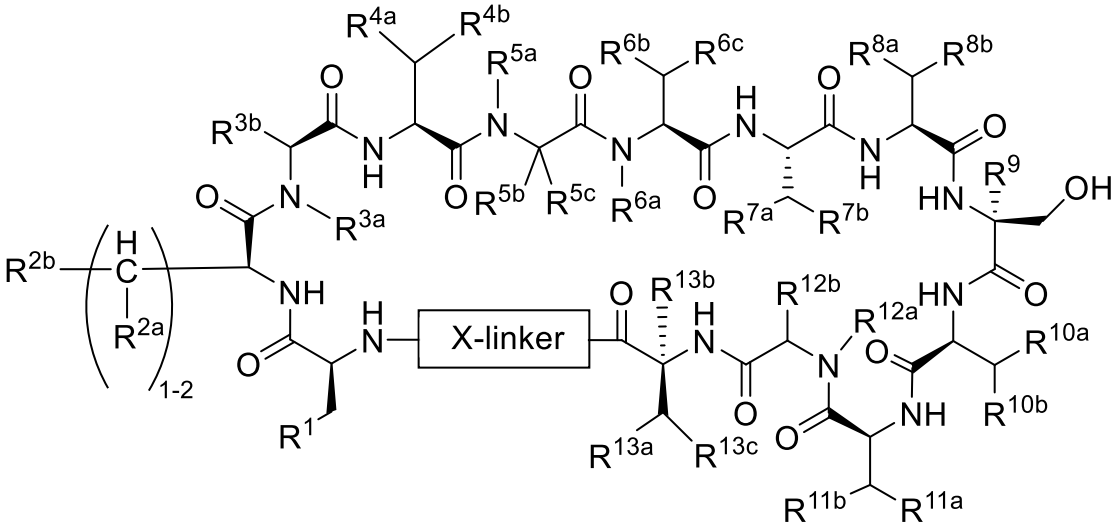
SUMMARY OF THE DISCLOSURE

The present disclosure provides certain cyclic peptides that reduce inflammation by selectively inhibiting TNFR1 to specifically attenuate the proinflammatory activities of TNFα mediated by TNFR1 signaling, and to spare / passively enable TNFα–TNFR2 pro-homeostatic signaling. These cyclic peptides can be valuable pharmaceutically active compounds for the treatment of prevalent autoimmune and inflammatory diseases including ulcerative colitis (UC), Crohn's disease (CD), collectively referred to as inflammatory bowel diseases (IBD), as well as rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), psoriasis and other inflammatory conditions that can be treated by blockade of TNFα signaling like psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, hidradenitis suppurativa, and other dermatological disorders, as well as other neurological, neurodegenerative, metabolic and ocular disorders.

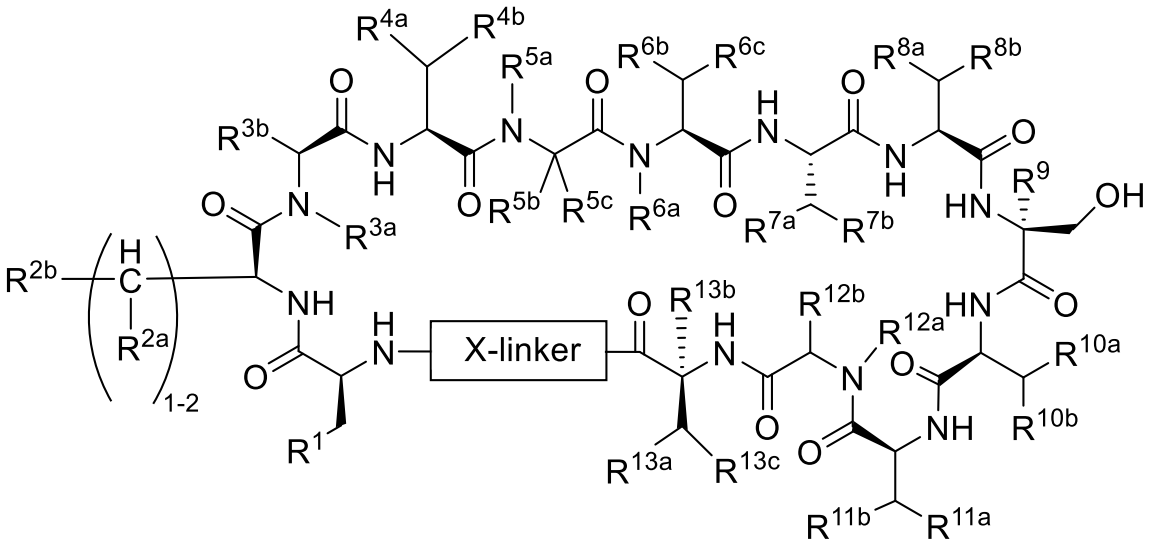
The present disclosure provides compounds of Formula (I)



(I),

and their pharmaceutically acceptable salts.

In one aspect, the present disclosure provides ac compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein



(I)

R^1 is selected from hydrogen, C_{1-10} alkyl, $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl$)$oxy$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_3N^+(C_{0-6}$ alkyl), aryl$(C_{0-10}$ alkyl), heteroaryl$(C_{0-10}$ alkyl), (C_{3-12})cycloalkyl$(C_{0-10}$ alkyl), heterocycloalkyl$(C_{0-10}$ alkyl), C_{1-10} fluoroalkyl, C_{2-10} alkenyl, $(C_{0-6}$ alkyl$)$carbonylamino$(C_{0-6}$ alkyl), $(C_{0-6}$ alkyl$)_{0-2}$ aminocarbonyl$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ aminocarbonylamino$(C_{0-6}$ alkyl), arylcarbonylamino$(C_{0-6}$ alkyl), arylaminocarbonyl$(C_{0-6}$ alkyl), heteroarylcarbonylamino$(C_{0-6}$ alkyl), heteroarylaminocarbonyl$(C_{0-6}$ alkyl), C_{1-6} alkyloxy, $(C_{1-6}$ alkyl$)$oxy$(C_{0-6}$ alkyl), $((C_{3-12})$cycloalkyl$)$oxy$(C_{0-6}$ alkyl), $((C_{3-12})$cycloalkyl C_{0-6} alkyl$)$oxy$(C_{0-6}$ alkyl), $(C_{0-6}$ alkyl$)$carboxy$(C_{0-6}$ alkyl), $N^-{=}N^+{=}N{-}(C_{0-6}$ alkyl), and $H_2N{-}C(=NH)NH{-}(C_{0-6}$ alkyl),

wherein **R^1** is substituted by 0, 1, 2, 3, or 4 **R^{1a}** substituents each independently selected from C_{1-6} alkyl, amino, cyano, halo, hydroxy, (C_{3-12})cycloalkyloxy, and C_{1-6} alkyloxy;

each **R^{2a}** is independently selected from hydrogen, hydroxy, C_{1-4} alkyl, fluoro, and C_{1-4} alkyloxy;

R^{2b} is selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said heteroaryl contains at least one nitrogen atom,

wherein **R^{2b}** is substituted by 0, 1, or 2 **R^{2c}** independently selected from C_{1-6} alkyl, amino$(C_{0-6}$ alkyl$)$, $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-6}$ alkyl$)$, $(C_{1-6}$ alkyl$)_3N^+(C_{0-6}$ alkyl),

aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), hydroxy, C_{1-6} alkyloxy, halo, (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyloxy), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyloxy), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), carboxy(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), C_{1-6} haloalkyl, C_{1-6} haloalkyloxy, and C_{1-6} alkyloxy;

R^{3a} is selected from hydrogen, hydroxy, hydroxy(C_{1-6} alkyl), amino, amino(C_{1-6} alkyl), C_{1-10} alkyl, (C_{3-12})cycloalkyl(C_{0-10} alkyl), (C_{0-6} alkyl)thio(C_{1-6} alkyl), and carboxy(C_{1-6} alkyl), wherein **R^{3a}** may be substituted by 0, 1, or 2 **R^{3c}** substituents;

R^{3b} is selected from hydrogen, C_{1-10} alkyl, hydroxy(C_{1-6} alkyl), amino(C_{1-10} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-10} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl), C_{1-6} haloalkyl, aryl(C_{0-10} alkyl), heteroaryl(C_{0-10} alkyl), (C_{3-12})cycloalkyl(C_{0-10} alkyl), heterocycloalkyl(C_{0-10} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), (C_{3-12})cycloalkyloxy(C_{1-6} alkyl), carboxy(C_{1-6} alkyl), aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{1-6} alkyl), aminocarbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{1-6} alkyl), (C_{0-6} alkyl)thio(C_{1-6} alkyl), (C_{1-6} alkyl)SO_2(C_{1-6} alkyl), and (C_{1-6} alkyl)sulfinyl(C_{1-6} alkyl), wherein **R^{3b}** may be substituted by 0, 1, or 2 **R^{3c}** substituents;

each **R^{3c}** is independently selected from halo, C_{1-6} alkyl, amino, (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$–, (C_{1-6} alkyl)SO_2(C_{0-6} alkyl), cyano, cyano(C_{1-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), (C_{1-6} alkyl)oxy(C_{0-6} alkyl), aminocarbonyl(C_{0-6} alkyl), and (C_{0-6}) carboxy(C_{0-6} alkyl);

and wherein **R^{3a}** and **R^{3b}**, together with the atoms to which they are attached, may form a saturated ring system, wherein said saturated ring system may be substituted by 0, 1, or 2 **R^{3c}** substituents;

R^{4a} is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, and fluoro;

R^{4b} is selected from bicyclic heteroaryl(C_{0-3} alkyl), and bicyclic aryl(C_{0-3} alkyl),

wherein **R^{4b}** is substituted with 0, 1, or 2 **R^{4c}** substituents each independently selected from halo, hydroxy, cyano, nitro, carboxy, carboxy(C_{1-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{5a} is selected from hydrogen, C_{1-10} alkyl, C_{1-10} fluoroalkyl, carboxy(C_{1-10} alkyl), hydroxy, hydroxy(C_{1-10} alkyl), cyano(C_{1-10} alkyl), heterocycloalkyl(C_{0-10} alkyl), aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{1-6} alkyl), (carboxy(C_{1-10}

alkyl))oxy(C_{1-6} alkyl), aryl(C_{0-6} alkyl), (C_{3-12})cycloalkyl(C0-6 alkyl), heteroaryl(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-10} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), and C_{1-10} fluoroalkyl, and wherein **R^{5a}** is substituted by 0, 1, or 2 **R^{5d}** substituents;

R^{5b} is selected from hydrogen, C_{1-10} alkyl, hydroxy(C_{1-10} alkyl), carboxy(C_{1-6} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{1-6} alkyl), carboxy(C_{1-10} alkyl)oxy(C_{1-6} alkyl), cyano(C_{1-10} alkyl), amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl), heterocycloalkyl(C_{0-10} alkyl), (C_{3-12})cycloalkyl(C_{0-10} alkyl), and C_{1-10} haloalkyl, wherein **R^{5b}** is substituted by 0, 1, 2, or 3 **R^{5e}** substituents,

wherein **R^{5a}** and **R^{5b}**, together with the atoms to which they are attached, form a saturated mono- or bi-cyclic ring, wherein said mono- or bi-cyclic ring is substituted with 0, 1, 2, or 3 **R^{5d}** and 0, 1, 2, or 3 **R^{5e}**;

each **R^{5d}** is independently selected from selected from halo, hydroxy, hydroxy(C_{1-10} alkyl), C_{1-10} alkyl, carboxy, carboxy(C_{1-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino (C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino (C_{0-6} alkyl), (carboxy(C_{1-6} alkyl))oxy(C_{1-6} alkyl), cyano(C_{0-6} alkyl), tetrazolyl(C_{0-6} alkyl), and C_{1-6} haloalkyl, and two **R^{5d}** substituents together with the atom they are attached to may join together to form a saturated ring;

each **R^{5e}** is independently selected from halo, hydroxy, hydroxy(C_{1-10} alkyl), C_{1-10} alkyl, carboxy, carboxy(C_{1-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino

(C_{0-6} alkyl), (carboxy(C_{1-6} alkyl))oxy(C_{1-6} alkyl), cyano(C_{0-6} alkyl), tetrazolyl(C_{0-6} alkyl), and C_{1-6} haloalkyl, and two $\mathbf{R^{5e}}$ substituents together with the atom they are attached to may join together to form a saturated ring;

$\mathbf{R^{5c}}$ is hydrogen, C_{1-4} alkyl, hydroxy(C_{1-4} alkyl), C_{1-4} alkyloxy, or (C_{1-4} alkyl)oxy (C_{1-4} alkyl);

$\mathbf{R^{6a}}$ is selected from hydrogen, hydroxy, amino, C_{1-4} alkyloxy, and C_{1-6} alkyl;

$\mathbf{R^{6b}}$ is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{6c}}$ is selected from C_{1-10} alkyl, C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), C_{1-10} haloalkyl, aryl(C_{0-6} alkyl), heteroaryl(C_{0-10} alkyl), (C_{1-6} alkyl)SO_2(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), amino(C_{0-6} alkyl), (C1-6 alkyl)$_{0-2}$ amino(C_{0-6} alkyl), aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl) carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), and carboxy(C_{0-6} alkyl);

$\mathbf{R^{7a}}$ is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{7b}}$ is selected from aryl(C_{0-6} alkyl), heteroaryl(C_{0-6} alkyl), and (C_{3-12})cycloalkyl(C_{0-6} alkyl),

wherein $\mathbf{R^{7b}}$ is substituted by 0, 1, 2, or 3 $\mathbf{R^{7c}}$ substituents each independently selected from C_{1-6} alkyl, C_{1-10} fluoroalkyl, C_{1-10} fluoroalkyloxy, (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-5} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-5} alkyl), carboxy(C_{0-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl (C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), halo, –(C_{0-5} alkyl)–($S(=O)_2OH$), –(C_{0-5} alkyl)–($S(=O)_2NH_2$), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), aminocarbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), C_{1-10} haloalkyl, C_{1-10} haloalkyloxy, and (C_{1-6} alkyl)oxy(C_{0-6} alkyl);

$\mathbf{R^{8a}}$ is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, C_{1-6} fluoroalkyl, C_{1-4} fluoroalkyloxy, and halo;

$\mathbf{R^{8b}}$ is selected from bicyclic aryl(C_{0-3} alkyl) and bicyclic heteroaryl(C_{0-3} alkyl),

wherein $\mathbf{R^{8b}}$ is substituted by 0, 1, or 2 $\mathbf{R^{8c}}$ substituents each independently selected from C_{1-4} alkyl, halo, cyano, nitro, carboxy, amino, hydroxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkyloxy, C_{1-6} alkyloxy, amino(C_{1-3} alkyl), and hydroxy(C_{1-6} alkyl);

$\mathbf{R^{9}}$ is selected from hydrogen, and C_{1-4} alkyl;

$\mathbf{R^{10a}}$ is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{10b}}$ is selected from (C_{3-12})cycloalkyl(C_{0-3} alkyl), aryl(C_{0-3} alkyl), and heteroaryl(C_{0-3} alkyl), wherein said heteroaryl contains 1, 2, or 3 nitrogen atoms,

wherein $\mathbf{R^{10b}}$ is substituted by 0, 1, or 2 $\mathbf{R^{10c}}$ wherein each $\mathbf{R^{10c}}$ is independently selected from C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-6} haloalkyl, C_{1-10} fluoroalkyloxy, amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), cyano, halo, aminocarbonyl, aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl) carbonylamino(C_{0-6} alkyl), carboxy(C_{0-6} alkyl), (C_{1-6} alkoxy)carbonyl(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), –(C_{0-5} alkyl)–(S(=O)$_2$OH), –(C_{0-5} alkyl)–(S(=O)$_2$NH$_2$), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{0-6} alkyl), C_{1-6} haloalkyloxy, (C_{3-12}) cycloalkyl(C_{0-6} alkyl), and heterocycloalkyl(C_{0-6} alkyl);

$\mathbf{R^{11a}}$ is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{11b}}$ is selected from aryl(C_{0-3} alkyl), heteroaryl(C_{0-3} alkyl), wherein said heteroaryl contains 1, 2, or 3 nitrogen atoms, and H_2N–C(=NH)NH–(C_{1-6} alkyl),

wherein $\mathbf{R^{11b}}$ is substituted by 0, 1, 2, 3, or 4 $\mathbf{R^{11c}}$ substituents each independently selected from C_{1-6} alkyl, amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), cyano, halo, aminocarbonyl, aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), carboxy(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino (C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{0-6} alkyl), C_{1-6} haloalkyloxy, C_{1-6} haloalkyl, (C_{3-12})cycloalkyl(C_{0-6} alkyl), heterocycloalkyl(C_{0-6} alkyl), ((C_{1-6} alkyl)carbonyl)heterocycloalkyl(C_{0-10} alkyl), and ((C_{1-6} alkyl)carbonyloxy) heterocycloalkyl(C_{0-10} alkyl);

R12a is selected from hydrogen, hydroxy, amino, C_{1-10} alkyl, and (C_{3-12})cycloalkyl $(C_{0-6}$ alkyl);

R12b is selected from hydrogen, C_{1-10} alkyl, and (C_{3-12})cycloalkyl$(C_{0-6}$ alkyl);

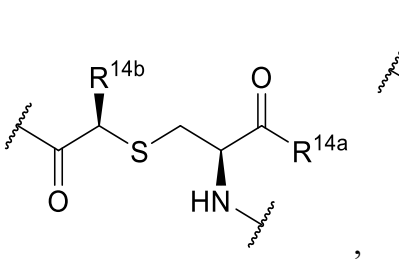
wherein **R12a** and **R12b**, together with the atoms to which they are attached, may form a saturated ring;

R13a is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

R13b is selected from hydrogen, and C_{1-4} alkyl;

R13c is selected from a bicyclic nitrogen-containing heteroaryl having 1 or 2 nitrogen and bicyclic-aryl and wherein **R13c** is substituted independently by 0, 1, or 2 **R13d** substituents each independently selected from halo, C_{1-6} alkyl, carboxy$(C_{0-4}$ alkyl), C_{1-4} haloalkyloxy, and C_{1-4} alkyloxy;

X-linker is selected from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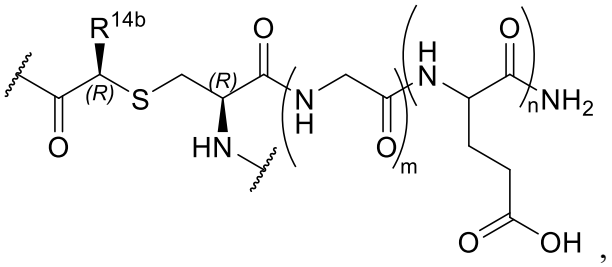
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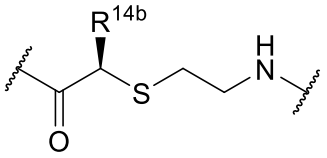
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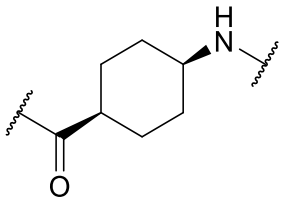
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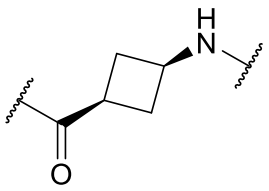
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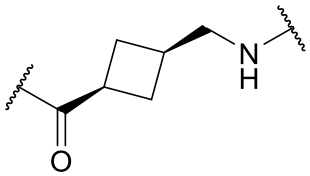
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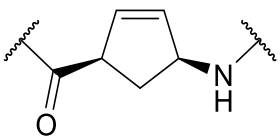
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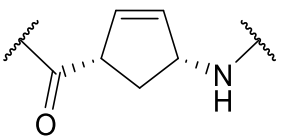
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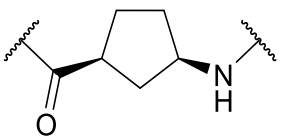
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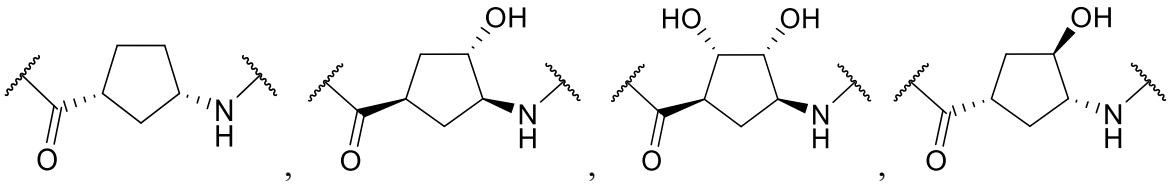

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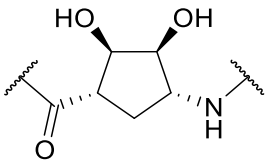


;

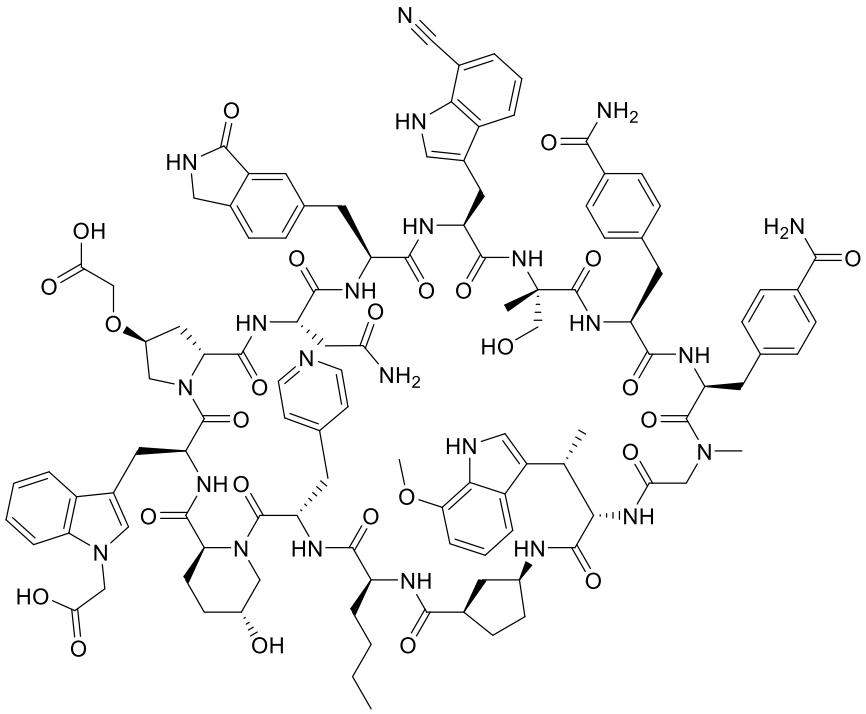
wherein $\mathbf{R^{14a}}$ is selected from amino, hydroxy, $(C_{1-6}$ alkyl$)_{0-2}$ amino, and C_{1-6} alkyloxy;

m is selected from 1, 2, 3, or 4;

n is selected from 1, 2, 3, or 4; and

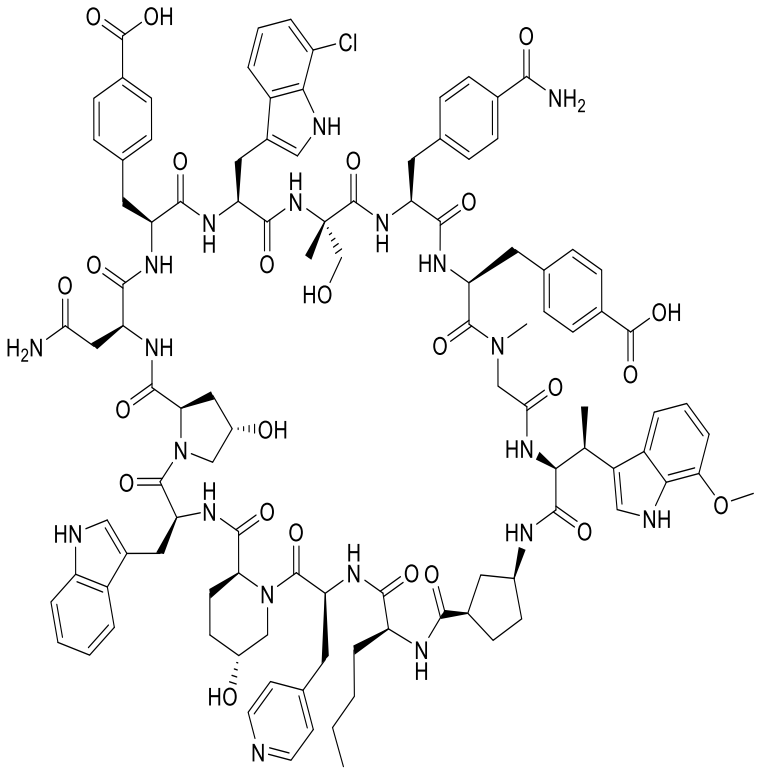
$\mathbf{R^{14b}}$ is selected from hydrogen, C_{1-8} alkyl, aryl(C_{0-6} alkyl), and heteroaryl(C_{0-6} alkyl), wherein $\mathbf{R^{14b}}$ is substituted by 0, 1, 2, or 3 halo groups.

In another aspect, the present disclosure provides the compound of **SEQ ID NO: 22**



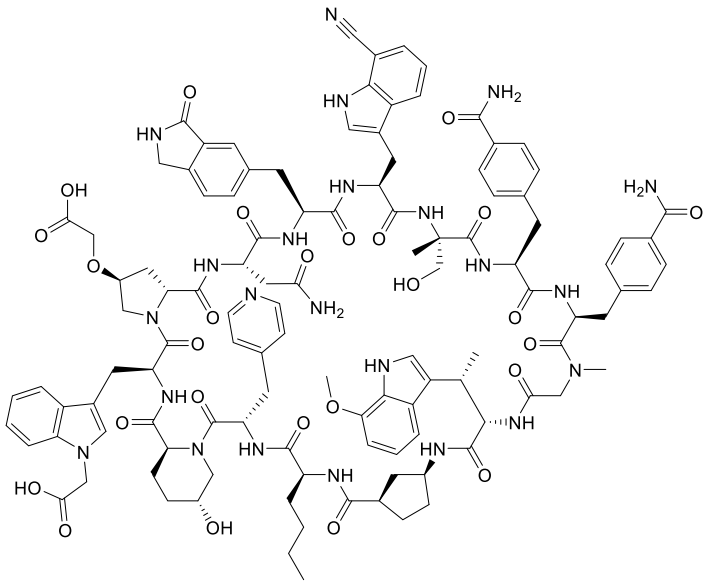
SEQ ID NO: 22.

In another aspect, the present disclosure provides the compound of **SEQ ID NO: 247**



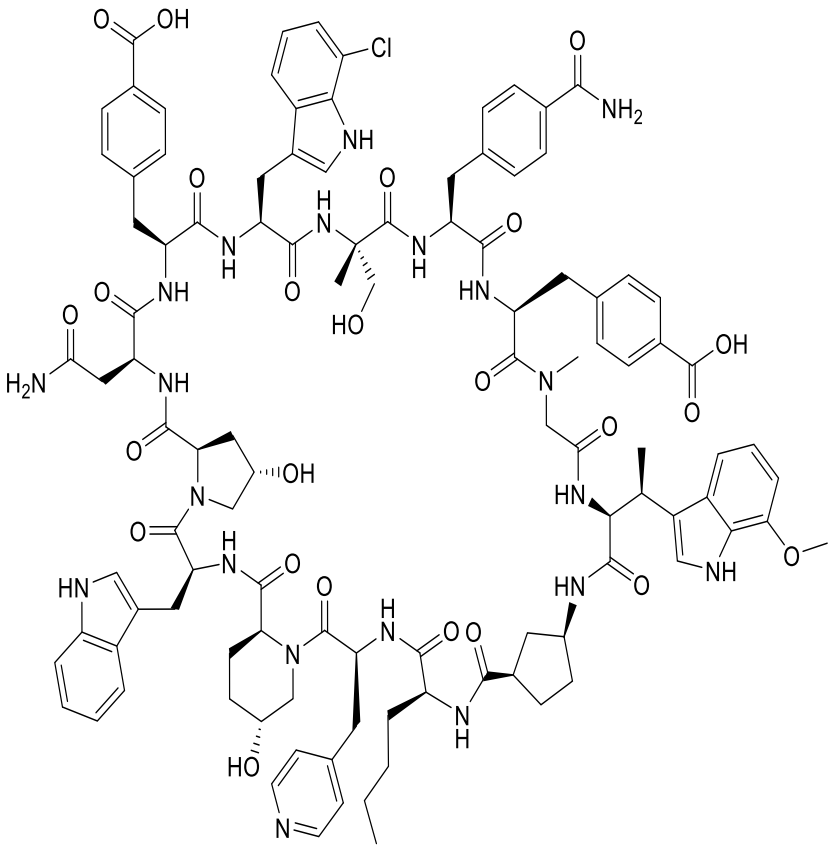
SEQ ID NO: 247.

In another aspect, the present disclosure provides the compound of **SEQ ID NO: 22**



SEQ ID NO: 22, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides the compound of **SEQ ID NO: 247**



SEQ ID NO: 247, or a pharmaceutically acceptable salt thereof.

The compounds of the present disclosure have the potential to provide superior, more durable efficacy over non-selective anti-TNFα SOC, through inhibition of TNFR1-driven inflammation that concomitantly spares TNFR2-dependent homeostasis, mucosal/tissue healing, and immune regulation. Accordingly, the present disclosure also provides a method for treating autoimmune and inflammatory diseases (*e.g.*, ulcerative colitis, Crohn's disease, collectively referred to as IBD, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and hidradenitis suppurativa) comprising administering a therapeutically effective amount of the

compound of the disclosure to a subject in need thereof. In some examples, the administration comprises an oral administration of the compound.

In another aspect, the present disclosure provides use of a compound as defined herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases to a subject in need of such treatment, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt thereof for use in therapy.

In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis and Crohn's disease.

In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

The disclosure furthermore provides processes for preparing compounds of the disclosure and pharmaceutical compositions which comprise compounds of the disclosure and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound as defined herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides the pharmaceutical composition as defined herein for use in treating IBD and other TNFα-driven inflammatory diseases, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

In another aspect, the present disclosure provides use of a compound as defined herein or the pharmaceutical composition as defined herein in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis and Crohn's disease.

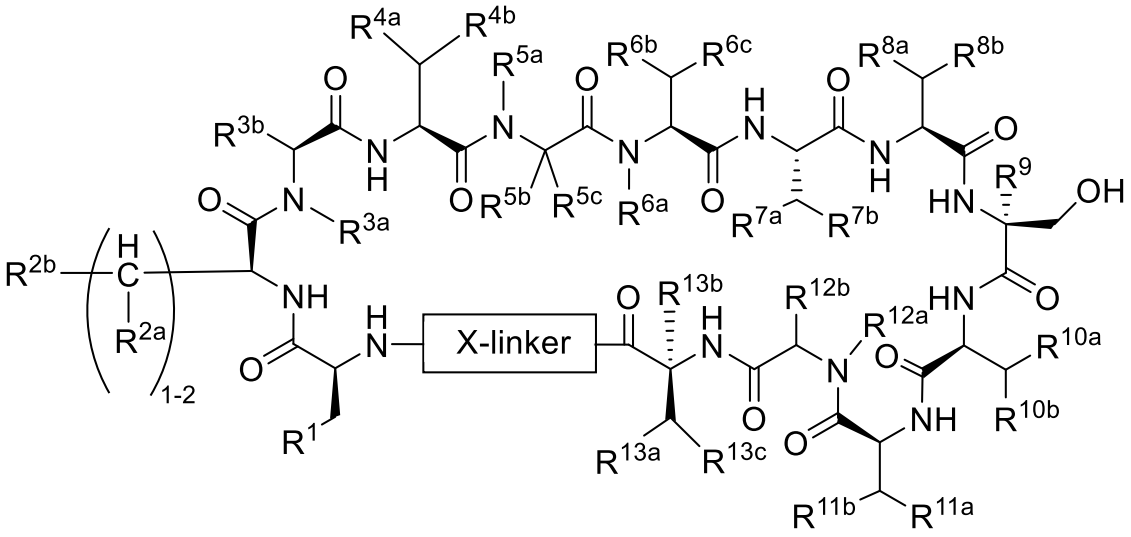
In another aspect, the present disclosure provides use of a compound as defined herein or the pharmaceutical composition as defined herein in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

In another aspect, the present disclosure provides a compound as defined herein or the pharmaceutical composition as defined herein for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the Disclosure

In one embodiment, the present disclosure provides a compound having structural Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

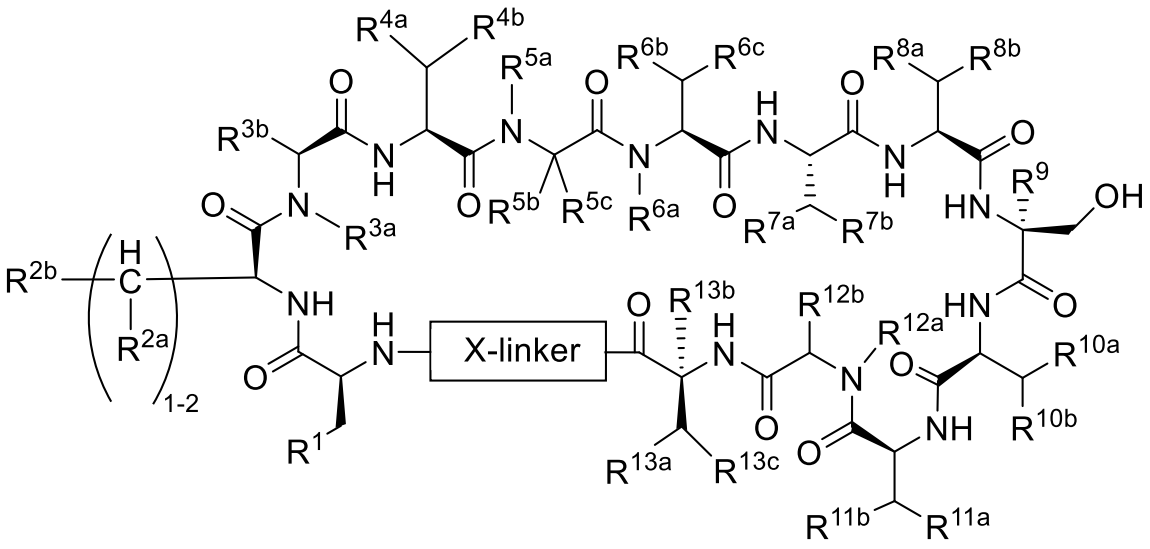
R^1 is selected from hydrogen, C_{1-10} alkyl, $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl$)$oxy$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_3N^+(C_{0-6}$ alkyl), aryl$(C_{0-10}$ alkyl), heteroaryl$(C_{0-10}$ alkyl), (C_{3-12})cycloalkyl$(C_{0-10}$ alkyl), heterocycloalkyl$(C_{0-10}$ alkyl), C_{1-10} fluoroalkyl, C_{2-10} alkenyl, $(C_{0-6}$ alkyl$)$carbonylamino$(C_{0-6}$ alkyl), $(C_{0-6}$ alkyl$)_{0-2}$ aminocarbonyl$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ aminocarbonylamino$(C_{0-6}$ alkyl),

arylcarbonylamino(C_{0-6} alkyl), arylaminocarbonyl(C_{0-6} alkyl), heteroarylcarbonylamino(C_{0-6} alkyl), heteroarylaminocarbonyl(C_{0-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{0-6} alkyl), ((C_{3-12})cycloalkyl)oxy(C_{0-6} alkyl), ((C_{3-12})cycloalkyl C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{0-6} alkyl)carboxy(C_{0-6} alkyl), $N^-=N^+=N$–(C_{0-6} alkyl), and H_2N–C(=NH)NH–(C_{0-6} alkyl),

CLAIMS

What is claimed is:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein



(I)

R1 is selected from hydrogen, C_{1-10} alkyl, $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ amino$(C_{0-10}$ alkyl$)$oxy$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_3N^+(C_{0-6}$ alkyl), aryl$(C_{0-10}$ alkyl), heteroaryl$(C_{0-10}$ alkyl), (C_{3-12})cycloalkyl$(C_{0-10}$ alkyl), heterocycloalkyl$(C_{0-10}$ alkyl), C_{1-10} fluoroalkyl, C_{2-10} alkenyl, $(C_{0-6}$ alkyl$)$carbonylamino$(C_{0-6}$ alkyl), $(C_{0-6}$ alkyl$)_{0-2}$ aminocarbonyl$(C_{0-6}$ alkyl), $(C_{1-6}$ alkyl$)_{0-2}$ aminocarbonylamino$(C_{0-6}$ alkyl), arylcarbonylamino$(C_{0-6}$ alkyl), arylaminocarbonyl$(C_{0-6}$ alkyl), heteroarylcarbonylamino$(C_{0-6}$ alkyl), heteroarylaminocarbonyl$(C_{0-6}$ alkyl), C_{1-6} alkyloxy, $(C_{1-6}$ alkyl$)$oxy$(C_{0-6}$ alkyl), $((C_{3-12})$cycloalkyl$)$oxy$(C_{0-6}$ alkyl), $((C_{3-12})$cycloalkyl C_{0-6} alkyl$)$oxy$(C_{0-6}$ alkyl), $(C_{0-6}$ alkyl$)$carboxy$(C_{0-6}$ alkyl), $N^-{=}N^+{=}N{-}(C_{0-6}$ alkyl), and $H_2N{-}C(=NH)NH{-}(C_{0-6}$ alkyl),

wherein **R1** is substituted by 0, 1, 2, 3, or 4 **R1a** substituents each independently selected from C_{1-6} alkyl, amino, cyano, halo, hydroxy, (C_{3-12})cycloalkyloxy, and C_{1-6} alkyloxy;

each **R2a** is independently selected from hydrogen, hydroxy, C_{1-4} alkyl, fluoro, and C_{1-4} alkyloxy;

$\mathbf{R^{2b}}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein said heteroaryl contains at least one nitrogen atom,

wherein $\mathbf{R^{2b}}$ is substituted by 0, 1, or 2 $\mathbf{R^{2c}}$ independently selected from $C_{1\text{-}6}$ alkyl, amino($C_{0\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ amino($C_{0\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_3N^+$($C_{0\text{-}6}$ alkyl), aminocarbonyl($C_{0\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ aminocarbonyl($C_{0\text{-}6}$ alkyl), hydroxy, $C_{1\text{-}6}$ alkyloxy, halo, ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ amino($C_{0\text{-}6}$ alkyloxy), ($C_{1\text{-}6}$ alkyl)$_3N^+$($C_{0\text{-}6}$ alkyloxy), ($C_{1\text{-}6}$ alkyloxy)carbonyl($C_{0\text{-}6}$ alkyl), carboxy($C_{0\text{-}6}$ alkyl), carboxy($C_{1\text{-}6}$ alkyl)oxy($C_{0\text{-}6}$ alkyl), $C_{1\text{-}6}$ haloalkyl, $C_{1\text{-}6}$ haloalkyloxy, and $C_{1\text{-}6}$ alkyloxy;

$\mathbf{R^{3a}}$ is selected from hydrogen, hydroxy, hydroxy($C_{1\text{-}6}$ alkyl), amino, amino($C_{1\text{-}6}$ alkyl), $C_{1\text{-}10}$ alkyl, ($C_{3\text{-}12}$)cycloalkyl($C_{0\text{-}10}$ alkyl), ($C_{0\text{-}6}$ alkyl)thio($C_{1\text{-}6}$ alkyl), and carboxy($C_{1\text{-}6}$ alkyl), wherein $\mathbf{R^{3a}}$ may be substituted by 0, 1, or 2 $\mathbf{R^{3c}}$ substituents;

$\mathbf{R^{3b}}$ is selected from hydrogen, $C_{1\text{-}10}$ alkyl, hydroxy($C_{1\text{-}6}$ alkyl), amino($C_{1\text{-}10}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ amino($C_{1\text{-}10}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_3N^+$($C_{1\text{-}6}$ alkyl), $C_{1\text{-}6}$ haloalkyl, aryl($C_{0\text{-}10}$ alkyl), heteroaryl($C_{0\text{-}10}$ alkyl), ($C_{3\text{-}12}$)cycloalkyl($C_{0\text{-}10}$ alkyl), heterocycloalkyl($C_{0\text{-}10}$ alkyl), ($C_{1\text{-}6}$ alkyl)oxy($C_{1\text{-}6}$ alkyl), ($C_{3\text{-}12}$)cycloalkyloxy($C_{1\text{-}6}$ alkyl), carboxy($C_{1\text{-}6}$ alkyl), aminocarbonyl($C_{1\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ aminocarbonyl($C_{1\text{-}6}$ alkyl), aminocarbonylamino($C_{1\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ aminocarbonylamino($C_{1\text{-}6}$ alkyl), ($C_{0\text{-}6}$ alkyl)thio($C_{1\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)SO_2($C_{1\text{-}6}$ alkyl), and ($C_{1\text{-}6}$ alkyl)sulfinyl($C_{1\text{-}6}$ alkyl), wherein $\mathbf{R^{3b}}$ may be substituted by 0, 1, or 2 $\mathbf{R^{3c}}$ substituents;

each $\mathbf{R^{3c}}$ is independently selected from halo, $C_{1\text{-}6}$ alkyl, amino, ($C_{1\text{-}6}$ alkyl)$_{0\text{-}2}$ amino($C_{0\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)$_3N^+$–, ($C_{1\text{-}6}$ alkyl)SO_2($C_{0\text{-}6}$ alkyl), cyano, cyano($C_{1\text{-}6}$ alkyl), hydroxy, hydroxy($C_{1\text{-}6}$ alkyl), ($C_{1\text{-}6}$ alkyl)oxy($C_{0\text{-}6}$ alkyl), aminocarbonyl($C_{0\text{-}6}$ alkyl), and ($C_{0\text{-}6}$) carboxy($C_{0\text{-}6}$ alkyl);

and wherein $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$, together with the atoms to which they are attached, may form a saturated ring system, wherein said saturated ring system may be substituted by 0, 1, or 2 $\mathbf{R^{3c}}$ substituents;

$\mathbf{R^{4a}}$ is selected from hydrogen, $C_{1\text{-}6}$ alkyl, hydroxy, $C_{1\text{-}4}$ alkyloxy, and fluoro;

$\mathbf{R^{4b}}$ is selected from bicyclic heteroaryl($C_{0\text{-}3}$ alkyl), and bicyclic aryl($C_{0\text{-}3}$ alkyl),

wherein $\mathbf{R^{4b}}$ is substituted with 0, 1, or 2 $\mathbf{R^{4c}}$ substituents each independently selected from halo, hydroxy, cyano, nitro, carboxy, carboxy(C_{1-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), C_{1-6} alkyl, and C_{1-6} haloalkyl;

$\mathbf{R^{5a}}$ is selected from hydrogen, C_{1-10} alkyl, C_{1-10} fluoroalkyl, carboxy(C_{1-10} alkyl), hydroxy, hydroxy(C_{1-10} alkyl), cyano(C_{1-10} alkyl), heterocycloalkyl(C_{0-10} alkyl), aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{1-6} alkyl), (carboxy(C_{1-10} alkyl))oxy(C_{1-6} alkyl), aryl(C_{0-6} alkyl), (C_{3-12})cycloalkyl(C0-6 alkyl), heteroaryl(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-10} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), and C_{1-10} fluoroalkyl, and wherein $\mathbf{R^{5a}}$ is substituted by 0, 1, or 2 $\mathbf{R^{5d}}$ substituents;

$\mathbf{R^{5b}}$ is selected from hydrogen, C_{1-10} alkyl, hydroxy(C_{1-10} alkyl), carboxy(C_{1-6} alkyl), (C_{1-6} alkyl)oxy(C_{1-6} alkyl), aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{1-6} alkyl), carboxy(C_{1-10} alkyl)oxy(C_{1-6} alkyl), cyano(C_{1-10} alkyl), amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino(C_{1-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl), heterocycloalkyl(C_{0-10} alkyl), (C_{3-12})cycloalkyl(C_{0-10} alkyl), and C_{1-10} haloalkyl, wherein $\mathbf{R^{5b}}$ is substituted by 0, 1, 2, or 3 $\mathbf{R^{5e}}$ substituents,

wherein $\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$, together with the atoms to which they are attached, form a saturated mono- or bi-cyclic ring, wherein said mono- or bi-cyclic ring is substituted with 0, 1, 2, or 3 $\mathbf{R^{5d}}$ and 0, 1, 2, or 3 $\mathbf{R^{5e}}$;

each $\mathbf{R^{5d}}$ is independently selected from selected from halo, hydroxy, hydroxy(C_{1-10} alkyl), C_{1-10} alkyl, carboxy, carboxy(C_{1-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino (C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino (C_{0-6} alkyl), (carboxy(C_{1-6} alkyl))oxy(C_{1-6} alkyl), cyano(C_{0-6} alkyl), tetrazolyl(C_{0-6} alkyl),

and C_{1-6} haloalkyl, and two $\mathbf{R^{5d}}$ substituents together with the atom they are attached to may join together to form a saturated ring;

each $\mathbf{R^{5e}}$ is independently selected from halo, hydroxy, hydroxy(C_{1-10} alkyl), C_{1-10} alkyl, carboxy, carboxy(C_{1-6} alkyl), C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{1-6} alkyl)carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{2-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{1-6} alkyl)carbonylamino (C_{0-6} alkyl), (carboxy(C_{1-6} alkyl))oxy(C_{1-6} alkyl), cyano(C_{0-6} alkyl), tetrazolyl(C_{0-6} alkyl), and C_{1-6} haloalkyl, and two $\mathbf{R^{5e}}$ substituents together with the atom they are attached to may join together to form a saturated ring;

$\mathbf{R^{5c}}$ is hydrogen, C_{1-4} alkyl, hydroxy(C_{1-4} alkyl), C_{1-4} alkyloxy, or (C_{1-4} alkyl)oxy (C_{1-4} alkyl);

$\mathbf{R^{6a}}$ is selected from hydrogen, hydroxy, amino, C_{1-4} alkyloxy, and C_{1-6} alkyl;

$\mathbf{R^{6b}}$ is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{6c}}$ is selected from C_{1-10} alkyl, C_{1-6} alkyloxy, (C_{1-6} alkyl)oxy(C_{1-6} alkyl), C_{1-10} haloalkyl, aryl(C_{0-6} alkyl), heteroaryl(C_{0-10} alkyl), (C_{1-6} alkyl)SO_2(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), amino(C_{0-6} alkyl), (C1-6 alkyl)$_{0-2}$ amino(C_{0-6} alkyl), aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl) carbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), and carboxy(C_{0-6} alkyl);

$\mathbf{R^{7a}}$ is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, and fluoro;

$\mathbf{R^{7b}}$ is selected from aryl(C_{0-6} alkyl), heteroaryl(C_{0-6} alkyl), and (C_{3-12})cycloalkyl(C_{0-6} alkyl),

wherein $\mathbf{R^{7b}}$ is substituted by 0, 1, 2, or 3 $\mathbf{R^{7c}}$ substituents each independently selected from C_{1-6} alkyl, C_{1-10} fluoroalkyl, C_{1-10} fluoroalkyloxy, (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-5} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-5} alkyl), carboxy(C_{0-6} alkyl), (C_{1-6} alkyloxy)carbonyl(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl (C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), halo, –(C_{0-5} alkyl)–($S(=O)_2OH$), –(C_{0-5} alkyl)– ($S(=O)_2NH_2$), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl)oxy(C_{0-6}

alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), aminocarbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), C_{1-10} haloalkyl, C_{1-10} haloalkyloxy, and (C_{1-6} alkyl)oxy(C_{0-6} alkyl);

R^{8a} is selected from hydrogen, C_{1-6} alkyl, hydroxy, C_{1-4} alkyloxy, C_{1-6} fluoroalkyl, C_{1-4} fluoroalkyloxy, and halo;

R^{8b} is selected from bicyclic aryl(C_{0-3} alkyl) and bicyclic heteroaryl(C_{0-3} alkyl),

wherein **R^{8b}** is substituted by 0, 1, or 2 **R^{8c}** substituents each independently selected from C_{1-4} alkyl, halo, cyano, nitro, carboxy, amino, hydroxy, C_{1-6} fluoroalkyl, C_{1-6} fluoroalkyloxy, C_{1-6} alkyloxy, amino(C_{1-3} alkyl), and hydroxy(C_{1-6} alkyl);

R^{9} is selected from hydrogen, and C_{1-4} alkyl;

R^{10a} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

R^{10b} is selected from (C_{3-12})cycloalkyl(C_{0-3} alkyl), aryl(C_{0-3} alkyl), and heteroaryl(C_{0-3} alkyl), wherein said heteroaryl contains 1, 2, or 3 nitrogen atoms,

wherein **R^{10b}** is substituted by 0, 1, or 2 **R^{10c}** wherein each **R^{10c}** is independently selected from C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-6} haloalkyl, C_{1-10} fluoroalkyloxy, amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), cyano, halo, aminocarbonyl, aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonylamino(C_{0-6} alkyl), (C_{1-6} alkyl) carbonylamino(C_{0-6} alkyl), carboxy(C_{0-6} alkyl), (C_{1-6} alkoxy)carbonyl(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), –(C_{0-5} alkyl)–(S(=O)$_2$OH), –(C_{0-5} alkyl)–(S(=O)$_2$NH$_2$), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{0-6} alkyl), C_{1-6} haloalkyloxy, (C_{3-12}) cycloalkyl(C_{0-6} alkyl), and heterocycloalkyl(C_{0-6} alkyl);

R^{11a} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

R^{11b} is selected from aryl(C_{0-3} alkyl), heteroaryl(C_{0-3} alkyl), wherein said heteroaryl contains 1, 2, or 3 nitrogen atoms, and H_2N–C(=NH)NH–(C_{1-6} alkyl),

wherein **R^{11b}** is substituted by 0, 1, 2, 3, or 4 **R^{11c}** substituents each independently selected from C_{1-6} alkyl, amino, amino(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl), hydroxy, hydroxy(C_{1-6} alkyl), cyano, halo, aminocarbonyl,

aminocarbonyl(C_{1-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ aminocarbonyl(C_{0-6} alkyl), carboxy(C_{0-6} alkyl), carboxy(C_{1-6} alkyl)oxy(C_{0-6} alkyl), amino(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_{0-2}$ amino (C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)$_3N^+$(C_{0-6} alkyl)oxy(C_{0-6} alkyl), (C_{1-6} alkyl)oxy(C_{0-6} alkyl), C_{1-6} haloalkyloxy, C_{1-6} haloalkyl, (C_{3-12})cycloalkyl(C_{0-6} alkyl), heterocycloalkyl(C_{0-6} alkyl), ((C_{1-6} alkyl)carbonyl)heterocycloalkyl(C_{0-10} alkyl), and ((C_{1-6} alkyl)carbonyloxy) heterocycloalkyl(C_{0-10} alkyl);

R^{12a} is selected from hydrogen, hydroxy, amino, C_{1-10} alkyl, and (C_{3-12})cycloalkyl (C_{0-6} alkyl);

R^{12b} is selected from hydrogen, C_{1-10} alkyl, and (C_{3-12})cycloalkyl(C_{0-6} alkyl);

wherein **R^{12a}** and **R^{12b}**, together with the atoms to which they are attached, may form a saturated ring;

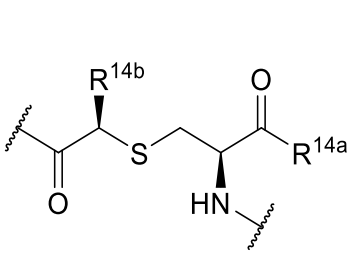
R^{13a} is selected from hydrogen, hydroxy, C_{1-6} alkyl, C_{1-4} alkyloxy, and fluoro;

R^{13b} is selected from hydrogen, and C_{1-4} alkyl;

R^{13c} is selected from a bicyclic nitrogen-containing heteroaryl having 1 or 2 nitrogen and bicyclic-aryl and wherein **R^{13c}** is substituted independently by 0, 1, or 2 **R^{13d}** substituents each independently selected from halo, C_{1-6} alkyl, carboxy(C_{0-4} alkyl), C_{1-4} haloalkyloxy, and C_{1-4} alkyloxy;



is selected from



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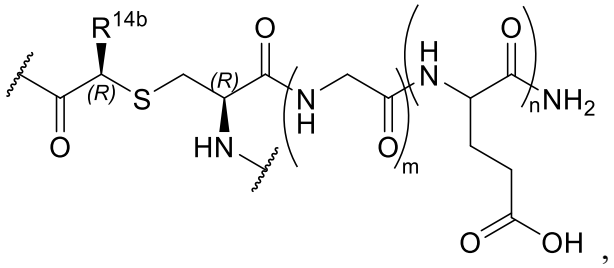

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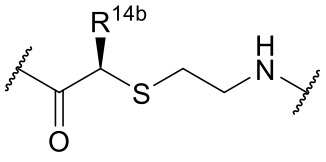

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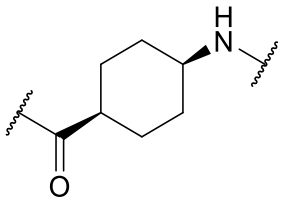

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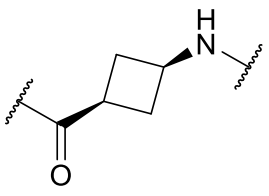

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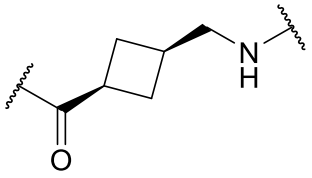
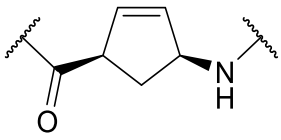
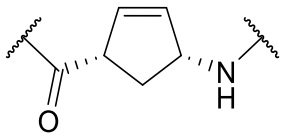
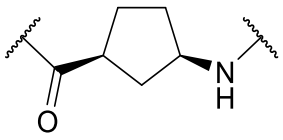
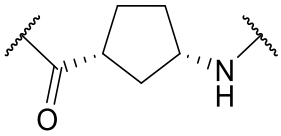
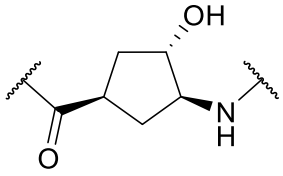
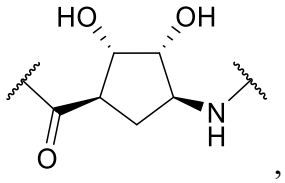
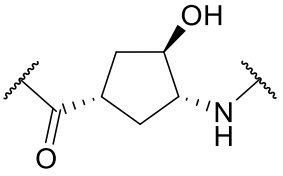
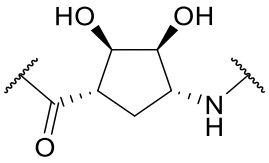
 ,  ,  ,  ,

 ,  ,  ,  , and

 ;

wherein $\mathbf{R^{14a}}$ is selected from amino, hydroxy, $(C_{1-6}$ alkyl$)_{0-2}$ amino, and C_{1-6} alkyloxy;

m is selected from 1, 2, 3, or 4;

n is selected from 1, 2, 3, or 4; and

$\mathbf{R^{14b}}$ is selected from hydrogen, C_{1-8} alkyl, aryl(C_{0-6} alkyl), and heteroaryl(C_{0-6} alkyl), wherein $\mathbf{R^{14b}}$ is substituted by 0, 1, 2, or 3 halo groups.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is selected from aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl, phenyl, phenylmethyl, phenylethyl, phenylpropyl, styryl, biphenyl, naphthyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, furyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, biphenylmethyl, naphthylmethyl, pyridylmethyl, pyridazinylmethyl, pyrimidylmethyl, pyrazinylmethyl, imidazolylmethyl, pyrazolylmethyl, furylmethyl, thiophenylmethyl, oxazolylmethyl, isoxazolylmethyl, thiazolylmethyl, isothiazolylmethyl, oxadiazolylmethyl, bicyclo[1.1.1.]pentyl, (bicyclo[1.1.1.]pentyl)methyl, phenylcarbonylaminoethyl, aminocarbonylmethyl, aminocarbonylethyl, aminocarbonylpropyl, aminocarbonylisopropyl, aminocarbonylbutyl, aminocarbonylaminomethyl, aminocarbonylaminoethyl, aminocarbonylaminopropyl, aminocarbonylaminobutyl, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, isohexyl, *n*-heptyl, *n*-octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, adamantyl,

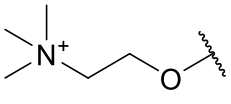
carboxy, carboxymethyl, carboxyethyl, azidomethyl, azidoethyl, azidopropyl, phenylaminocarbonylmethyl, pyridylaminocarbonylmethyl, (pyridylcarbonylamino)methyl, guanidino, guanidinomethyl, guanidinoethyl, guanidinopropyl, guanidinobutyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, pentafluoroethyl, fluoropropyl, difluoropropyl, trifluoropropyl, pentafluoropropyl, heptafluoropropyl, trifluorobutyl, *N*,*N*,*N*-trimethylmethylammonium, *N*,*N*,*N*-trimethyleth-1-ylammonium, *N*,*N*,*N*-trimethylpropan-1-ylammonium, *N*,*N*,*N*-trimethylbut-1-ylammonium, methylamino, methylaminomethyl, methylaminoethyl, methylaminopropyl, methylaminobutyl, dimethylamino, dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, dimethylaminobutyl, ethylamino, ethylaminomethyl, ethylaminoethyl, ethylaminopropyl, ethylaminobutyl, diethylamino, diethylaminomethyl, diethylaminoethyl, diethylaminopropyl, diethylaminobutyl, aminoethoxy, aminoethoxymethyl, isoxazolylcarbonylaminomethyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, cyclopropoxymethyl, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclopropylmethoxyethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, vinyl, prop-2-enyl, but-3-enyl, and pent-4-enyl.

3. The compound of claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein:

each $\mathbf{R^{1a}}$ substituent is independently selected from $C_{1\text{-}6}$ alkyl, amino, cyano, halo, and hydroxy;

each $\mathbf{R^{2a}}$ substituent is independently selected from hydrogen, hydroxy, methyl, ethyl, methoxy, ethoxy, fluoro;

$\mathbf{R^{2b}}$ is selected from phenyl, benzyl, biphenyl, naphthyl, pyridyl, pyridazinylpyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, and bicyclo[1.1.1]pentyl; and

each $\mathbf{R^{2c}}$ substituent is independently selected from aminomethyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, *tert*-butyl, fluoro, chloro, bromo, iodo, aminoethoxy, *N*-methylaminoethoxy, *N*-ethylaminoethoxy, *N*,*N*-dimethylaminoethoxy,  , carboxy, carboxymethoxy, (carboxymethoxy)methyl, aminocarbonyl, *N*,*N*-dimethylaminocarbonyl, and aminocarbonylmethyl.

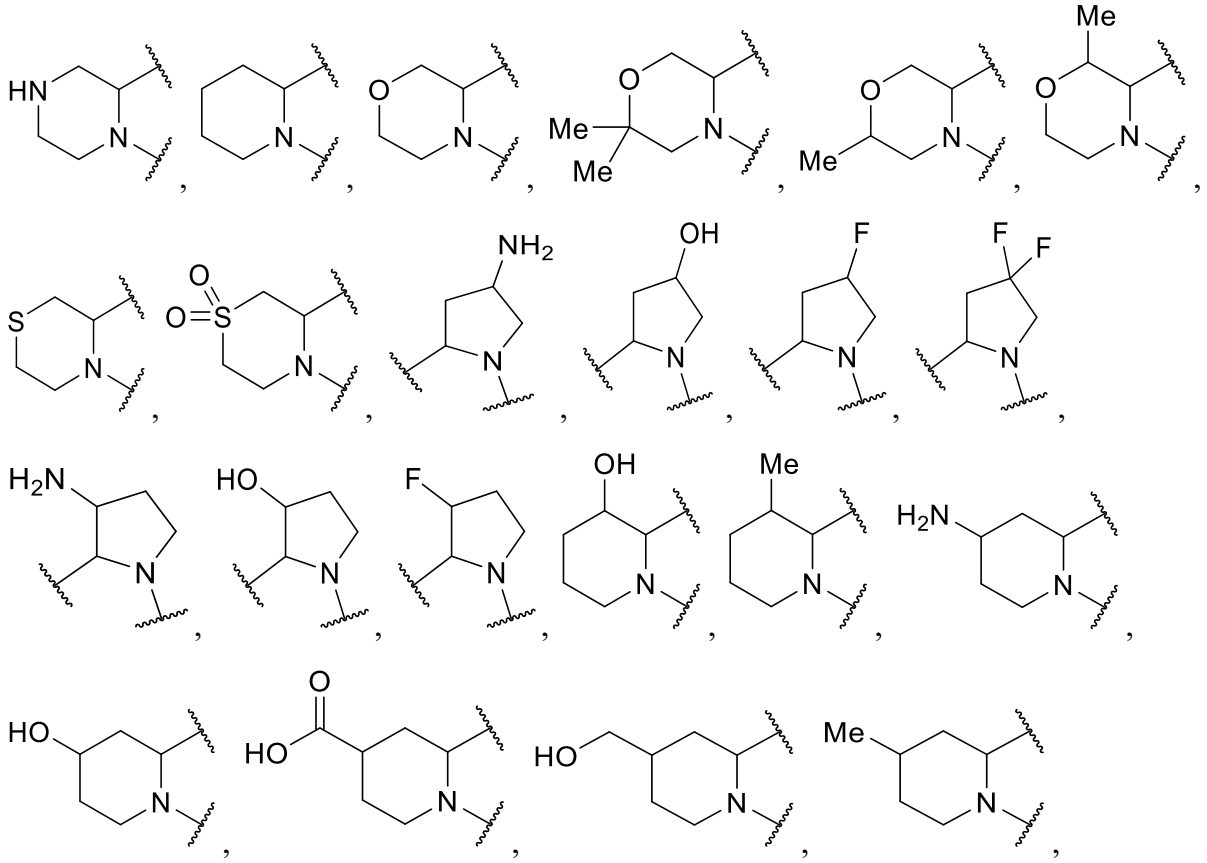
4. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein

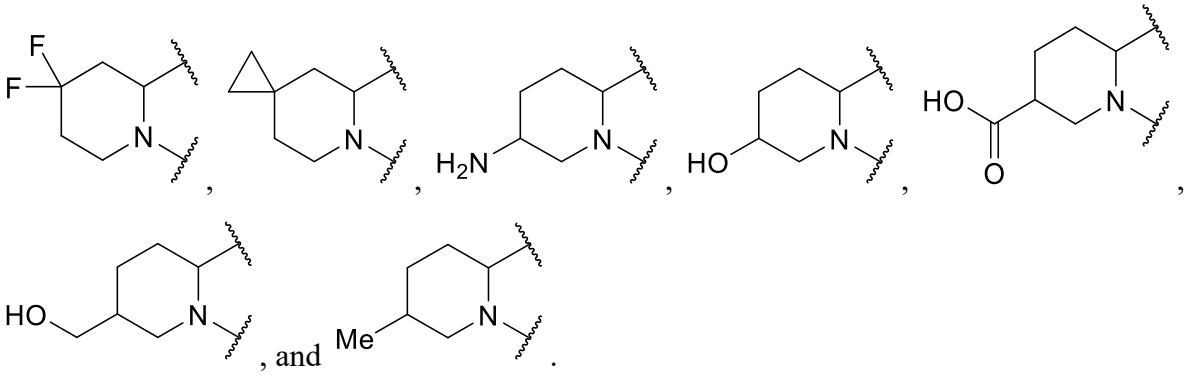
R^{3a} is selected from hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, cyclobutyl, cyclobutylmethyl, cyclobutylethyl, aminoethyl, aminopropyl, aminobutyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, thioethyl, and thiopropyl, wherein **R^{3a}** may be substituted by 0, 1, or 2 **R^{3c}** substituents each independently selected from fluoro, chloro, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amino, aminomethyl, *N*-methylamino, *N*-methylaminomethyl, *N*-ethylamino, *N*-ethylaminomethyl, *N*,*N*-dimethylamino, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylamino, *N*,*N*-diethylaminomethyl, *N*,*N*,*N*-trimethylammonium, *N*,*N*,*N*-trimethylmethylammonium, hydroxy, hydroxymethyl, $–SO_2CH_3$, $–CH_2SO_2CH_3$, $–CH_2CH_2SO_2CH_3$, cyano, cyanomethyl, methoxy, ethoxy, methoxymethyl, methoxyethyl, carboxy, carboxymethyl, and carboxyethyl; and

R^{3b} is selected from hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmetyl, cyclopentylmethyl, cyclohexylmethyl, bicyclo[1.1.1]pentylmethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, hydroxypropyl, 3-hydroxypropyl, 1-methyl-1-hydroxyethyl, hydroxyisopropyl, hydroxybutyl, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, aminomethyl, 2-aminoethyl, *N*-methylaminomethyl, *N*,*N*-dimethylaminomethyl, *N*-methylaminoethyl, *N*,*N*-dimethylaminoethyl, *N*-methylaminopropyl, *N*,*N*-dimethylaminopropyl, 1-aminopropyl, 2-aminopropyl, 3-aminopropyl, 2-aminoprop-2-yl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, benzyl, 3-pyridinylmethyl, 4-pyridinylmethyl, imidazolylmethyl, thiazolylmethyl, oxazolylmethyl, thiophenylmethyl, furanylmethyl, pyrazolylmethyl, *N*-pyrazolylmethyl, 1-phenylethyl, 1-(4-pyridinyl)ethyl, aminocarbonylmethyl, aminocarbonylethyl, aminocarbonylpropyl, (*N*,*N*-dimethyl)aminocarbonylmethyl, (*N*,*N*-dimethyl)aminocarbonylethyl, thiomethyl, thioethyl, thiopropyl, $–CH_2CH_2SO_2CH_3$, carboxymethyl, carboxyethyl, 2-carboxyethyl, carboxypropyl, 3-carboxypropyl, carboxybutyl, 4-carboxybutyl, piperazinylmethyl, morpholinomethyl, piperidinylmethyl, azetidinylmethyl, tetrahydropyranylmethyl, aminocarbonylaminomethyl, aminocarbonylaminoethyl,

aminocarbonylaminopropyl, and aminocarbonylaminobutyl, wherein **R^{3b}** may be substituted by 0, 1, or 2 **R^{3c}** substituents each independently selected from fluoro, chloro, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amino, aminomethyl, *N*-methylamino, *N*-methylaminomethyl, *N*-ethylamino, *N*-ethylaminomethyl, *N*,*N*-dimethylamino, *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylamino, *N*,*N*-diethylaminomethyl, *N*,*N*,*N*-trimethylammonium, *N*,*N*,*N*-trimethylmethylammonium, hydroxy, hydroxymethyl, $–SO_2CH_3$, $–CH_2SO_2CH_3$, $–CH_2CH_2SO_2CH_3$, cyano, cyanomethyl, methoxy, ethoxy, methoxymethyl, methoxyethyl, carboxy, carboxymethyl, and carboxyethyl.

5. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein **R^{3a}** and **R^{3b}**, together with the atoms to which they are attached, form a saturated ring system substituted by 0, 1, or 2, **R^{3d}** substituents, said saturated ring system is selected from:





, and .

6. The compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein

R^{4a} is selected from hydrogen, methyl, ethyl, propyl, hydroxy, methoxy, and fluoro;

R^{4b} is selected from indolyl, naphthyl, quinolinyl, pyrrolo[2,3-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridine, 1*H*-pyrazolo[3,4-*b*]pyridine, indazolyl, benzothiazolyl, and benzothiophenyl, wherein **R^{4b}** substituted with 0, 1, or 2 **R^{4c}** substituents each independently selected from fluoro, chloro, bromo, iodo, cyano, nitro, hydroxy, methyl, ethyl, propyl, isopropyl, carboxy, carboxymethyl, and carboxyethyl;

R^{5a} is selected from hydrogen, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, isobutyl, cyclobutyl, *n*-pentyl, isopentyl, neopentyl, cyclopentyl, cyclobutyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, phenyl, benzyl, phenylethyl, phenylpropyl, oxazolylmethyl, thiazolylmethyl, imidazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, oxazolylethyl, thiazolylethyl, imidazolylethyl, triazolylethyl, oxadiazolylethyl, thiadiazolylethyl, oxazolylpropyl, thiazolylpropyl, imidazolylpropyl, triazolylpropyl, oxadiazolylpropyl, thiadiazolylpropyl, azetidinylmethyl, azetidinylethyl, oxetanylmethyl, oxetanylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, tetrahydrofuranylmethyl, tetrahydrofuranylethyl, piperidinylmethyl, piperidinylethyl, piperazinylmethyl, piperazinylethyl, tetrahydropyranylmethyl, tetrahydropyranylmethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, hydroxybutyl, 3-hydroxy-2,2-dimethylpropyl, cyclopropylmethyl, 1-hydroxypropan-2-yl, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxyisopropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, cyanomethyl, cyanoethyl, cyanopropyl, cyanobutyl, carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-aminoethyl, 3-aminopropyl, 3-amino-2,2-dimethylpropyl,

cyclopropylmethyl, 4-aminobutyl, aminomethylcarbonylaminoethyl, aminoethylcarbonylaminoethyl, aminomethylcarbonylaminopropyl, aminoethylaminocarbonylmethyl, aminoethylaminocarbonylethyl, aminoethylaminocarbonylpropyl, aminohexylcarbonylaminoethyl, aminohexylcarbonylaminoethyl, (*N*-methylamino)ethyl, (*N*-methylamino)propyl, (*N*-ethylamino)ethyl, (*N*,*N*-diethylamino)propyl, (*N*,*N*-dimethylamino)ethyl, (*N*,*N*-dimethylamino)propyl, (*N*,*N*-diethylamino)ethyl, (*N*,*N*-diethylamino)propyl, (*N*,*N*,*N*-trimethylammonium)ethyl, (*N*,*N*,*N*-trimethylammonium)propyl, (*N*,*N*,*N*-triethylammonium)ethyl, (*N*,*N*,*N*-triethylammonium)propyl, (*N*-methylamino)methylcarbonylaminoethyl, (*N*-methylamino)ethylcarbonylaminoethyl, (*N*-methylamino)methylcarbonylaminopropyl, (*N*-ethylamino)methylcarbonylaminoethyl, (*N*-ethylamino)ethylcarbonylaminoethyl, (*N*-ethylamino)methylcarbonylaminopropyl, (*N*-methylamino)pentylcarbonylaminoethyl, (*N*-methylamino)pentylcarbonylaminoethyl, (*N*-methylamino)pentylcarbonylaminopropyl, (*N*,*N*-dimethylamino)methylcarbonylaminoethyl, (*N*,*N*-dimethylamino)ethylcarbonylaminoethyl, (*N*,*N*-dimethylamino)methylcarbonylaminopropyl, (*N*,*N*-diethylamino)methylcarbonylaminoethyl, (*N*,*N*-diethylamino)ethylcarbonylaminoethyl, (*N*,*N*-diethylamino)methylcarbonylaminopropyl, (*N*,*N*-dimethylamino)pentylcarbonylaminoethyl, (*N*,*N*-dimethylamino)pentylcarbonylaminoethyl, (*N*,*N*-dimethylamino)pentylcarbonylaminopropyl, *N*,*N*,*N*-trimethyl-ethan-1-ammonium, *N*,*N*,*N*-trimethyl-propan-1-ammonium, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminoethyl, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylaminoethyl, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminopropyl, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylaminopropyl, (*N*,*N*,*N*-trimethylammonium)pentylcarbonylaminoethyl, (*N*,*N*,*N*-trimethylammonium)pentylcarbonylaminopropyl, (carboxymethyl)oxyethyl, and (carboxymethyl)oxypropyl, wherein $\mathbf{R^{5a}}$ is substituted by 0, 1, 2, or 3 $\mathbf{R^{5d}}$ substituents each independently selected from chloro, fluoro, hydroxy, hydroxymethyl, hydroxyethyl, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, cyclobutyl, *n*-pentyl, isopentyl, neopentyl, carboxy, carboxymethyl, carboxyethyl, methoxy, ethoxy, methoxymethyl, methoxyethyl, methoxypropyl, amino, aminomethyl, aminoethyl, *N*-methylamino, (*N*-methylamino)methyl, (*N*-methylamino)ethyl, *N*,*N*-dimethylamino, (*N*,*N*-dimethylamino)methyl, (*N*,*N*-dimethylamino)ethyl, *N*,*N*-diethylamino, (*N*,*N*-diethylamino)methyl, (*N*,*N*-diethylamino)ethyl, aminomethylcarbonylamino, aminoethylcarbonylamino, aminopentylcarbonylamino, aminomethylcarbonylaminomethyl, aminoethylcarbonylaminomethyl, (*N*-

methylamino)methylcarbonylamino, (*N*-methylamino)ethylcarbonylamino, (*N*-methylamino)methylcarbonylaminomethyl, (*N*-methylamino)ethylcarbonylaminomethyl, (*N*,*N*-dimethylamino)methylcarbonylamino, (*N*,*N*-dimethylamino)ethylcarbonylamino, (*N*,*N*-dimethylamino)methylcarbonylaminomethyl, (*N*,*N*-dimethylamino)ethylcarbonylaminomethyl, (*N*,*N*-diethylamino)methylcarbonylamino, (*N*,*N*-diethylamino)ethylcarbonylamino, (*N*,*N*-diethylamino)methylcarbonylaminomethyl, (*N*,*N*-diethylamino)ethylcarbonylaminomethyl, *N*,*N*,*N*-trimethylammonium, (*N*,*N*,*N*-trimethylammonium)methyl, (*N*,*N*,*N*-trimethylammonium)ethyl, (*N*,*N*,*N*-trimethylammonium)ethoxy, (*N*,*N*,*N*-trimethylammonium)ethoxymethyl, (*N*,*N*,*N*-trimethylammonium)methylcarbonylamino, (*N*,*N*,*N*-triethylammonium)methylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)pentylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminomethyl, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylaminomethyl, cyano, cyanomethyl, cyanoethyl, tetrazoyl, tetrazoylmethyl, tetrazoylethyl, carboxymethoxy, carboxyethoxy, carboxymethoxymethyl, and carboxyethoxymethyl;

R^{5b} is selected from hydrogen, methyl, ethyl, isopropyl, *n*-propyl, cyclopropyl, isobutyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, cyclobutyl, cyclopropylmethyl, oxetanylmethyl, tetrahydrofurylmethyl, tetrahydropyranylmethyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxymethyl, methoxyethyl, methoxypropyl, carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, (carboxymethoxy)methyl, (carboxymethoxy)ethyl, (carboxyethoxy)methyl, (carboxyethoxy)ethyl, aminomethyl, aminoethyl, aminopropyl, aminobutyl, (*N*-methylamino)methyl, (*N*-methylamino)ethyl, (*N*-methylamino)propyl, (*N*-methylamino)butyl, (*N*,*N*-dimethylamino)methyl, (*N*,*N*-dimethylamino)ethyl, (*N*,*N*-dimethylamino)propyl, (*N*,*N*-dimethylamino)butyl, (*N*,*N*-diethylamino)methyl, (*N*,*N*-diethylamino)ethyl, (*N*,*N*-diethylamino)propyl, (*N*,*N*-diethylamino)butyl, *N*,*N*,*N*-trimethylmethan-1-ylammonium, *N*,*N*,*N*-trimethylethan-1-ylammonium, *N*,*N*,*N*-triethylethan-1-ylammonium, *N*,*N*,*N*-trimethylpropan-1-ylammonium, *N*,*N*,*N*-trimethylbutan-1-ylammonium, (*N*,*N*,*N*-trimethylammonium)ethoxymethyl, (*N*,*N*,*N*-trimethylammonium)ethoxyethyl, (*N*,*N*,*N*-triethylammonium)ethoxyethyl, (*N*,*N*,*N*-trimethylammonium)ethoxypropyl, (*N*,*N*,*N*-trimethylammonium)ethoxybutyl, aminocarbonylmethyl, aminocarbonylethyl, aminocarbonylpropyl, aminocarbonylbutyl, (*N*-methylamino)carbonylmethyl, (*N*-methylamino)carbonylethyl, (*N*-methylamino)carbonylpropyl, (*N*-methylamino)carbonylbutyl, (*N*,*N*-dimethylamino)carbonylmethyl, (*N*,*N*-dimethylamino)carbonylethyl, (*N*,*N*-dimethylamino)carbonylpropyl, (*N*,*N*-

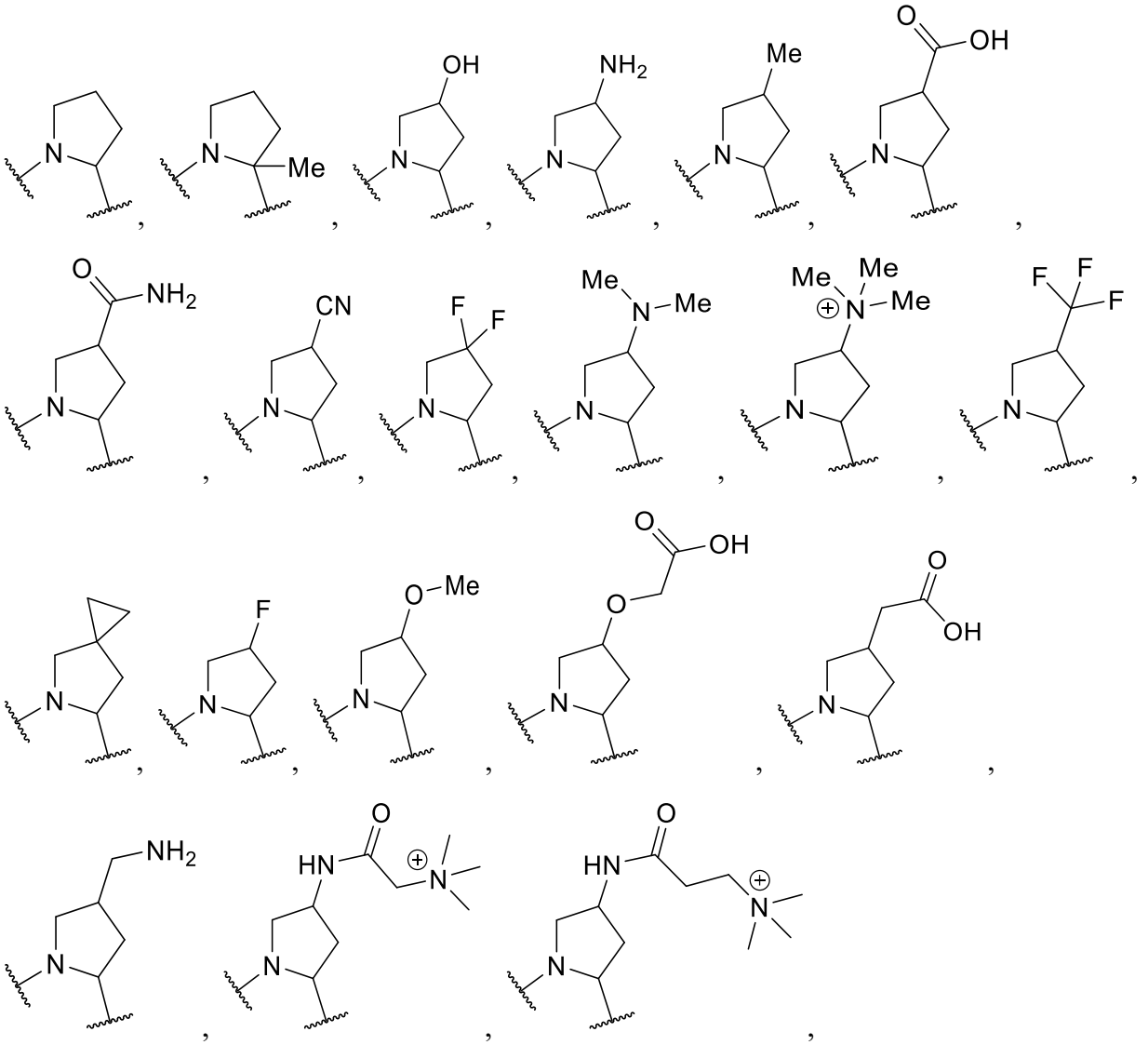
dimethylamino)carbonylbutyl, aminomethylcarbonylaminoethyl, aminomethylcarbonylaminopropyl, aminoethylcarbonylaminoethyl, aminoethylcarbonylaminopropyl, (*N*,*N*-dimethylamino)methylcarbonylaminoethyl, (*N*,*N*-dimethylamino)methylcarbonylaminopropyl, (*N*,*N*-dimethylamino)ethylcarbonylaminoethyl, (*N*,*N*-dimethylamino)ethylcarbonylaminopropyl, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminoethyl, (*N*,*N*,*N*-triethylammonium)methylcarbonylaminoethyl, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminopropyl, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylaminoethyl, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylaminopropyl, (*N*,*N*,*N*-trimethylammonium)ethoxyethyl, (*N*,*N*,*N*-trimethylammonium)ethoxypropyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, cyanomethyl, cyanoethyl, cyanopropyl, cyanoisopropyl, and cyanobutyl, wherein $\mathbf{R^{5b}}$ is substituted by 0, 1, 2, or 3 $\mathbf{R^{5e}}$ substituents each independently selected from chloro, fluoro, hydroxy, hydroxymethyl, hydroxyethyl, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, cyclobutyl, *n*-pentyl, isopentyl, neopentyl, carboxy, carboxymethyl, carboxyethyl, methoxy, ethoxy, methoxymethyl, methoxyethyl, methoxypropyl, amino, aminomethyl, aminoethyl, *N*-methylamino, (*N*-methylamino)methyl, (*N*-methylamino)ethyl, *N*,*N*-dimethylamino, (*N*,*N*-dimethylamino)methyl, (*N*,*N*-dimethylamino)ethyl, *N*,*N*-diethylamino, (*N*,*N*-diethylamino)methyl, (*N*,*N*-diethylamino)ethyl, aminomethylcarbonylamino, aminoethylcarbonylamino, aminopentylcarbonylamino, aminomethylcarbonylaminomethyl, aminoethylcarbonylaminomethyl, (*N*-methylamino)methylcarbonylamino, (*N*-methylamino)ethylcarbonylamino, (*N*-methylamino)methylcarbonylaminomethyl, (*N*-methylamino)ethylcarbonylaminomethyl, (*N*,*N*-dimethylamino)methylcarbonylamino, (*N*,*N*-dimethylamino)ethylcarbonylamino, (*N*,*N*-dimethylamino)methylcarbonylaminomethyl, (*N*,*N*-dimethylamino)ethylcarbonylaminomethyl, (*N*,*N*-diethylamino)methylcarbonylamino, (*N*,*N*-diethylamino)ethylcarbonylamino, (*N*,*N*-diethylamino)methylcarbonylaminomethyl, (*N*,*N*-diethylamino)ethylcarbonylaminomethyl, *N*,*N*,*N*-trimethylammonium, (*N*,*N*,*N*-trimethylammonium)methyl, (*N*,*N*,*N*-trimethylammonium)ethyl, (*N*,*N*,*N*-trimethylammonium)ethoxy, (*N*,*N*,*N*-trimethylammonium)ethoxymethyl, (*N*,*N*,*N*-trimethylammonium)methylcarbonylamino, (*N*,*N*,*N*-triethylammonium)methylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)ethylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)pentylcarbonylamino, (*N*,*N*,*N*-trimethylammonium)methylcarbonylaminomethyl, (*N*,*N*,*N*-

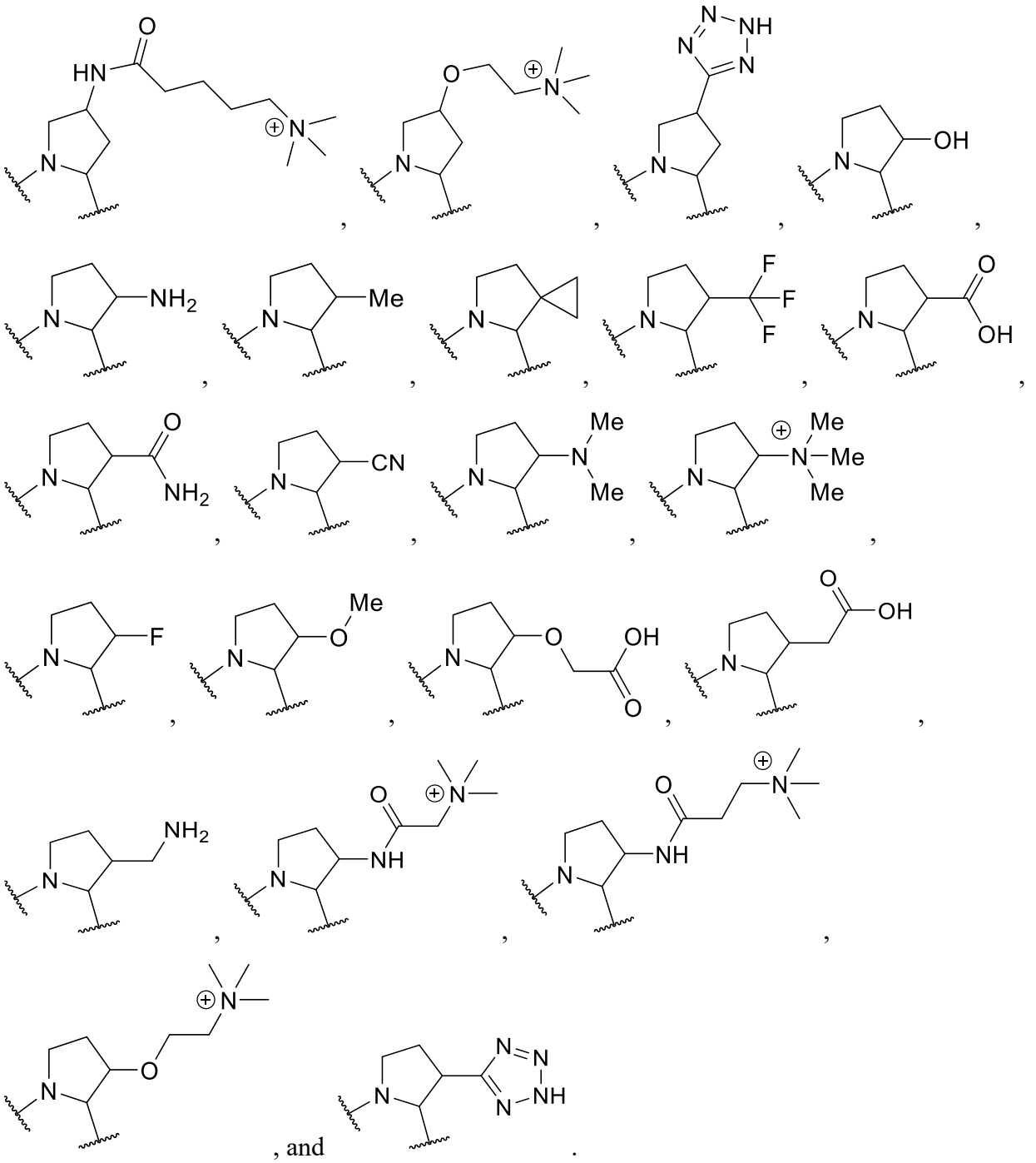
trimethylammonium)ethylcarbonylaminomethyl, cyano, cyanomethyl, cyanoethyl, tetrazoyl, tetrazoylmethyl, tetrazoylethyl, carboxymethoxy, carboxyethoxy, carboxymethoxymethyl, and carboxyethoxymethyl; and

$\mathbf{R^{5c}}$ is hydrogen, methyl, or ethyl.

7. The compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein

$\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$, together with the atoms to which they are attached, form a saturated mono- or bi-cyclic ring system substituted with 0, 1, 2, or 3 $\mathbf{R^{5d}}$ and 0, 1, 2, or 3 $\mathbf{R^{5e}}$ substituents, wherein said mono- or bi-cyclic ring system is selected from:





8. The compound of any one of claims 1-7 or a pharmaceutically acceptable salt thereof, wherein

R^{6a} is selected from hydrogen, hydroxy, methyl, ethyl, propyl, and methoxy;

R^{6b} is selected from hydrogen, hydroxy, methyl, ethyl, propyl, methoxy, and ethoxy;

$\mathbf{R^{6c}}$ is selected from aminocarbonyl, (aminocarbonyl)methyl, (aminocarbonyl)ethyl, (aminocarbonyl)propyl, (*N*-methylamino)carbonyl, (*N*-methylamino)carbonylmethyl, (*N*-methylamino)carbonylethyl, (*N*-methylamino)carbonylpropyl, (*N*,*N*-dimethylamino)carbonyl, (*N*,*N*-dimethylamino)carbonylmethyl, (*N*,*N*-dimethylamino)carbonylethyl, (*N*,*N*-dimethylamino) carbonylpropyl, (*N*,*N*-diethylamino)carbonyl, (*N*,*N*-diethylamino)carbonylmethyl, (*N*,*N*-diethylamino)carbonylethyl, (*N*,*N*-diethylamino)carbonylpropyl, aminocarbonylamino, (aminocarbonylamino)methyl, (aminocarbonylamino)ethyl, (aminocarbonylamino)propyl, methoxy, methoxymethyl, methoxyethyl, ethoxy, ethoxymethyl, ethoxyethyl, methylsulfonyl, (methylsulfonyl)methyl, (methylsulfonyl)ethyl, (methylsulfonyl)propyl, amino, aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, carboxy, carboxymethyl, carboxyethyl, hydroxy, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, trifluoromethyl, 2,2,2-trifluoroethyl, methyl, ethyl, isopropyl, *n*-propyl, isobutyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, phenyl, and benzyl;

$\mathbf{R^{7a}}$ is selected from hydrogen, methyl, ethyl, hydroxy, methoxy, and ethoxy;

$\mathbf{R^{7b}}$ is selected from phenyl, biphenyl, naphthyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, furyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, 3-oxoisoindolinyl, and bicyclo[1.1.1]pentyl;

$\mathbf{R^{7c}}$ is selected from fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, carboxy, carboxymethyl, methoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonyl, carboxymethoxy, carboxyethoxy, carboxymethoxymethyl, aminocarbonyl, aminocarbonylmethyl, (*N*,*N*-dimethylamino)carbonyl, (*N*,*N*-dimethylamino)carbonylmethyl, amino, aminomethyl, *N*,*N*-dimethylamino, (*N*,*N*-dimethylamino)methyl, (*N*,*N*-diethylamino)methyl, *N*,*N*,*N*-trimethylammonium, *N*,*N*,*N*-trimethylmethylammonium, *N*,*N*,*N*-triethylmethylammonium, methyl, ethyl, propyl, isopropyl, difluoromethyl, trifluoromethyl, $–SO_2OH$,$–CH_2SO_2OH$, $–SO_2NH_2$, $–CH_2SO_2NH_2$, aminoethoxy, aminoethoxymethyl, (*N*,*N*-dimethylamino)ethoxy, *N*,*N*,*N*-trimethyleth-1-oxy-ammonium, aminocarbonylamino, and aminocarbonylaminomethyl;

$\mathbf{R^{8a}}$ is selected from hydrogen, methyl, ethyl, hydroxy, methoxy, and ethoxy;

$\mathbf{R^{8b}}$ is selected from indolyl, naphthyl, indolylmethyl, naphthylmethyl, quinolinyl, pyrrolo[2,3-*b*]pyridinyl, indazolyl, benzothiazolyl, and benzothiophenyl;

each $\mathbf{R^{8c}}$ independently is selected from methyl, ethyl, isopropyl, fluoro, chloro, bromo, iodo, cyano, amino, aminomethyl, nitro, hydroxy, hydroxymethyl, carboxy, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, methoxy, ethoxy, and trifluoromethoxy; and

$\mathbf{R^{9}}$ is selected from hydrogen, methyl, ethyl, and propyl.

9. The compound of any one of claims 1-8 or a pharmaceutically acceptable salt thereof, wherein

$\mathbf{R^{10a}}$ is selected from hydrogen, hydroxy, methyl, ethyl, propyl, methoxy, ethoxy, and propoxy;

$\mathbf{R^{10b}}$ is selected from phenyl, benzyl, biphenyl, biphenylmethyl, pyridyl, pyridylmethyl, pyridazinyl, pyrimidyl, pyrazinyl, imidazolyl, imidazolylmethyl, pyrazolyl, furyl, furylmethyl, oxazolyl, oxazolylmethyl, thiazolyl, indolyl, [1,2,4]triazolo[1,5-*a*]pyridine, and bicyclo[1.1.1] pentyl;

$\mathbf{R^{10c}}$ is independently selected from methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, isobutyl, cyclobutyl, *n*-pentyl, isopentyl, neopentyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, fluoro, chloro, bromo, iodo, hydroxy, hydroxymethyl, hydroxyethyl, cyano, amino, aminomethyl, aminoethyl, *N*-methylamino, (*N*-methylamino)methyl, (*N*-methylamino)ethyl, *N*,*N*-dimethylamino, (*N*,*N*-dimethylamino)methyl, (*N*,*N*-dimethylamino)ethyl, *N*,*N*,*N*-trimethylammonium, *N*,*N*,*N*-trimethylmethan-ylammonium, aminocarbonyl, aminocarbonylmethyl, aminocarbonylethyl, (*N*-methylamino)carbonyl, (*N*-methylamino) carbonylmethyl, (*N*,*N*-dimethylamino)carbonyl, (*N*,*N*-dimethylamino)carbonylmethyl, aminocarbonylamino, aminocarbonylaminomethyl, methylcarbonylamino, methylcarbonylaminomethyl, carboxy, carboxymethyl, carboxyethyl, methoxycarboxy, carboxymethoxy, carboxyethoxy, carboxymethoxymethyl, carboxyethoxymethyl, $–S(=O)_2OH$, $–CH_2(S(=O)_2OH)$, $–S(=O)_2NH_2$, $–CH_2(S(=O)_2NH_2)$, aminoethoxy, aminopropoxy, (*N*-methylamino)ethoxy, (*N*-ethylamino)ethoxy, (*N*,*N*-dimethylamino)ethoxy, (*N*,*N*-diethylamino) ethoxy, (*N*,*N*,*N*-trimethylammonium)ethoxy, methoxy, ethoxy, methoxymethyl, ethoxymethyl, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy;

$\mathbf{R^{11a}}$ is selected from hydrogen, hydroxy, methyl, ethyl, methoxy, and ethoxy;

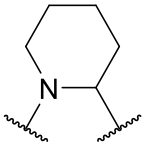
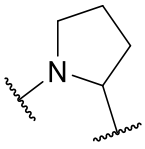
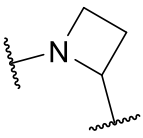
R11b is selected from (H_2N–C(=NH)–NH)methyl, (H_2N–C(=NH)–NH)ethyl, (H_2N–C(=NH)–NH)propyl, (H_2N–C(=NH)–NH)butyl, phenyl, benzyl, pyridinyl, pyridinylmethyl, indolyl, indolylmethyl, pyridazinyl, pyridazinylmethyl, pyrimidyl, pyrimidylmethyl, pyrazinyl, pyrazinylmethyl, imidazolyl, imidazolylmethyl, pyrazolyl, pyrazolylmethyl, [1,2,4]triazolo[1,5-*a*]pyridine, oxazolyl, oxazolylmethyl, thiazolyl, and thiazolylmethyl;

each **R11c** is independently selected from fluoro, chloro, bromo, iodo, (carboxymethyl)oxy, (carboxymethyl)oxymethyl, (carboxyethyl)oxy, hydroxy, hydroxymethyl, hydroxyethyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, carboxy, carboxymethyl, aminocarbonyl, aminocarbonylmethyl, (*N*-methylamino)carbonyl, (*N*-methylamino) carbonylmethyl, (*N*,*N*-dimethylamino)carbonyl, (*N*,*N*-dimethylamino)carbonylmethyl, amino, *N*-methylamino, *N*,*N*-dimethylamino, *N*,*N*-diethylamino, aminomethyl, (*N*,*N*-dimethylamino) methyl, (*N*,*N*-diethylamino)methyl, *N*,*N*,*N*-trimethylammonium, *N*,*N*,*N*-trimethylmeth-1-yl-ammonium, *N*,*N*,*N*-triethylammonium, *N*,*N*,*N*-triethylmeth-1-yl-ammonium, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, difluoromethyl, trifluoromethyl, aminoethoxy, aminopropoxy, aminoethoxymethyl, (*N*,*N*-dimethylamino)ethoxy, *N*,*N*,*N*-trimethyleth-1-yloxy-ammonium, cyano, and methylcarbonylpiperazyl [(*N*-acetyl)piperazyl;

R12a is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, and isopropyl; and

R12b is selected from hydrogen, methyl, ethyl, and propyl.

10. The compound of any one of claims 1-8 or a pharmaceutically acceptable salt thereof, wherein

R12a and **R12b**, together with the atoms to which they are attached form a saturated ring selected from  ,  , and  .

11. The compound of any one of claims 1-10 or a pharmaceutically acceptable salt thereof, wherein:

R13a is hydrogen, methyl, or propyl;

R13b is hydrogen or methyl;

R^{13c} is selected from indolyl, pyrrolo[2,3-*b*]pyridinyl, quinolinyl, indazolyl, and naphthyl;

R^{13c} is selected from indolyl, and pyrrolo[2,3-*b*]pyridinyl;

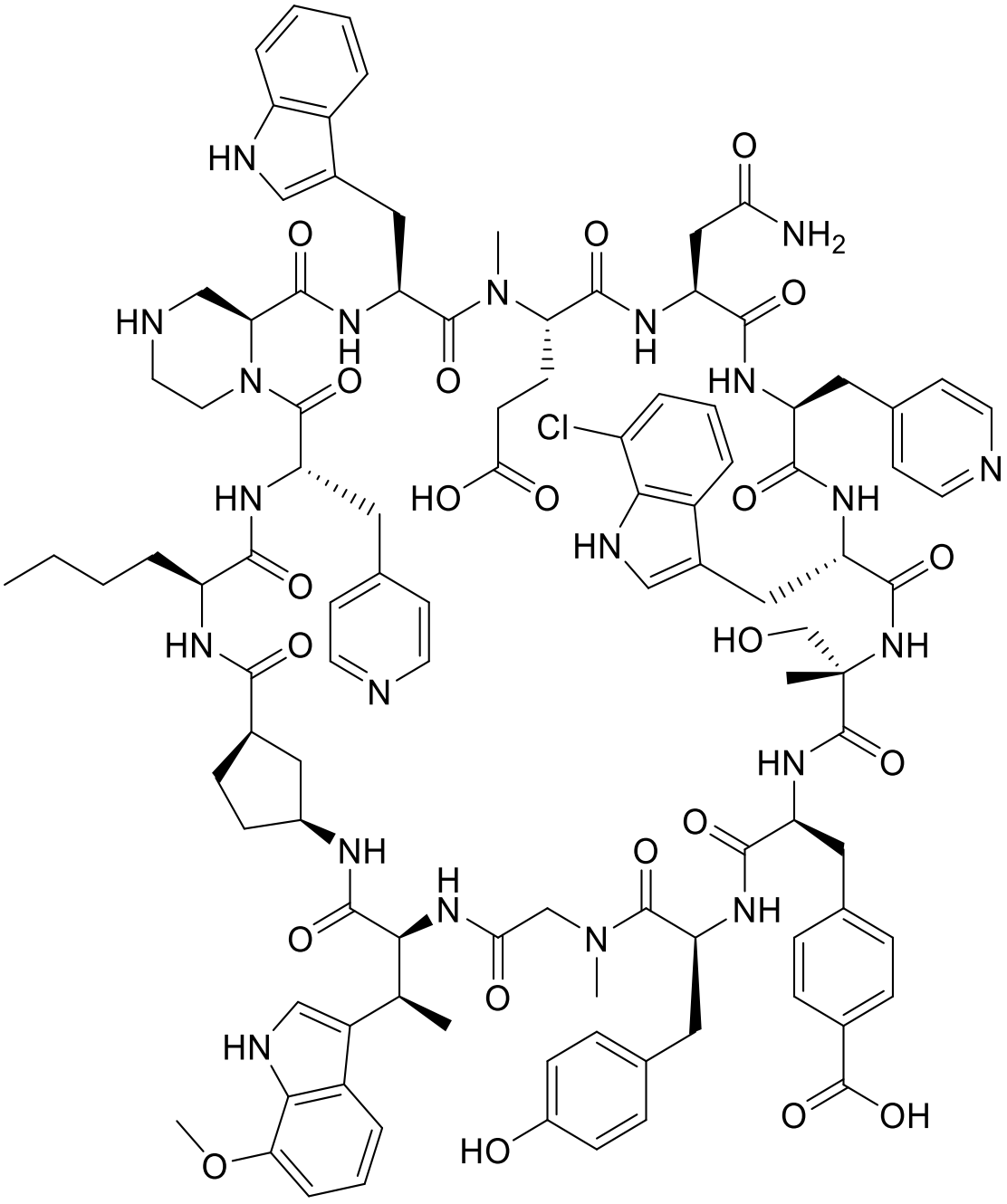
each **R^{13d}** independently is selected from fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, carboxy, carboxymethyl, methoxy, difluoromethoxy, trifluoromethoxy, and ethoxy;

each **R^{14a}** independently is selected from amino, hydroxy, *N*-methylamino, *N*,*N*-dimethylamino, *N*-ethylamino, methoxy, and ethoxy; and

each **R^{14b}** independently is selected from hydrogen, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *n*-pentyl, isopentyl, neopentyl, trifluoromethyl, trifluoroethyl, phenyl, benzyl, chlorophenyl, dichlorophenyl, fluorophenyl, difluorophenyl, bromophenyl, iodophenyl, chlorobenzyl, dichlorobenzyl, fluorobenzyl, difluorobenzyl, bromobenzyl, iodobenzyl, naphthyl, naphthylmethyl, pyrazolyl, pyrazolylmethyl, indolyl, indolylmethyl, imidazolyl, imidazolylmethyl, pyridyl, and pyridylmethyl.

12. The compound of any one of claims 1-11 selected from the group consisting of SEQ ID NOS: 1-289, or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-11 selected from the group consisting of (**SEQ ID NOS: 5**, **10**, **18**, **22**, **30**, **31**, **41**, **45**, **48**, **51**, **52**, **53**, **60**, **68**, **77**, **83**, **87**, **104**, **183**, **196**, **206**, **210**, **214**, **221**, **229**, **237**, **247**, **250**, **254**, **257**, and **265** respectively, in order of appearance):



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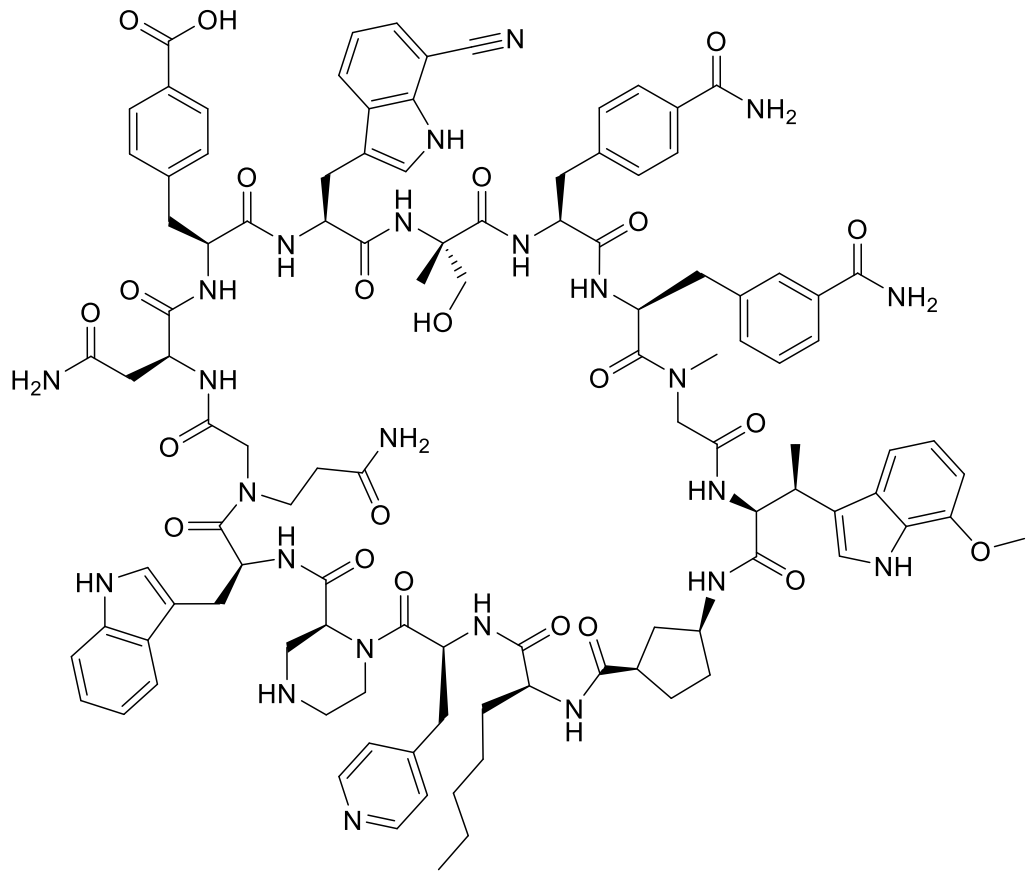

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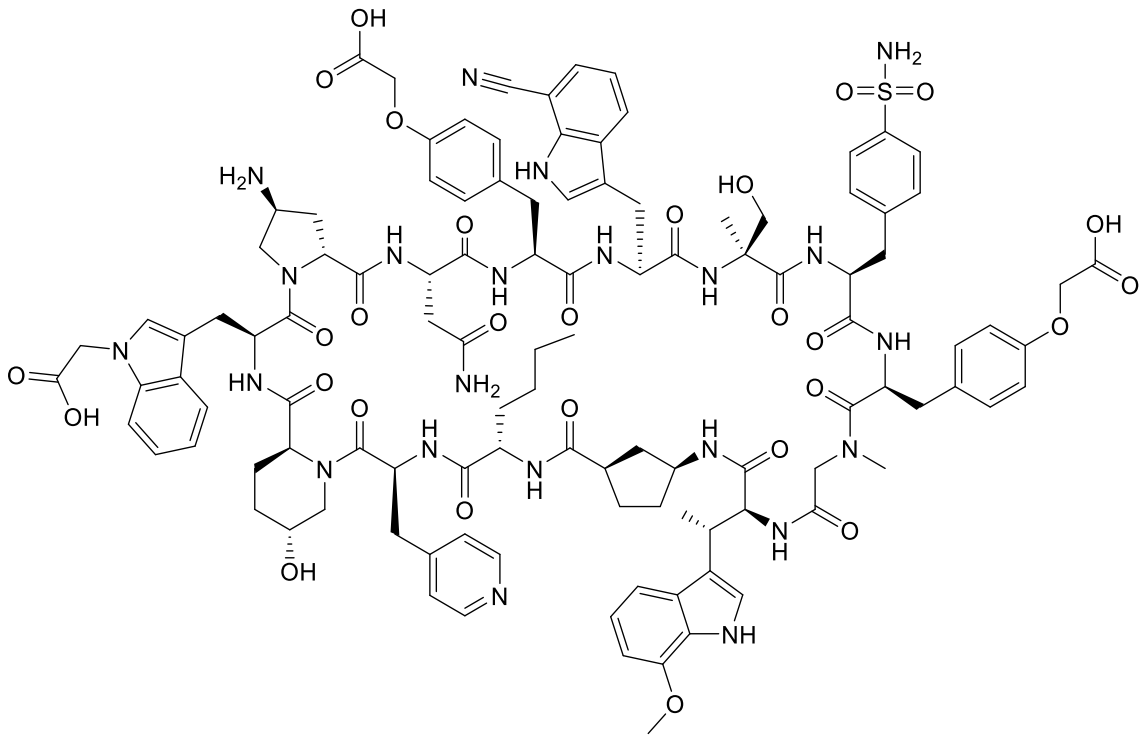

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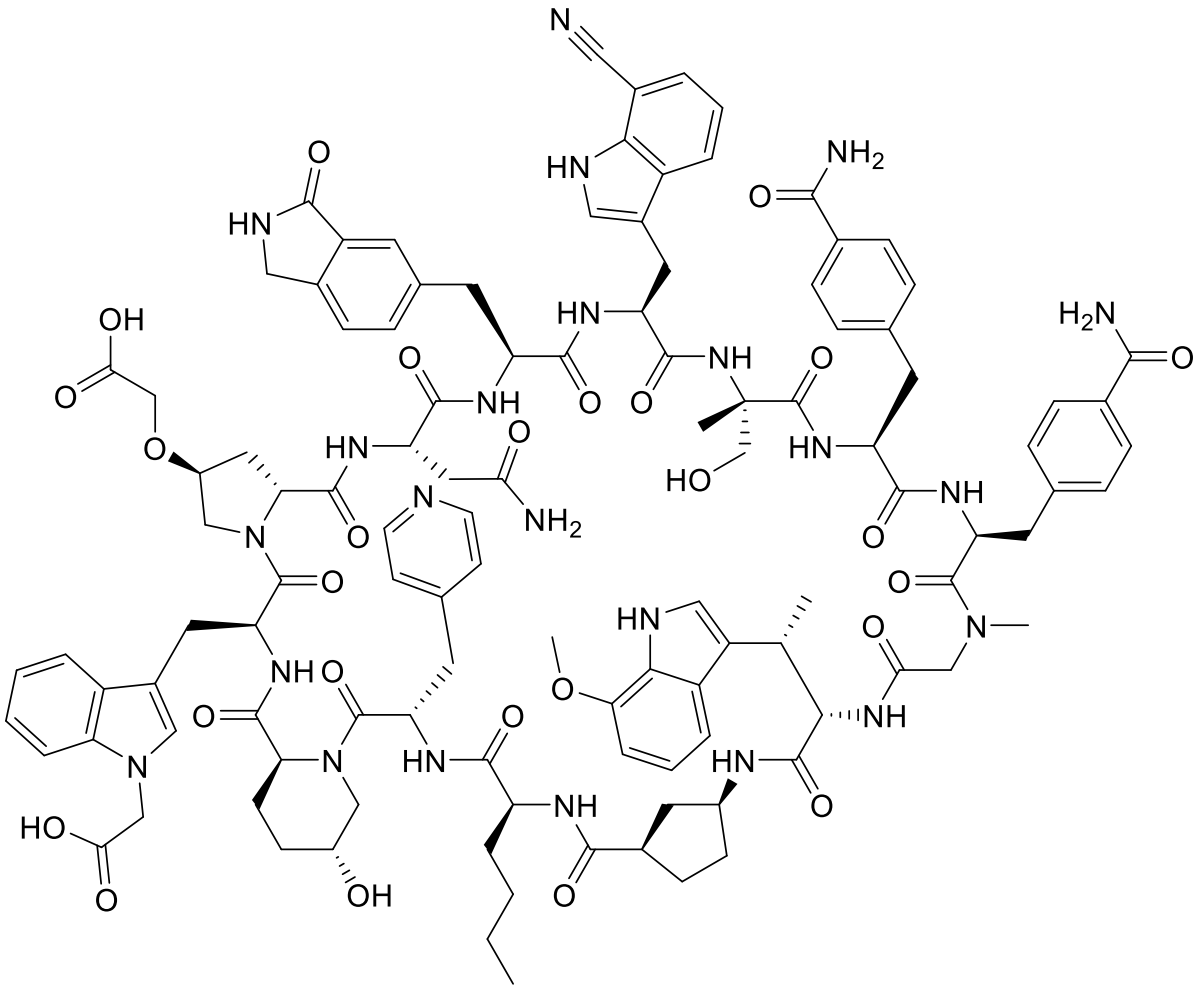

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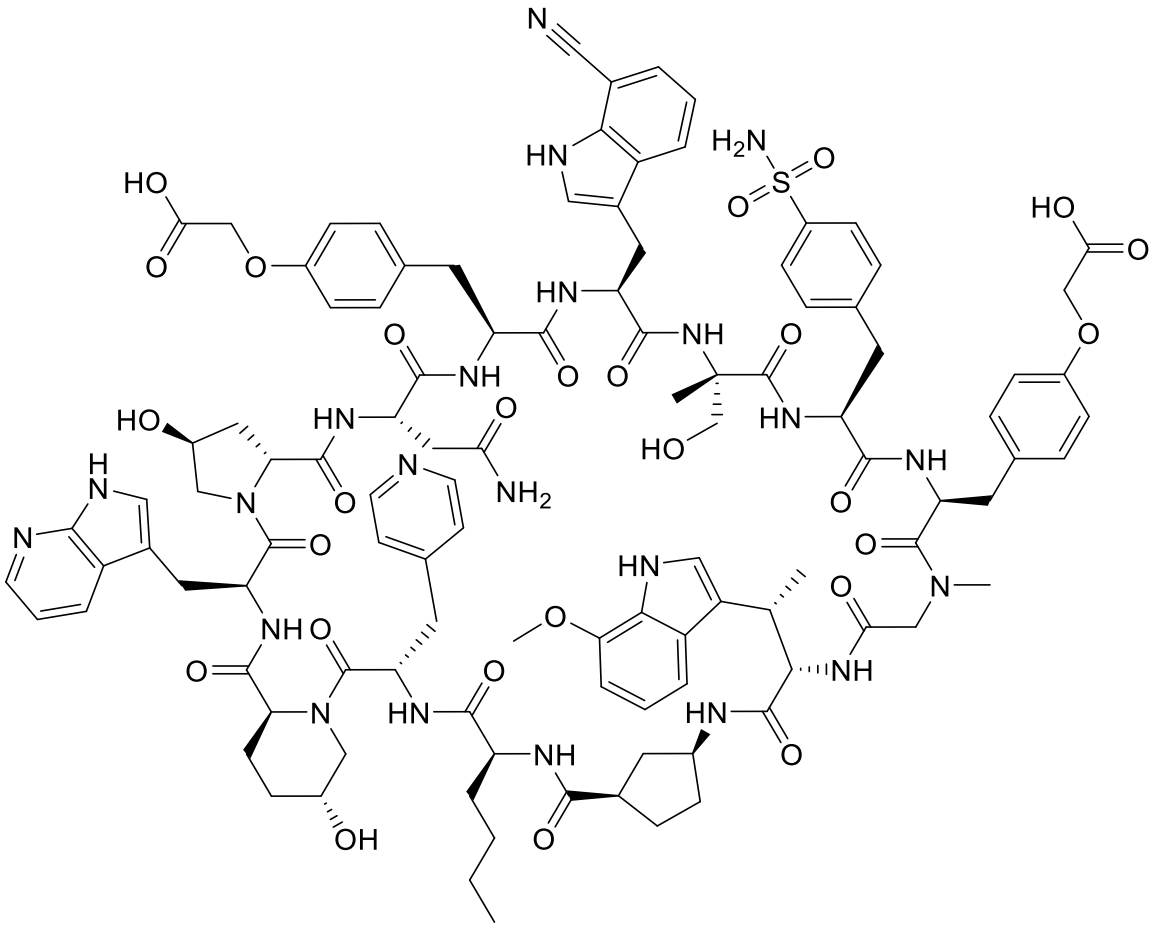

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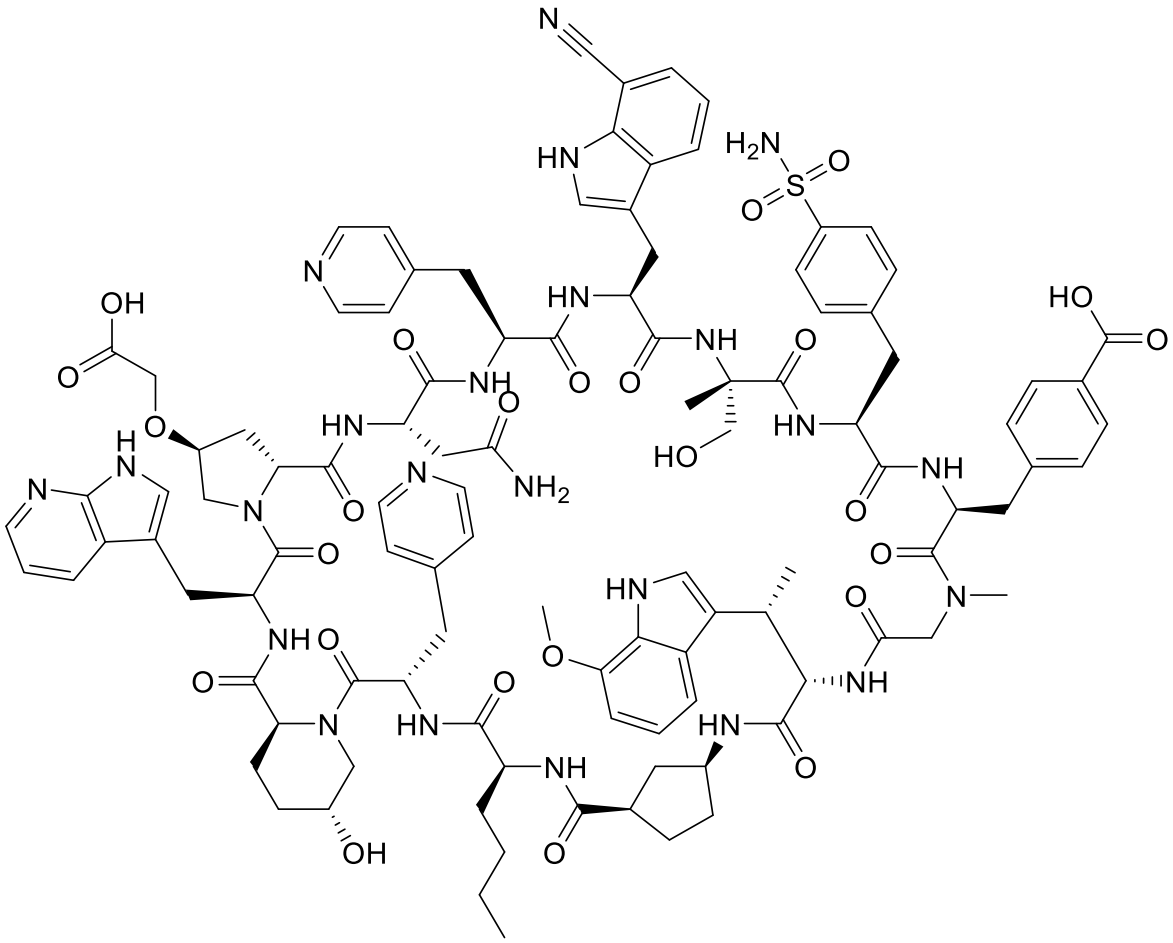

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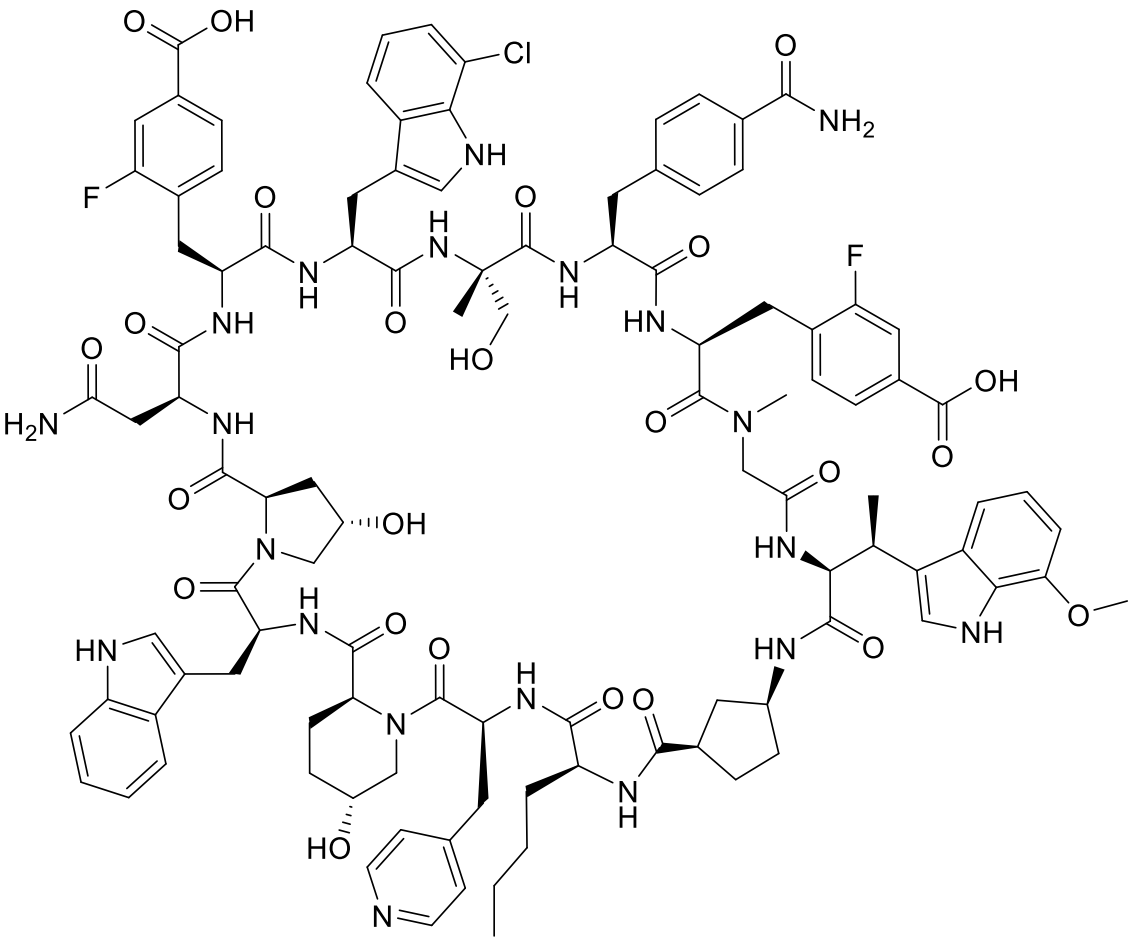

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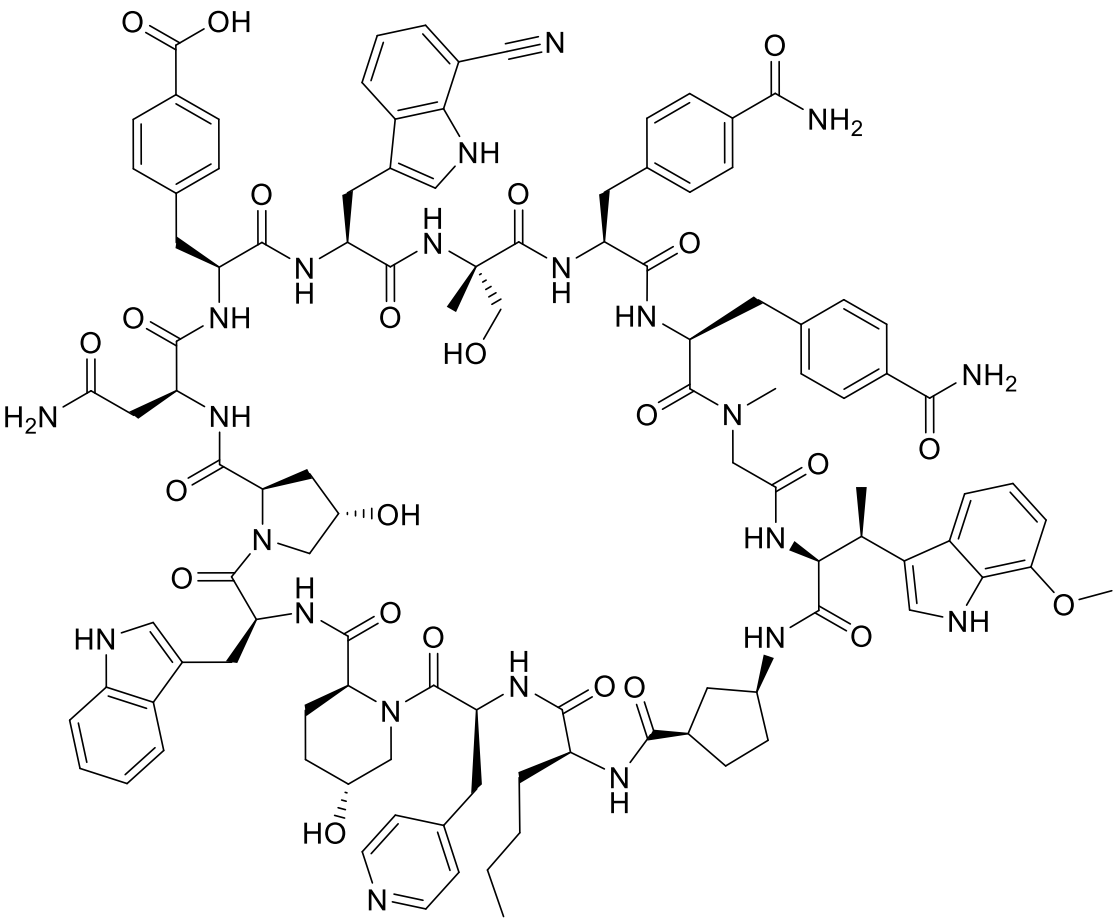

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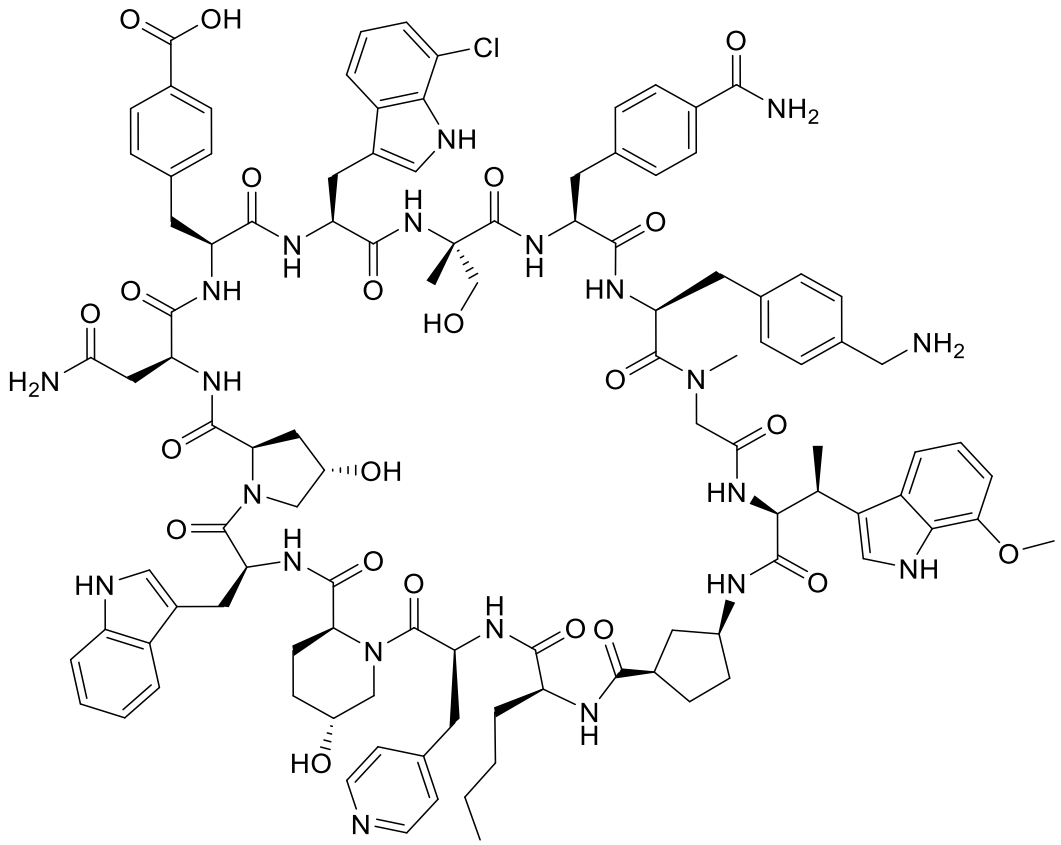

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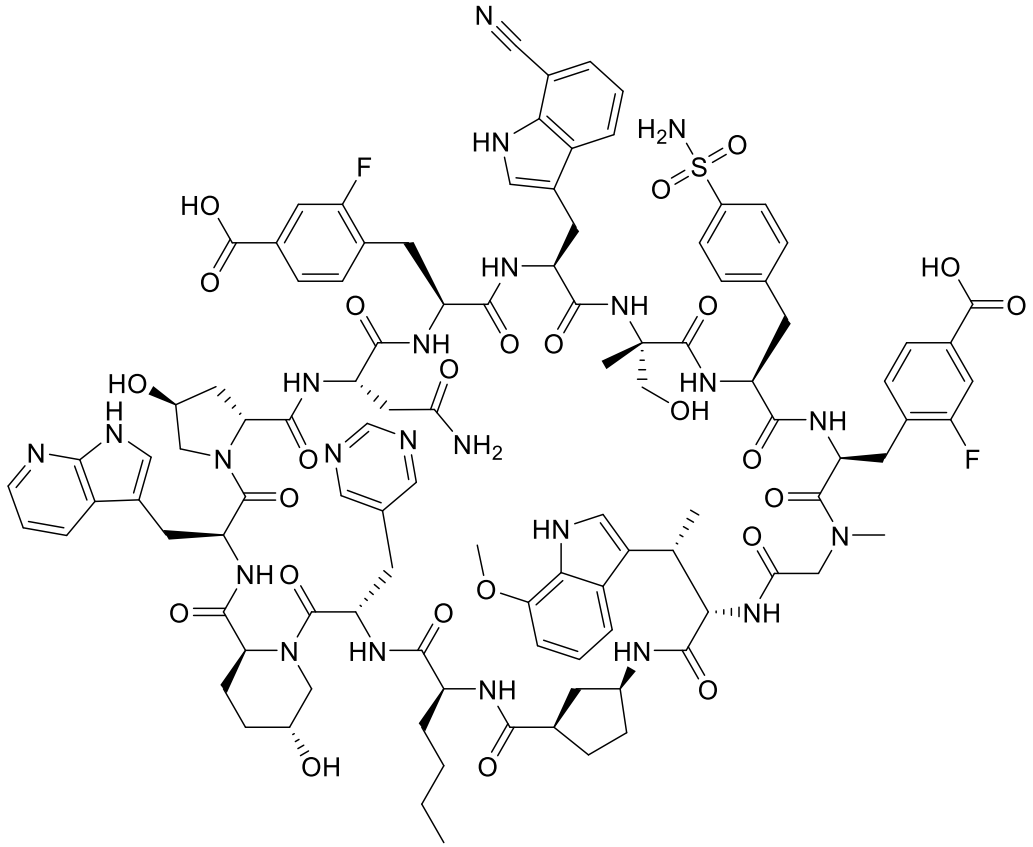

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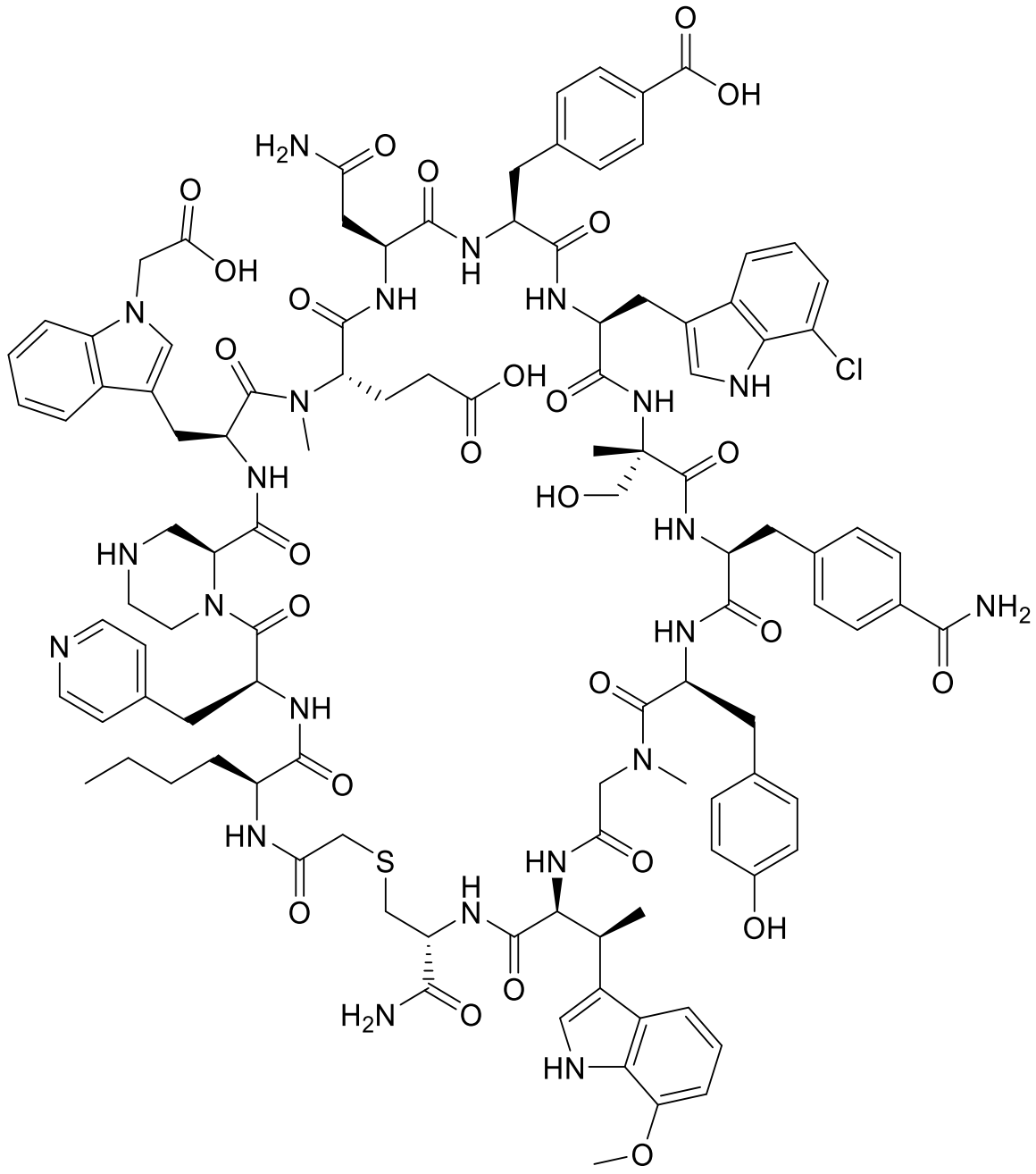

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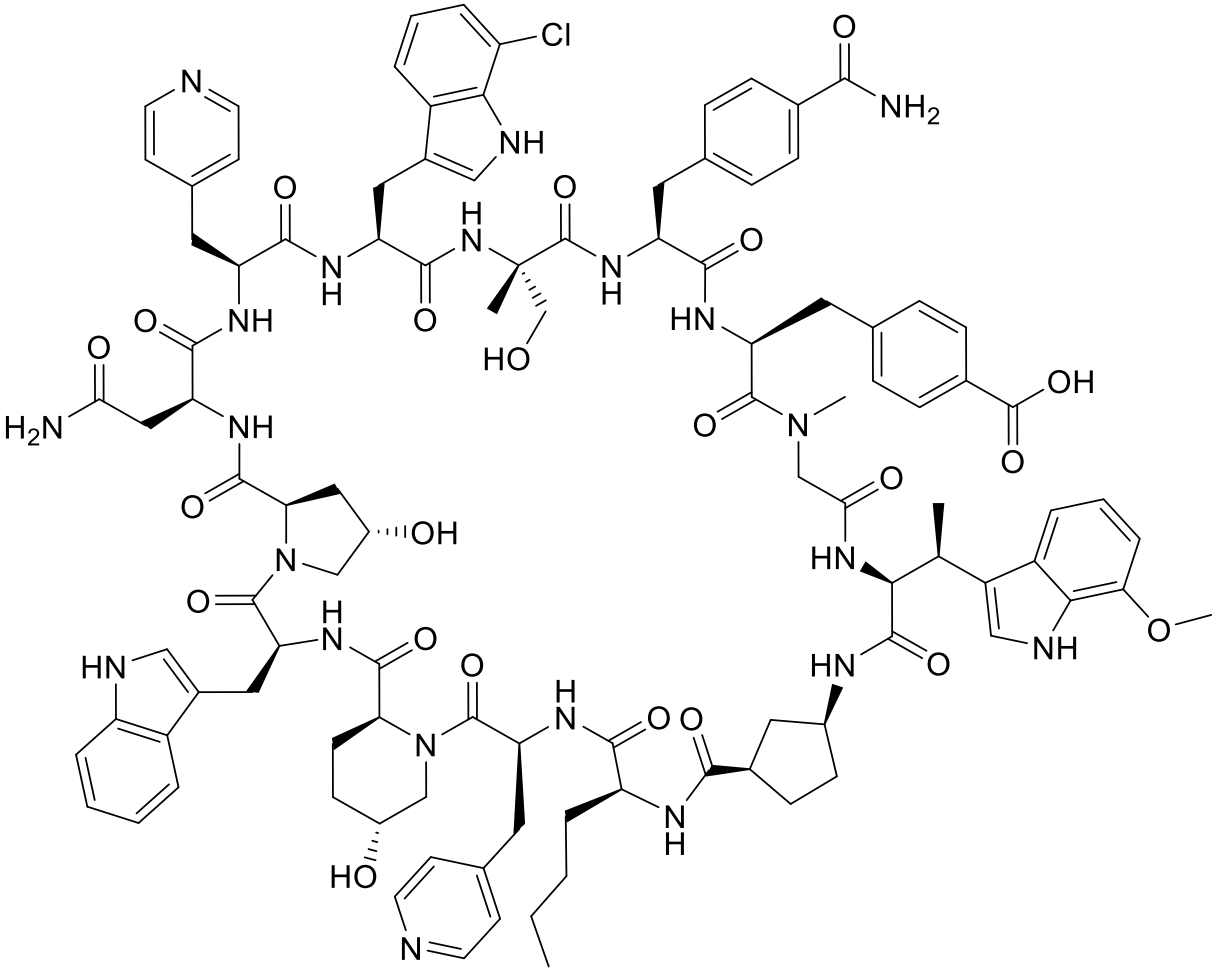

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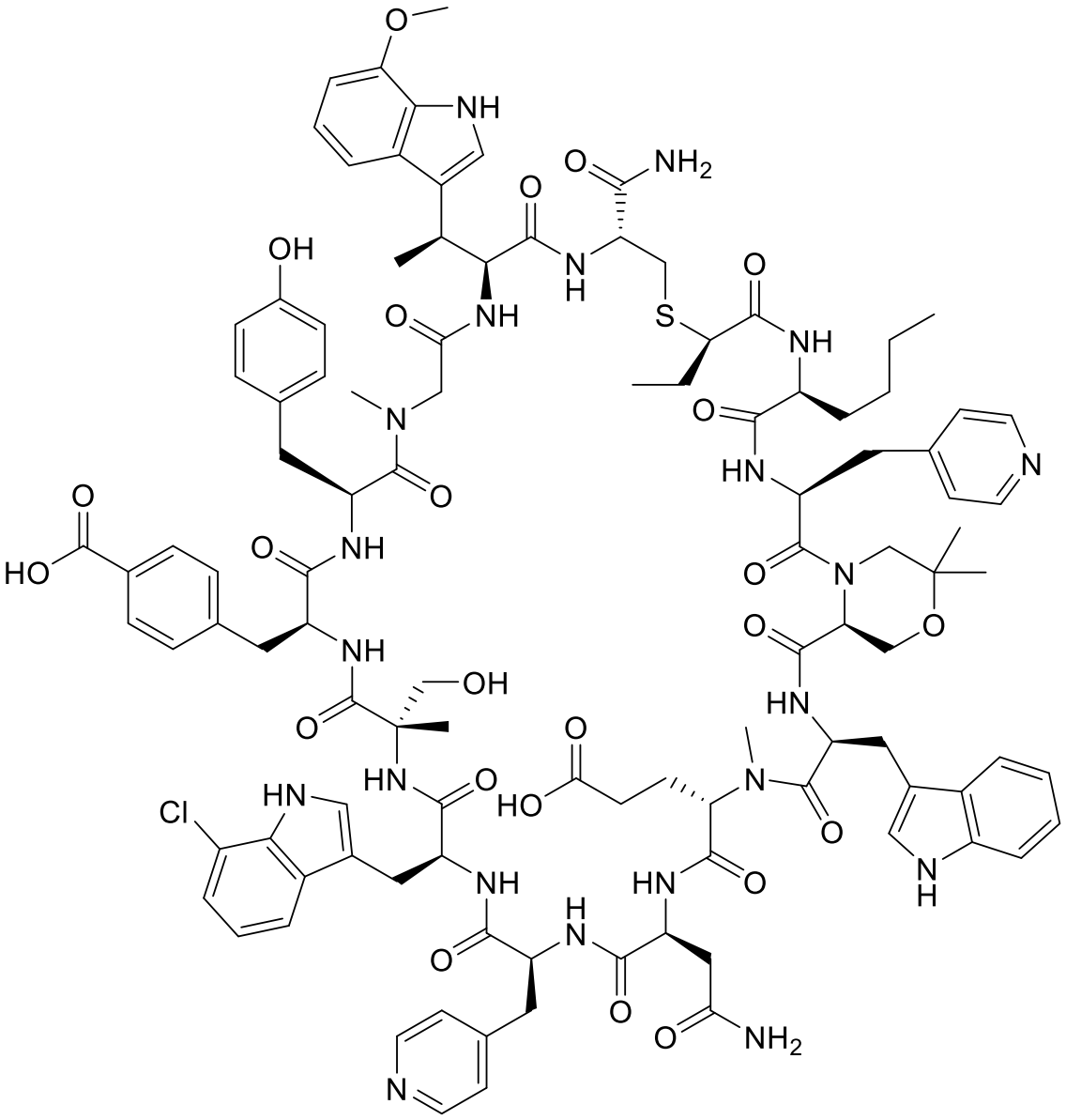

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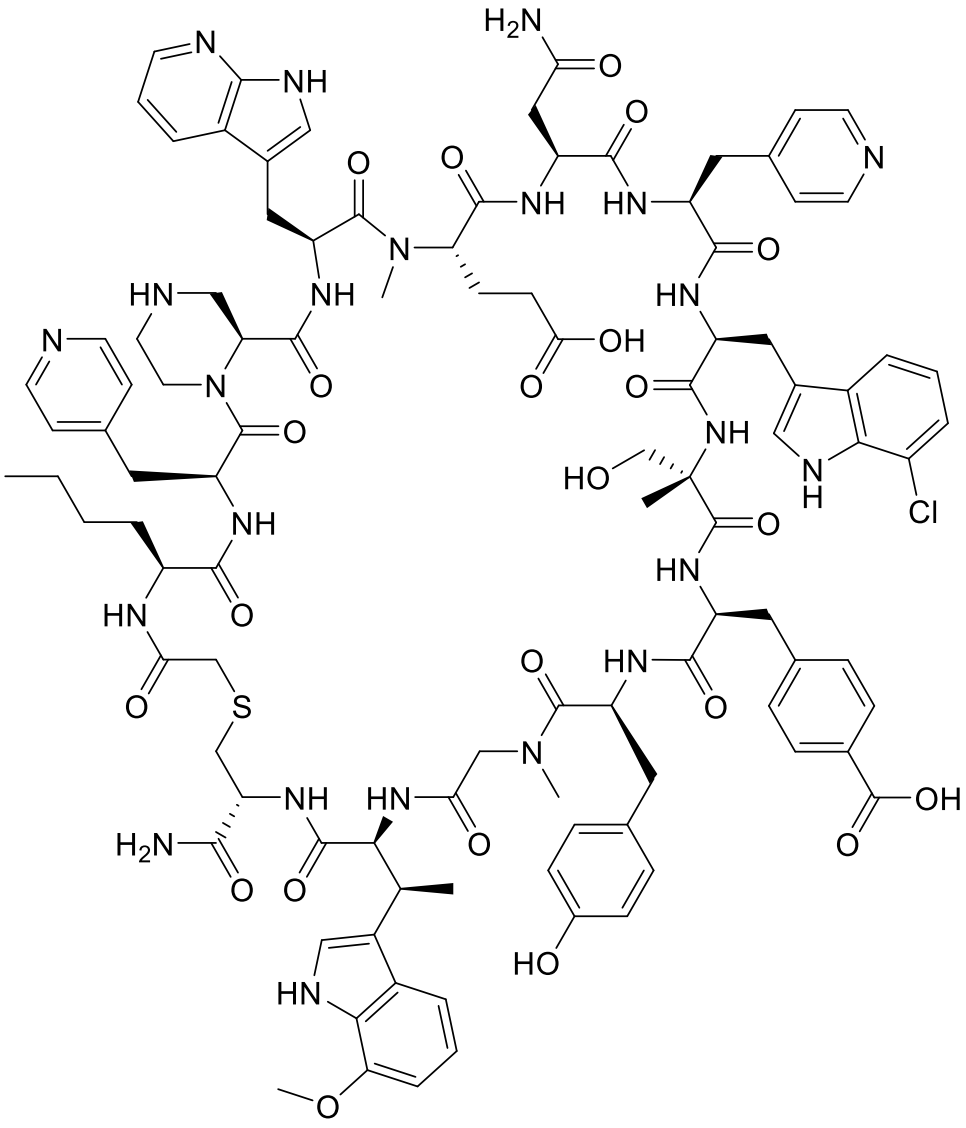

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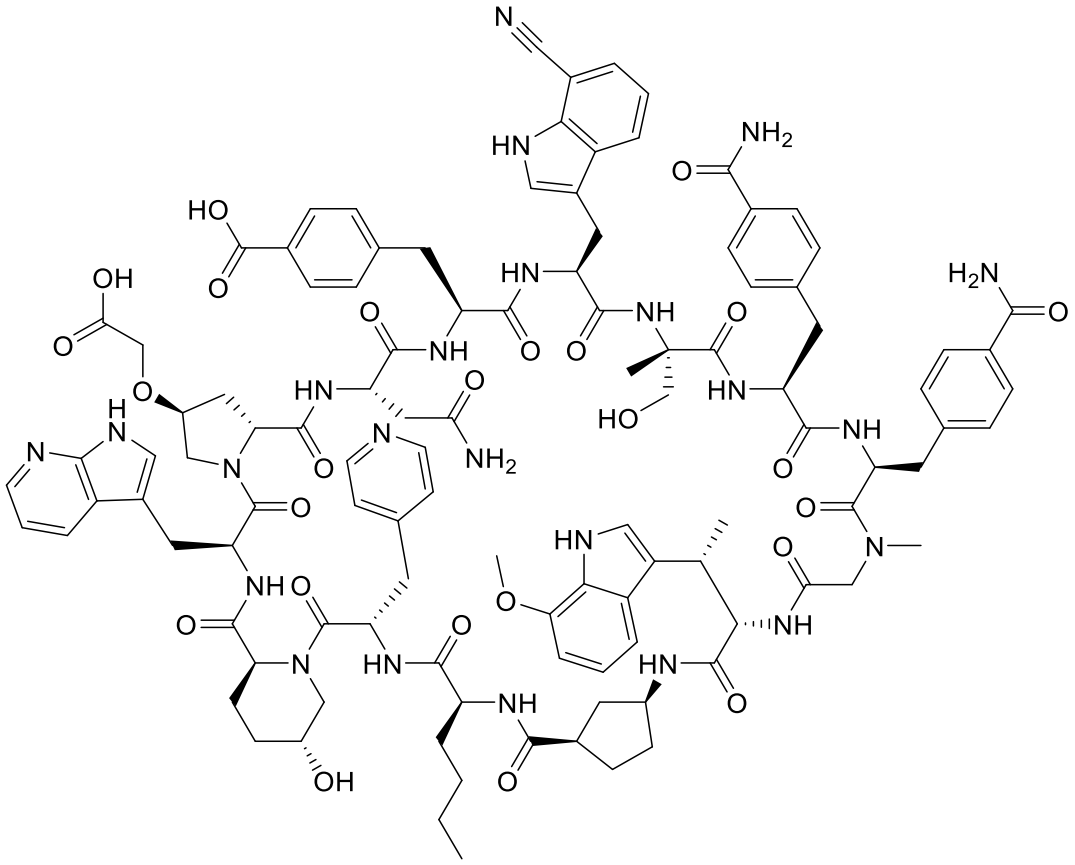

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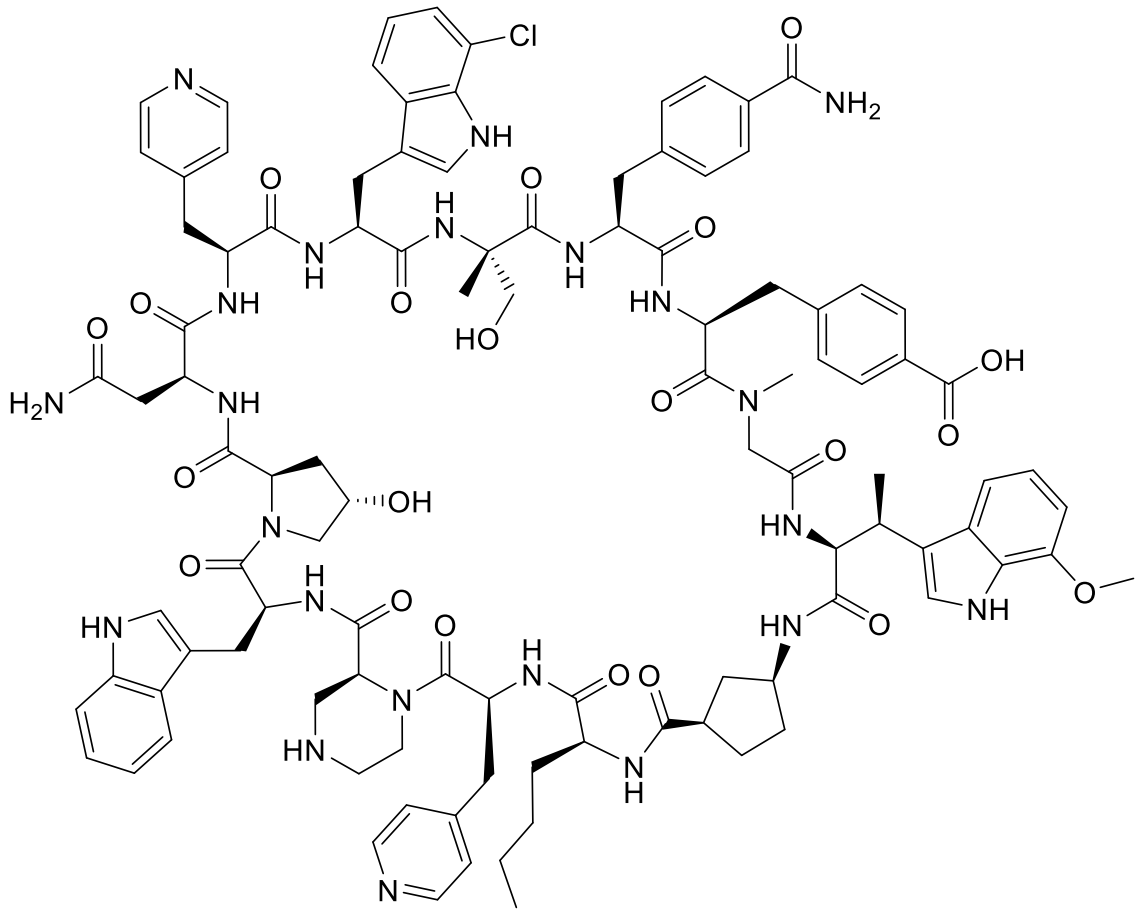

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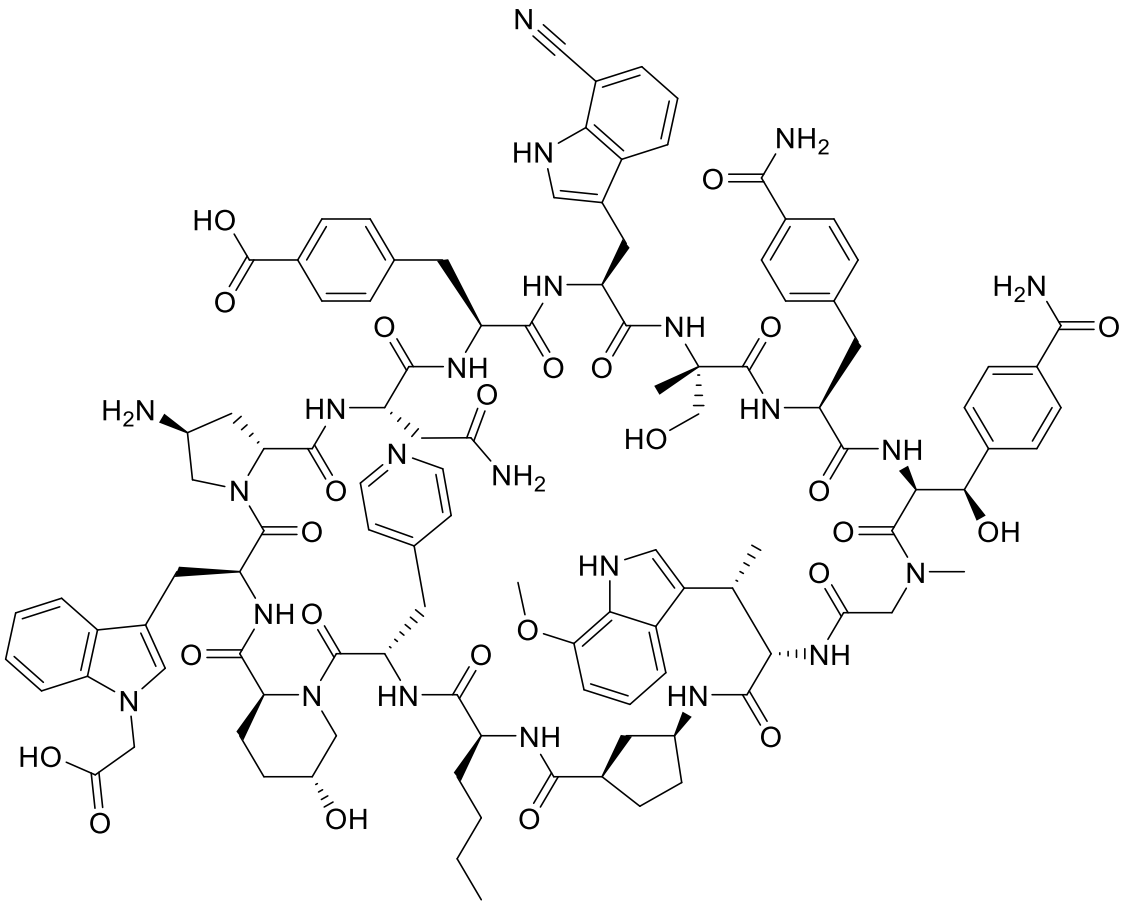

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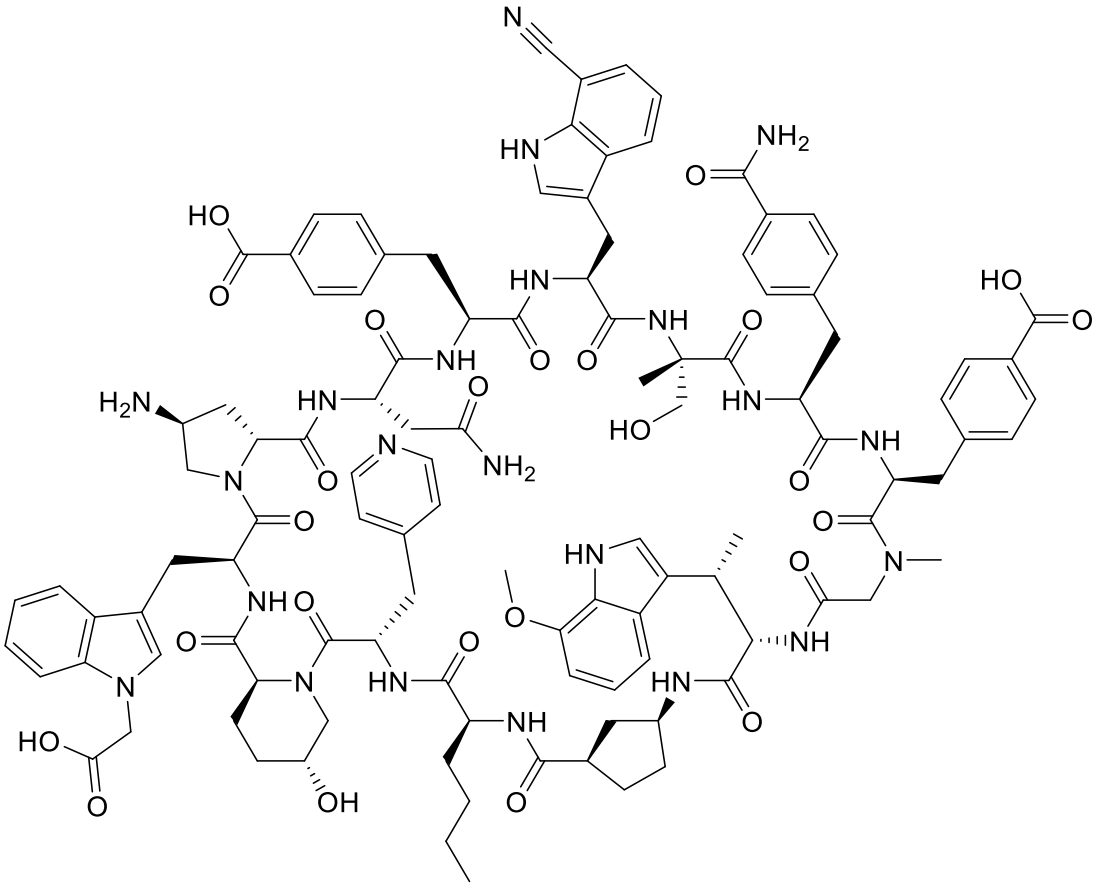

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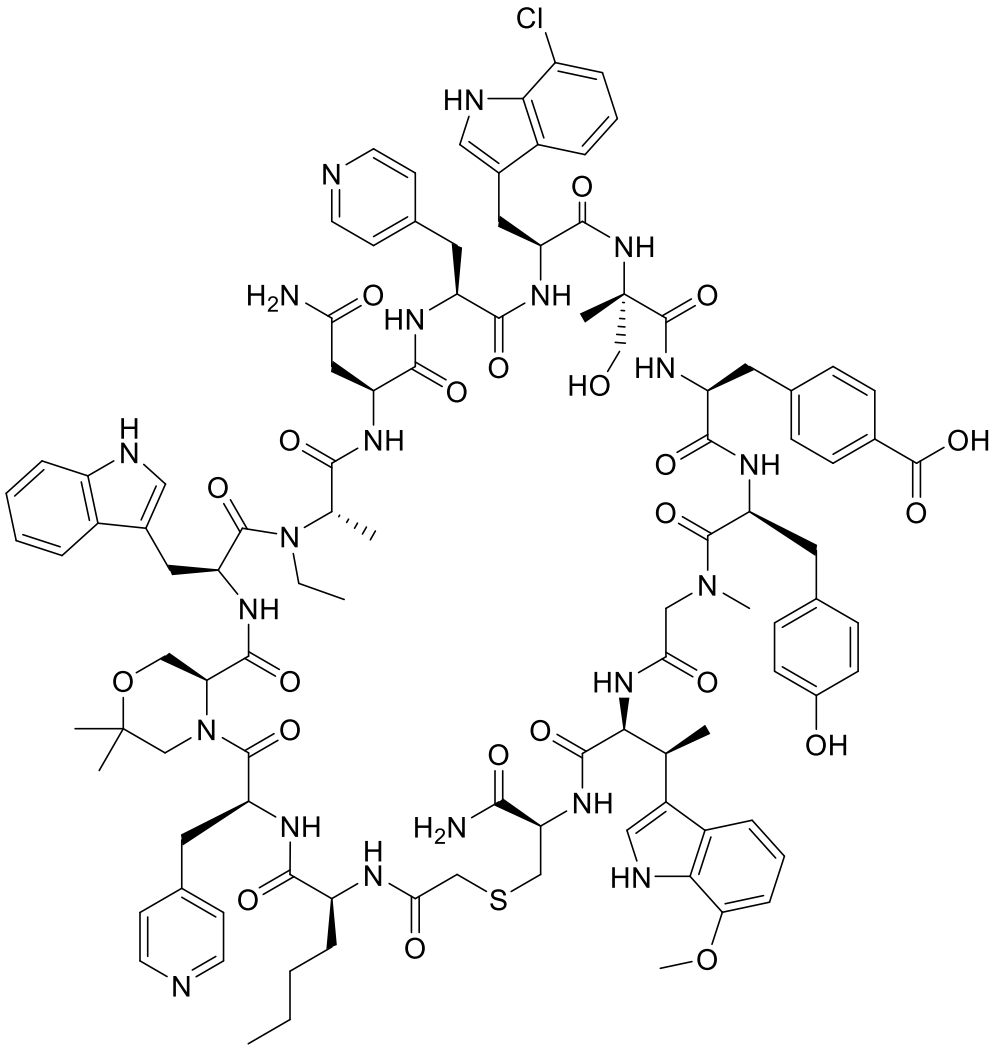

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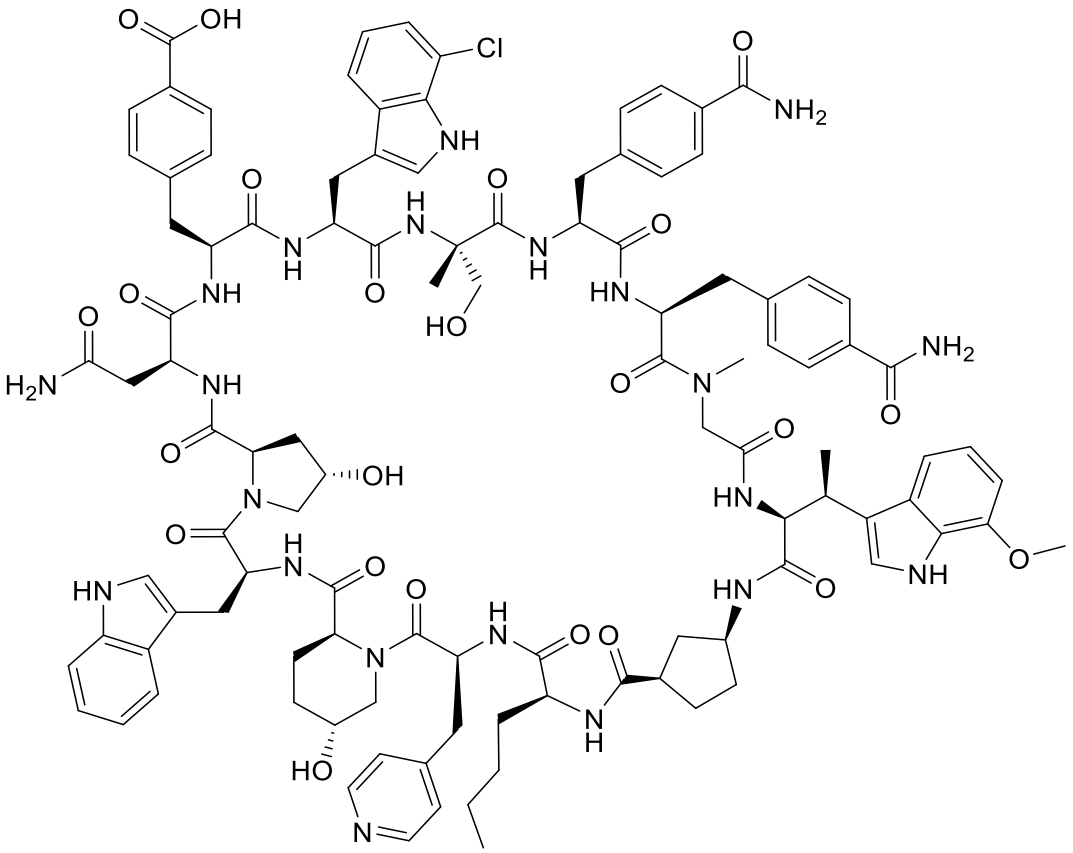

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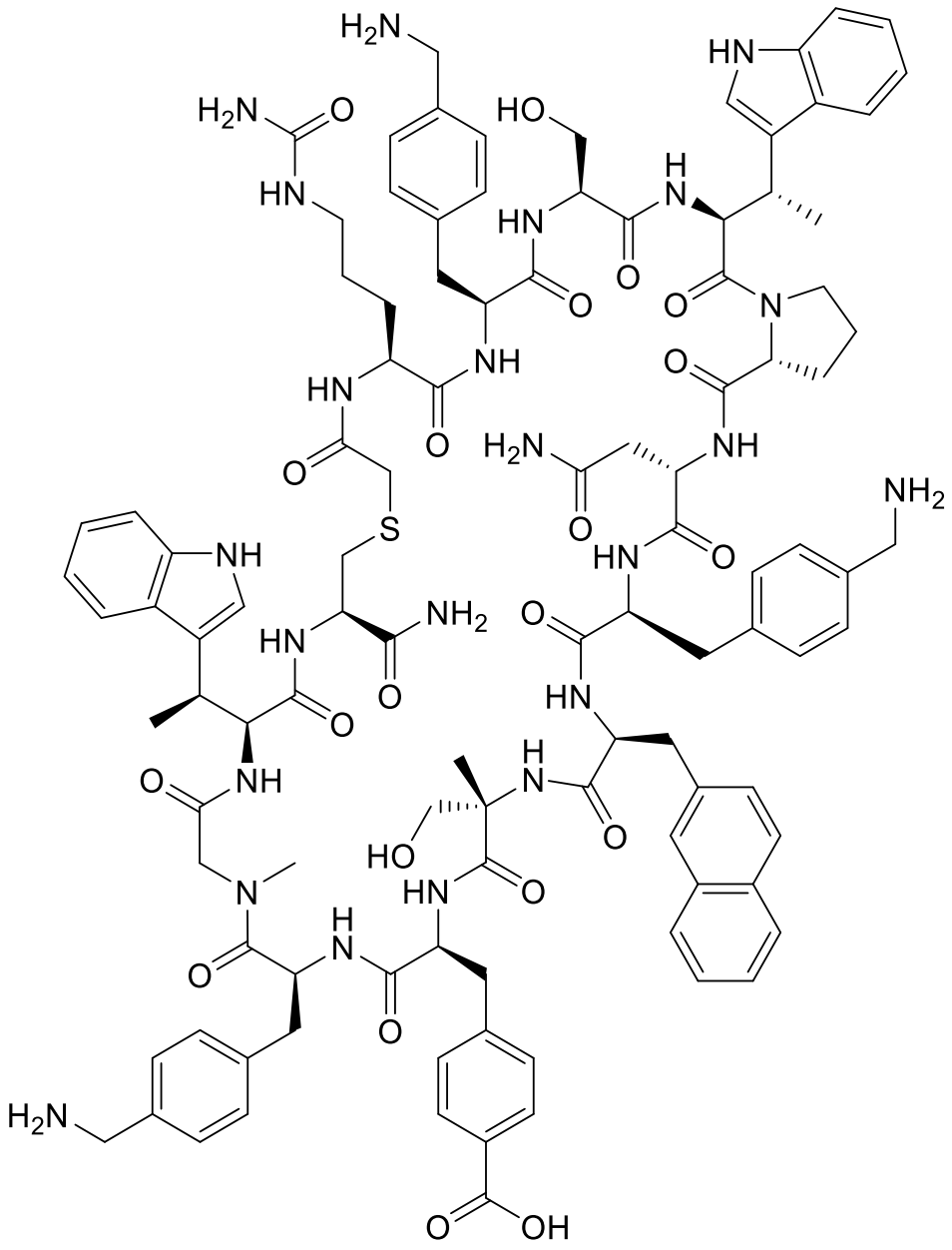

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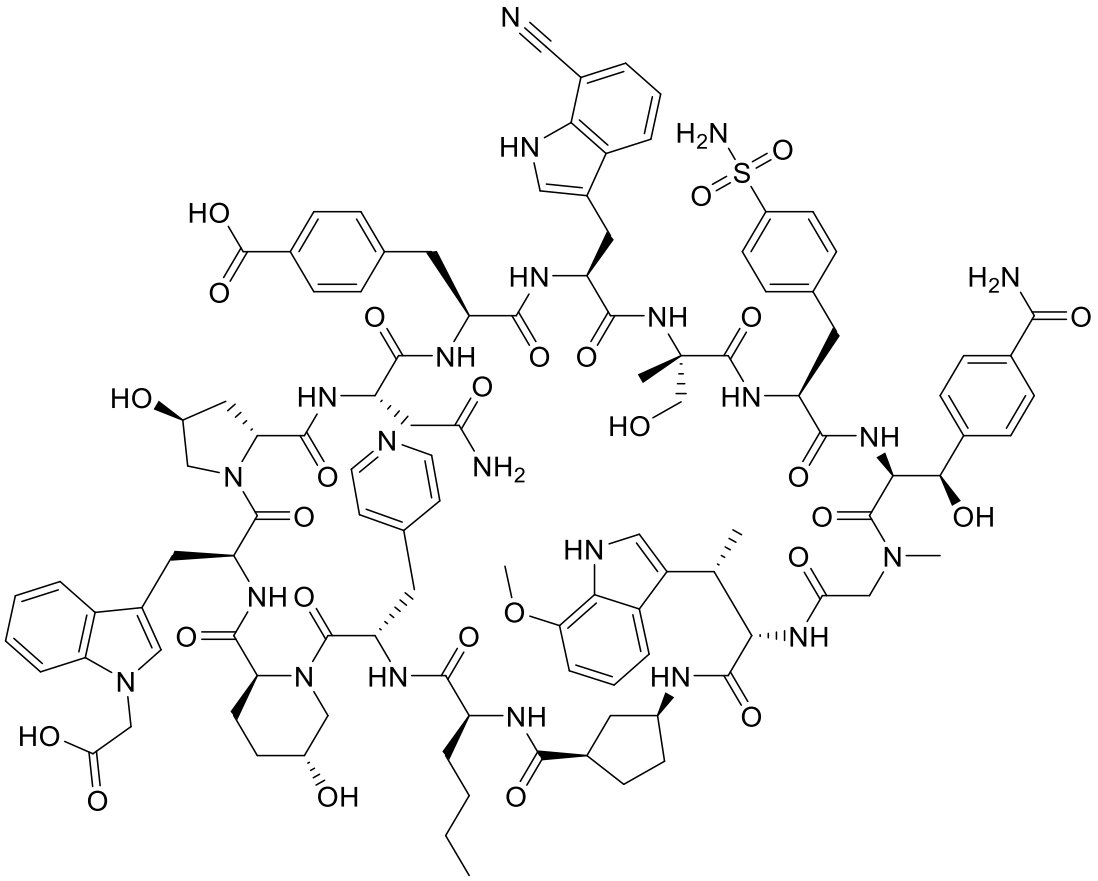

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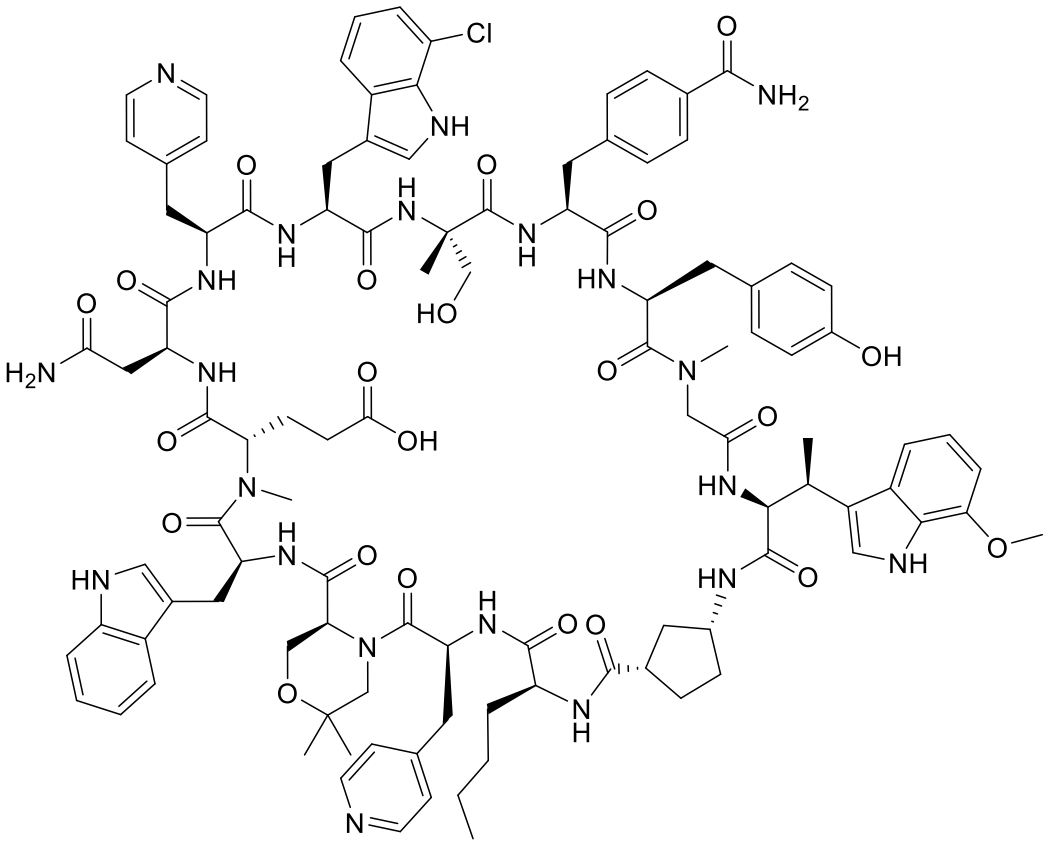

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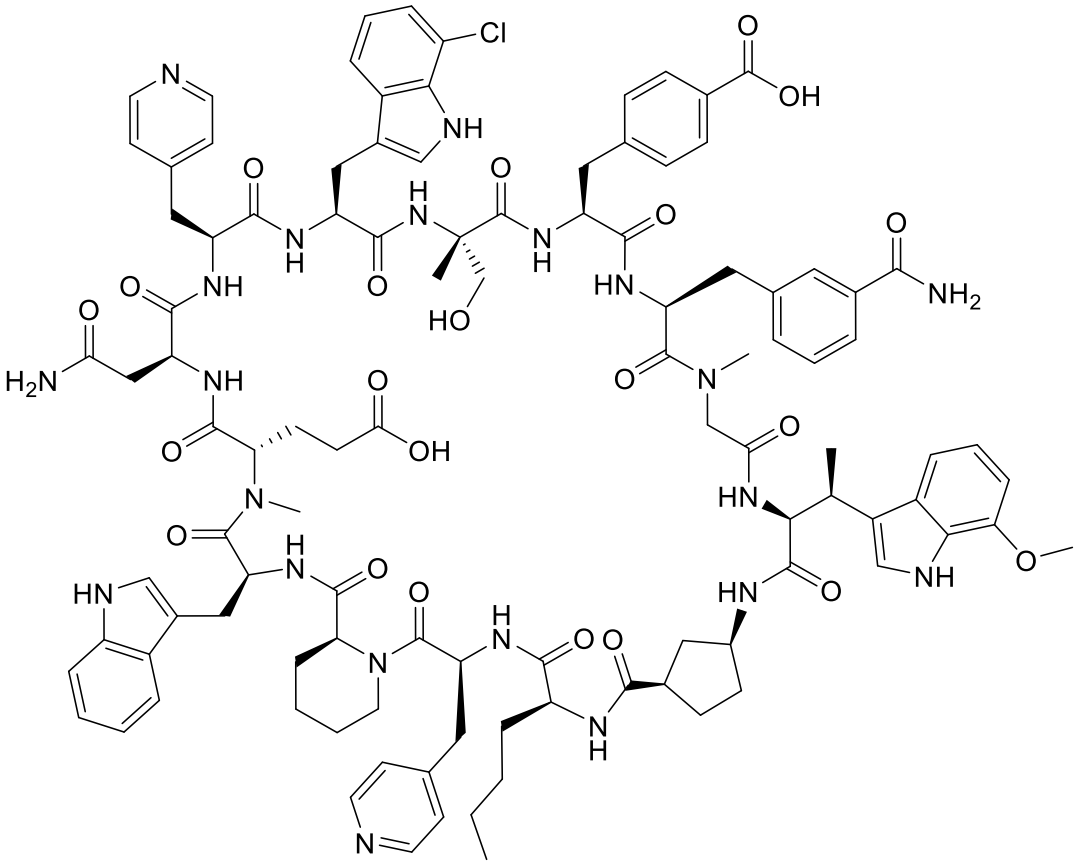

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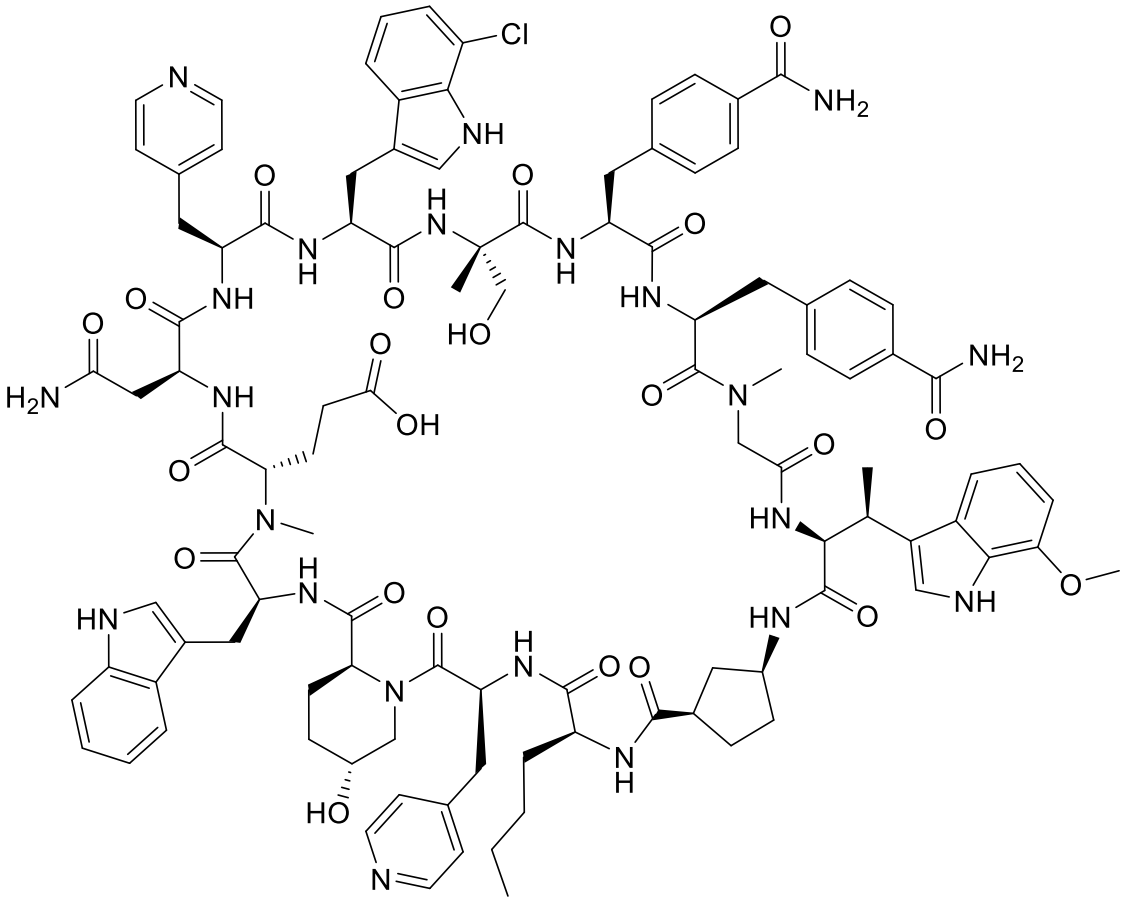
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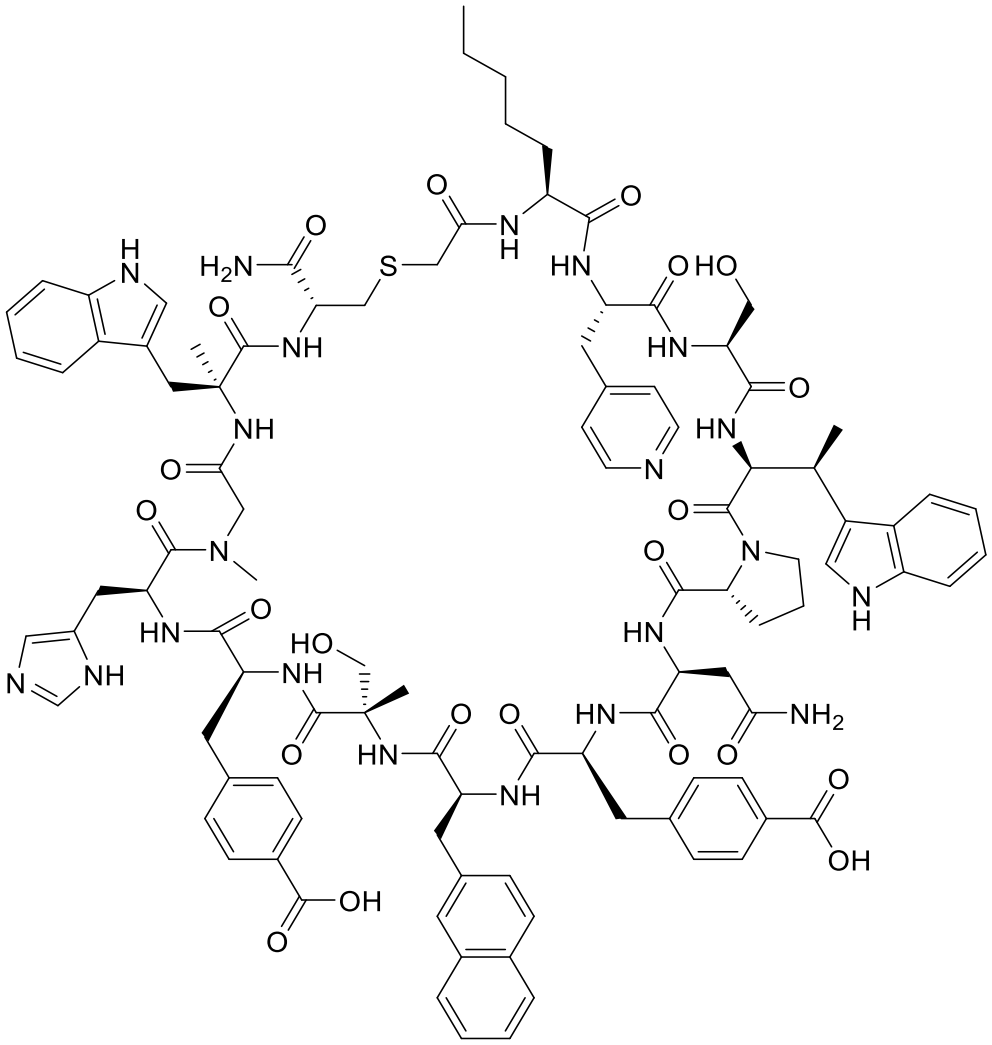

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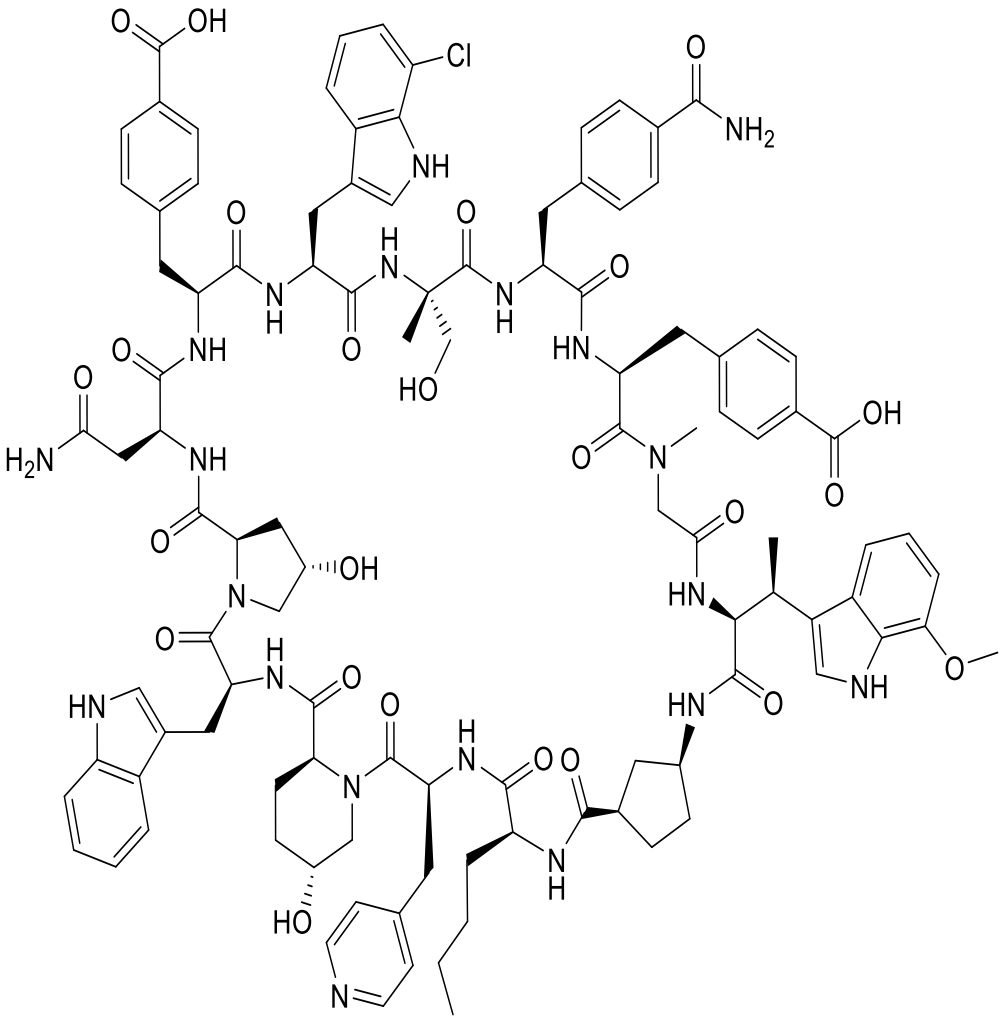
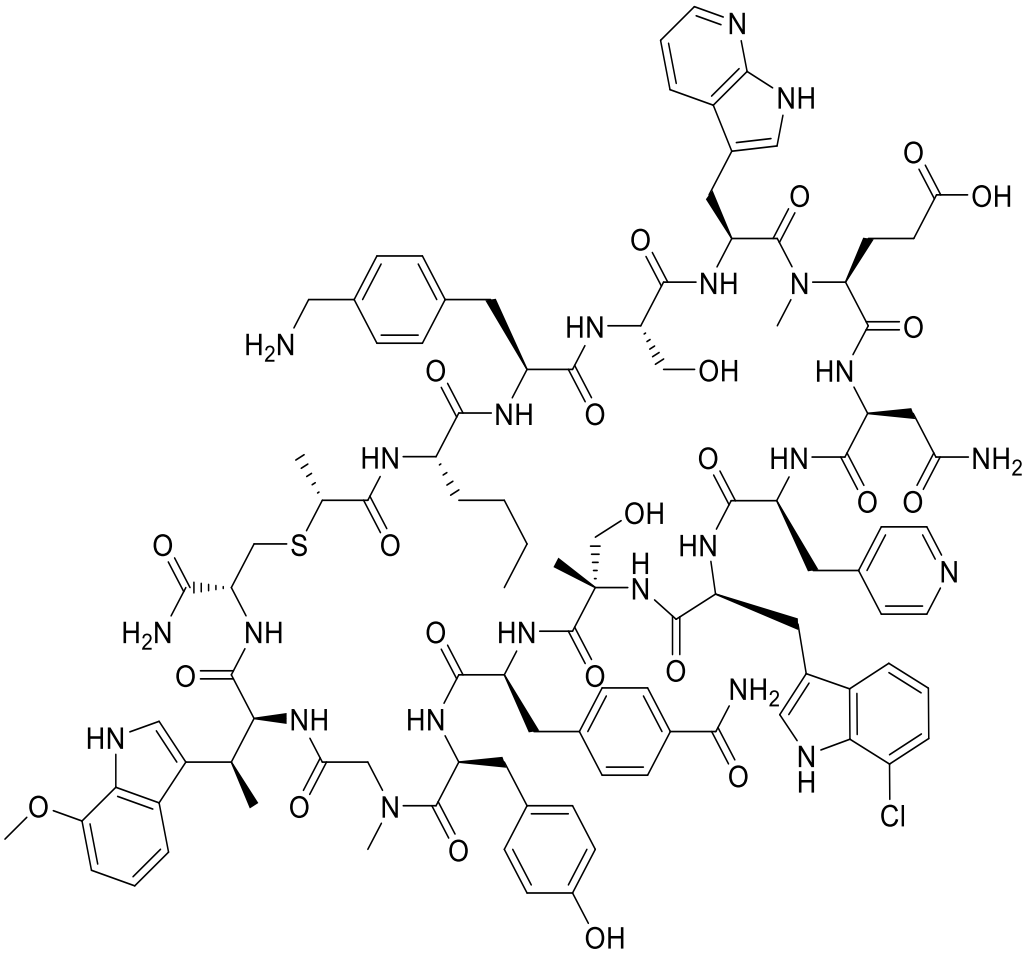


SEQ ID NO: 237,

SEQ ID NO: 247,



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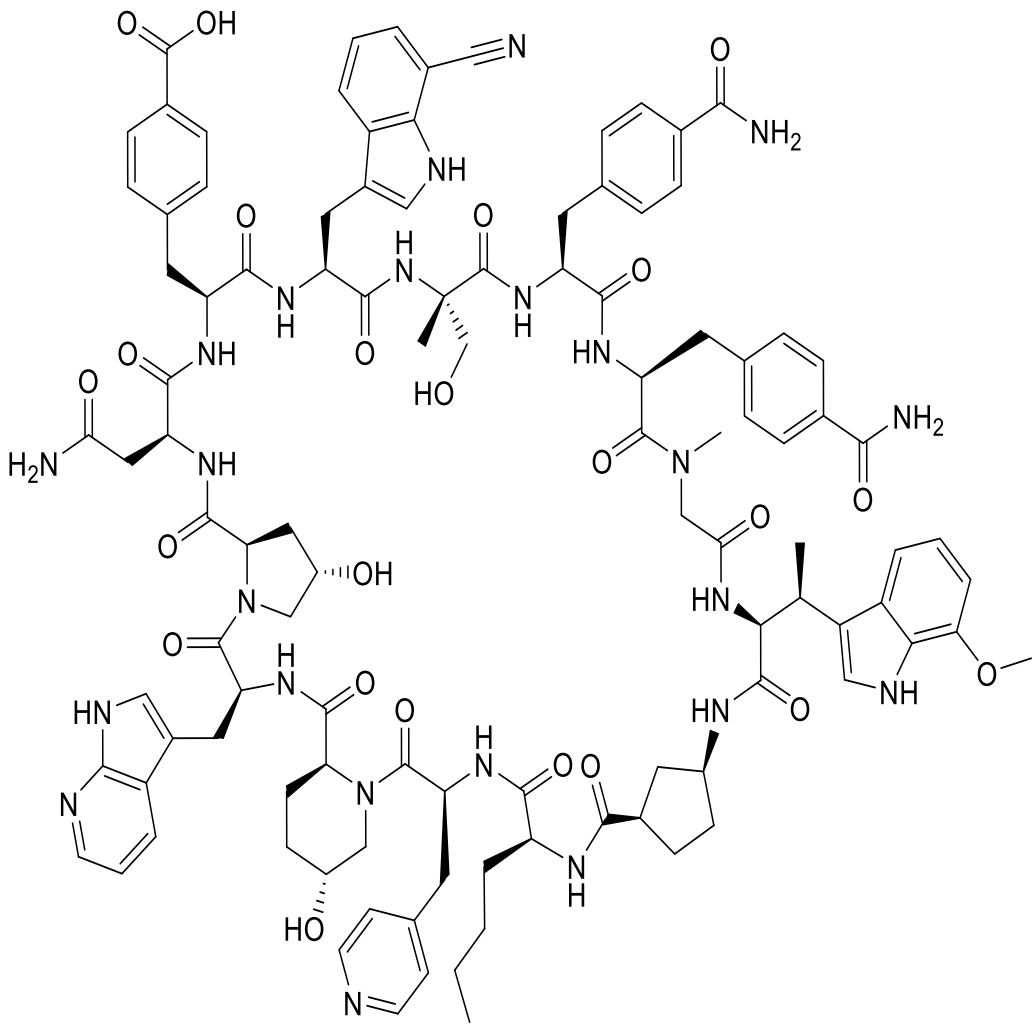

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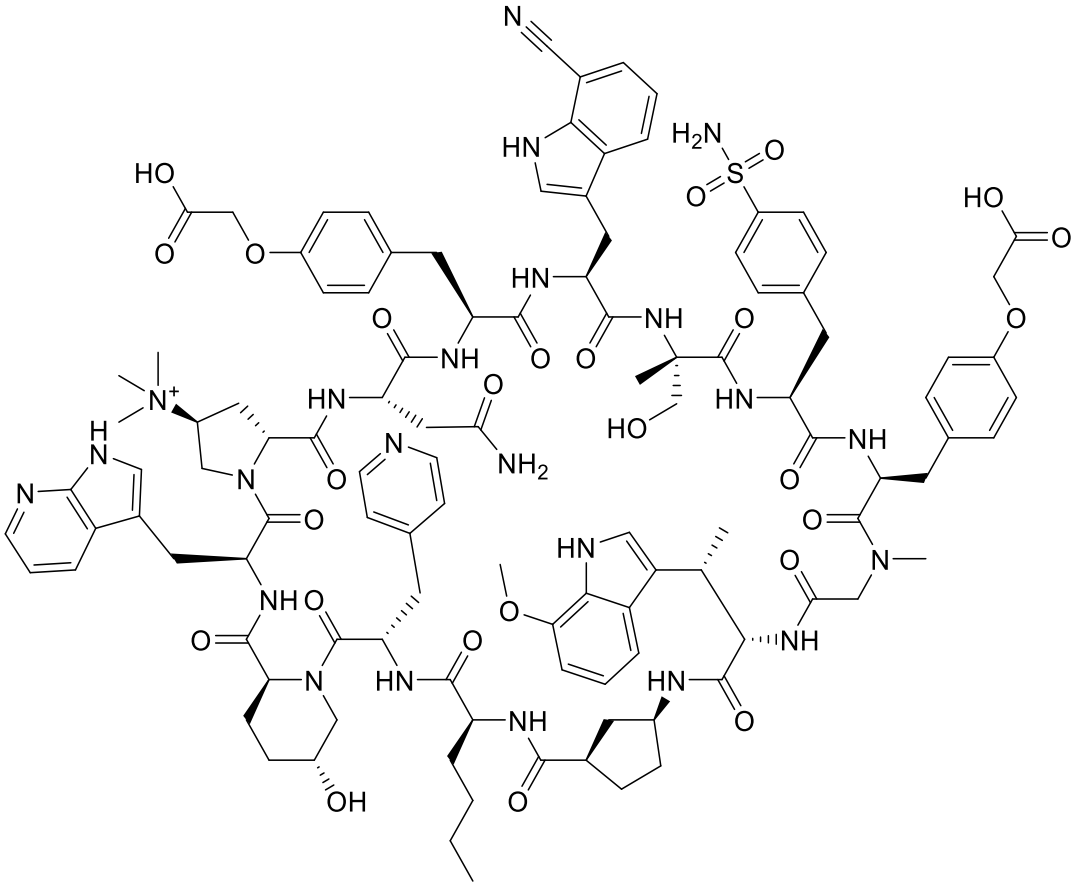
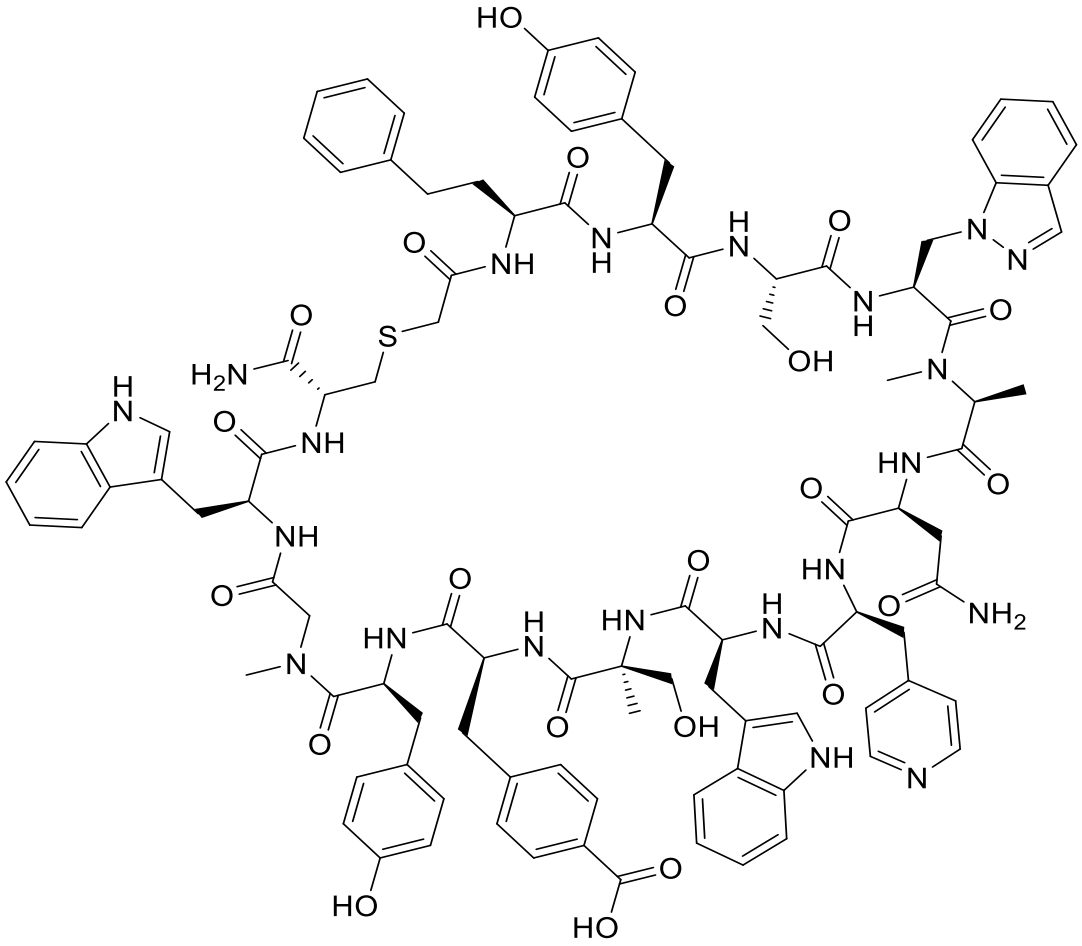


SEQ ID NO: 257; and



SEQ ID NO: 265,

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising the compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. Use of a compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases to a subject in need of such treatment, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

16. The use according to claim 15, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis and Crohn's disease.

17. The use according to claim 15, wherein said IBD and other TNFα-driven inflammatory diseases are selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

18. The use of any one of claims 15 - 17 wherein an effective amount of the compound or a pharmaceutically acceptable salt thereof is to be administered orally to the subject.

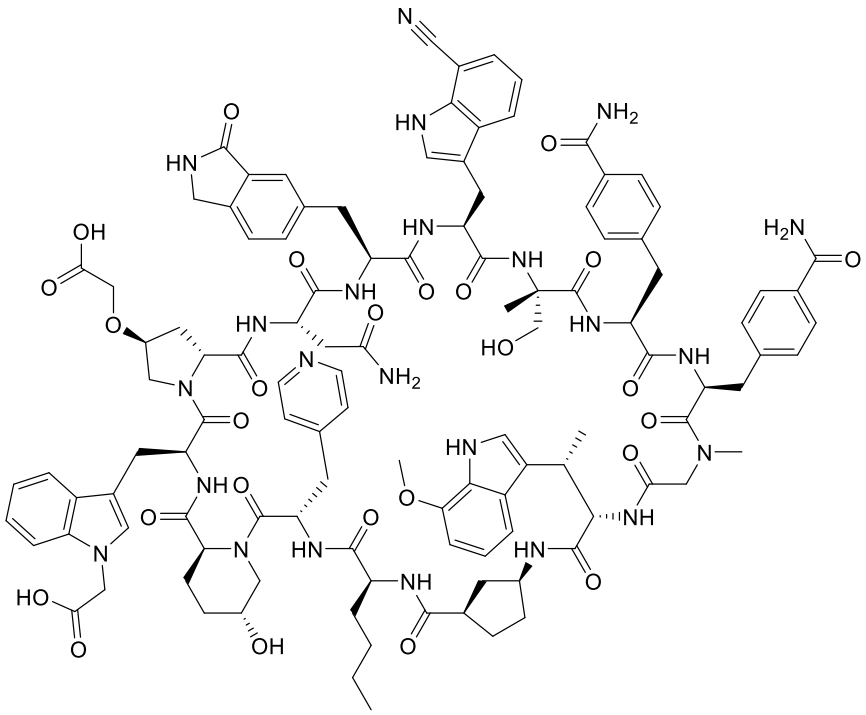
19. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof for use in therapy.

20. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

21. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis and Crohn's disease.

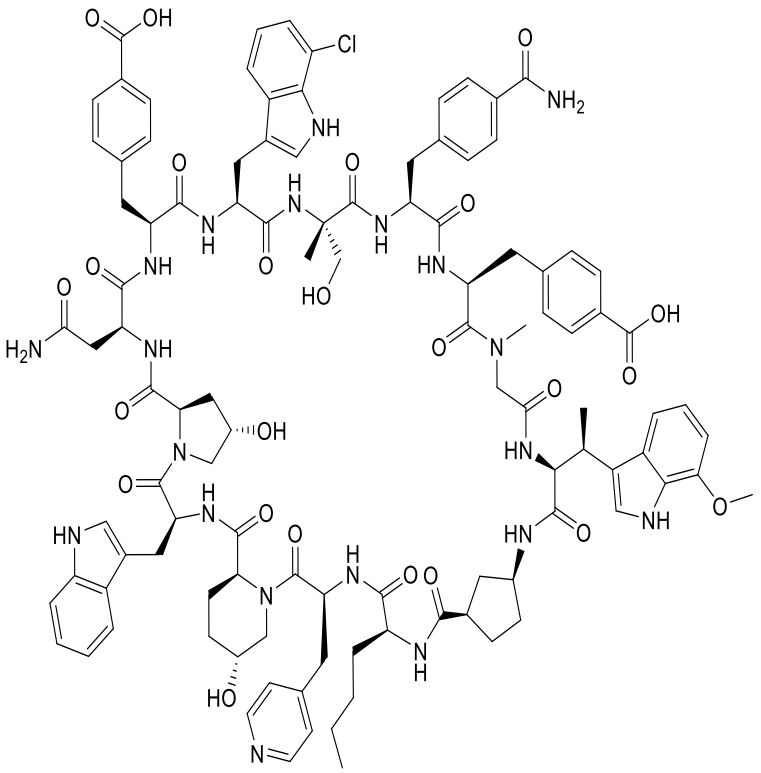
22. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof for use in treating IBD and other TNFα-driven inflammatory diseases selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

23. The compound of **SEQ ID NO: 22**



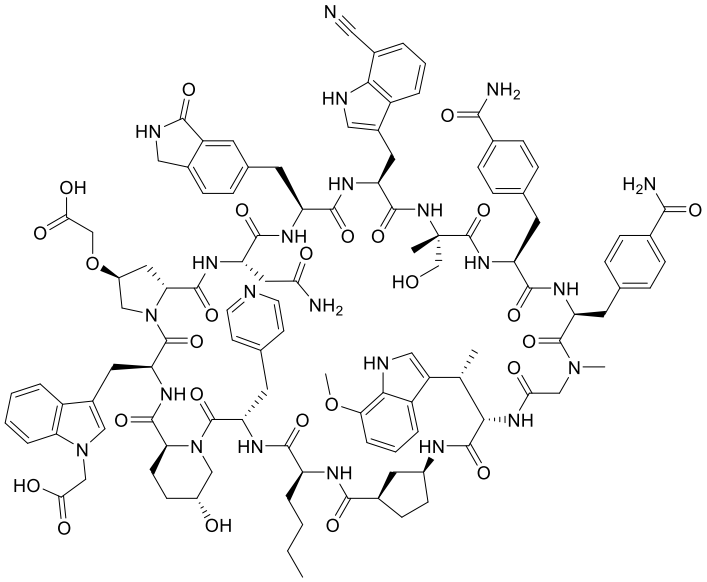
SEQ ID NO: 22.

24. The compound of **SEQ ID NO: 247**



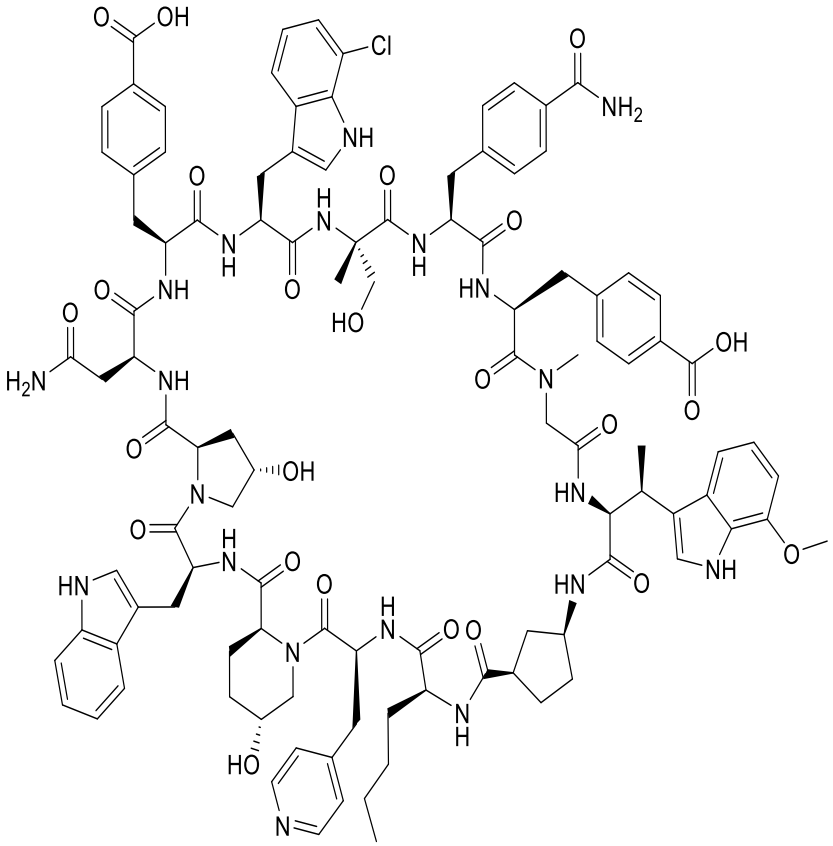
SEQ ID NO: 247.

25. The compound of **SEQ ID NO: 22**



SEQ ID NO: 22, or a pharmaceutically acceptable salt thereof.

26. The compound of **SEQ ID NO: 247**



SEQ ID NO: 247, or a pharmaceutically acceptable salt thereof.

27. A pharmaceutical composition comprising the compound of any one of claims 23-26, and a pharmaceutically acceptable carrier.

28. The pharmaceutical composition according to claim 27 for use in treating IBD and other TNFα-driven inflammatory diseases, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

29. The pharmaceutical composition for use according to claim 28, wherein said IBD and other TNFα-driven inflammatory diseases are selected from ulcerative colitis and Crohn's disease.

30. The pharmaceutical composition for use according to claim 28, wherein said IBD and other TNFα-driven inflammatory diseases are selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

31. The pharmaceutical composition of claim 27 or the pharmaceutical composition for use according to any one of claims 28 – 30, wherein the effective amount of the compound is to be administered orally to the subject.

32. Use of a compound of any one of claims 23-26 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis, Crohn's disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

33. Use of a compound of any one of claims 23-26 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases selected from ulcerative colitis and Crohn's disease.

34. Use of a compound of any one of claims 23-26 or the pharmaceutical composition of claim 27 in the manufacture of a medicament for treating IBD and other TNFα-driven inflammatory diseases selected from rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and hidradenitis suppurativa.

35. A compound of any one of claims 23-26 or the pharmaceutical composition of claim 27 for use in therapy.