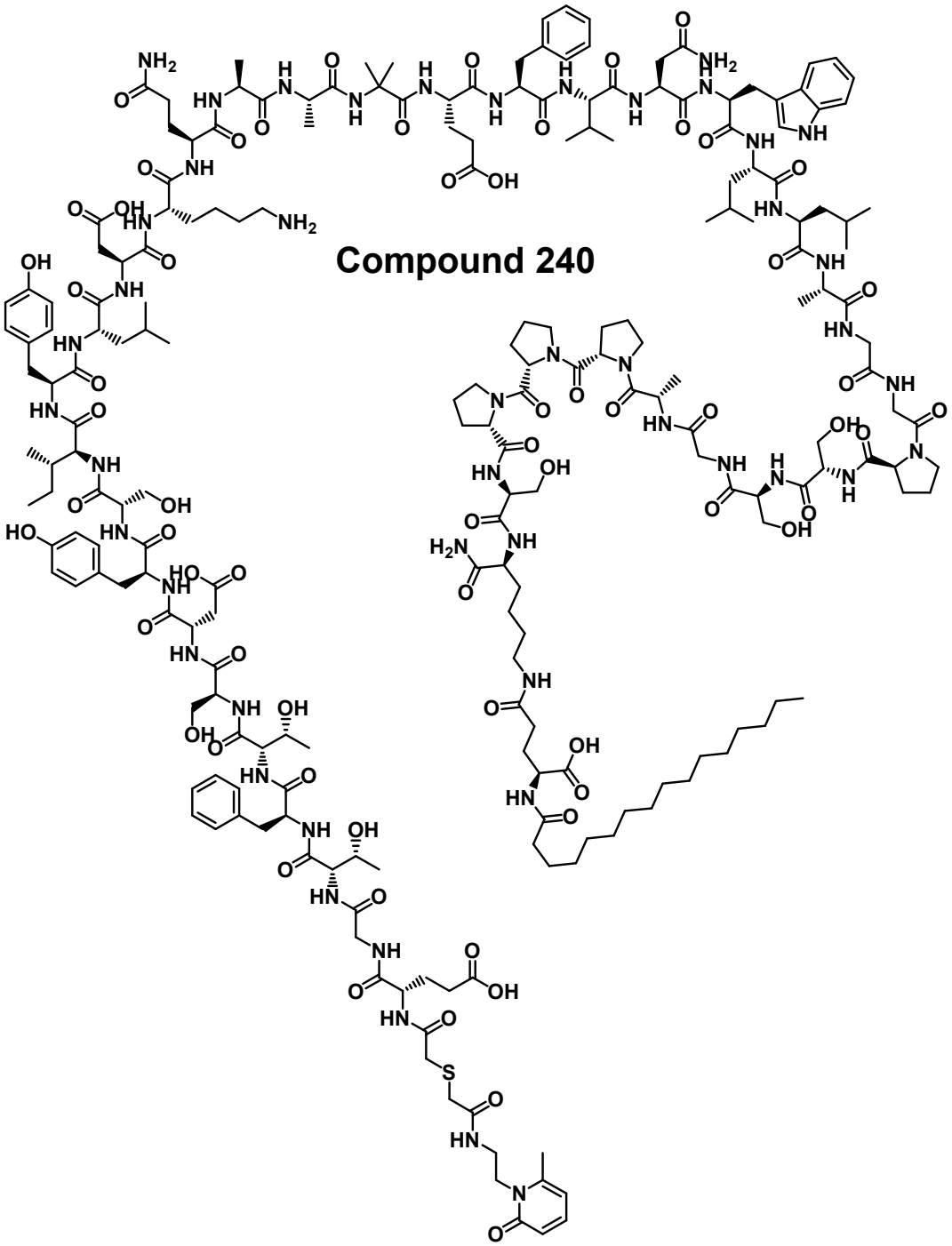
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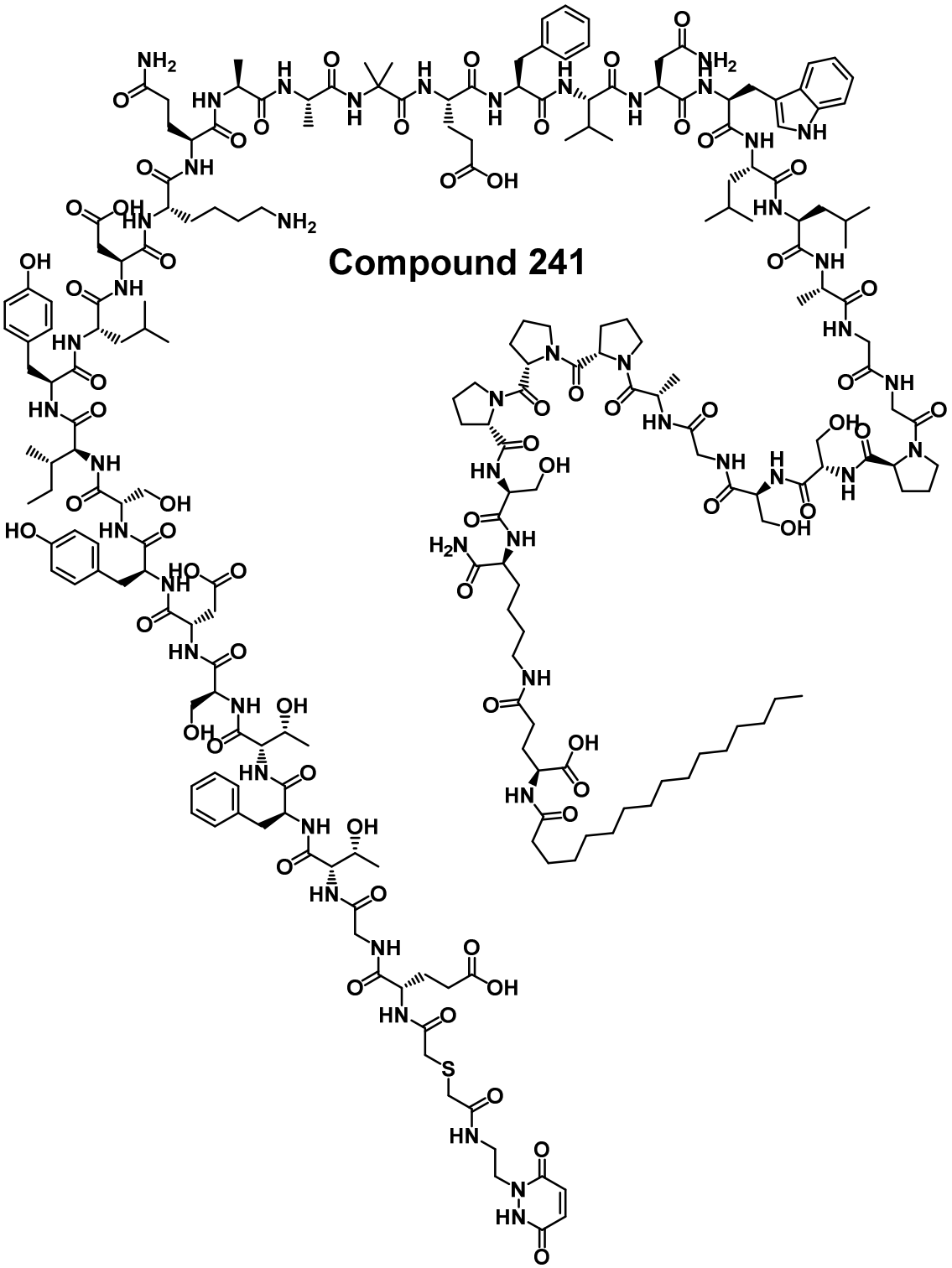
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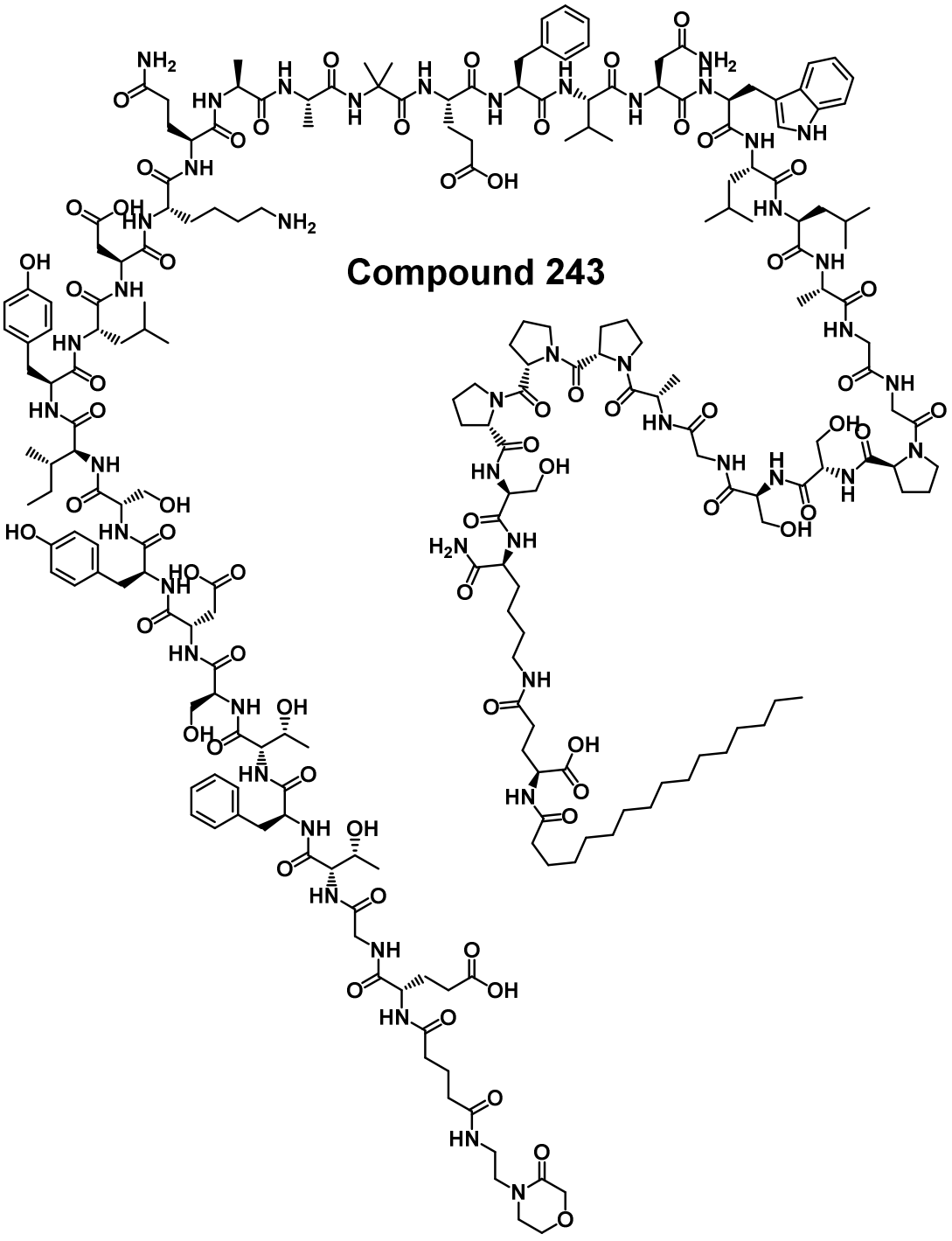
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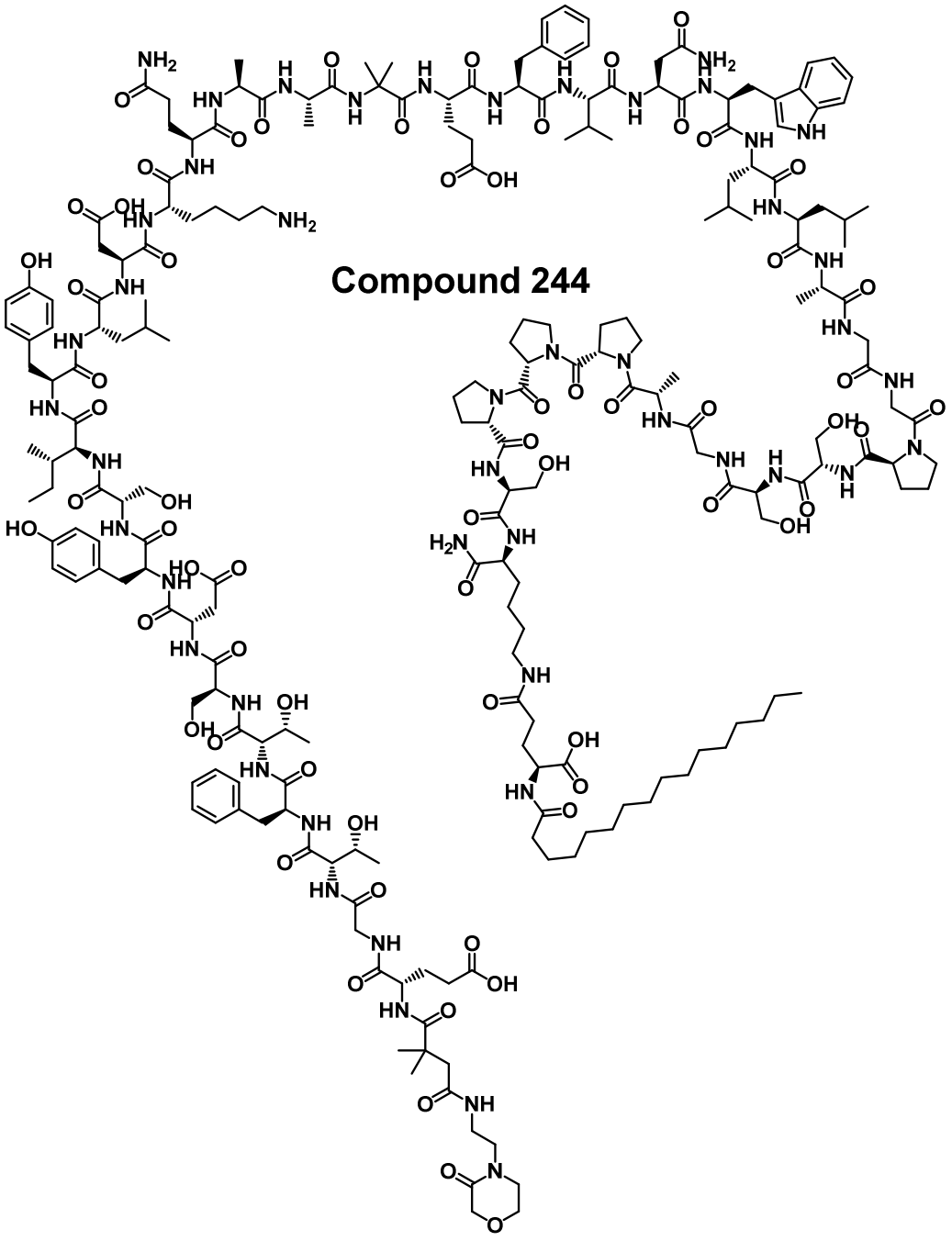
Compound 240

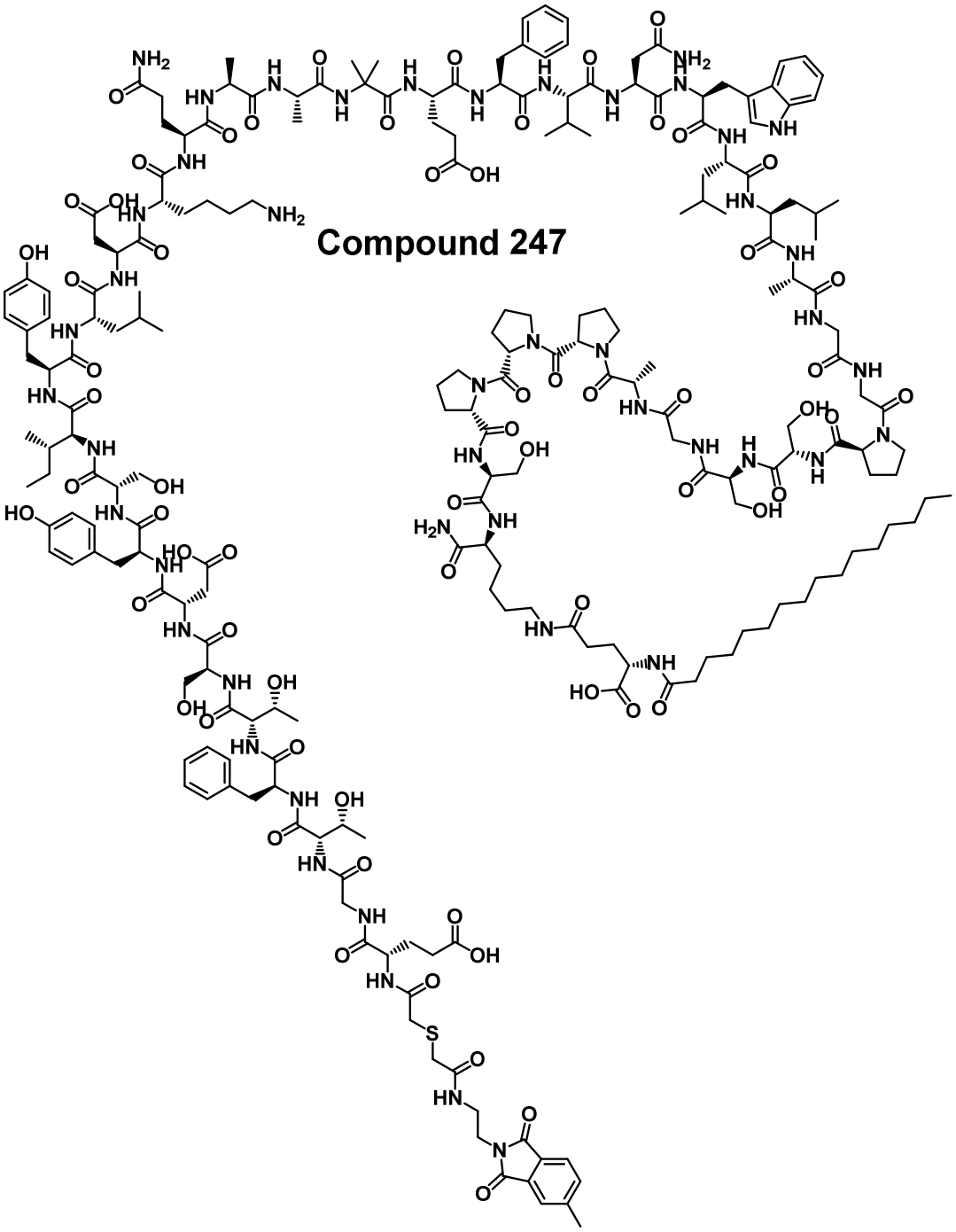


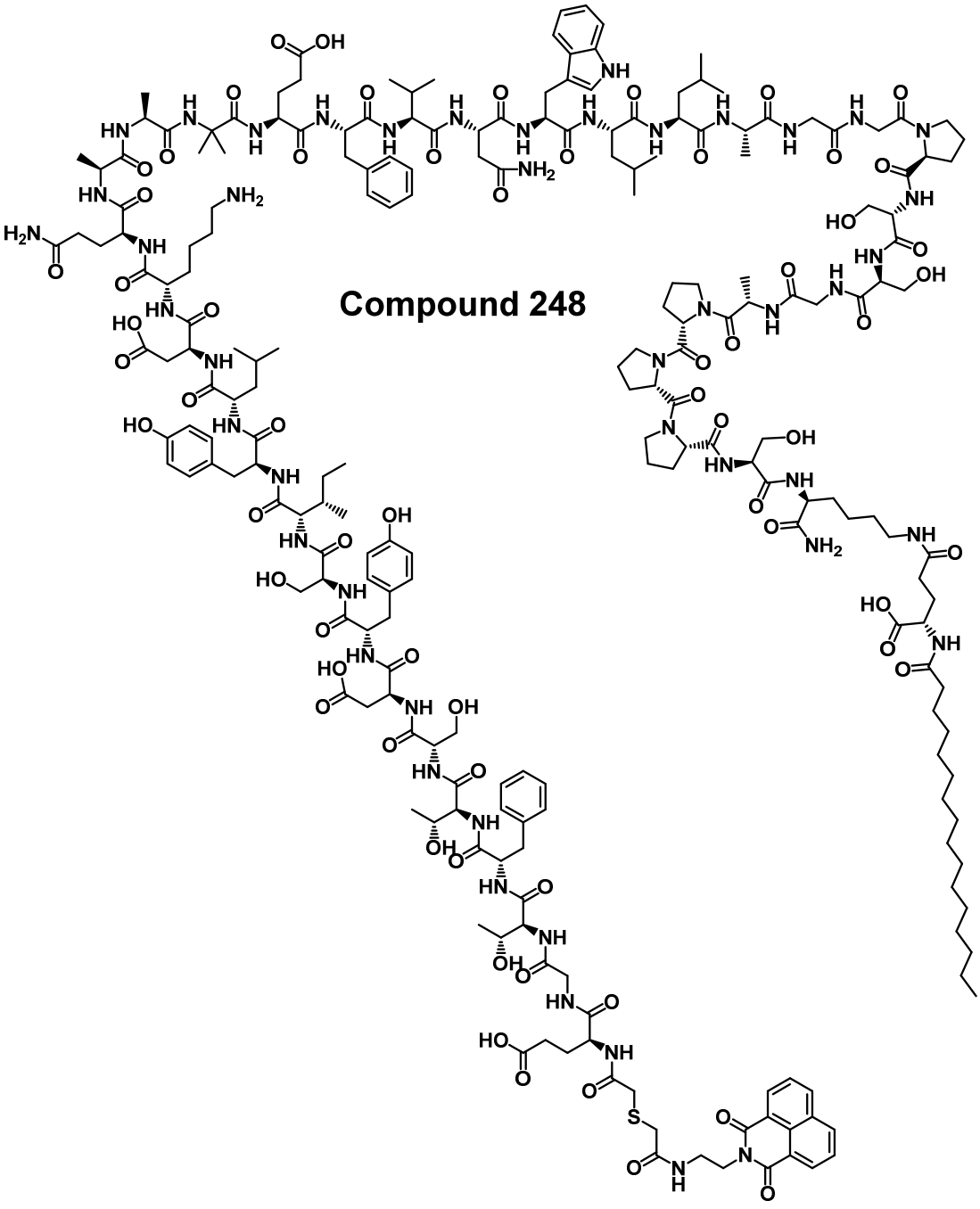
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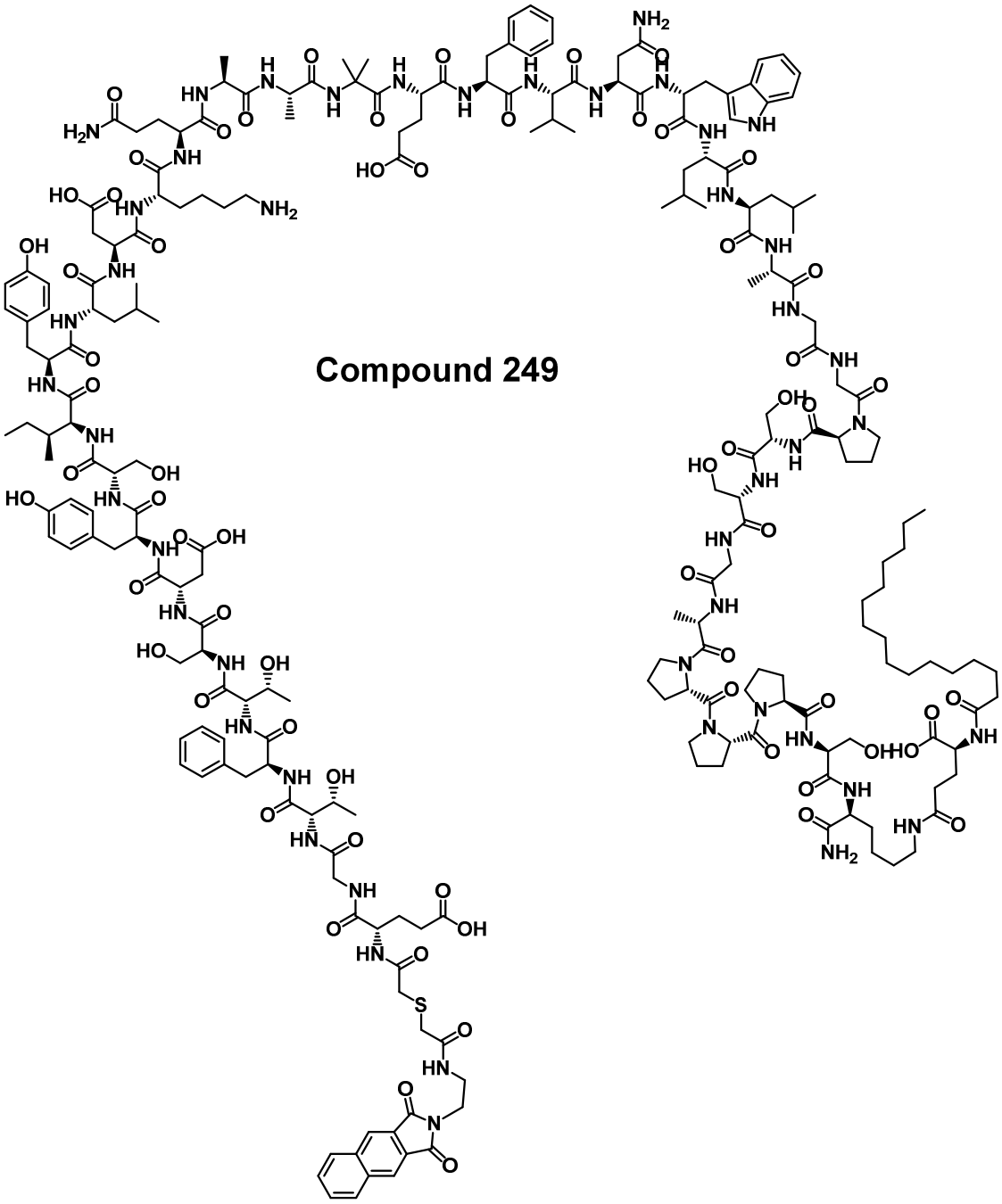
Compound 243


Compound 244

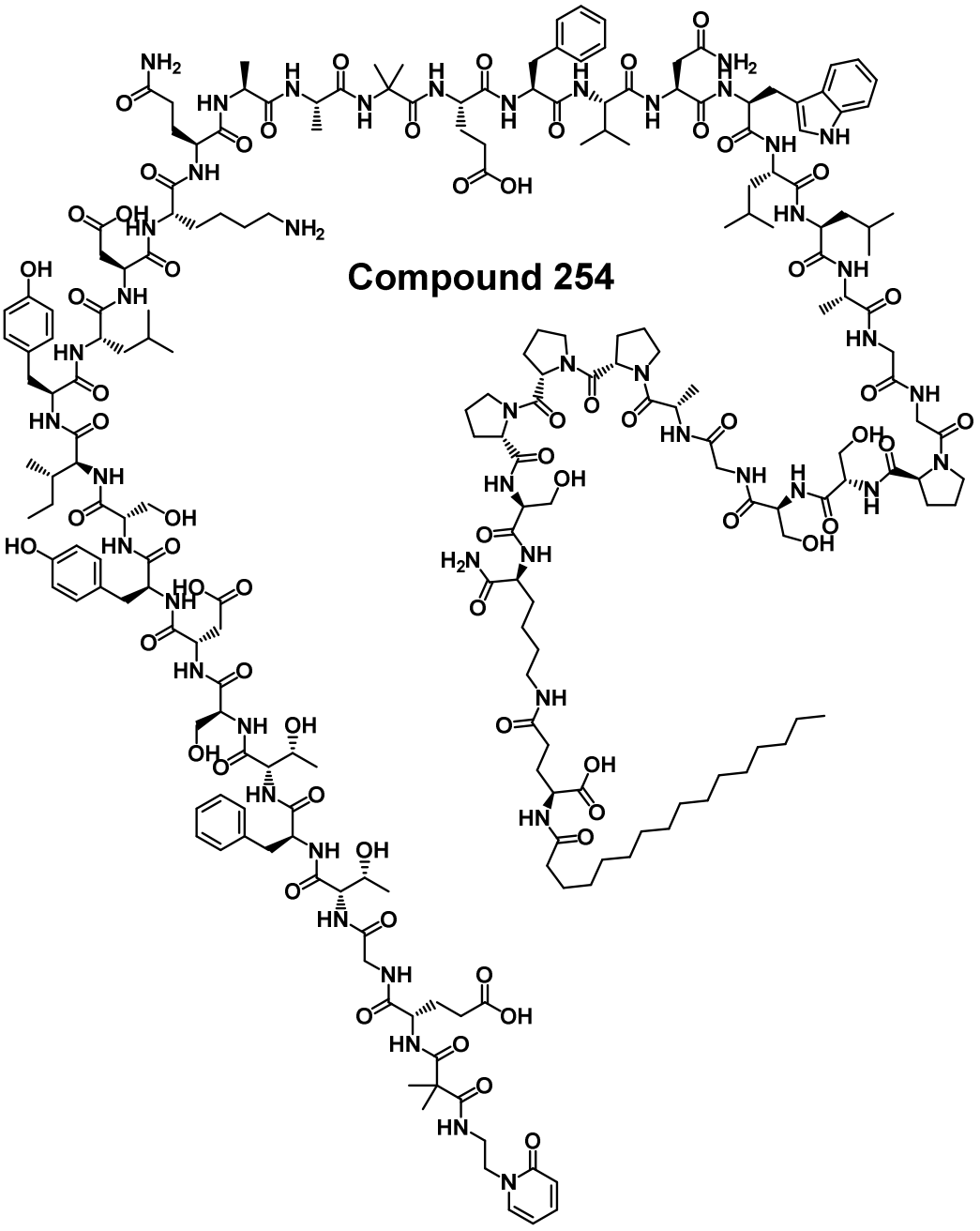

Compound 247



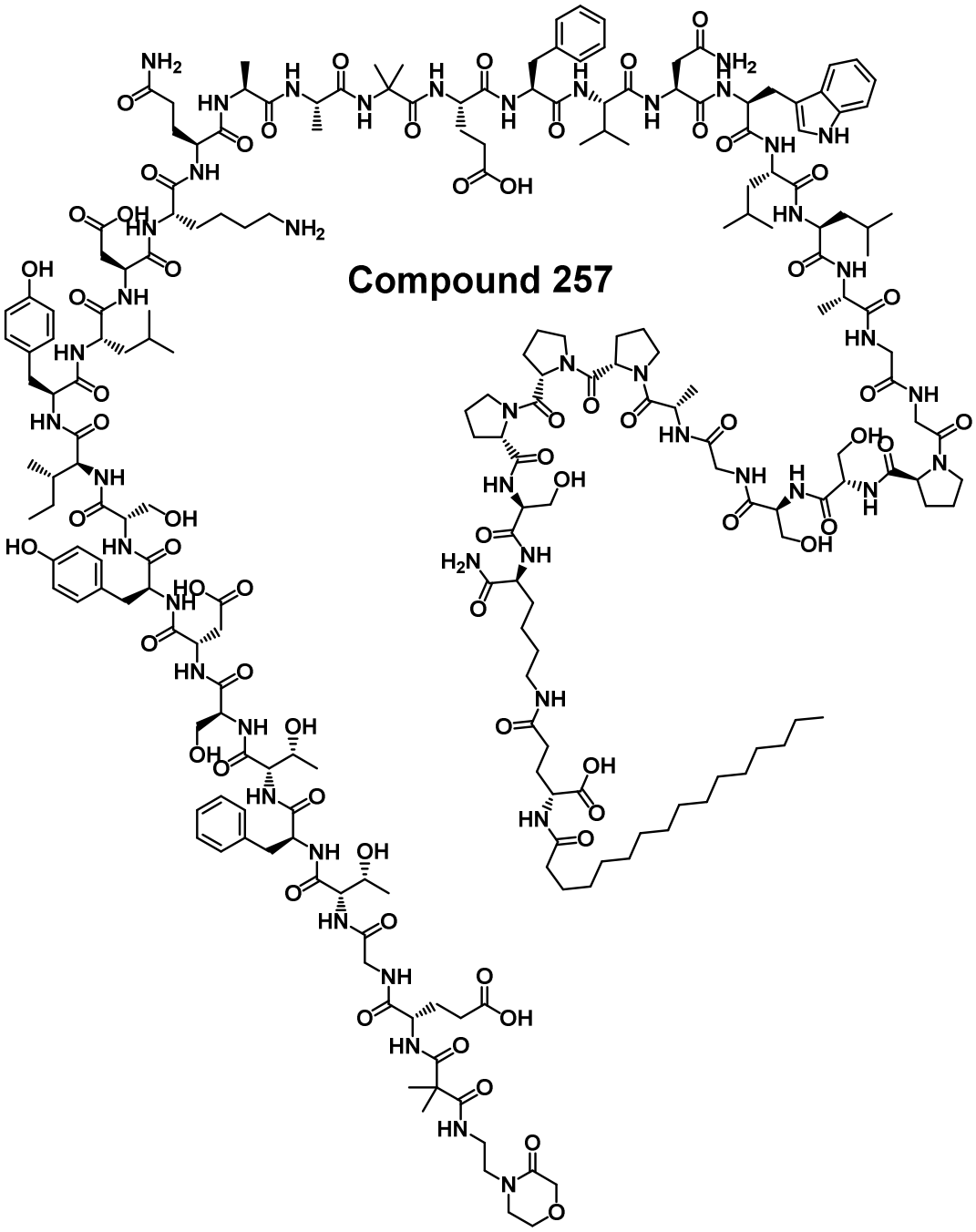
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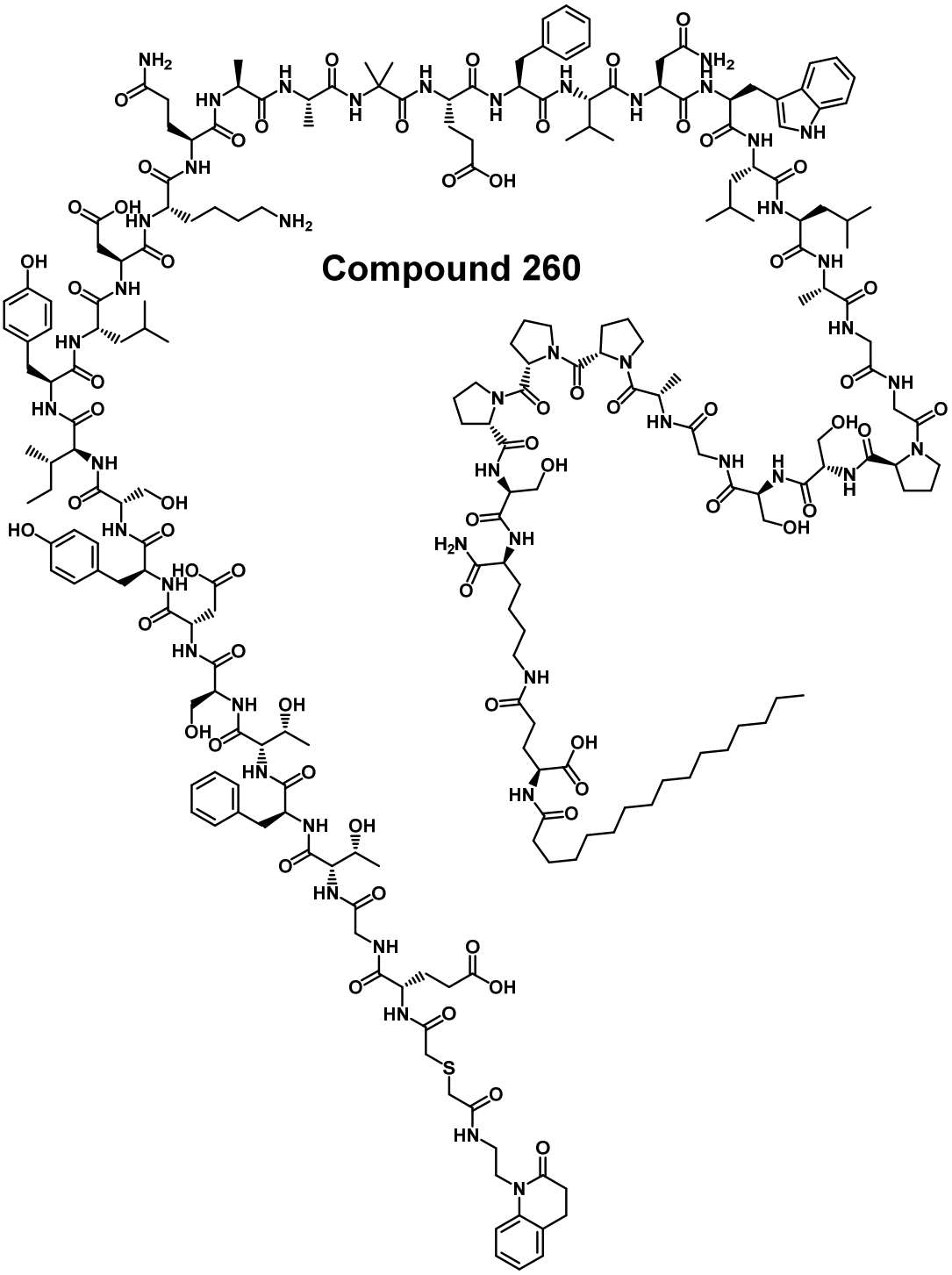


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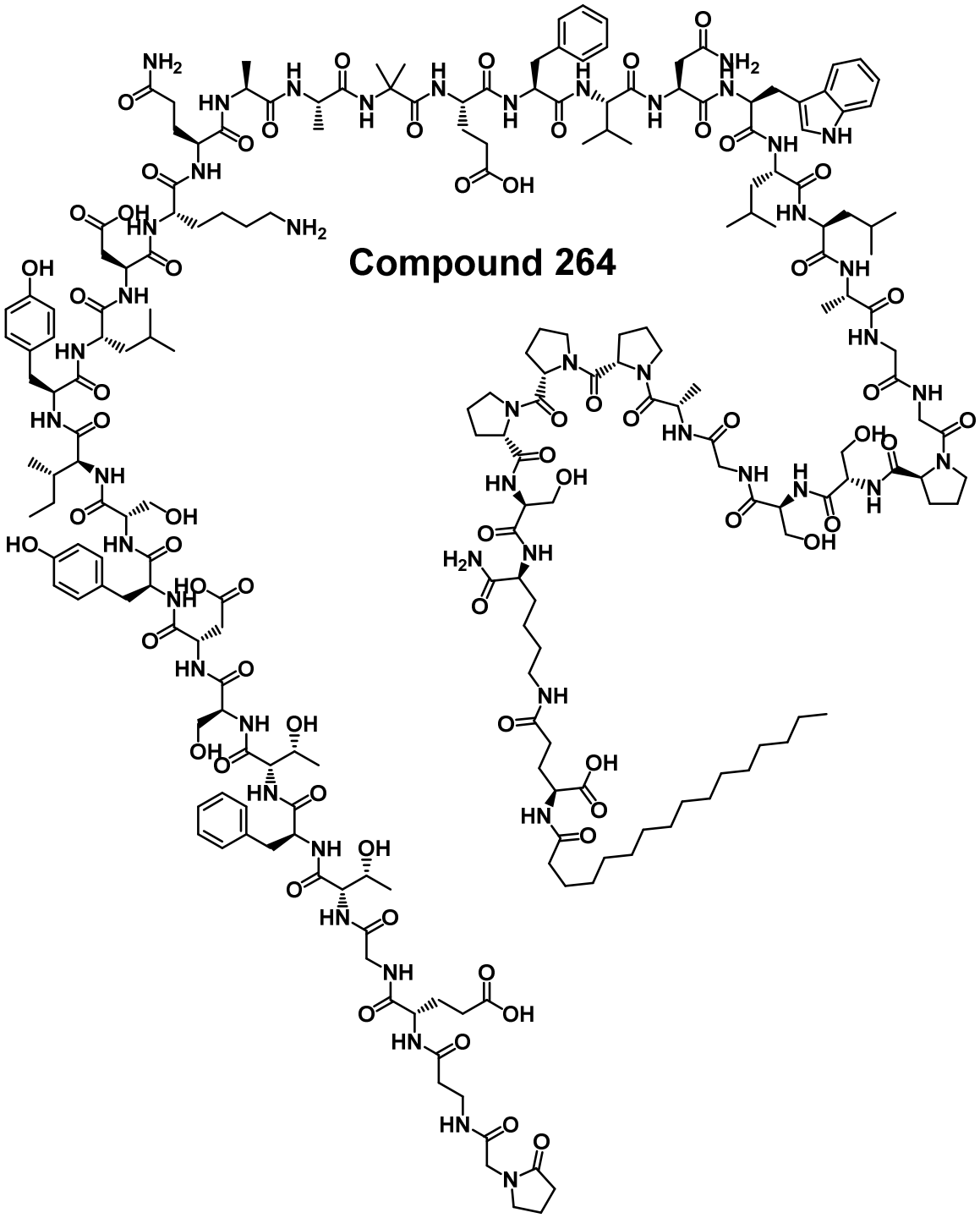


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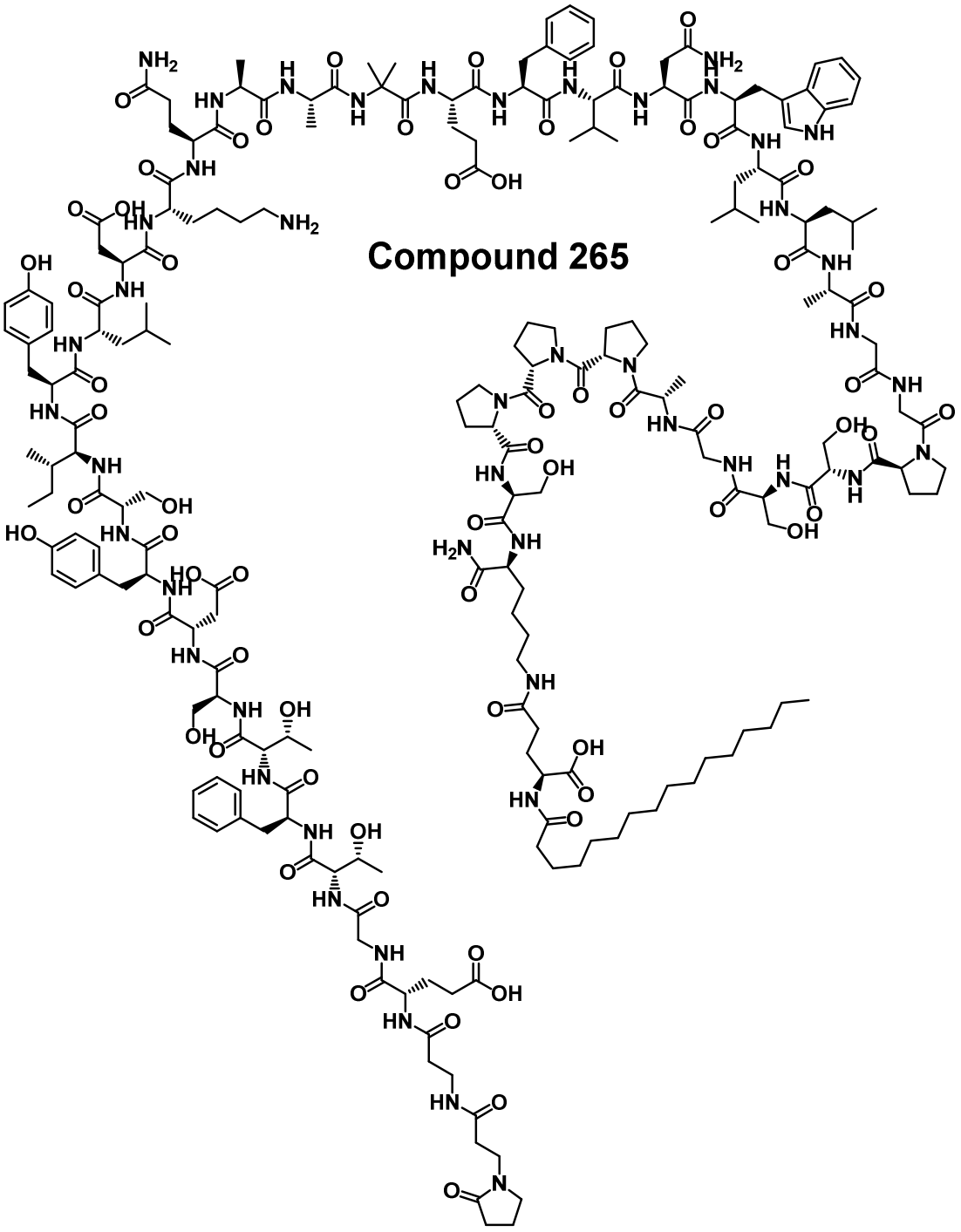

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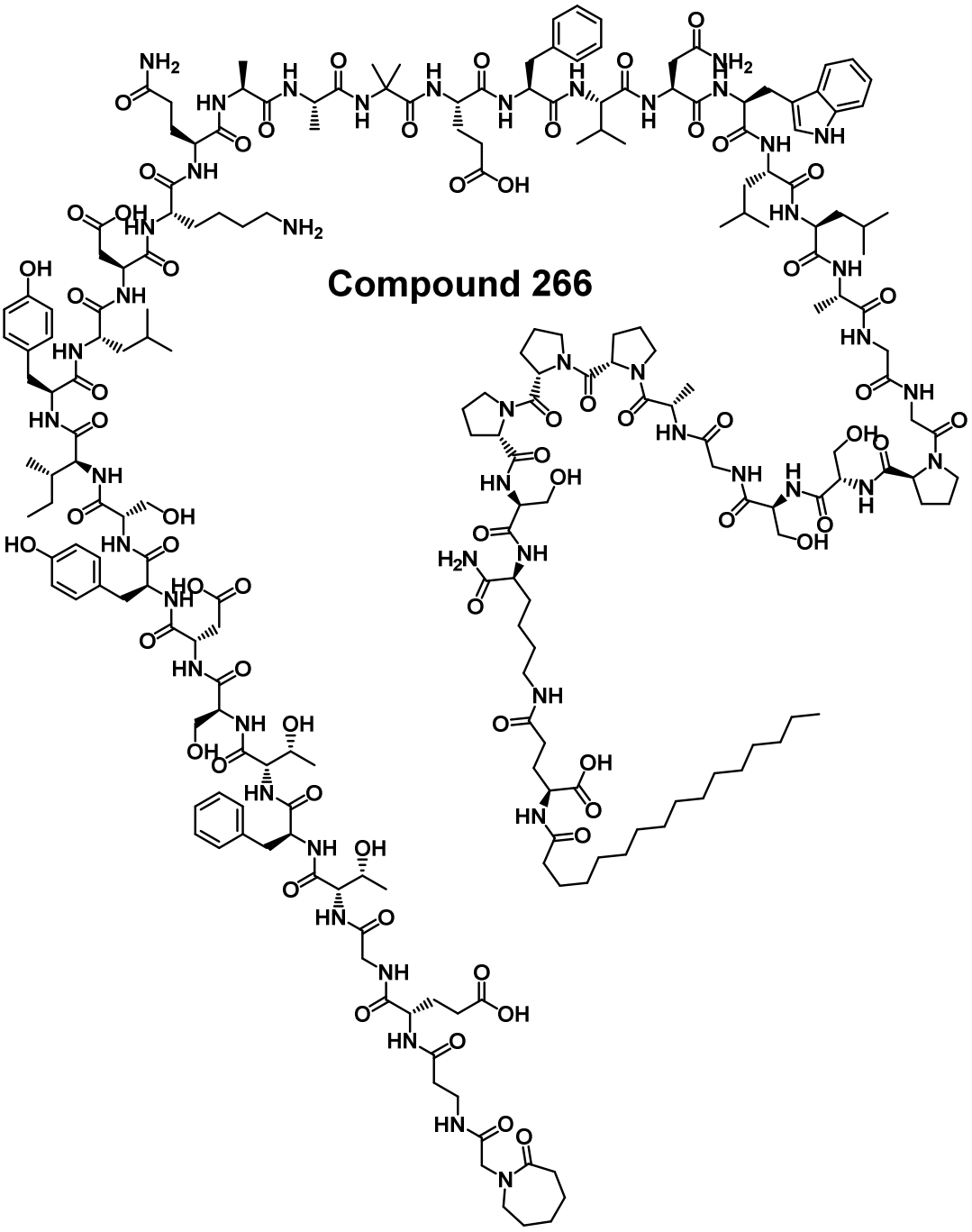
Compound 260



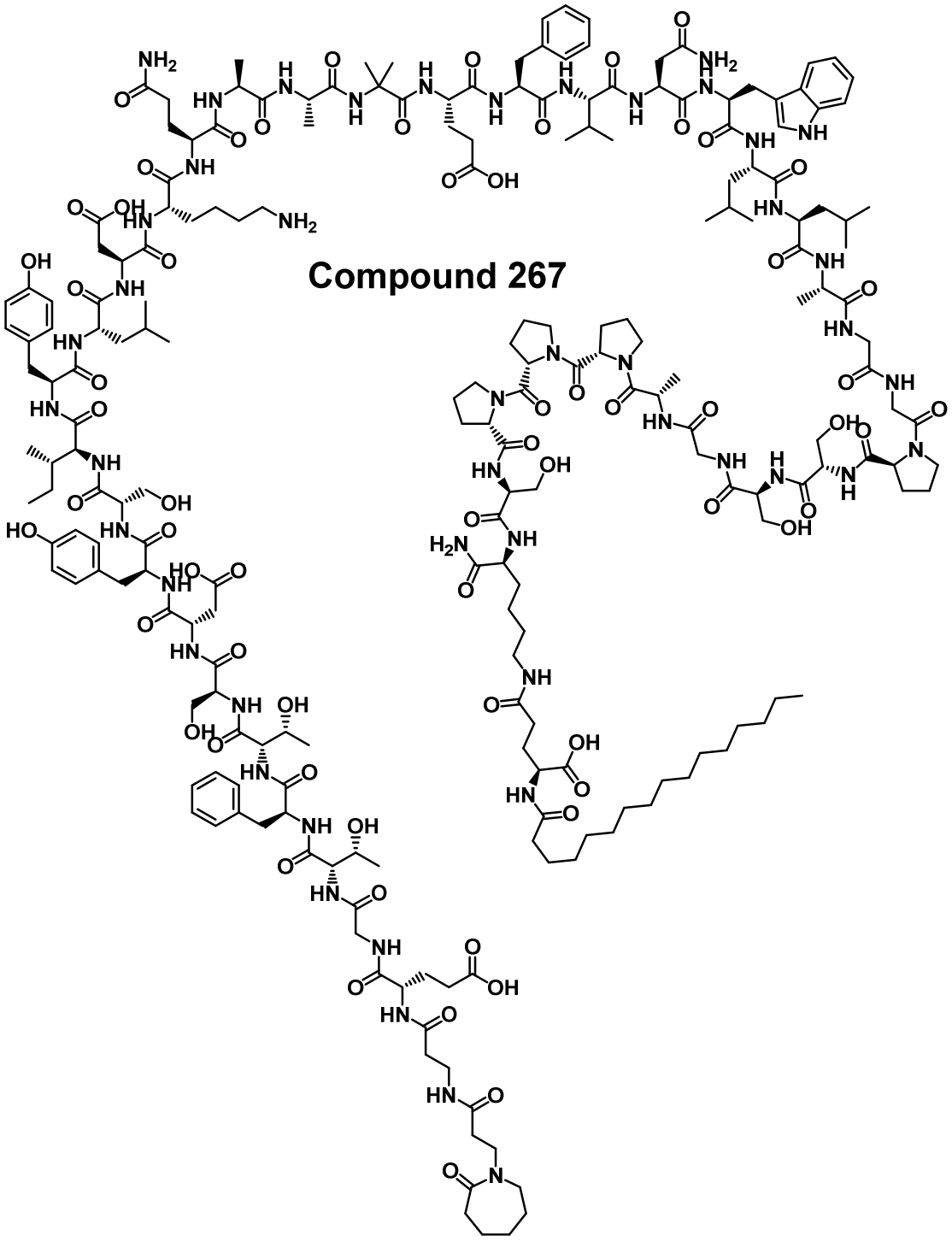
Compound 264



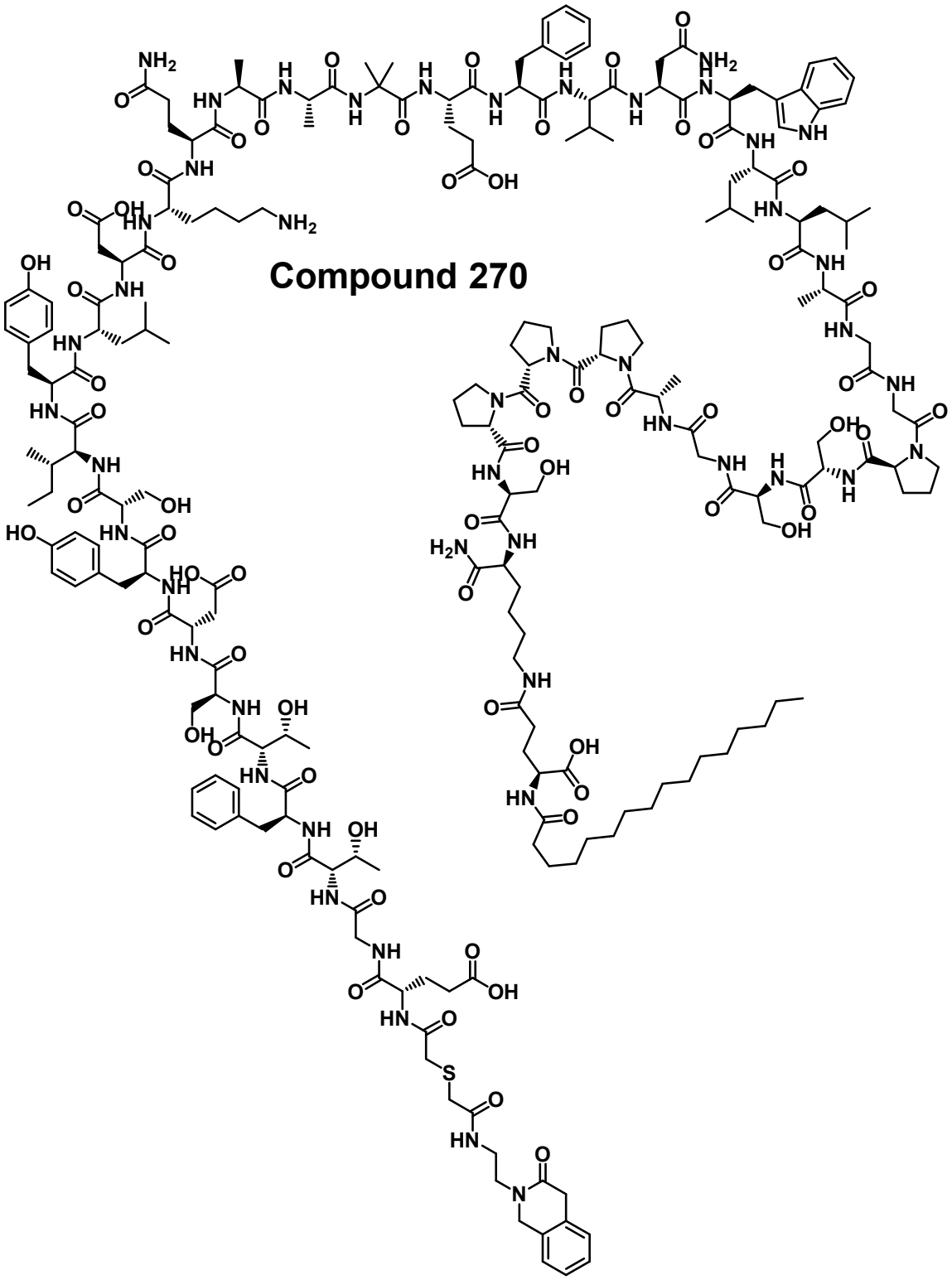
Compound 265

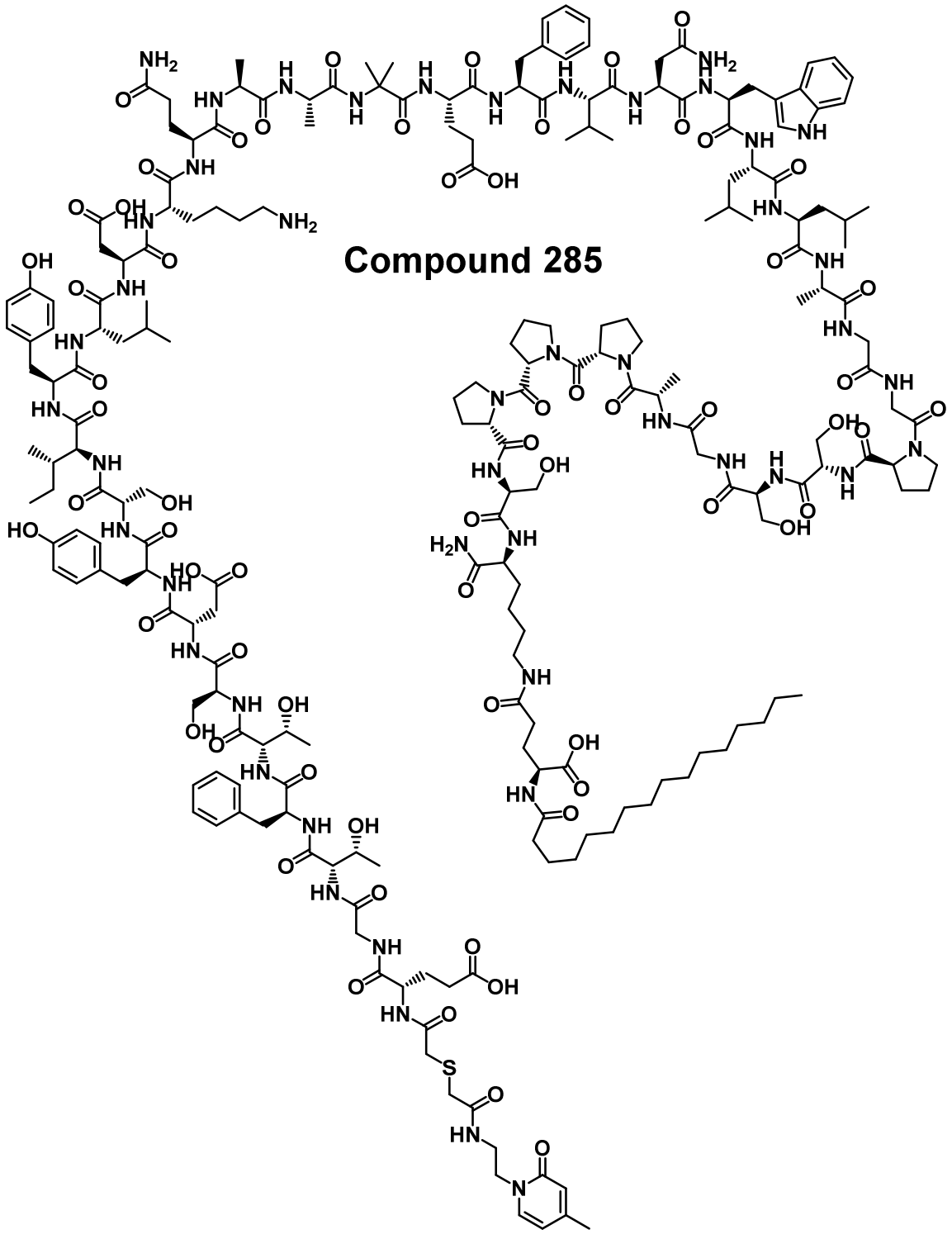


Compound 266

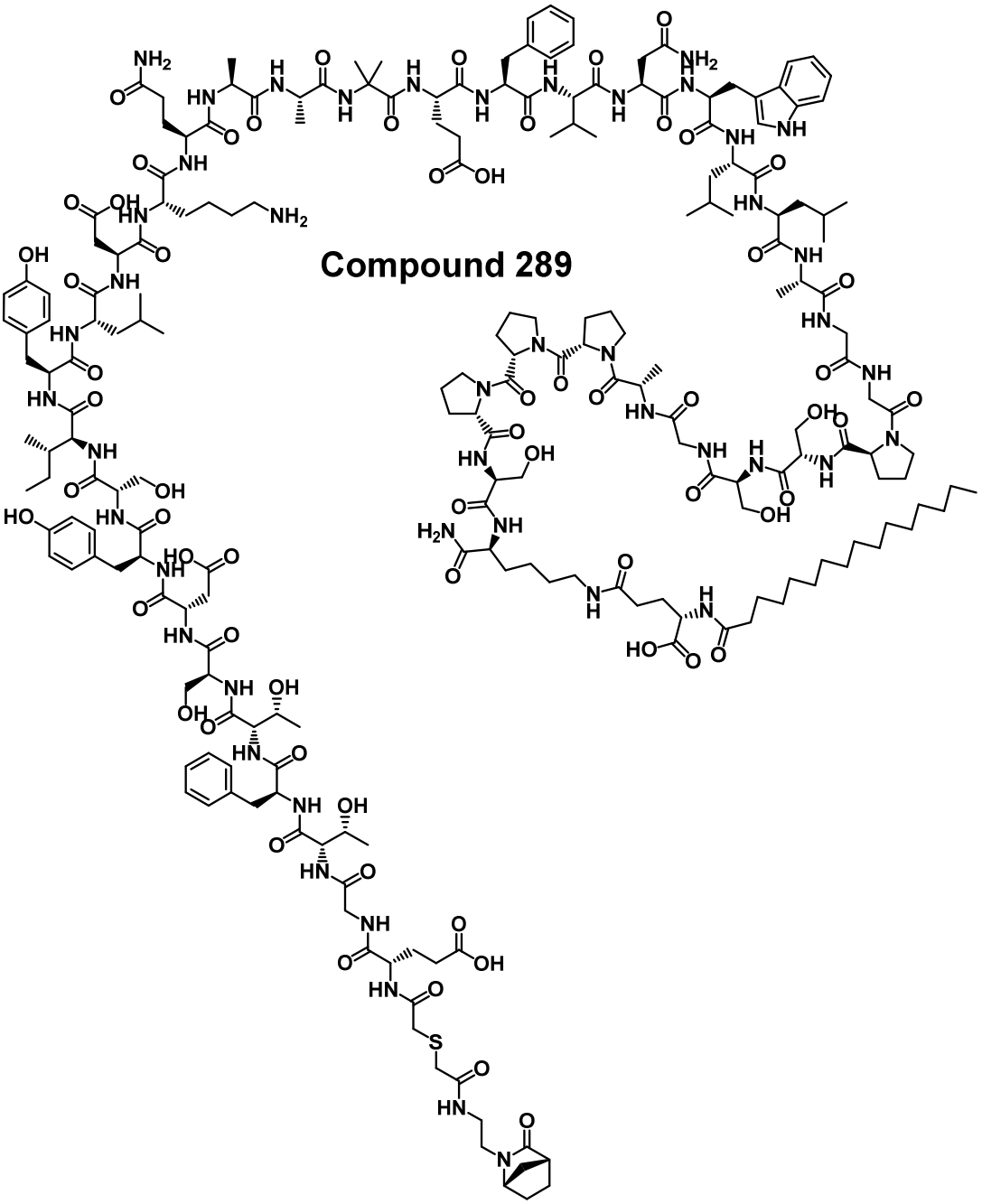


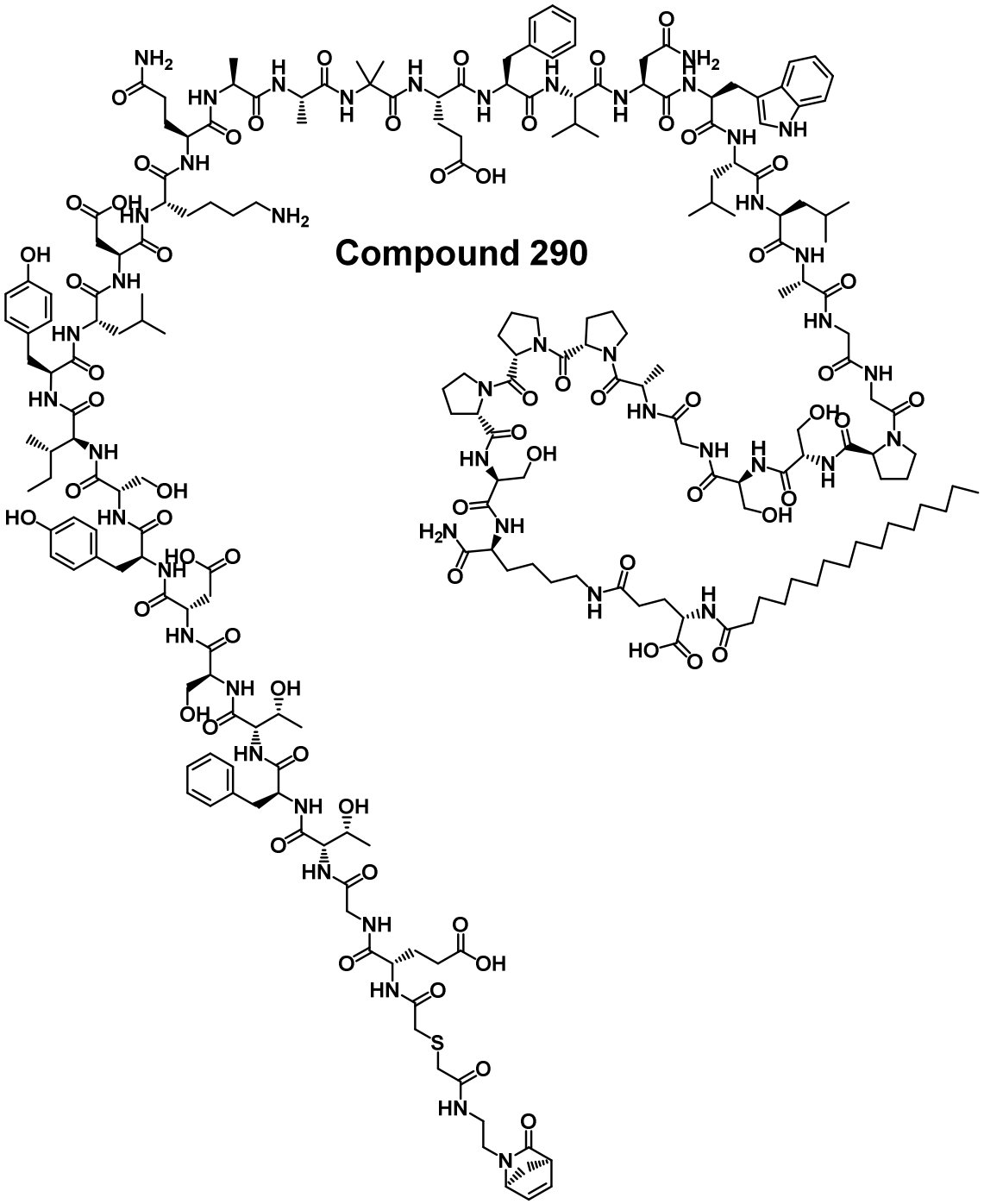
Compound 267

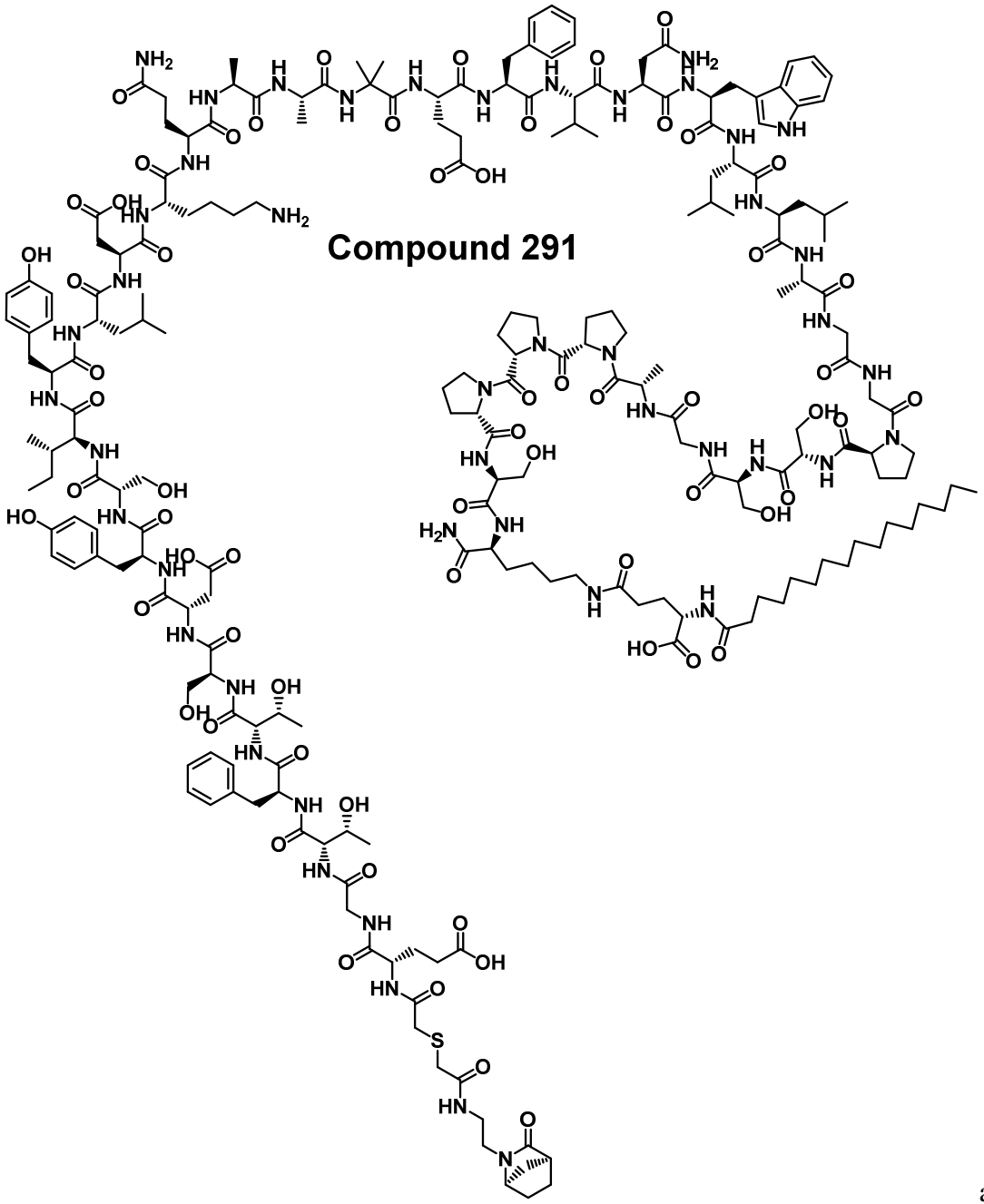

Compound 270



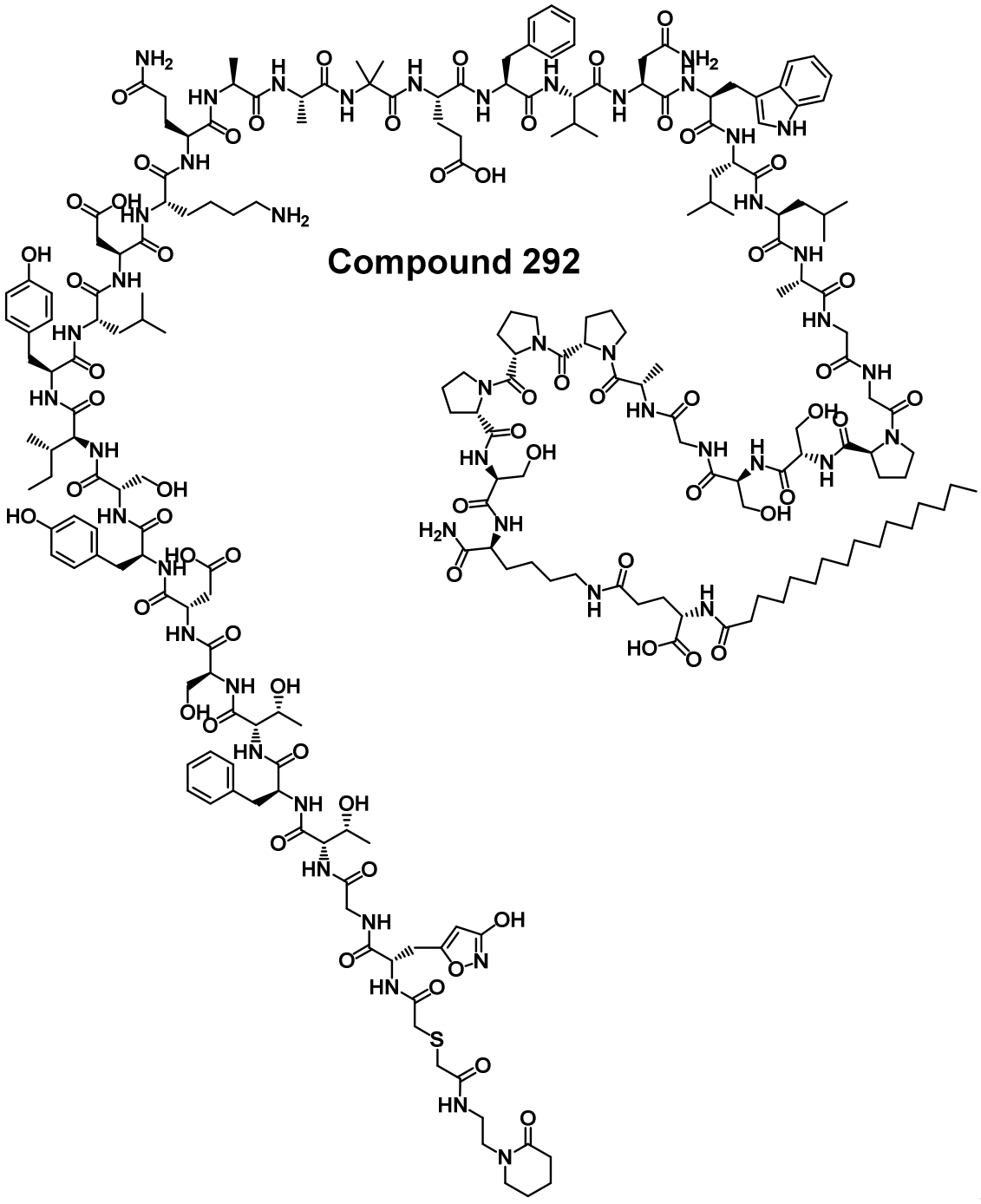
Compound 285


Compound 289

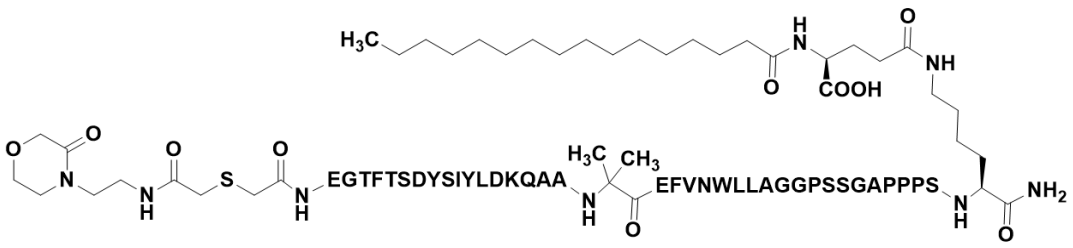

Compound 290

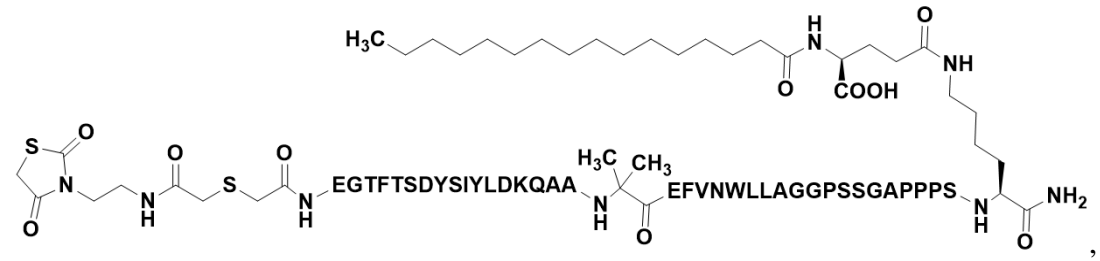


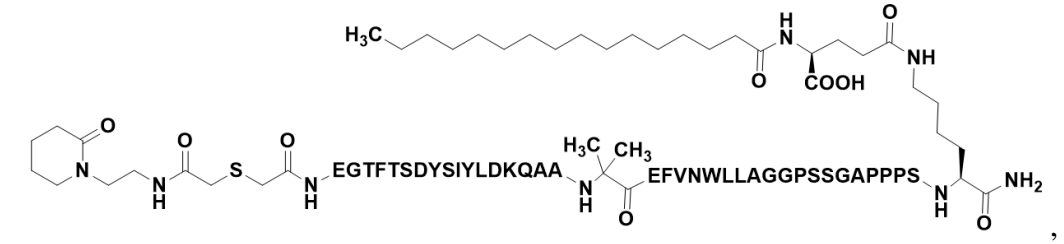
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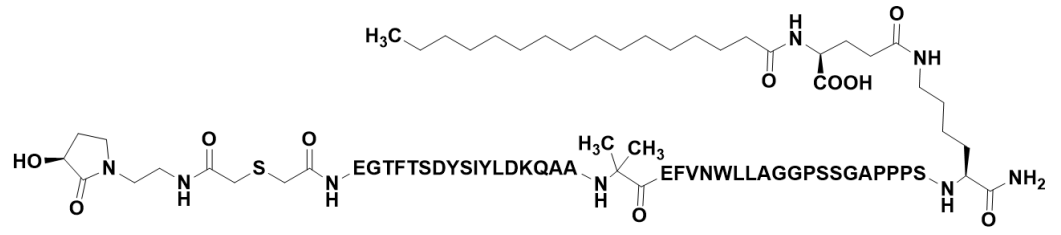


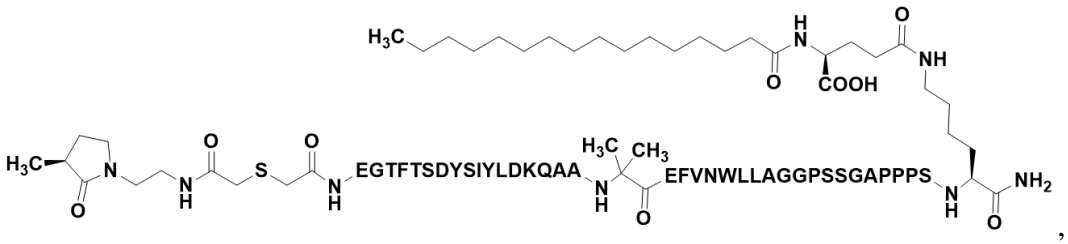
31. A compound selected from the group consisting of:

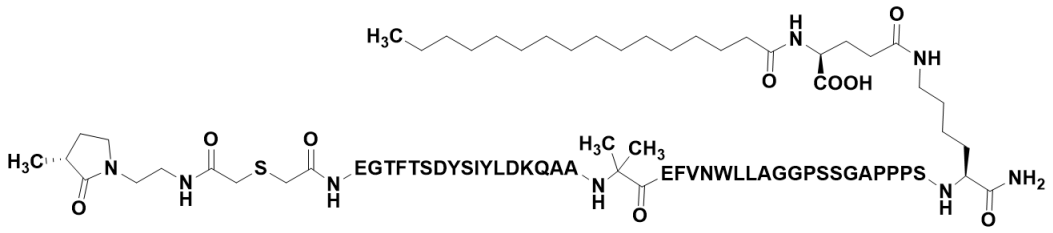

H3C
O
N
H
O
NH
COOH
O
O
N
O
O
NH
S
O
N
H
EGTFTSDYSIYLDKQAA
H3C
CH3
N
H
O
EFVNWLLAGGPSSGAPPPS
N
H
NH2
O
,


H3C
O
N
H
O
NH
COOH
O
S
O
N
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NH
S
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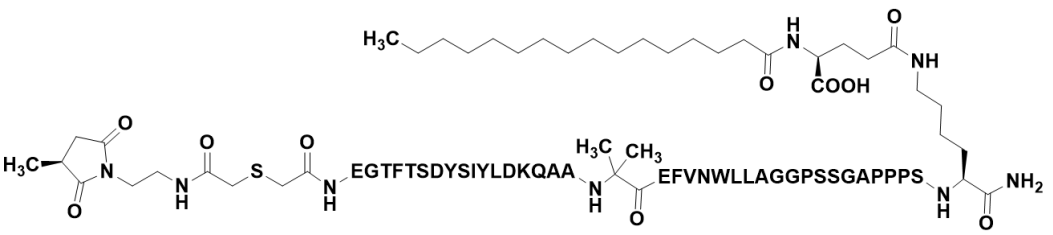

H3C
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NH
COOH
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O
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NH
S
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H
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H3C
CH3
N
H
O
EFVNWLLAGGPSSGAPPPS
N
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NH2
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,


H3C
O
N
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NH
COOH
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HO
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NH
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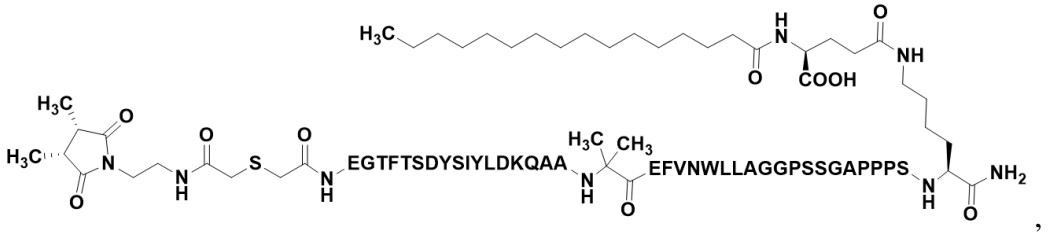

H3C
O
N
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NH
COOH
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H3C
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O
NH
S
O
N
H
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CH3
N
H
O
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N
H
NH2
O
,



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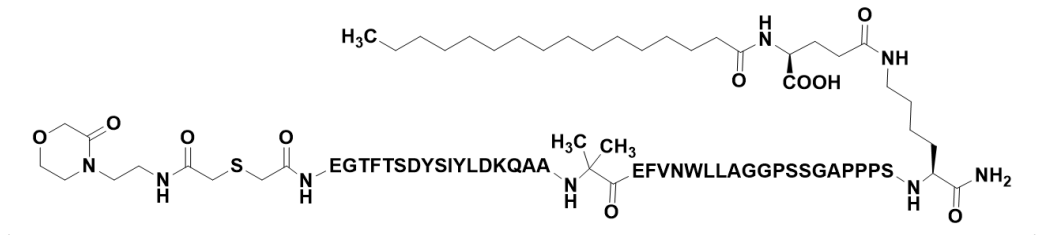
, and



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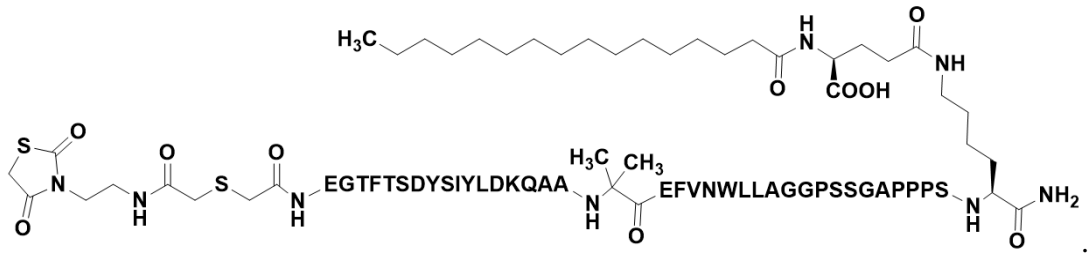
or a pharmaceutically acceptable salt thereof.

32. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:

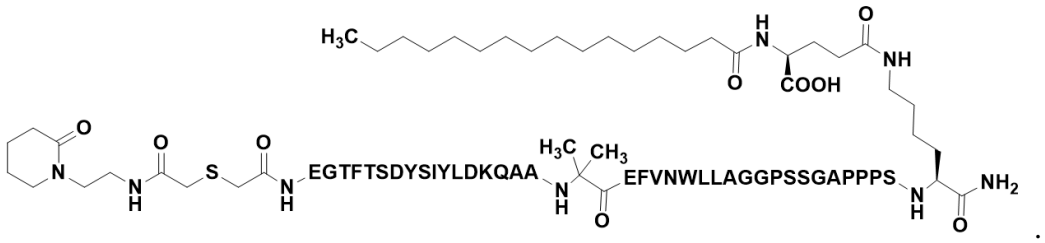


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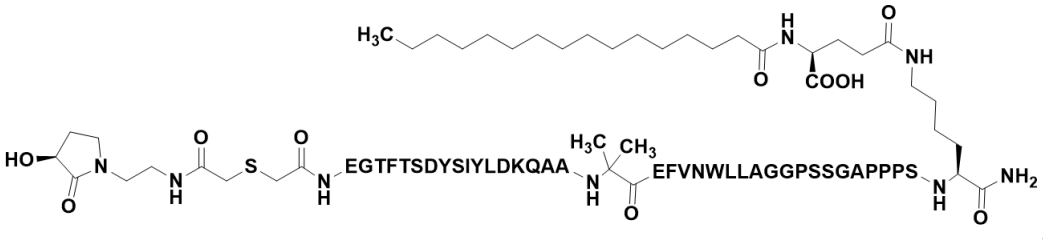
33. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



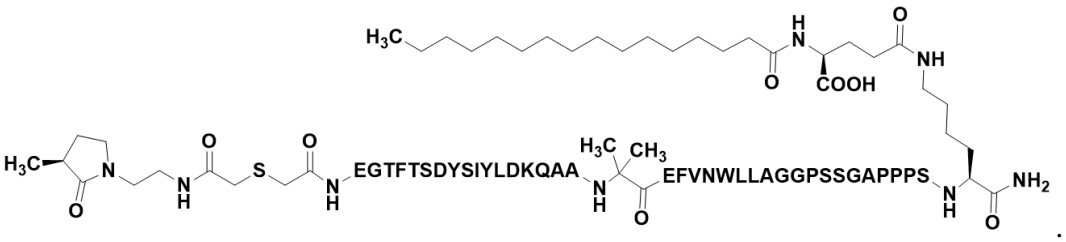
34. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



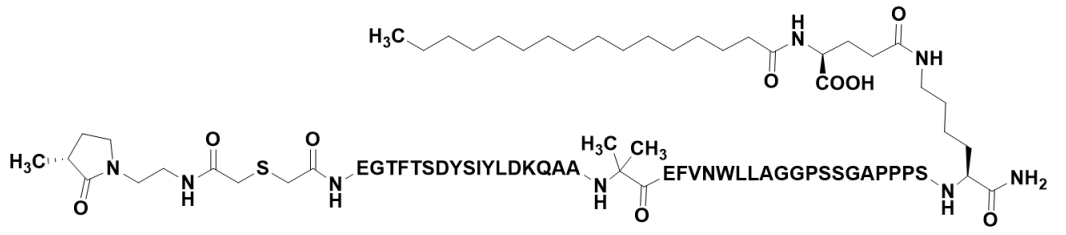
35. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



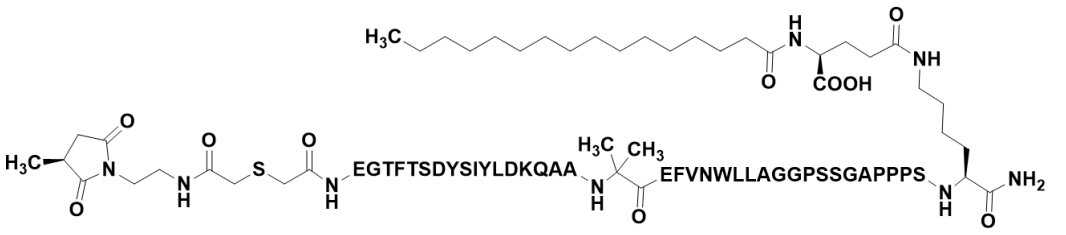
36. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



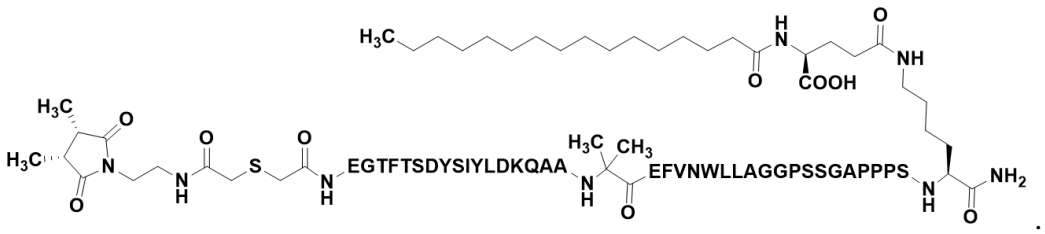
37. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



38. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



39. The compound, or pharmaceutically acceptable salt thereof, of claim 31, wherein the compound is:



40. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof of any one of claims 1-39 and one or more pharmaceutically acceptable excipients.

41. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for modulating glucagon-like peptide-1 receptor (GLP-1R) and/or gastric inhibitory polypeptide receptor (GIPR) activity.

42. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for increasing insulin levels in a human subject in need of such increasing.

43. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for decreasing glucose levels in a human subject in need of such decreasing.

44. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for

treating diabetes, NASH, obesity, fatty liver disease, or steatohepatitis in a human subject in need thereof.

45. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for treating type 2 diabetes mellitus in a human subject in need thereof.

46. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for treating obesity in a human subject in need thereof.

47. The use of claim 46, wherein the medicament is to be administered to the subject in combination with a diet therapy or an exercise therapy.

48. Use of the compound, or pharmaceutically acceptable salt thereof, of any one of claims 1-39 or the pharmaceutical composition of claim 40 in the manufacture of a medicament for treating metabolic syndrome, diabetes, obesity, obesity-related disorders, impaired glucose tolerance, insulin resistance, non-alcoholic steatohepatitis (NASH), fatty liver disease, steatohepatitis, brain insulin resistance, mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, dementia, 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, neuropathy,

Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis (ALS), glaucoma, Creutzfeld-Jakob Disease, bovine spongiform encephalopathy, cognitive dysfunction, chronic wasting syndrome, osteoporosis, post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodistrophy in liver disease, coronary artery disease, peripheral artery disease, cerebrovascular disease, hypertension, retinopathy, nephropathy, bone fracture, or altered bone metabolism caused by renal failure, haemodialysis, bone fracture, bone surgery, aging, or pregnancy.