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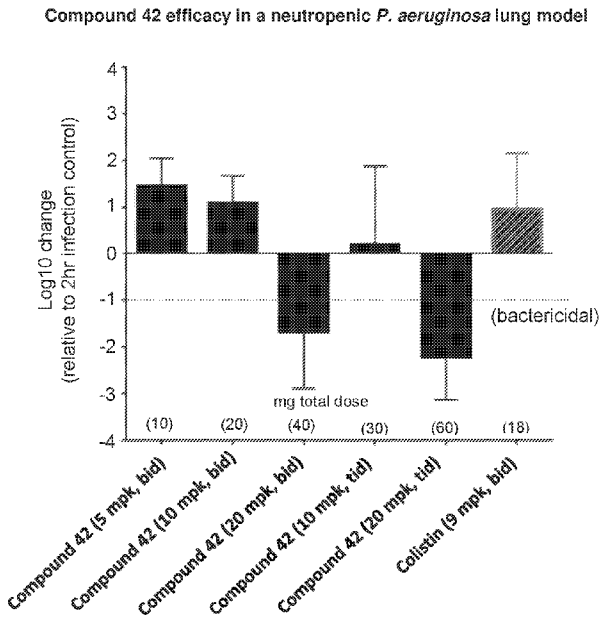
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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF BACTERIAL INFECTIONS

FIG. 1



(57) Abstract: Compositions and methods for the treatment of bacterial infections include compounds containing a cyclic heptapeptide. In particular, compounds can be used in the treatment of bacterial infections caused by Gram-negative bacteria.

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[Continued on next page]

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COMPOSITIONS AND METHODS FOR THE TREATMENT OF BACTERIAL INFECTIONS

Background

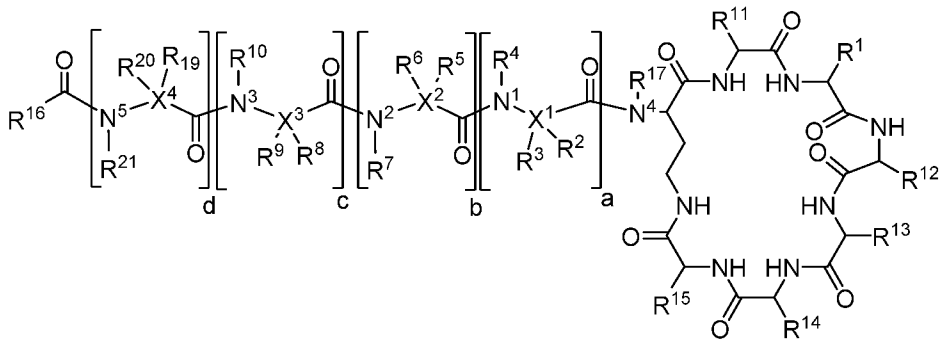
The need for novel antibacterial treatments for bacterial infections is significant and especially critical in the medical field. Antibacterial resistance is a serious global healthcare threat. Polymyxins are a class of antibiotics that exhibit potent antibacterial activities against Gram-negative bacteria. However, the use of polymyxins as an antibiotic has been limited due to the associated toxicity and adverse effects (e.g., nephrotoxicity). Moreover, *mcr-1*, a plasmid-borne gene conferring bacterial resistance to polymyxins, has a high potential for dissemination and further threatens the efficacy of this class of antibiotics.

Because of the shortcomings of existing antibacterial treatments, combined with the emergence of multidrug-resistant Gram-negative bacteria, there is a need in the art for improved antibacterial therapies having greater efficacy, bioavailability, and reduced toxicity.

Summary

The disclosure relates to compounds, compositions, and methods for inhibiting bacterial growth (e.g., Gram-negative bacterial growth) and for the treatment of bacterial infections (e.g., Gram-negative bacterial infections). In particular, such compounds contain a cyclic heptapeptide (e.g., a polymyxin core). The cyclic heptapeptide binds to lipopolysaccharides (LPS) in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization of the Gram-negtaive bacteria to other antibiotics.

In one aspect, the invention features a compound described by formula (I):



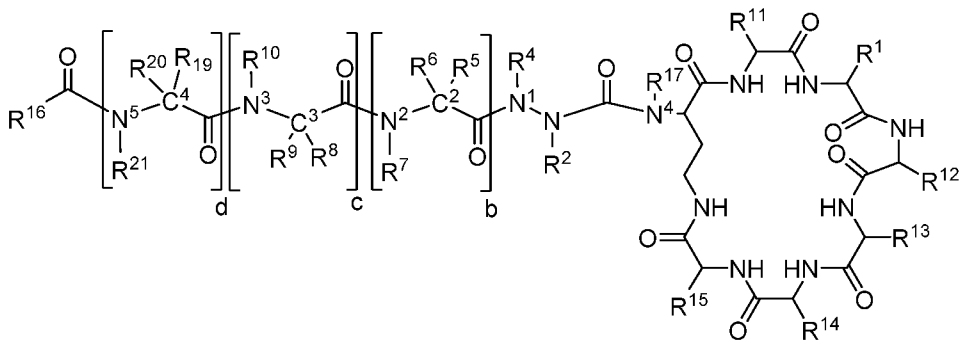
(I)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or

optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein at least one of X^1, X^2, X^3, and X^4 is a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; (vii) R^{19}, R^{20}, and X^4; or (viii) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (I-1):

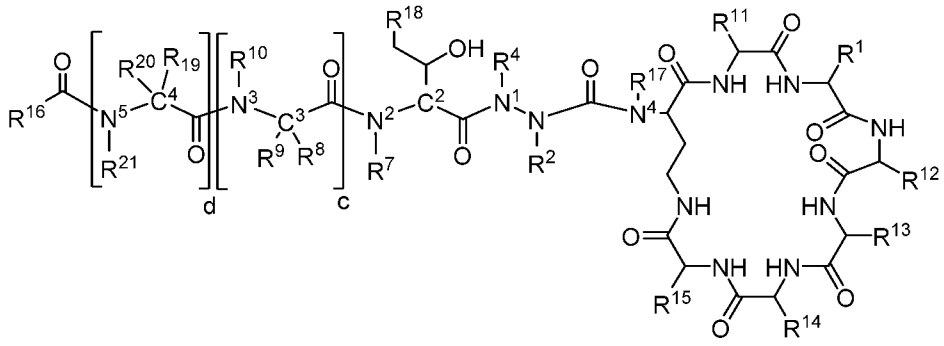


(I-1)

wherein each of b, c, and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^5, R^6, and C^2; (ii) R^6, R^7, N^2, and C^2; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (I-2):

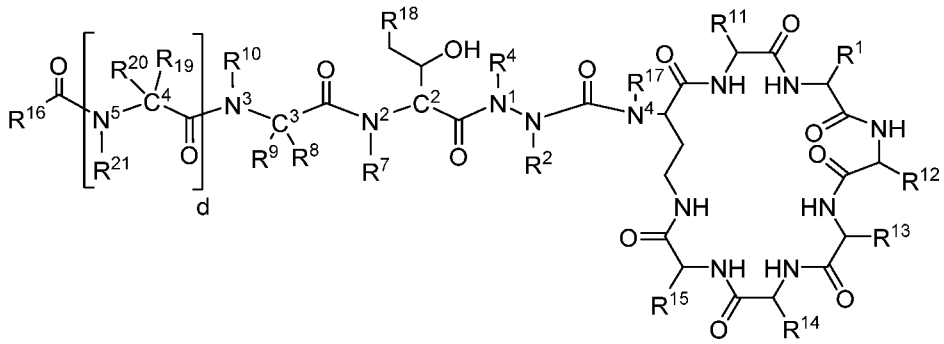


(I-2)

wherein each of c and d is, independently, 0 or 1; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally

substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (I-3):

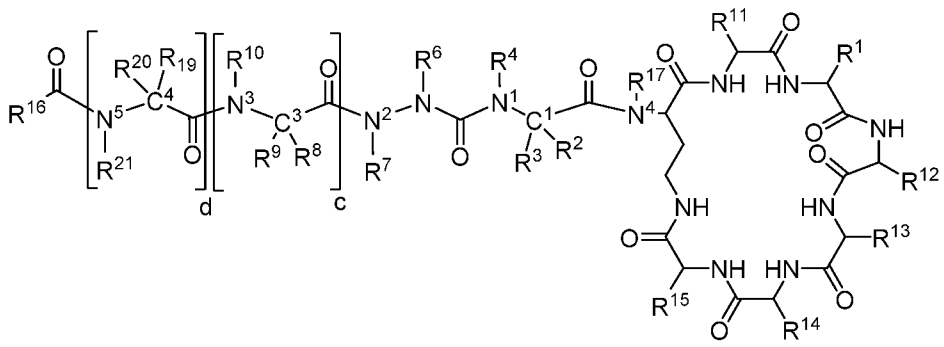


(I-3)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^8, R^9, and C^3; (ii) R^9, R^{10}, N^3, and C^3; (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4.

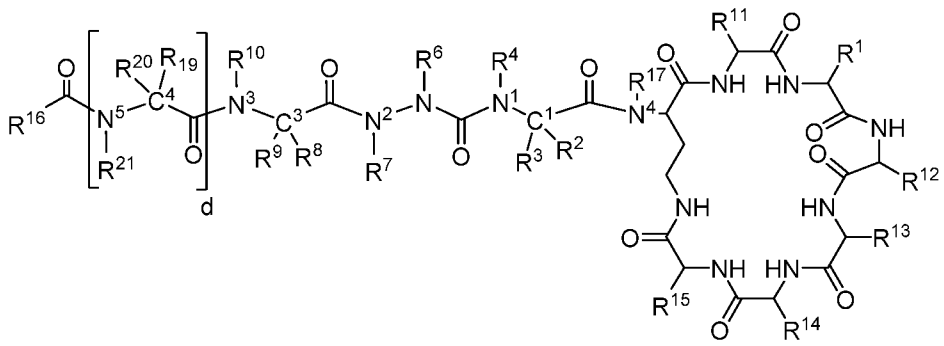
In some embodiments, the compound is described by formula (I-4):



(I-4)

wherein each of c and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (I-5):

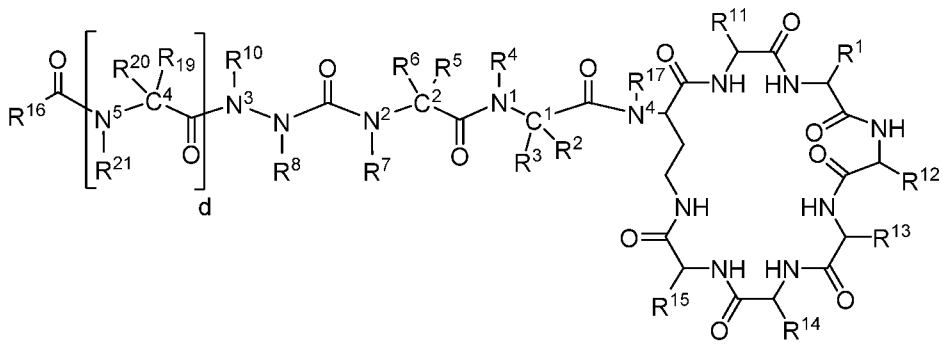


(I-5)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (I-6):

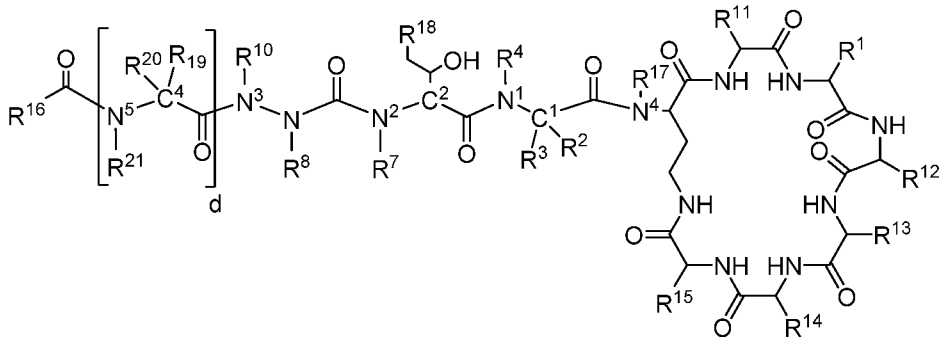


(I-6)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; or (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (I-7):

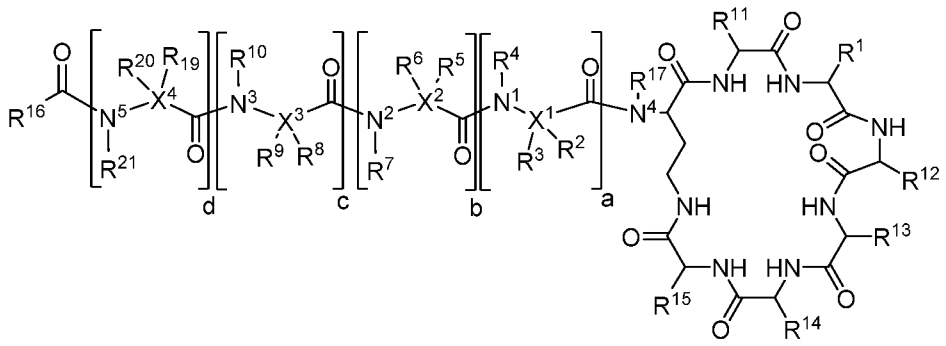


(I-7)

wherein d is 0 or 1; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; or (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (II):

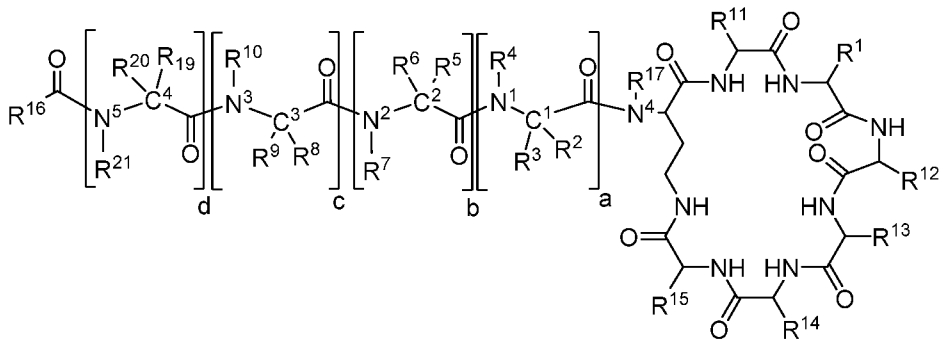


(II)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is C1-C3 alkyl or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (II-1):

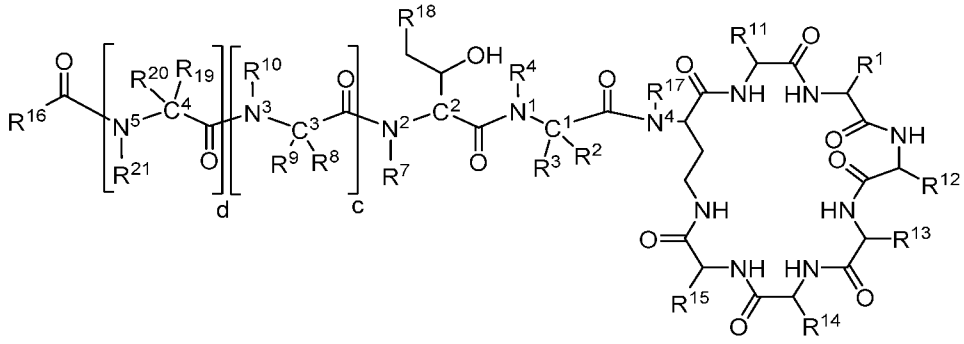


(II-1)

wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and each of a, b, c, and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

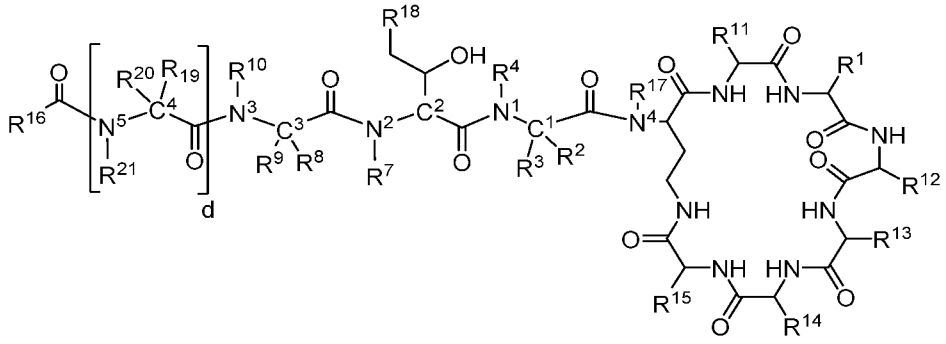
In some embodiments, the compound is described by formula (II-2):



(II-2)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is C1-C3 alkyl or C2-C3 alkamino; and each of c and d is, independently, 0 or 1,or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (II-3):

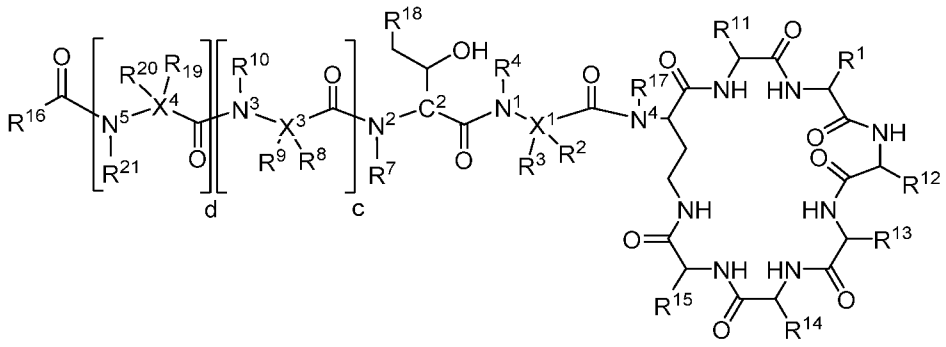


(II-3)

wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (III):



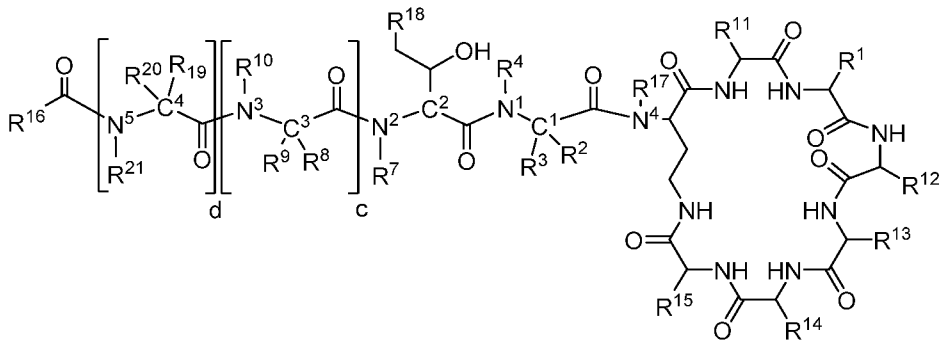
(III)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20

cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^8, R^9, and X^3; (iv) R^9, R^{10}, N^3, and X^3; (v) R^{19}, R^{20}, and X^4; or (vi) R^{19}, R^{20}, N^5, and X^4.

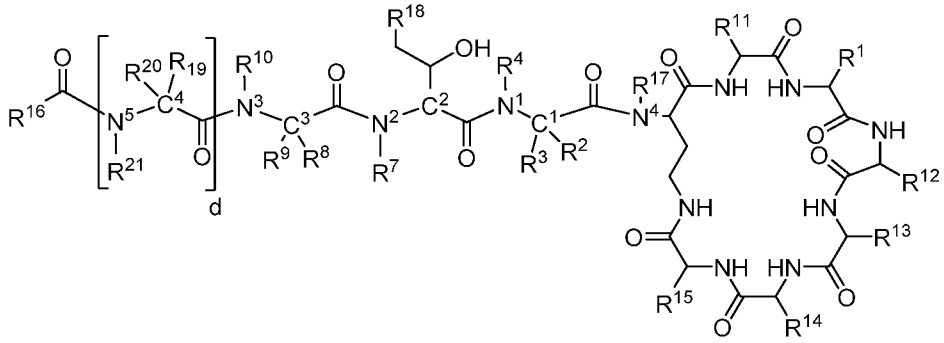
In some embodiments, the compound is described by formula (III-1):



(III-1)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and each of c and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (III-2):

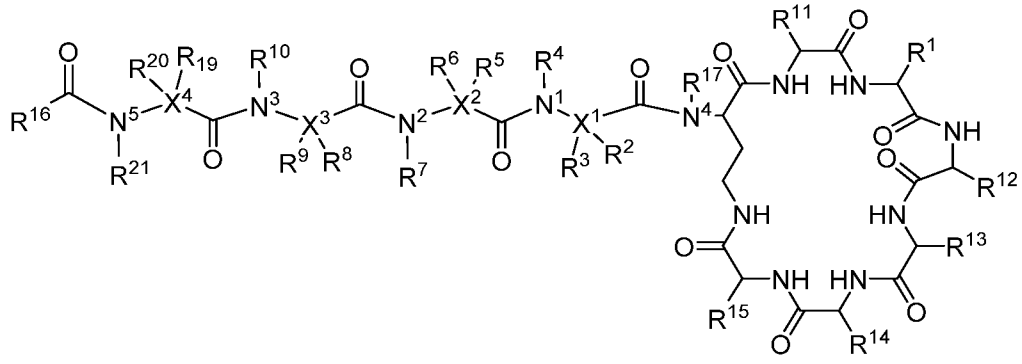


(III-2)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and d is 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (IV):



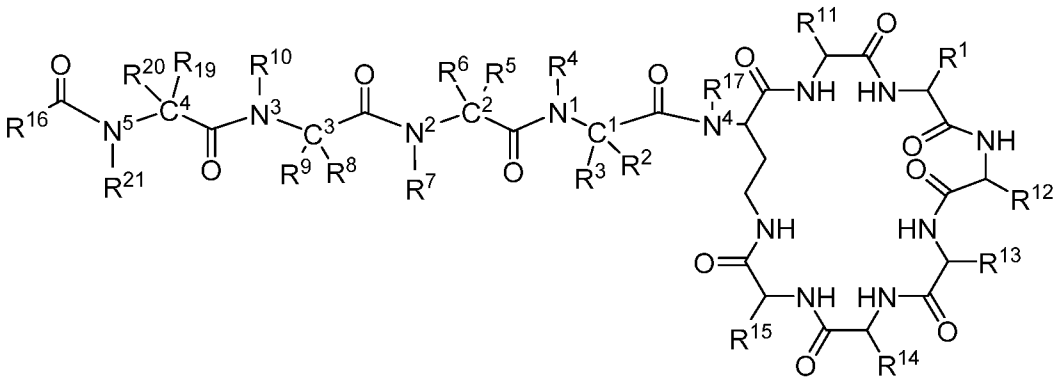
(IV)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally

substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (IV-1):

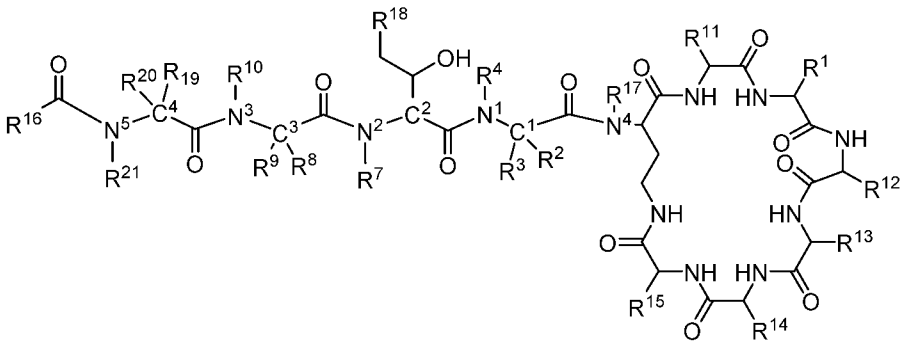


(IV-1)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (IV-2):



(IV-2)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl.

In some embodiments, each of R^1 and R^{12} is a lipophilic moiety; each of R^{11}, R^{13}, and R^{14} is, independently, optionally substituted C1-C5 alkamino, a polar moiety, or a positively charged moiety; and/or R^{15} is a polar moiety.

In some embodiments, each of R^1 and R^{12} is a lipophilic moiety.

In some embodiments, each lipophilic moiety is, independently, optionally substituted C1-C20 alkyl, optionally substituted C5-C15 aryl, optionally substituted C6-C35 alkaryl, or optionally C5-C10 substituted heteroaryl.

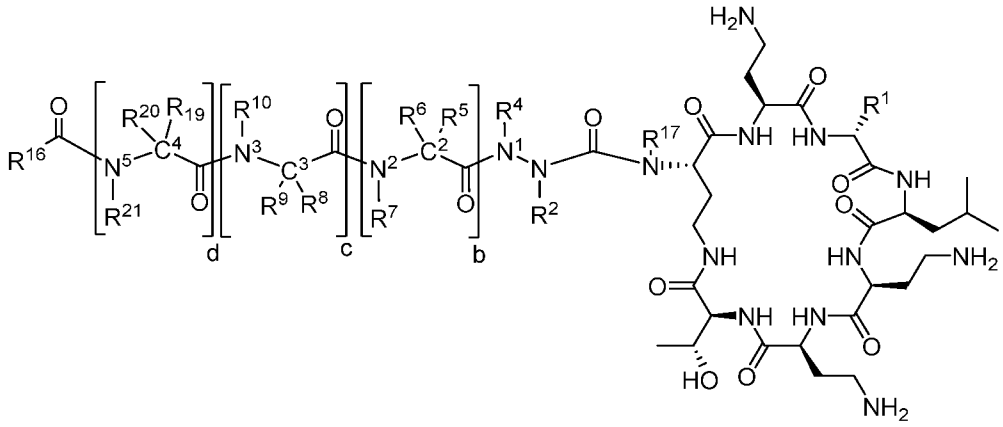
In some embodiments, each lipophilic moiety is, independently, C1-C8 alkyl, methyl substituted C2-C4 alkyl, (C1-C10)alkylene(C6)aryl, phenyl substituted (C1-C10)alkylene(C6)aryl, or alkyl substituted C4-C9 heteroaryl.

In some embodiments, each lipophilic moiety is, independently, benzyl, isobutyl, sec-butyl, isopropyl, n-propyl, methyl, biphenylmethyl, n-octyl, or methyl substituted indolyl.

In some embodiments, R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl. In some embodiments, R^{11}, R^{13}, and R^{14} is independently optionally substituted C1-C5 alkamino (e.g., $CH_2CH_2NH_2$).

In some embodiments, R^{15} is a polar moiety. In some embodiments, each polar moiety includes a hydroxyl group, a carboxylic acid group, an ester group, or an amide group. In some embodiments, each polar moiety is hydroxyl substituted C1-C4 alkyl (e.g., $CHCH_3OH$).

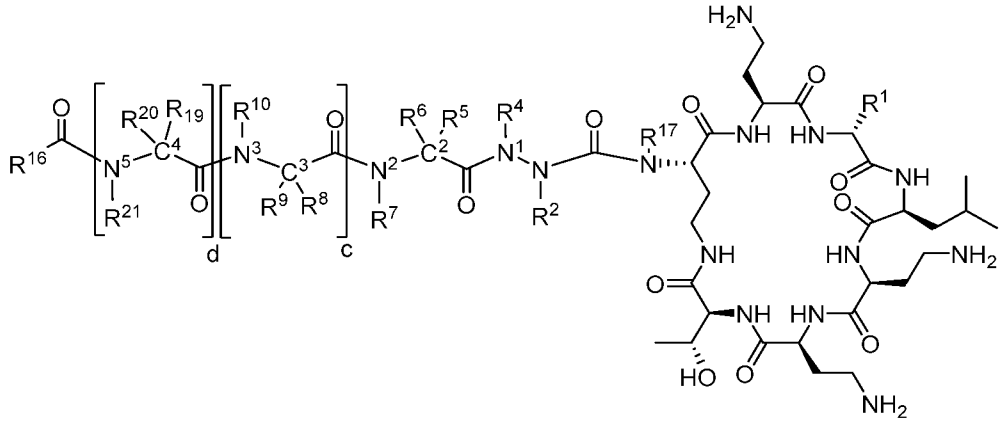
In some embodiments, the compound is described by formula (V):



(V)

wherein R^1 is benzyl or $CH_2CH(CH_3)_2$, or a pharmaceutically acceptable salt thereof.

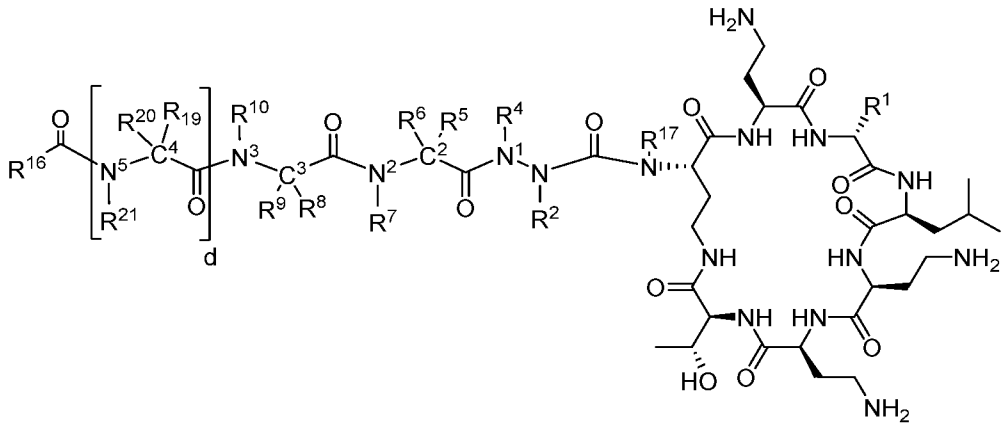
In some embodiments, the compound is described by formula (V-1):



(V-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, or a pharmaceutically acceptable salt thereof.

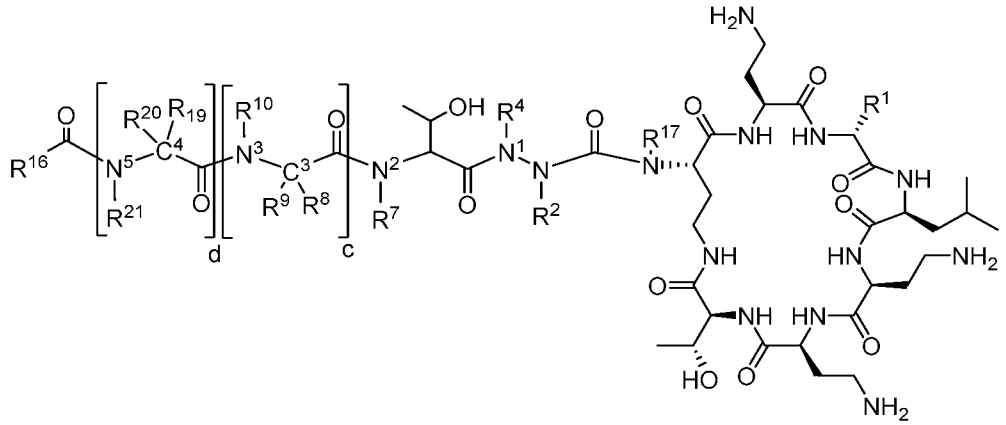
In some embodiments, the compound is described by formula (V-2):



(V-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, or a pharmaceutically acceptable salt thereof.

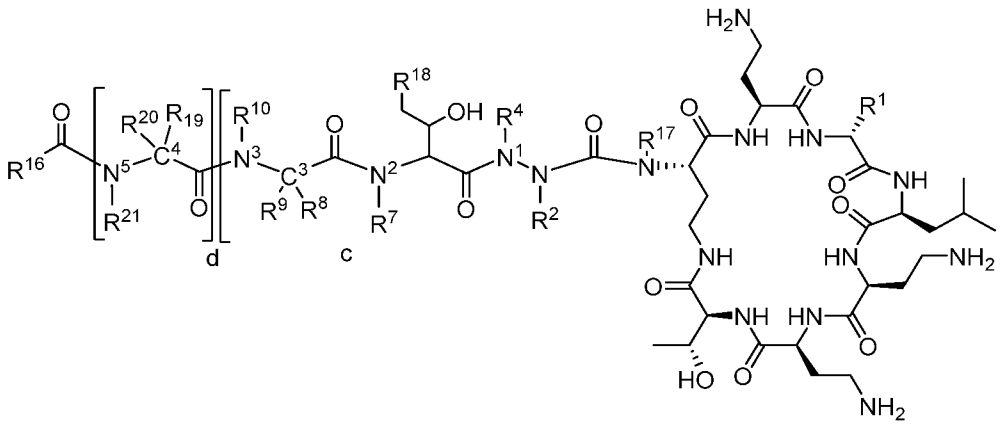
In some embodiments, the compound is described by formula (V-3):



(V-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (V-4):

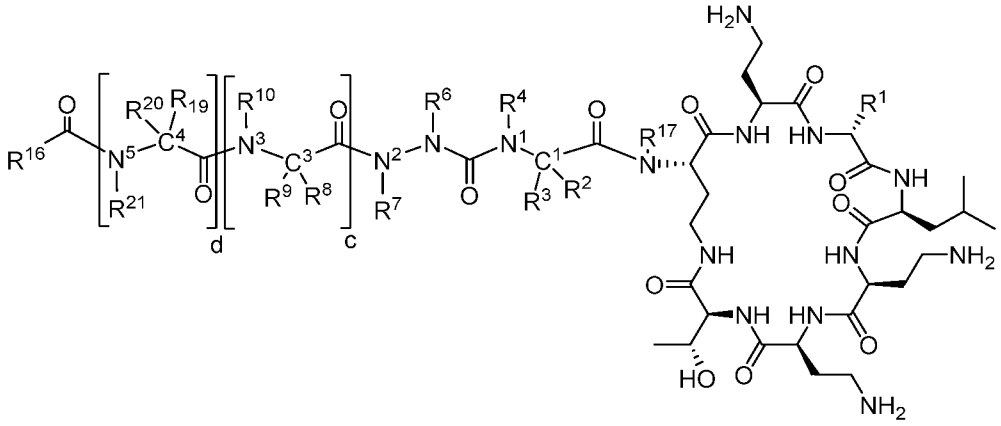


(V-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl. In some embodiments, R^2 is H or C1-C8 alkyl.

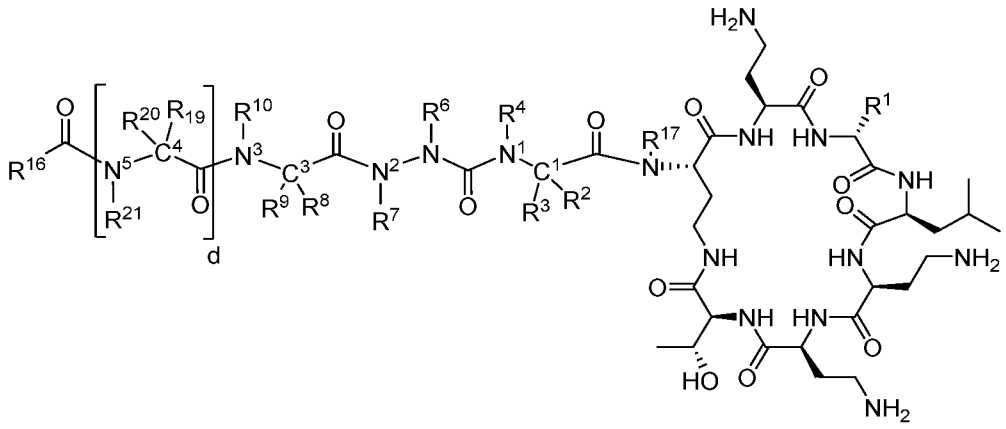
In some embodiments, the compound is described by formula (VI):



(VI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (VI-1):

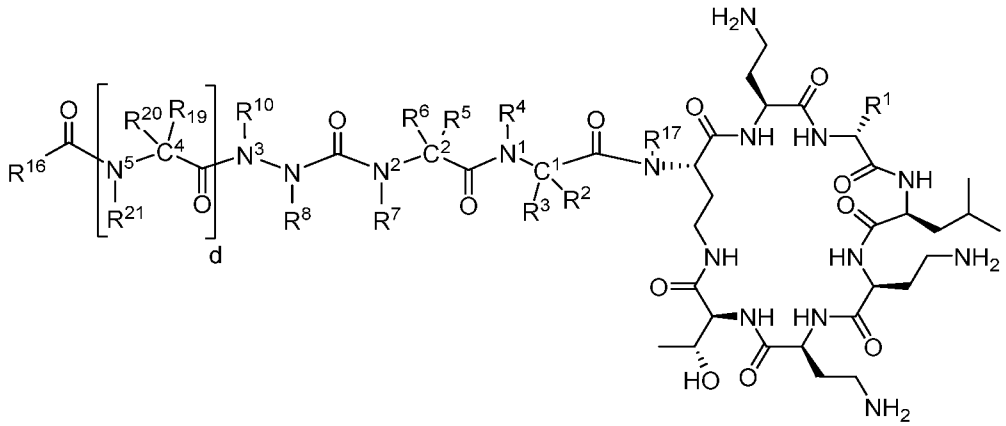


(VI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, or a pharmaceutically acceptable salt thereof.

In some embodiments, R^6 is H or C1-C8 alkyl.

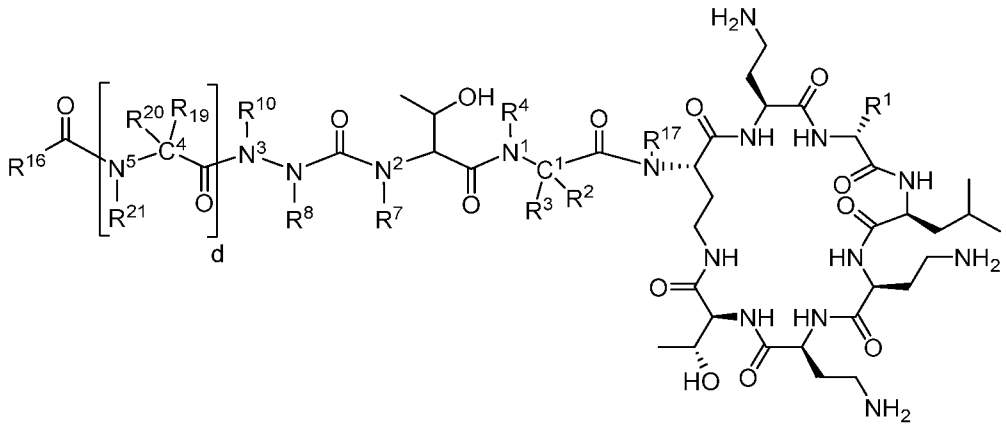
In some embodiments, the compound is described by formula (VII):



(VII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, or a pharmaceutically acceptable salt thereof.

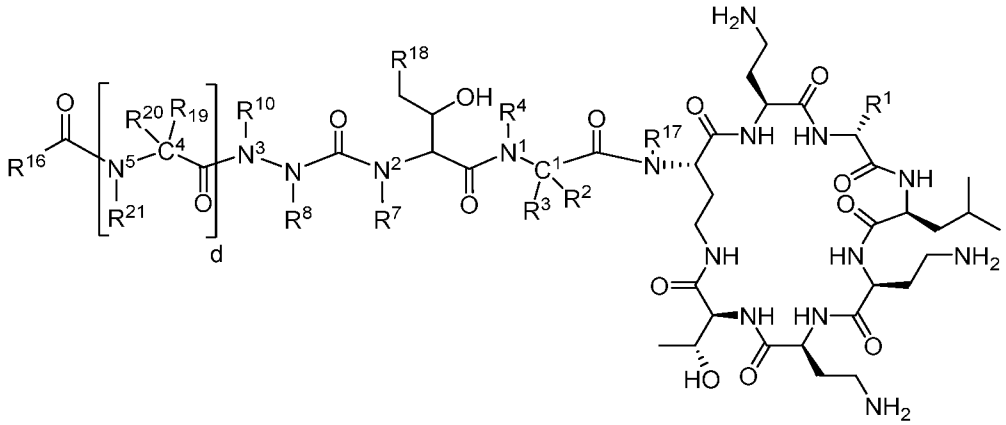
In some embodiments, the compound is described by formula (VII-1):



(VII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (VII-2):



(VII-2)

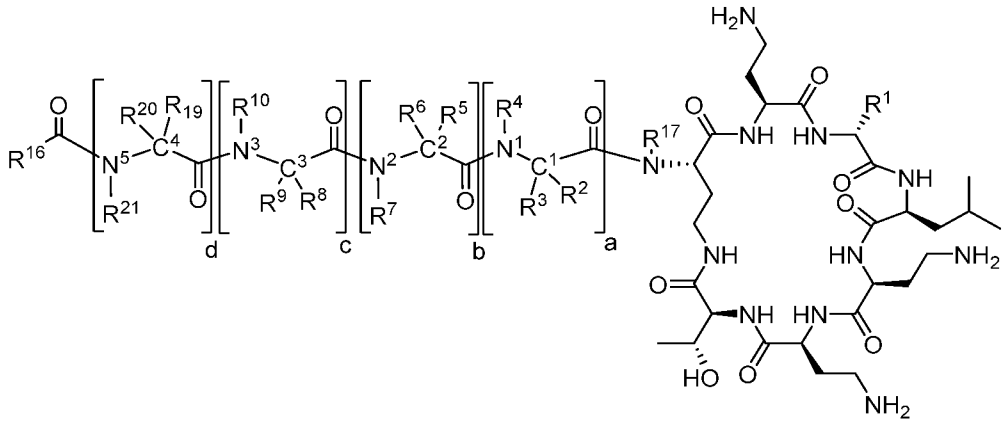
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl. In some embodiments, R^8 is independently H or C1-C8 alkyl. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl.

In some embodiments, R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

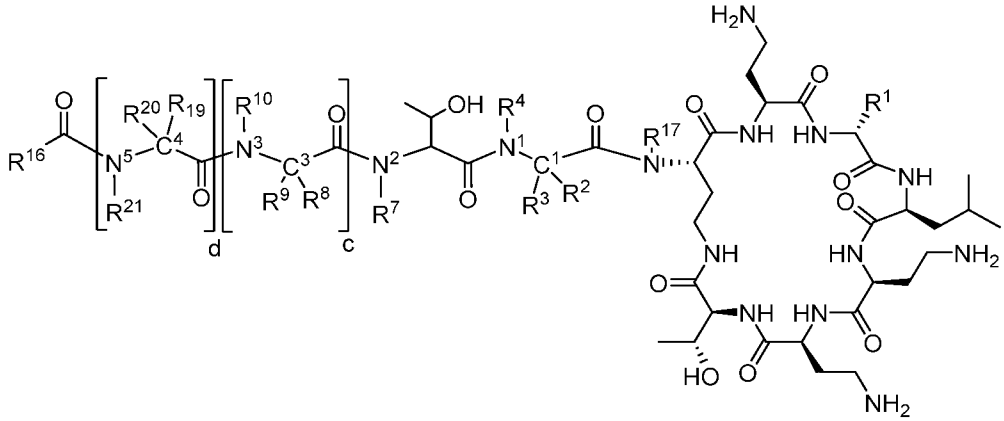
In some embodiments, the compound is described by formula (VIII):



(VIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

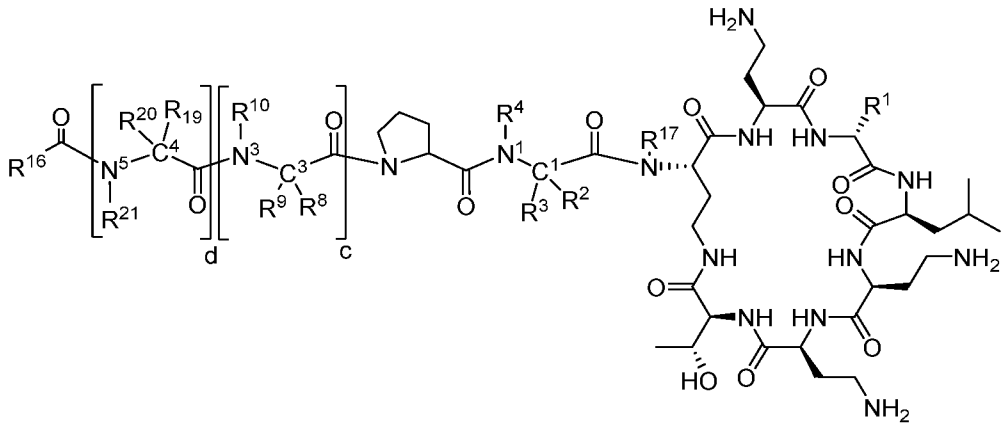
In some embodiments, the compound is described by formula (VIII-1):



(VIII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

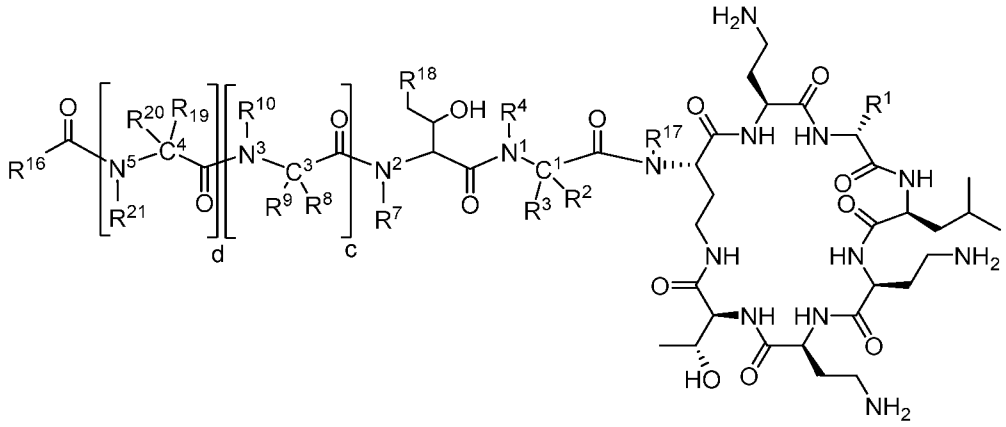
In some embodiments, the compound is described by formula (VIII-2):



(VIII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (VIII-3):



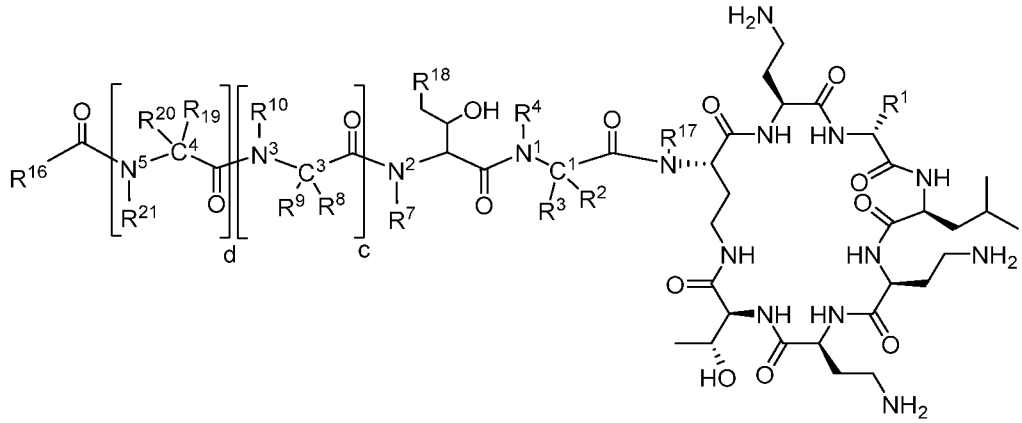
(VIII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{17} is C1-C3 alkyl or C2-C3 alkamino; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl. In some embodiments, R^{17} is methyl. In some embodiments, R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In some embodiments, the compound is described by formula (IX):

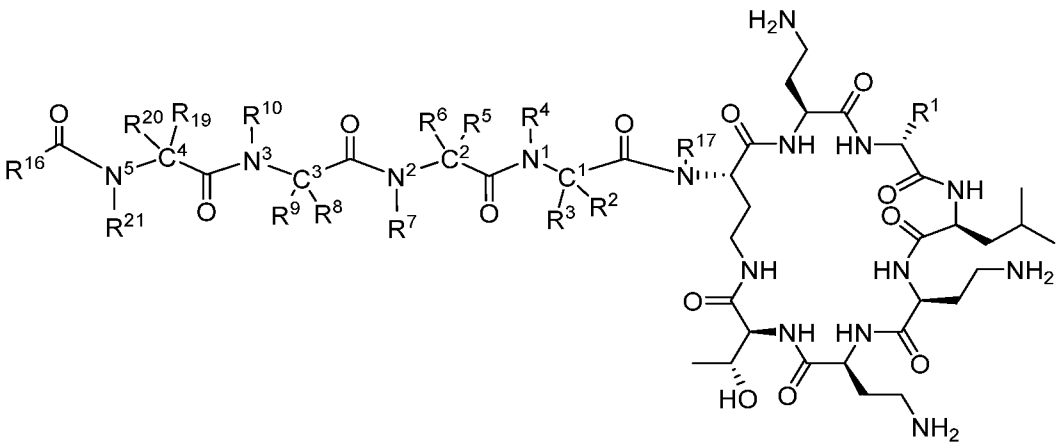


(IX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

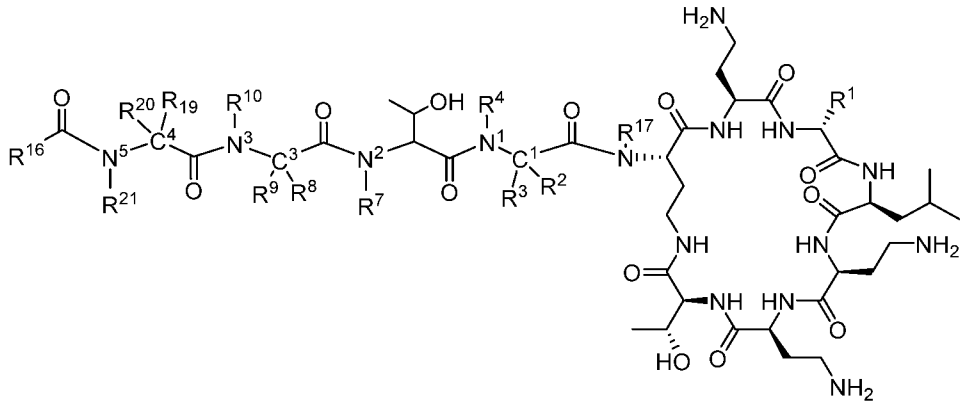
In some embodiments, the compound is described by formula (X):



(X)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

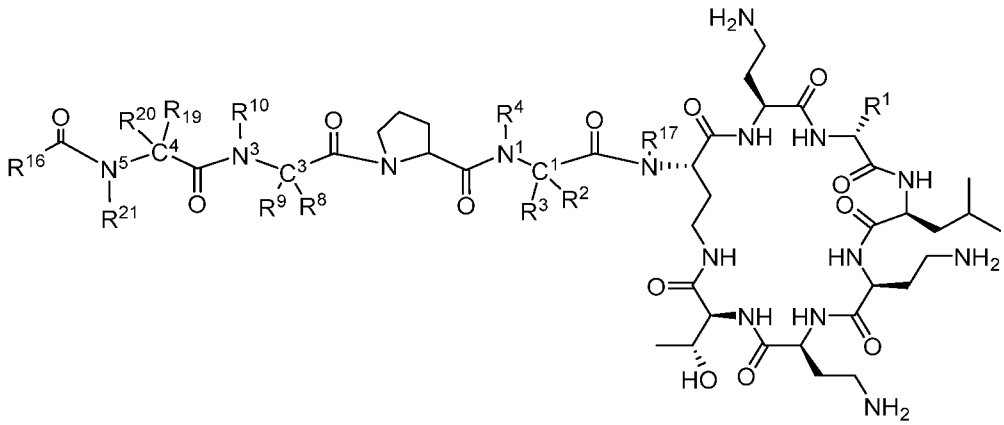
In some embodiments, the compound is described by formula (X-1):



(X-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (X-2):

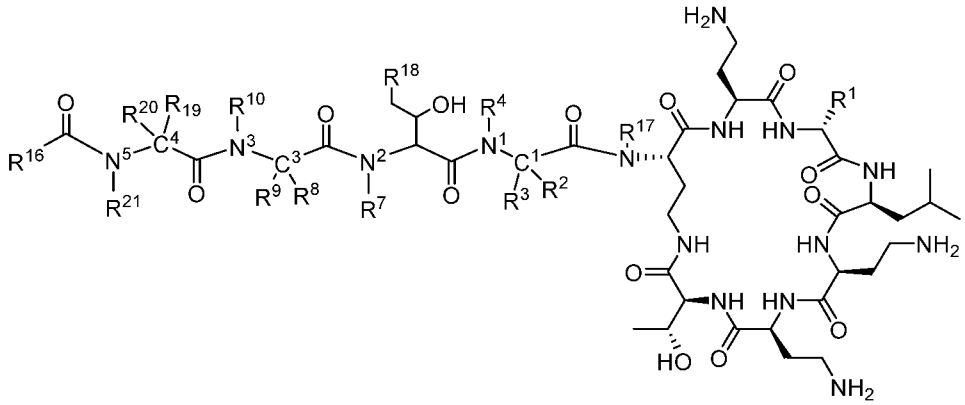


(X-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally

substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (X-3):

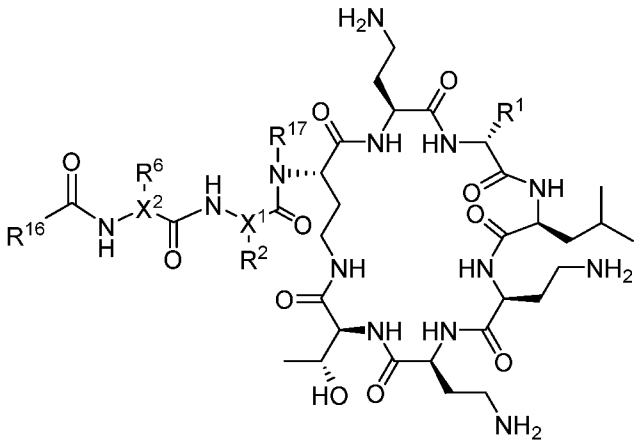


(X-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$.

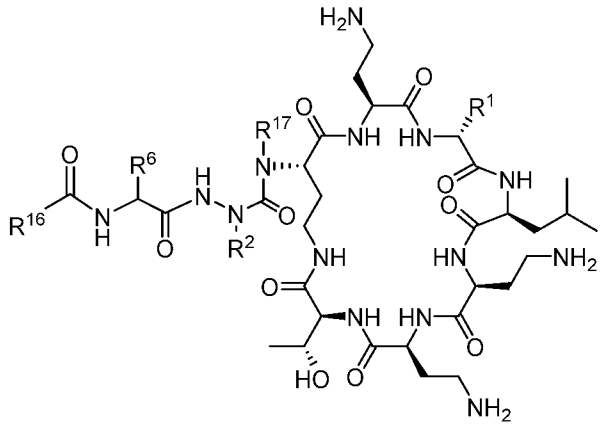
In some embodiments, the compound is described by formula (XI):



(XI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2 and R^6 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and each of X^1 and X^2 is a carbon atom or a nitrogen atom, wherein at least one of X^1 and X^2 is a nitrogen atom,or a pharmaceutically acceptable salt thereof.

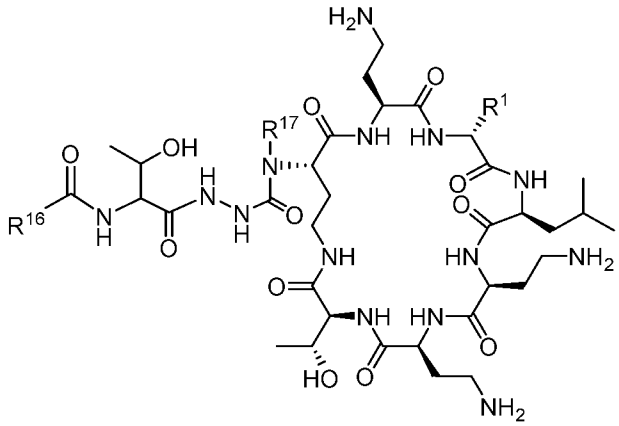
In some embodiments, the compound is described by formula (XI-1):



(XI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

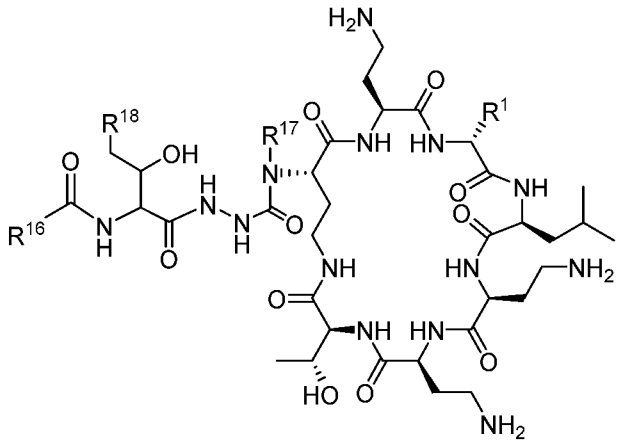
In some embodiments, the compound is described by formula (XI-2):



(XI-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XI-3):

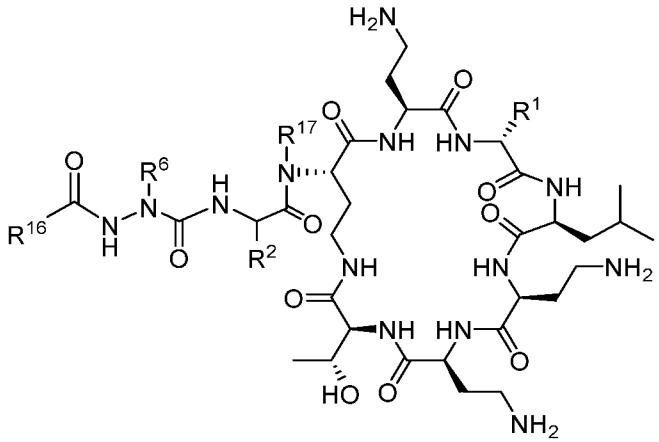


(XI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

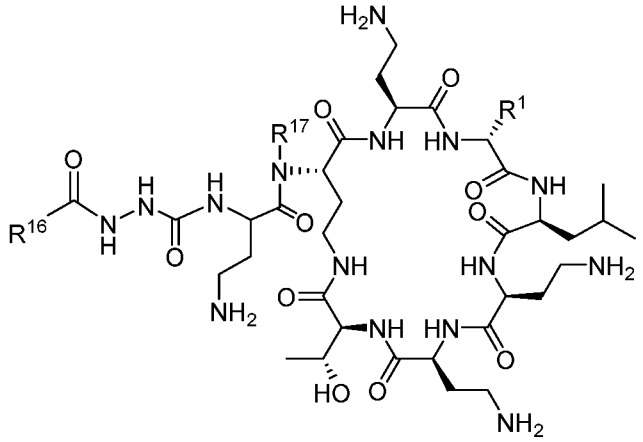
In some embodiments, the compound is described by formula (XI-4):



(XI-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

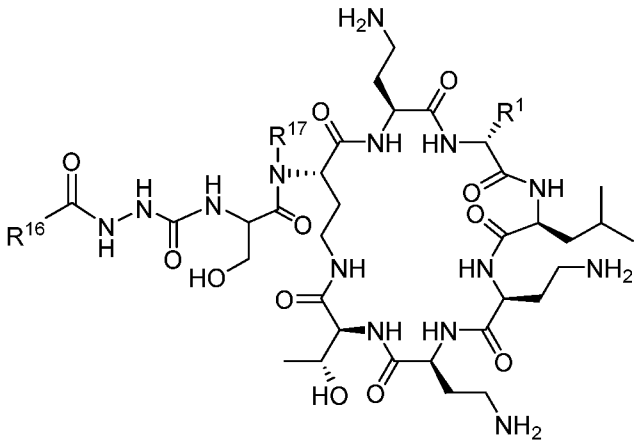
In some embodiments, the compound is described by formula (XI-5):



(XI-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and or a pharmaceutically acceptable salt thereof.

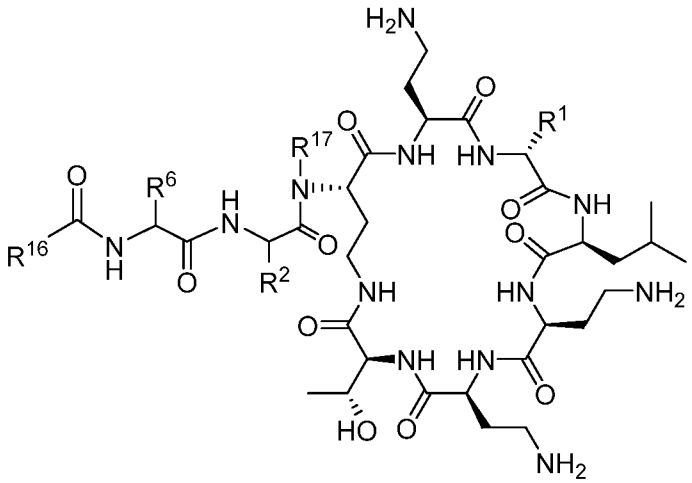
In some embodiments, the compound is described by formula (XI-6):



(XI-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and or a pharmaceutically acceptable salt thereof.

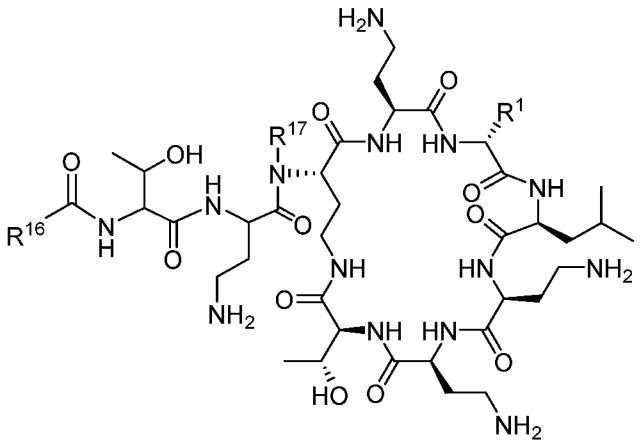
In some embodiments, the compound is described by formula (XII):



(XII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

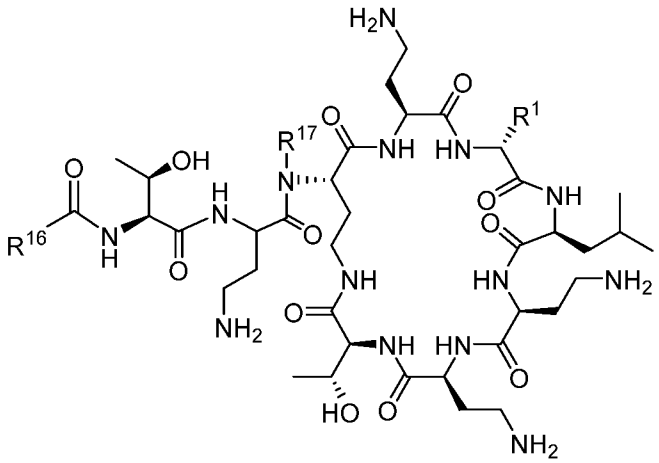
In some embodiments, the compound is described by formula (XII-1):



(XII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

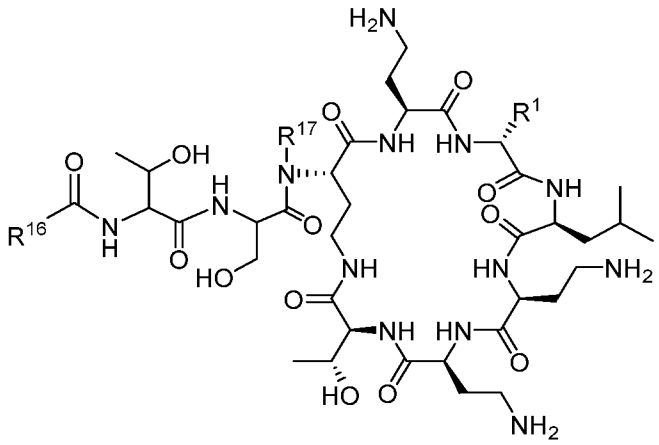
In some embodiments, the compound is described by formula (XII-2):



(XII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

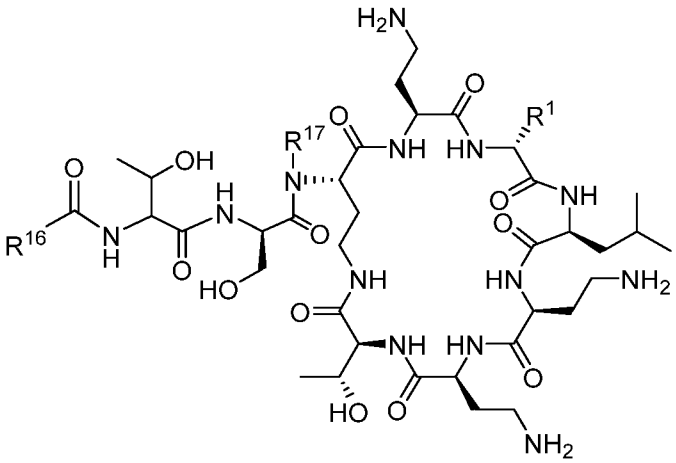
In some embodiments, the compound is described by formula (XII-3):



(XII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

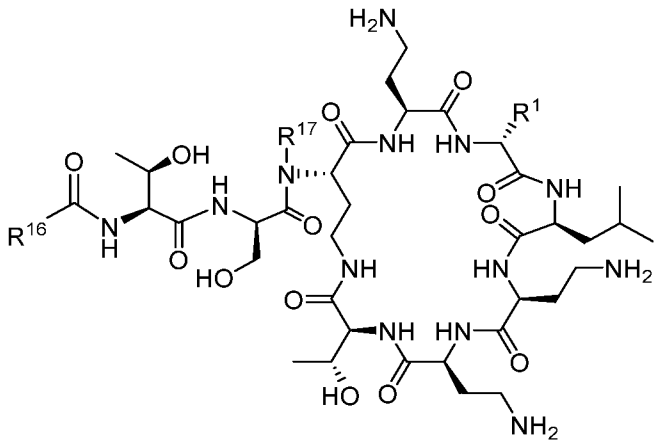
In some embodiments, the compound is described by formula (XII-4):



(XII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

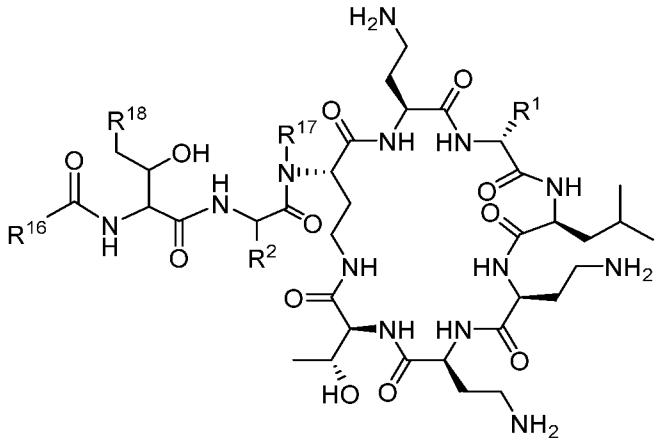
In some embodiments, the compound is described by formula (XII-5):



(XII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIII):

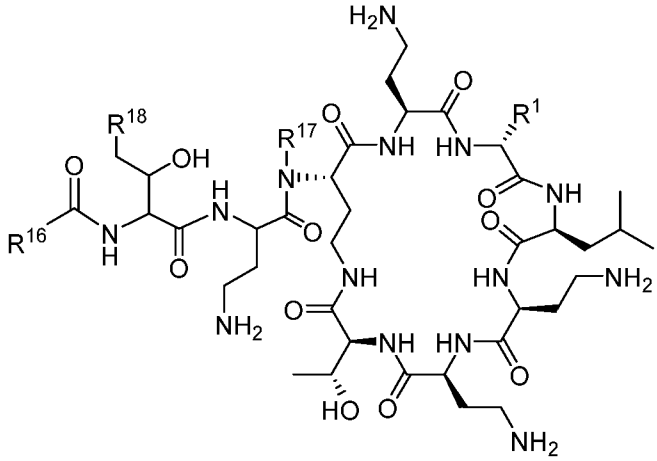


(XIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^2 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

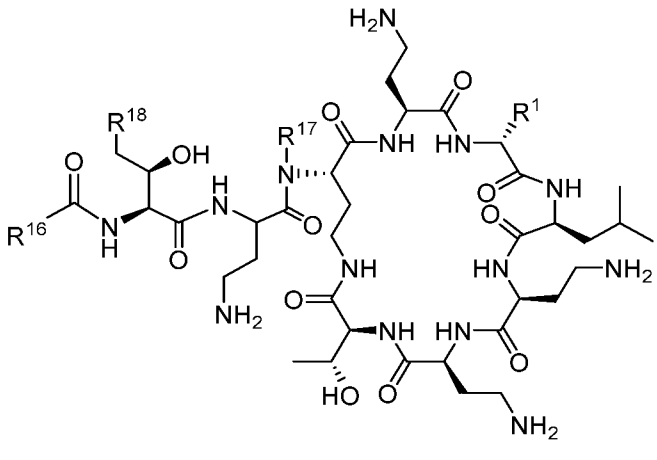
In some embodiments, the compound is described by formula (XIII-1):



(XIII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIII-2):

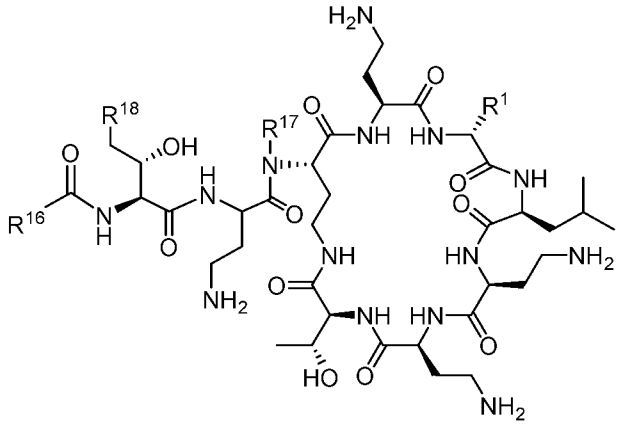


(XIII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

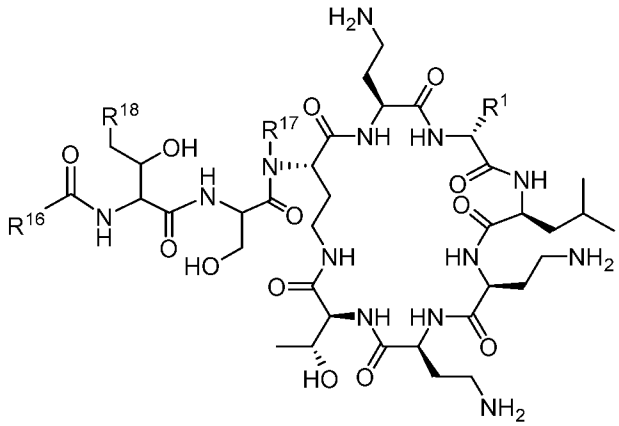
In some embodiments, the compound is described by formula (XIII-3):



(XIII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIII-4):

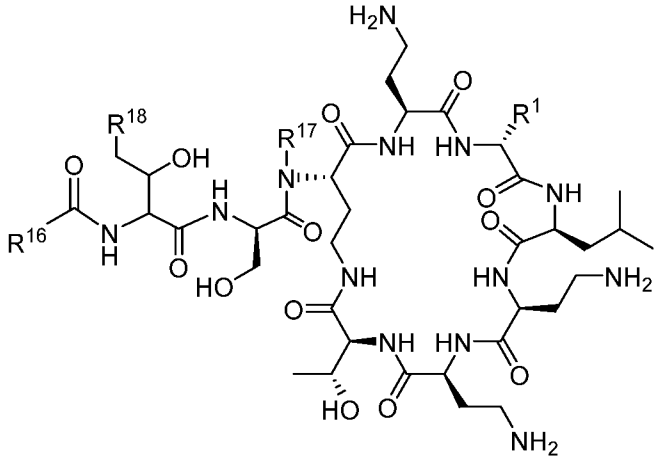


(XIII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

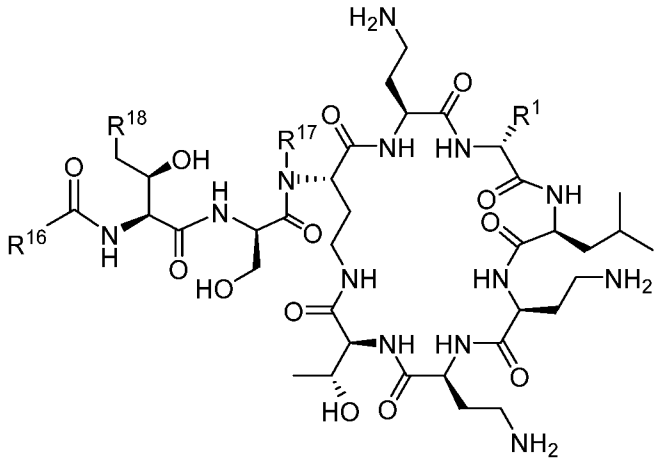
In some embodiments, the compound is described by formula (XIII-5):



(XIII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIII-6):



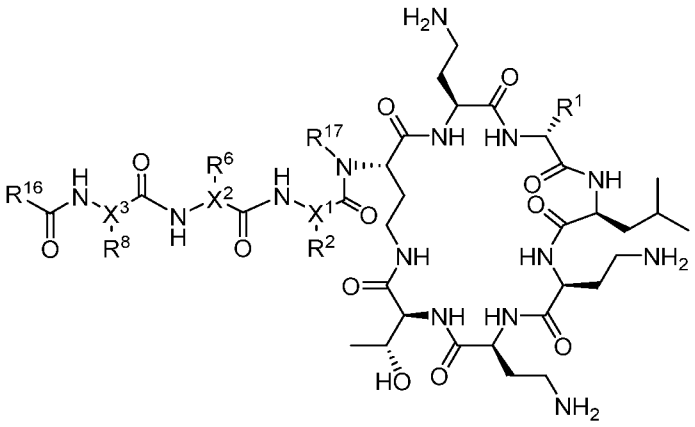
(XIII-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

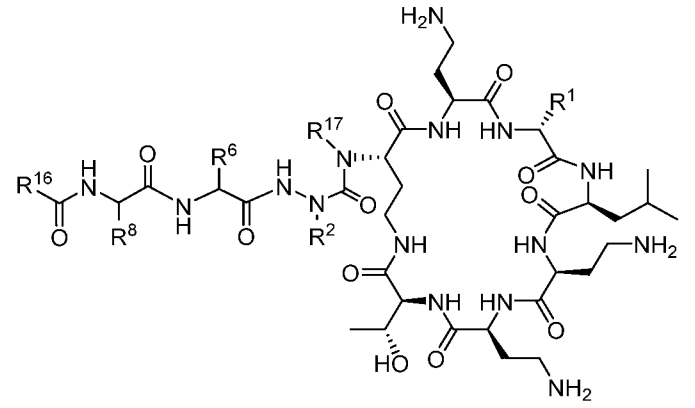
In some embodiments, the compound is described by formula (XIV):



(XIV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and each of X^1, X^2, and X^3 is, independently, a carbon atom or a nitrogen atom, wherein at least one of X^1, X^2, and X^3 is a nitrogen atom, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIV-1):

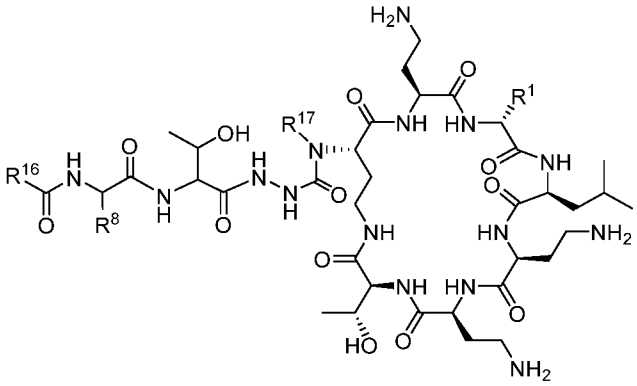


(XIV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar

moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

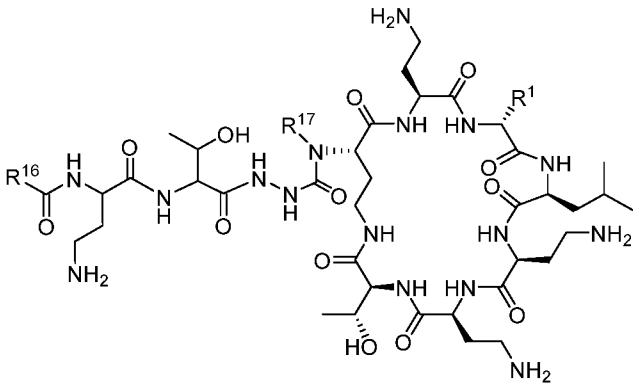
In some embodiments, the compound is described by formula (XIV-2):



(XIV-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^8 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

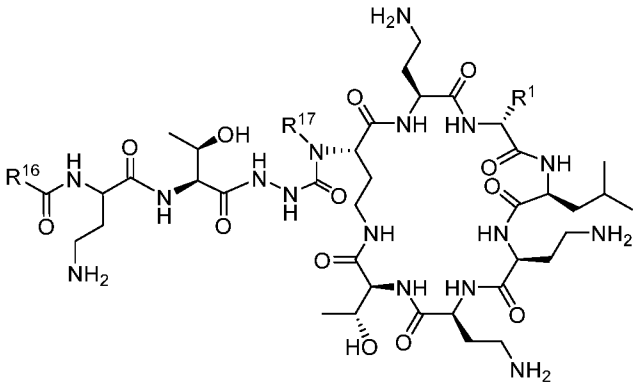
In some embodiments, the compound is described by formula (XIV-3):



(XIV-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

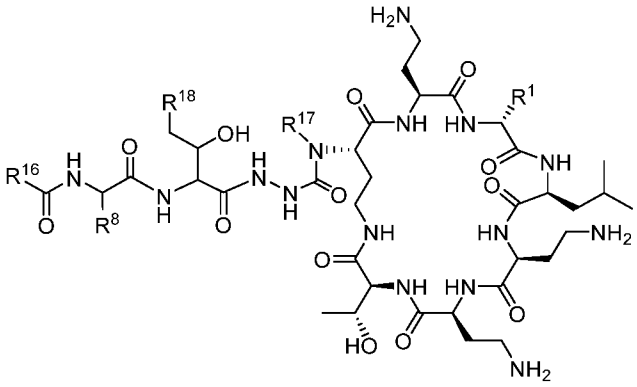
In some embodiments, the compound is described by formula (XIV-4):



(XIV-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

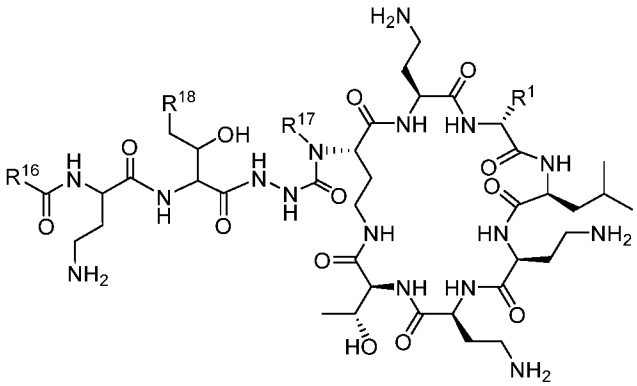
In some embodiments, the compound is described by formula (XIV-5):



(XIV-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^8 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

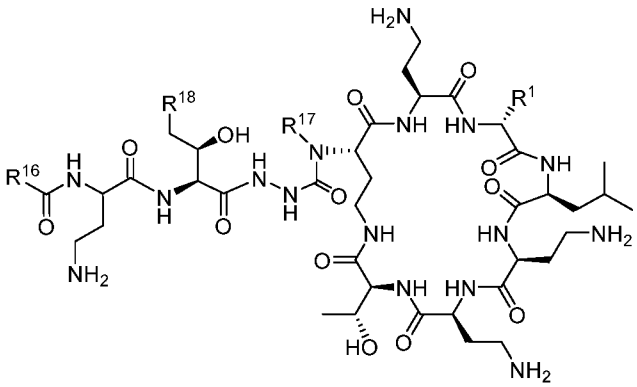
In some embodiments, the compound is described by formula (XIV-6):



(XIV-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIV-7):

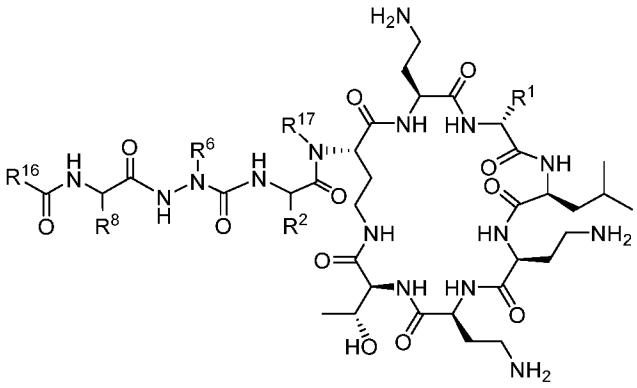


(XIV-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

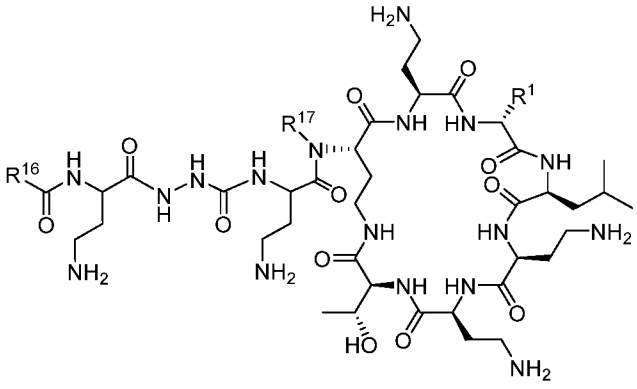
In some embodiments, the compound is described by formula (XIV-8):



(XIV-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

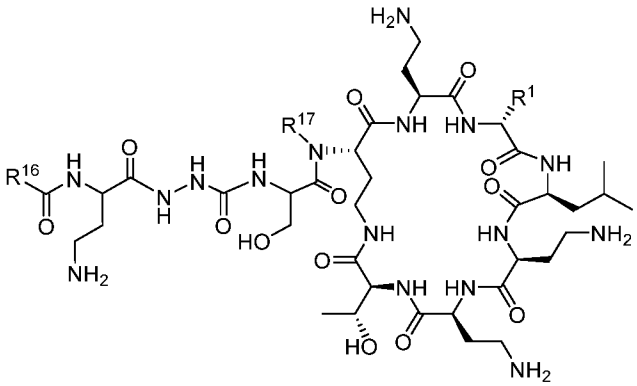
In some embodiments, the compound is described by formula (XIV-9):



(XIV-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

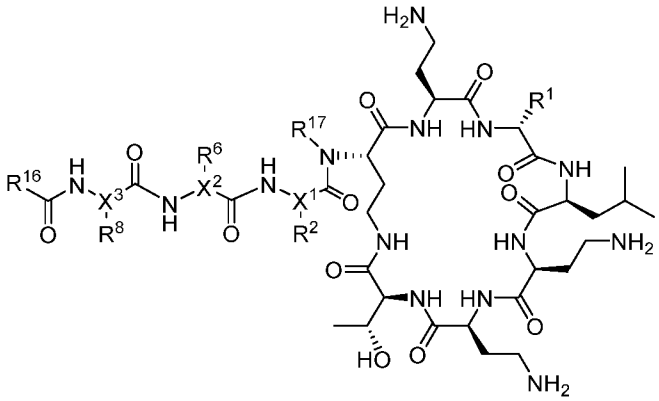
In some embodiments, the compound is described by formula (XIV-10):



(XIV-10)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

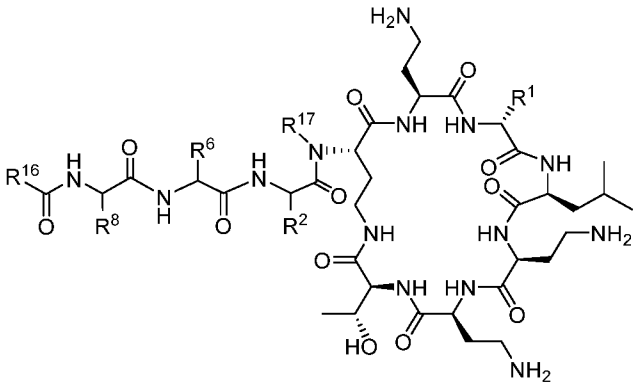
In some embodiments, the compound is described by formula (XV):



(XV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

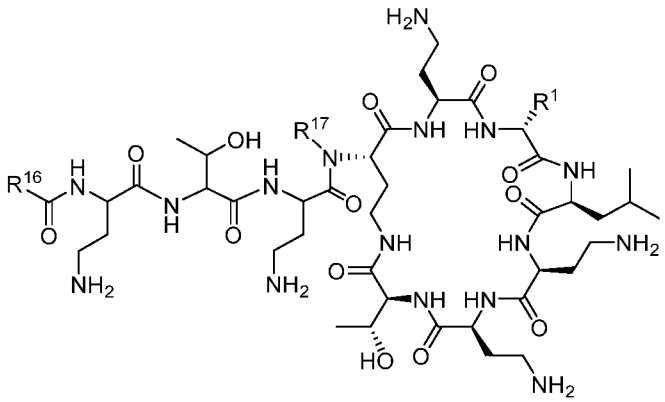
In some embodiments, the compound is described by formula (XV-1):



(XV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

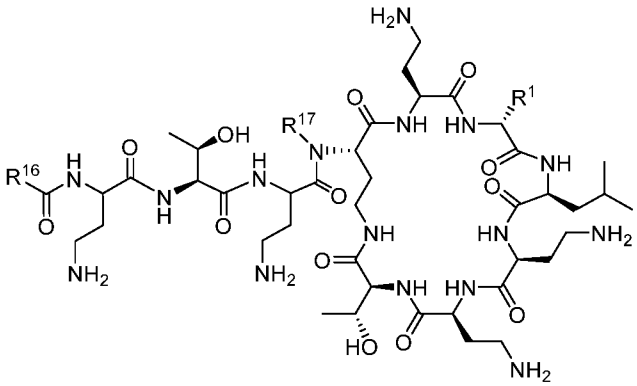
In some embodiments, the compound is described by formula (XV-2):



(XV-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

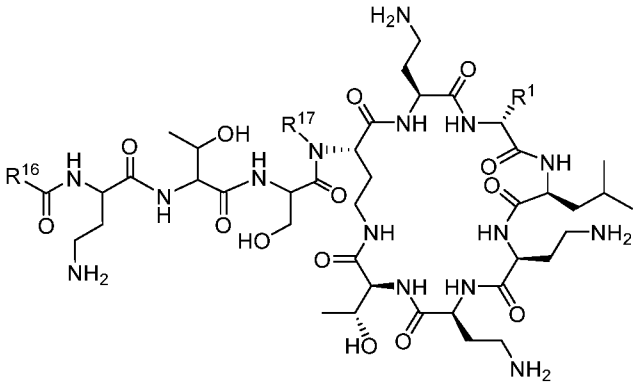
In some embodiments, the compound is described by formula (XV-3):



(XV-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

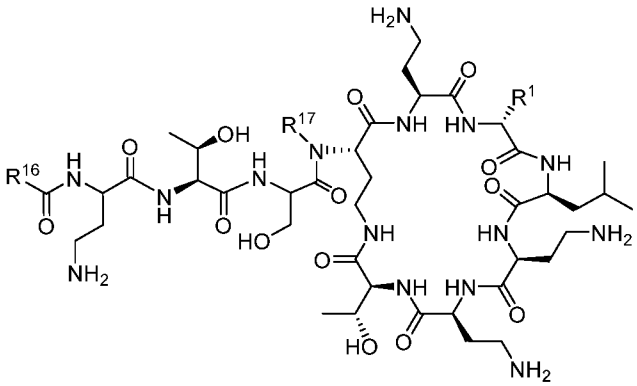
In some embodiments, the compound is described by formula (XV-4):



(XV-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

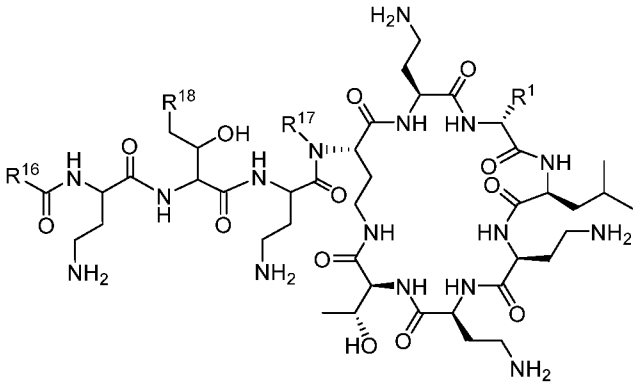
In some embodiments, the compound is described by formula (XV-5):



(XV-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

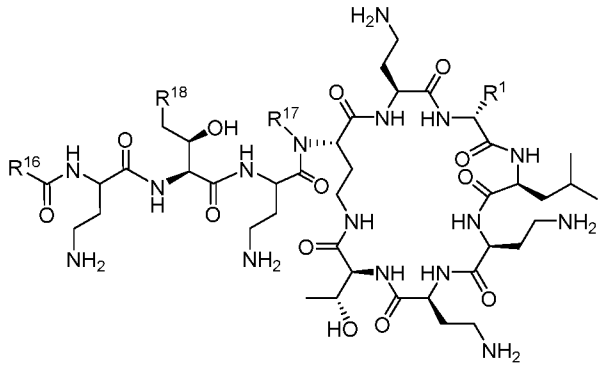
In some embodiments, the compound is described by formula (XV-6):



(XV-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XV-7):

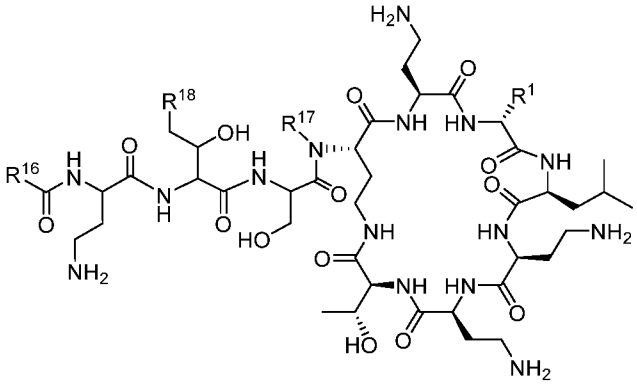


(XV-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or

optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino,or a pharmaceutically acceptable salt thereof.

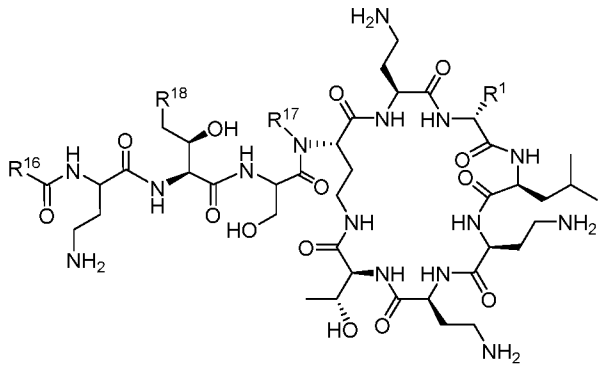
In some embodiments, the compound is described by formula (XV-8):



(XV-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XV-9):



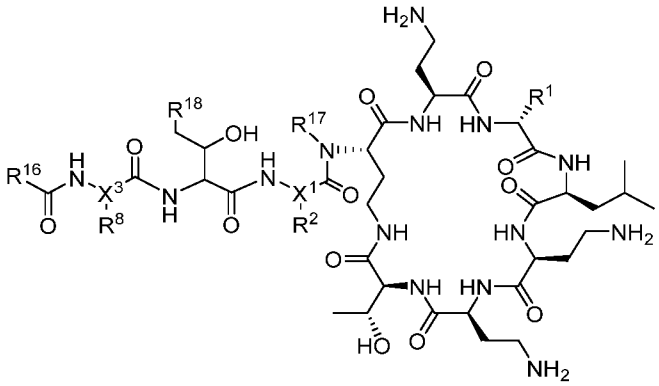
(XV-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or

optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

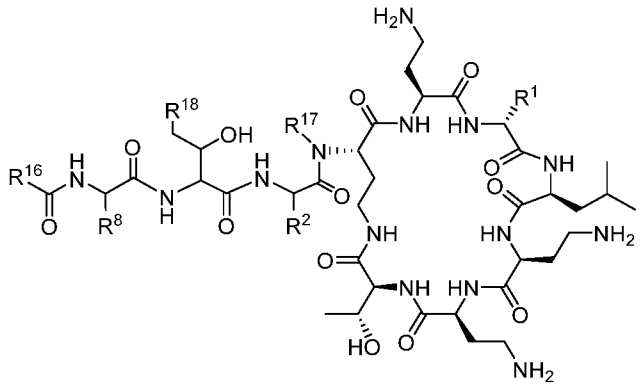
In some embodiments, the compound is described by formula (XVI):



(XVI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2 and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

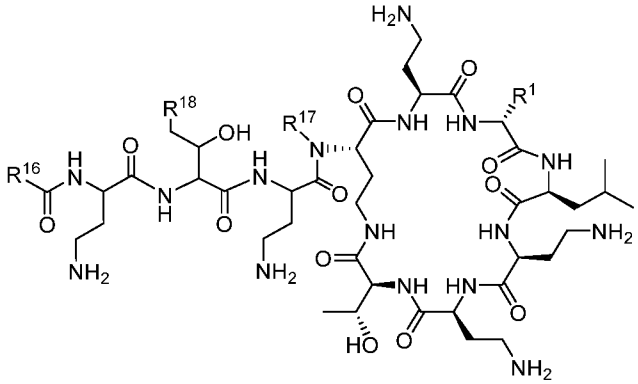
In some embodiments, the compound is described by formula (XVI-1):



(XVI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

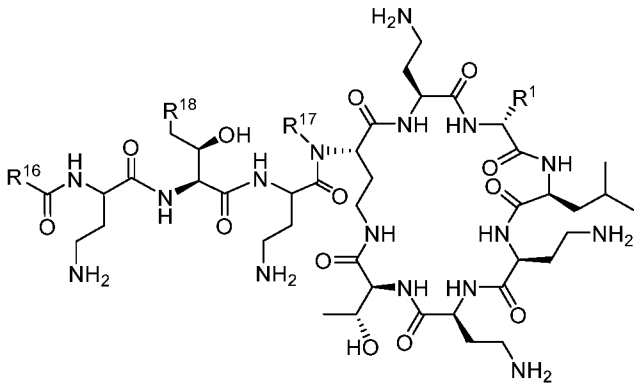
In some embodiments, the compound is described by formula (XVI-2):



(XVI-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVI-3):

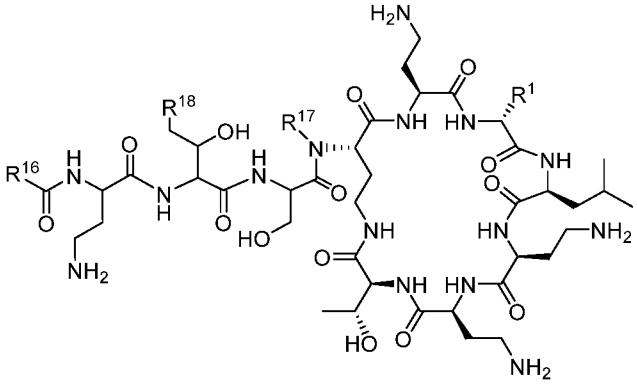


(XVI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-

C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

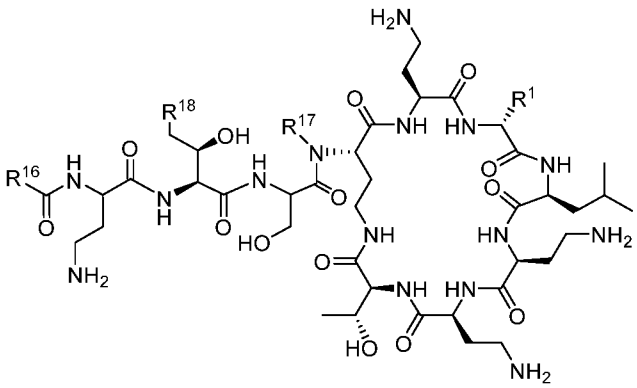
In some embodiments, the compound is described by formula (XVI-4):



(XVI-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVI-5):



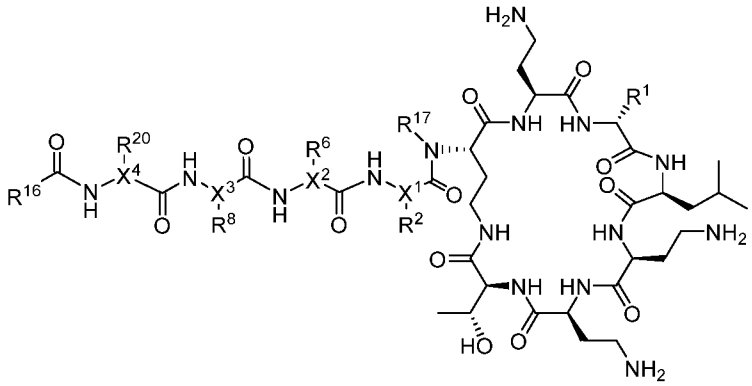
(XVI-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

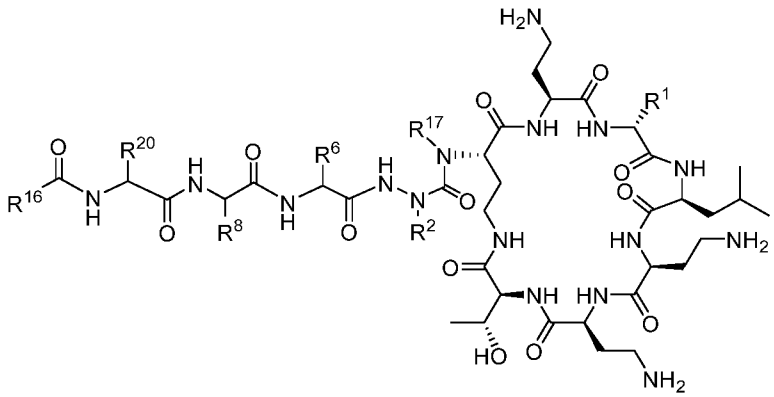
In some embodiments, the compound is described by formula (XVII):



(XVII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and each of X^1, X^2, and X^3 is, independently, a carbon atom or a nitrogen atom, wherein at least one of X^1, X^2, and X^3 is a nitrogen atom, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVII-1):

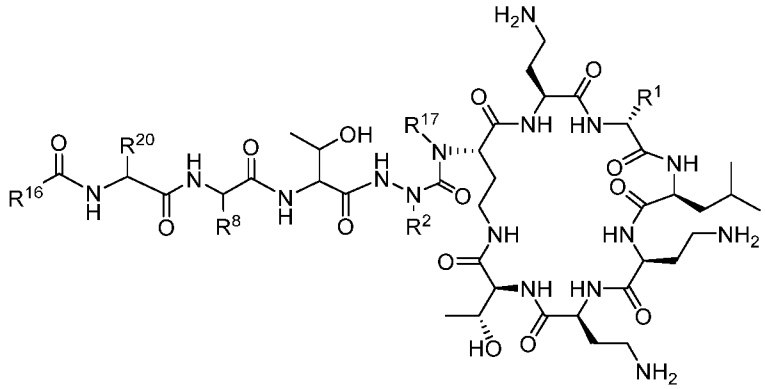


(XVII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally

substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

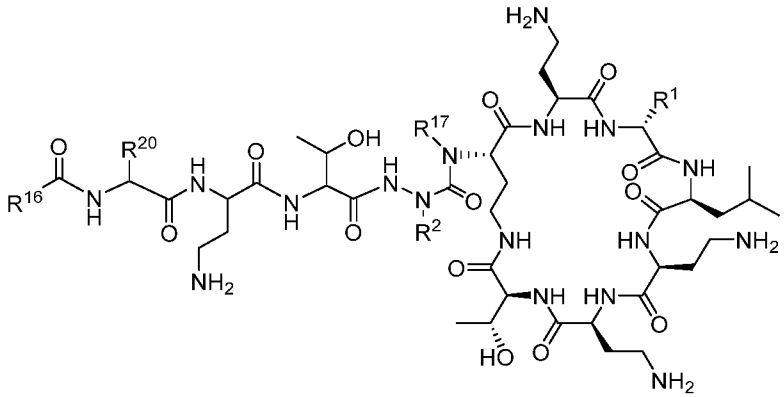
In some embodiments, the compound is described by formula (XVII-2):



(XVII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVII-3):

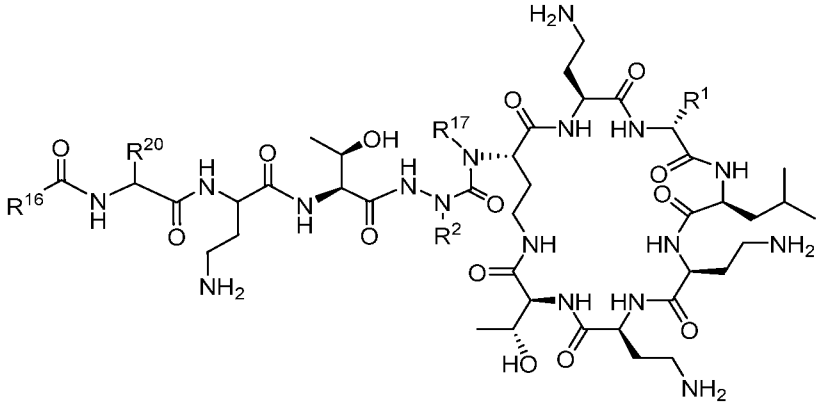


(XVII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl,

optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

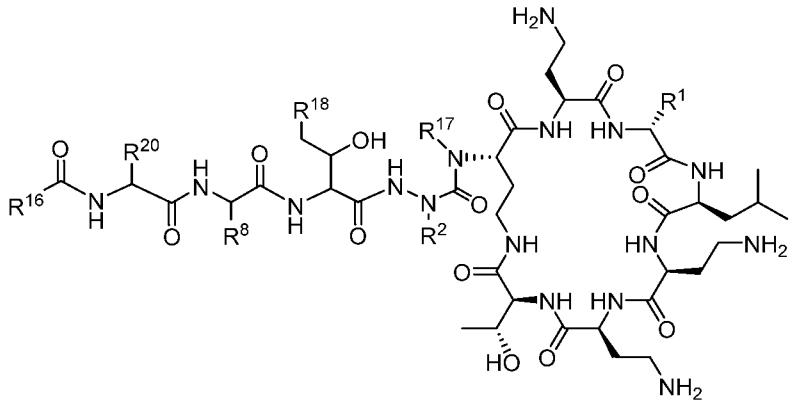
In some embodiments, the compound is described by formula (XVII-4):



(XVII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVII-5):

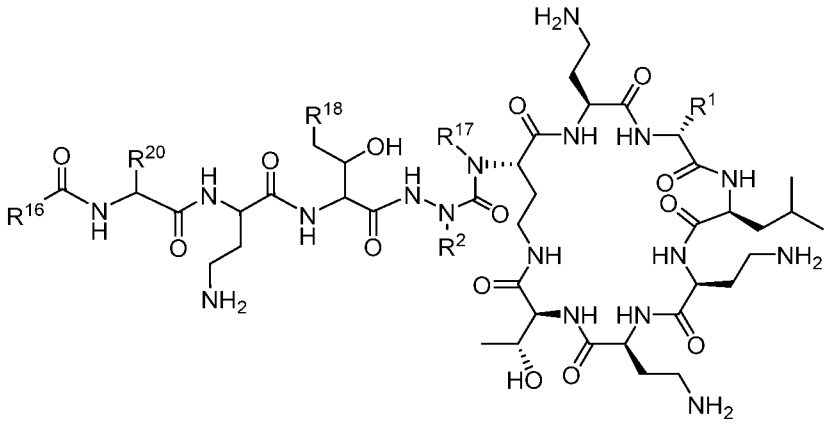


(XVII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally

substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

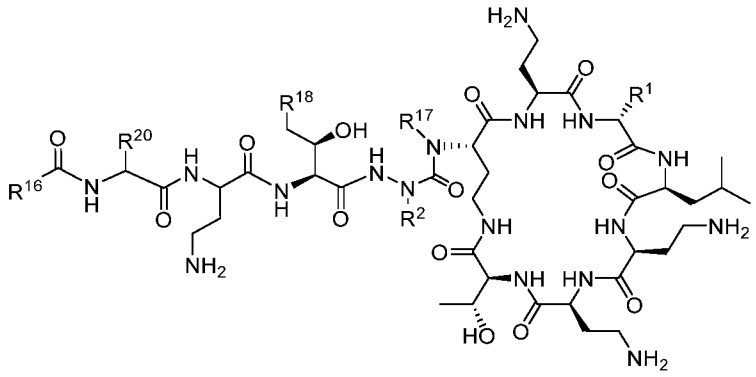
In some embodiments, the compound is described by formula (XVII-6):



(XVII-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVII-7):

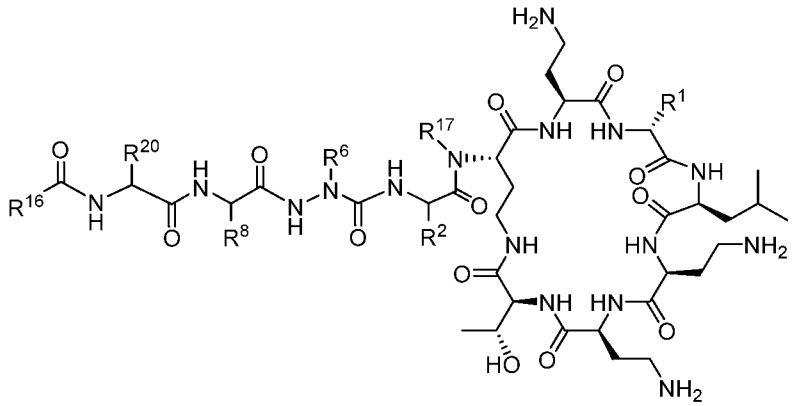


(XVII-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

In some embodiments, the compound is described by formula (XVII-8):

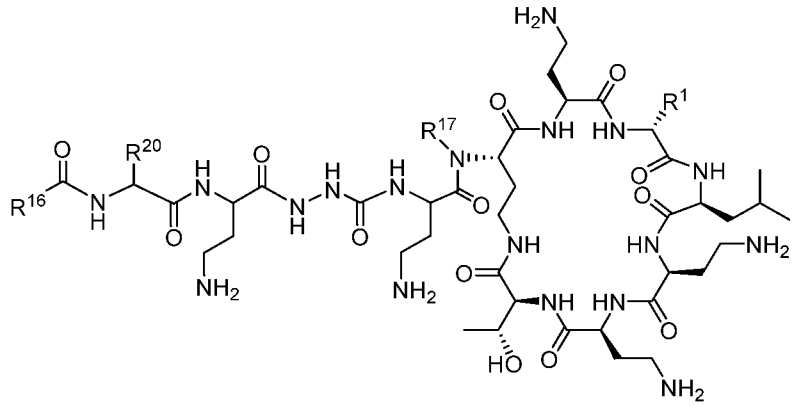


(XVII-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively

charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

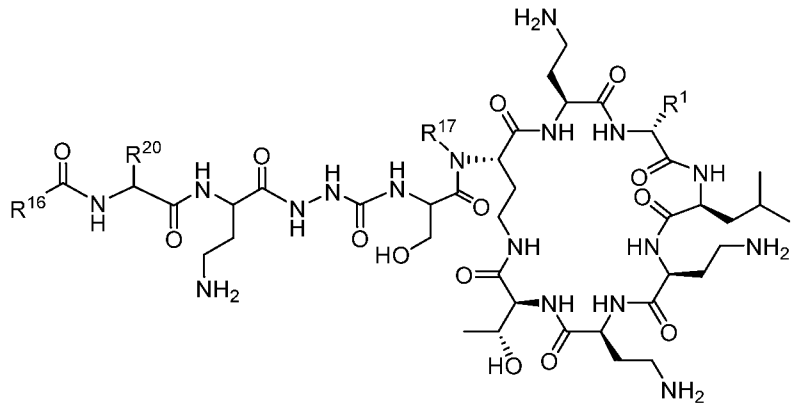
In some embodiments, the compound is described by formula (XVII-9):



(XVII-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVII-10):

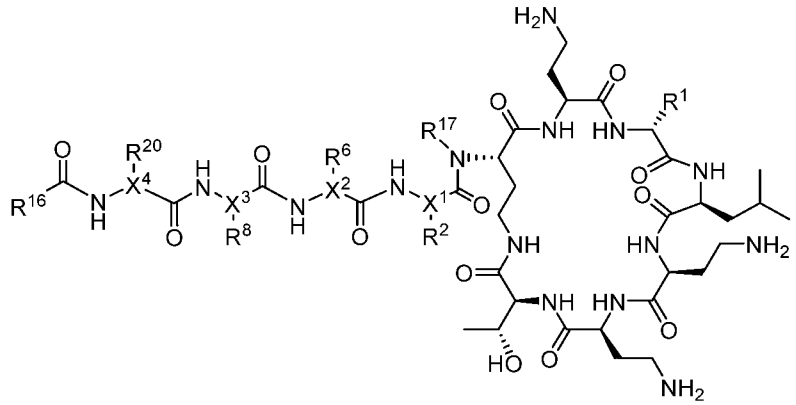


(XVII-10)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted

furanylmethyl; and R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

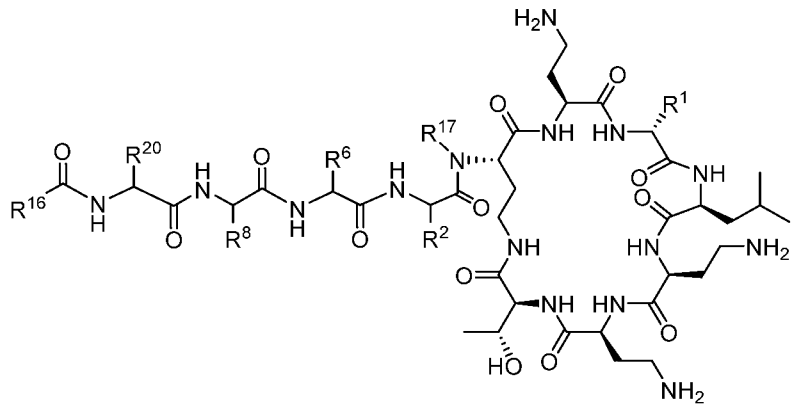
In some embodiments, the compound is described by formula (XVIII):



(XVIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

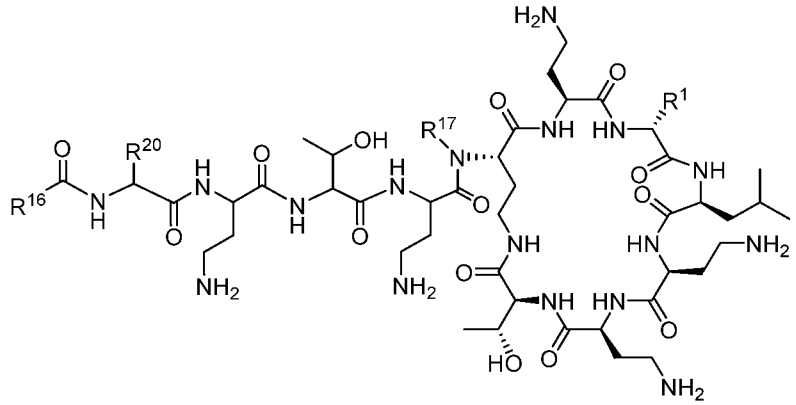
In some embodiments, the compound is described by formula (XVIII-1):



(XVIII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

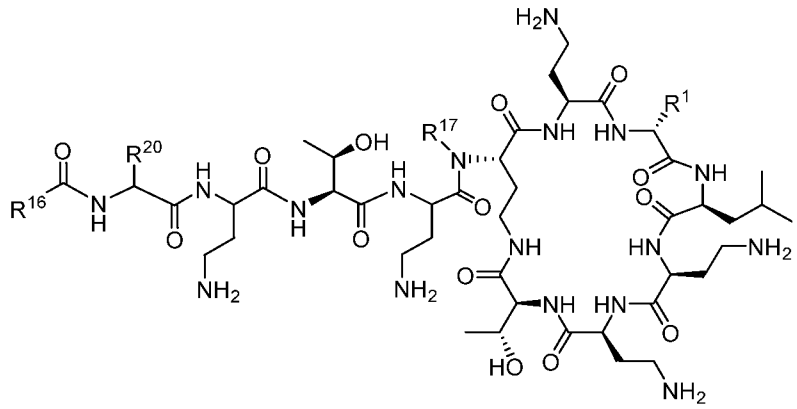
In some embodiments, the compound is described by formula (XVIII-2):



(XVIII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

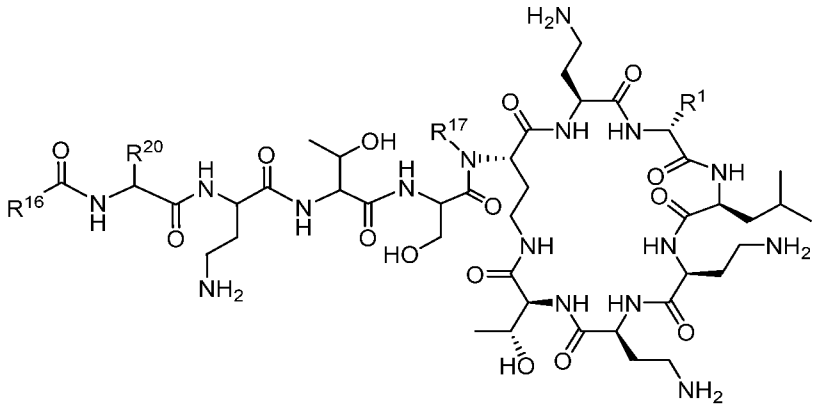
In some embodiments, the compound is described by formula (XVIII-3):



(XVIII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVIII-4):

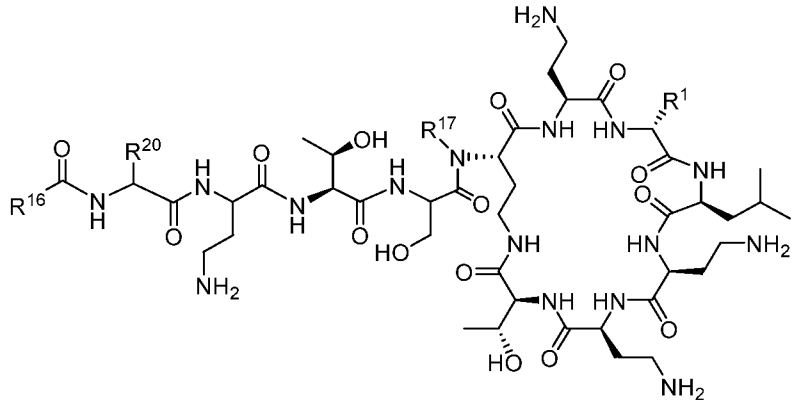


(XVIII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or

optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

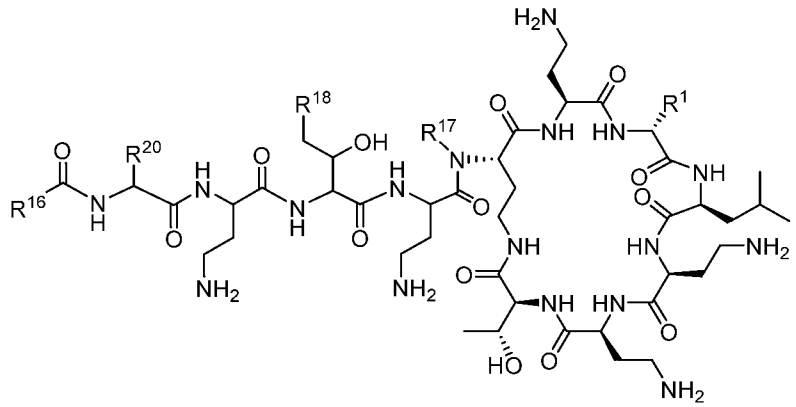
In some embodiments, the compound is described by formula (XVIII-5):



(XVIII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; andR^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVIII-6):

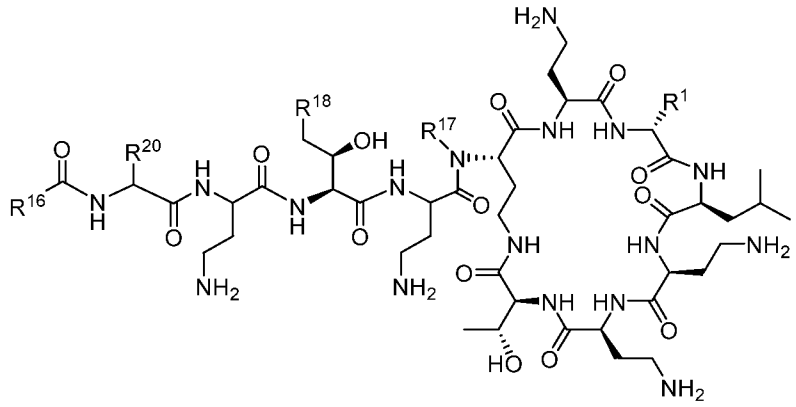


(XVIII-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20

heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

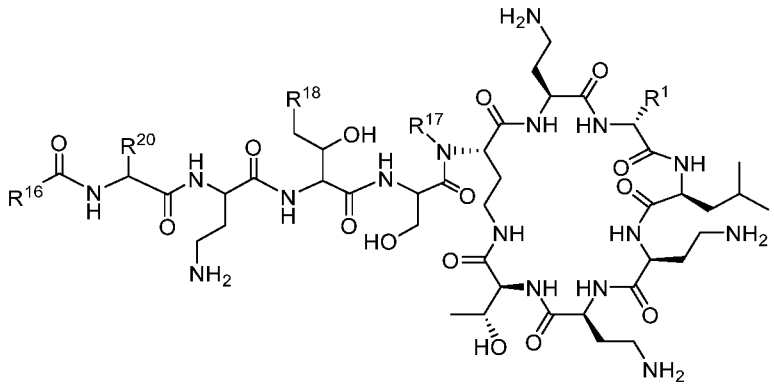
In some embodiments, the compound is described by formula (XVIII-7):



(XVIII-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

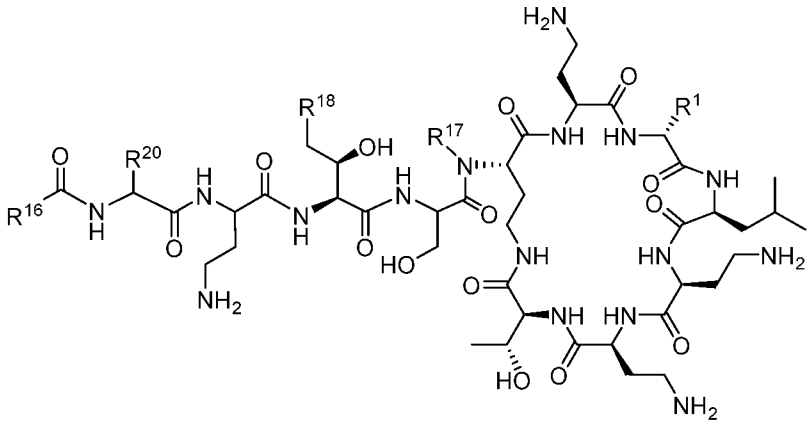
In some embodiments, the compound is described by formula (XVIII-8):



(XVIII-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XVIII-9):



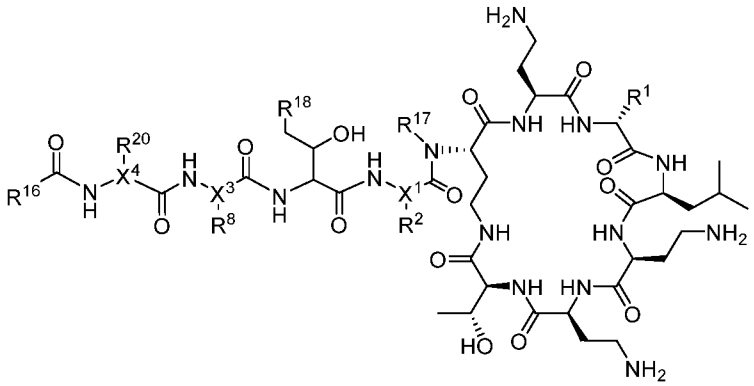
(XVIII-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally

substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino, or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

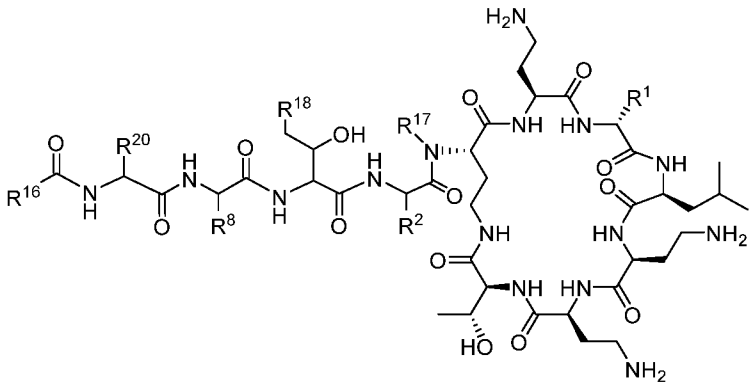
In some embodiments, the compound is described by formula (XIX):



(XIX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

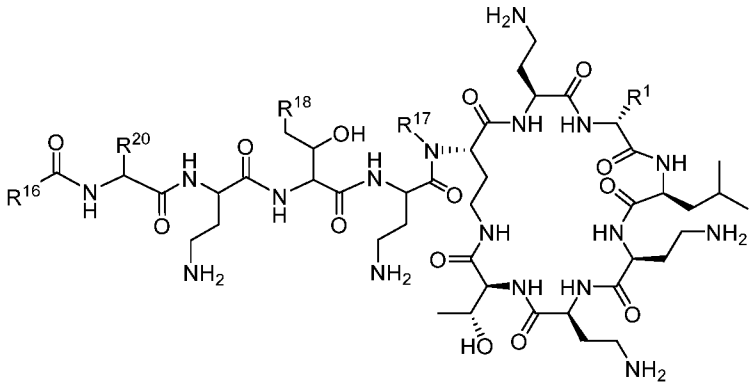
In some embodiments, the compound is described by formula (XIX-1):



(XIX-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIX-2):

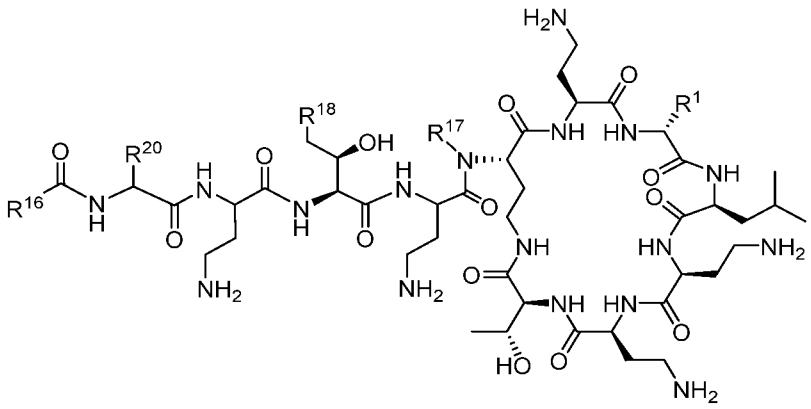


(XIX-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl,

optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

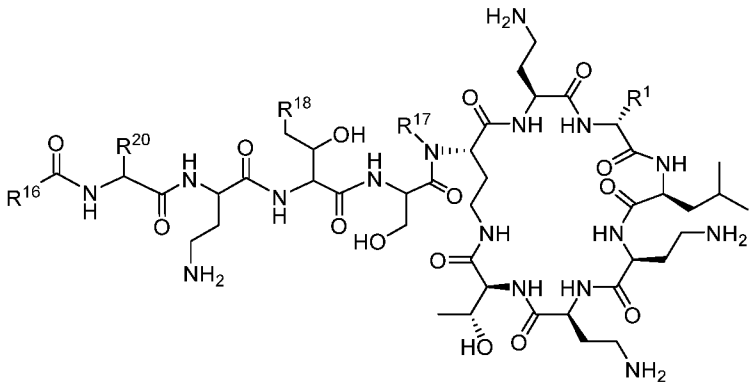
In some embodiments, the compound is described by formula (XIX-3):



(XIX-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

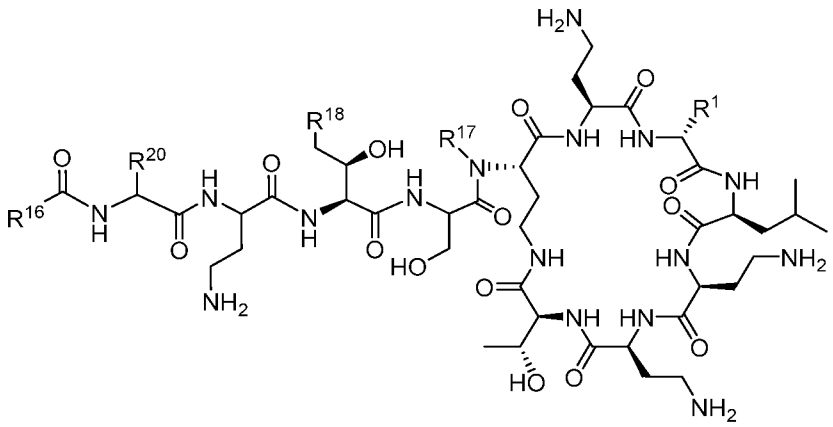
In some embodiments, the compound is described by formula (XIX-4):



(XIX-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XIX-5):



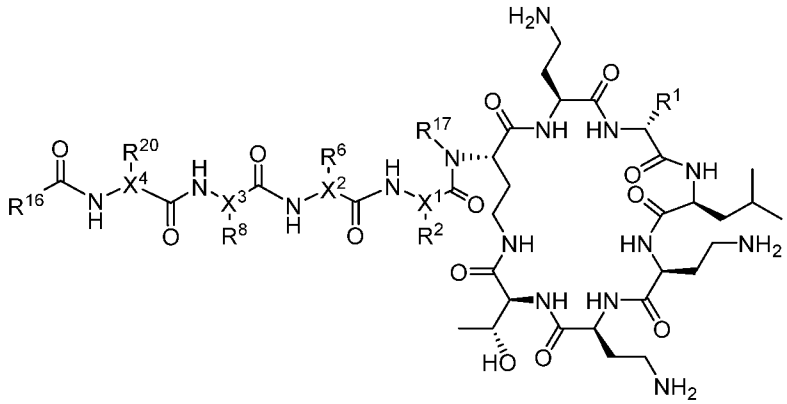
(XIX-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally

substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

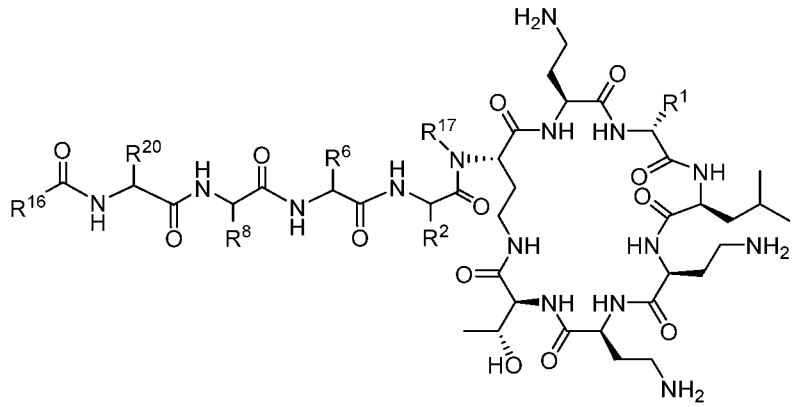
In some embodiments, the compound is described by formula (XX):



(XX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

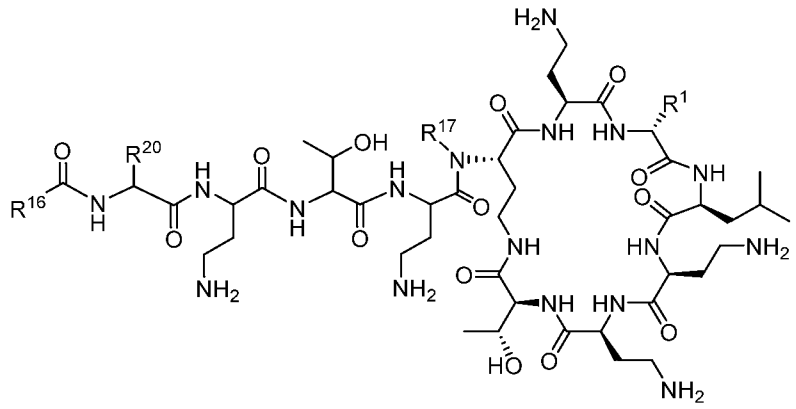
In some embodiments, the compound is described by formula (XX-1):



(XX-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XX-2):

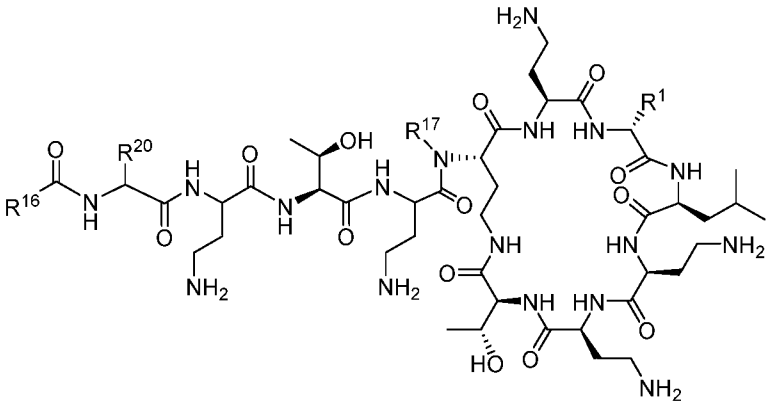


(XX-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl,

optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

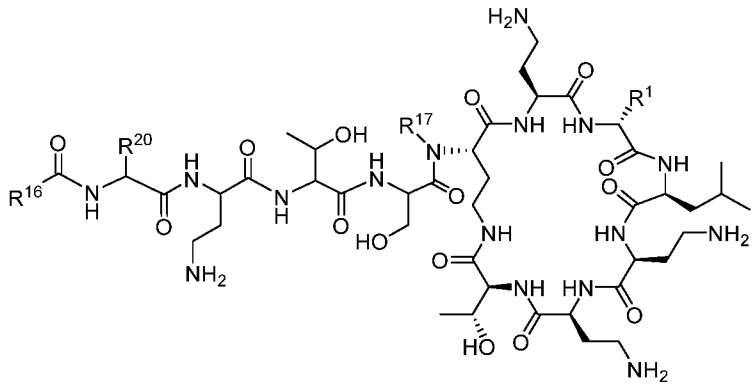
In some embodiments, the compound is described by formula (XX-3):



(XX-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

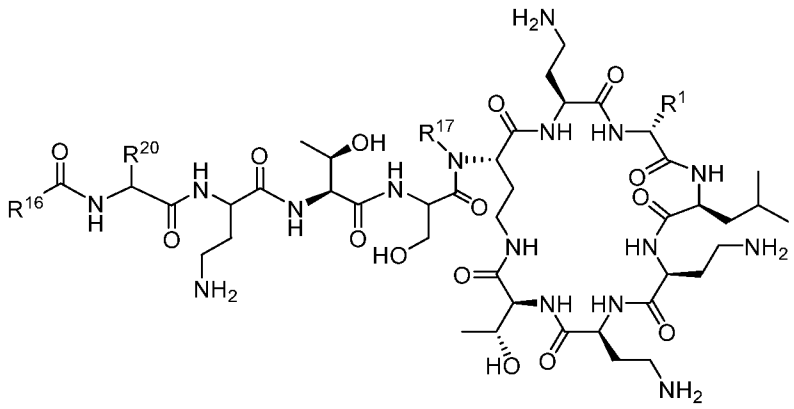
In some embodiments, the compound is described by formula (XX-4):



(XX-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XX-5):

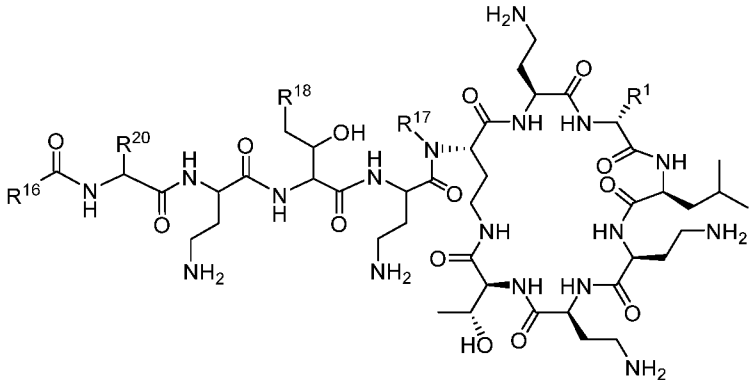


(XX-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally

substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

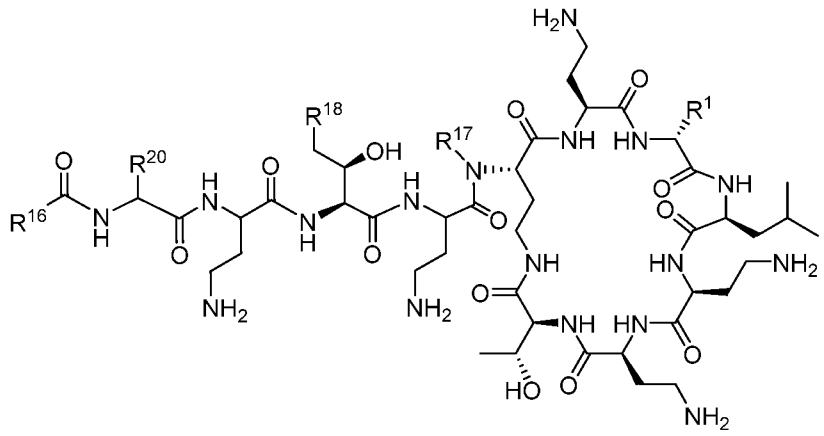
In some embodiments, the compound is described by formula (XX-6):



(XX-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

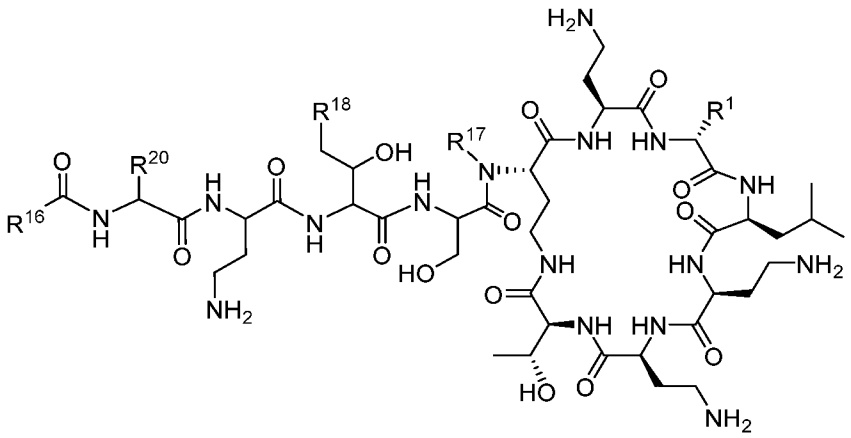
In some embodiments, the compound is described by formula (XX-7):



(XX-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

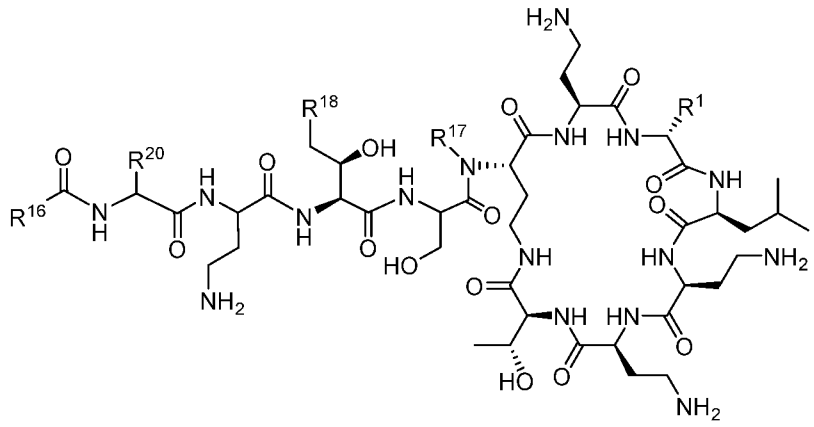
In some embodiments, the compound is described by formula (XX-8):



(XX-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XX-9):

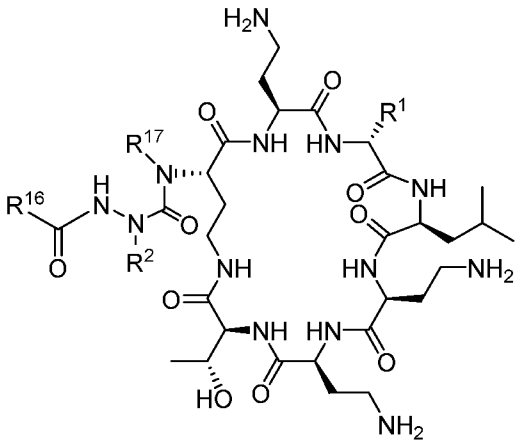


(XX-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl, or a pharmaceutically acceptable salt thereof

In some embodiments, R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

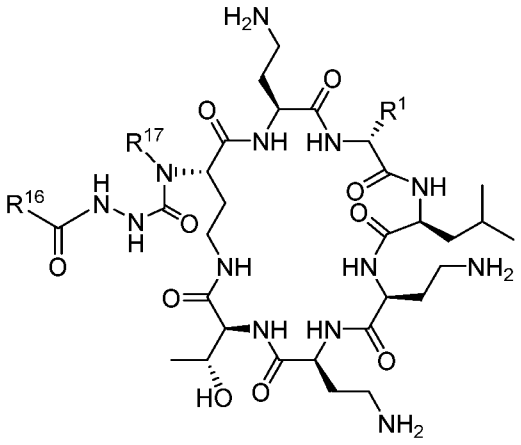
In some embodiments, the compound is described by formula (XXI):



(XXI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^2 is a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

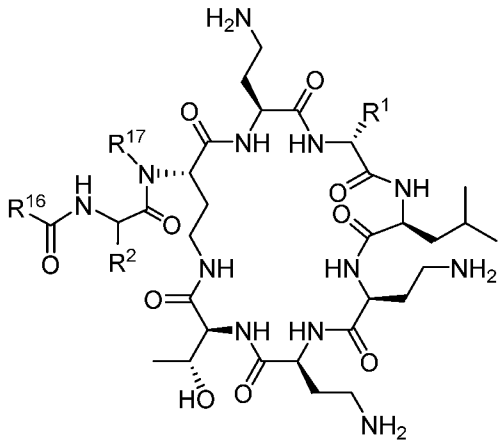
In some embodiments, the compound is described by formula (XXI-1):



(XXI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; or a pharmaceutically acceptable salt thereof.

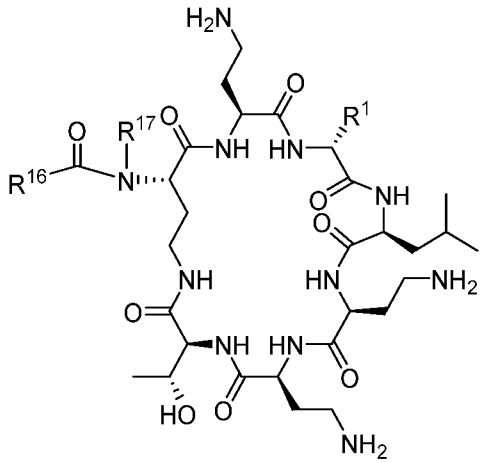
In some embodiments, the compound is described by formula (XXII):



(XXII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^2 is a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

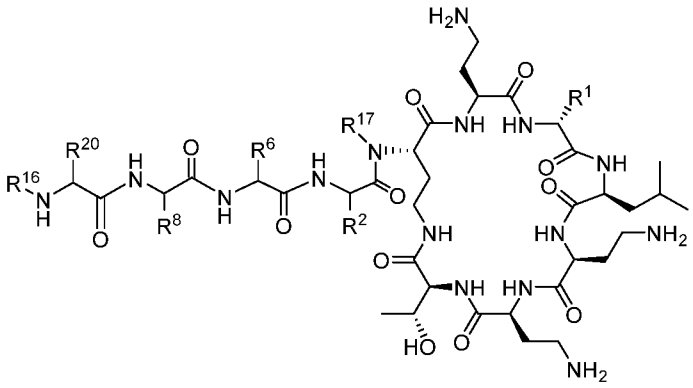
In some embodiments, the compound is described by formula (XXIII):



(XXIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{17} is C1-C3 alkyl or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

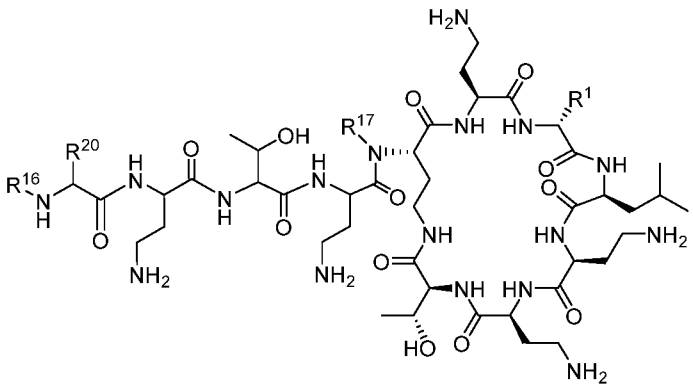
In another aspect, the invention features a compound described by formula (XXIV):



(XXIV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, and R^8, is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{20} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, optionally substituted C6-C35 heteroalkaryl, or absent; and R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXIV-1):

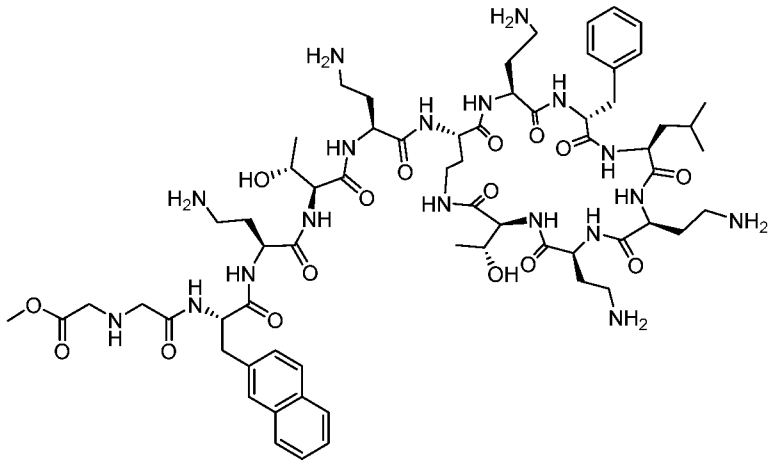


(XXIV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted

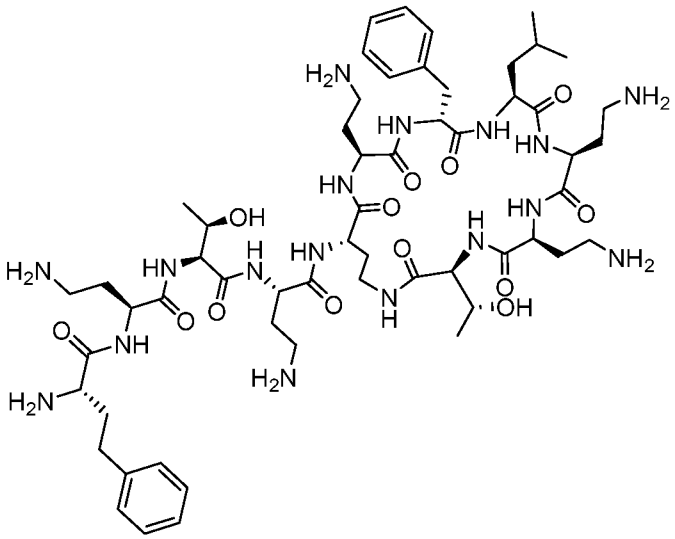
furanylmethyl; and R^{20} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; and R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, optionally substituted C6-C35 heteroalkaryl, or absent; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is:



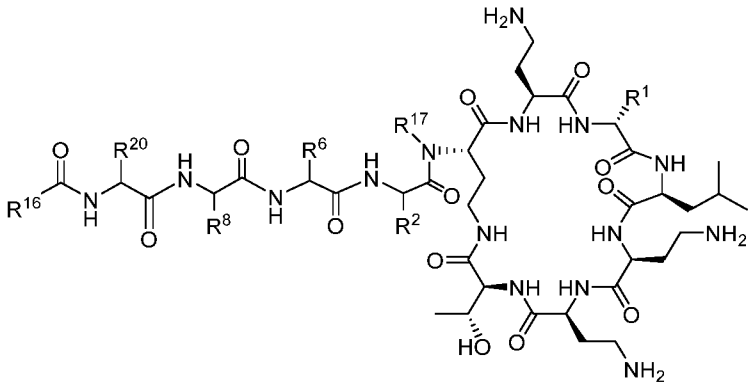
Compound 52.

In some embodiments, the compound is:



Compound 53.

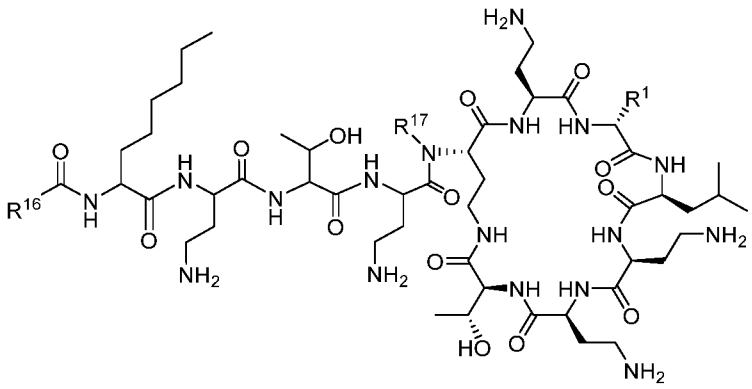
In another aspect, the invention features a compound described by formula (XXV):



(XXV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, R^8, and R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; and R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

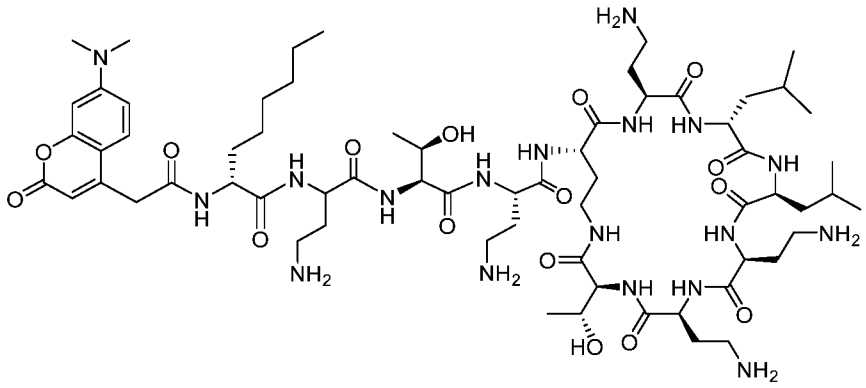
In some embodiments, the compound is described by formula (XXV-1):



(XXV-1)

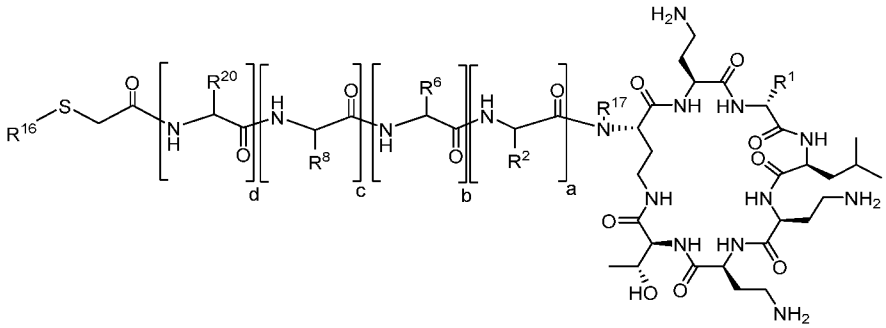
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{16} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is:



Compound 51.

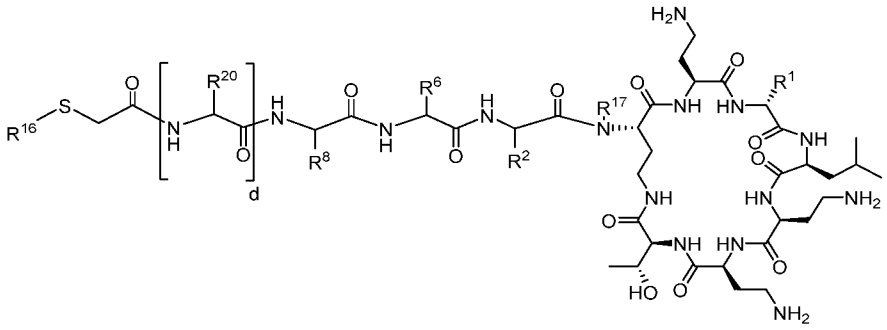
In another aspect, the invention features a compound described by formula (XXVI):



(XXVI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and each of a, b, c, and d is, independently, 0 or 1, or a pharmaceutically acceptable salt thereof.

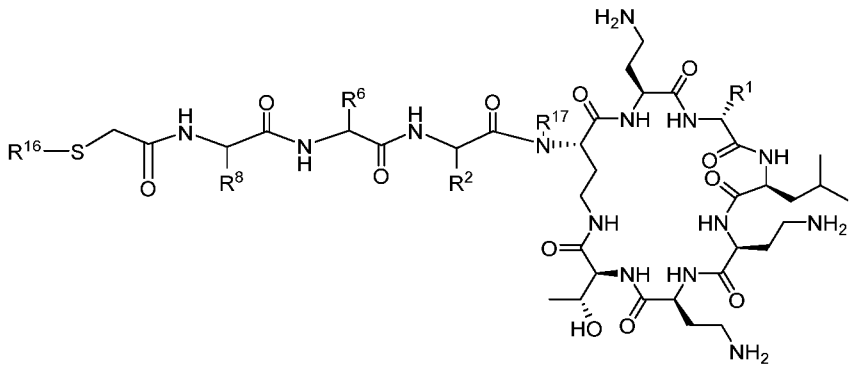
In some embodiments, the compound is described by formula (XXVI-1):



(XXVI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXVI-2):

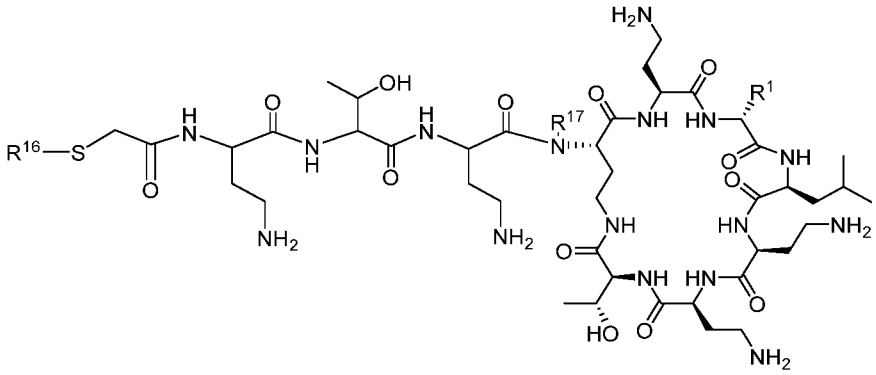


(XXVI-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and each of R^2, R^6, and R^8 is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally

substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXVI-3):

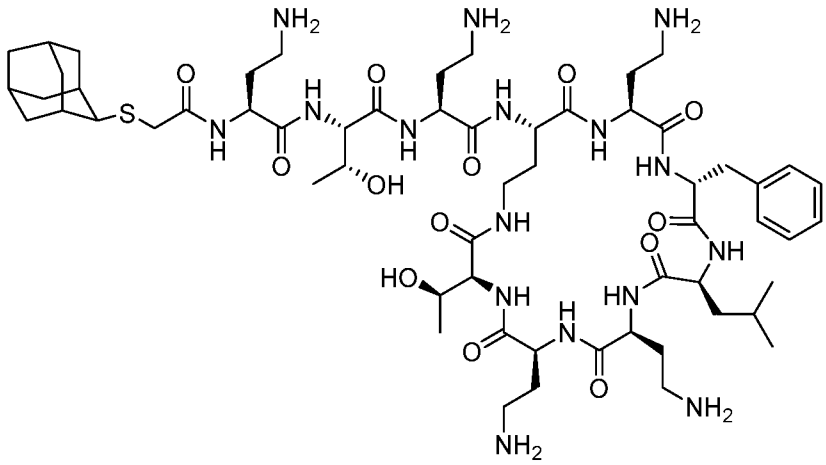


(XXVI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

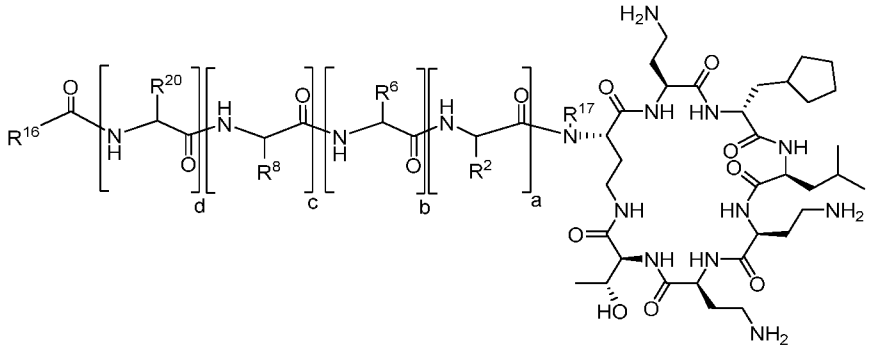
In some embodiments, R^{16} is adamantyl.

In some embodiments, the compound is:



Compound 54.

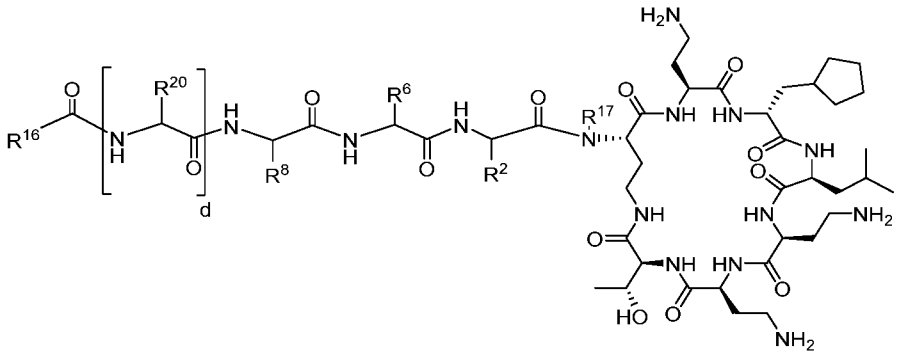
In another aspect, the invention features a compound described by formula (XXVII):



(XXVII)

wherein each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and each of a, b, c, and d is, independently, 0 or 1, or a pharmaceutically acceptable salt thereof.

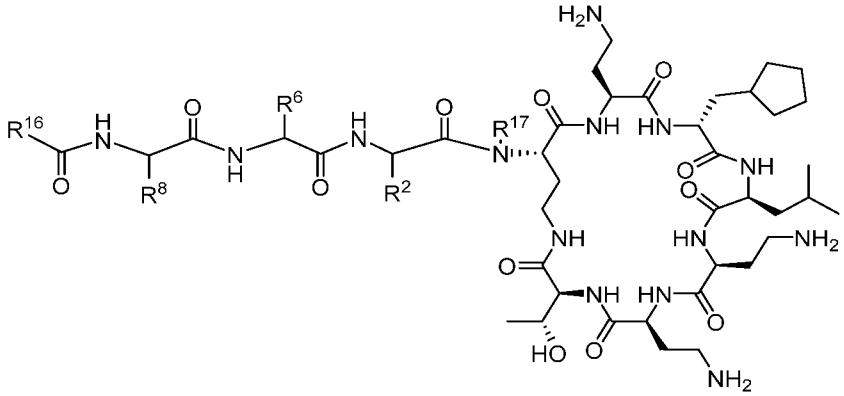
In some embodiments, the compound is described by formula (XXVII-1):



(XXVII-1)

wherein each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXVII-2):

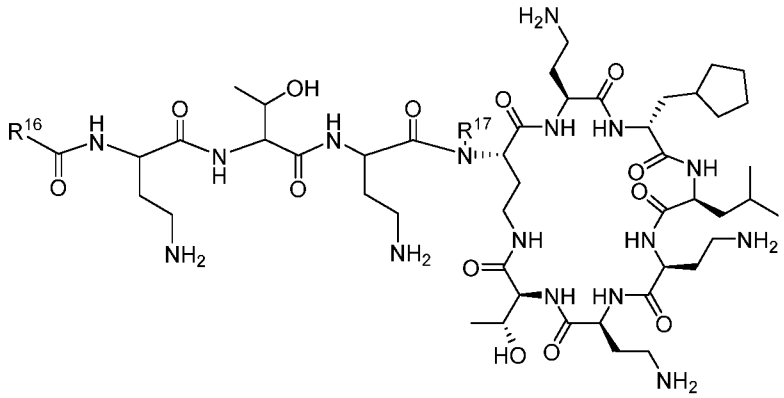


(XXVII-2)

wherein each of R^2, R^6, and R^8 is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally

substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

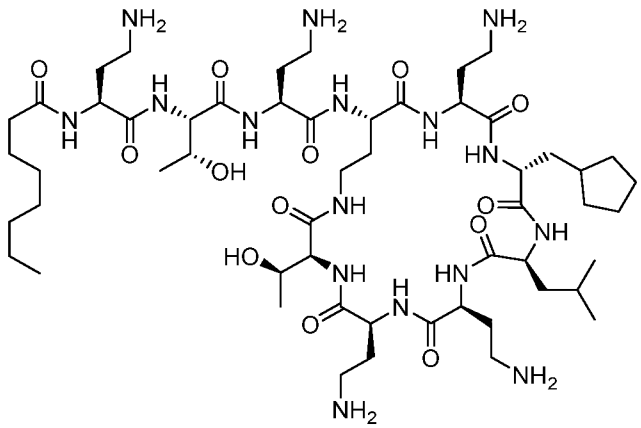
In some embodiments, the compound is described by formula (XXVII-3):



(XXVII-3)

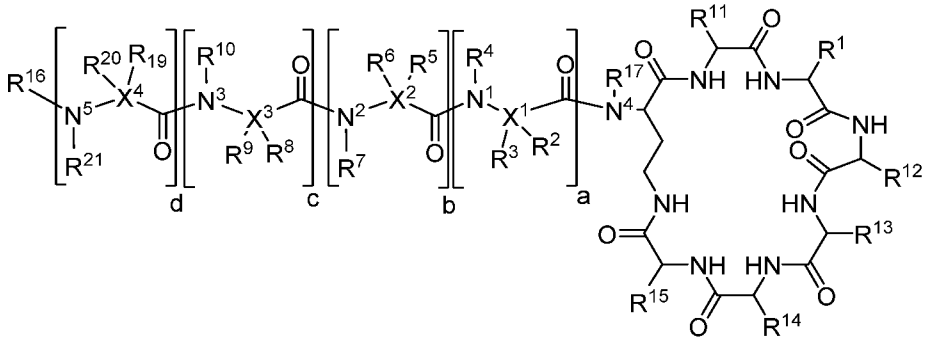
wherein R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is:



Compound 55.

In another aspect, the invention features a compound described by formula (XXVIII):

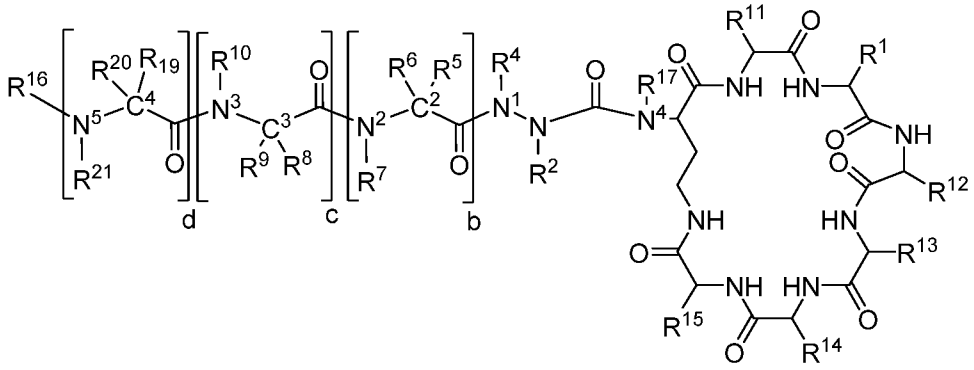


(XXVIII)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein at least one of X^1, X^2, X^3, and X^4 is a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; (vii) R^{19}, R^{20}, and X^4; or (viii) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (XXVIII-1):

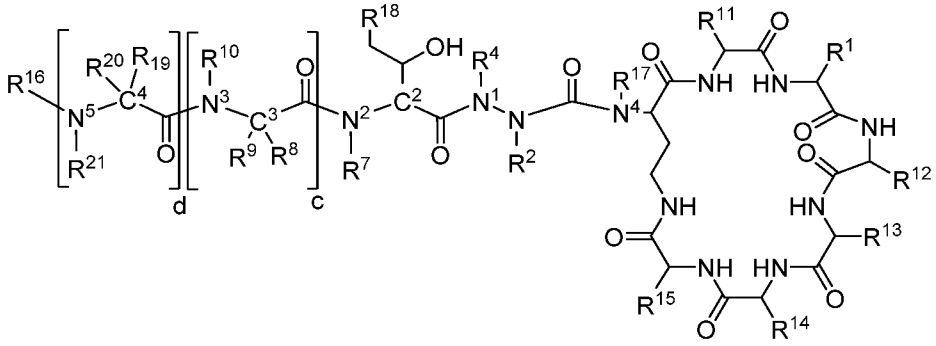


(XXVIII-1)

wherein each of b, c, and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^5, R^6, and C^2; (ii) R^6, R^7, N^2, and C^2; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

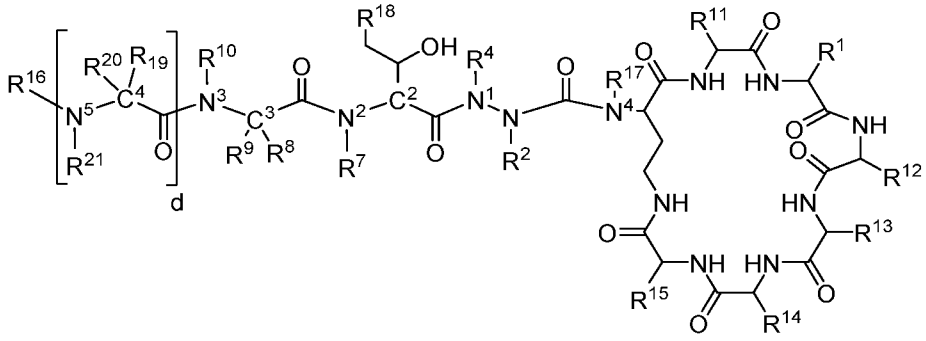
In some embodiments, the compound is described by formula (XXVIII-2):



(XXVIII-2)

wherein each of c and d is, independently, 0 or 1; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXVIII-3):

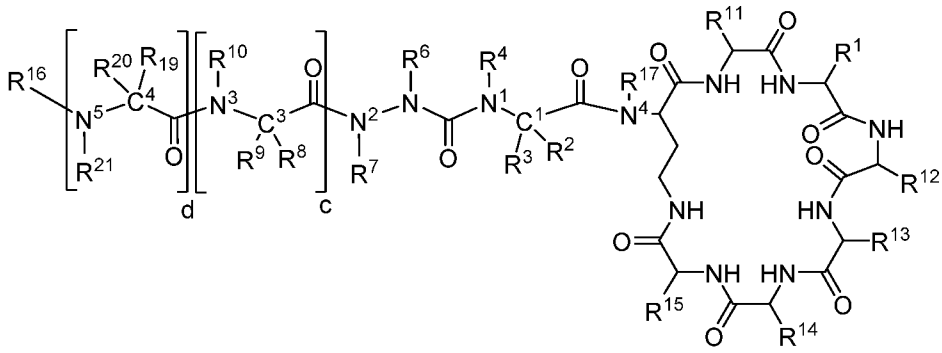


(XXVIII-3)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^8, R^9, and C^3; (ii) R^9, R^{10}, N^3, and C^3; (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4.

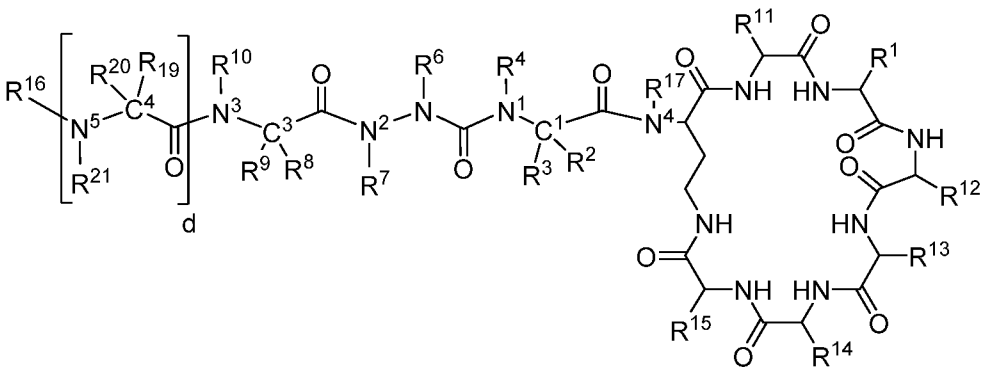
In some embodiments, the compound is described by formula (XXVIII-4):



(XXVIII-4)

wherein each of c and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXVIII I-5):

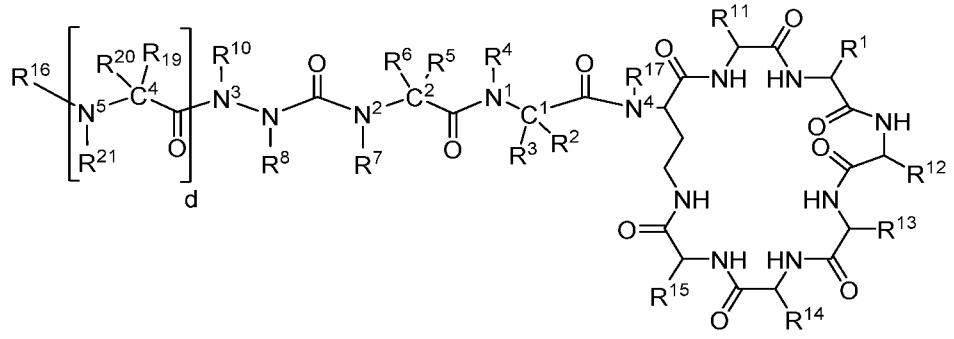


(XXVIII-5)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (XXVIII-6):

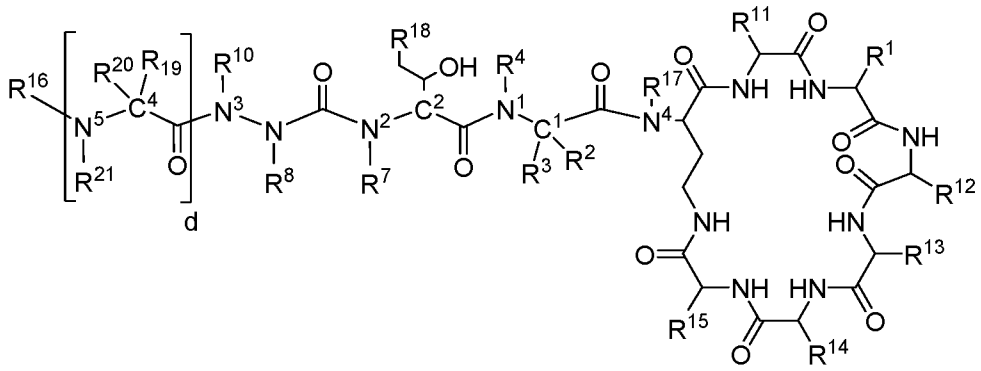


(XXVIII-6)

wherein d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; or (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (XXVIII-7):

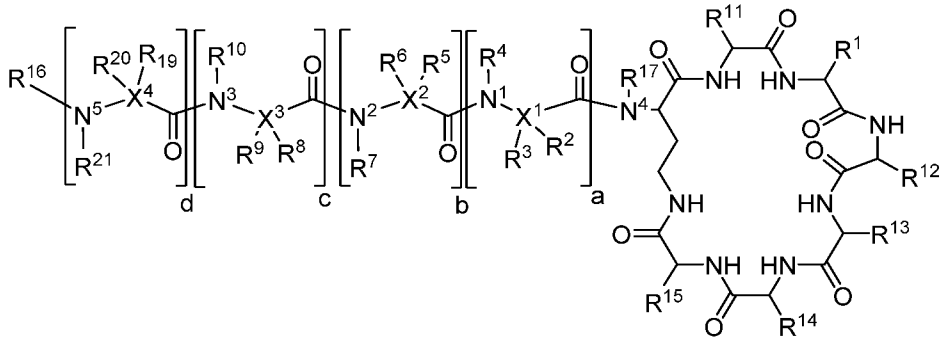


(XXVIII-7)

wherein d is 0 or 1; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; or (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (XXIX):

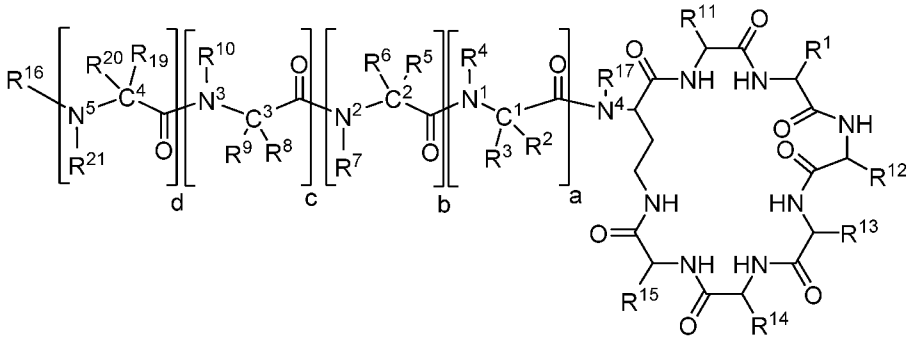


(XXIX)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is C1-C3 alkyl or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (XXIX-1):

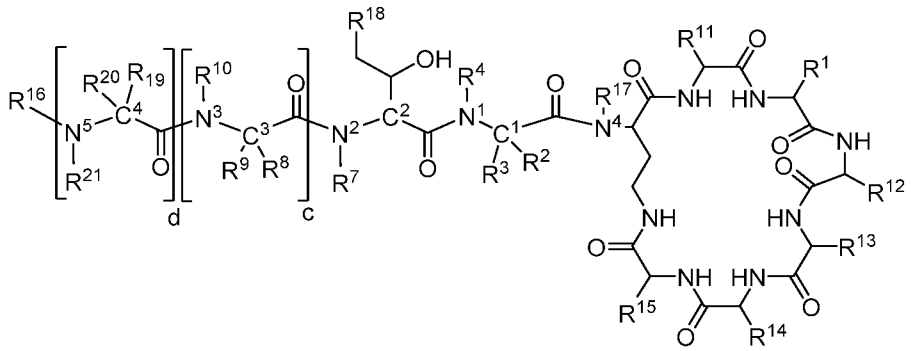


(XXIX-1)

wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and each of a, b, c, and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

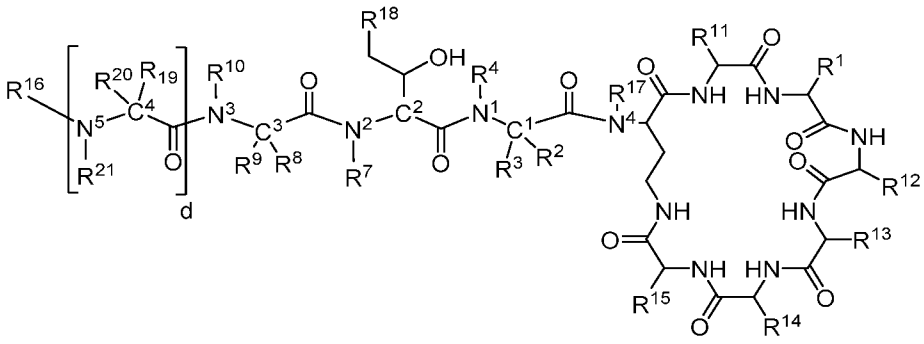
In some embodiments, the compound is described by formula (XXIX-2):



(XXIX-2)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is C1-C3 alkyl or C2-C3 alkamino; and each of c and d is, independently, 0 or 1,or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXIX-3):

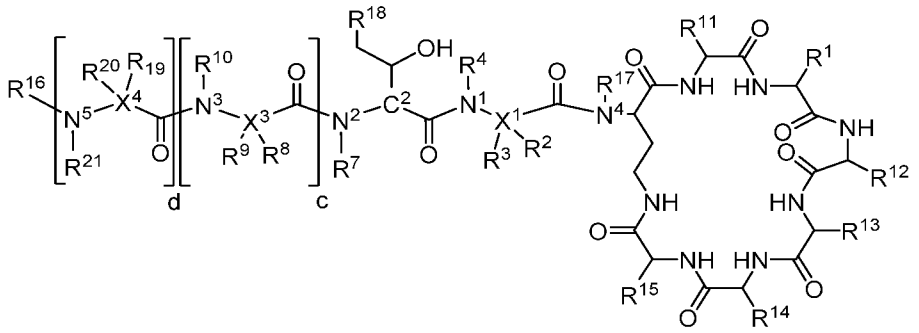


(XXIX-3)

wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and d is 0 or 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (XXX):



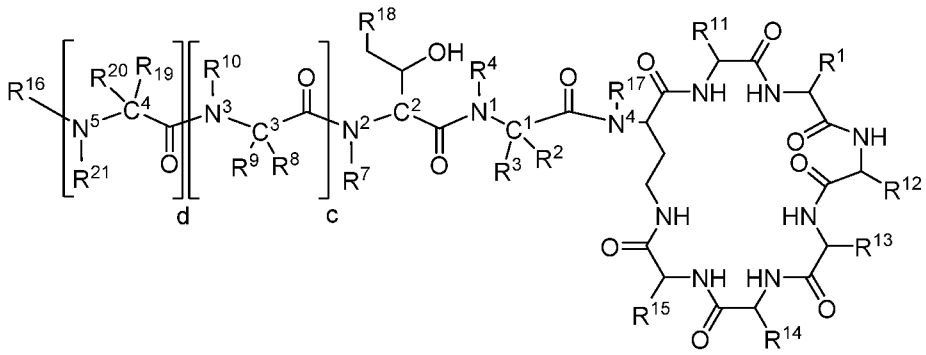
(XXX)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20

cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of a, b, c, and d is, independently, 0 or 1; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^8, R^9, and X^3; (iv) R^9, R^{10}, N^3, and X^3; (v) R^{19}, R^{20}, and X^4; or (vi) R^{19}, R^{20}, N^5, and X^4.

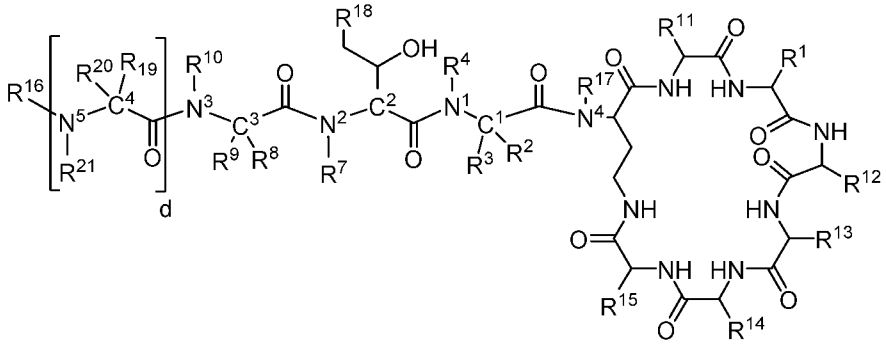
In some embodiments, the compound is described by formula (XXX-1):



(XXX-1)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and each of c and d is, independently, 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXX-2):

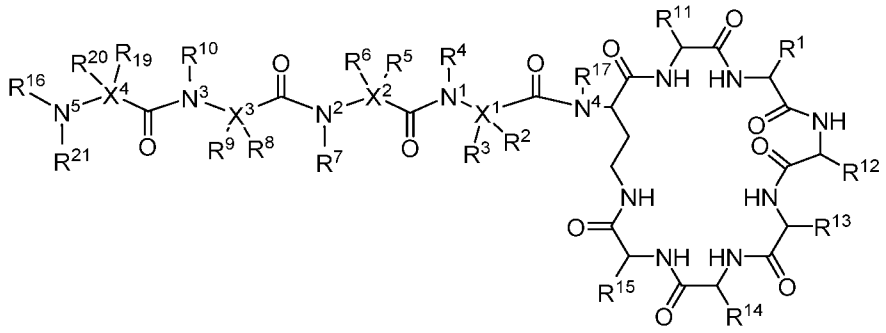


(XXX-2)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and d is 0 or 1; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl. In some embodiments, R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

In another aspect, the invention features a compound described by formula (XXXI):



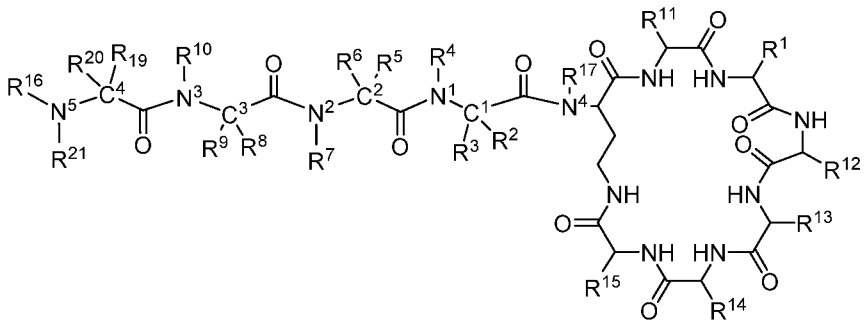
(XXXI)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H; R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H; R^{15} is a lipophilic moiety or a polar moiety; R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20

heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring; R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom, wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

In some embodiments, the compound is described by formula (XXXI-1):

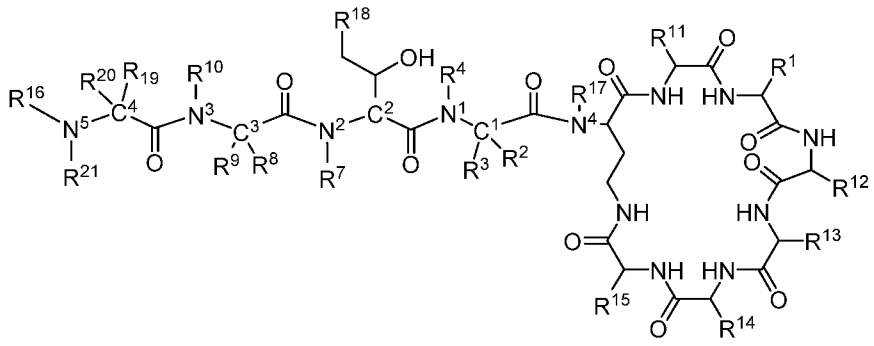


(XXXI-1)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

In some embodiments, the compound is described by formula (XXXI-2):

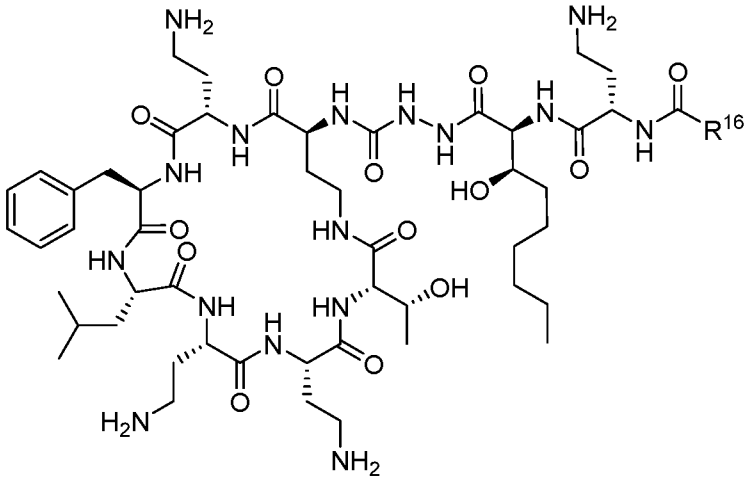


(XXXI-2)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; and R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound includes at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4. In some embodiments, R^{17} is H. In some embodiments, R^{17} is methyl.

In some embodiments, the compound is described by formula (XXXII):

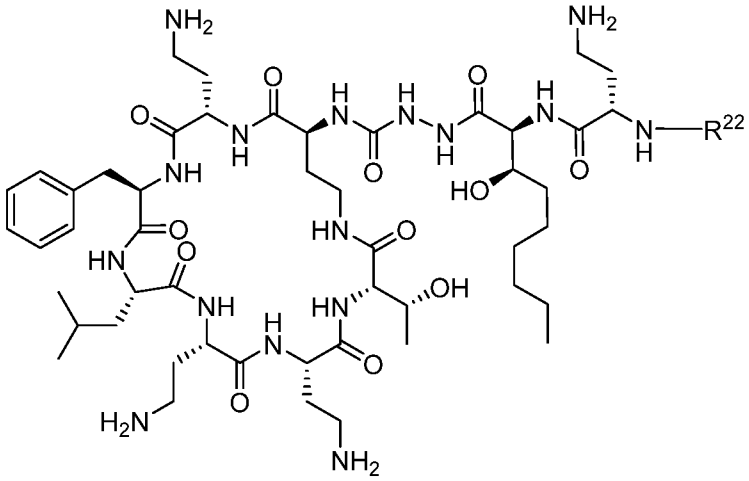


(XXXII)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

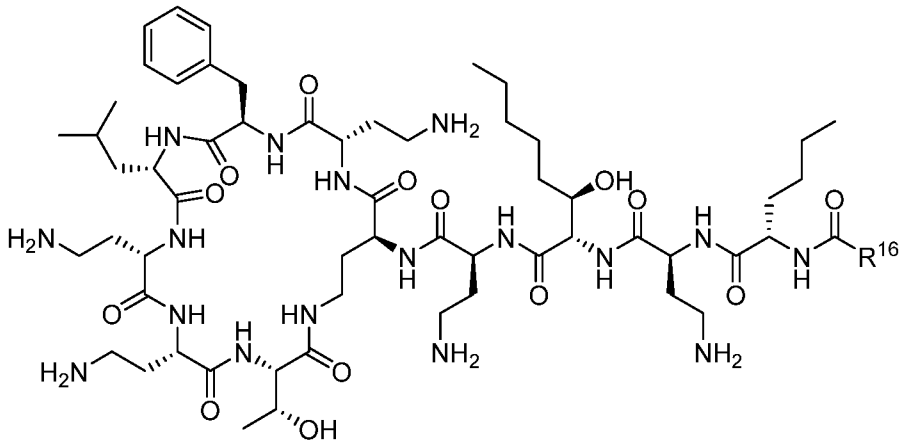
In some embodiments, the compound is described by formula (XXXIII):



(XXXIII)

wherein R^{22} is H, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

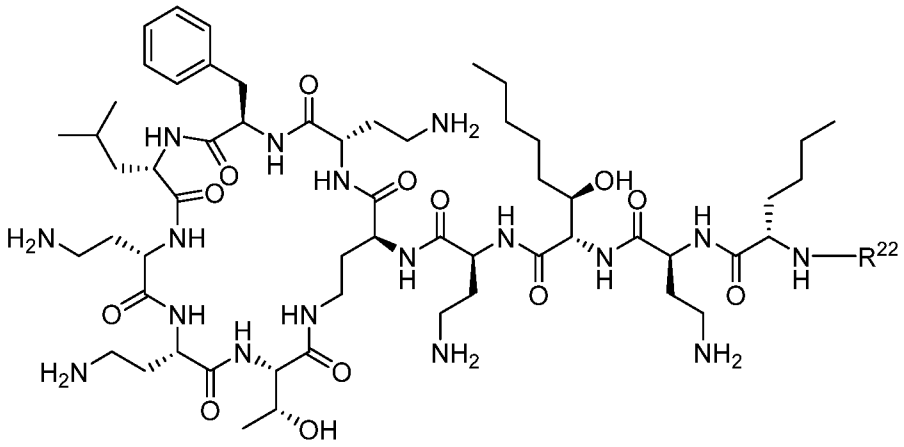
In some embodiments, the compound is described by formula (XXXIV):



(XXXIV)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

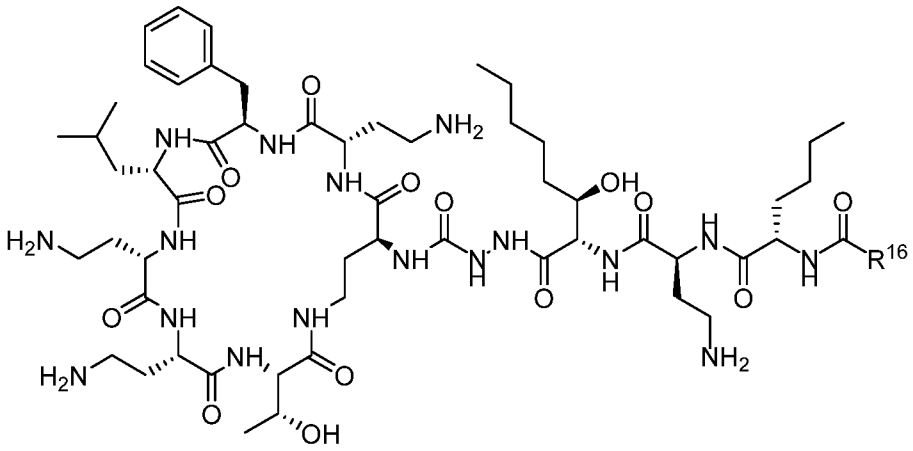
In some embodiments, the compound is described by formula (XXXV):



(XXXV)

wherein R^{22} is H, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

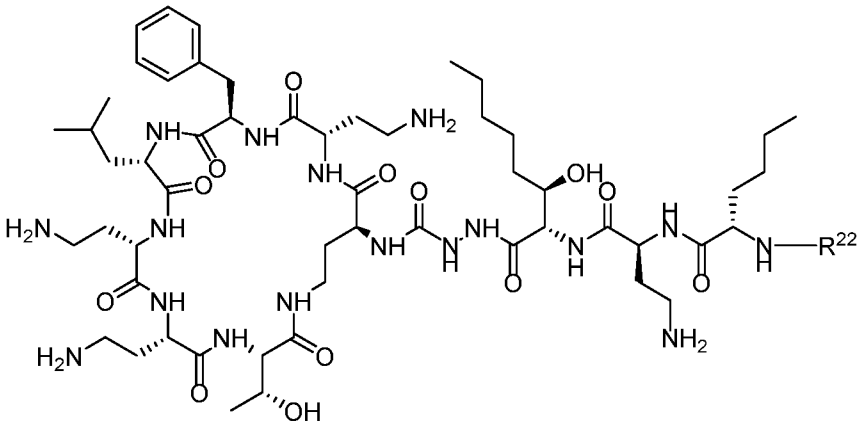
In some embodiments, the compound is described by formula (XXXVI):



(XXXVI)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

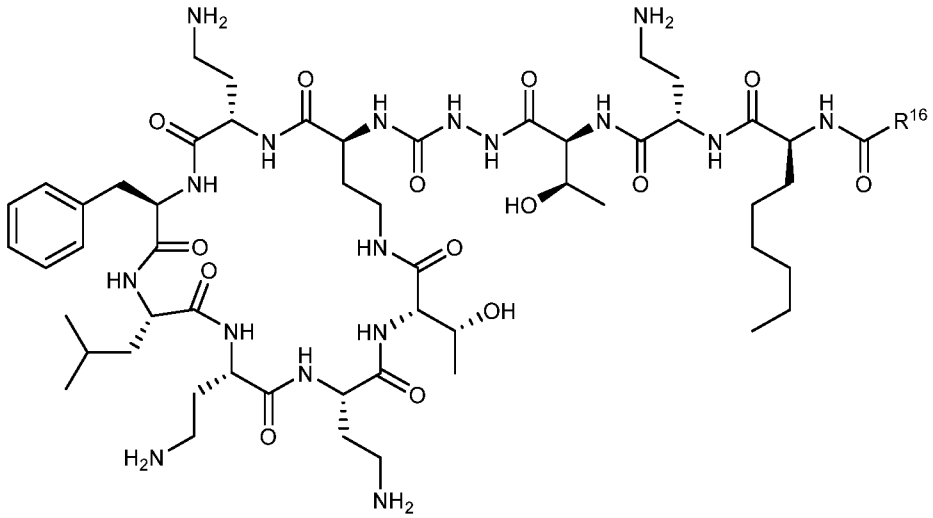
In some embodiments, the compound is described by formula (XXXVII):



(XXXVII)

wherein R^{22} is H, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

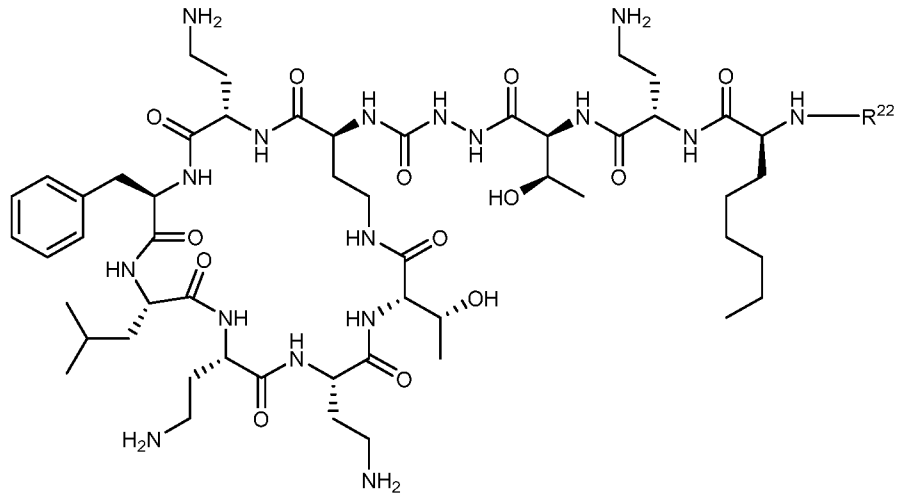
In some embodiments, the compound is described by formula (XXXVIII):



(XXXVIII)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

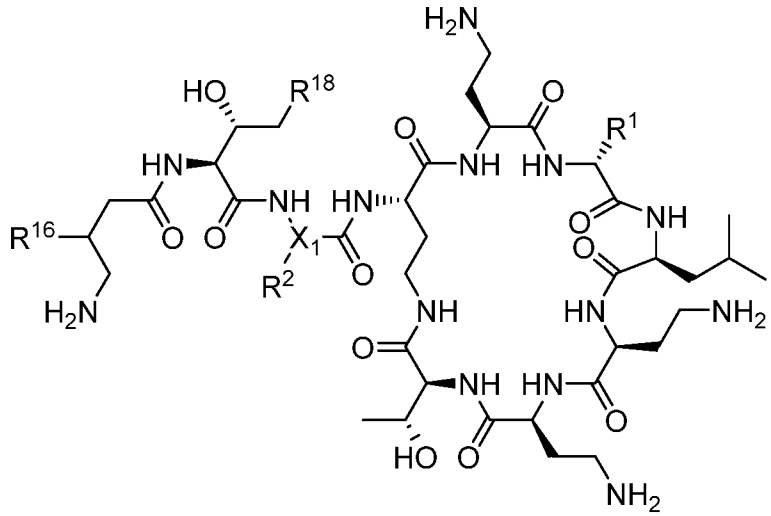
In some embodiments, the compound is described by formula (XXXIX):



(XXXIX)

wherein R^{22} is H, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; or a pharmaceutically acceptable salt thereof.

In another aspect, the invention features a compound described by formula (XXXX):

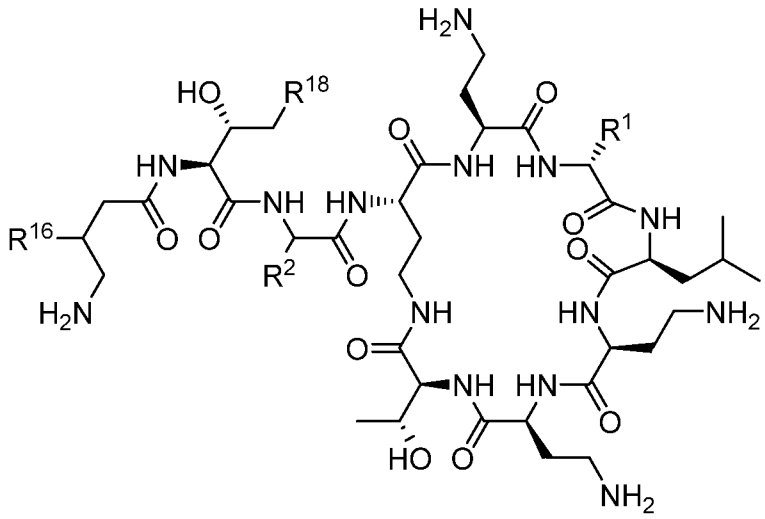


(XXXX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or

optionally substituted C6-C35 heteroalkaryl; R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and X_1 is a carbon atom or a nitrogen atom, or a pharmaceutically acceptable salt thereof.

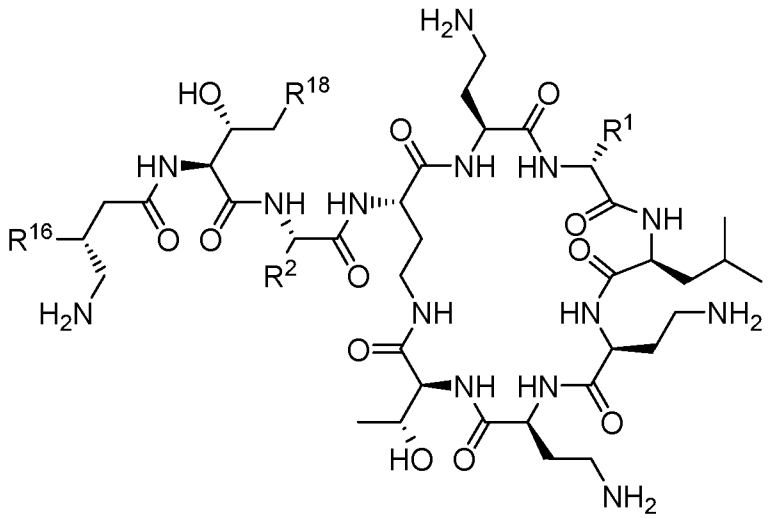
In some embodiments, the compound is described by formula (XXXX-1):



(XXXX-1)

or a pharmaceutically acceptable salt thereof.

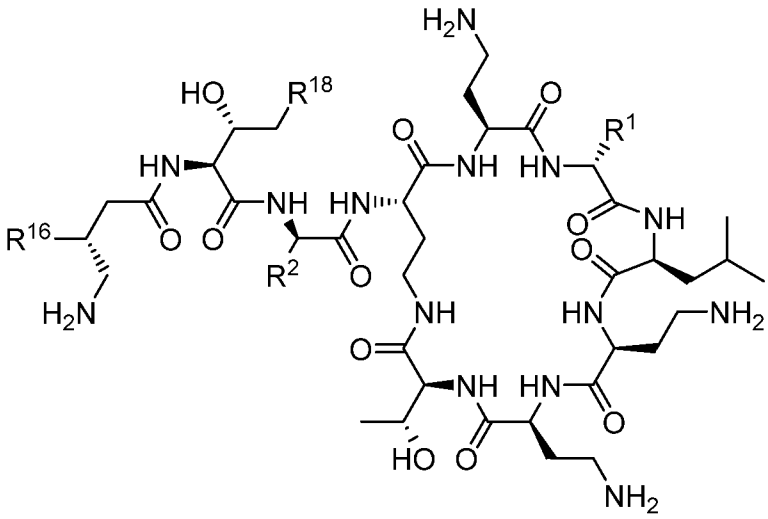
In some embodiments, the compound is described by formula (XXXX-2):



(XXXX-2)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXXX-3):

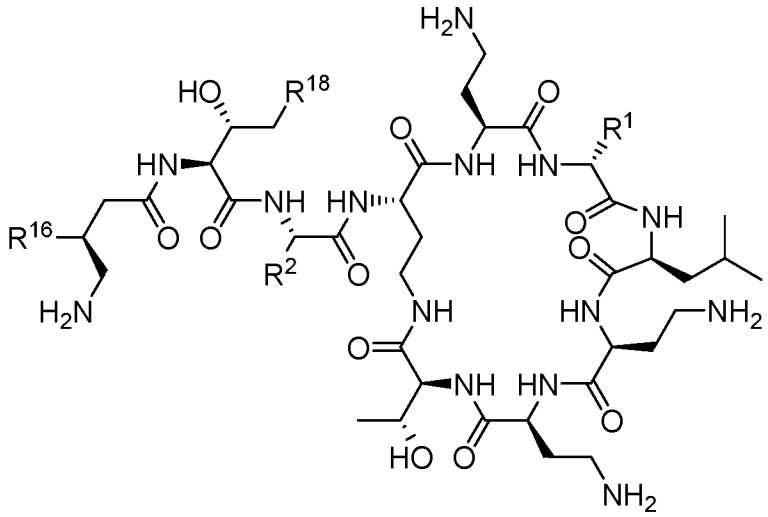


(XXXX-3)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl,

optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

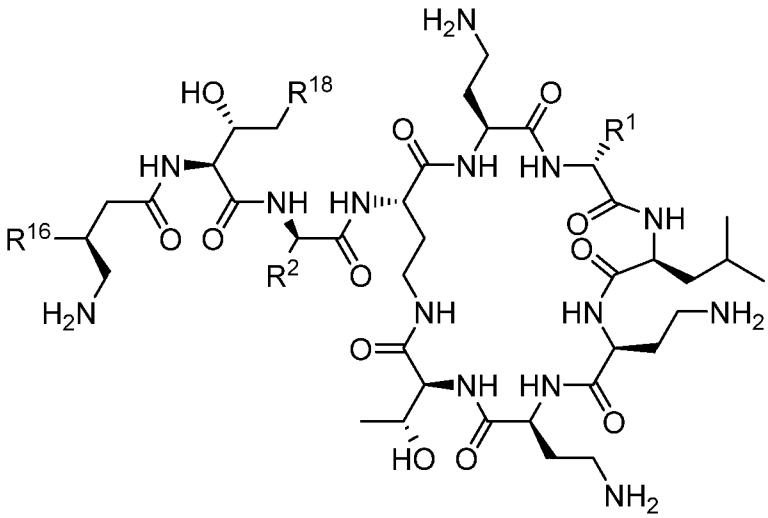
In some embodiments, the compound is described by formula (XXXX-4):



(XXXX-4)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXXX-5):

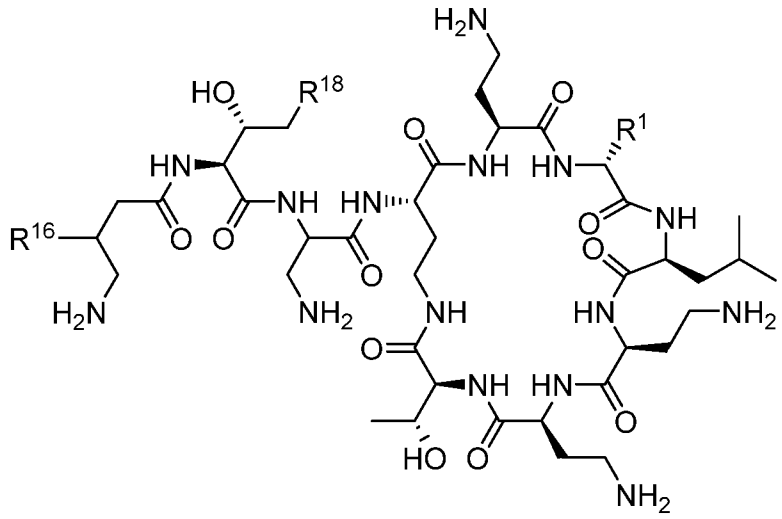


(XXXX-5)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl,

optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

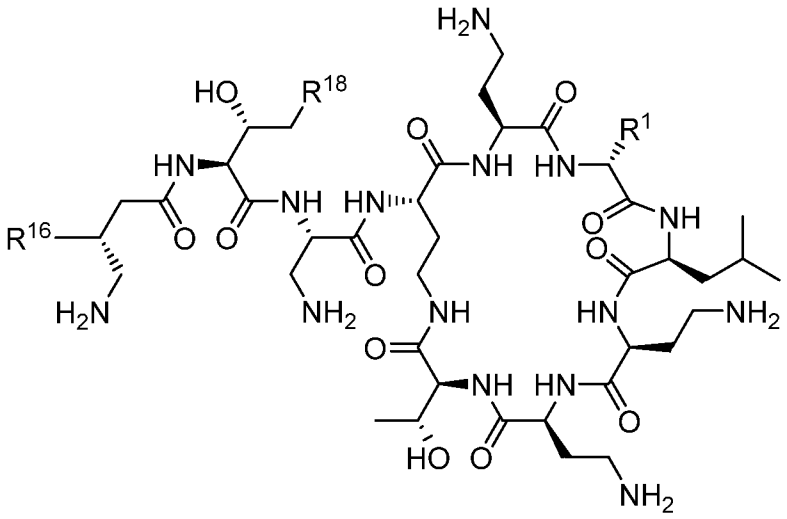
In some embodiments, the compound is described by formula (XXXX-6):



(XXXX-6)

or a pharmaceutically acceptable salt thereof.

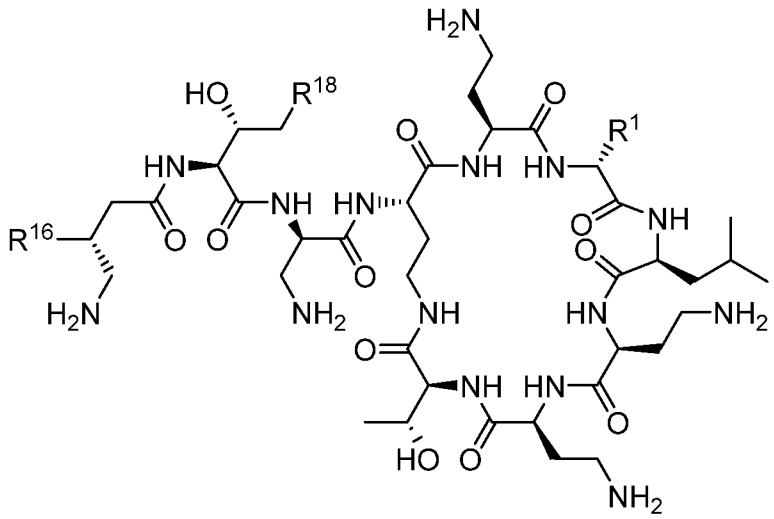
In some embodiments, the compound is described by formula (XXXX-7):



(XXXX-7)

or a pharmaceutically acceptable salt thereof.

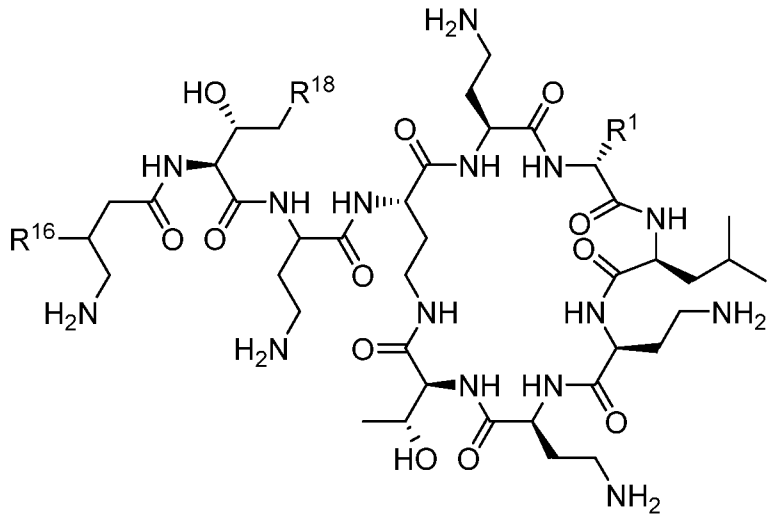
In some embodiments, the compound is described by formula (XXXX-8):



(XXXX-8)

or a pharmaceutically acceptable salt thereof.

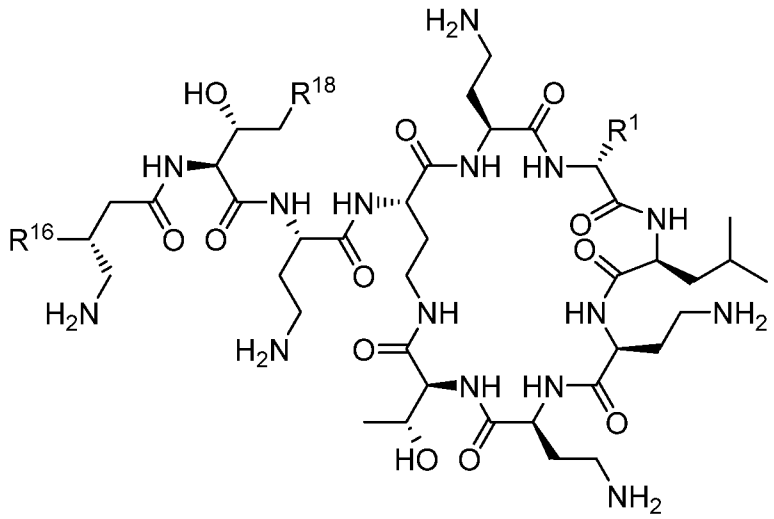
In some embodiments, the compound is described by formula (XXXX-9):



(XXXX-9)

or a pharmaceutically acceptable salt thereof.

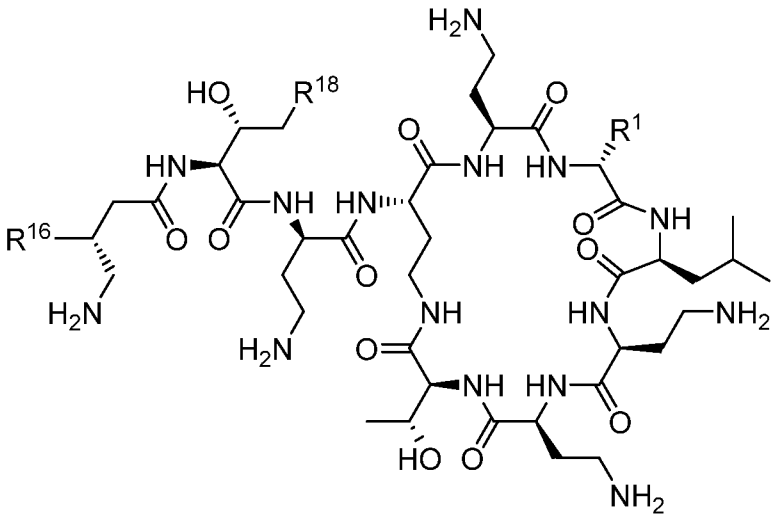
In some embodiments, the compound is described by formula (XXXX-10):



(XXXX-10)

or a pharmaceutically acceptable salt thereof.

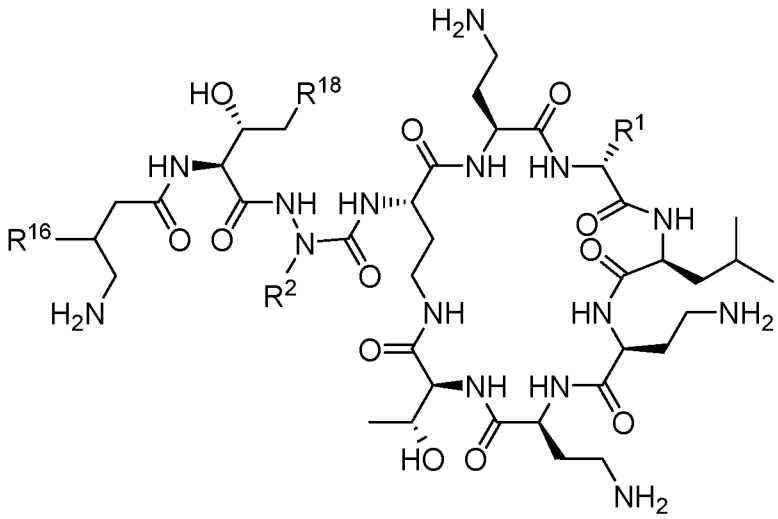
In some embodiments, the compound is described by formula (XXXX-11):



(XXXX-11)

or a pharmaceutically acceptable salt thereof.

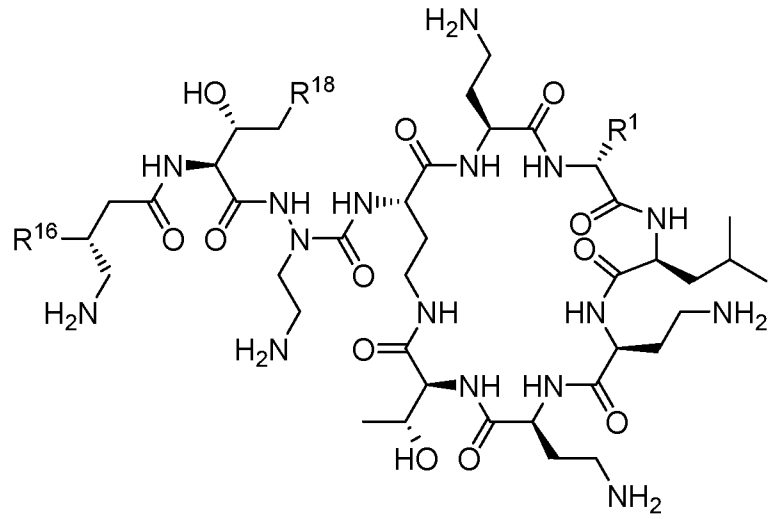
In some embodiments, the compound is described by formula (XXXX-12):



(XXXX-12)

wherein R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C2-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

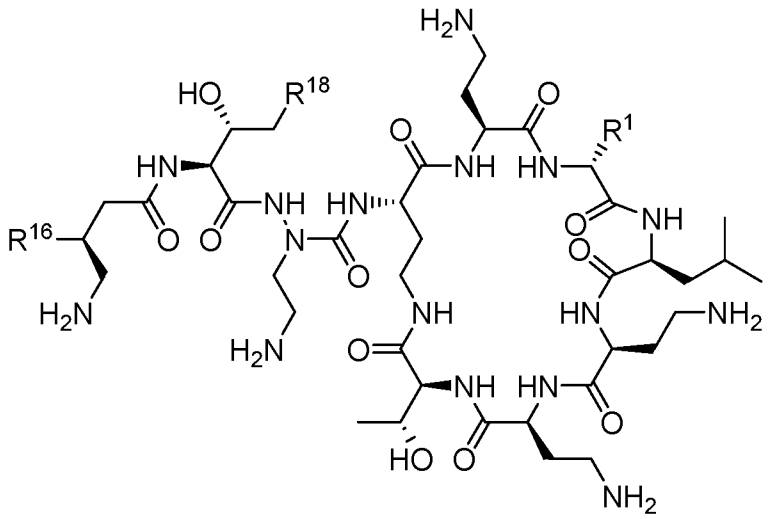
In some embodiments, the compound is described by formula (XXXX-13):



(XXXX-13)

or a pharmaceutically acceptable salt thereof.

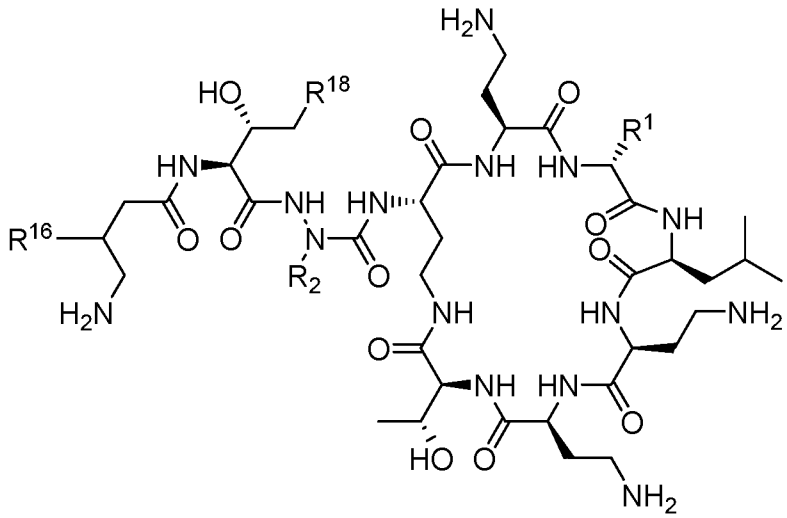
In some embodiments, the compound is described by formula (XXXX-14):



(XXXX-14)

or a pharmaceutically acceptable salt thereof.

In another aspect, the invention features a compound described by formula (XXXXI):

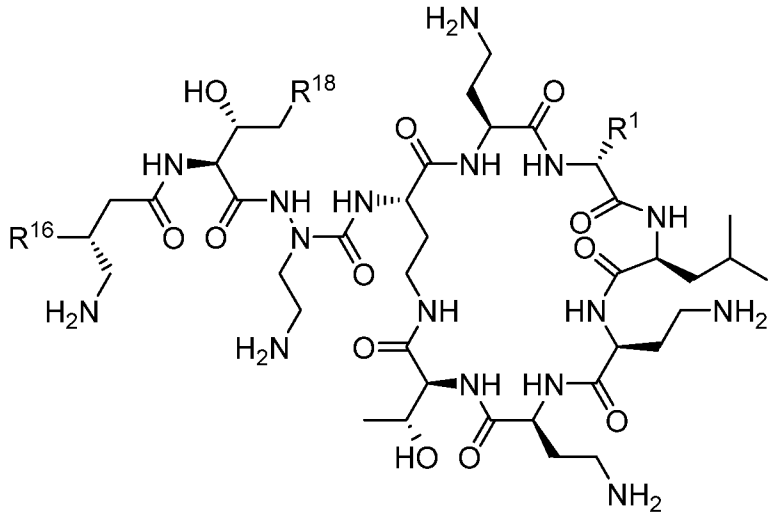


(XXXXI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C2-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; R^{18} is H, a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20

heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl, or a pharmaceutically acceptable salt thereof.

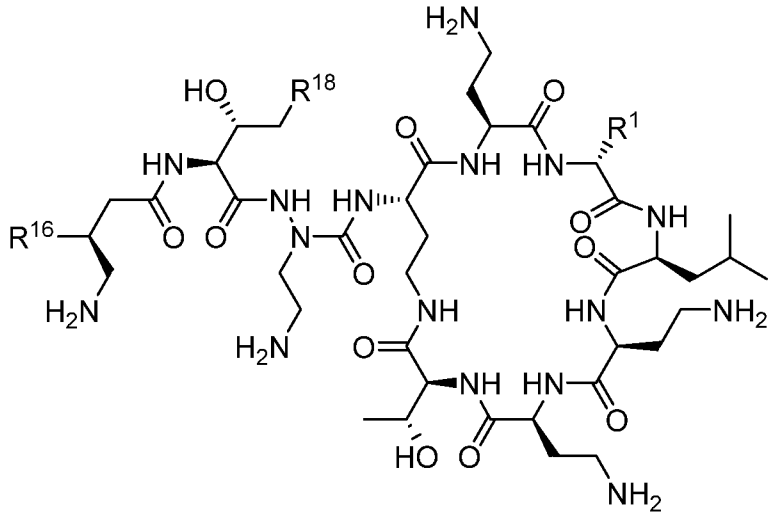
In some embodiments, the compound is described by formula (XXXXI-1):



(XXXXI-1)

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is described by formula (XXXXI-2):



(XXXXI-2)

or a pharmaceutically acceptable salt thereof.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is 3-chlorophenyl, 4-chlorophenyl, benzyl, 3-methylphenyl, isobutyl,

cyclohexyl, or phenyl. In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is 3-chlorophenyl.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is H. In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} and R^{21} are H.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^1 is benzyl or $CH_2CH(CH_3)_2$.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^2 is optionally substituted C1-C5 alkamino (e.g., CH_2NH_2 or $CH_2CH_2NH_2$). In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^2 is a polar moiety. In some embodiments, the polar moiety includes a hydroxyl group, a carboxylic acid group, an ester group, or an amide group. In some embodiments, the polar moiety is hydroxyl substituted C1-C4 alkyl (e.g., $CHCH_3OH$ or CH_2OH). In other embodiments, R^2 is H.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^6 is a polar moiety. In some embodiments, the polar moiety includes a hydroxyl group, a carboxylic acid group, an ester group, or an amide group. In some embodiments, the polar moiety is hydroxyl substituted C1-C4 alkyl (e.g., $CHCH_3OH$ or CH_2OH). In other embodiments, R^6 is H.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^8 is optionally substituted C1-C5 alkamino (e.g., CH_2NH_2 or $CH_2CH_2NH_2$). In some embodiments, R^8 is optionally substituted C5-C15 aryl (e.g., naphthyl). In other embodiments, R^8 is H.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{17} is H. In other embodiments, R^{17} is methyl.

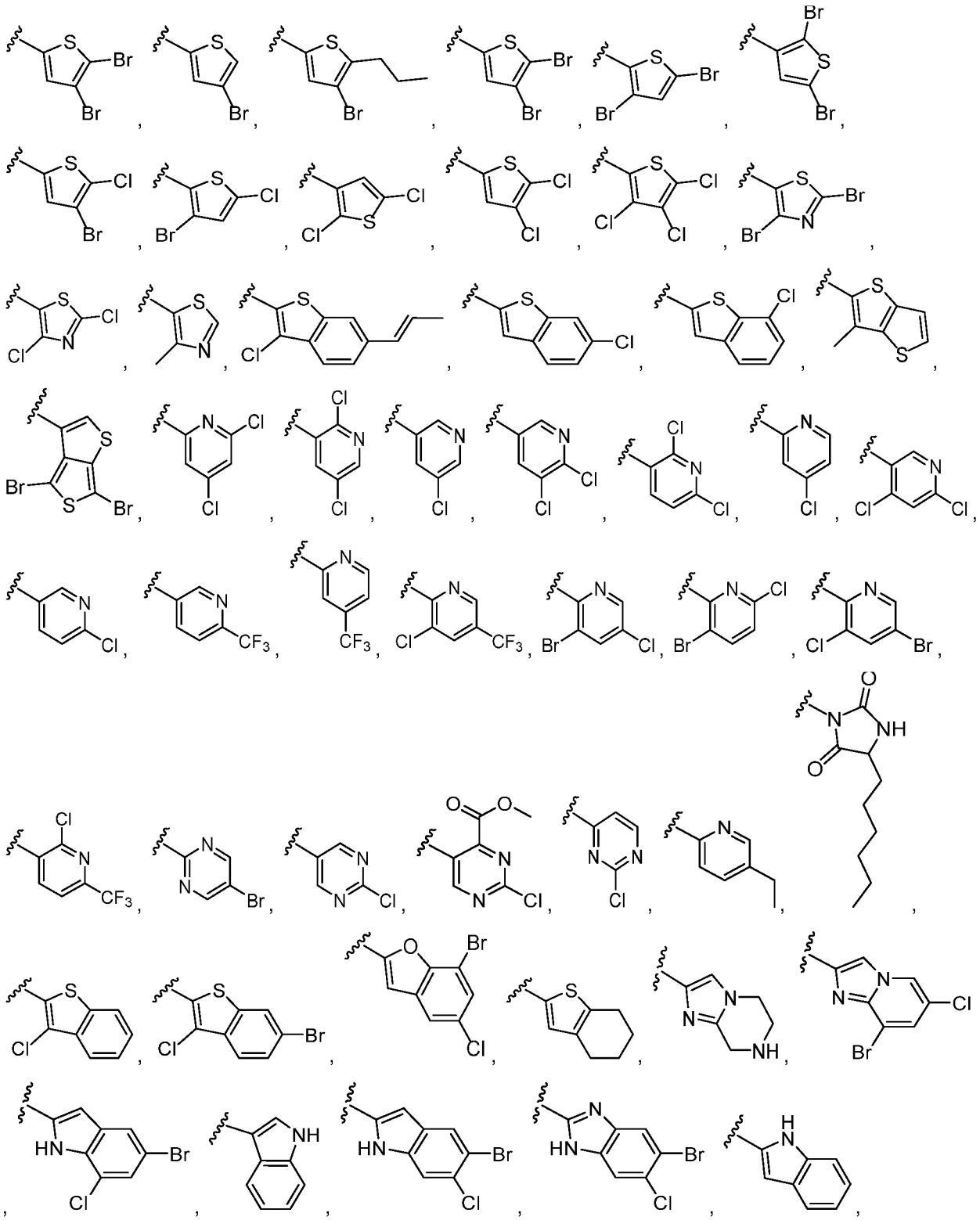
In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

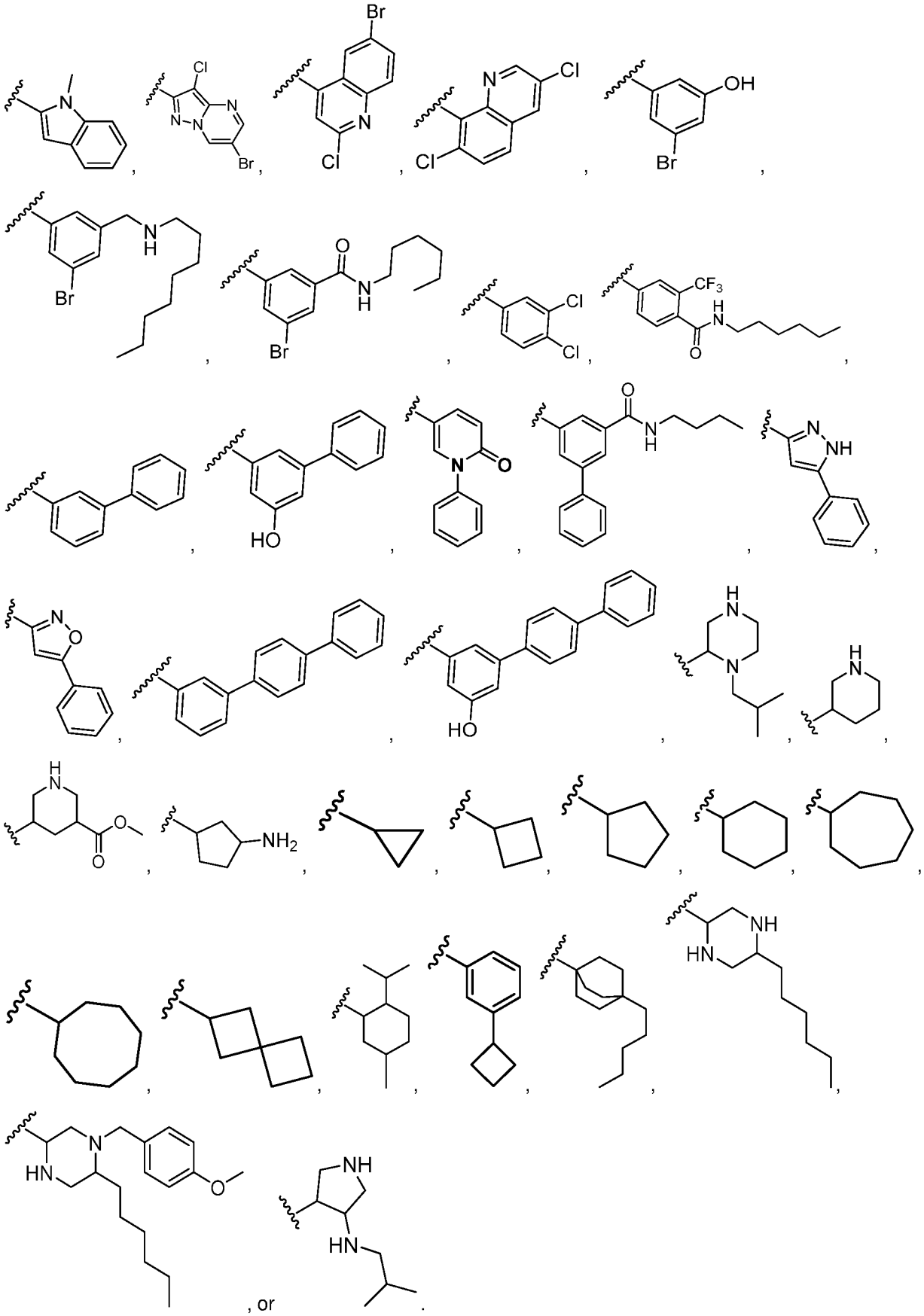
In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{20} is optionally substituted C1-C20 alkyl or optionally substituted C6-C35 alkaryl. In some embodiments, R^{20} is $CH_2CH_2CH_2CH_3$ or $CH_2CH_2CH_2CH_2CH_2CH_3$. In some embodiments, R^{20} is naphthylmethyl.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl. In some embodiments, R^{16} is optionally substituted pyrrolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, thiphenyl, thiolanyl, furanyl, tetrahydrofuranyl, pyridinyl, piperidinyl, pyrimidinyl, pyrazinyl, azepinyl, 1,4-diazepinyl, 4F-pyranyl, tetrahydropyranyl, indolyl, quinolyl, isoquinolyl, chromanyl, purinyl, pteridinyl, triazolyl, benzotriazolyl. In some embodiments, R^{16} is optionally substituted phenyl, naphthyl, or phenanthrene. In some embodiments, R^{16} is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl,

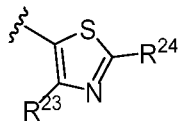
cyclohexyl, cycloheptyl, cyclooctyl, or cyclononyl. In some embodiments, R^{16} is optionally substituted biphenyl or terphenyl. In some embodiments, R^{16} is optionally substituted C1-C20 alkyl.

In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is



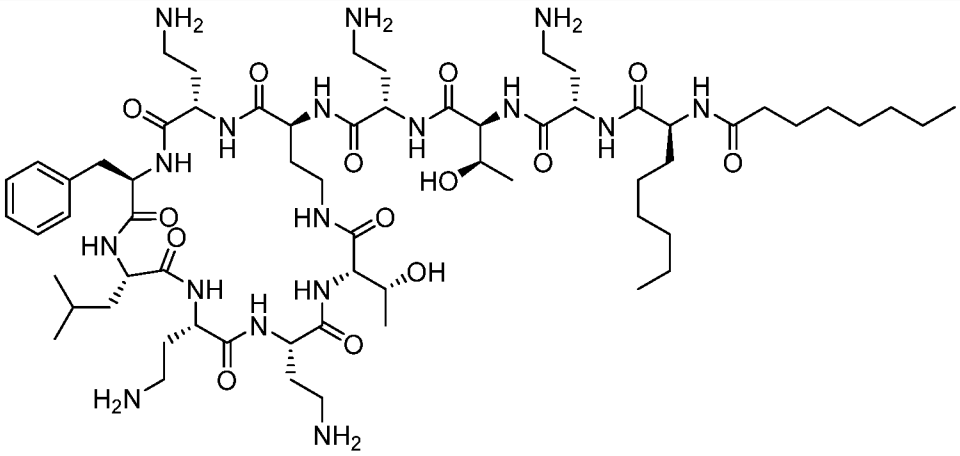
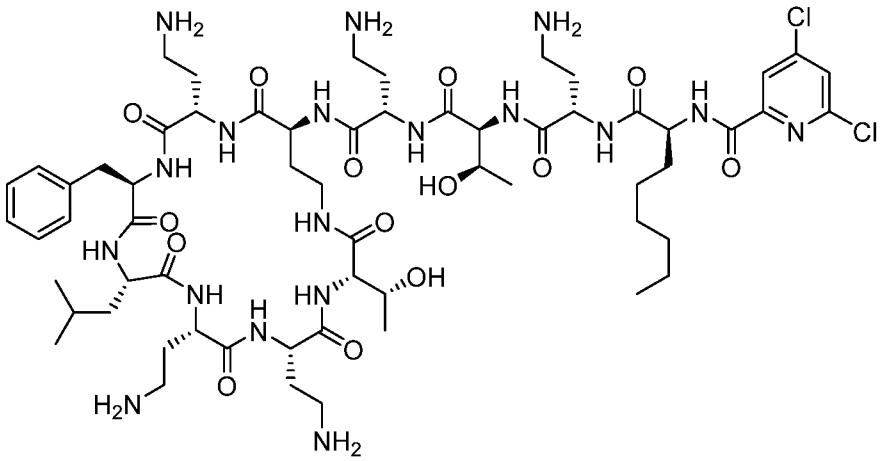


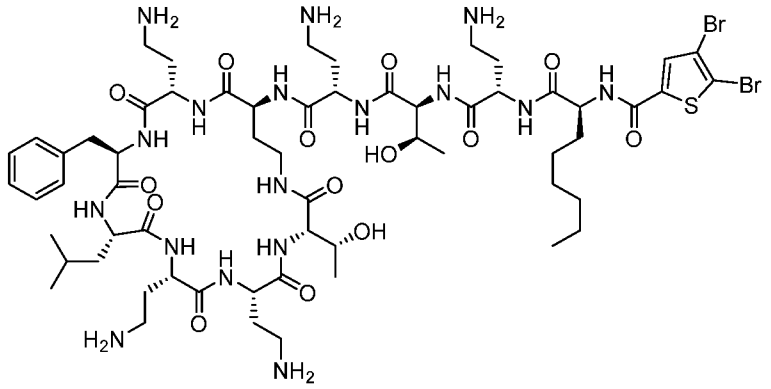
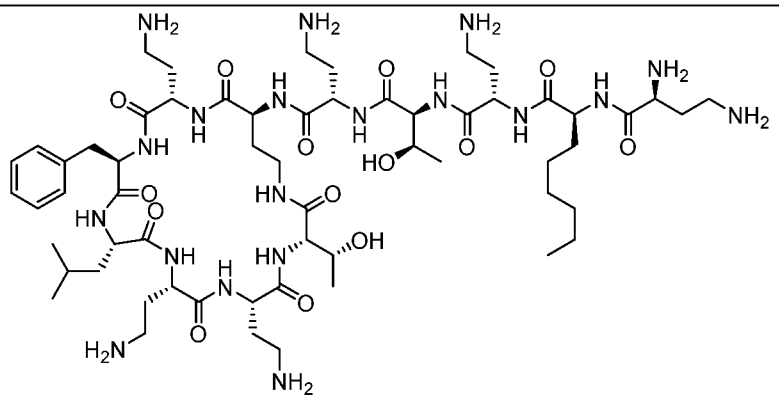
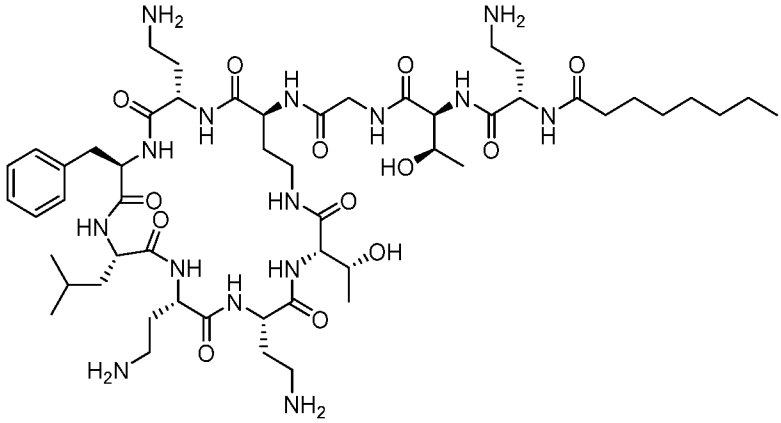
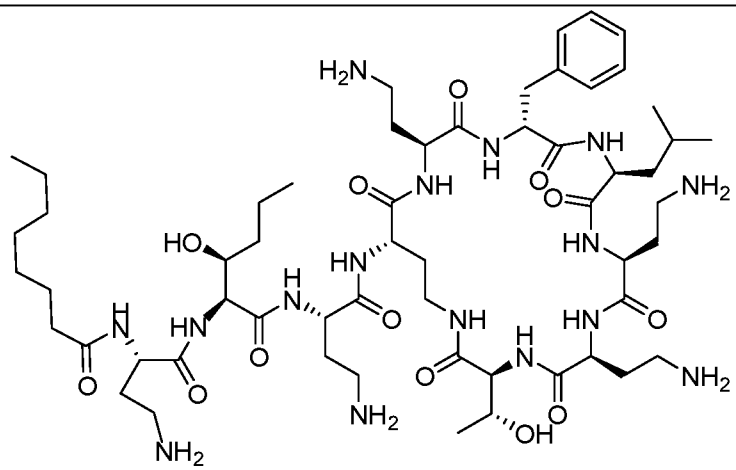
In some embodiments of any of the aspects described herein (e.g., in some embodiments of any of formulas (I)-(XXXXI)), R^{16} is an optionally substituted thiazolyl, for example, an optionally substituted

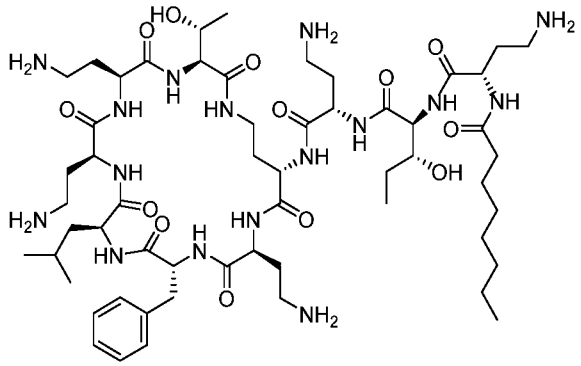
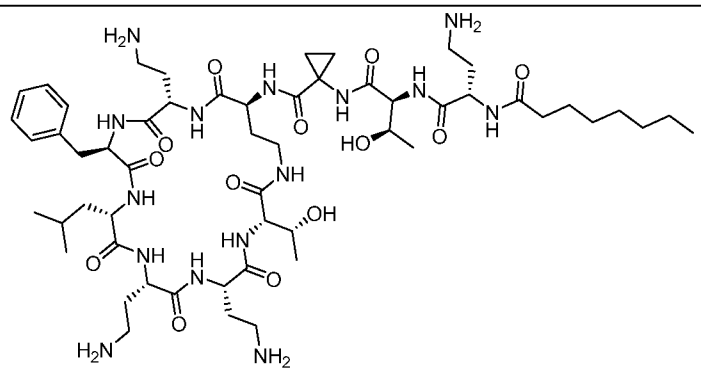
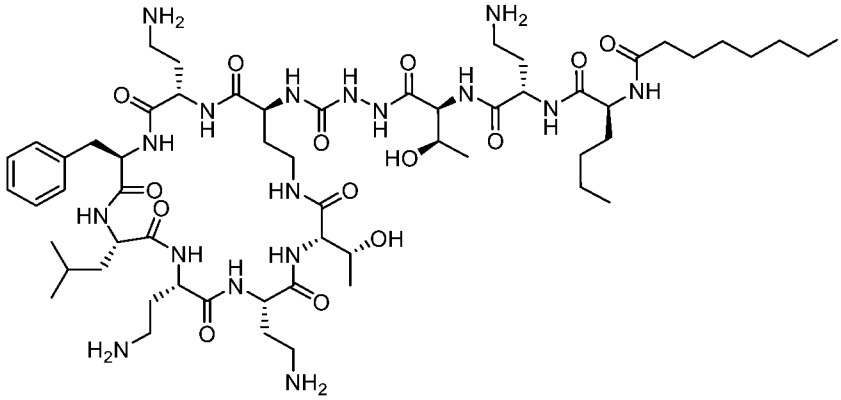
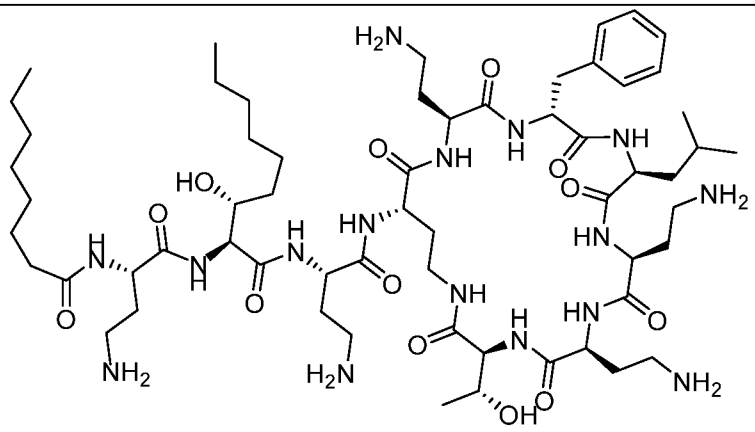
thiazolyl having the structure , wherein R^{23} and R^{24} are each, independently selected from H, amino, hydroxyl, halo (e.g., Cl, Br, or F), C1-C8 alkyl (e.g., methyl, ethyl, or propyl), C2-C8 alkamino, C2-C8 alkenyl, or C2-C8 alkynyl.

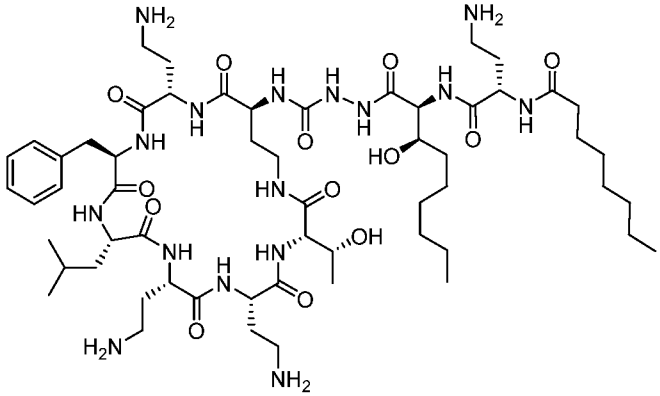
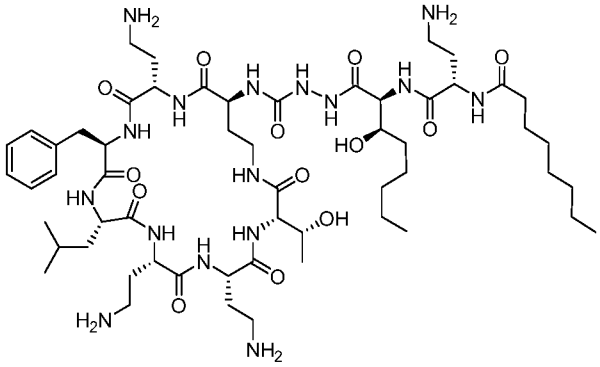
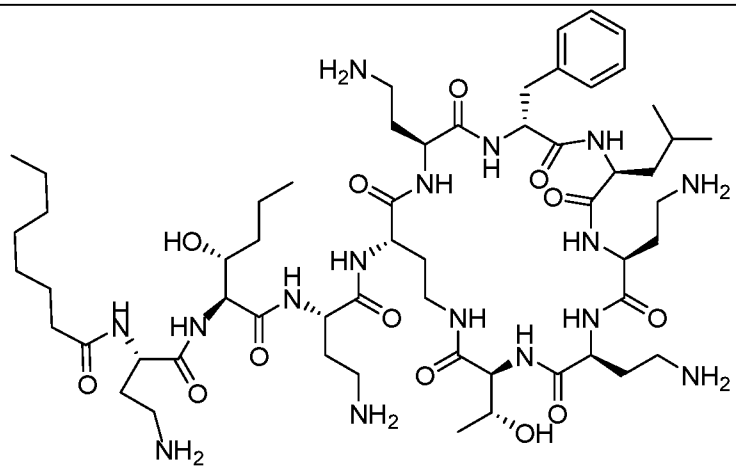
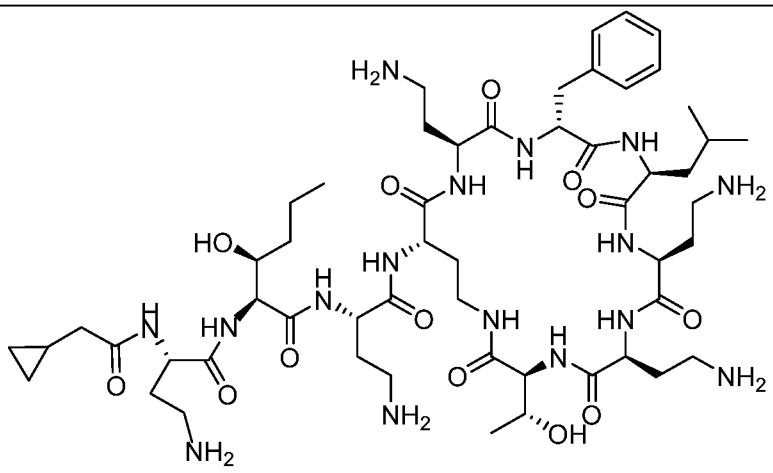
In another aspect, the invention includes a compound of Table 1, or a pharmaceutically acceptable salt thereof.

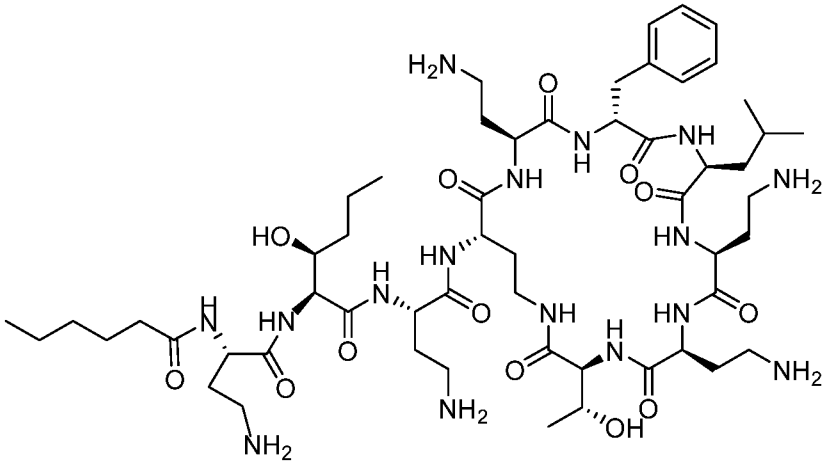
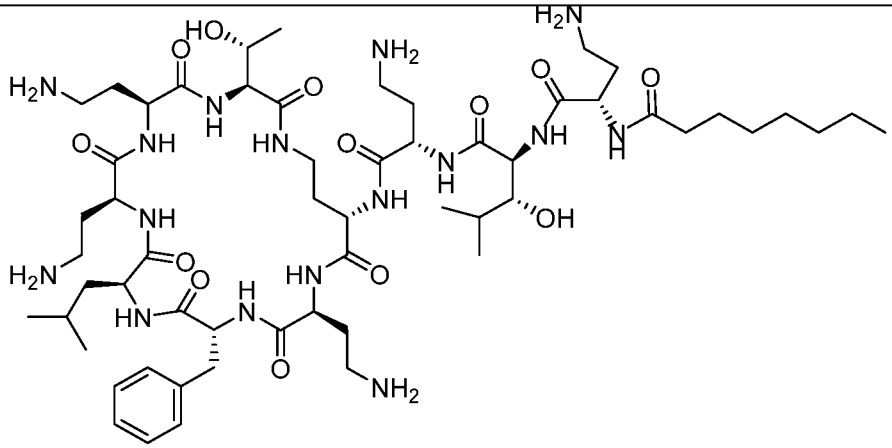
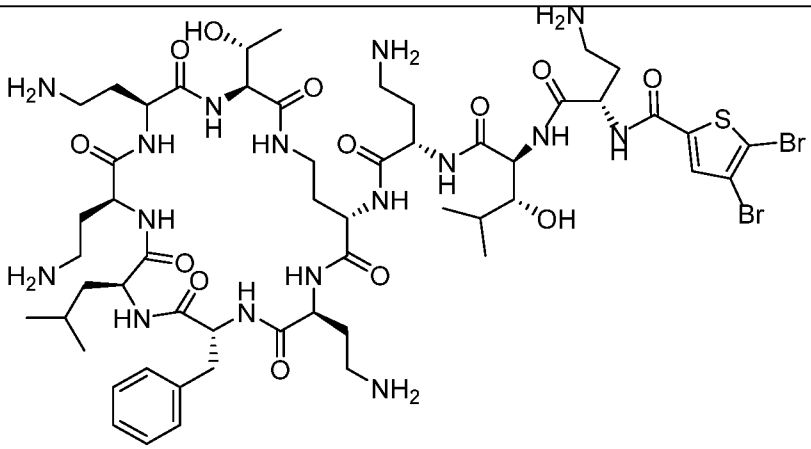
Table 1.

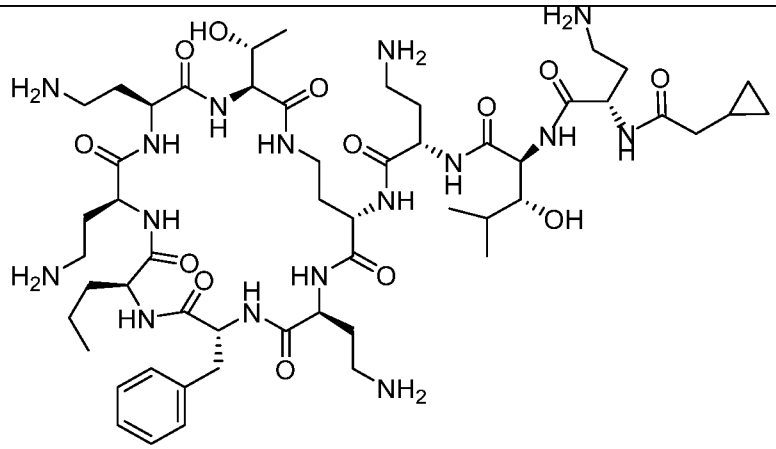
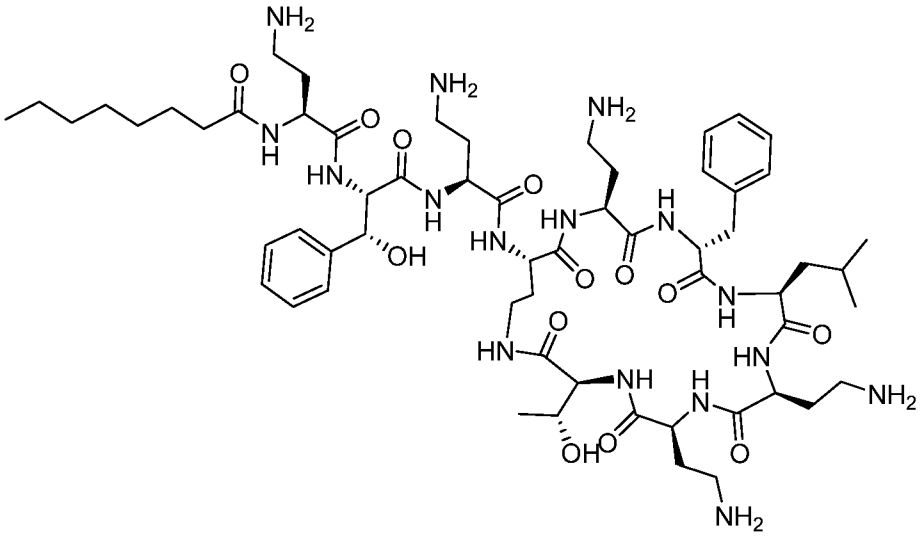
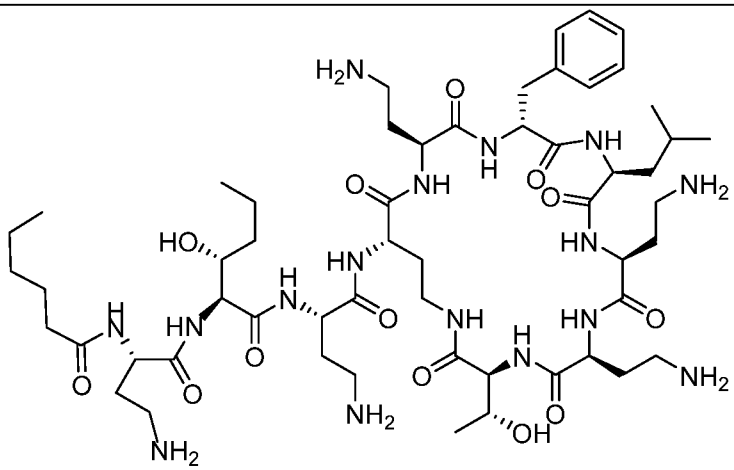
Compound No.	Structure
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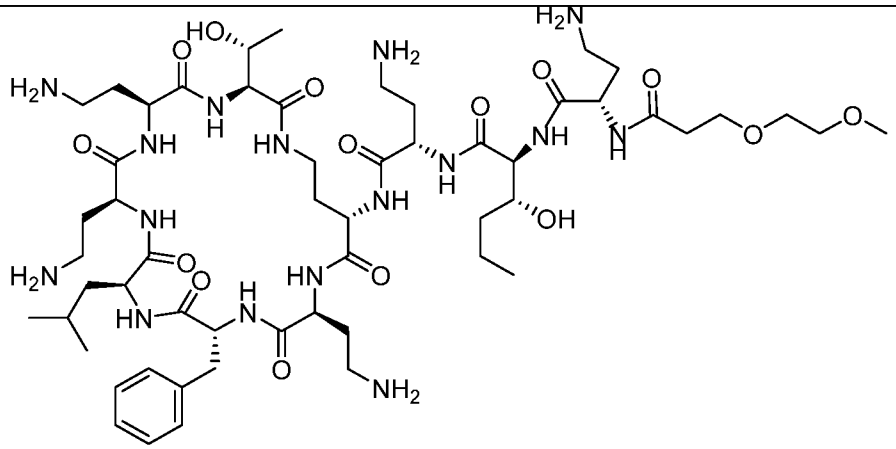
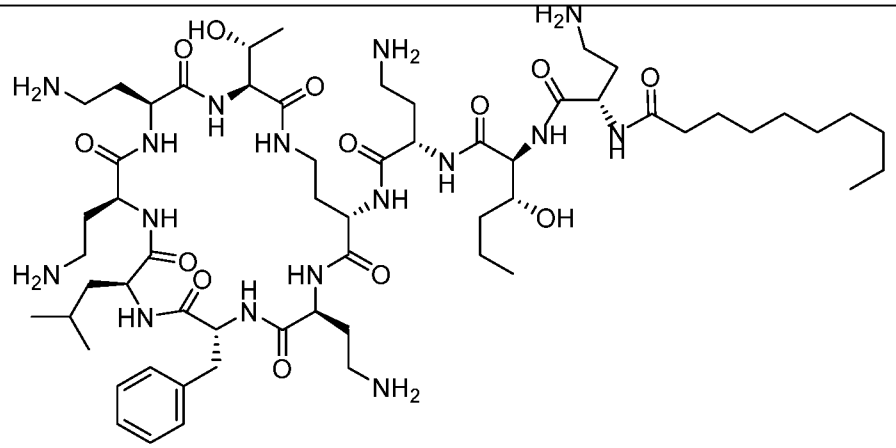
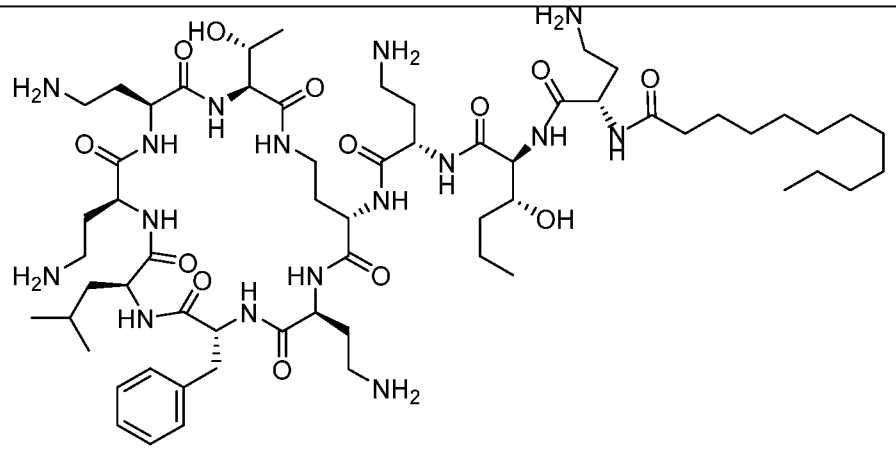
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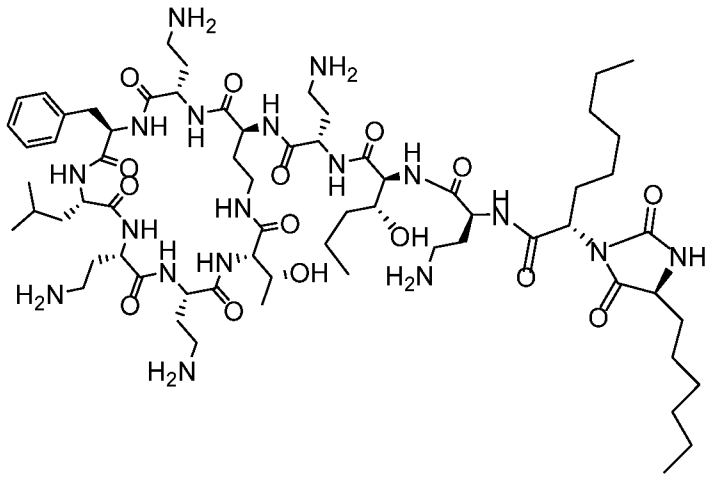
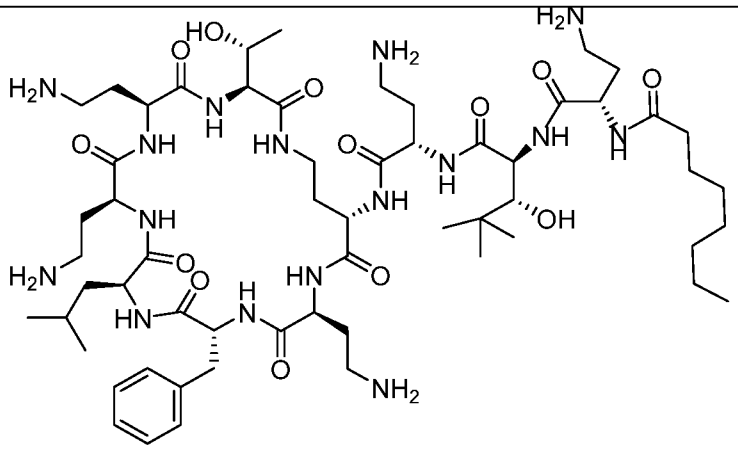
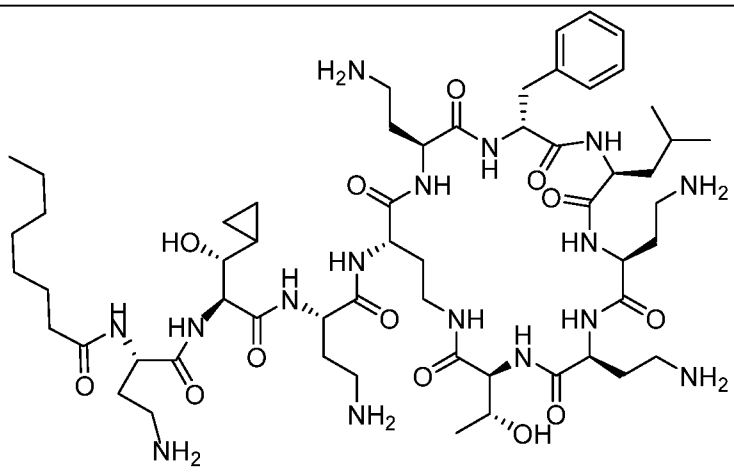
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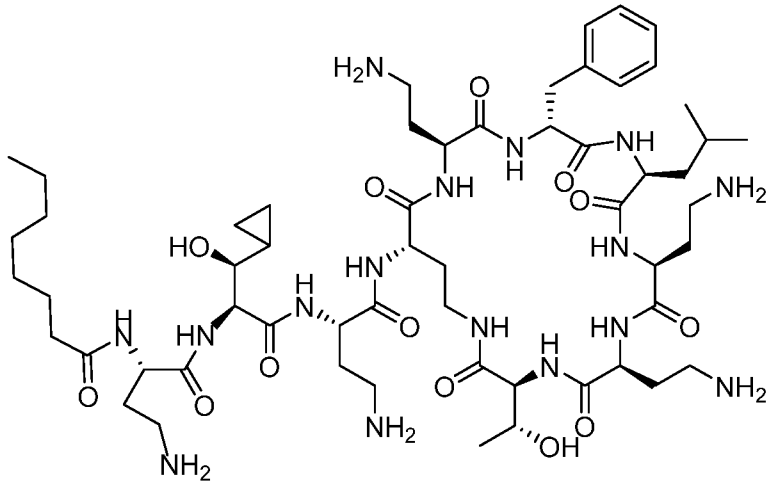
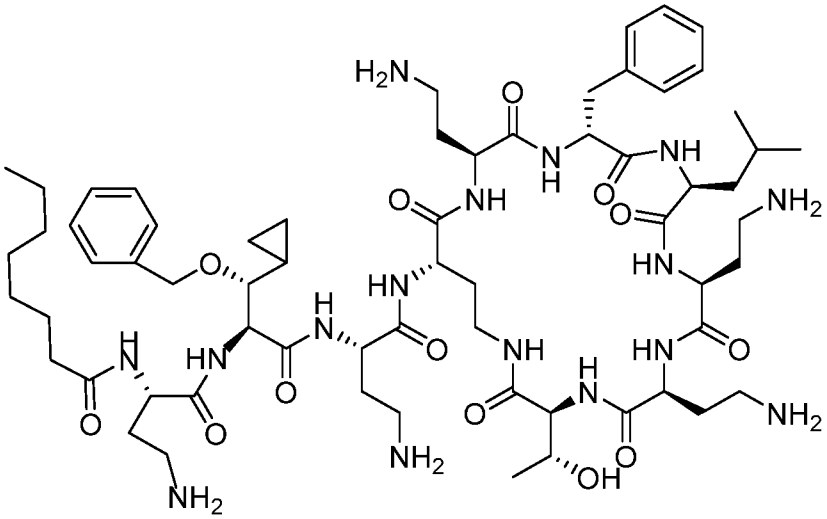
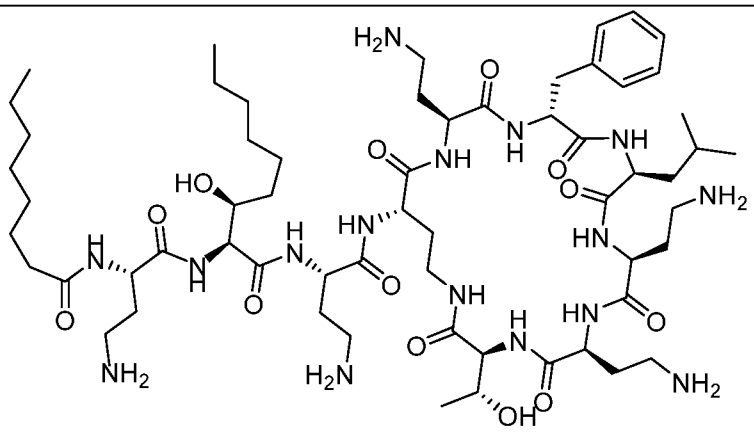
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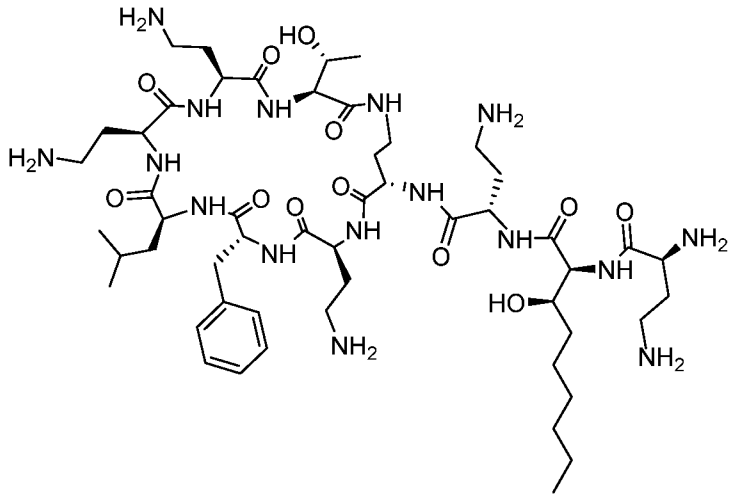
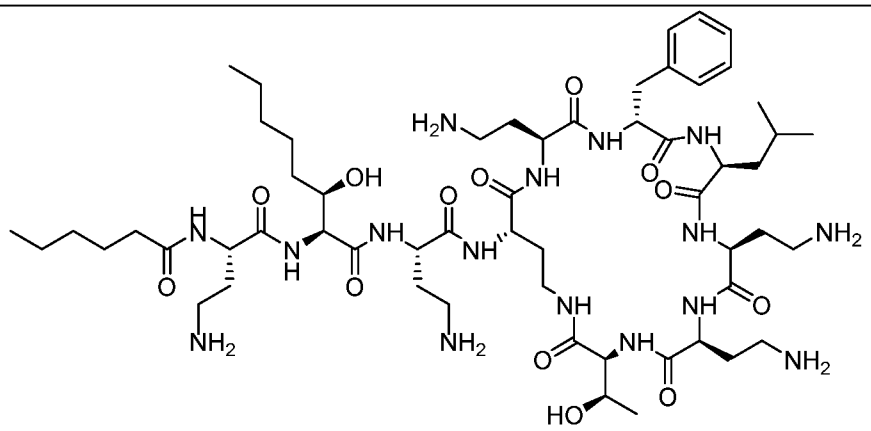
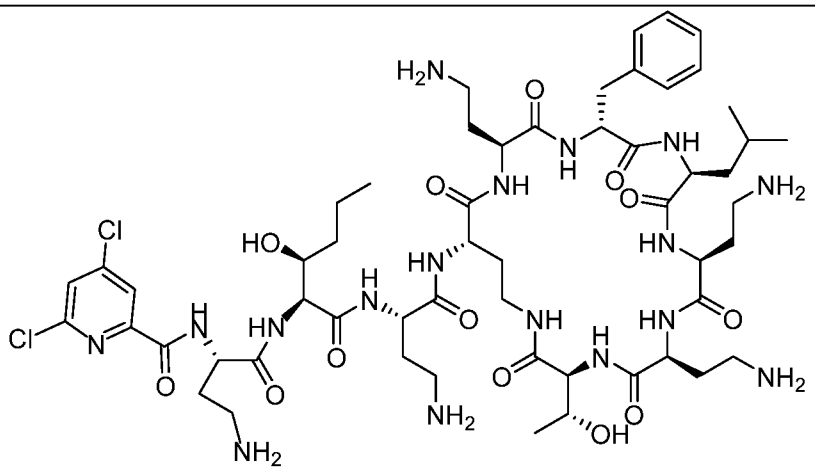
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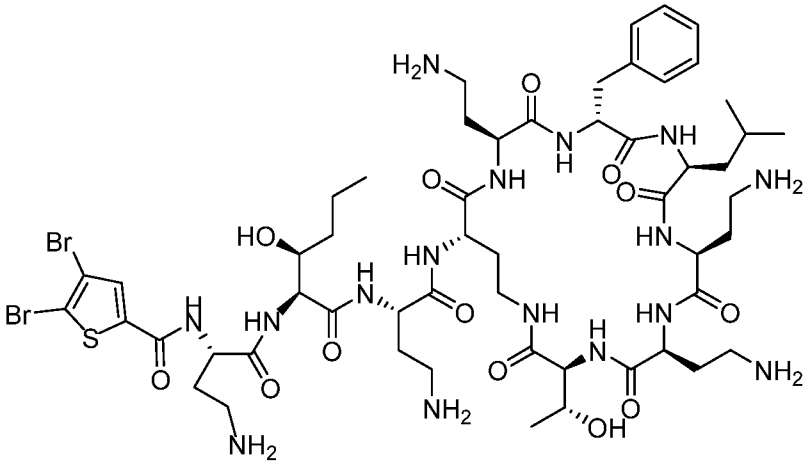
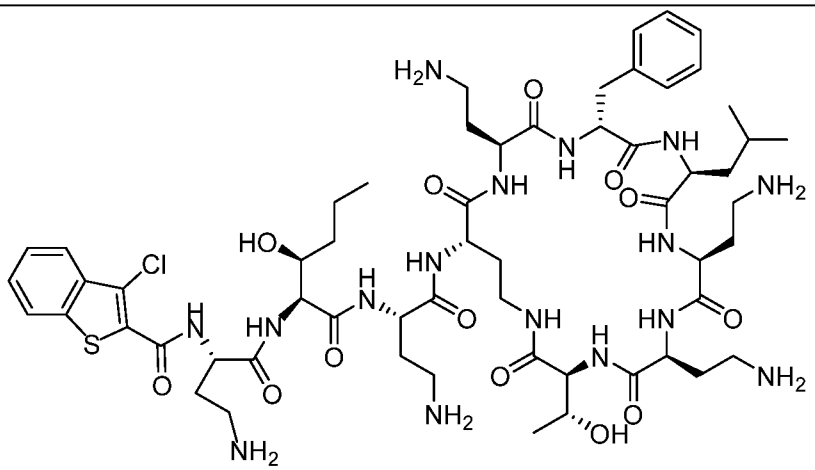
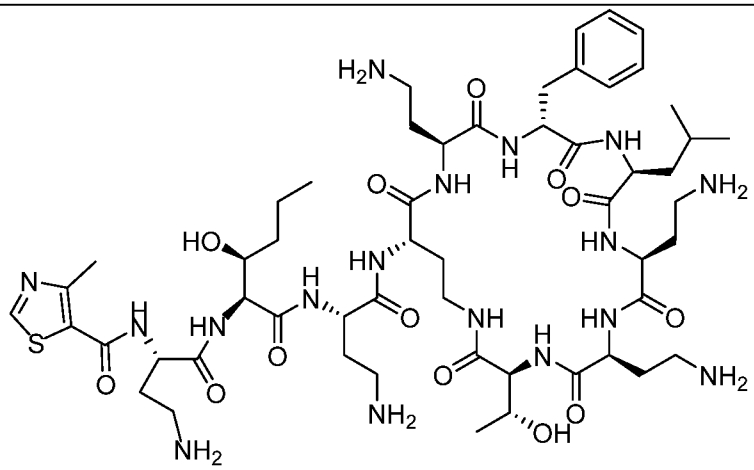
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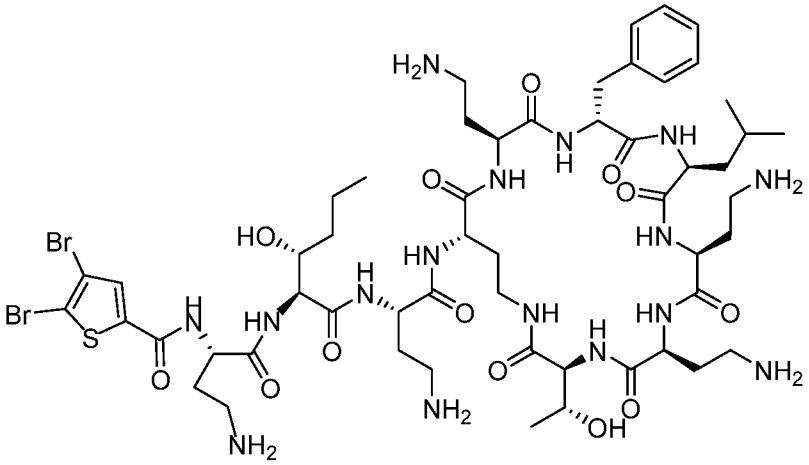
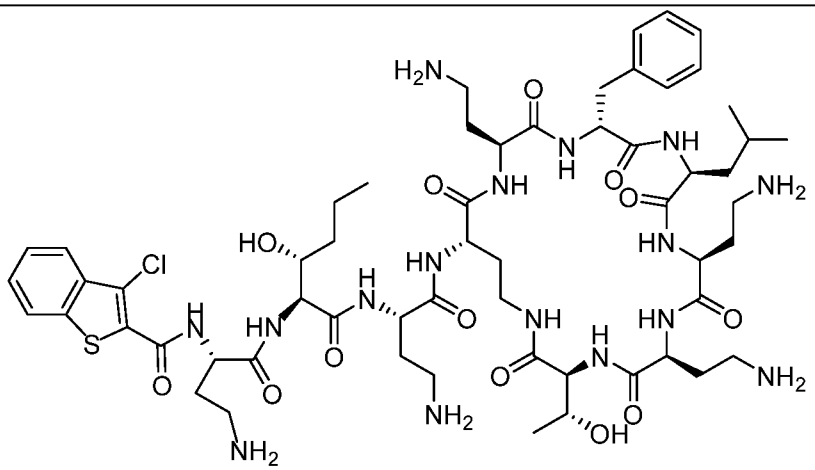
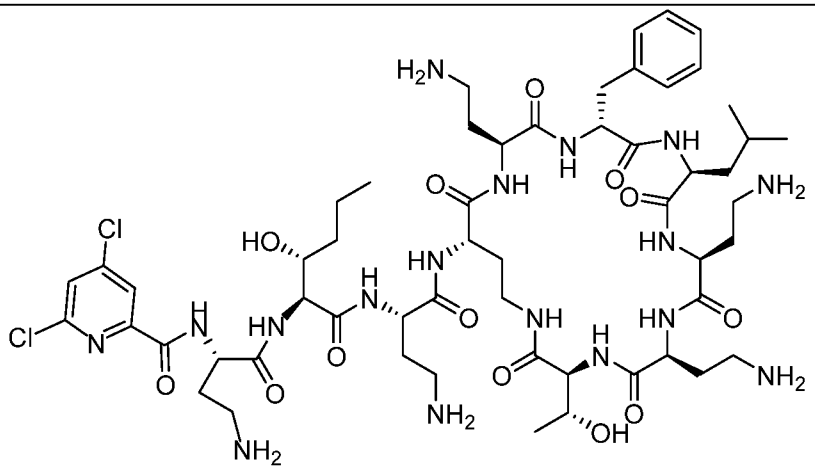
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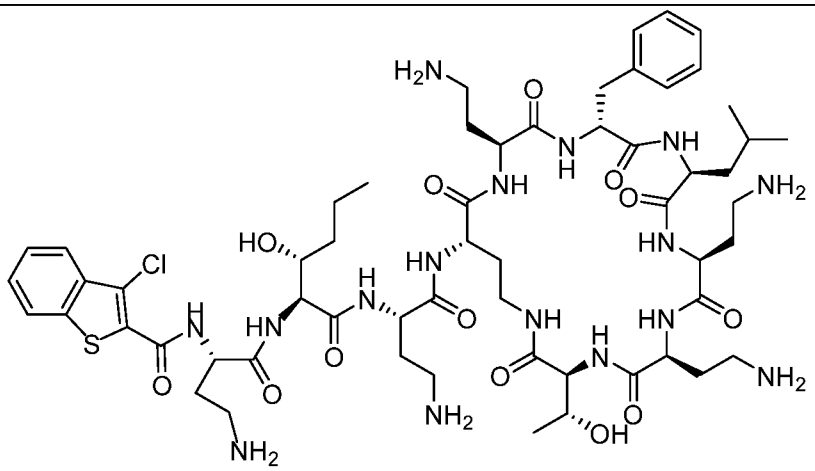
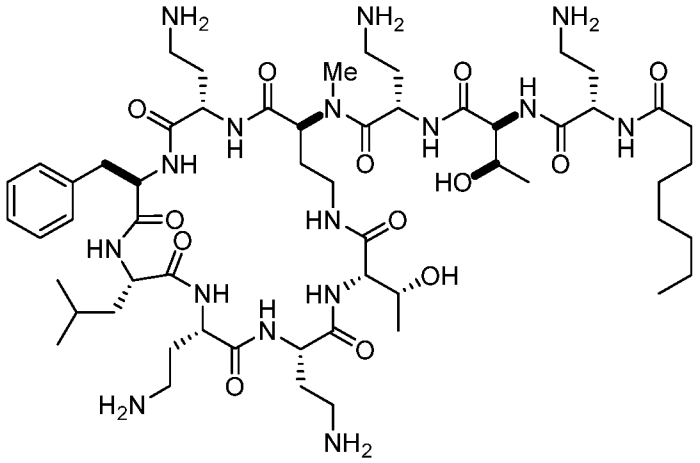
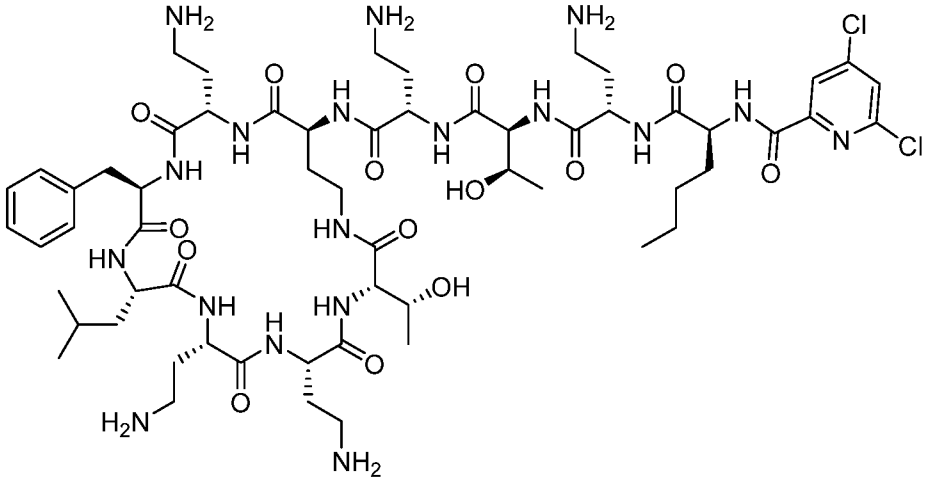
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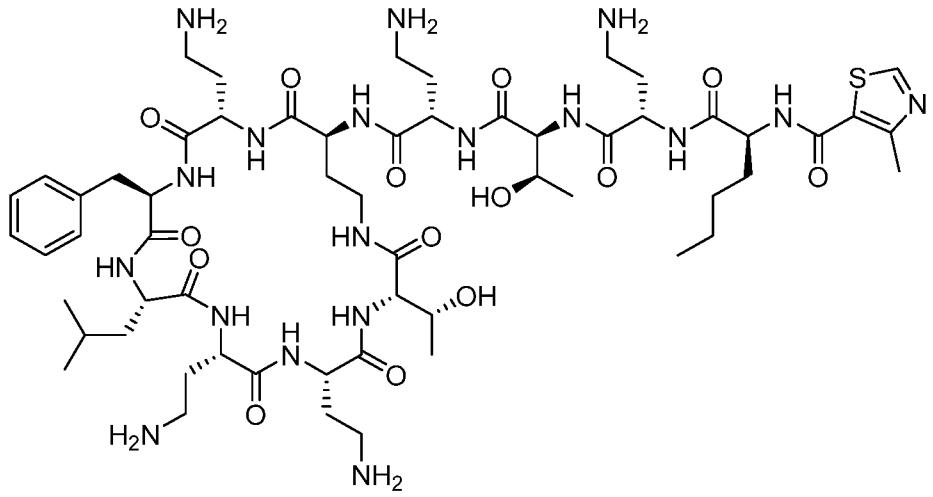
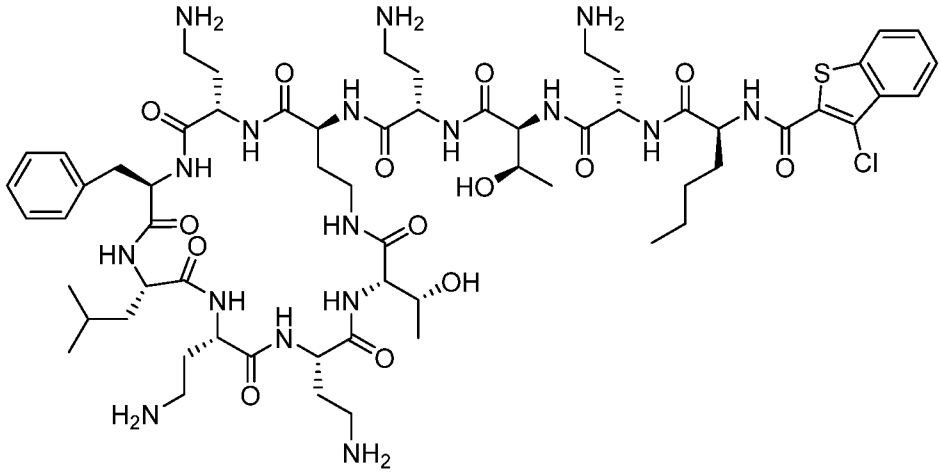
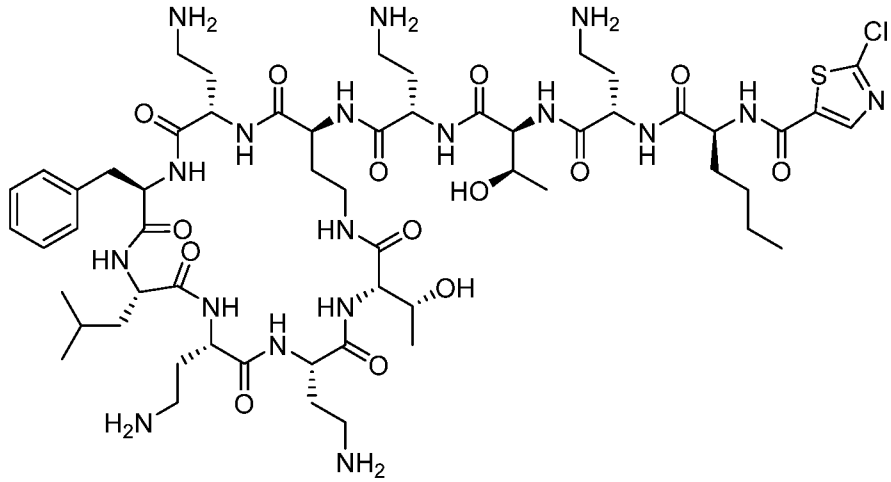
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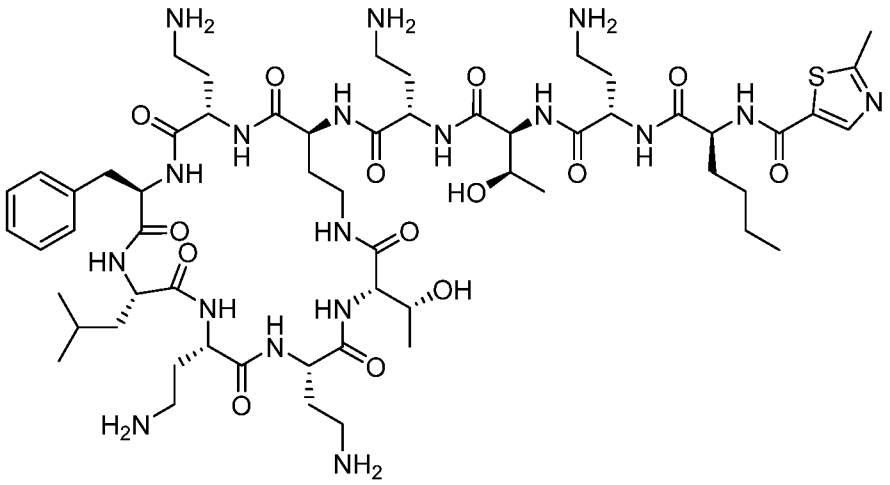
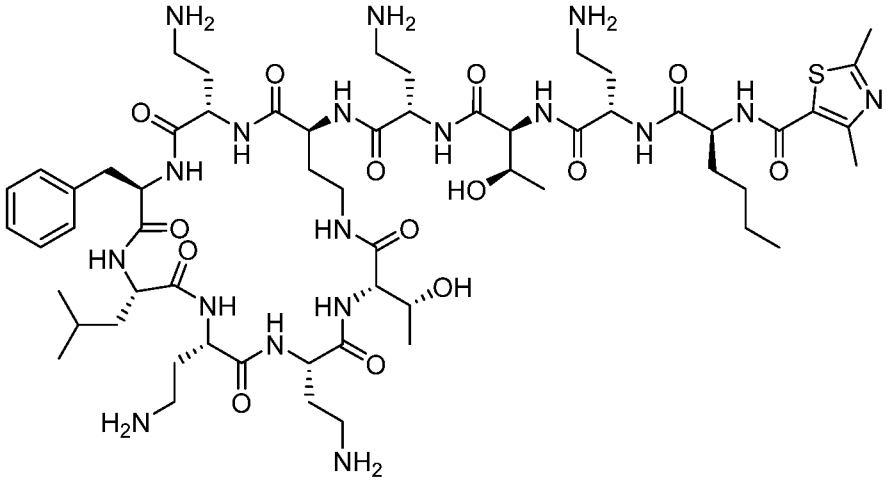
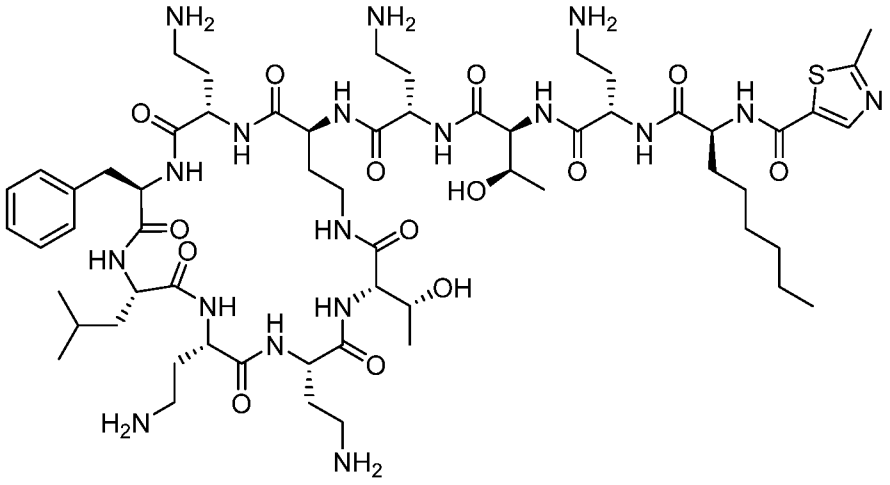
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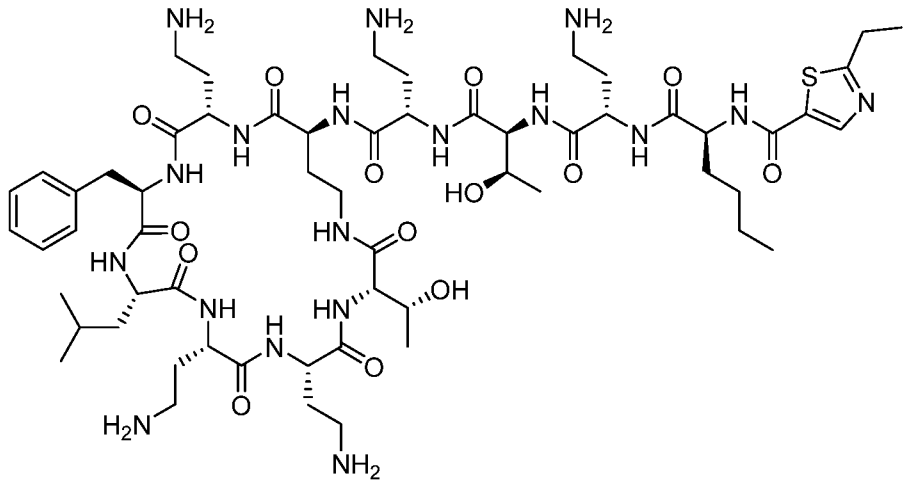
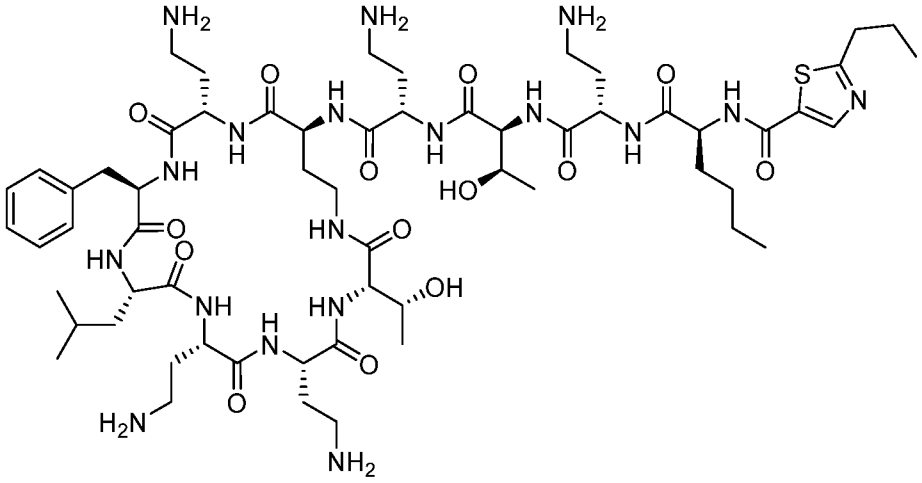
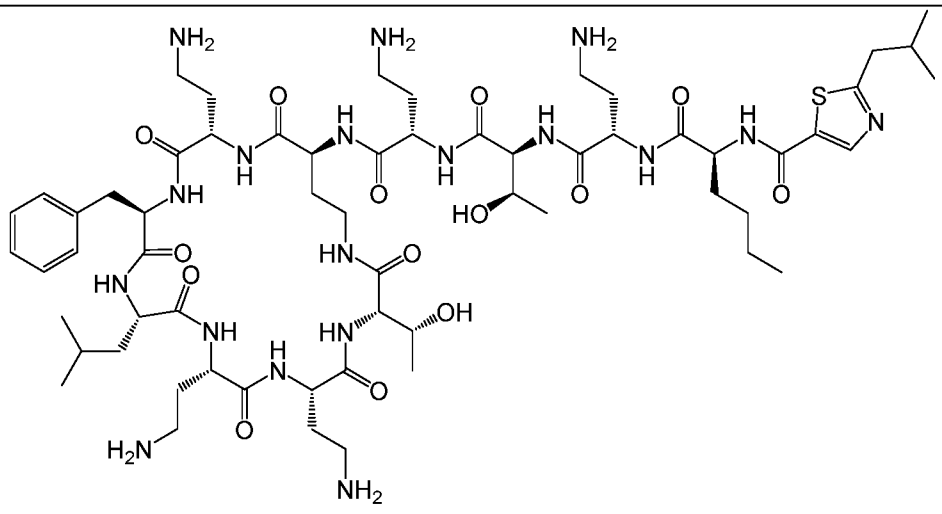
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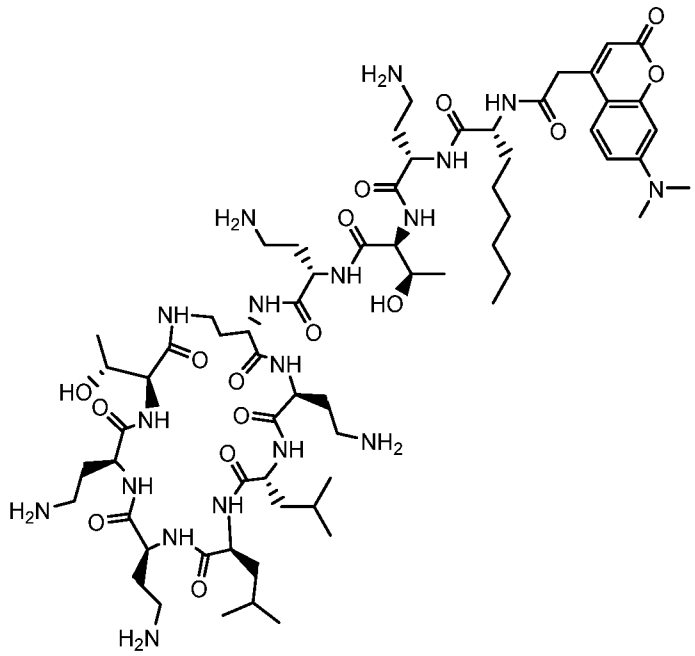
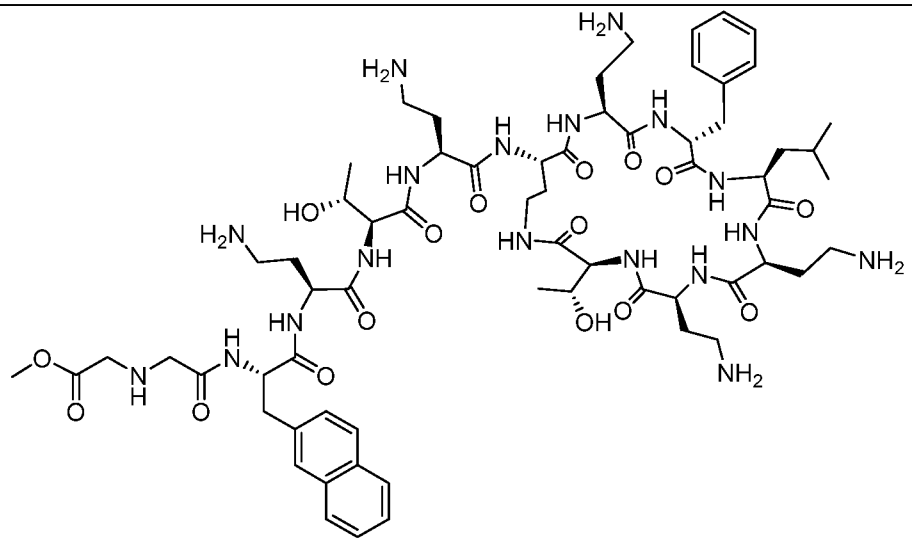
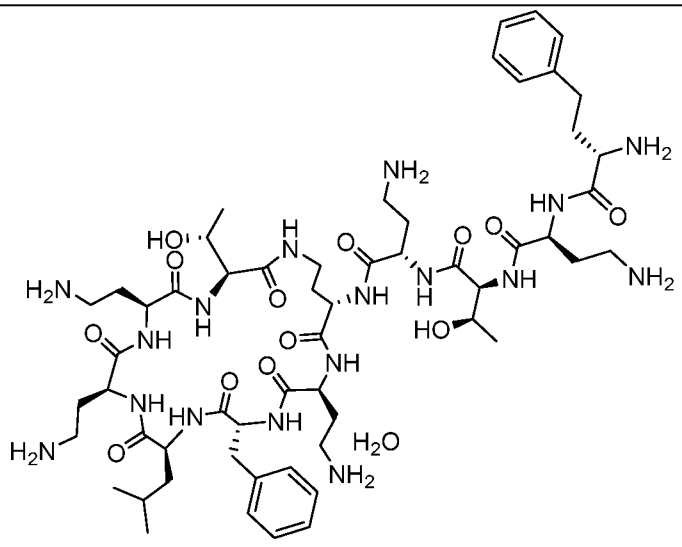
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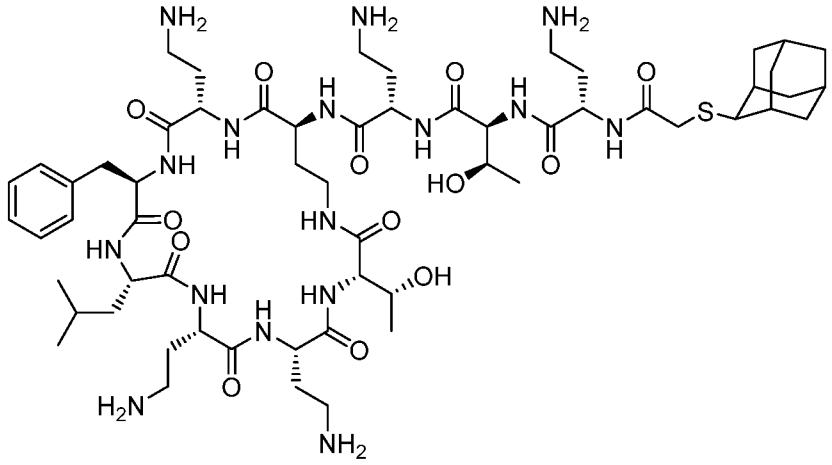
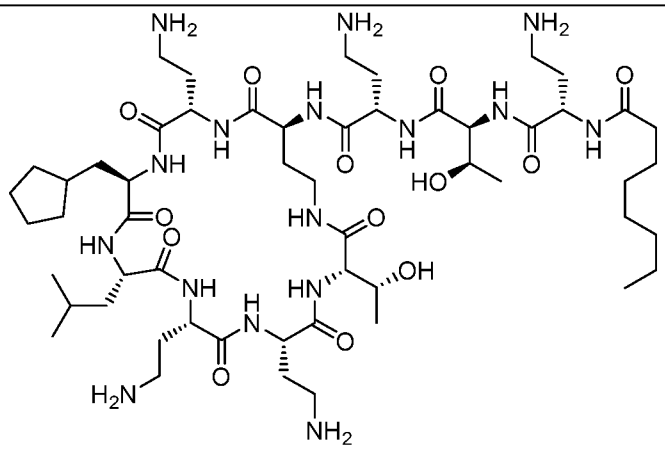
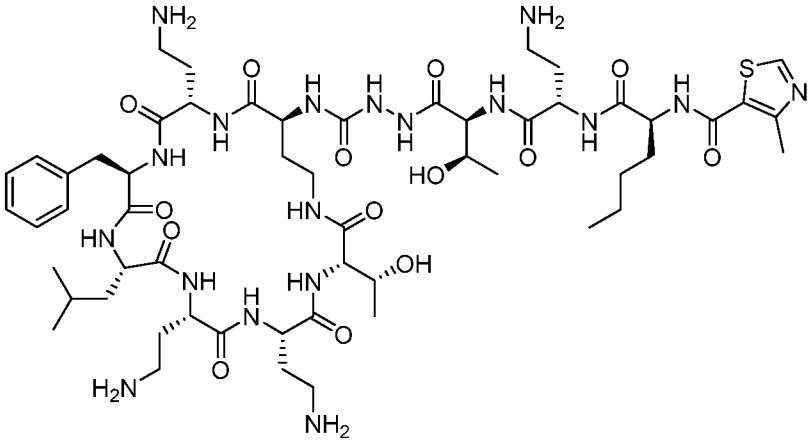
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In some embodiments of any of the aspects described herein, a compound of the invention includes a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1, where if a is 1 and b, c, and d are each 0, then the R^{16} is directly attached (e.g., by a covalent bond) to N^1 (e.g., there is no carbonyl between R^{16} and N^1). In some embodiments, R^{16} and R^4 are H.

In some embodiments of any of the aspects described herein, a compound of the invention includes a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1, where if a and b are each 1, and c and d are each 0, then the R^{16} is directly attached (e.g., by a covalent bond) to N^2 (e.g., there is no carbonyl between R^{16} and N^2). In some embodiments, R^{16} and R^7 are H.

In some embodiments of any of the aspects described herein, a compound of the invention includes a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1, where if a, b, and c are each 1, and d is 0, then the R^{16} is directly attached (e.g., by a covalent bond) to N^3 (e.g., there is no carbonyl between R^{16} and N^3). In some embodiments, R^{16} and R^{10} are H.

In some embodiments of any of the aspects described herein, a compound of the invention includes a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1, where if a, b, c, and d are each 1, then the R^{16} is directly attached (e.g., by a covalent bond) to N^5 (e.g., there is no carbonyl between R^{16} and N^5). In some embodiments, R^{16} and R^{21} are H.

In another aspect, the invention features a pharmaceutical composition including a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition further includes an antibacterial agent. In some embodiments, the antibacterial agent is selected from the group consisting of linezolid, tedizolid, posizolid, radezolid, retapamulin, valnemulin, tiamulin, azamulin, lefamulin, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin g, penicillin v, piperacillin, penicillin g, temocillin, ticarcillin, amoxicillin clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (tmp-smx), sulfonamidochrysoidine, eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone, capreomycin, cycloserine, ethambutol(bs), ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole, and trimethoprim, prodrugs thereof, and pharmaceutically acceptable salts thereof. In some embodiments, a prodrug of tedizolid is tedizolid phosphate. In some embodiments, the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, levofloxacin, rifampicin, linezolid, erythromycin, or solithromycin. In some embodiments, the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, or levofloxacin.

In another aspect, the invention features a method of protecting against or treating a bacterial infection in a subject including administering to said subject a compound of any of aspects described

herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). In some embodiments, the method further includes administering to the subject an antibacterial agent.

In another aspect, the invention features a method of protecting against or treating a bacterial infection in a subject including administering to said subject (1) a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and (2) an antibacterial agent.

In another aspect, the invention features a method of inducing immune cell activation of the immune response in a subject having a bacterial infection including administering to said subject a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). In some embodiments, the method further includes administering to the subject an antibacterial agent.

In another aspect, the invention features a method of inducing immune cell activation of the immune response in a subject having a bacterial infection, said method including administering to said subject (1) a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and (2) an antibacterial agent.

In some embodiments, a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and a antibacterial agent are administered substantially simultaneously. In other embodiments, the compound and the antibacterial agent are administered separately. In further embodiments, the compound is administered first, followed by administering of the antibacterial agent alone. In further embodiments, the antibacterial agent is administered first, followed by administering of the compound alone.

In some embodiments, a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and an antibacterial agent are administered substantially simultaneously, followed by administering of the compound or the antibacterial agent alone. In some embodiments, the compound or the antibacterial agent is administered first, followed by administering of the compound and the antibacterial agent substantially simultaneously.

In some embodiments, administration of a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and an antibacterial agent together lowers the MIC of each of the compound and the antibacterial agent relative to the MIC of each of the compound and the antibacterial agent when each is used alone.

In some embodiments, the compound (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and/or the antibacterial agent is administered intramuscularly, intravenously, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally, locally, by inhalation, by injection, or by infusion.

In another aspect, the invention features a method of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria including contacting the bacteria or a site susceptible to bacterial growth with a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-

(XXXXI) or a compound of Table 1). In some embodiments, the method further includes contacting the bacteria or the site susceptible to bacterial growth with an antibacterial agent.

In another aspect, the invention features a method of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria, including contacting the bacteria or a site susceptible to bacterial growth with (1) a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and (2) an antibacterial agent.

In some embodiments, the antibacterial agent is selected from the group consisting of linezolid, tedizolid, posizolid, radezolid, retapamulin, valnemulin, tiamulin, azamulin, lefamulin, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin g, penicillin v, piperacillin, penicillin g, temocillin, ticarcillin, amoxicillin clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (tmp-smx), sulfonamidochrysoidine, eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone, capreomycin, cycloserine, ethambutol(bs), ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole, and trimethoprim, prodrugs thereof, and pharmaceutically acceptable salts thereof.

In some embodiments, a prodrug of tedizolid is tedizolid phosphate. In some embodiments, the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, levofloxacin, rifampicin, linezolid, erythromycin, or solithromycin. In some embodiments, the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, or levofloxacin.

In some embodiments, the bacterial infection is caused by Gram-negative bacteria. In other embodiments, the bacterial infection is caused by a resistant strain of bacteria. In some embodiments, the resistant strain of bacteria possesses the *mcr-1* gene, the *mcr-2* gene, and/or a chromosomal mutation conferring polymyxin resistance. In some embodiments, the resistant strain of bacteria possesses the *mcr-1* gene. In some embodiments, the resistant strain of bacteria possesses the *mcr-2* gene. In some embodiments, the resistant strain of bacteria possesses a chromosomal mutation conferring polymyxin resistance. In some embodiments, the resistant strain of bacteria is a resistant strain of *E. coli*.

In another aspect, the invention features a method of preventing lipopolysaccharides (LPS) in Gram-negative bacteria from activating an immune system in a subject, including administering to the subject a compound of any of aspects described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). In some embodiments, the method prevents LPS from activating a macrophage. In some embodiments, the method prevents LPS-induced nitric oxide production from a macrophage.

Definitions

The term "cyclic heptapeptide" or "cycloheptapeptide," as used herein, refers to certain compounds that bind to lipopolysaccharides (LPS) in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization to other antibiotics. Cyclic heptapeptides or cycloheptapeptides comprise seven natural or non-natural α-amino acid residues, such as D- or L-amino acid residues, in a closed ring. Generally, cyclic heptapeptides are formed by linking the α-carboxyl group of one amino acid to the α-amino group or the γ-amino group of another amino acid and cyclizing. The cyclic heptapeptide comprises a heterocycle comprising carbon and nitrogen ring members, which may be substituted, for example, with amino acid side chains. One nitrogen from an α-amino group in the cyclic heptapeptide, however, is not a ring member and is branched from a ring member of the heterocycle. Thus, this nitrogen is directly attached to a ring member, such as a carbon atom (e.g., an α-carbon atom). This nitrogen atom serves as an attachment point for the cyclic heptapeptide to a peptide (e.g., a linear peptide including 1-5 amino acid residue(s)), and thus is referred to herein as a "linking nitrogen." The linking nitrogen is directly attached to the ring of the cyclic heptapeptide and is not derived from a side chain, such as an ethylamine side chain. The linking nitrogen in a compound of, e.g., any one of formulas (I)-(XXXXI), is N^4.

In some embodiments, a peptide including one or more (e.g., 1-5; 1, 2, 3, 4, or 5) amino acid residues (e.g., natural and/or non-natural amino acid residues) may be covalently attached to a linking nitrogen (e.g., N^4, the nitrogen from an α-amino group) in the cyclic heptapeptide ring. Cyclic heptapeptides may be derived from polymyxins (e.g., naturally existing polymyxins and non-natural polymyxins) and/or octapeptins (e.g., naturally existing octapeptins and non-natural octapeptins). Examples of naturally existing polymyxins include, but are not limited to, polymyxin B_1, polymyxin B_2, polymyxin B_3, polymyxin B_4, polymyxin B_5, polymyxin B_6, polymyxin B_1-Ile, polymyxin B_2-Ile, polymyxin C_1, polymyxin C_2, polymyxin S_1, polymyxin T_1, polymyxin T_2, polymyxin A_1, polymyxin A_2, polymyxin D_1, polymyxin D_2, polymyxin E_1 (colistin A), polymyxin E_2 (colistin B), polymyxin E_3, polymyxin E_4, polymyxin E_7, polymyxin E_1-Ile, polymyxin E_1-Val, polymyxin E_1-Nva, polymyxin E_2-Ile, polymyxin E_2-Val, polymyxin E_2-Nva, polymyxin E_8-Ile, polymyxin M_1, and polymyxin M_2. In other embodiments, a cyclic heptapeptide may be entirely synthetic and prepared by standard peptide methodology as known in the art.

The term "covalently attached" refers to two parts of a compound that are linked to each other by a covalent bond formed between two atoms in the two parts of the compound. For example, in the compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI)), when a is 0, b is covalently attached to N^4, which means that when a is 0, an atom in b forms a covalent bond with N^4 in

the compound. Similarly, when a is 1 and b is 0, c is covalently attached to N^1; when b is 1, and c is 0, d is covalently attached to b; and when c is 1 and d is 0, $R^{16}C(O)$ is covalently attached to c.

The term "lipophilic moiety," as used herein, refers to a portion, substituent, or functional group of a compound that is, in general, hydrophobic and non-polar. A moiety is lipophilic if it has a hydrophobicity determined using a cLogP value of greater than 0, such as about 0.25 or greater, about 0.5 or greater, about 1 or greater, about 2 or greater, 0.25-5, 0.5-4 or 2-3. As used herein, the term "cLogP" refers to the calculated partition coefficient of a molecule or portion of a molecule. The partition coefficient is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium (e.g., octanol and water) and measures the hydrophobicity or hydrophilicity of a compound. A variety of methods are available in the art for determining cLogP. For example, in some embodiments, cLogP can be determined using quantitative structure-property relationship algorithims known in the art (e.g., using fragment based prediction methods that predict the logP of a compound by determining the sum of its non-overlapping molecular fragments). Several algorithims for calculating cLogP are known in the art including those used by molecular editing software such as CHEMDRAW® Pro, Version 12.0.2.1092 (Camrbridgesoft, Cambridge, MA) and MARVINSKETCH® (ChemAxon, Budapest, Hungary). A moiety is considered lipophilic if it has a cLogP value described above in at least one of the above methods. A lipophilic moiety having the stated cLogP value will be considered lipophilic, even though it may have a positive charge or a polar substituent.

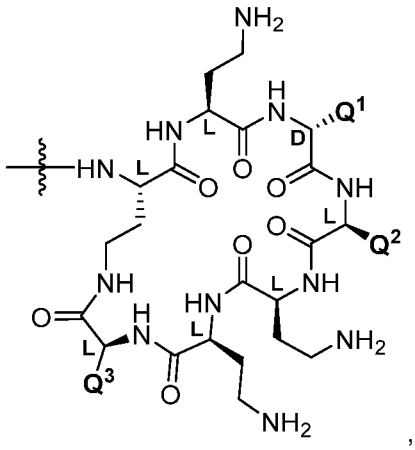
In some embodiments, a lipophilic moiety contains entirely hydrocarbons. In some embodiments, a lipophilic moiety may contain one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms independently selected from N, O, and S (e.g., an indolyl), or one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, halo groups, which, due to the structure of the moiety and/or small differences in electronegativity between the heteroatoms or halo groups and the hydrocarbons, do not induce significant chemical polarity into the lipophilic moiety. Thus, in some embodiments, a lipophilic moiety having, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms and/or, e.g., 1-4, 1-3, 1, 2, 3, or 4, halo atoms may still be considered non-polar. In some embodiments, a lipophilic moiety may be optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heteroalkenyl, optionally substituted heteroalkynyl, or optionally substituted heteroaryl, or halo forms thereof, wherein the optional substituents are also lipophilic (such as alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, or heteroaryl) or are not lipophilic but do not change the overall lipophilic character of the moiety, i.e., the moiety has a cLogP value of greater than 0. For example, octanol contains a polar group, OH, but is still a lipophilic moiety. In some embodiments, a lipophilic moiety may be benzyl, isobutyl, sec-butyl, isopropyl, n-propyl, methyl, biphenylmethyl, n-octyl, or substituted indolyl (e.g., alkyl substituted indolyl). In some embodiments, a lipophilic moiety may be the side chain of a hydrophobic amino acid residue, e.g., leucine, isoleucine, alanine, phenylalanine, valine, and proline, or groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and pyrrolidinyl. In some embodiments, lipophilic moieties of the compounds described herein may interact with the hydrophobic portions of lipid A (e.g., fatty acid side chains of lipid A) when the compounds bind to the membrane of bacterial cells (e.g., Gram-negative bacterial cells). Due to its position on the cyclic heptapeptide, one or more of R^1, R^{12}, and R^{15}may be a lipophilic moiety.

The term "positively charged moiety," as used herein, refers to a portion, substituent, or functional group of a compound that contains at least one positive charge. In some embodiments, a positively charged moiety contains one or more (e.g., 1-4, 1-3, 1, 2, 3, or 4) heteroatoms independently selected from N, O, and S, for example. In some embodiments, a positively charged moiety may possess a pH-dependent positive charge, e.g., the moiety becomes a positively charged moiety at physiological pH (e.g., pH 7), such as $-NH_3^+$, $-(CH_2)_4NH_2$, $-(CH_2)_3NH_2$, $-(CH_2)_2NH_2$, $-CH_2NH_2$, $-(CH_2)_4N(CH_3)_2$, $-(CH_2)_3N(CH_3)_2$, $-(CH_2)_2N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-(CH_2)_4NH(CH_3)$, $-(CH_2)_3NH(CH_3)$,$-(CH_2)_2NH(CH_3)$, and $-CH_2NH(CH_3)$. In some embodiments, a positively charged moiety may be optionally substituted alkamino, optionally substituted heteroalkyl (e.g., optionally substituted heteroalkyl containing 1-3 nitrogens; $-(CH_2)_4$-guanidinium, $-(CH_2)_3$-guanidinium, $-(CH_2)_2$-guanidinium, $-CH_2$-guanidinium), optionally substituted heterocycloalkyl (e.g., optionally substituted heterocycloalkyl containing 1-3 nitrogens), or optionally substituted heteroaryl (e.g., optionally substituted heteroaryl containing 1-3 nitrogens; $-(CH_2)_4$-imidazole, $-(CH_2)_3$-imidazole, $-(CH_2)_2$-imidazole, $-CH_2$-imidazole). In some embodiments, a positively charged moiety may be pH independent such as $-CH_2N(CH_3)_3^+$, $-(CH_2)_2N(CH_3)_3^+$, $-(CH_2)_3N(CH_3)_3^+$, or $-(CH_2)_4N(CH_3)_3^+$. Thus, substituents may transform an otherwise lipophilic moiety such as optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heteroalkenyl, optionally substituted heteroalkynyl, or optionally substituted heteroaryl, or halo forms thereof, to a positively charged moiety with the addition of a substituent that imparts a positive charge or a pH dependent positive charge, such as guanidinyl, $-NH_3^+$, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, and/or $-N(CH_3)_3^+$. In some embodiments, a positively charged moiety may be the side chain of an amino acid residue (e.g., a natural or non-natural amino acid residue, such as a D- or L-amino acid residue, that is positively charged at physiological pH (e.g., pH 7), such as the side chain of a basic amino acid residue (e.g., arginine, lysine, histidine, ornithine, diaminobuteric acid, or diaminopropionic acid). In some embodiments, positively charged moieties of the compounds described herein interact with the negatively charged portions of lipid A (e.g., phosphates of lipid A) when the compounds bind to the membrane of bacterial cells (e.g., Gram-negative bacterial cells). Due to its position on the cyclic heptapeptide, one or more of R^{11}, R^{13}, and R^{14} may be a positively charged moiety.

The term "polar moiety," as used herein, refers to a portion, substituent, or functional group of a compound that has a chemical polarity induced by atoms with different electronegativity. The polarity of a polar moiety is dependent on the electronegativity between atoms within the moiety and the asymmetry of the structure of the moiety. In some embodiments, a polar moiety contains one or more (e.g., 1-4, 1-3, 1, 2, 3, or 4) heteroatoms independently selected from N, O, and S, which may induce chemical polarity in the moiety by having different electronegativity from carbon and hydrogen. In general, a polar moiety interacts with other polar or charged molecules. In some embodiments, a polar moiety may be optionally substituted alkamino, optionally substituted heteroalkyl (e.g., N- and/or O-containing heteroalkyl; $-(CH_2)_4$-carboxylic acid, $-(CH_2)_3$-carboxylic acid, $-(CH_2)_2$-carboxylic acid, $-CH_2$-carboxylic acid), optionally substituted heterocycloalkyl (e.g., N- and/or O-containing heterocycloalkyl), or optionally substituted heteroaryl (e.g., N- and/or O-containing heteroaryl). In some embodiments, a polar moiety may $-CH(CH_3)OH$, $-CH_2OH$, $-(CH_2)_2CONH_2$, $-CH_2CONH_2$, $-CH_2COOH$, or $-(CH_2)_2COOH$. Thus,

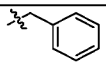
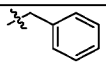
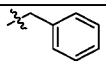
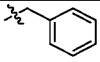
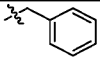
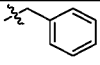
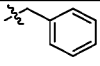
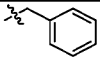
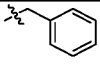
substituents may transform an otherwise lipophilic moiety such optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heteroalkenyl, optionally substituted heteroalkynyl, or optionally substituted heteroaryl, or halo forms thereof, to a polar moiety with the addition of a substituent that imparts polarity, such as -OH, -COOH, -COOR, or -$CONR_2$, in which R is H or C1-C4 alkyl. In some embodiments, a polar moiety may be the side chain or a polar or charged amino acid residue (e.g., threonine, serine, glutamine, asparagine, arginine, lysine histidine, aspartic acid, and glutamic acid). In some embodiments, a polar moiety is the side chain of threonine. In some embodiments, polar moieties of the compounds described herein interact with the negatively charged portions of lipid A (e.g., phosphates of lipid A) when the compounds bind to the membrane of bacterial cells (e.g., Gram-negative bacterial cells). Due to its position on the cyclic heptapeptide, one or more of R^1, R^{12}, and R^{15} may be a polar moiety.

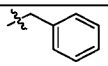
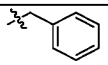
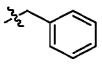
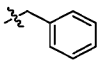
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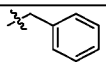
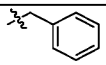
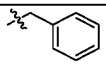
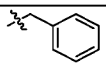
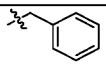
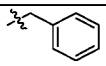
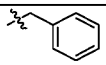
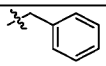
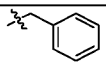
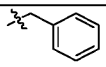
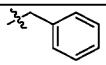
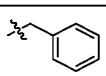
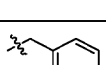
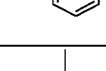


,

wherein Q^1, Q^2 and Q^3 are as follows:

Q^1	Q^2	Q^3
		
		
		
		
		
		
		
		
		
		

Q^1	Q^2	Q^3
		
		
		
		
		
		
		
		
		
		
		
		
		
		
Q^1	Q^2	Q^3

Q^1	Q^2	Q^3
		
		
		
		
		
		
		
		
		
		
		
		
		
		

Q^1	Q^2	Q^3
		
		
		
		
		
		
		
		
D-Leu	L-Thr	
D-Leu	L-Ala	
D-Leu	L-Val	
D-Nle	L-Thr	
D-Leu	L-Ser	
D-Thr	L-Leu	
D-Val	L-Thr	
D-Thr	L-Thr	
D-Val	L-Val	
D-Leu	L-Thr	
D-Leu	L-Ala	
D-Leu	L-Abu	

wherein "D-Nle" is D-norleucine, "L-Abu" is L-2-aminobutyric acid, and "〰" refers to the point of attachment of the polymyxin core to the remainder of the compounds disclosed herein (e.g., a peptide having 1-5 amino acids).

The terms "alkyl," "alkenyl," and "alkynyl," as used herein, include straight-chain and branched-chain monovalent substituents, as well as combinations of these, containing only C and H when unsubstituted. When the alkyl group includes at least one carbon-carbon double bond or carbon-carbon

triple bond, the alkyl group can be referred to as an "alkenyl" or "alkynyl" group respectively. The monovalency of an alkyl, alkenyl, or alkynyl group does not include the optional substituents on the alkyl, alkenyl, or alkynyl group. For example, if an alkyl, alkenyl, or alkynyl group is attached to a compound, monovalency of the alkyl, alkenyl, or alkynyl group refers to its attachment to the compound and does not include any additional substituents that may be present on the alkyl, alkenyl, or alkynyl group. In some embodiments, the alkyl or heteroalkyl group may contain, e.g., 1-20. 1-18, 1-16, 1-14, 1-12, 1-10, 1-8, 1-6, 1-4, or 1-2 carbon atoms (e.g., C1-C20, C1-C18, C1-C16, C1-C14, C1-C12, C1-C10, C1-C8, C1-C6, C1-C4, or C1-C2). In some embodiments, the alkenyl, heteroalkenyl, alkynyl, or heteroalkynyl group may contain, e.g., 2-20, 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, or 2-4 carbon atoms (e.g., C2-C20, C2-C18, C2-C16, C2-C14, C2-C12, C2-C10, C2-C8, C2-C6, or C2-C4). Examples include, but are not limited to, methyl, ethyl, isobutyl, sec-butyl, tert-butyl, 2-propenyl, and 3-butynyl.

The term "cycloalkyl," as used herein, represents a monovalent saturated or unsaturated non-aromatic cyclic alkyl group. A cycloalkyl may have, e.g., three to twenty carbons (e.g., a C3-C7, C3-C8, C3-C9, C3-C10, C3-C11, C3-C12, C3-C14, C3-C16, C3-C18, or C3-C20 cycloalkyl). Examples of cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. When the cycloalkyl group includes at least one carbon-carbon double bond, the cycloalkyl group can be referred to as a "cycloalkenyl" group. A cycloalkenyl may have, e.g., four to twenty carbons (e.g., a C4-C7, C4-C8, C4-C9, C4-C10, C4-C11, C4-C12, C4-C14, C4-C16, C4-C18, or C4-C20 cycloalkenyl). Exemplary cycloalkenyl groups include, but are not limited to, cyclopentenyl, cyclohexenyl, and cycloheptenyl. When the cycloalkyl group includes at least one carbon-carbon triple bond, the cycloalkyl group can be referred to as a "cycloalkynyl" group. A cycloalkynyl may have, e.g., eight to twenty carbons (e.g., a C8-C9, C8-C10, C8-C11, C8-C12, C8-C14, C8-C16, C8-C18, or C8-C20 cycloalkynyl). The term "cycloalkyl" also includes a cyclic compound having a bridged multicyclic structure in which one or more carbons bridges two non-adjacent members of a monocyclic ring, e.g., bicyclo[2.2.1.]heptyl and adamantane. The term "cycloalkyl" also includes bicyclic, tricyclic, and tetracyclic fused ring structures, e.g., decalin and spiro cyclic compounds.

The term "aryl," as used herein, refers to any monocyclic or fused ring bicyclic or tricyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system, e.g., phenyl, naphthyl, or phenanthrene. In some embodiments, a ring system contains 5-15 ring member atoms or 5-10 ring member atoms. An aryl group may have, e.g., five to fifteen carbons (e.g., a C5-C6, C5-C7, C5-C8, C5-C9, C5-C10, C5-C11, C5-C12, C5-C13, C5-C14, or C5-C15 aryl). The term "heteroaryl" also refers to such monocyclic or fused bicyclic ring systems containing one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms selected from O, S and N. A heteroaryl group may have, e.g., two to fifteen carbons (e.g., a C2-C3, C2-C4, C2-C5, C2-C6, C2-C7, C2-C8, C2-C9. C2-C10, C2-C11, C2-C12, C2-C13, C2-C14, or C2-C15 heteroaryl). The inclusion of a heteroatom permits inclusion of 5-membered rings to be considered aromatic as well as 6-membered rings. Thus, typical heteroaryl systems include, e.g., pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, benzoisoxazolyl, and imidazolyl. Because tautomers are possible, a group such as phthalimido is also considered heteroaryl. In some embodiments, the aryl or heteroaryl group is a 5- or 6-membered aromatic rings system

optionally containing 1-2 nitrogen atoms. In some embodiments, the aryl or heteroaryl group is an optionally substituted phenyl, pyridyl, indolyl, pyrimidyl, pyridazinyl, benzothiazolyl, benzimidazolyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, or imidazopyridinyl. In some embodiments, the aryl group is phenyl. In some embodiments, an aryl group may be optionally substituted with a substituent such an aryl substituent, e.g., biphenyl.

The term "alkaryl," refers to an aryl group that is connected to an alkylene, alkenylene, or alkynylene group. In general, if a compound is attached to an alkaryl group, the alkylene, alkenylene, or alkynylene portion of the alkaryl is attached to the compound. In some embodiments, an alkaryl is C6-C35 alkaryl (e.g., C6-C16, C6-C14, C6-C12, C6-C10, C6-C9, C6-C8, C7, or C6 alkaryl), in which the number of carbons indicates the total number of carbons in both the aryl portion and the alkylene, alkenylene, or alkynylene portion of the alkaryl. Examples of alkaryls include, but are not limited to, (C1-C8)alkylene(C6-C12)aryl, (C2-C8)alkenylene(C6-C12)aryl, or (C2-C8)alkynylene(C6-C12)aryl. In some embodiments, an alkaryl is benzyl or phenethyl. In a heteroalkaryl, one or more heteroatoms selected from N, O, and S may be present in the alkylene, alkenylene, or alkynylene portion of the alkaryl group and/or may be present in the aryl portion of the alkaryl group. In an optionally substituted alkaryl, the substituent may be present on the alkylene, alkenylene, or alkynylene portion of the alkaryl group and/or may be present on the aryl portion of the alkaryl group.

The term "amino," as used herein, represents $-N(R^x)_2$ or $-N^+(R^x)_3$, where each R^x is, independently, H, alkyl, alkenyl, alkynyl, aryl, alkaryl, cycloalkyl, or two R^x combine to form a heterocycloalkyl. In some embodiment, the amino group is $-NH_2$.

The term "alkamino," as used herein, refers to an amino group, described herein, that is attached to an alkylene (e.g., C1-C5 alkylene), alkenylene (e.g., C2-C5 alkenylene), or alkynylene group (e.g., C2-C5 alkenylene). In general, if a compound is attached to an alkamino group, the alkylene, alkenylene, or alkynylene portion of the alkamino is attached to the compound. The amino portion of an alkamino refers to $-N(R^x)_2$ or $-N^+(R^x)_3$, where each R^x is, independently, H, alkyl, alkenyl, alkynyl, aryl, alkaryl, cycloalkyl, or two R^x combine to form a heterocycloalkyl. In some embodiment, the amino portion of an alkamino is $-NH_2$. An example of an alkamino group is C1-C5 alkamino, e.g., C2 alkamino (e.g., $CH_2CH_2NH_2$ or $CH_2CH_2N(CH_3)_2$). In a heteroalkamino group, one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms selected from N, O, and S may be present in the alkylene, alkenylene, or alkynylene portion of the heteroalkamino group. In some embodiments, an alkamino group may be optionally substituted. In a substituted alkamino group, the substituent may be present on the alkylene, alkenylene, or alkynylene portion of the alkamino group and/or may be present on the amino portion of the alkamino group.

The term "alkamide," as used herein, refers to an amide group that is attached to an alkylene (e.g., C1-C5 alkylene), alkenylene (e.g., C2-C5 alkenylene), or alkynylene (e.g., C2-C5 alkenylene) group. In general, if a compound is attached to an alkamide group, the alkylene, alkenylene, or alkynylene portion of the alkamide is attached to the compound. The amide portion of an alkamide refers to $-C(O)-N(R^x)_2$, where each R^x is, independently, H, alkyl, alkenyl, alkynyl, aryl, alkaryl, cycloalkyl, or two R^x combine to form a heterocycloalkyl. In some embodiment, the amide portion of an alkamide is $-C(O)NH_2$. An alkamide group may be $-(CH_2)_2-C(O)NH_2$ or $-CH_2-C(O)NH_2$. In a heteroalkamide group, one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms selected from N, O, and S may be present in the

alkylene, alkenylene, or alkynylene portion of the heteroalkamide group. In some embodiments, an alkamide group may be optionally substituted. In a substituted alkamide group, the substituent may be present on the alkylene, alkenylene, or alkynylene portion of the alkamide group and/or may be present on the amide portion of the alkamide group.

The terms "alkylene," "alkenylene," and "alkynylene," as used herein, refer to divalent groups having a specified size. In some embodiments, an alkylene may contain, e.g., 1-20, 1-18, 1-16, 1-14, 1-12, 1-10, 1-8, 1-6, 1-4, or 1-2 carbon atoms (e.g., C1-C20, C1-C18, C1-C16, C1-C14, C1-C12, C1-C10, C1-C8, C1-C6, C1-C4, or C1-C2). In some embodiments, an alkenylene or alkynylene may contain, e.g., 2-20, 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, or 2-4 carbon atoms (e.g., C2-C20, C2-C18, C2-C16, C2-C14, C2-C12, C2-C10, C2-C8, C2-C6, or C2-C4). Alkylene, alkenylene, and/or alkynylene includes straight-chain and branched-chain forms, as well as combinations of these. The divalency of an alkylene, alkenylene, or alkynylene group does not include the optional substituents on the alkylene, alkenylene, or alkynylene group. Alkylene, alkenylene, and/or alkynylene groups can be substituted by the groups typically suitable as substituents for alkyl, alkenyl and alkynyl groups as set forth herein. For example, C=O is a C1 alkylene that is substituted by an oxo (=O). For example, -HCR-C≡C- may be considered as an optionally substituted alkynylene and is considered a divalent group even though it has an optional substituent, R. Heteroalkylene, heteroalkenylene, and/or heteroalkynylene groups refer to alkylene, alkenylene, and/or alkynylene groups including one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms, e.g., N, O, and S. For example, a polyethylene glycol (PEG) polymer or a PEG unit $-(CH_2)_2-O-$ in a PEG polymer is considered a heteroalkylene containing one or more oxygen atoms.

The term "cycloalkylene," as used herein, refers to a divalent cyclic group linking together two parts of a compound. For example, one carbon within the cycloalkylene group may be linked to one part of the compound, while another carbon within the cycloalkylene group may be linked to another part of the compound. A cycloalkylene group may include saturated or unsaturated non-aromatic cyclic groups. A cycloalkylene may have, e.g., three to twenty carbons in the cyclic portion of the cycloalkylene (e.g., a C3-C7, C3-C8, C3-C9, C3-C10, C3-C11, C3-C12, C3-C14, C3-C16, C3-C18, or C3-C20 cycloalkylene). When the cycloalkylene group includes at least one carbon-carbon double bond, the cycloalkylene group can be referred to as a "cycloalkenylene" group. A cycloalkenylene may have, e.g., four to twenty carbons in the cyclic portion of the cycloalkenylene (e.g., a C4-C7, C4-C8, C4-C9. C4-C10, C4-C11, C4-C12, C4-C14, C4-C16, C4-C18, or C4-C20 cycloalkenylene). When the cycloalkylene group includes at least one carbon-carbon triple bond, the cycloalkylene group can be referred to as a "cycloalkynylene" group. A cycloalkynylene may have, e.g., four to twenty carbons in the cyclic portion of the cycloalkynylene (e.g., a C4-C7, C4-C8, C4-C9. C4-C10, C4-C11, C4-C12, C4-C14, C4-C16, C4-C18, or C8-C20 cycloalkynylene). A cycloalkylene group can be substituted by the groups typically suitable as substituents for alkyl, alkenyl and alkynyl groups as set forth herein. Heterocycloalkylene refers to a cycloalkylene group including one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms, e.g., N, O, and S. Examples of cycloalkylenes include, but are not limited to, cyclopropylene and cyclobutylene. A tetrahydrofuran may be considered as a heterocycloalkylene.

The term "arylene," as used herein, refers to a multivalent (e.g., divalent or trivalent) aryl group linking together multiple (e.g., two or three) parts of a compound. For example, one carbon within the

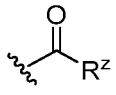
arylene group may be linked to one part of the compound, while another carbon within the arylene group may be linked to another part of the compound. An arylene may have, e.g., five to fifteen carbons in the aryl portion of the arylene (e.g., a C5-C6, C5-C7, C5-C8, C5-C9. C5-C10, C5-C11, C5-C12, C5-C13, C5-C14, or C5-C15 arylene). An arylene group can be substituted by the groups typically suitable as substituents for alkyl, alkenyl and alkynyl groups as set forth herein. Heteroarylene refers to an aromatic group including one or more, e.g., 1-4, 1-3, 1, 2, 3, or 4, heteroatoms, e.g., N, O, and S. A heteroarylene group may have, e.g., two to fifteen carbons (e.g., a C2-C3, C2-C4, C2-C5, C2-C6, C2-C7, C2-C8, C2-C9. C2-C10, C2-C11, C2-C12, C2-C13, C2-C14, or C2-C15 heteroarylene).

The term "optionally substituted," as used herein, refers to having 0, 1, or more substituents, such as 0-25, 0-20, 0-10 or 0-5 substituents. Substituents include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, alkaryl, acyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkaryl, halogen, oxo, cyano, nitro, amino, alkamino, hydroxy, alkoxy, alkanoyl, carbonyl, carbamoyl, guanidinyl, ureido, amidinyl, any of the groups or moieties described above, and hetero versions of any of the groups or moieties described above. Substituents include, but are not limited to, F, Cl, methyl, phenyl, benzyl, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, OCF_3, SiR_3, and NO_2, wherein each R is, independently, H, alkyl, alkenyl, aryl, heteroalkyl, heteroalkenyl, or heteroaryl, and wherein two of the optional substituents on the same or adjacent atoms can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3–8 members, or two of the optional substituents on the same atom can be joined to form an optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3–8 members.

An optionally substituted group or moiety refers to a group or moiety (e.g., any one of the groups or moieties described above) in which one of the atoms (e.g., a hydrogen atom) is optionally replaced with another substituent. For example, an optionally substituted alkyl may be an optionally substituted methyl, in which a hydrogen atom of the methyl group is replaced by, e.g., OH. As another example, a substituent on a heteroalkyl or its divalent counterpart, heteroalkylene, may replace a hydrogen on a carbon or a hydrogen on a heteroatom such as N. For example, the hydrogen atom in the group -R-NH-R- may be substituted with an alkamide substituent, e.g., $-R-N[(CH_2C(O)N(CH_3)_2]-R$. Generally, an optional substituent is a noninterfering substituent. A "noninterfering substituent" refers to a substituent that leaves the ability of the compounds described herein (e.g., compounds of any one of formulas (I)-(XXXXI)) to either bind to lipopolysaccharides (LPS) or to kill or inhibit the growth of Gram-negative bacteria qualitatively intact. Thus, in some embodiments, the substituent may alter the degree of such activity. However, as long as the compound retains the ability to bind to LPS and/or to kill or inhibit the growth of Gram-negative bacteria, the substituent will be classified as "noninterfering." In some aspects, a noninterfering substituent leaves the ability of a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI)) to kill or inhibit the growth of Gram-negative bacteria qualitatively intact as determined by measuring the minimum inhibitory concentration (MIC) against at least one Gram-negative bacteria as known in the art, wherein the MIC is 128 μg/mL or less (e.g., 110 μg/mL or less, 100 μg/mL or less, 90 μg/mL or less, 80 μg/mL or less, 70 μg/mL or less, 60 μg/mL or less, 50 μg/mL or less, 40 μg/mL or less, 30 μg/mL or less, 20 μg/mL or less, or 10 μg/mL or less). In some aspects, a

noninterfering substituent leaves the ability of a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI)) to bind to lipopolysaccharides (LPS) from the cell membrane of Gram-negative bacteria qualitatively intact, as determined by an LPS binding assay, wherein the compound shows a value of about 10% or greater displacement of a fluorogenic substrate at 250 μM of the compound.

The term "hetero," when used to describe a chemical group or moiety, refers to having at least one heteroatom that is not a carbon or a hydrogen, e.g., N, O, and S. Any one of the groups or moieties described above may be referred to as hetero if it contains at least one heteroatom. For example, a heterocycloalkyl, heterocycloalkenyl, or heterocycloalkynyl group refers to a cycloalkyl, cycloalkenyl, or cycloalkynyl group that has one or more heteroatoms independently selected from, e.g., N, O, and S. An example of a heterocycloalkenyl group is a maleimido. For example, a heteroaryl group refers to an aromatic group that has one or more heteroatoms independently selected from, e.g., N, O, and S. One or more heteroatoms may also be included in a substituent that replaced a hydrogen atom in a group or moiety as described herein. For example, in an optionally substituted heteroaryl group, if one of the hydrogen atoms in the heteroaryl group is replaced with a substituent (e.g., methyl), the substituent may also contain one or more heteroatoms (e.g., methanol).

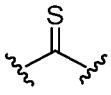
The term "acyl," as used herein, refers to a group having the structure: , wherein R^z is an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, alkamino, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaryl, heteroalkaryl, or heteroalkamino.

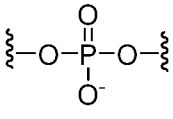
The term "halo" or "halogen," as used herein, refers to any halogen atom, e.g., F, Cl, Br, or I. Any one of the groups or moieties described herein may be referred to as a "halo moiety" if it contains at least one halogen atom, such as haloalkyl.

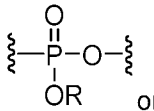
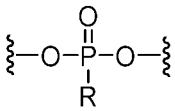
The term "hydroxyl," as used herein, represents an -OH group.

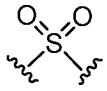
The term "oxo," as used herein, refers to a substituent having the structure =O, where there is a double bond between an atom and an oxygen atom.

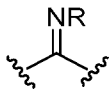
The term "carbonyl," as used herein, refers to a group having the structure: .

The term "thiocarbonyl," as used herein, refers to a group having the structure: 

The term "phosphate," as used herein, represents the group having the structure: .

The term "phosphoryl," as used herein, represents the group having the structure:  or .

The term "sulfonyl," as used herein, represents the group having the structure: .

The term "imino," as used herein, represents the group having the structure: , wherein R is an optional substituent.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 5th Edition (John Wiley & Sons, New York, 2014), which is incorporated herein by reference. *N*-protecting groups include, e.g., acyl, aryloyl, and carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, carboxybenzyl (CBz), 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acid residues such as alanine, leucine, phenylalanine; sulfonyl-containing groups such as benzenesulfonyl and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyl oxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl (BOC), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl; alkaryl groups such as benzyl, triphenylmethyl, and benzyloxymethyl; and silyl groups such as trimethylsilyl.

The term "amino acid," as used herein, means naturally occurring amino acids and non-naturally occurring amino acids.

The term "naturally occurring amino acids," as used herein, means amino acids including Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val.
The term "non-naturally occurring amino acid," as used herein, means an alpha amino acid that is not naturally produced or found in a mammal. Examples of non-naturally occurring amino acids include D-amino acids; an amino acid having an acetylaminomethyl group attached to a sulfur atom of a cysteine; a pegylated amino acid; the omega amino acids of the formula $NH_2(CH_2)_nCOOH$ where n is 2-6, neutral nonpolar amino acids, such as sarcosine, t-butyl alanine, t-butyl glycine, N-methyl isoleucine, and norleucine; oxymethionine; phenylglycine; citrulline; methionine sulfoxide; cysteic acid; ornithine; diaminobutyric acid; 3-aminoalanine; 3-hydroxy-D-proline; 2,4-diaminobutyric acid; 2-aminopentanoic acid; 2-aminooctanoic acid, 2-carboxy piperazine; piperazine-2-carboxylic acid, 2-amino-4-phenylbutanoic acid; 3-(2-naphthyl)alanine, and hydroxyproline. Other amino acids are α-aminobutyric acid, α-amino-α-methylbutyrate, aminocyclopropane-carboxylate, aminoisobutyric acid, aminonorbornyl-carboxylate, L-

cyclohexylalanine, cyclopentylalanine, L-N-methylleucine, L-N-methylmethionine, L-N-methylnorvaline, L-N-methylphenylalanine, L-N-methylproline, L-N-methylserine, L-N-methyltryptophan, D-ornithine, L-N-methylethylglycine, L-norleucine, α-methyl-aminoisobutyrate, α-methylcyclohexylalanine, D-α-methylalanine, D-α-methylarginine, D-α-methylasparagine, D-α-methylaspartate, D-α-methylcysteine, D-α-methylglutamine, D-α-methylhistidine, D-α-methylisoleucine, D-α-methylleucine, D-α-methyllysine, D-α-methylmethionine, D-α-methylornithine, D-α-methylphenylalanine, D-α-methylproline, D-α-methylserine, D-N-methylserine, D-α-methylthreonine, D-α-methyltryptophan, D-α-methyltyrosine, D-α-methylvaline, D-N-methylalanine, D-N-methylarginine, D-N-methylasparagine, D-N-methylaspartate, D-N-methylcysteine, D-N-methylglutamine, D-N-methylglutamate, D-N-methylhistidine, D-N-methylisoleucine, D-N-methylleucine, D-N-methyllysine, N-methylcyclohexylalanine, D-N-methylornithine, N-methylglycine, N-methylaminoisobutyrate, N-(1-methylpropyl)glycine, N-(2-methylpropyl)glycine, D-N-methyltryptophan, D-N-methyltyrosine, D-N-methylvaline, γ-aminobutyric acid, L-t-butylglycine, L-ethylglycine, L-homophenylalanine, L-α-methylarginine, L-α-methylaspartate, L-α-methylcysteine, L-α-methylglutamine, L-α-methylhistidine, L-α-methylisoleucine, L-α-methylleucine, L-α-methylmethionine, L-α-methylnorvaline, L-α-methylphenylalanine, L-α-methylserine, L-α-methyltryptophan, L-α-methylvaline, N-(N-(2,2-diphenylethyl) carbamylmethylglycine, 1-carboxy-1-(2,2-diphenyl-ethylamino) cyclopropane, 4-hydroxyproline, ornithine, 2-aminobenzoyl (anthraniloyl), D-cyclohexylalanine, 4-phenyl-phenylalanine, L-citrulline, α-cyclohexylglycine, L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, L-thiazolidine-4-carboxylic acid, L-homotyrosine, L-2-furylalanine, L-histidine (3-methyl), N-(3-guanidinopropyl)glycine, O-methyl-L-tyrosine, O-glycan-serine, meta-tyrosine, nor-tyrosine, L-N,N′,N″-trimethyllysine, homolysine, norlysine, N-glycan asparagine, 7-hydroxy-1,2,3,4-tetrahydro-4-fluorophenylalanine, 4-methylphenylalanine, bis-(2-picolyl)amine, pentafluorophenylalanine, indoline-2-carboxylic acid, 2-aminobenzoic acid, 3-amino-2-naphthoic acid, asymmetric dimethylarginine, L-tetrahydroisoquinoline-1-carboxylic acid, D-tetrahydroisoquinoline-1-carboxylic acid, 1-amino-cyclohexane acetic acid, D/L-allylglycine, 4-aminobenzoic acid, 1-amino-cyclobutane carboxylic acid, 2 or 3 or 4-aminocyclohexane carboxylic acid, 1-amino-1-cyclopentane carboxylic acid, 1-aminoindane-1-carboxylic acid, 4-amino-pyrrolidine-2-carboxylic acid, 2-aminotetraline-2-carboxylic acid, azetidine-3-carboxylic acid, 4-benzyl-pyrolidine-2-carboxylic acid, tert-butylglycine, b-(benzothiazolyl-2-yl)-alanine, b-cyclopropyl alanine, 5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid, (2R,4S)4-hydroxypiperidine-2-carboxylic acid, (2S,4S) and (2S,4R)-4-(2-naphthylmethoxy)-pyrolidine-2-carboxylic acid, (2S,4S) and (2S,4R)4-phenoxy-pyrrolidine-2-carboxylic acid, (2R,5S)and(2S,5R)-5-phenyl-pyrrolidine-2-carboxylic acid, (2S,4S)-4-amino-1-benzoyl-pyrrolidine-2-carboxylic acid, t-butylalanine, (2S,5R)-5-phenyl-pyrrolidine-2-carboxylic acid, 1-aminomethyl-cyclohexane-acetic acid, 3,5-bis-(2-amino)ethoxy-benzoic acid, 3,5-diamino-benzoic acid, 2-methylamino-benzoic acid, N-methylanthranylic acid, L-N-methylalanine, L-N-methylarginine, L-N-methylasparagine, L-N-methylaspartic acid, L-N-methylcysteine, L-N-methylglutamine, L-N-methylglutamic acid, L-N-methylhistidine, L-N-methylisoleucine, L-N-methyllysine, L-N-methylnorleucine, L-N-methylornithine, L-N-methylthreonine, L-N-methyltyrosine, L-N-methylvaline, L-N-methyl-t-butylglycine, L-norvaline, α-methyl-γ-aminobutyrate, 4,4′-biphenylalanine, α-methylcylcopentylalanine, α-methyl-α-napthylalanine, α-methylpenicillamine, N-(4-aminobutyl)glycine, N-(2-aminoethyl)glycine, N-(3-aminopropyl)glycine, N-amino-α-methylbutyrate, α-napthylalanine, N-benzylglycine, N-(2-

carbamylethyl)glycine, N-(carbamylmethyl)glycine, N-(2-carboxyethyl)glycine, N-(carboxymethyl)glycine, N-cyclobutylglycine, N-cyclodecylglycine, N-cycloheptylglycine, N-cyclohexylglycine, N-cyclodecylglycine, N-cylcododecylglycine, N-cyclooctylglycine, N-cyclopropylglycine, N-cycloundecylglycine, N-(2,2-diphenylethyl)glycine, N-(3,3-diphenylpropyl)glycine, N-(3-guanidinopropyl)glycine, N-(1-hydroxyethyl)glycine, N-(hydroxyethyl))glycine, N-(imidazolylethyl))glycine, N-(3-indolylyethyl)glycine, N-methyl-γ-aminobutyrate, D-N-methylmethionine, N-methylcyclopentylalanine, D-N-methylphenylalanine, D-N-methylproline, D-N-methylthreonine, N-(1-methylethyl)glycine, N-methyl-napthylalanine, N-methylpenicillamine, N-(p-hydroxyphenyl)glycine, N-(thiomethyl)glycine, penicillamine, L-α-methylalanine, L-α-methylasparagine, L-α-methyl-t-butylglycine, L-methylethylglycine, L-α-methylglutamate, L-α-methylhomophenylalanine, N-(2-methylthioethyl)glycine, L-α-methyllysine, L-α-methylnorleucine, L-α-methylornithine, L-α-methylproline, L-α-methylthreonine, L-α-methyltyrosine, L-N-methyl-homophenylalanine, N-(N-(3,3-diphenylpropyl) carbamylmethylglycine, L-pyroglutamic acid, D-pyroglutamic acid, O-methyl-L-serine, O-methyl-L-homoserine, 5-hydroxylysine, α-carboxyglutamate, phenylglycine, L-pipecolic acid (homoproline), L-homoleucine, L-lysine (dimethyl), L-2-naphthylalanine, L-dimethyldopa or L-dimethoxy-phenylalanine, L-3-pyridylalanine, L-histidine (benzoyloxymethyl), N-cycloheptylglycine, L-diphenylalanine, O-methyl-L-homotyrosine, L-β-homolysine, O-glycan-threoine, Ortho-tyrosine, L-N,N′-dimethyllysine, L-homoarginine, neotryptophan, 3-benzothienylalanine, isoquinoline-3-carboxylic acid, diaminopropionic acid, homocysteine, 3,4-dimethoxyphenylalanine, 4-chlorophenylalanine, L-1,2,3,4-tetrahydronorharman-3-carboxylic acid, adamantylalanine, symmetrical dimethylarginine, 3-carboxythiomorpholine, D-1,2,3,4-tetrahydronorharman-3-carboxylic acid, 3-aminobenzoic acid, 3-amino-1-carboxymethyl-pyridin-2-one, 1-amino-1-cyclohexane carboxylic acid, 2-aminocyclopentane carboxylic acid, 1-amino-1-cyclopropane carboxylic acid, 2-aminoindane-2-carboxylic acid, 4-amino-tetrahydrothiopyran-4-carboxylic acid, azetidine-2-carboxylic acid, b-(benzothiazol-2-yl)-alanine, neopentylglycine, 2-carboxymethyl piperidine, b-cyclobutyl alanine, allylglycine, diaminopropionic acid, homo-cyclohexyl alanine, (2S,4R)- 4-hydroxypiperidine-2-carboxylic acid, octahydroindole-2-carboxylic acid, (2S,4R) and (2S,4R)-4-(2-naphthyl), pyrrolidine-2-carboxylic acid, nipecotic acid, (2S,4R)and (2S,4S)-4-(4-phenylbenzyl) pyrrolidine-2-carboxylic acid, (3S)-1-pyrrolidine-3-carboxylic acid, (2S,4S)-4-tritylmercapto-pyrrolidine-2-carboxylic acid, (2S,4S)-4-mercaptoproline, t-butylglycine, N,N-bis(3-aminopropyl)glycine, 1-amino-cyclohexane-1-carboxylic acid, N-mercaptoethylglycine, and selenocysteine. In some embodiments, amino acid residues may be charged or polar. Charged amino acids include alanine, lysine, aspartic acid, or glutamic acid, or non-naturally occurring analogs thereof. Polar amino acids include glutamine, asparagine, histidine, serine, threonine, tyrosine, methionine, or tryptophan, or non-naturally occurring analogs thereof.

It is specifically contemplated that in some embodiments, a terminal amino group in the amino acid may be an amido group or a carbamate group.

The term “antibacterial agent,” as used herein, refers to an agent that is used in addition to one or more of the compounds described herein (e.g., compounds of any one of formulas (I)-(XXXXI) or a compound of Table 1) in methods of treating a bacterial infection (e.g., Gram-negative bacterial infection) and/or preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria. An antibacterial agent may be an agent that prevents the entrance of a bacteria (e.g., a Gram-negative bacteria) into a

subject's cells, tissues, or organs, inhibits the growth of a bacteria (e.g., a Gram-negative bacteria) in a subject's cells, tissues, or organs, and/or kills a bacteria (e.g., a Gram-negative bacteria) that is inside a subject's cells, tissues, or organs. Examples of antibacterial agents are described in detail further herein. In some embodiments, an antibacterial agent used in addition to a compound described herein is linezolid or tedizolid (e.g., tedizolid phosphate).

The term "bacterial infection," as used herein, refers to the invasion of a subject's cells, tissues, and/or organs by bacteria (e.g., Gram-negative bacteria), thus, causing an infection. In some embodiments, the bacteria may grow, multiply, and/or produce toxins in the subject's cells, tissues, and/or organs. In some embodiments, a bacterial infection can be any situation in which the presence of a bacterial population(s) is latent within or damaging to a host body. Thus, a subject is "suffering" from a bacterial infection when a latent bacterial population is detectable in or on the subject's body, an excessive amount of a bacterial population is present in or on the subject's body, or when the presence of a bacterial population(s) is damaging the cells, tissues, and/or organs of the subject.

The term "protecting against," as used herein, refers to preventing a subject from developing a bacterial infection (e.g., a Gram-negative bacterial infection) or decreasing the risk that a subject may develop a bacterial infection (e.g., a Gram-negative bacterial infection). Prophylactic drugs used in methods of protecting against a bacterial infection in a subject are often administered to the subject prior to any detection of the bacterial infection. In some embodiments of methods of protecting against a bacterial infection, a subject (e.g., a subject at risk of developing a bacterial infection) may be administered a compound described herein (e.g., a compound having any one of formulas (I)-(XXXXI) or a compound of Table 1) to prevent the bacterial infection development or decrease the risk of the bacterial infection development.

The term "treating" or "to treat," as used herein, refers to a therapeutic treatment of a bacterial infection (e.g., a Gram-negative bacterial infection) in a subject. In some embodiments, a therapeutic treatment may slow the progression of the bacterial infection, improve the subject's outcome, and/or eliminate the infection. In some embodiments, a therapeutic treatment of a bacterial infection (e.g., a Gram-negative bacterial infection) in a subject may alleviate or ameliorate of one or more symptoms or conditions associated with the bacterial infection, diminish the extent of the bacterial infection, stabilize (i.e., not worsening) the state of the bacterial infection, prevent the spread of the bacterial infection, and/or delay or slow the progress of the bacterial infection, as compare the state and/or the condition of the bacterial infection in the absence of the therapeutic treatment.

The phrase "LPS-induced nitric oxide (NO) production from a macrophage," as used herein, refers to the ability of the lipopolysaccharides (LPS) in Gram-negative bacteria to activate a macrophage and induce NO production from the macrophage. NO production from a macrophage in response to LPS is a signal of macrophage activation, which may lead to sepsis in a subject, e.g., a Gram-negative bacteria infected subject. The disclosure features compounds (e.g., compounds of any one of formulas (I)-(XXXXI) or a compound of Table 1) that are able to bind to LPS in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, thus neutralizing an immune response to LPS. NO production from a macrophage may be measured using available techniques in the art, e.g., a Griess assay.

The term "resistant strain of bacteria," as used herein, refers to a strain of bacteria (e.g., Gram-negative or Gram-positive bacteria) that is refractory to treatment with an antibiotic, such as an antibiotic described in the Detailed Description. Antibiotics that a strain of bacteria is resistant to do not include the compounds described herein (e.g., compounds of any one of formulas (I)-(XXXXI) or a compound of Table 1). Resistance may arise through natural resistance in certain types of bacteria, spontaneous random genetic mutations, and/or by inter- or intra-species horizontal transfer of resistance genes. In some embodiments, a resistant strain of bacteria contains a *mcr-1* gene, a *mcr-2* gene, an *mcr*-3 gene, an *mcr*-4 gene, an *mcr*-5 gene, an *mcr*-6 gene, an *mcr*-7 gene, and/or an *mcr*-8 gene. In some embodiments, a resistant strain of bacteria contains a chromosomal mutation conferring polymyxin resistance. In some embodiments, a resistant strain of bacteria contains a *mcr-1* gene, a *mcr-2* gene, an *mcr*-3 gene, an *mcr*-4 gene, an *mcr*-5 gene, an *mcr*-6 gene, an *mcr*-7 gene, and/or an *mcr*-8 gene in combination with other antibiotic resistance genes. In some embodiments, a resistant strain of bacteria is a resistant strain of *E. coli* (e.g., *E. coli* BAA-2469).

The term "subject," as used herein, can be a human, non-human primate, or other mammal, such as but not limited to dog, cat, horse, cow, pig, turkey, goat, fish, monkey, chicken, rat, mouse, and sheep. The term "substantially simultaneously," as used herein, refers to two or more events that occur at the same time or within a narrow time frame of each other. As disclosed herein, a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and an antibacterial agent (e.g., linezolid or tedizolid) may be administered substantially simultaneously, which means that the compound and the antibacterial agent are administered together (e.g., in one pharmaceutical composition) or separately but within a narrow time frame of each other, e.g., within 10 minutes, e.g., 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 minute, or 45, 30, 15, or 10 seconds of each other.

The term "therapeutically effective amount," as used herein, refers to an amount, e.g., pharmaceutical dose, effective in inducing a desired effect in a subject or in treating a subject having a condition or disorder described herein (e.g., a bacterial infection (e.g., a Gram-negative bacterial infection)). It is also to be understood herein that a "therapeutically effective amount" may be interpreted as an amount giving a desired therapeutic and/or preventative effect, taken in one or more doses or in any dosage or route, and/or taken alone or in combination with other therapeutic agents (e.g., an antibacterial agent described herein). For example, in the context of administering a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) that is used for the treatment of a bacterial infection, an effective amount of a compound is, for example, an amount sufficient to prevent, slow down, or reverse the progression of the bacterial infection as compared to the response obtained without administration of the compound.

As used herein, the term "pharmaceutical composition" refers to a medicinal or pharmaceutical formulation that contains at least one active ingredient (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) as well as one or more excipients and diluents to enable the active ingredient suitable for the method of administration. The pharmaceutical composition of the present disclosure includes pharmaceutically acceptable components that are compatible with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1).

As used herein, the term "pharmaceutically acceptable carrier" refers to an excipient or diluent in a pharmaceutical composition. For example, a pharmaceutically acceptable carrier may be a vehicle capable of suspending or dissolving the active compound (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). The pharmaceutically acceptable carrier must be compatible with the other ingredients of the formulation and not deleterious to the recipient. In the present disclosure, the pharmaceutically acceptable carrier must provide adequate pharmaceutical stability to a compound described herein. The nature of the carrier differs with the mode of administration. For example, for oral administration, a solid carrier is preferred; for intravenous administration, an aqueous solution carrier (e.g., WFI, and/or a buffered solution) is generally used.

The term "pharmaceutically acceptable salt," as used herein, represents salts of the compounds described herein (e.g., compounds of any one of formulas (I)-(XXXXI) or a compound of Table 1) that are, within the scope of sound medical judgment, suitable for use in methods described herein without undue toxicity, irritation, and/or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: *Pharmaceutical Salts: Properties, Selection, and Use* (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

The term "about," as used herein, indicates a deviation of ±5%. For example, about 10% refers to from 9.5% to 10.5%.

Definitions of abbreviations used in the disclosure are provided in Table 3 below:

Table 3

Abbreviation	Stands for
CAN	acetonitrile
CBZ, Cbz	carboxybenzyl
DCHA	dicyclohexylamine
DCM	dichloromethane
DIEA, DIPEA	N,N-diisopropylethylamine
DMF	dimethylformamide
EDC, EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
FMOC	fluorenylmethyloxycarbonyl
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOBT	hydroxybenzotriazole
PMBN	polymyxin B nonapeptide
PMEN	polymyxin E nonapeptide
RPLC	reversed phase liquid chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Other features and advantages of the compounds described herein will be apparent from the following Detailed Description and the claims.

Description of the Drawings

FIG. 1 is a graph showing the efficacy of Compound 42 (solid bars) compared to colistin (hatched bar) against *P. aeruginosa* in a neutropenic mouse pneumonia model. The total dose in mg of the administered compound is indicated on the x-axis, and the minimum activity to achieve bactericidal activity is indicated by a dashed line.

FIG. 2 is a graph showing KIM-1 protein levels in rats after subcutaneous administration of 50 mg/kg/day of colistin and Compound 42.

FIG. 3 is a graph showing the activity of selected compounds in a thigh model of infection with COL^R *E. coli* (*mcr*-1).

FIG. 4 is a graph showing the efficacy of Compounds 42, 54, and 55 in a neutropenic mouse *P. aeruginosa* lung model.

Detailed Description

The disclosure features compounds, compositions, and methods for the treatment of bacterial infections (e.g., Gram-negative bacterial infections). The compounds disclosed herein include a cyclic heptapeptide (e.g., a polymyxin core). The cyclic heptapeptide is covalently conjugated to a peptides (e.g., a peptide including a 1-5 amino acid residue(s)). The cyclic heptapeptides in the compounds described herein bind to lipopolysaccharides (LPS) in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization of the Gram-negtaive bacteria to other antibiotics.

I. Bacterial Infections

Pathogenic bacteria cause bacterial infections and diseases such as tuberculosis, pneumonia, and foodborne illnesses. Bacteria may be categorized into two major types: Gram-positive bacteria and Gram-negative bacteria. Gram-positive bacteria possess a thick cell wall containing multiple layers of peptidoglycan and teichoic acids, while Gram-negative bacteria have a relatively thin cell wall containing fewer layers of peptidoglycan that are surrounded by a second lipid membrane containing lipopolysaccharides (LPS) and lipoproteins. LPS, also called endotoxins, are composed of polysaccharides and lipid A. These differences in bacterial cell wall structure can produce differences in antibiotic susceptibility. Examples of Gram-positive bacteria include, but are not limited to, bacteria in the genus *Streptococcus* (e.g., *Streptococcus pyogenes*), bacteria in the genus *Staphylococcus* (e.g., Staphylococcus *cohnii*), bacteria in the genus *Corynebacterium* (e.g., *Corynebacterium auris*), bacteria in the genus *Listeria* (e.g., *Listeria grayi*), bacteria in the genus *Bacillus* (e.g., *Bacillus aerius*), and bacteria in the genus *Clostridium* (e.g., *Clostridium acetium*). Examples of Gram-negative bacteria include, but are not limited to, bacteria in the genus *Escherichia* (e.g., *Escherichia coli*), bacteria in the genus *Klebsiella* (e.g., *Klebsiella granulomatis, Klebsiella oxytoca, Klebsiella pneumoniae, Klebsiella terrigena,* and *Klebsiella variicola*), bacteria in the genus *Acinetobacter* (e.g., *Acinetobacter baumannii,*

Acinetobacter calcoaceticus, *Acinetobacter kookii*, and *Acinetobacter junii*), bacteria in the genus *Pseudomonas* (e.g., *Pseudomonas aeruginosa*), bacteria in the genus *Neisseria* (e.g., *Neisseria gonorrhoeae*), bacteria in the genus *Yersinia* (e.g., *Yersinia pestis*), bacteria in the genus *Vibrio* (e.g., *Vibrio cholerae*), bacteria in the genus *Campylobacter* (e.g., *Campylobacter jejuni*), and bacteria in the genus *Salmonella* (e.g., *Salmonella enterica*).

Bacteria may evolve to become more or fully resistant to antibiotics. Resistance may arise through natural resistance in certain types of bacteria, spontaneous random genetic mutations, and/or by inter- or intra-species horizontal transfer of resistance genes. Resistant bacteria are increasingly difficult to treat, requiring alternative medications or higher doses, which may be more costly or more toxic. Bacteria resistant to multiple antibiotics are referred to as multidrug resistant (MDR) bacteria. For example, the *mcr-1* gene encodes a phosphoethanolamine transferase (MCR-1) which confers resistance to colistin, a natural polymyxin, through modification of LPS. This is the first known horizontally-transferable resistance determinant for the polymyxin class of antibiotics. The *mcr-1* gene has also been found in bacterial strains which already possess resistance to other classes of antibiotics, such as in carbapenem-resistant *Enterobacteriaceae* (CRE). An *mcr-1* resistance plasmid refers to a bacterial plasmid that carries *mcr-1* alone or in combination with other antibiotic resistance genes. A *mcr-1* resistance plasmid refers to a bacterial plasmid that carries one or more antibiotic resistance genes. Examples of *mcr-1* resistance plasmids include, but are not limited to, pHNSHP45, pMR0516mcr, pESTMCR, pAF48, pAF23, pmcr1-IncX4, pmcr1-IncI2, pA31-12, pVT553, pICBEC72Hmcr, pE15004, pE15015, and pE15017.

In another example, the *mcr-2* gene also confers resistance to colistin. The *mcr-2* gene was identified in porcine and bovine colistin-resistance *E.coli* that did not contain *mcr-1* (Xavier et al., *Euro Surveill* 21(27), 2016). The *mcr-2* gene is a 1,617 bp phspoethanolamine transferase harbored on an IncX4 plasmid. The *mcr-2* gene has 76.7% nucleotide identity to *mcr-1*. Analysis of *mcr-2* harboring plasmids from *E.coli* isolates shows that the mobile element harboring *mcr-2* is an IS element of the IS_{1595} superfamily, which are distinguished by the presence of an $ISXO_2$-like transposase domain (Xavier et al., *supra*). The MCR-2 protein was predicted to have two domains, with domain 1 (1-229 residues) as a transporter and domain 2 (230-538 residues) as a transferase domain. An *mcr-2* resistance plasmid refers to a bacterial plasmid that carries *mcr-2* alone or in combination with other antibiotic resistance genes. A *mcr-2* resistance plasmid refers to a bacterial plasmid that carries one or more antibiotic resistance genes. *Mcr-2* resistance plasmids include, but are not limited to, pKP37-BE and pmcr2-IncX4. In another example, the *mcr*-3, *mcr*-4, *mcr*-5, *mcr*-6, *mcr*-7, and *mcr*-8 genes also confer resistance to colistin, described in Wang et al., *Emerging Microbes & Infections* 7:122 (2018), which is herein incorporated by reference in its entirety.

Furthermore, resistant strain *E. coli* BAA-2469 possesses the New Delhi metallo-β-lactamase (NDM-1) enzyme, which makes bacteria resistant to a broad range of β-lactam antibiotics. Additionally, *E. coli* BAA-2469 is also known to be resistatnt to penicillins (e.g., ticarcillin, ticarcillin/clavulanic acid, piperacillin, ampicillin, and ampicillin/sulbactam), cephalosporins (e.g., cefalotin, cefuroxime, cefuroxime, cefotetan, cefpodoxime, cefotaxime, ceftizoxime, cefazolin, cefoxitin, ceftazidime, ceftriaxone, and cefepime), carbapenems (e.g., doripenem, meropenem, ertapenem, imipenem), quinolones (e.g.,

nalidixic acid, moxifloxacin, norfloxacin, ciprofloxacin, and levofloxacin), aminoglycosides (e.g., amikacin, gentamicin, and tobramycin), and other antibiotics (e.g., tetracycline, tigecycline, nitrofurantoin, aztreonam, trimethoprim/sulfamethoxazole).

In some embodiments, a resistant strain of bacteria possesses the *mcr-1* gene, the *mcr-2* gene, the *mcr*-3 gene, the *mcr*-4 gene, the *mcr*-5 gene, the *mcr*-6 gene, the *mcr*-7 gene, the *mcr*-8 gene, and/or a chromosomal mutation conferring polymyxin resistance. In some embodiments, a resistant strain of bacteria is a resistant strain of *E. coli* (e.g., *E. coli* BAA-2469).

II. Compounds of the Disclosure

Provided herein are synthetic compounds useful in the treatment of bacterial infections (e.g., Gram-negative bacterial infections). The compounds disclosed herein include a cyclic heptapeptide (e.g., a polymyxin core). The cyclic heptapeptide is convalently conjugated to a peptide (e.g., a peptide including a 1-5 amino acid residue(s)). The peptide may further be conjugated to a terminal moiety (e.g., R^{16}, such as an optionally substituted alkamino, alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaryl, alkaryl, or heteroalkaryl moiety).

Without being bound by theory, in some aspects, compounds described herein bind to the cell membrane of Gram-negative bacteria (e.g., bind to LPS in the cell membrane of Gram-negative bacteria) through the interactions between the cyclic heptapeptides in the compounds and the cell membrane of Gram-negative bacteria. The binding of the compounds to the cell membrane of Gram-negative bacteria disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization of the Gram-negative bacteria to other antibiotics. In some embodiments, the initial association of the compounds with the bacterial cell membrane occurs through electrostatic interactions between the cyclic heptapepdies in the compounds and the anionic LPS in the outer membrane of Gram-negative bacteria, disrupting the arrangement of the cell membrane. Specifically, compounds described herein may bind to lipid A in the LPS. More specifically, the cyclic heptapeptides in the compounds described herein may bind to one or both phosphate groups in lipid A. In some embodiments, antibiotic-resistant bacteria (e.g., antibiotic-resistant, Gram-negative bacteria) has one phosphate group in lipid A. In some embodiments, compounds described herein may bind to multiple Gram-negative bacterial cells at the same time. The binding of the compounds described herein to the LPS may also displace Mg^{2+} and Ca^{2+} cations that bridge adjacent LPS molecules, causing, e.g., membrane permeabilization, leakage of cellular molecules, inhibition of cellular respiration, and/or cell death.

Compounds provided herein are described by any one of formulas (I)-(XXXXI) or a compound of Table 1. In some embodiments, the compounds described herein include a cyclic heptapeptide conjugated to peptide (e.g., a peptide including a 1-5 amino acid residue(s)). Compounds described herein may be synthesized using available chemical synthesis techniques in the art. In some embodiments, available functional groups in the cyclic heptapeptides and the linear peptide or the terminal moiety (e.g., R^{16}), e.g., amines, carboxylic acids, maleimides, bis-sulfones, azides, alkynes, and/or hydroxyl groups, may be used in making the compounds described herein. For example, the linking nitrogen (described further herein) in a cyclic heptapeptide may form an amide bond with the

carbon in a carboxylic acid group (e.g., in a peptide). A peptide including one or more (e.g., 1-5; 1, 2, 3, 4, or 5) amino acid residues (e.g., natural and/or non-natural amino acid residues) may be covalently attached to the linking nitrogen of the cyclic heptapeptide through forming an amide bond between the carbon in a carboxylic acid group in the peptide and the linking nitrogen. In cases where a functional group is not available for conjugation, a molecule may be derivatized using conventional chemical synthesis techniques that are well known in the art. In some embodiments, the compounds described herein contain one or more chiral centers. The compounds include each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers, enantiomers, and tautomers that can be formed.

Cyclic heptapeptide or polymyxin core

In some aspects, a cyclic heptapeptide or polymyxin core, as used herein, refers to certain compounds that bind to lipopolysaccharides (LPS) in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization to other antibiotics. In some aspects, cyclic heptapeptide, as used herein, refers to certain compounds that kill or inhibit the growth of Gram-negative bacteria as determined by measuring the minimum inhibitory concentration (MIC) against at least one Gram-negative bacteria as known in the art, wherein the MIC is 128 μg/mL or less (e.g., 110 μg/mL or less, 100 μg/mL or less, 90 μg/mL or less, 80 μg/mL or less, 70 μg/mL or less, 60 μg/mL or less, 50 μg/mL or less, 40 μg/mL or less, 30 μg/mL or less, 20 μg/mL or less, or 10 μg/mL or less).

Cyclic heptapeptides are composed of, at least, amino acid residues, each of which may, independently, may have a D- or L- configuration, assembled as a cyclic heptapeptide ring. A cyclic heptapeptide includes seven natural or non-natural amino acid residues attached to each other in a closed ring. The ring contains six bonds formed by linking the carbon in the α-carboxyl group of one amino acid residue to the nitrogen in the α-amino group of the adjacent amino acid residue and one bond formed by linking the carbon in the α-carboxyl group of one amino acid residue to the nitrogen in the γ-amino group in the side chain of the adjacent amino acid residue. For the amino acid residue whose nitrogen in the γ-amino group in the side chain participates in forming the ring, the nitrogen in the α-amino group of this amino acid residue does not participate directly in forming the ring and serves as the linking nitrogen (thus, referred to as the "linking nitrogen" herein) that links the cyclic heptapeptide or polymyxin core to a peptides (e.g., a peptide including a 1-5 amino acid residue(s)).

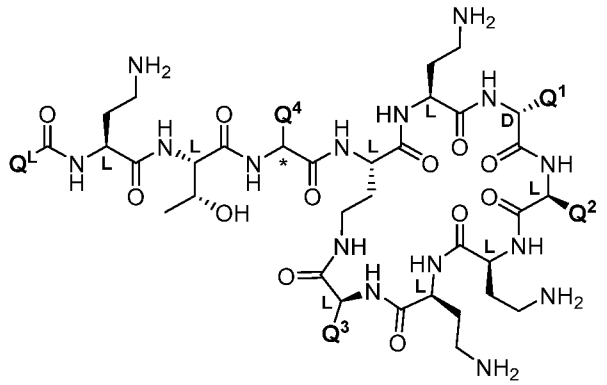
In some embodiments, a peptide including one or more (e.g., 1-5; 1, 2, 3, 4, or 5) amino acid residues (e.g., natural and/or non-natural amino acid residues) is covalently attached to the linking nitrogen of the cyclic heptapeptide or the polymyxin core.

In some embodiments, a terminal moiety (e.g., R^{16}, such as an optionally substituted alkamino, alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaryl, alkaryl, or heteroalkaryl moiety) is covalently attached the the free terminal amine of the peptide (e.g., via an amide bond). It is specifically contemplated that when the peptide is a tetrapeptide (e.g., a, b, c, and d are each 1), then the terminal moiety, R^{16} is a cyclic moiety (e.g., optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally

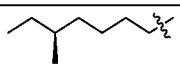
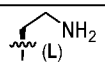
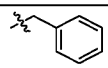
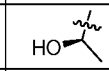
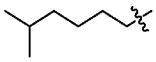
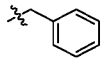
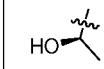
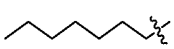
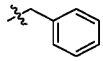
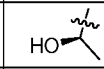
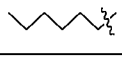
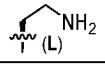
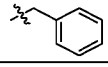
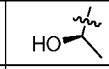
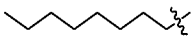
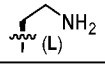
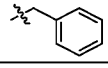
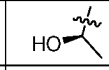
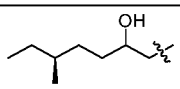
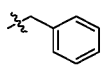
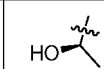
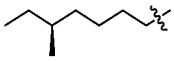
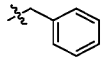
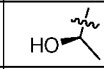
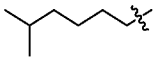
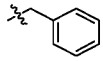
substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl).

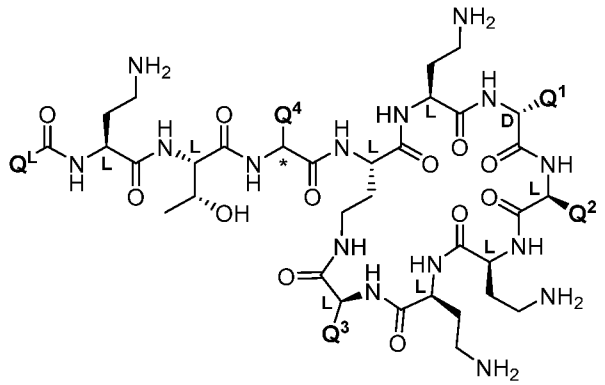
Cyclic heptapeptides or polymyxin cores may be derived from polymyxins (e.g., naturally existing polymyxins and non-natural polymyxins) and/or octapeptins (e.g., naturally existing octapeptins and non-natural octapeptins). In some embodiments, cyclic heptapeptides may be compounds described in Gallardo-Godoy et al., *J. Med. Chem.* 59:1068, 2016 (e.g., compounds 11-41 in Table 1 of Gallardo-Godoy et al.), which is incorporated herein by reference in its entirety. Examples of naturally existing polymyxins and their structures are shown in Table 2A. Examples of non-natural polymyxins and their structures are shown in Table 2B.

Table 2A. Natural polymyxins and their structures



* = stereochemistry varies and is indicated herein when known

Compound	Q^L	Q^4	Q^1	Q^2	Q^3
polymyxin B_1					
polymyxin B_2					
polymyxin B_3					
polymyxin B_4					
polymyxin B_5					
polymyxin B_6					
polymyxin B_1-Ile					
polymyxin B_2-Ile					
polymyxin C_1					
polymyxin C_2					
polymyxin S_1					
polymyxin T_1					



* = stereochemistry varies and is indicated herein when known

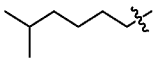
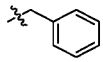
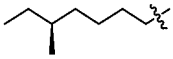
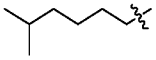
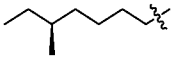
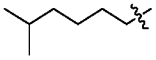
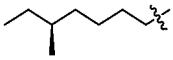
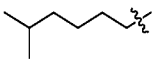
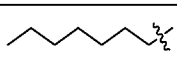
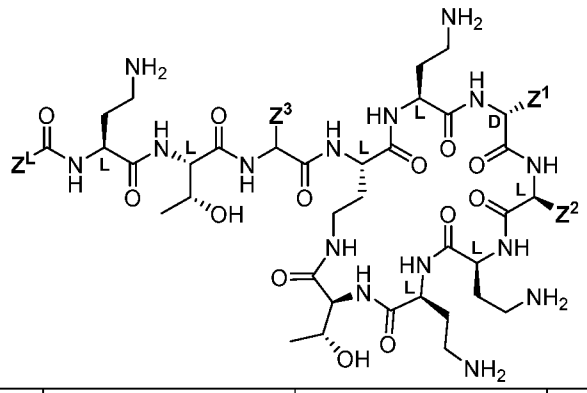
Compound	Q^L	Q^4	Q^1	Q^2	Q^3
polymyxin T_2					
polymyxin A_1					
polymyxin A_2					
polymyxin D_1					
polymyxin D_2					
polymyxin E_1 (colistin A)					
polymyxin E_2 (colistin B)					
polymyxin E_3					
polymyxin E_4					
polymyxin E_7					
polymyxin E_1-Ile					
polymyxin E_1-Val					
polymyxin E_1-Nva					
polymyxin E_2-Ile					
polymyxin E_2-Val					
polymyxin E_2-Nva					
polymyxin E_8-Ile					
polymyxin M_1					
polymyxin M_2					

Table 2B. Non-natural polymyxins and their structures
(Dab: diaminobutyric acid; Dap: diaminopropionic acid; Orn: ornithine;
Abu: 2-aminobutyric acid; Nle: norleucine)



Non-natural Compound	Z^L	Z^3	Z^1	Z^2
(i)	Octanoyl	L-Dab	D-Leu	L-Thr
(ii)	Octanoyl	L-Dab	D-Leu	L-Ala
(iii)	Octanoyl	L-Dab	D-Leu	L-Val
(iv)	Octanoyl	L-Dab	D-Nle	L-Thr
(v)	Octanoyl	L-Dab	D-Leu	L-Ser
(vi)	Octanoyl	L-Dab	D-Thr	L-Leu
(vii)	Octanoyl	L-Dab	D-Val	L-Thr
(viii)	Octanoyl	L-Dab	D-Thr	L-Thr
(ix)	Octanoyl	L-Dab	D-Val	L-Val
(x)	Octanoyl	L-Dap	D-Leu	L-Thr
(xi)	Octanoyl	L-Orn	D-Leu	L-Thr
(xii)	Octanoyl	L-Dap	D-Leu	L-Ala
(xiii)	Octanoyl	L-Dap	D-Leu	L-Abu
(xiv)	Octanoyl	D-Dap	D-Leu	L-Abu
(xv)	Octanoyl	L-Dab	D-Leu	L-Abu
(xvi)	Octanoyl	L-Dab	Cyclohexylmethyl	L-Thr
(xvii)	Octanoyl	L-Dab	Cyclopentylmethyl	L-Thr
(xviii)	Octanoyl	L-Dab	Cyclopropylmethyl	L-Thr
(xvix)	Octanoyl	L-Dab	Naphthylmethyl	L-Thr
(xx)	Octanoyl	L-Dab	Thiophenylmethyl	L-Thr
(xi)	Octanoyl	L-Dab	Furanylmethyl	L-Thr

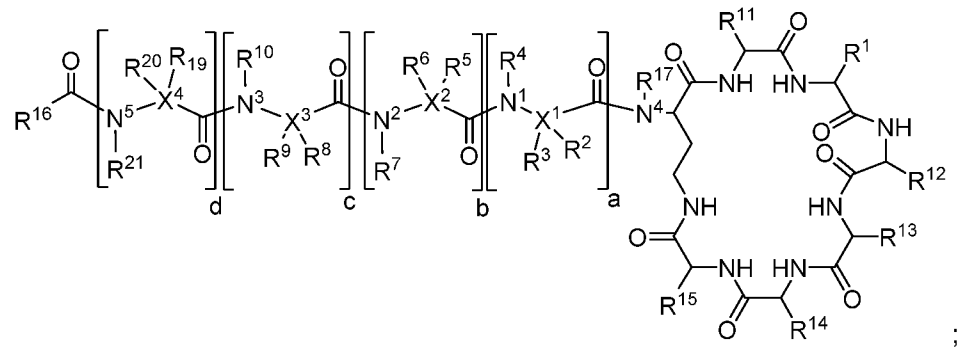
Cyclic heptapeptides linked to a linear peptide

The compounds described herein include a cyclic heptapeptide (e.g., a polymyxin core) covalently linked to a linear peptide (e.g., a 1-5 amino acid peptide, optionally conjugated to a terminal moiety).

In some embodiments, a peptide including one or more (e.g., 1-5; 1, 2, 3, 4, or 5) amino acid residues (e.g., natural and/or non-natural amino acid residues) is covalently attached to the linking nitrogen (e.g., N^4) of the cyclic heptapeptide or the polymyxin core.

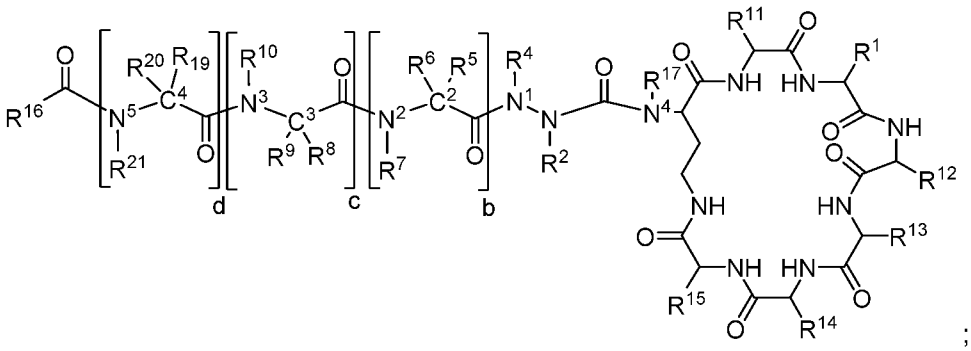
In some embodiments, a terminal moiety (e.g., R^{16}, such as an optionally substituted alkamino, alkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, heteroaryl, alkaryl, or heteroalkaryl moiety) is covalently attached the the free terminal amine of the peptide (e.g., via an amide bond). It is specifically contemplated that, in some embodiments, the peptide is a tetrapeptide (e.g., a, b, c, and d are each 1), and the terminal moiety, R^{16} is a cyclic moiety (e.g., optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl).

The disclosure provides a compound, or a pharmaceutically acceptable salt thereof, described by any one of formulas (I)-(XXXXI):



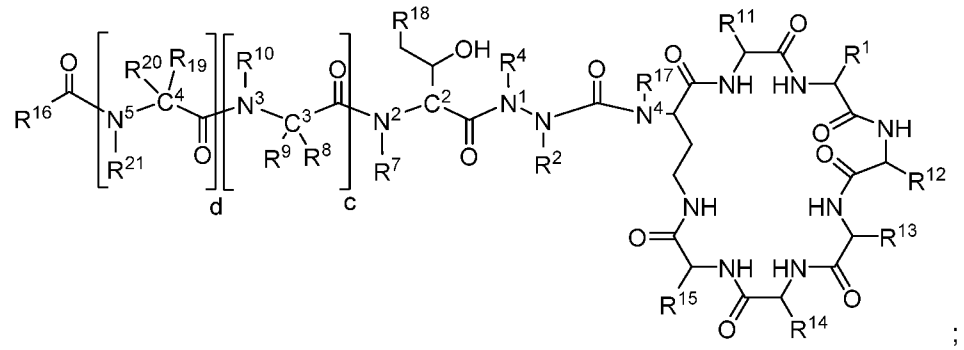
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(I)



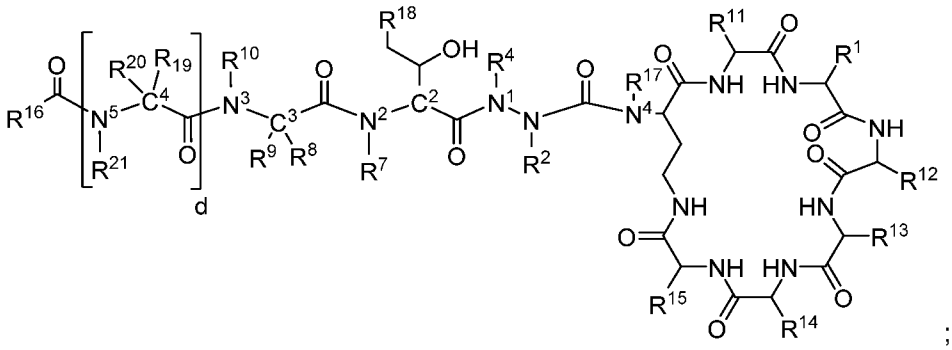
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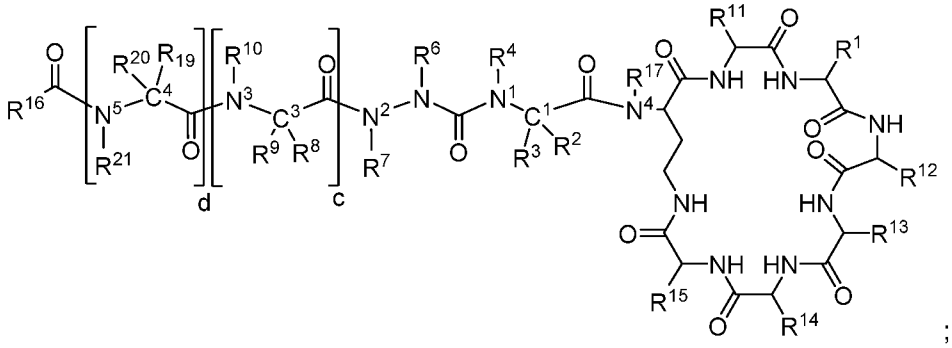
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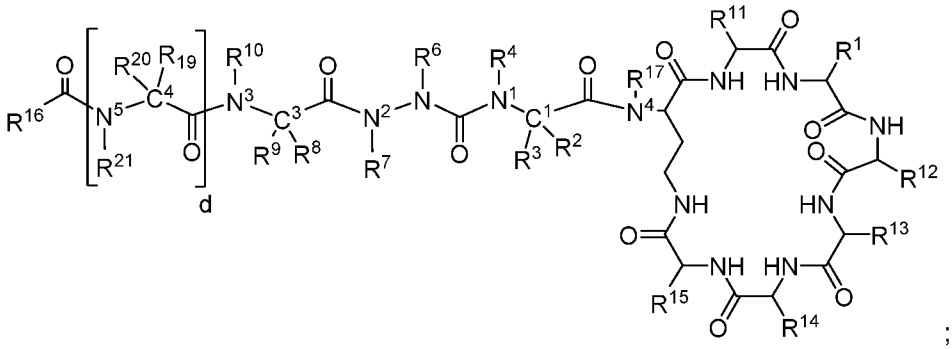
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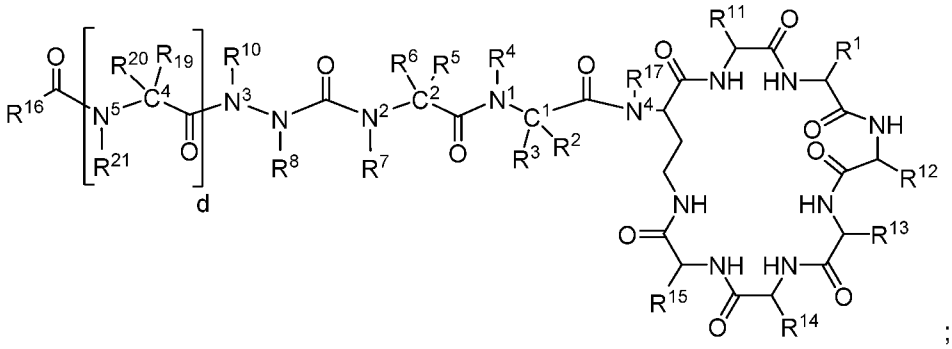
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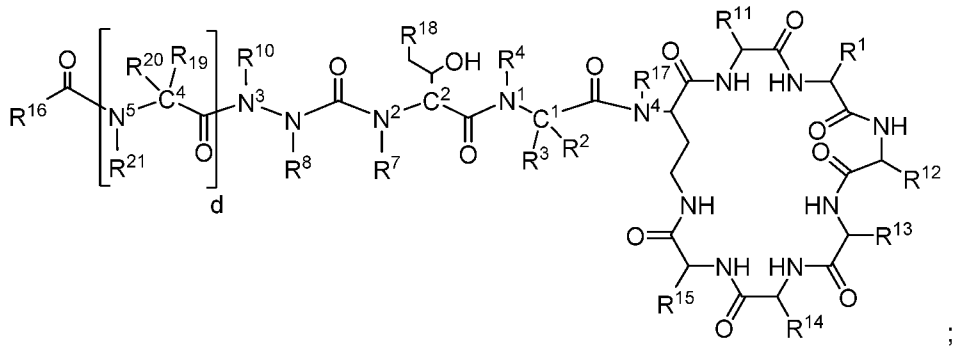
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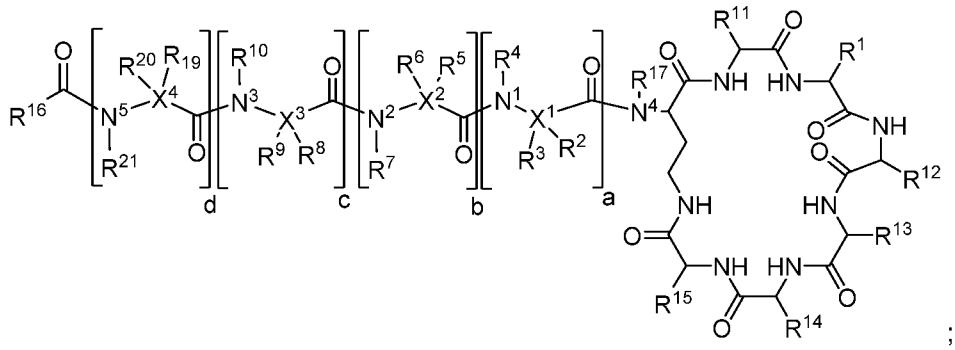
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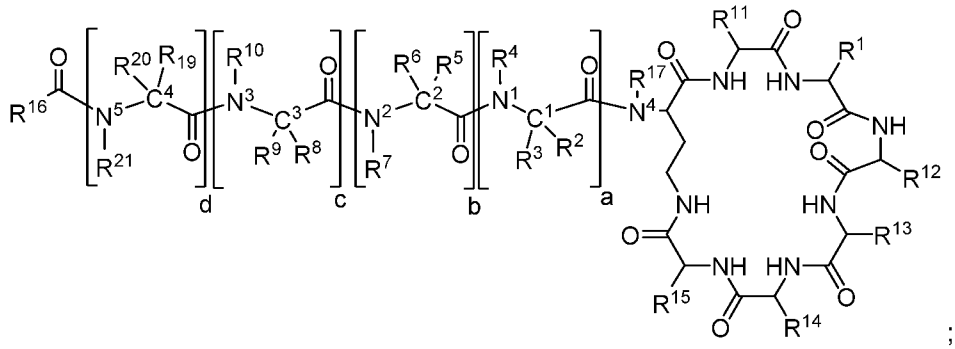
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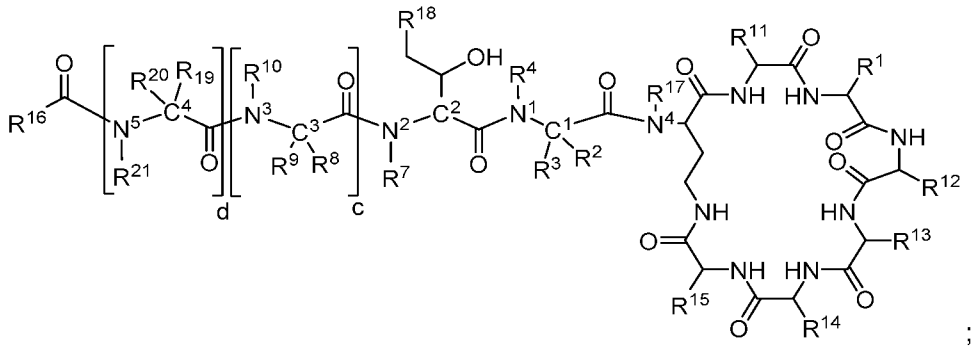
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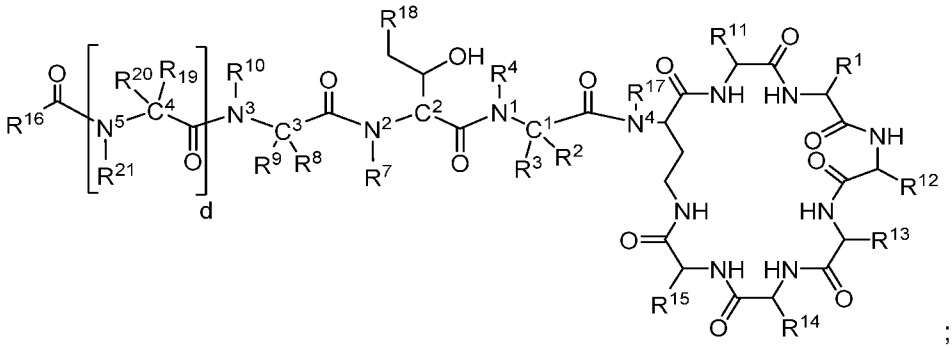
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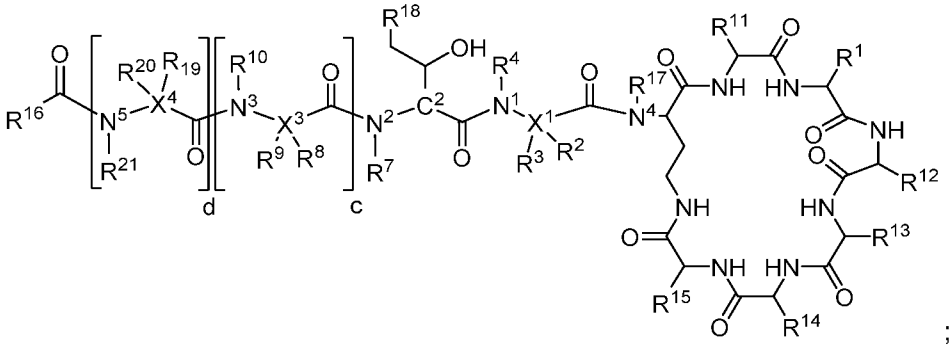
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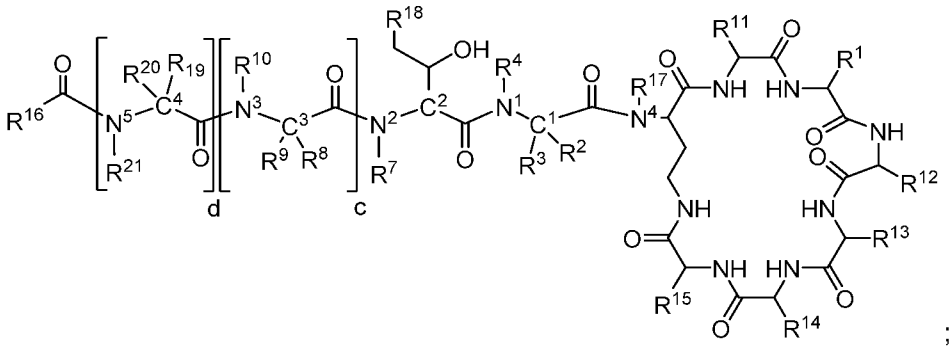
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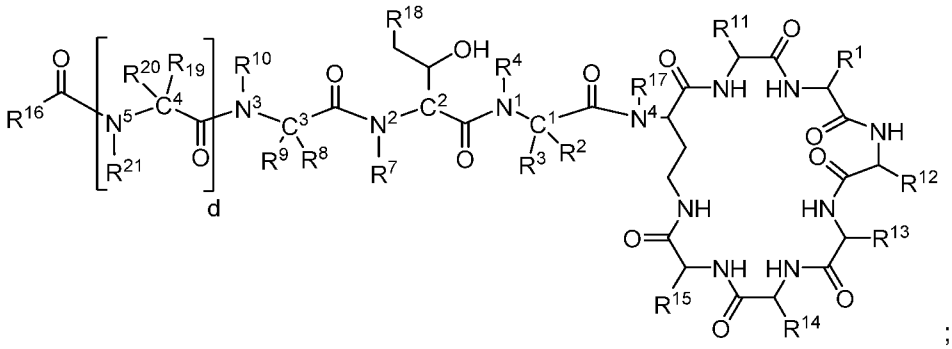
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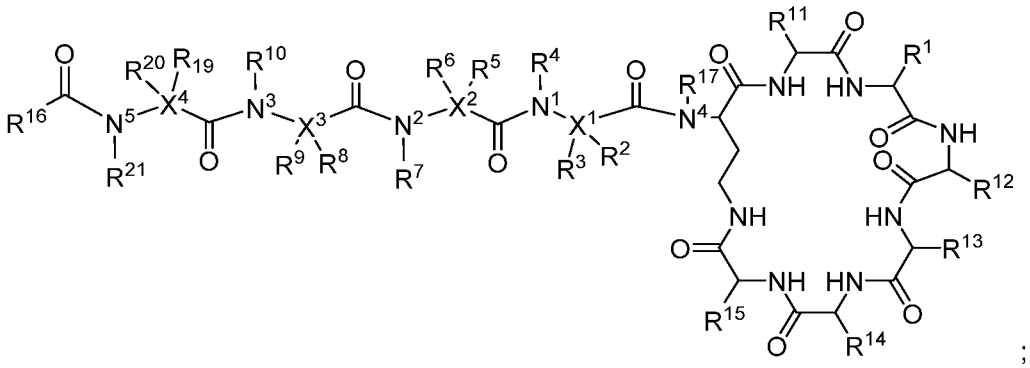
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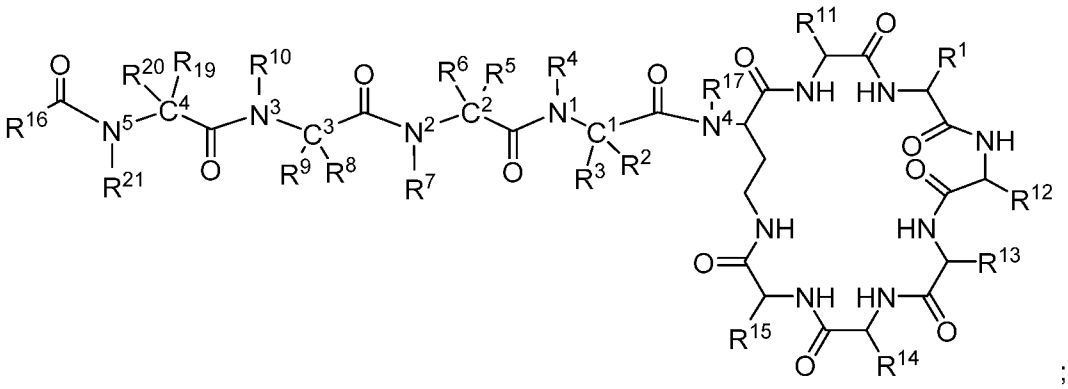
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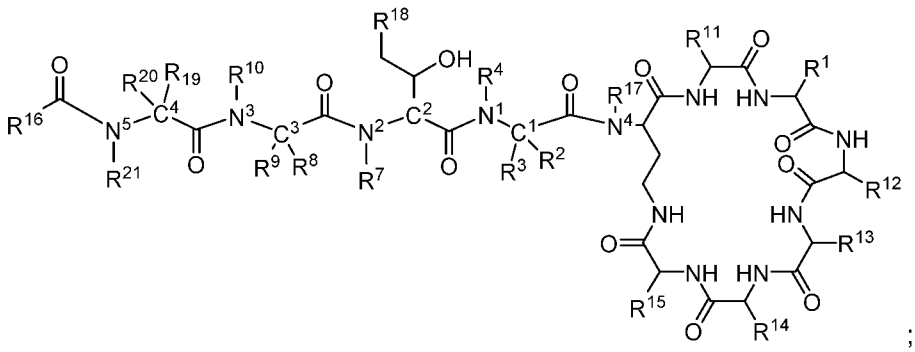
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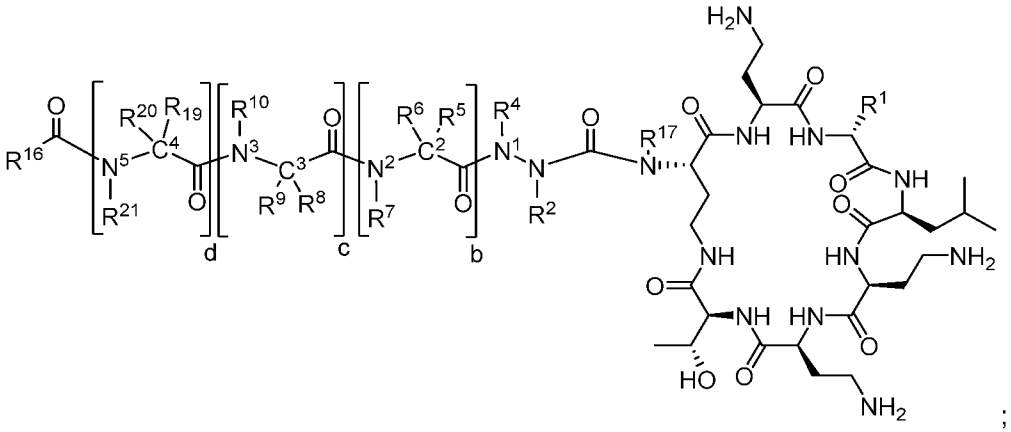
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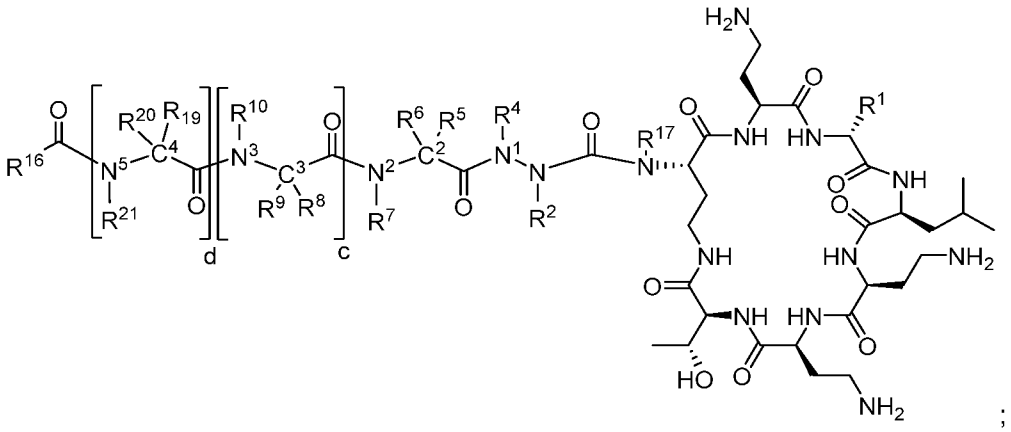
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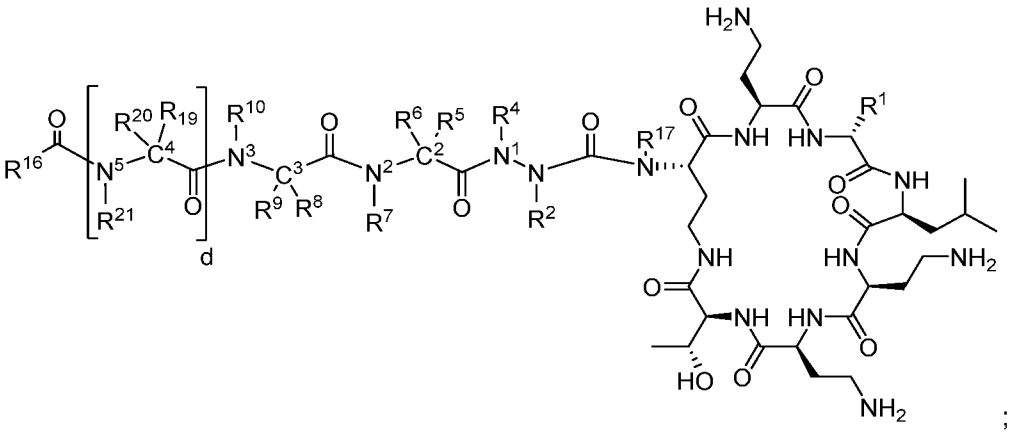
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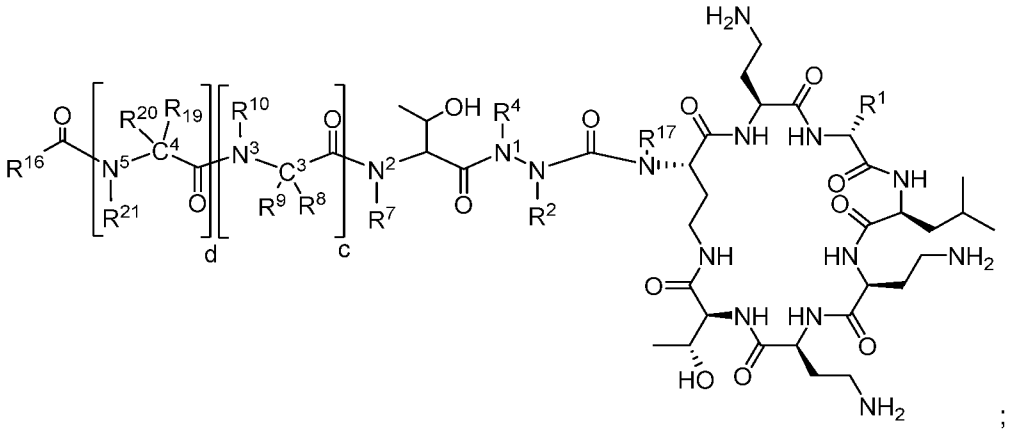
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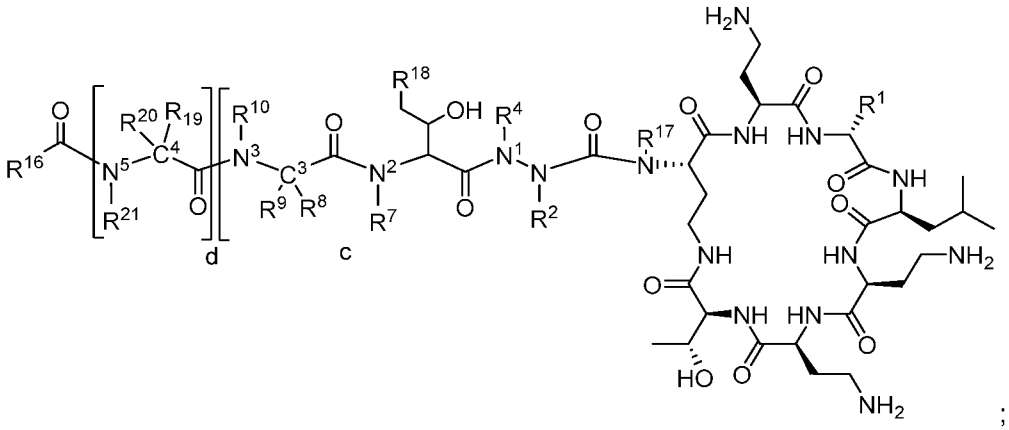
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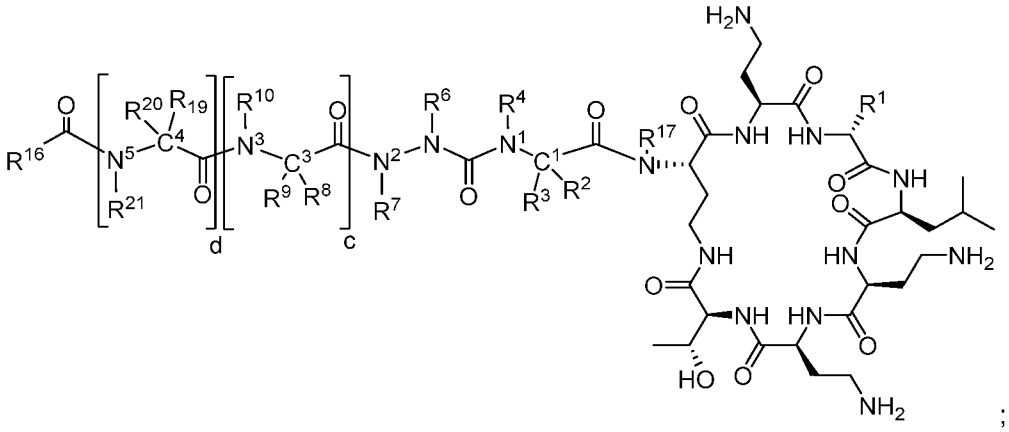
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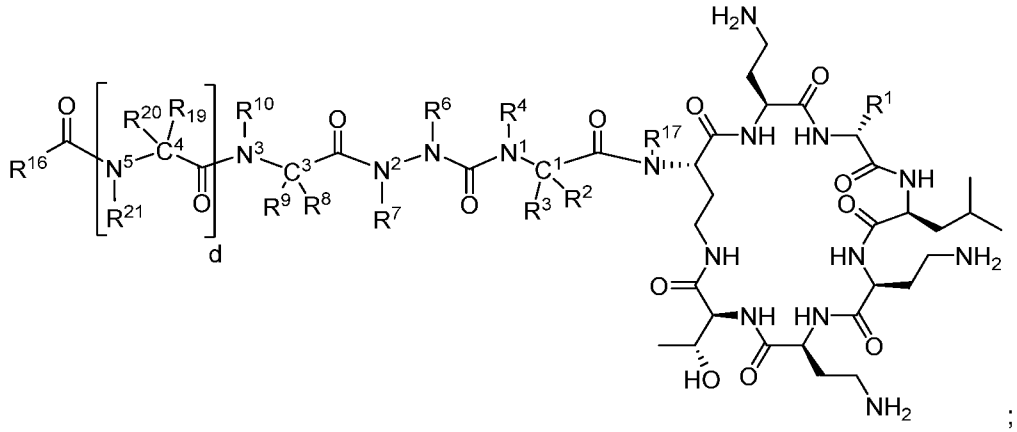
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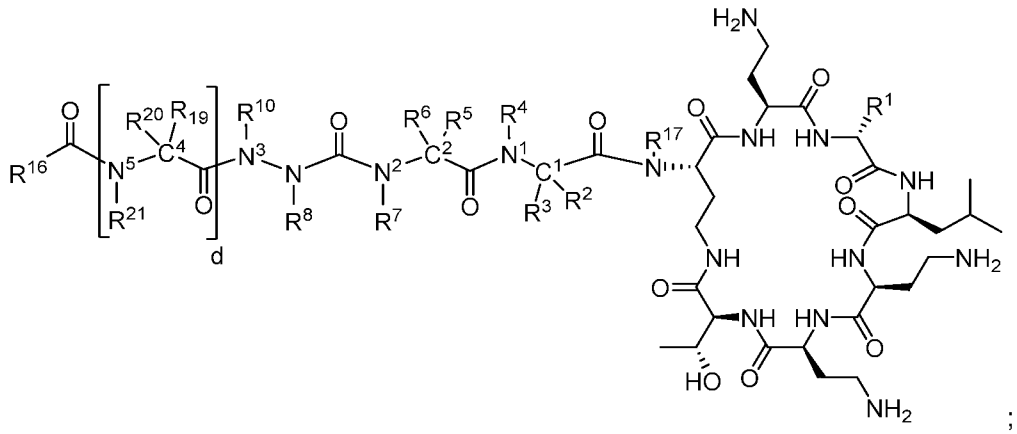
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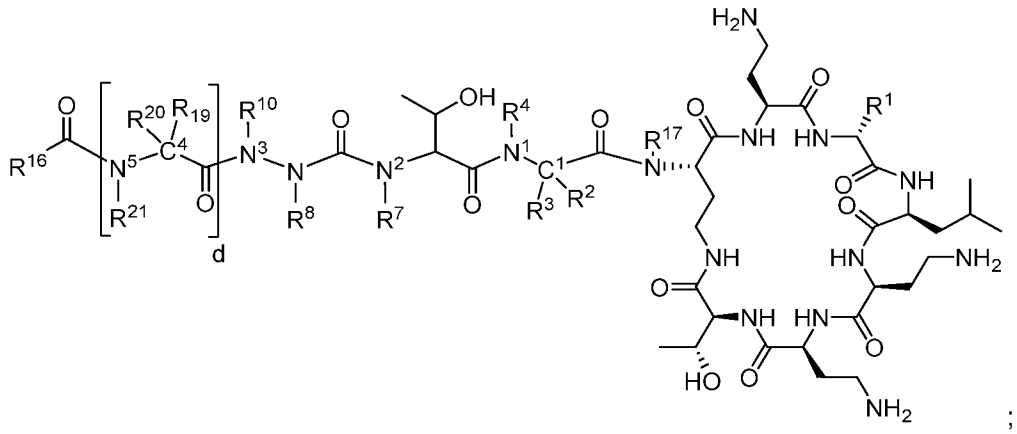
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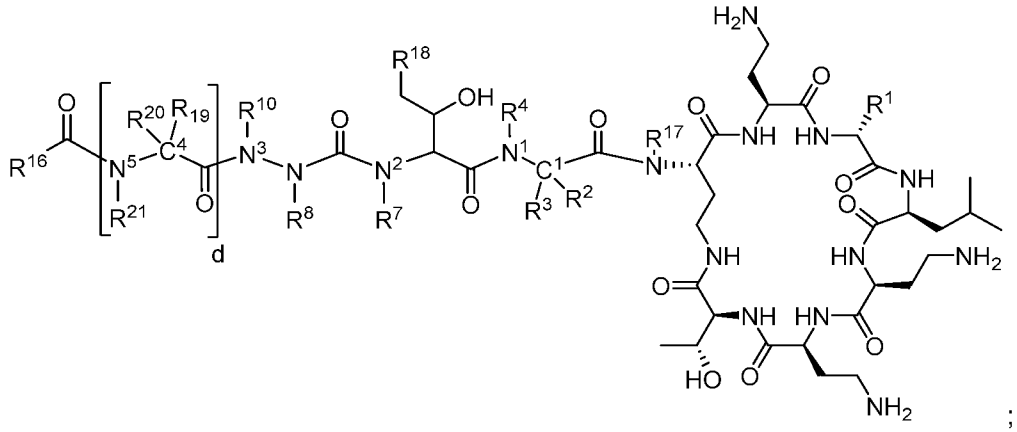
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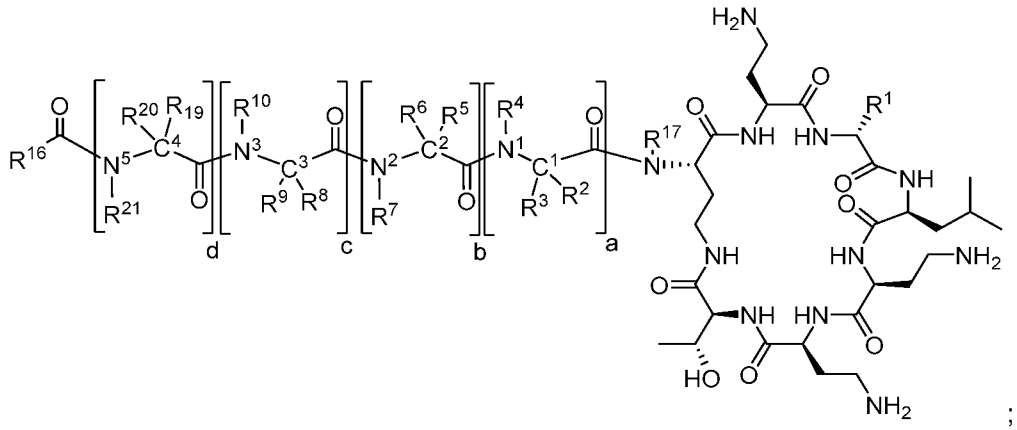
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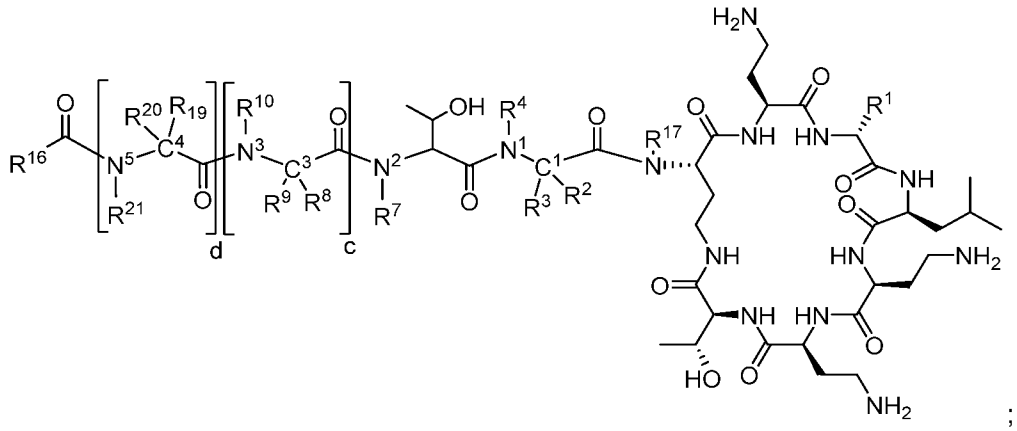
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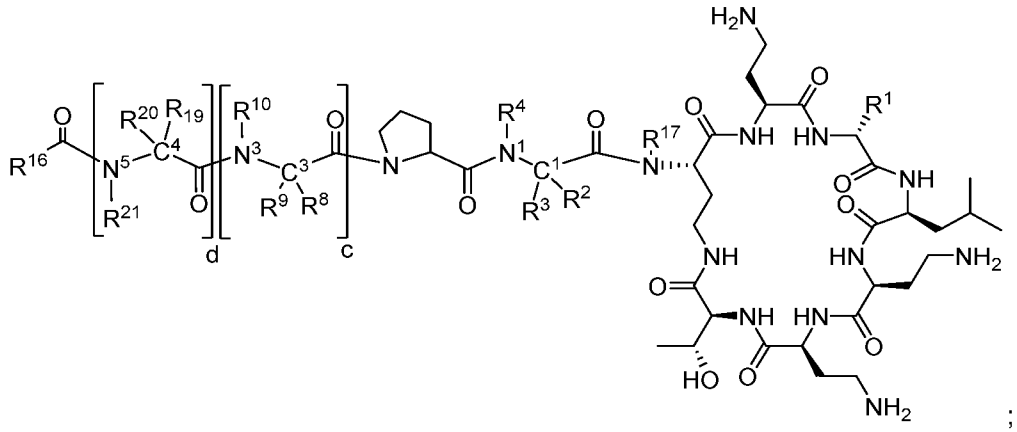
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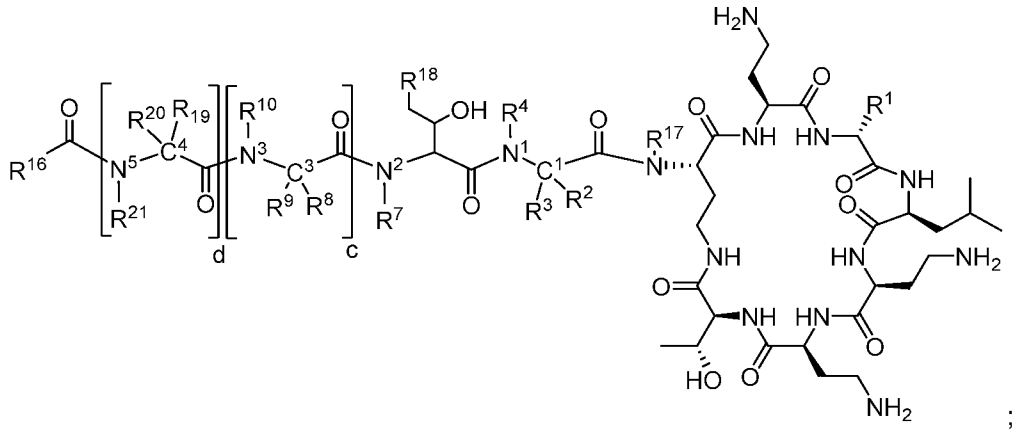
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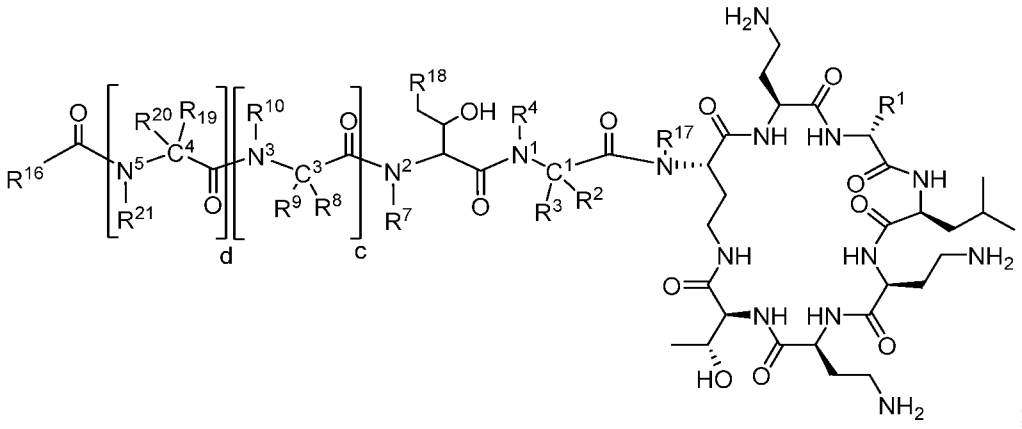
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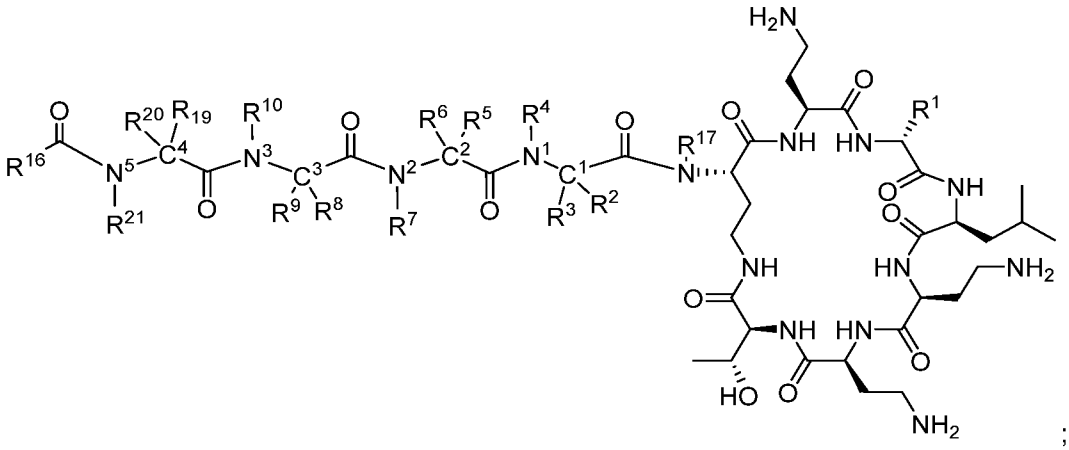
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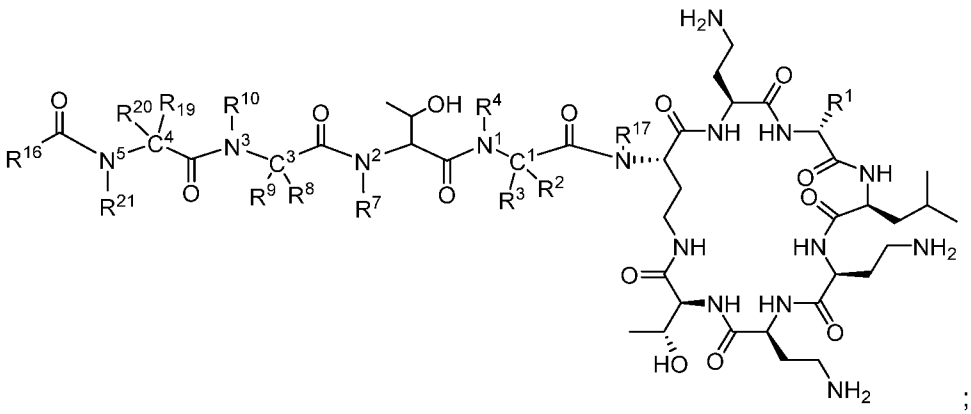
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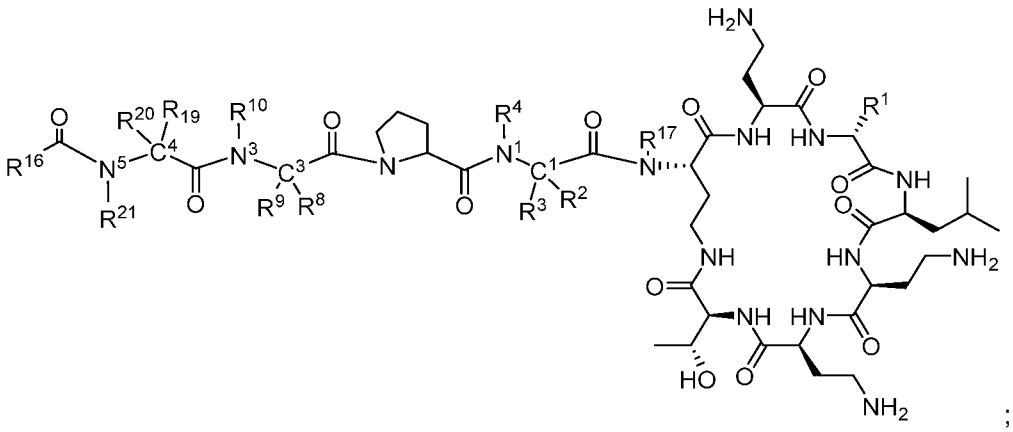
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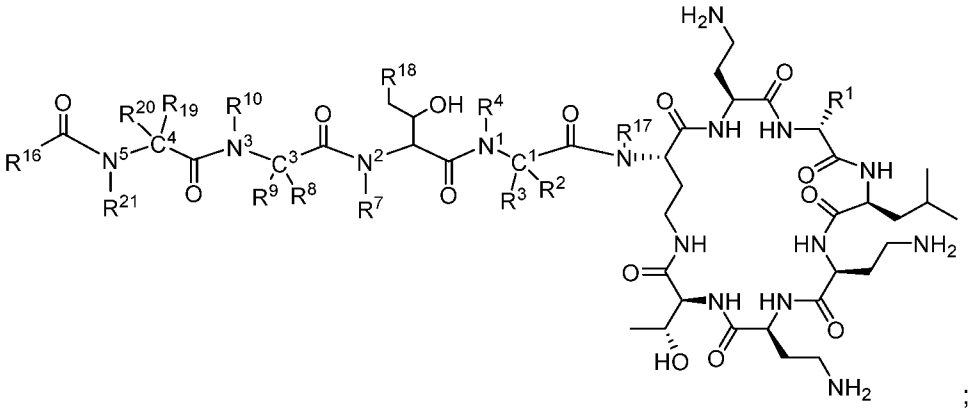
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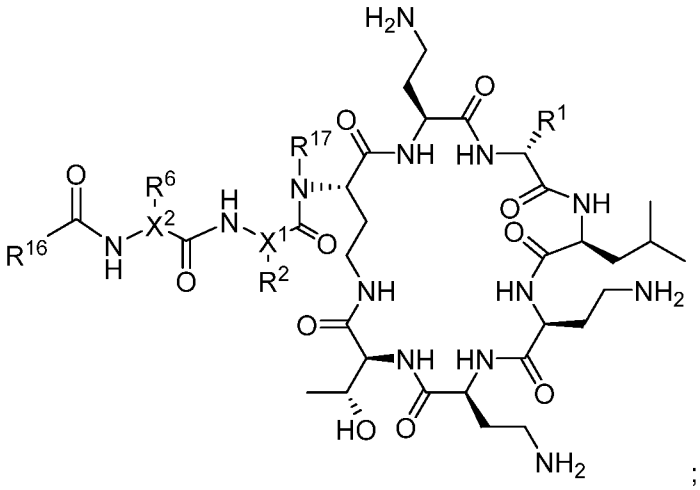
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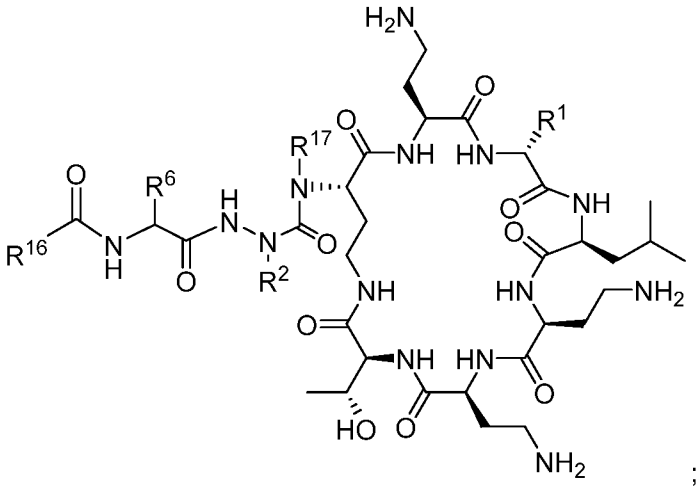
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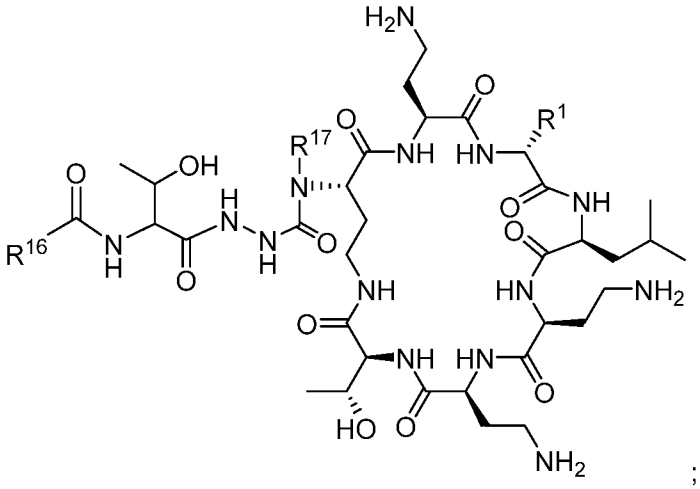
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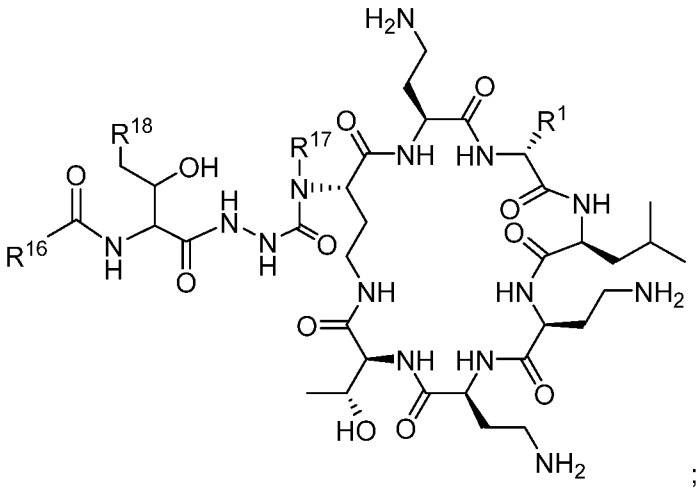
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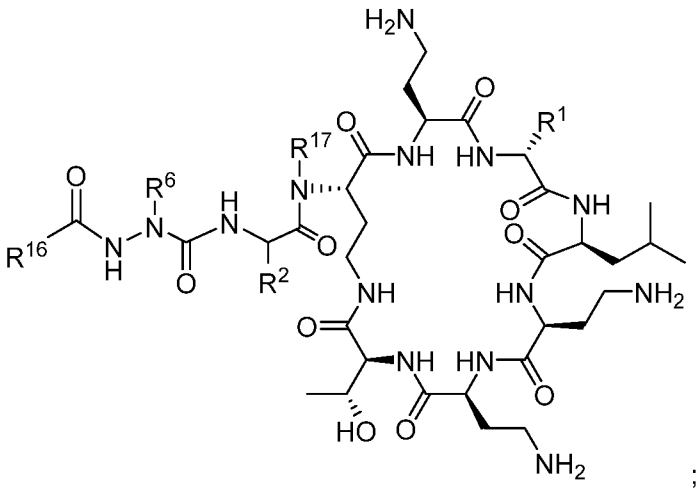
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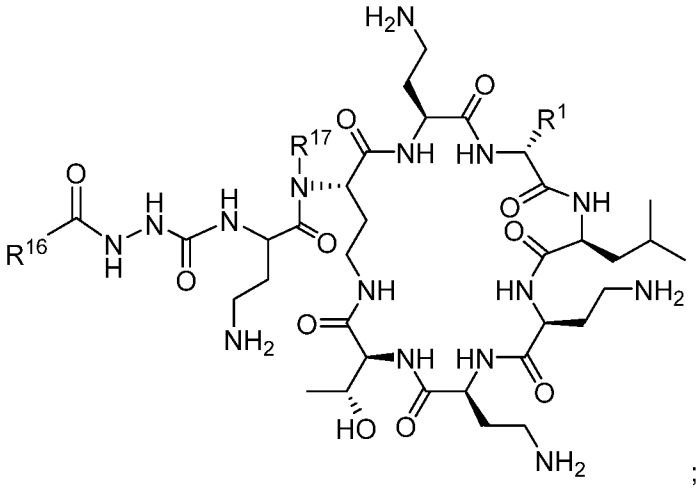
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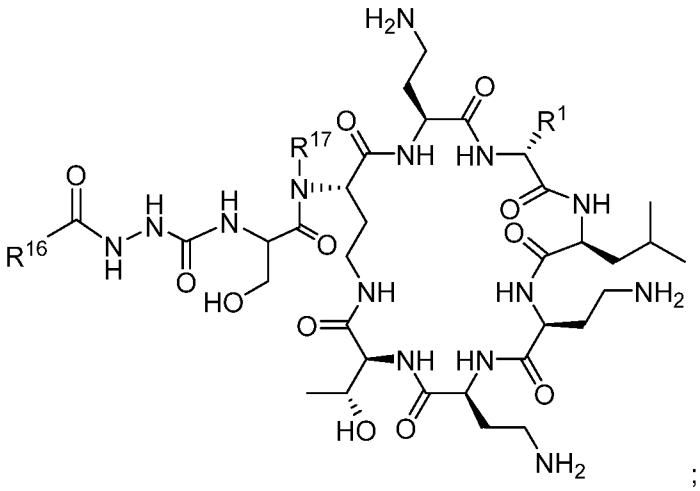
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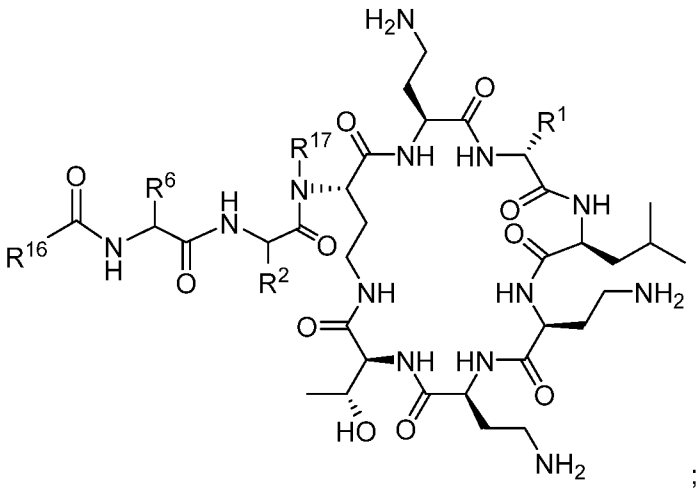
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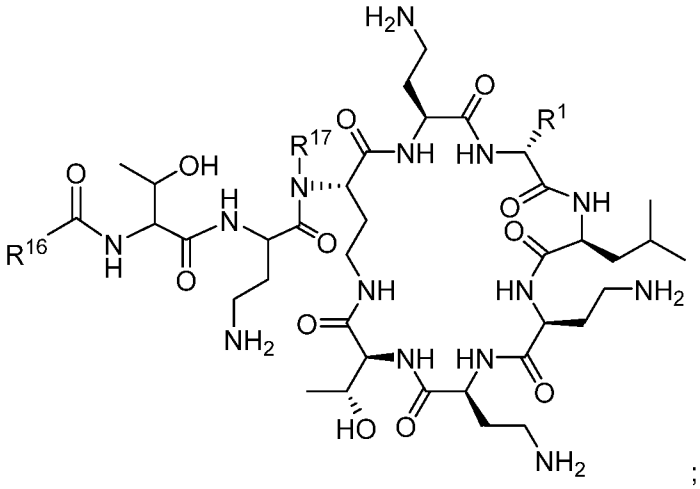
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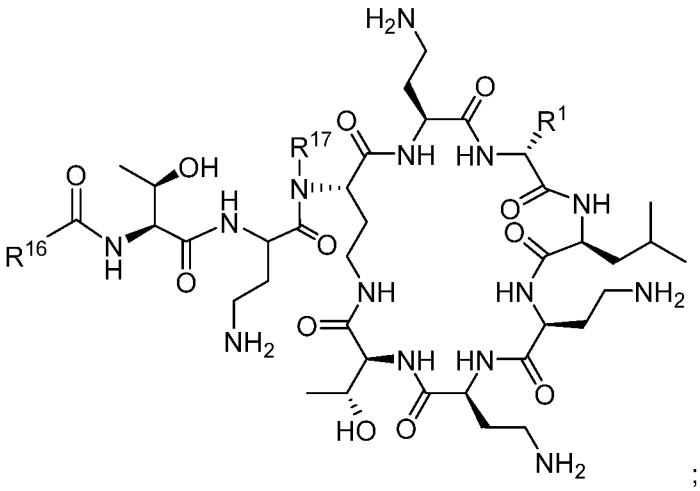
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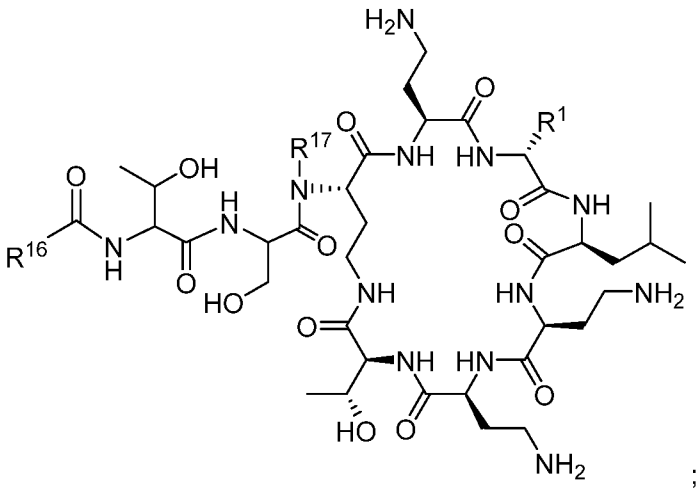
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(XII-1)



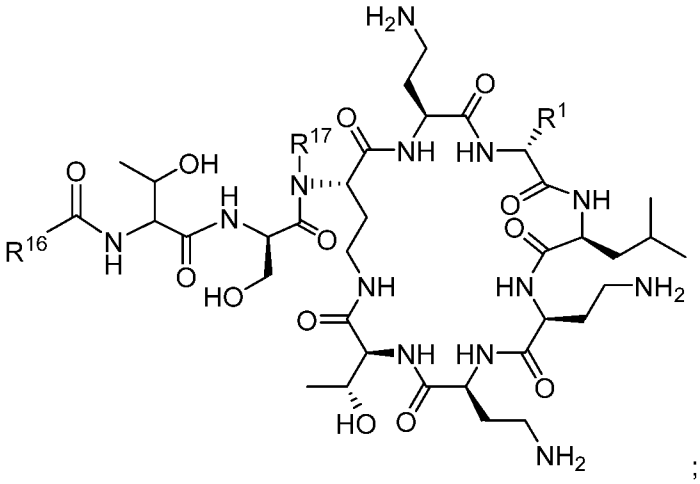
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(XII-2)



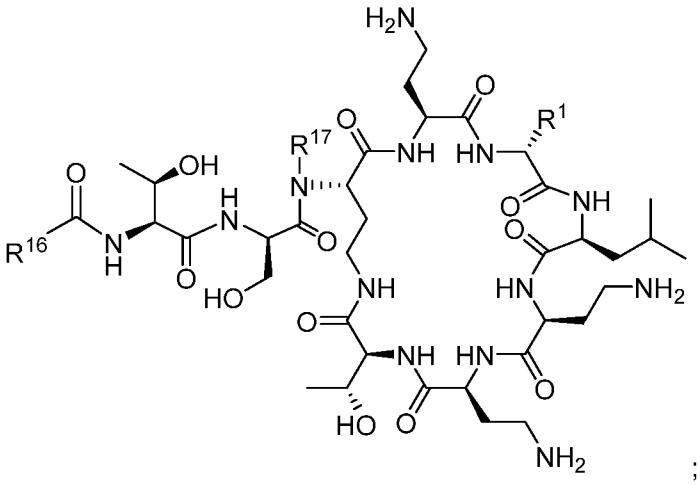
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(XII-3)



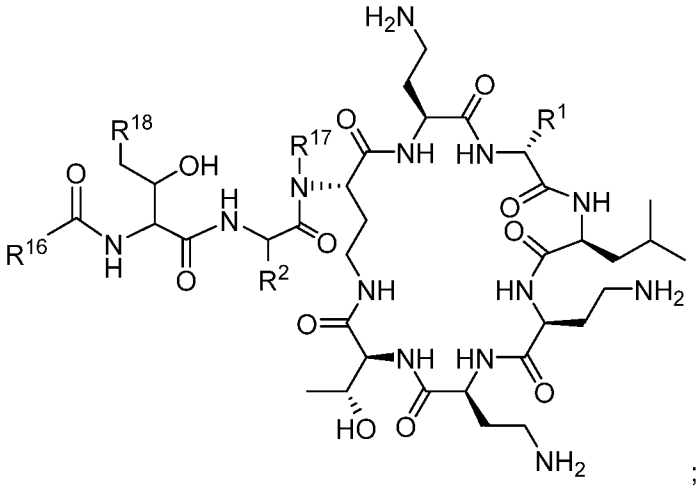
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(XII-4)



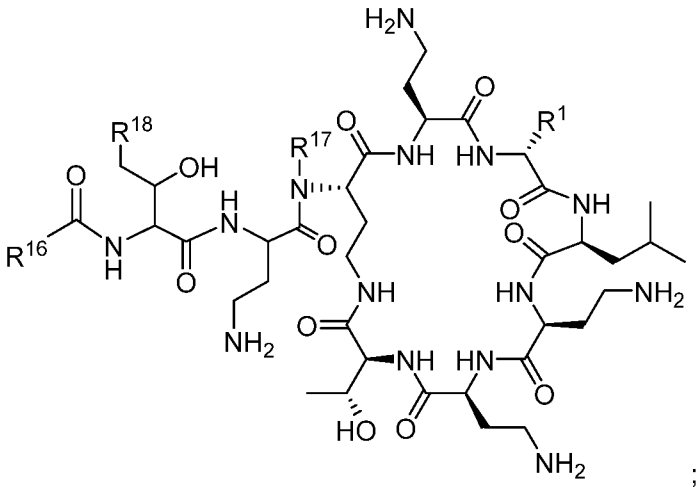
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(XII-5)



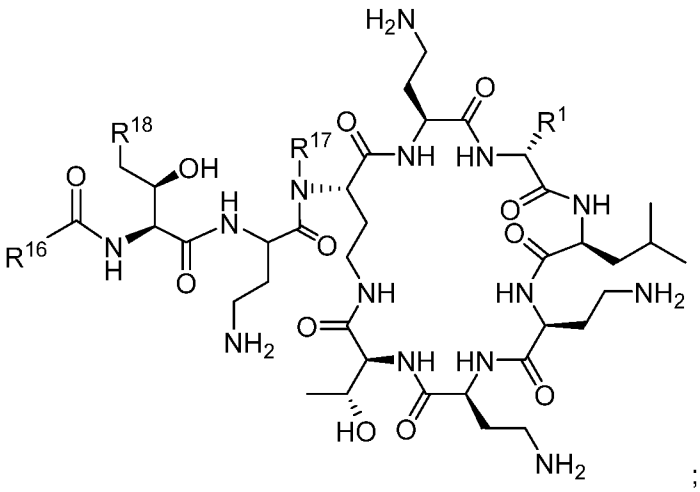
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(XIII)



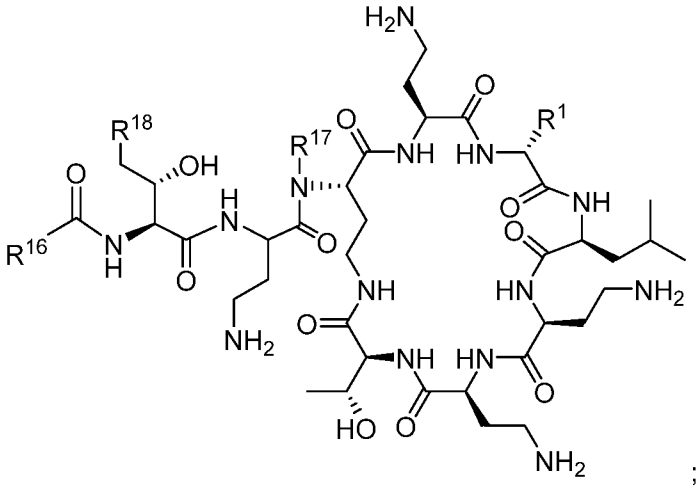
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(XIII-1)



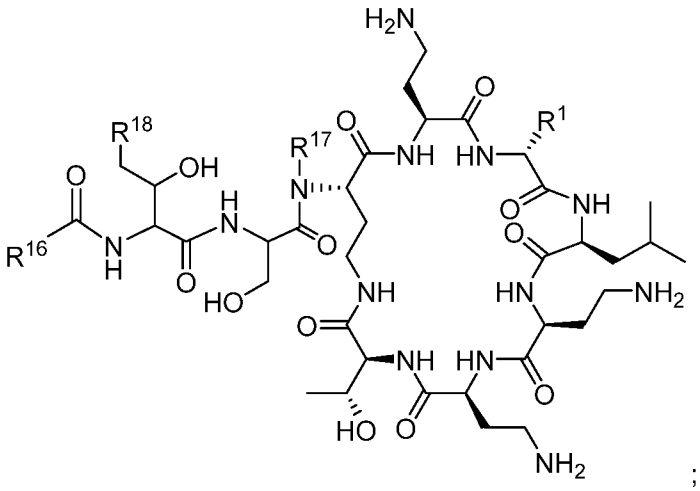
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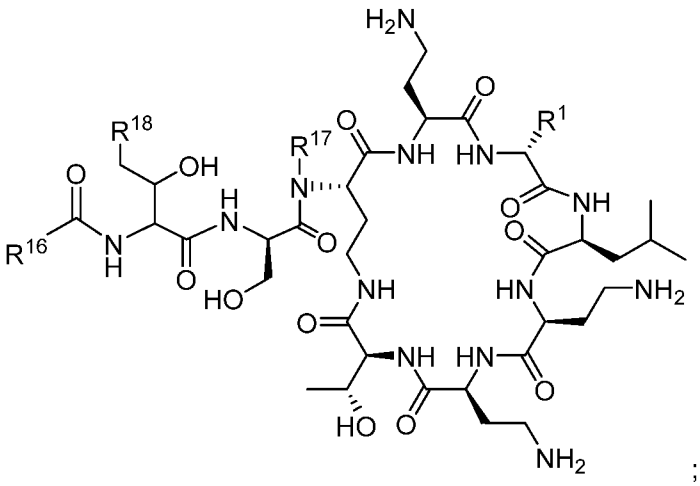
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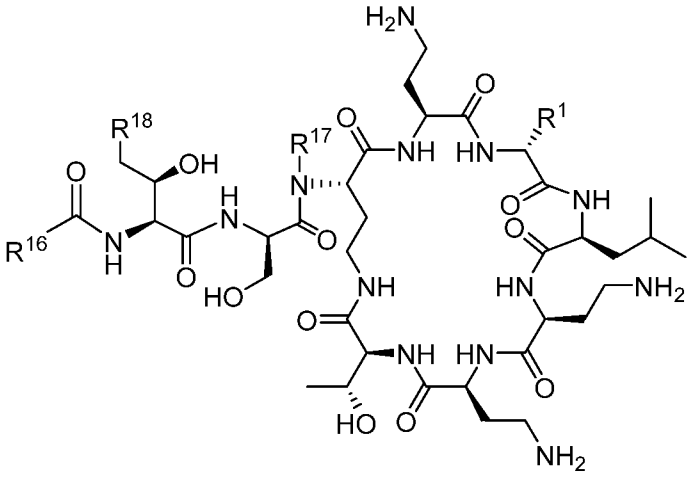
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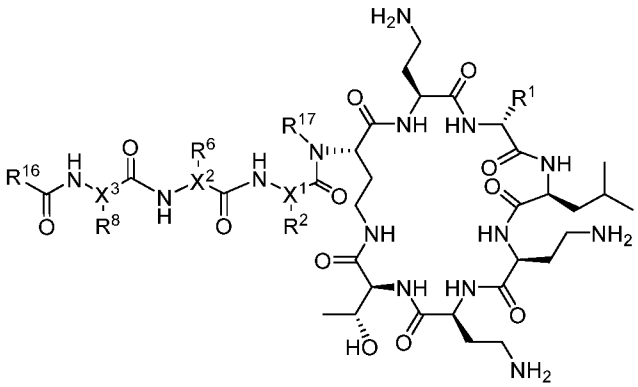
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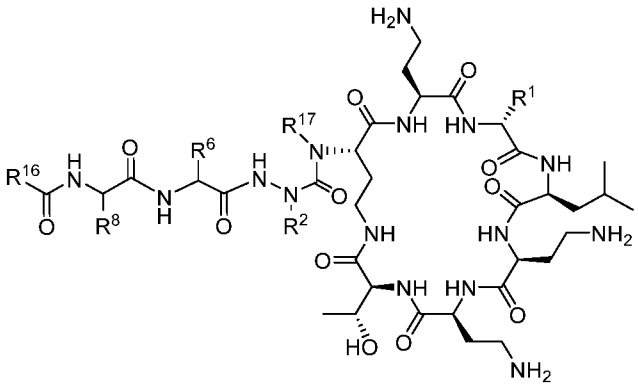
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(XIII-6)



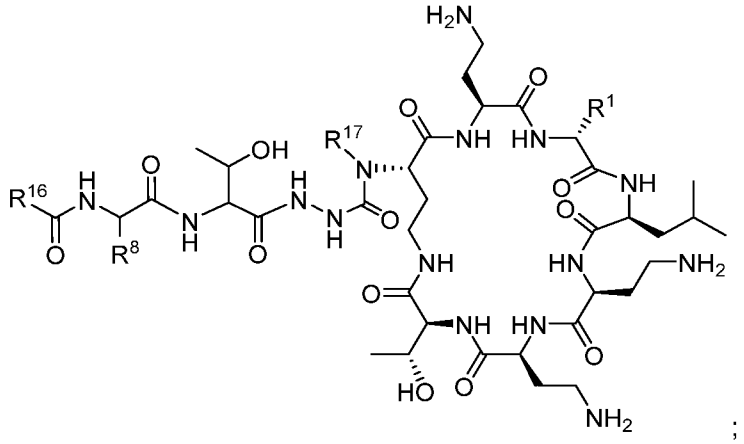
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(XIV)



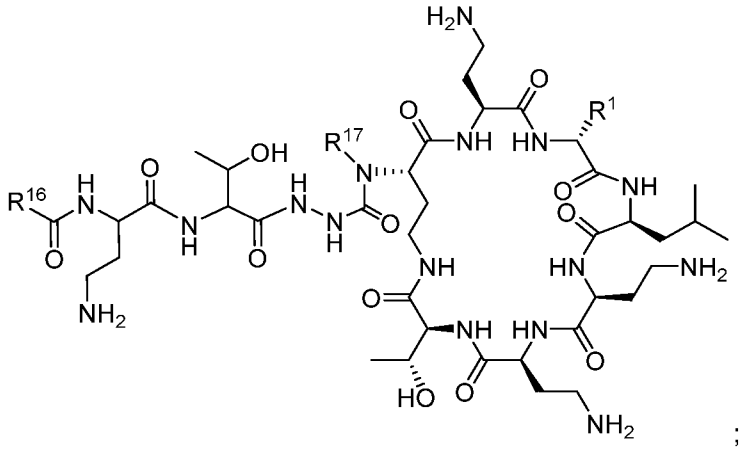
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(XIV-1)



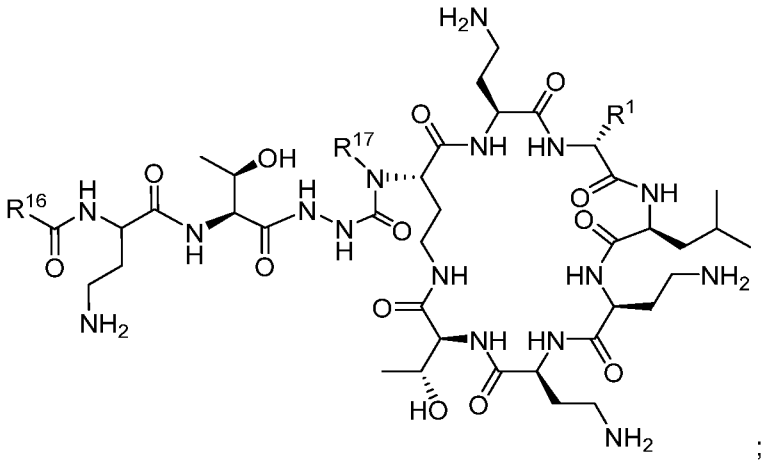
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(XIV-2)



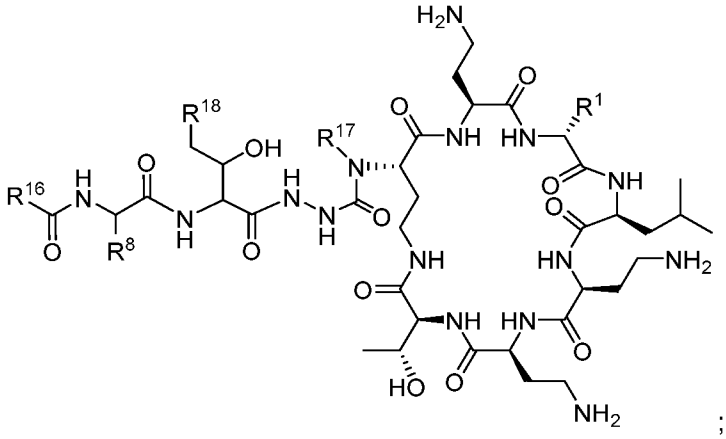
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(XIV-3)



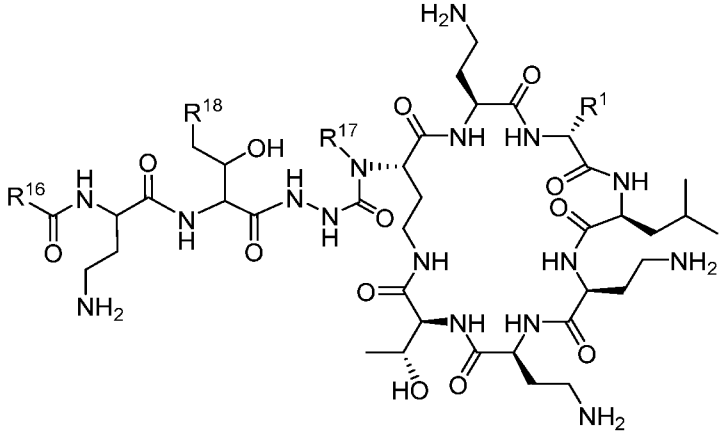
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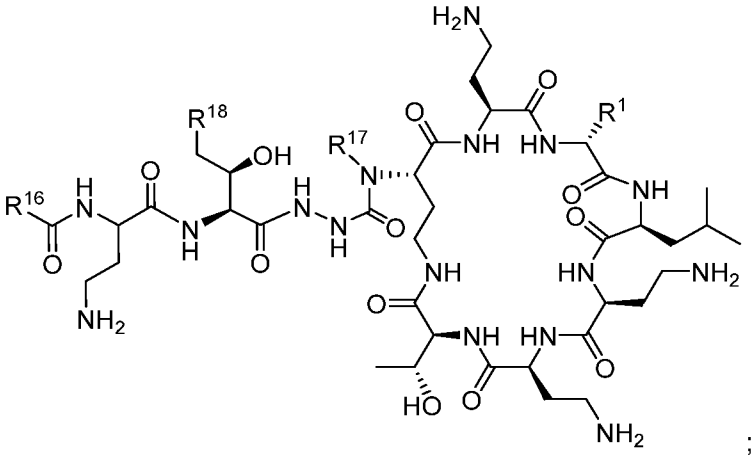
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(XIV-5)



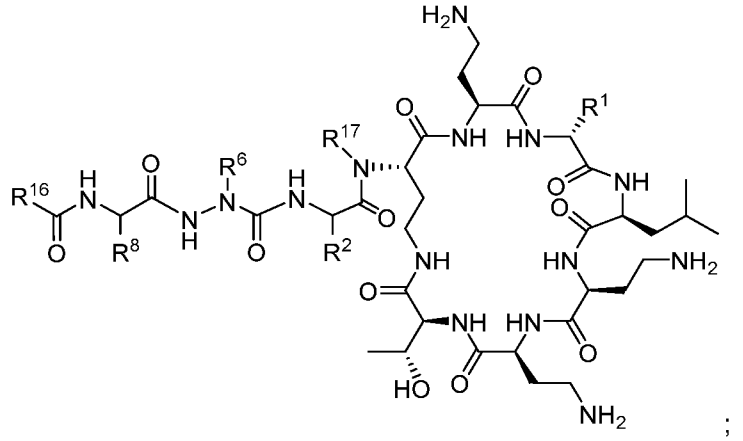
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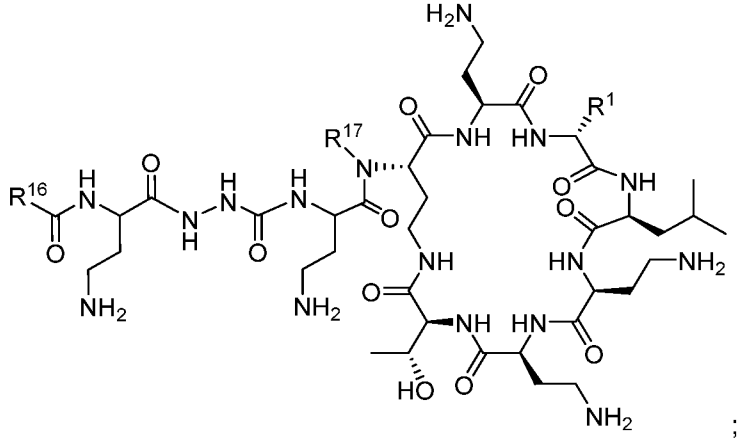
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(XIV-7)



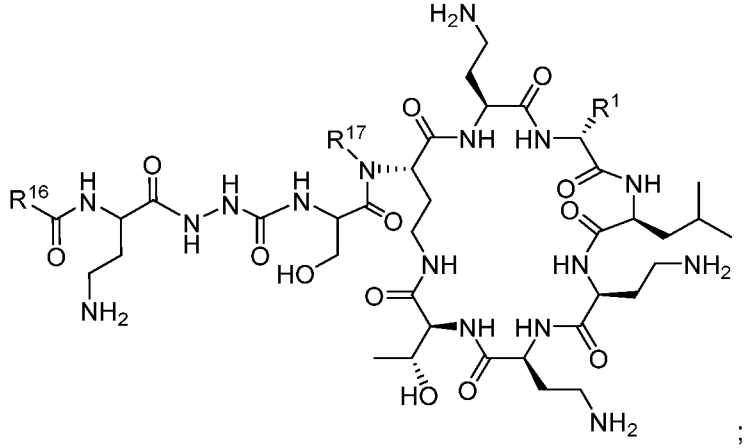
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(XIV-8)



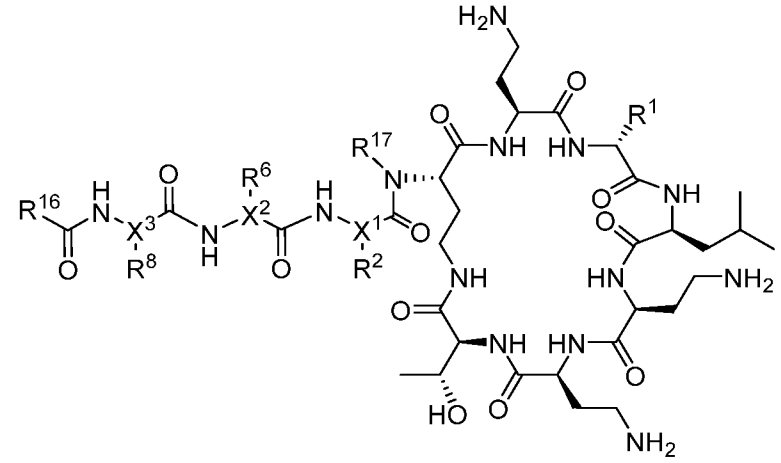
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(XIV-9)



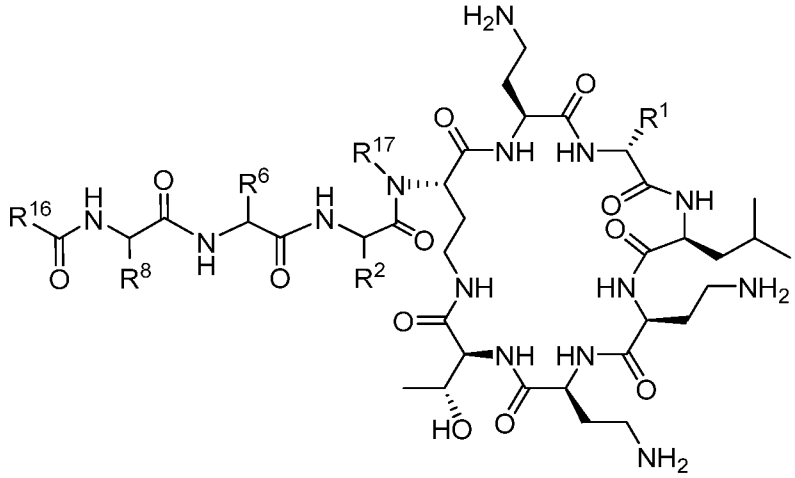
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(XIV-10)



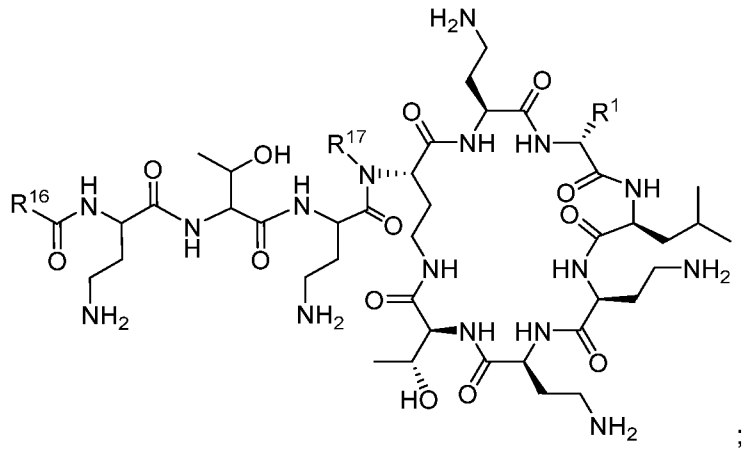
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(XV)



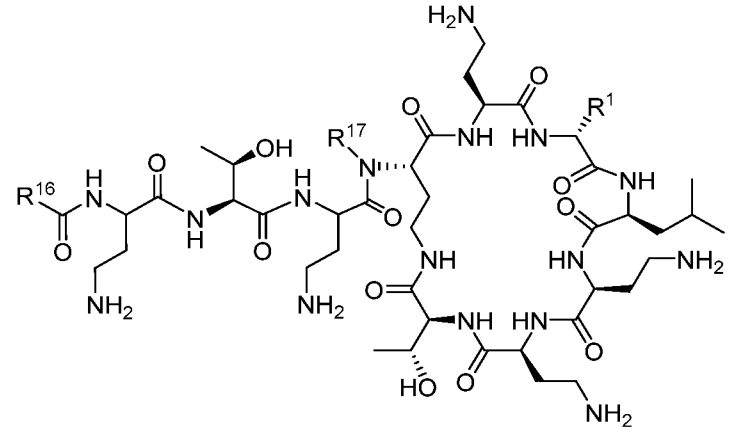
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(XV-1)



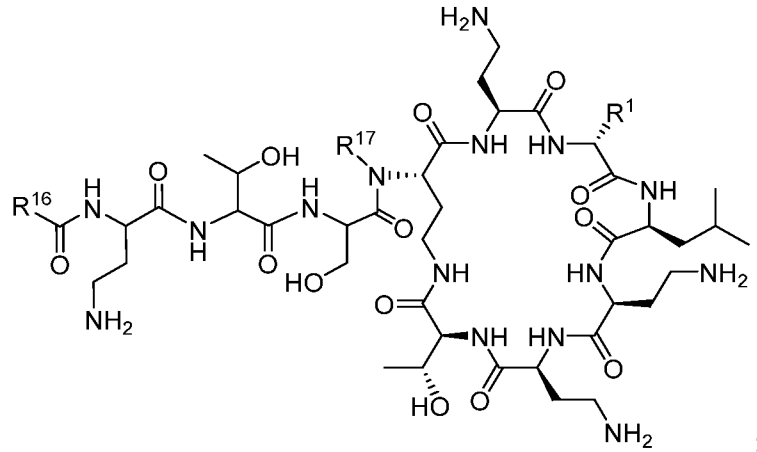
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(XV-2)



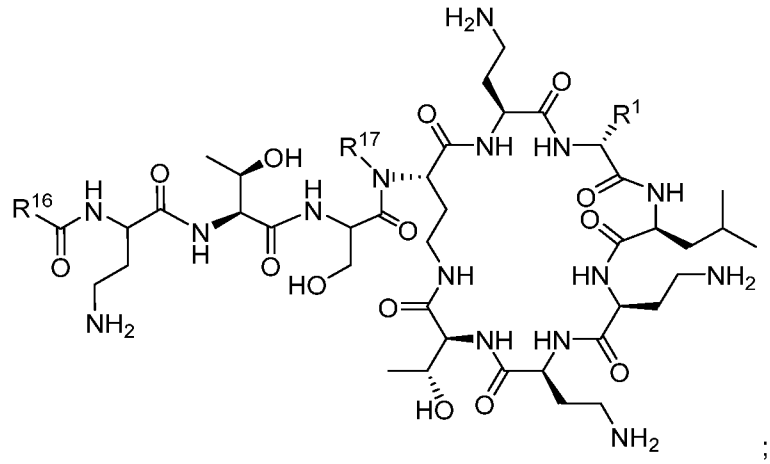
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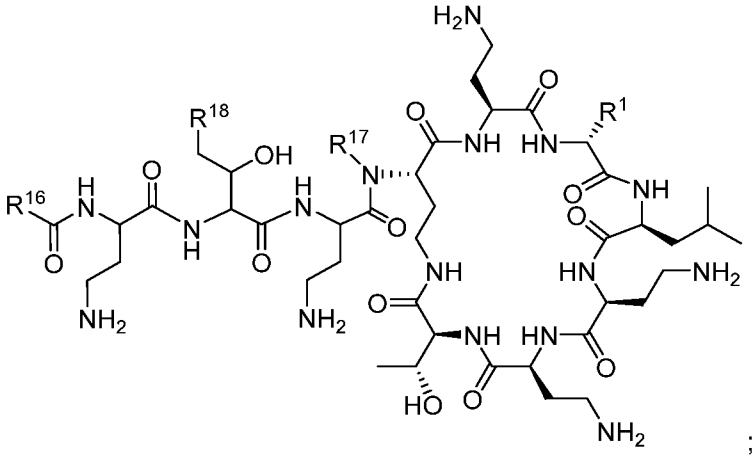
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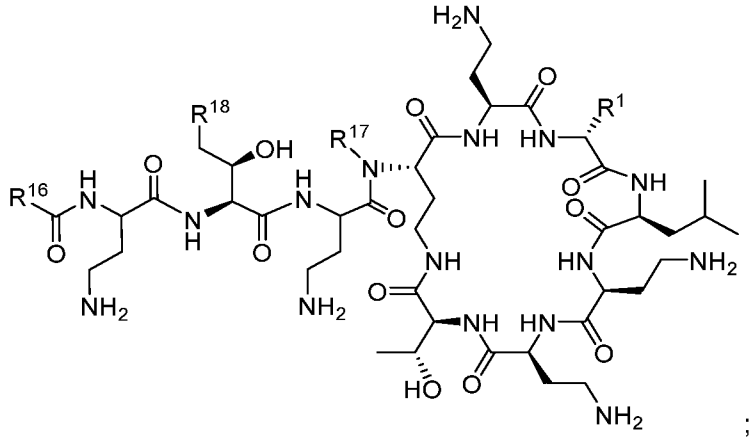
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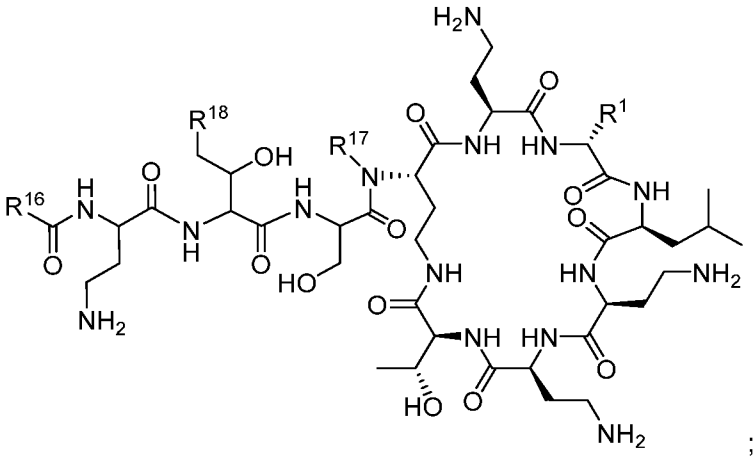
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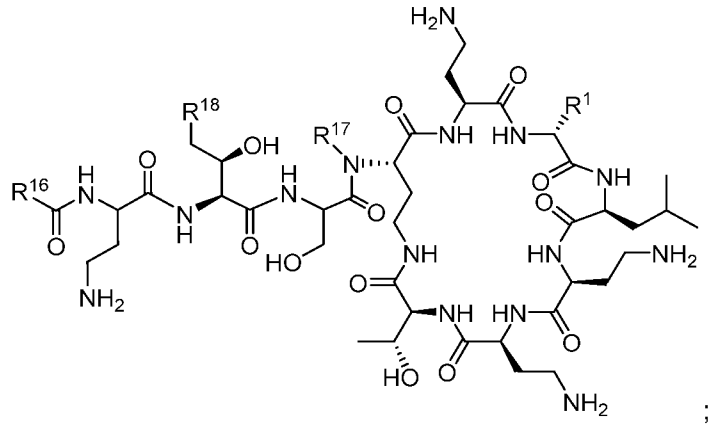
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(XV-7)



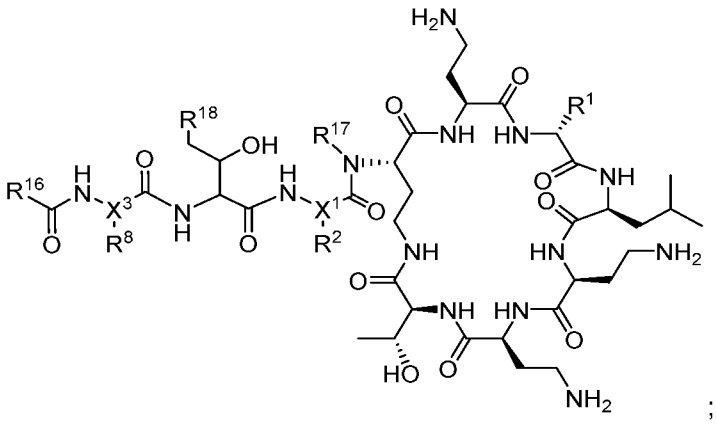
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(XV-8)



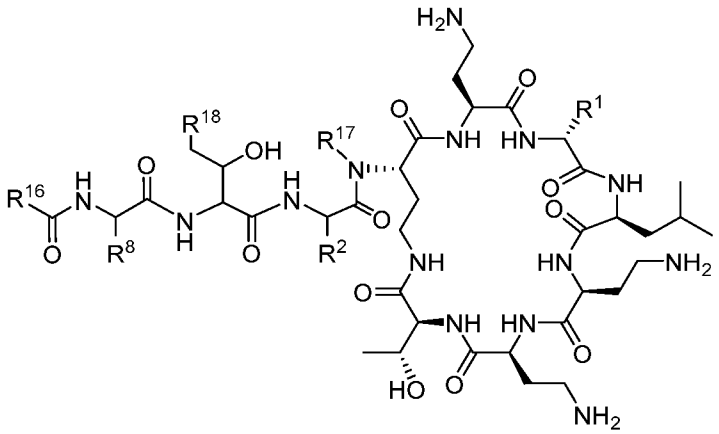
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(XV-9)



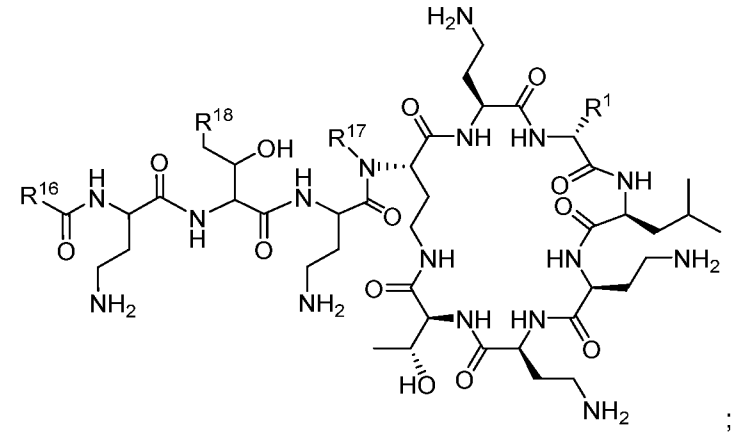
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(XVI)



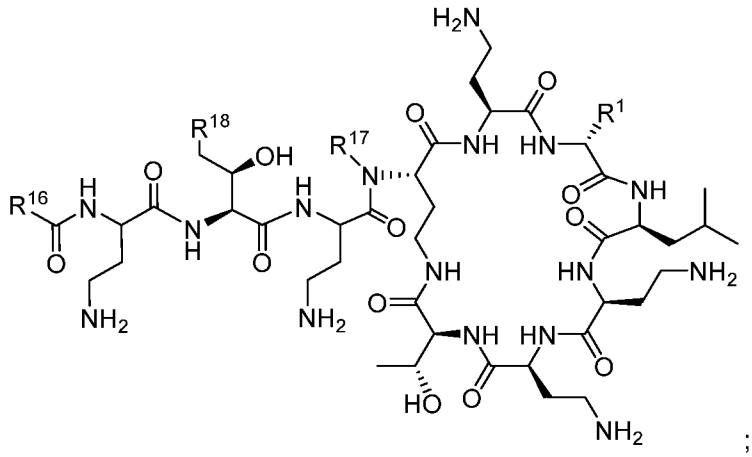
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(XVI-1)



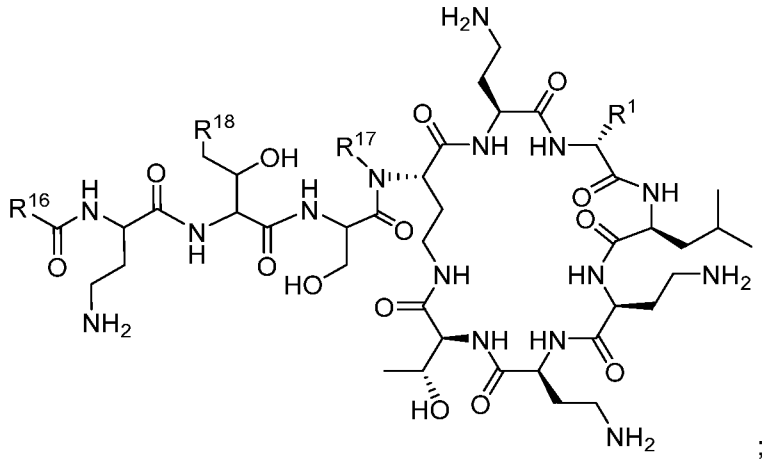
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(XVI-2)



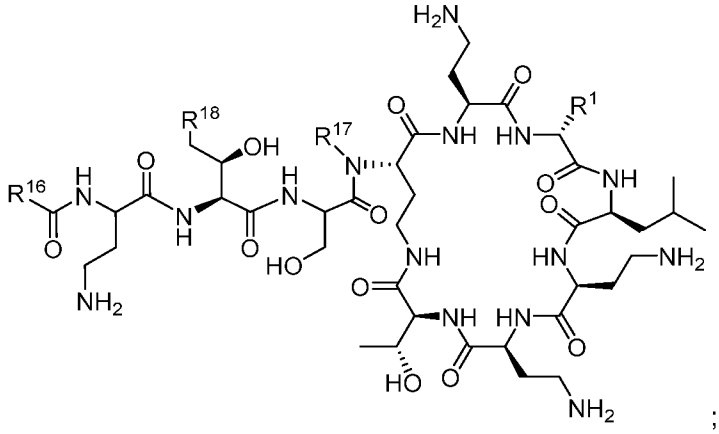
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(XVI-3)



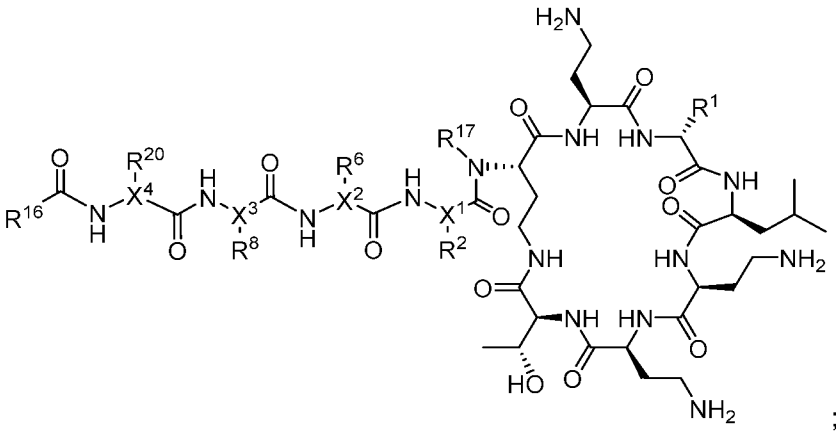
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(XVI-4)



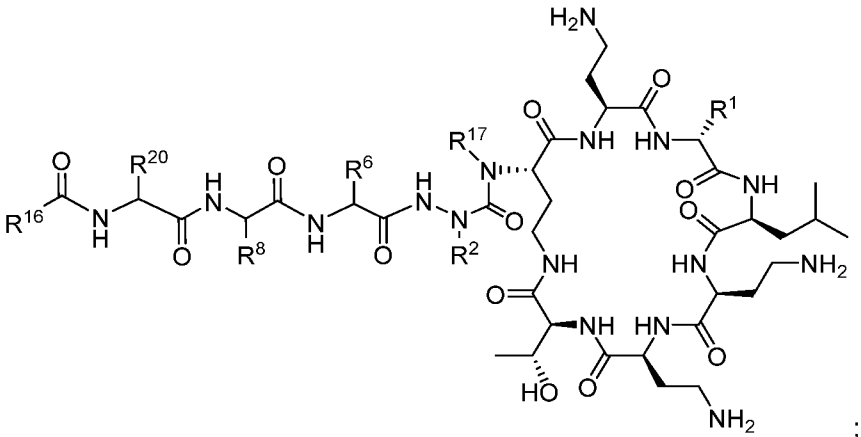
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(XVI-5)



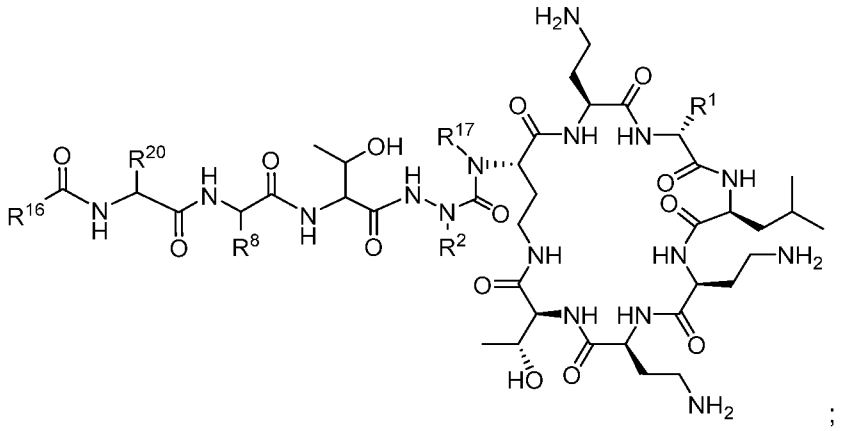
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(XVII)



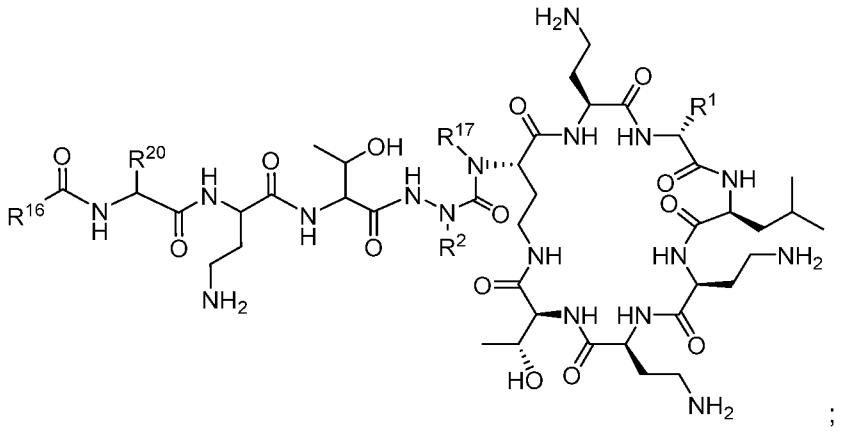
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(XVII-1)



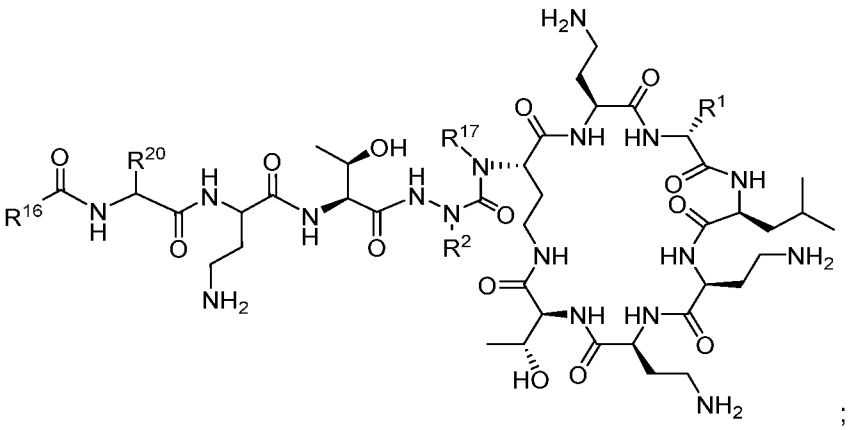
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(XVII-2)



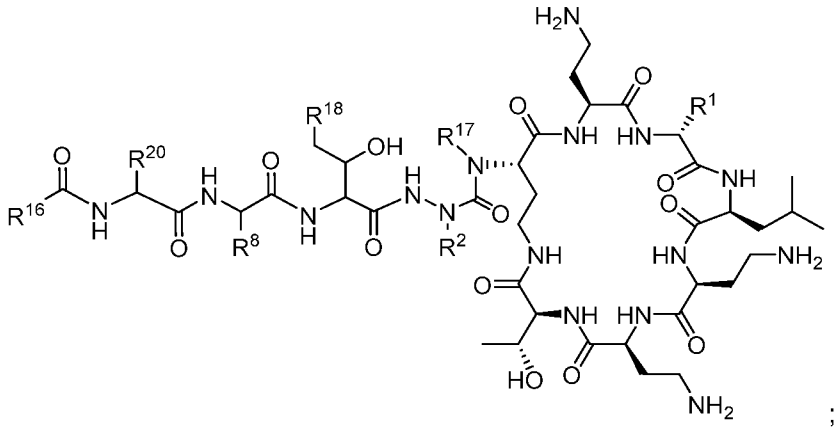
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(XVII-3)



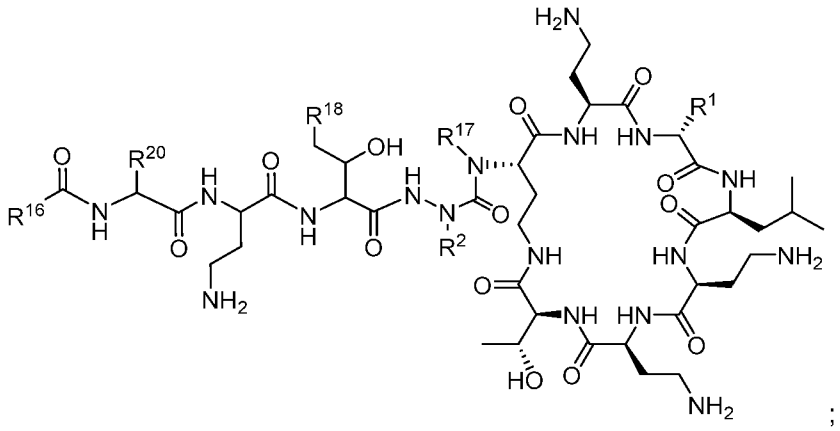
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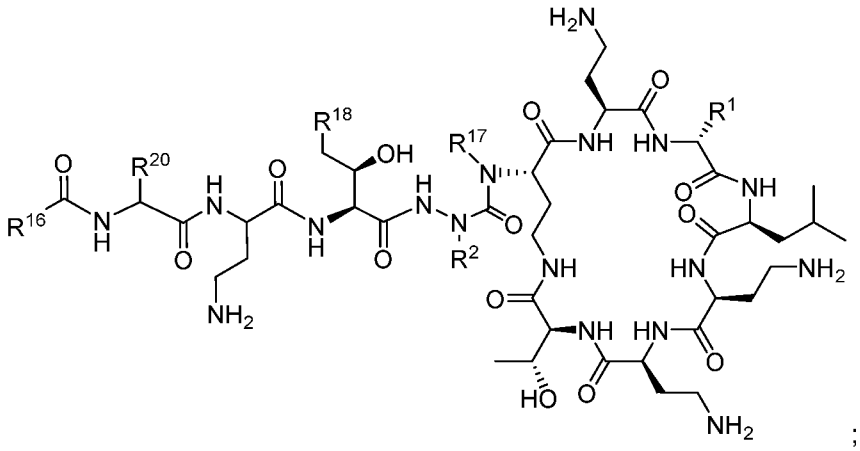
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(XVII-5)



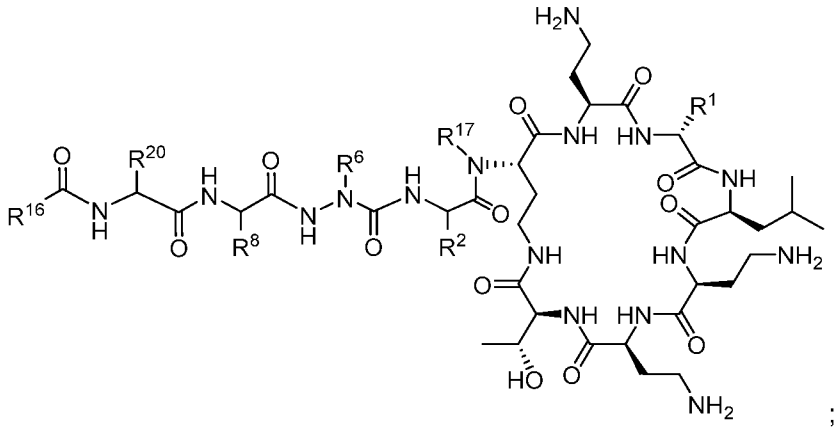
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(XVII-6)



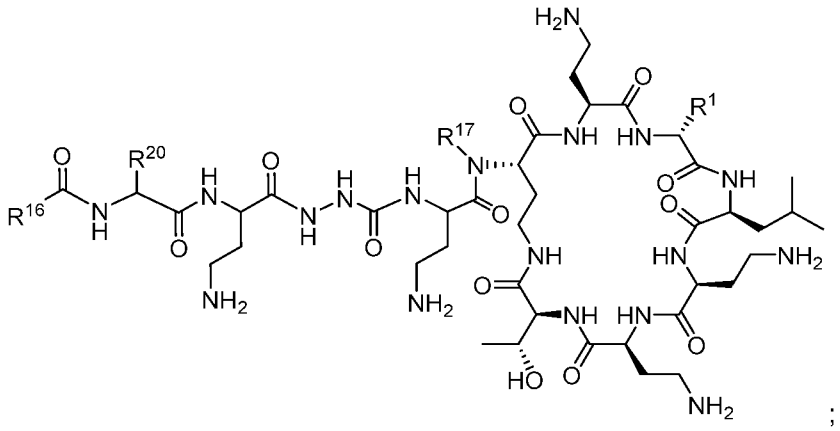
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(XVII-7)



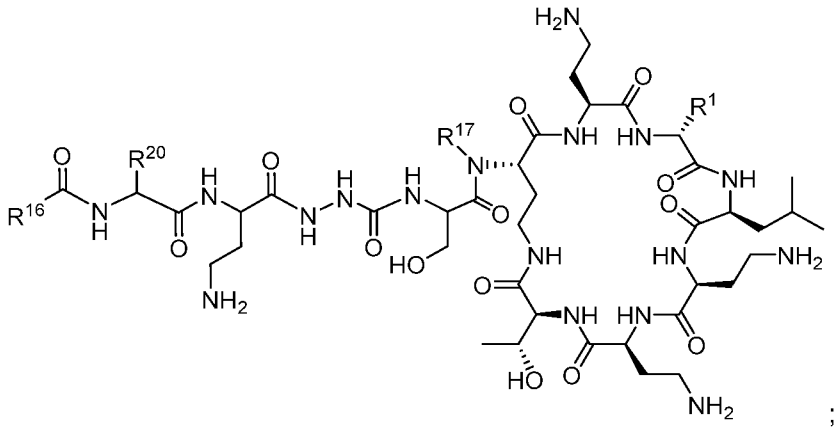
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(XVII-8)



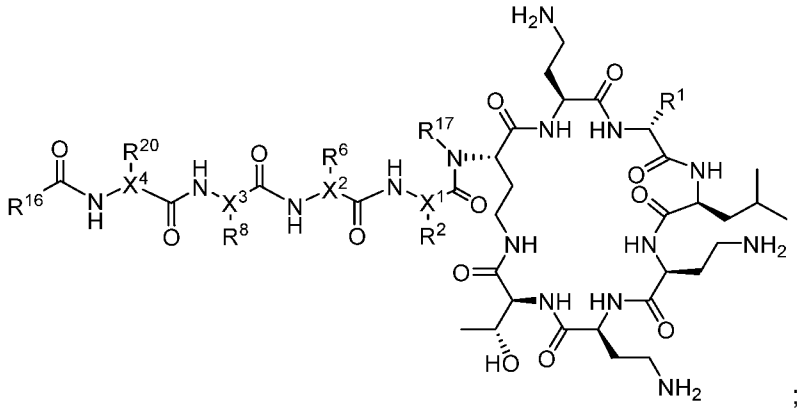
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(XVII-9)



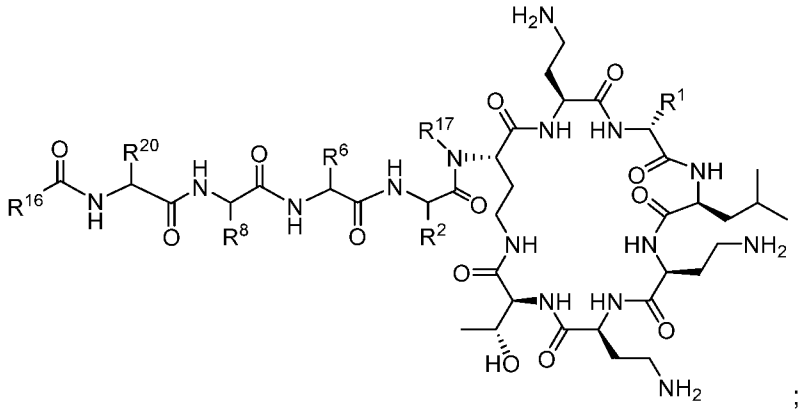
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(XVII-10)



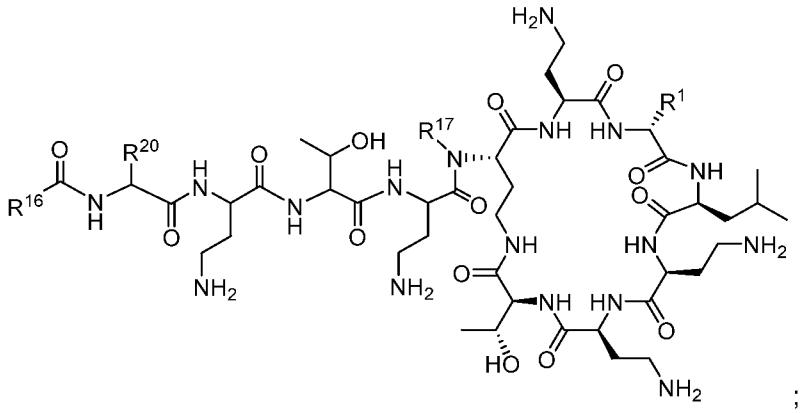
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(XVIII)



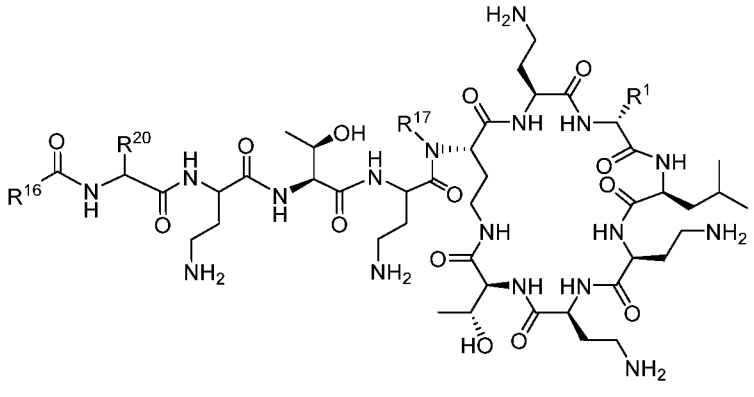
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(XVIII-1)



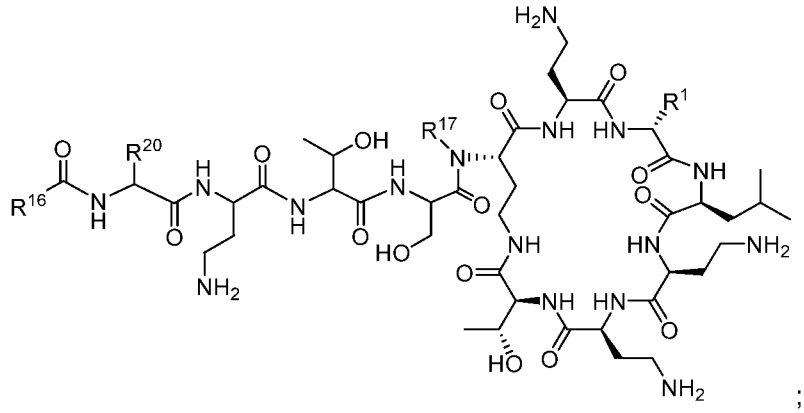
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(XVIII-2)



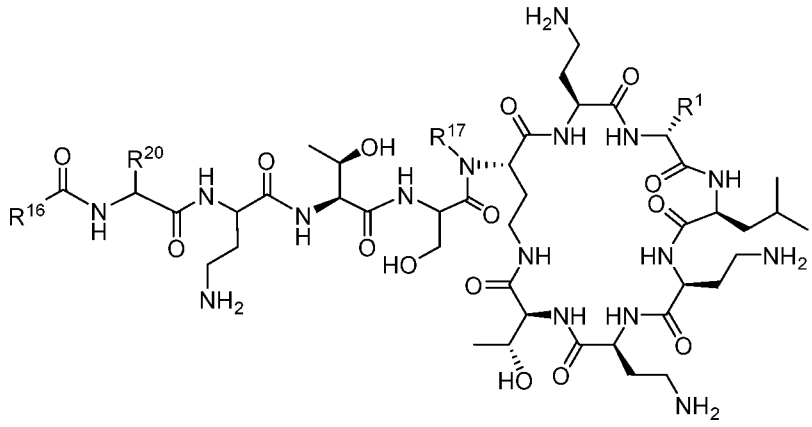
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(XVIII-3)



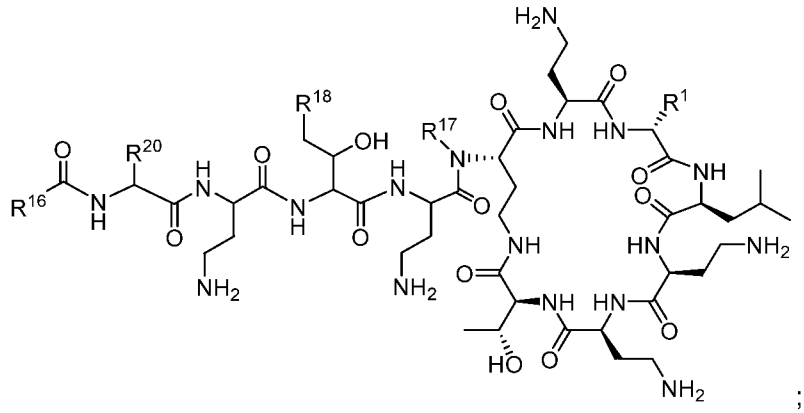
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(XVIII-4)



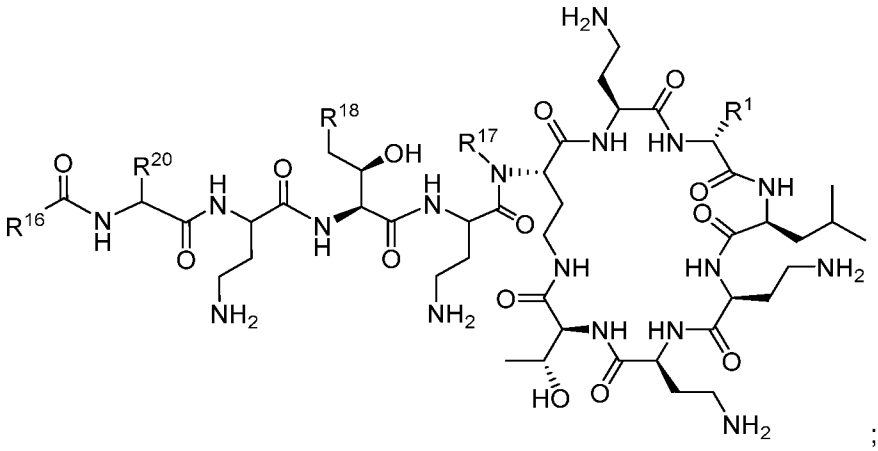
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(XVIII-5)



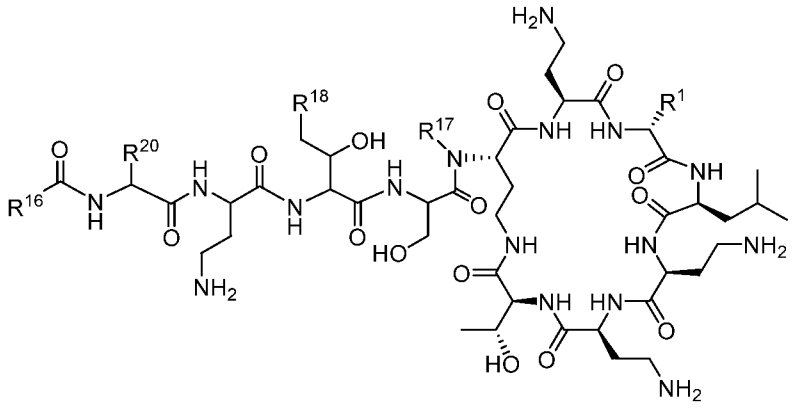
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(XVIII-6)



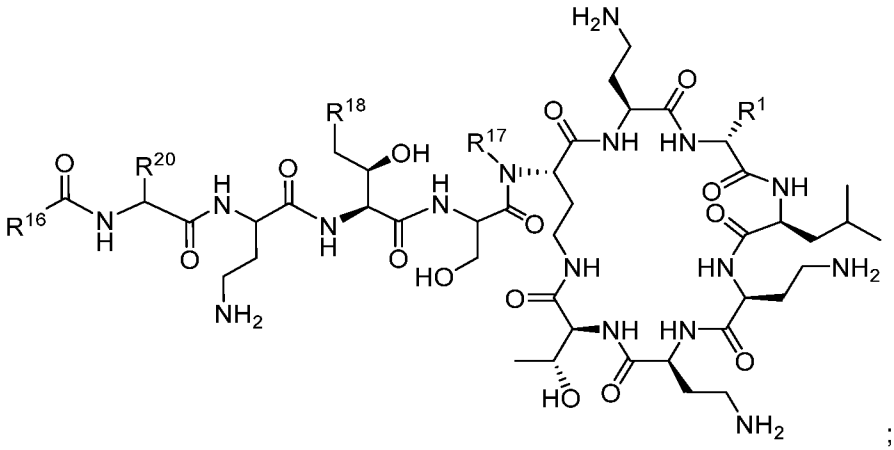
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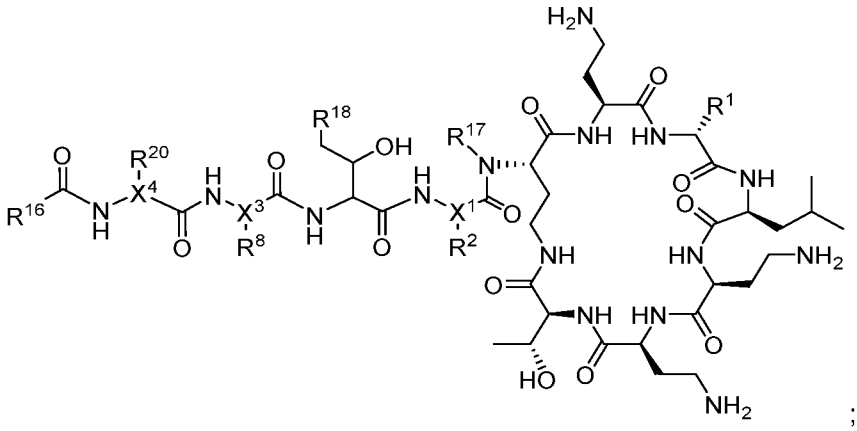
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(XVIII-8)



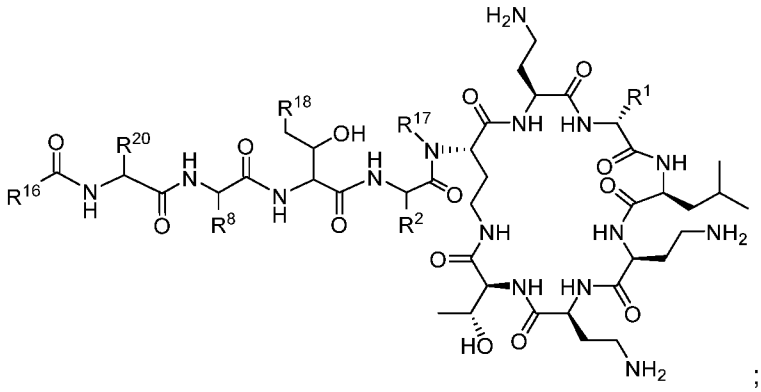
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(XVIII-9)



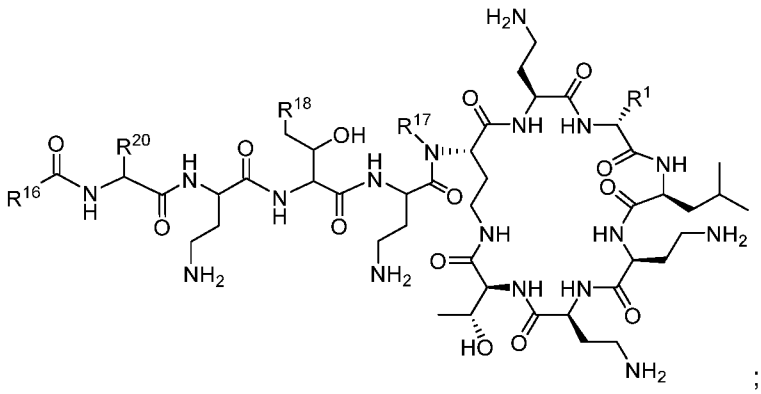
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(XIX)



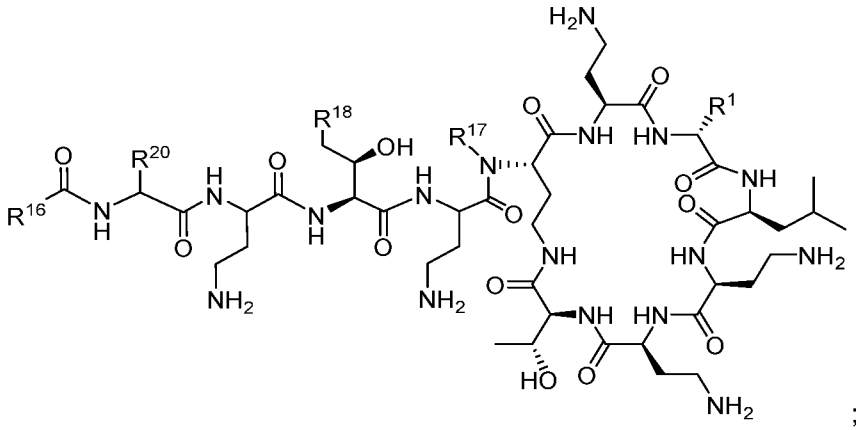
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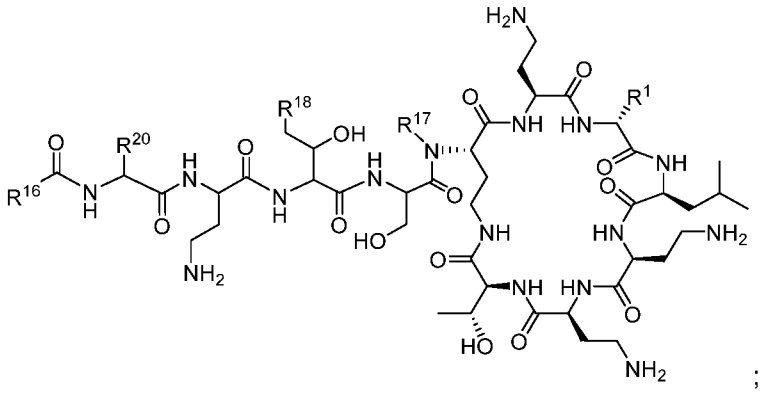
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(XIX-2)



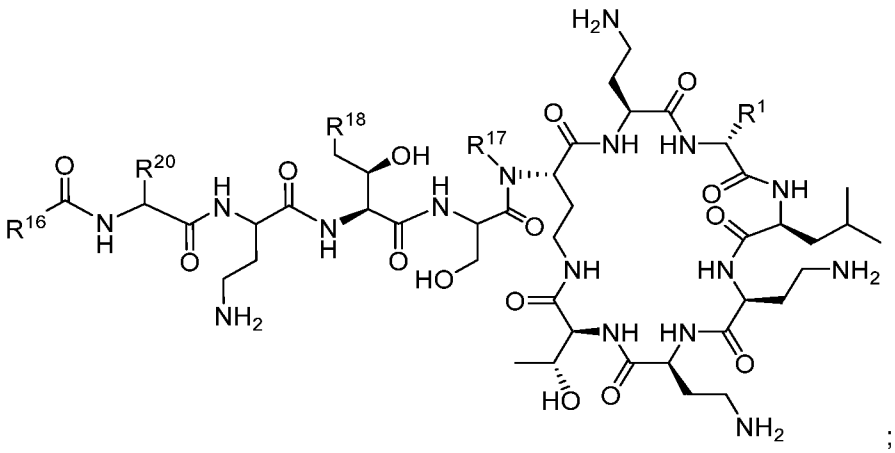
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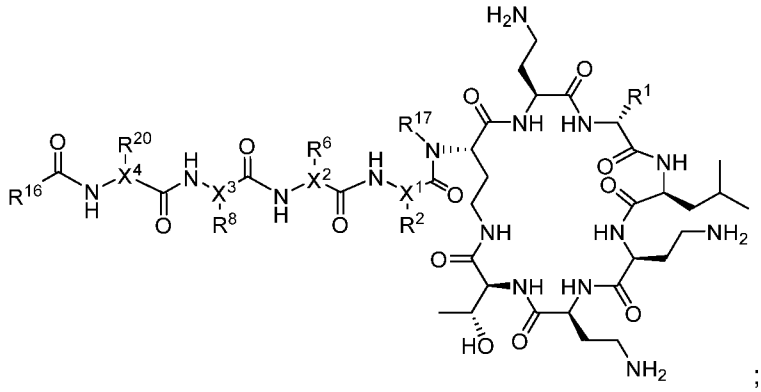
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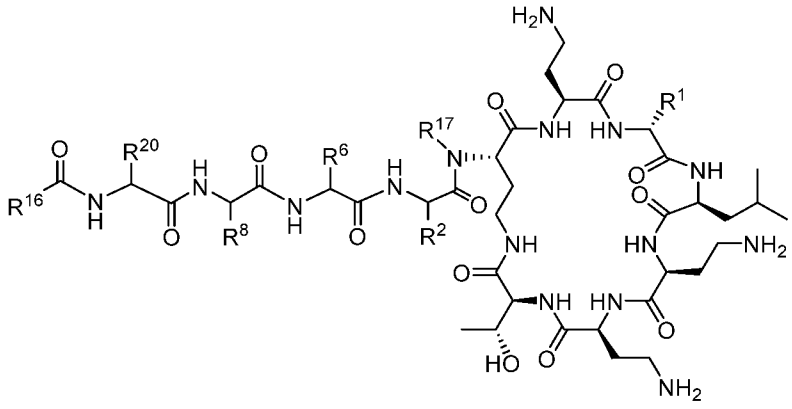
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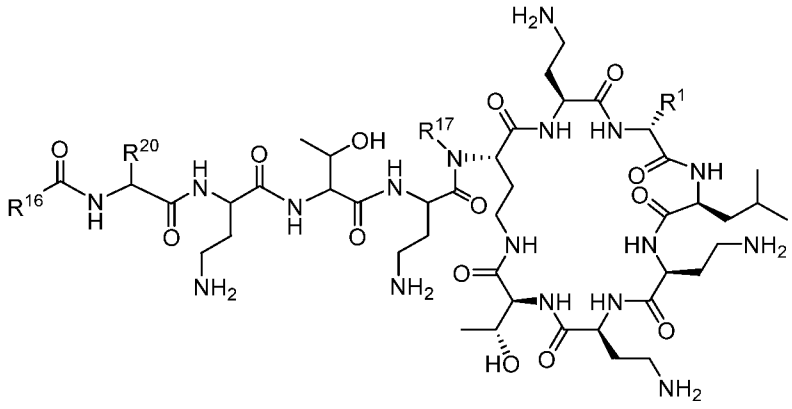
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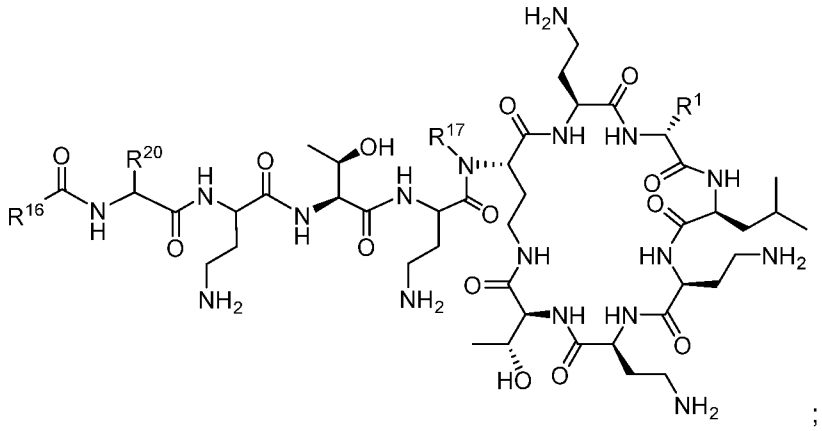
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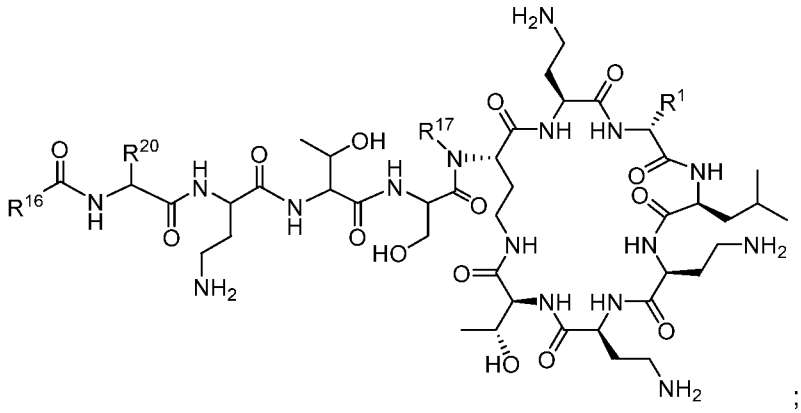
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(XX-2)



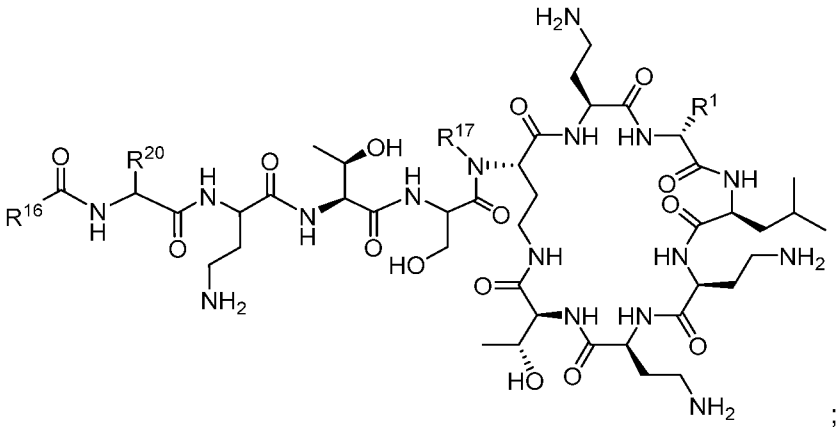
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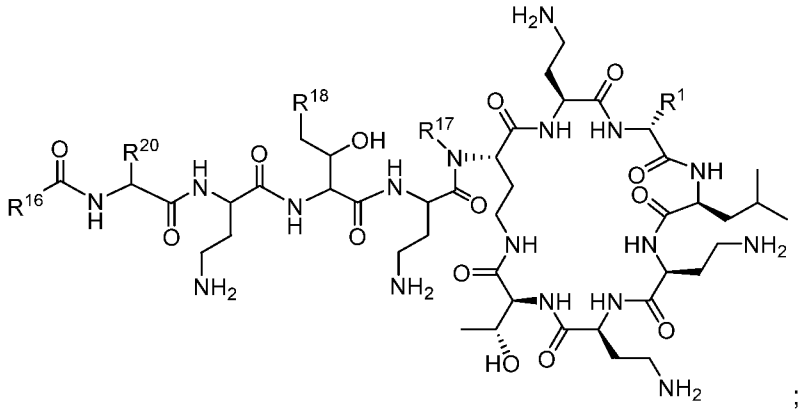
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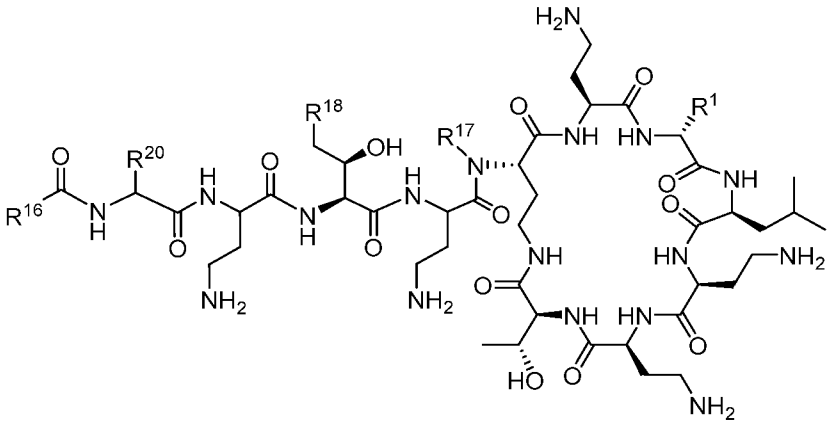
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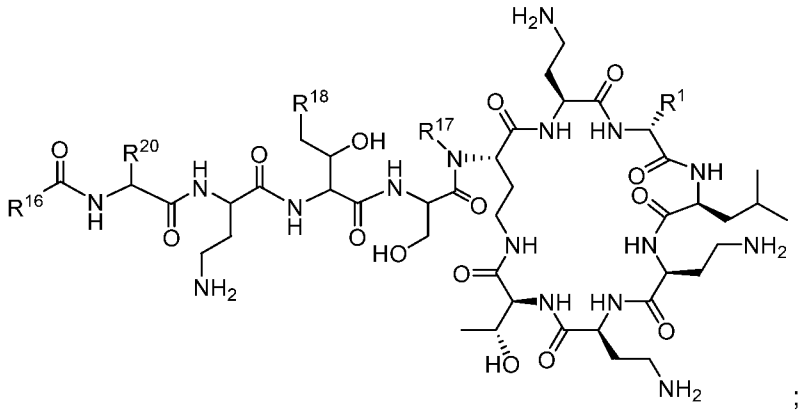
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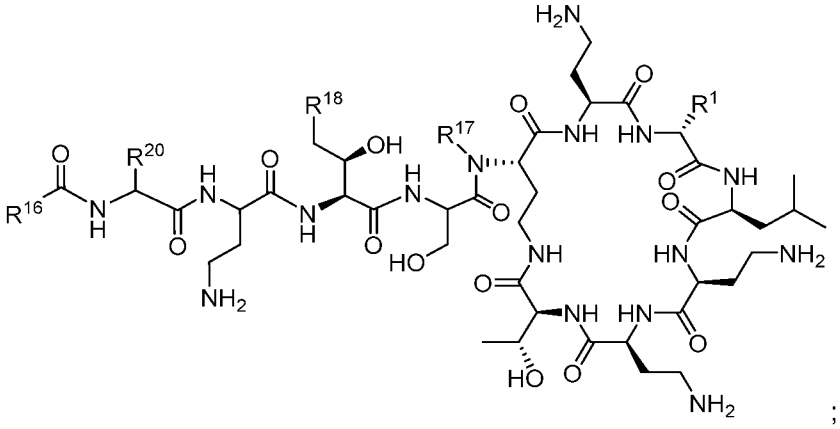
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(XX-7)



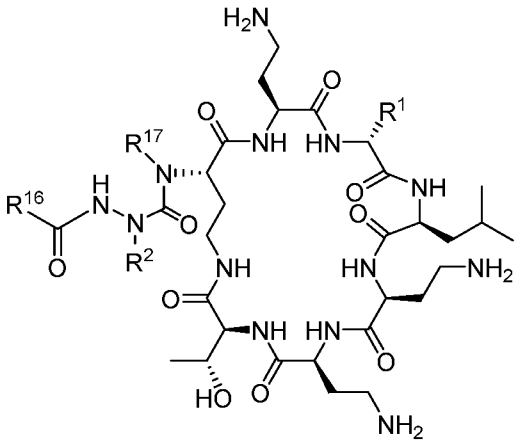
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(XX-8)



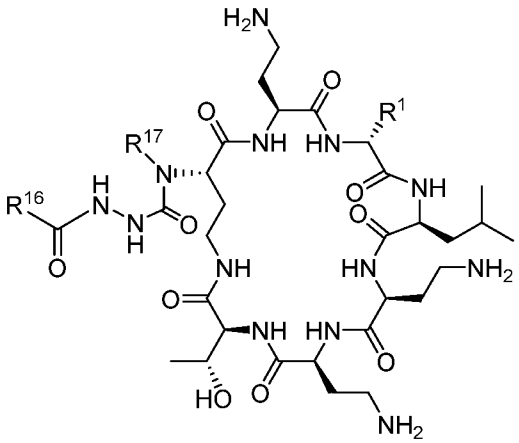
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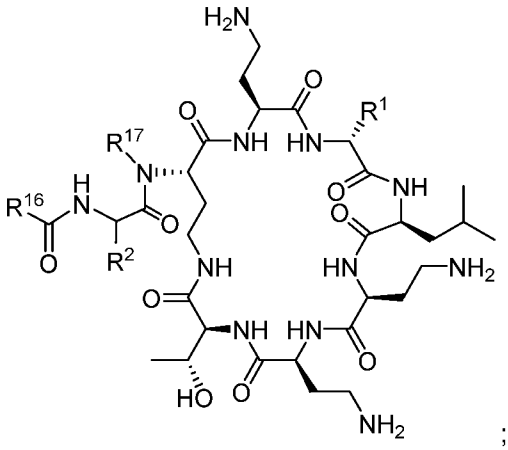
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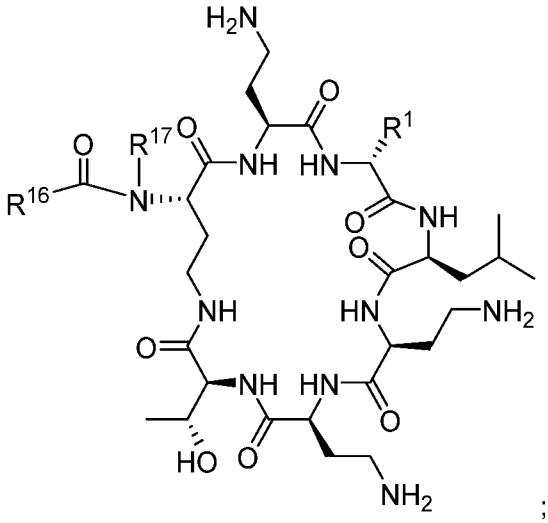
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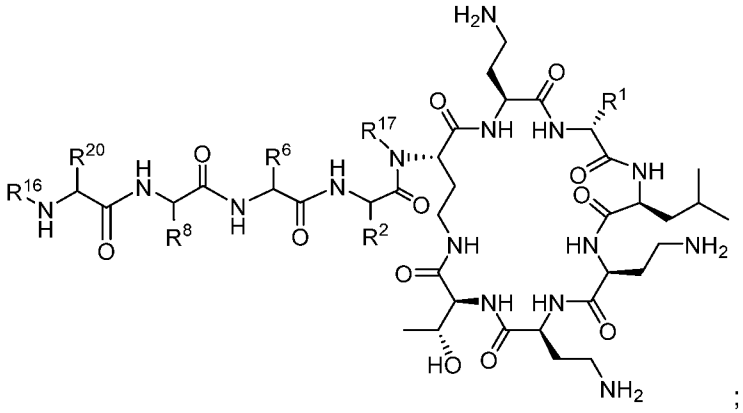
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(XXII)



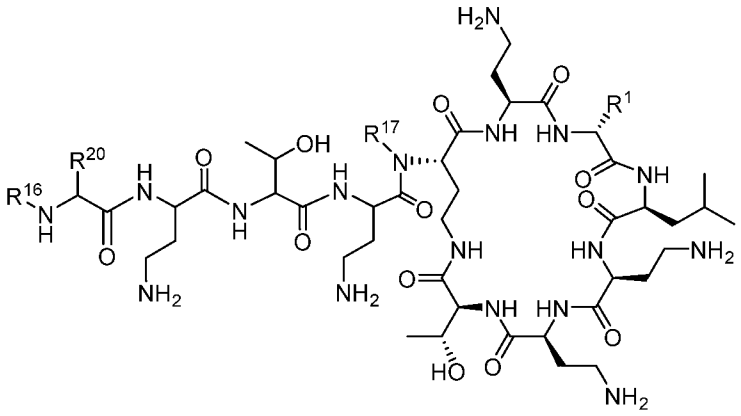
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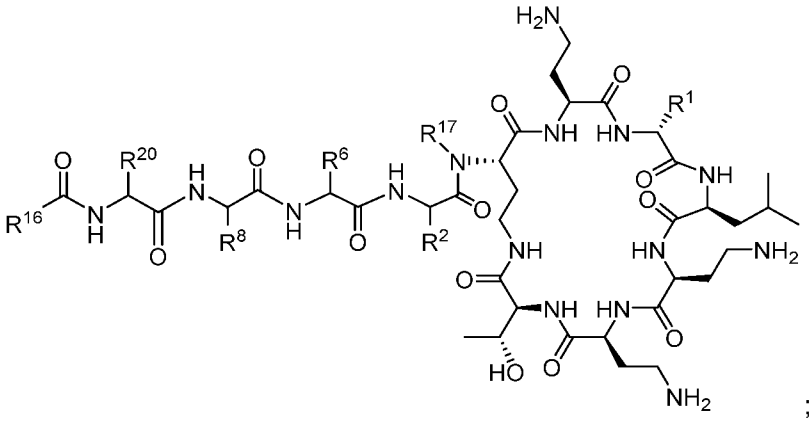
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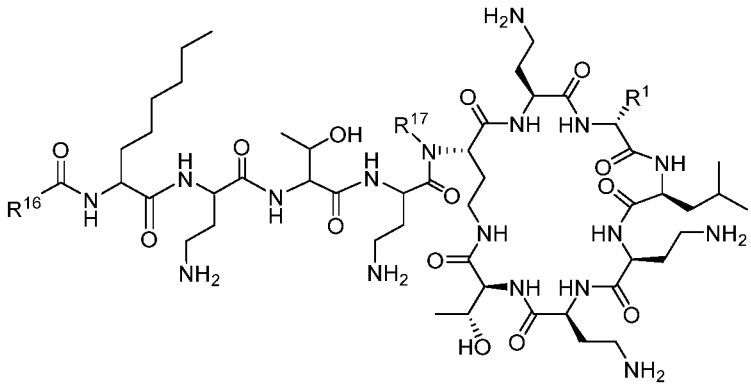
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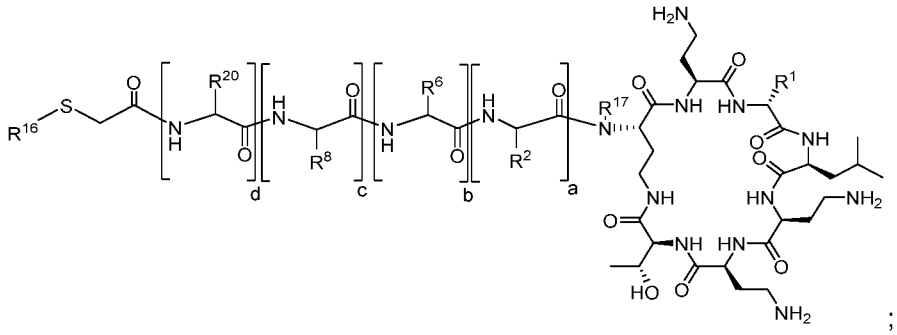
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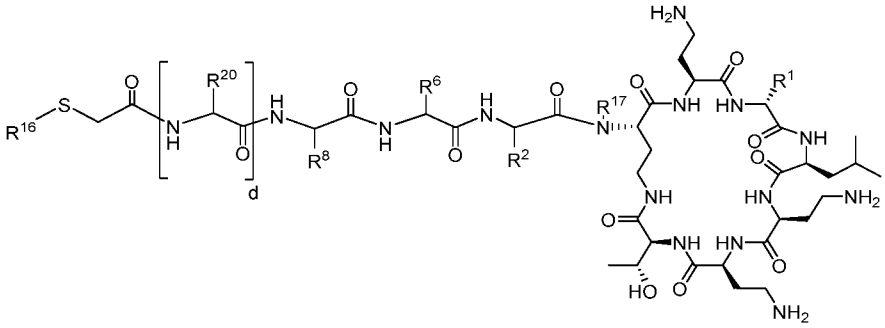
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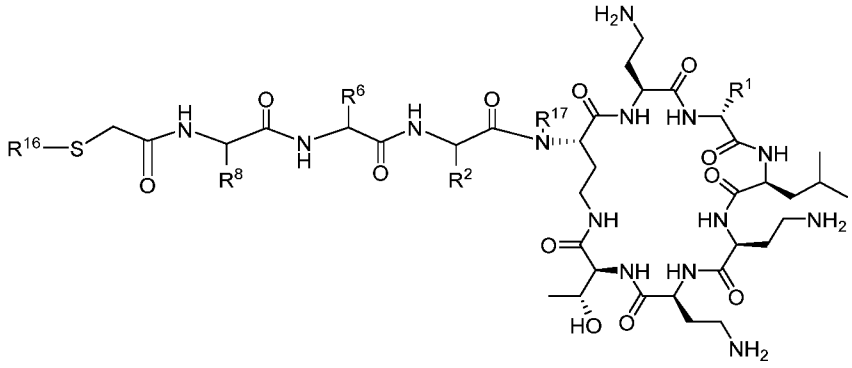
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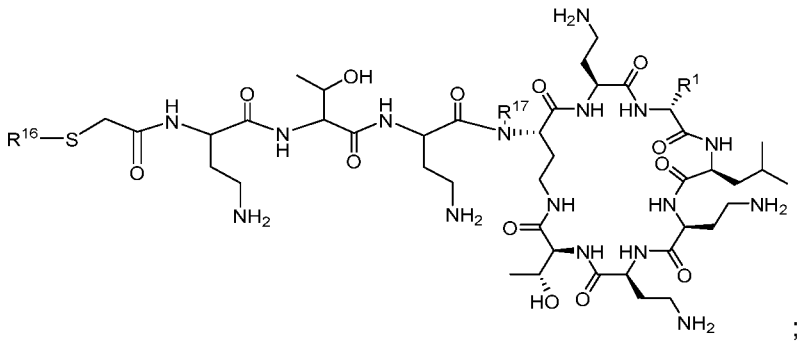
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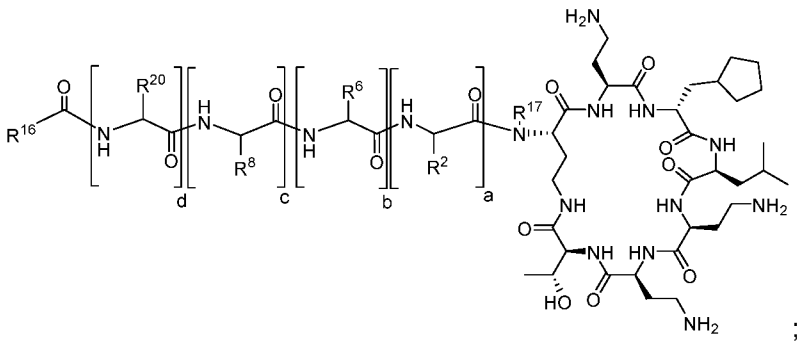
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(XXVI-2)



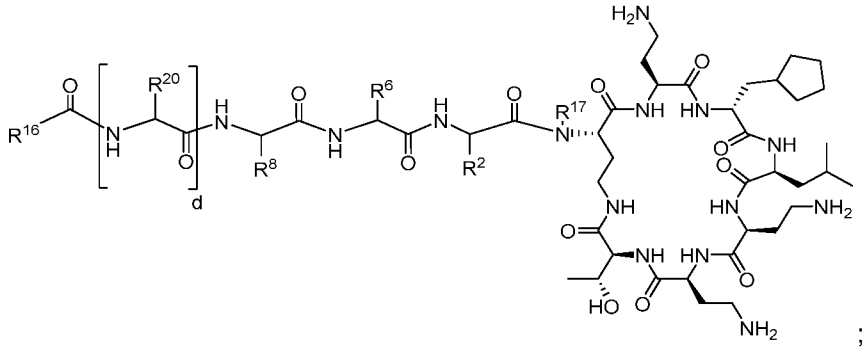
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(XXVI-3)



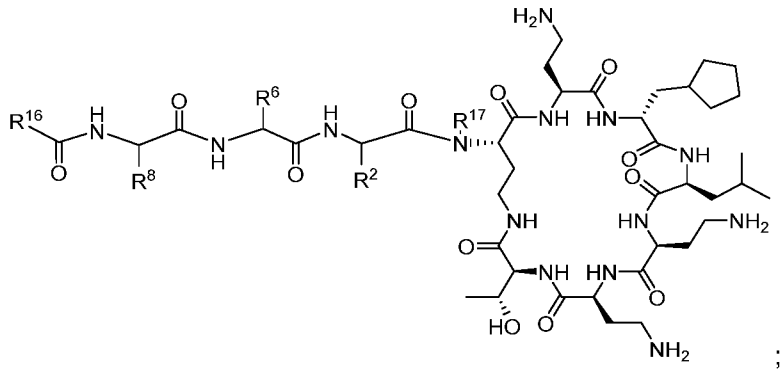
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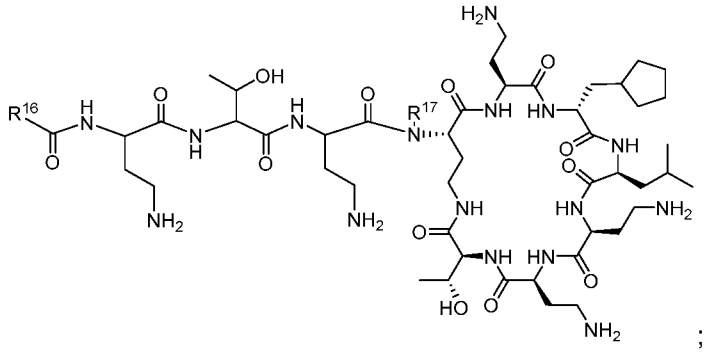
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(XXVII-1)



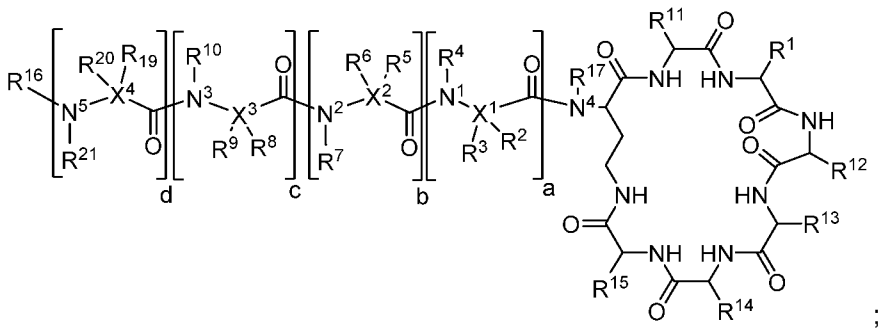
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(XXVII-2)



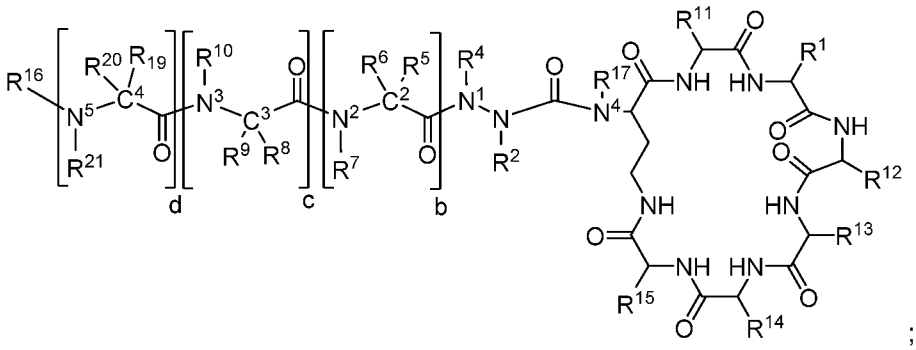
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(XXVII-3)



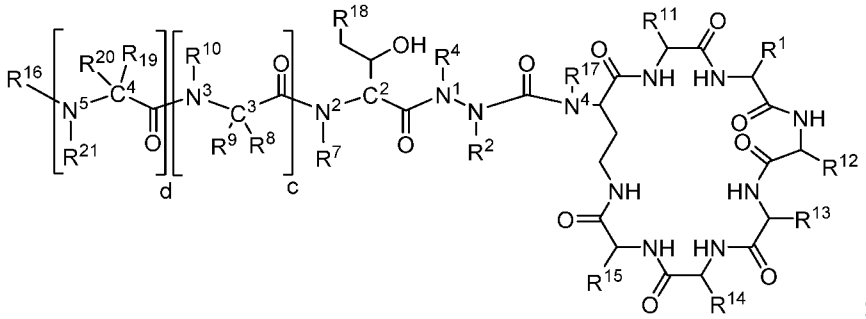
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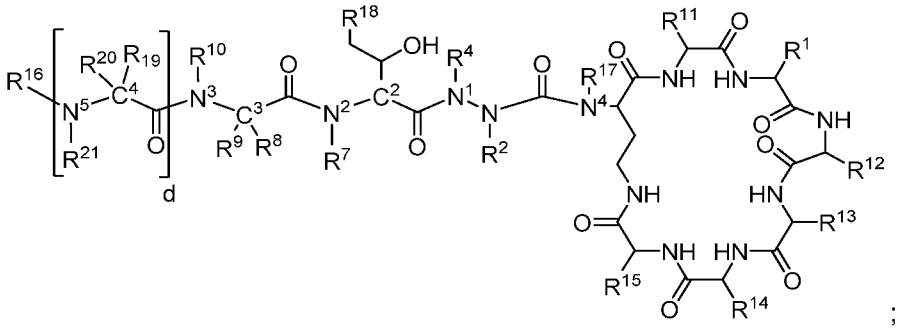
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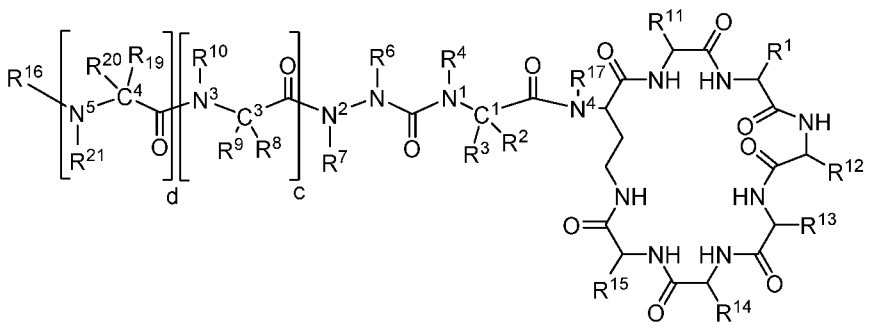
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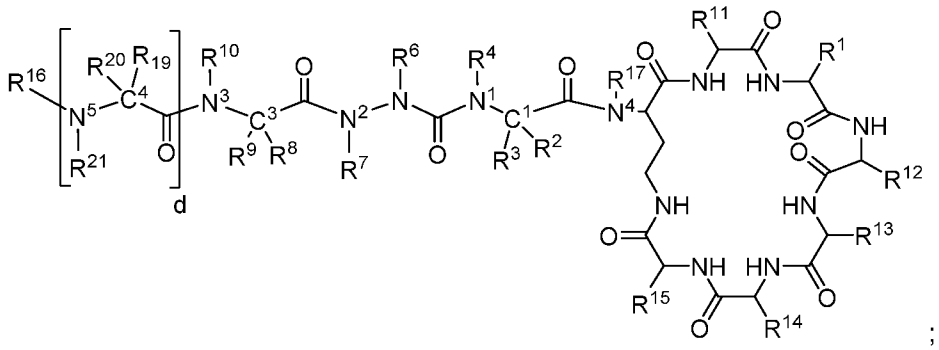
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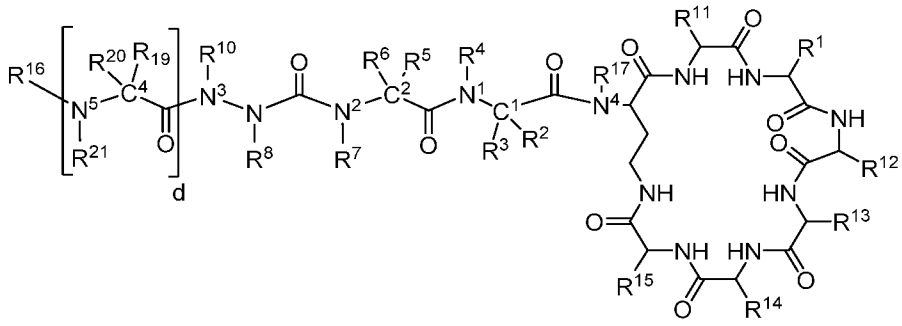
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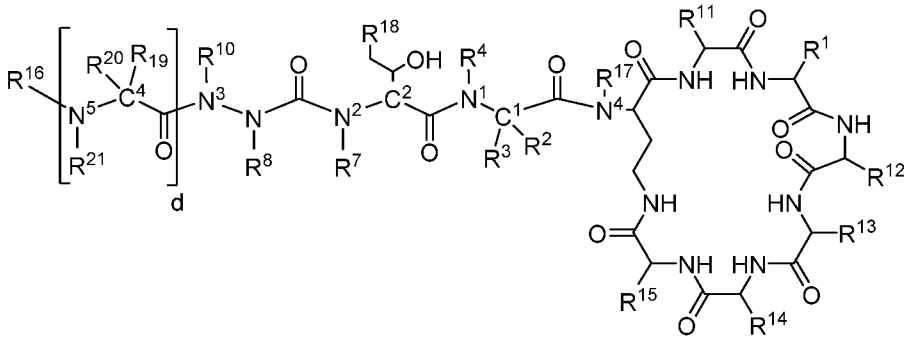
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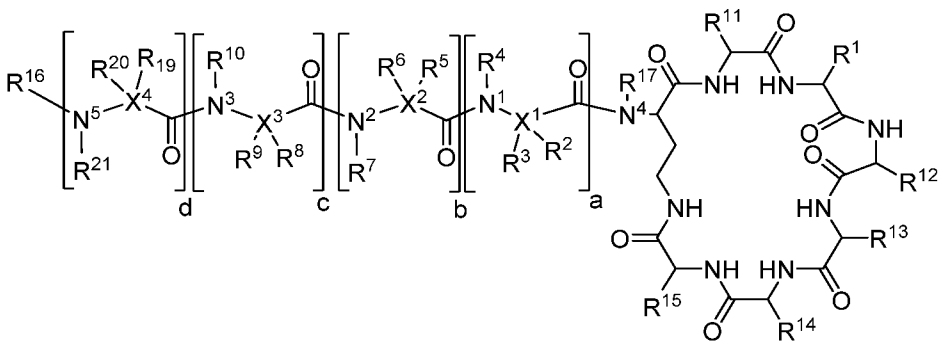
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(XXVIII-6)



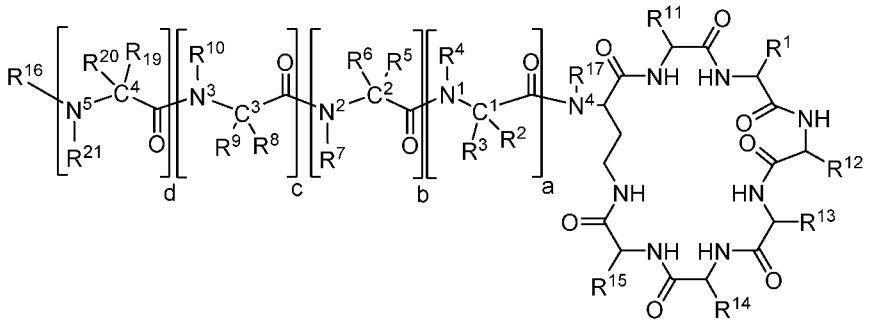
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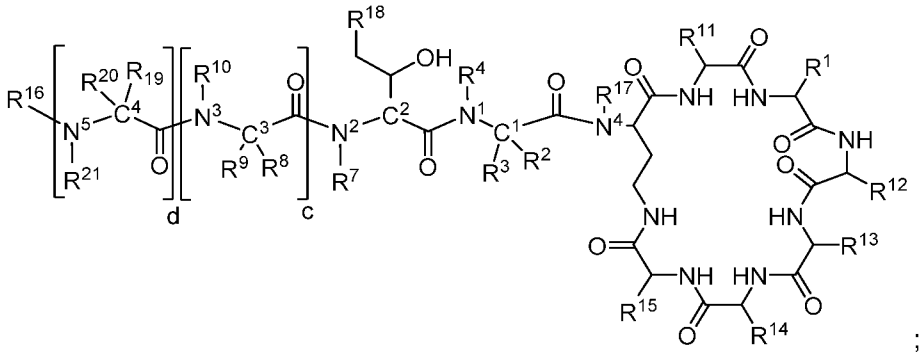
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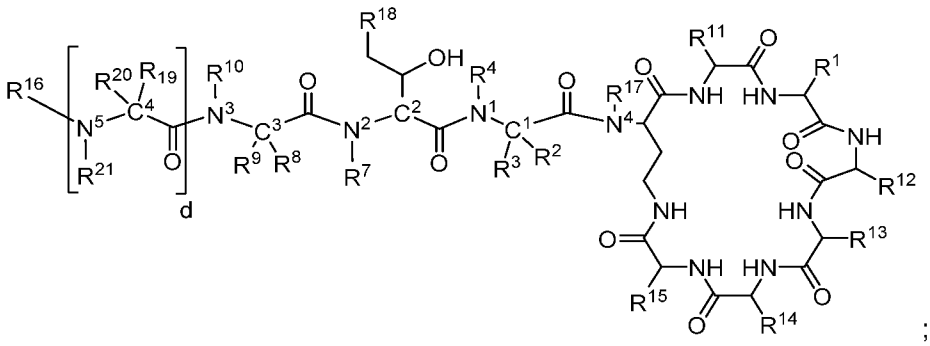
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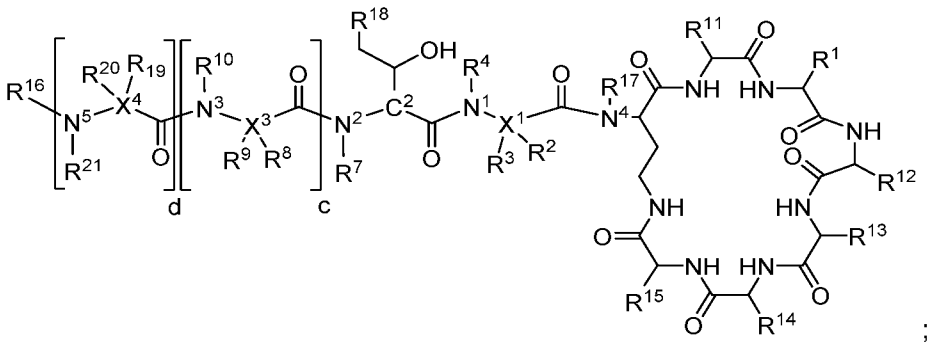
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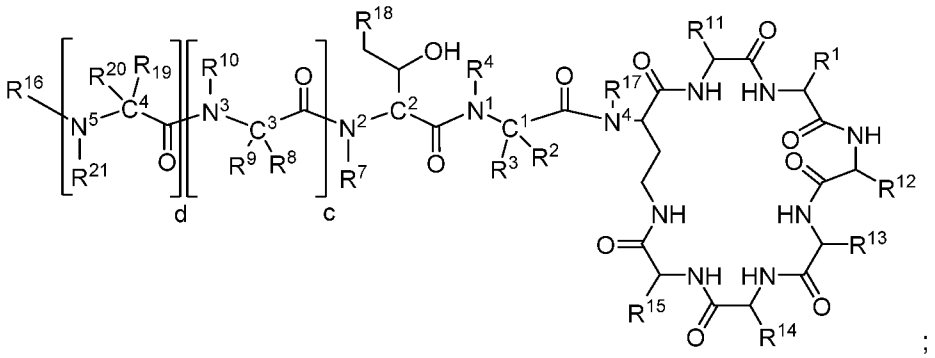
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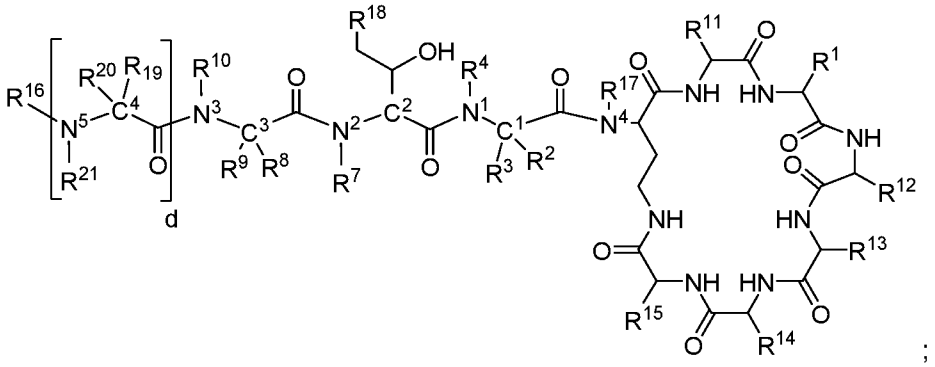
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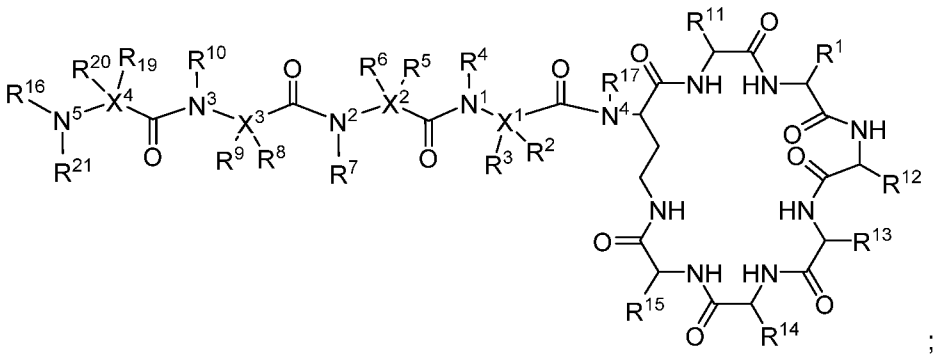
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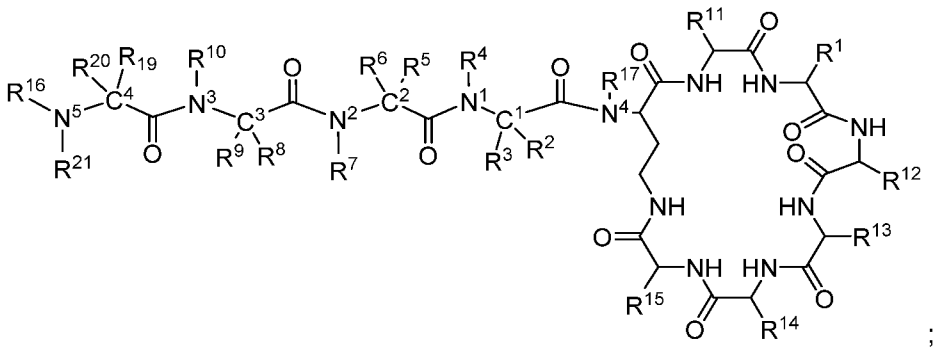
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(XXX-2)



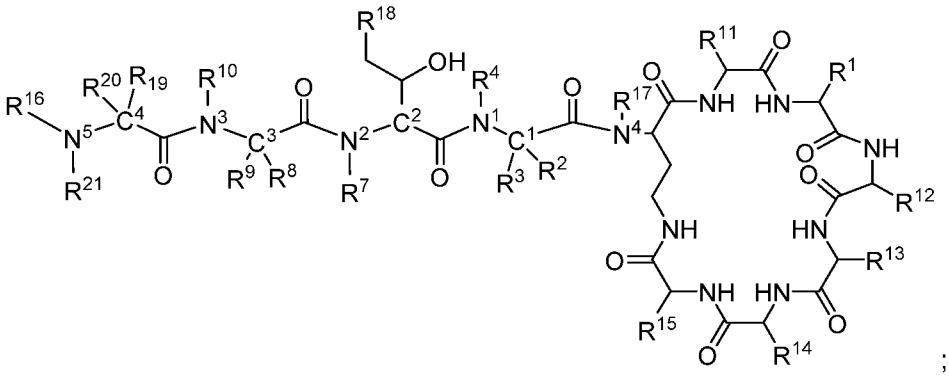
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(XXXI)



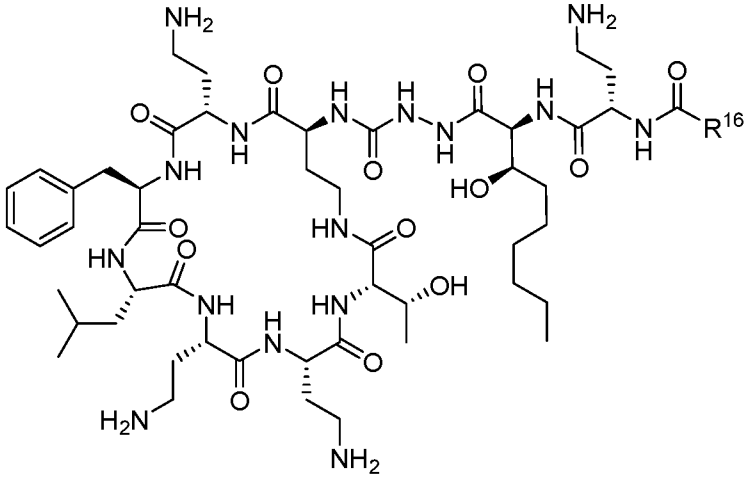
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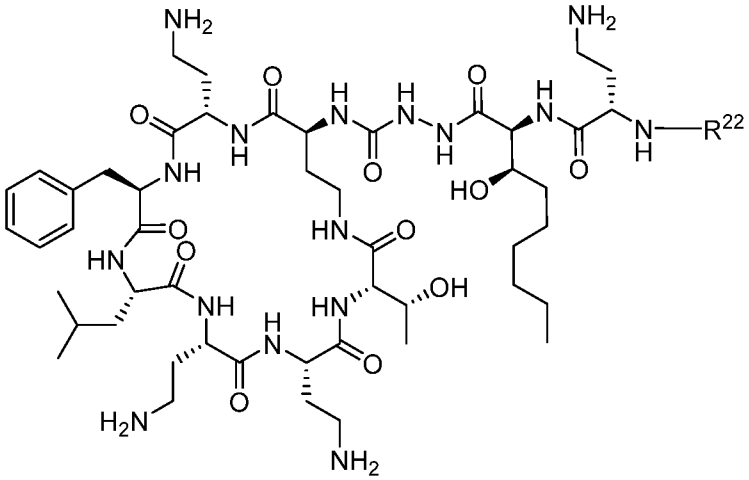
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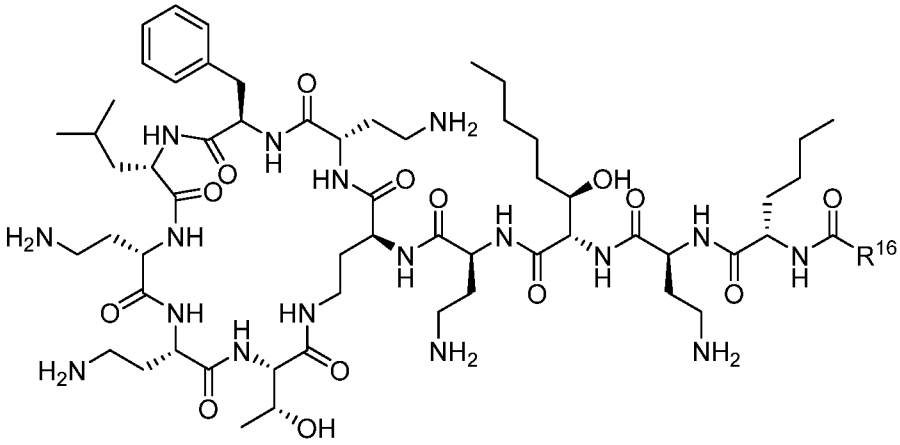
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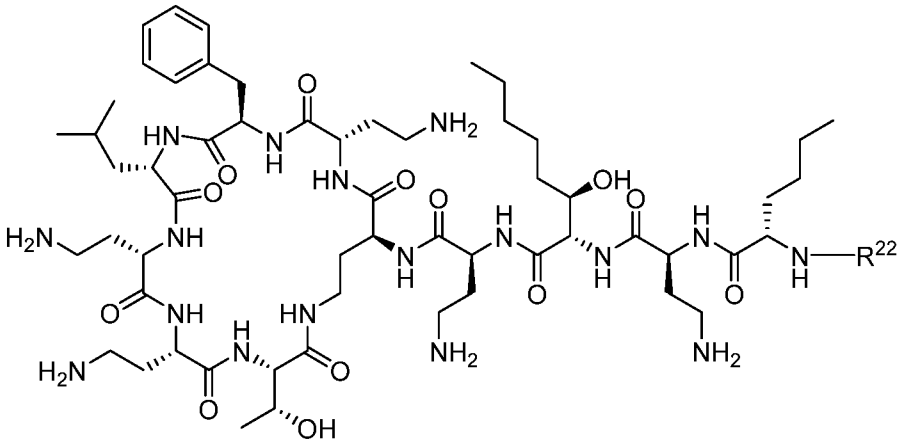
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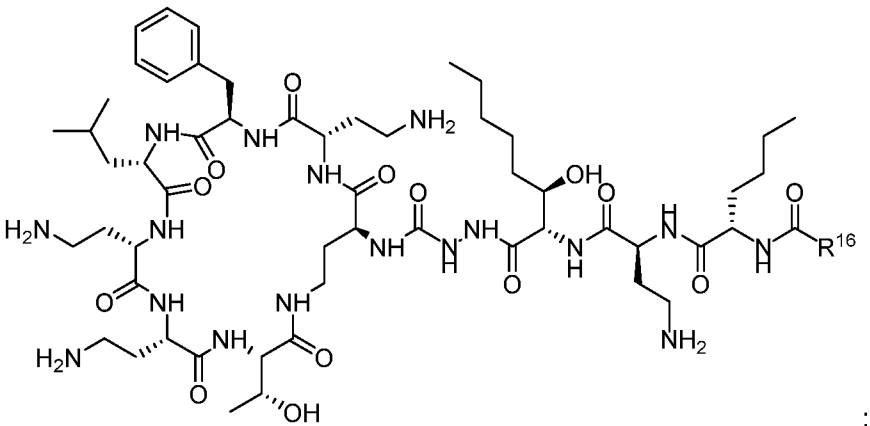
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(XXXIV)



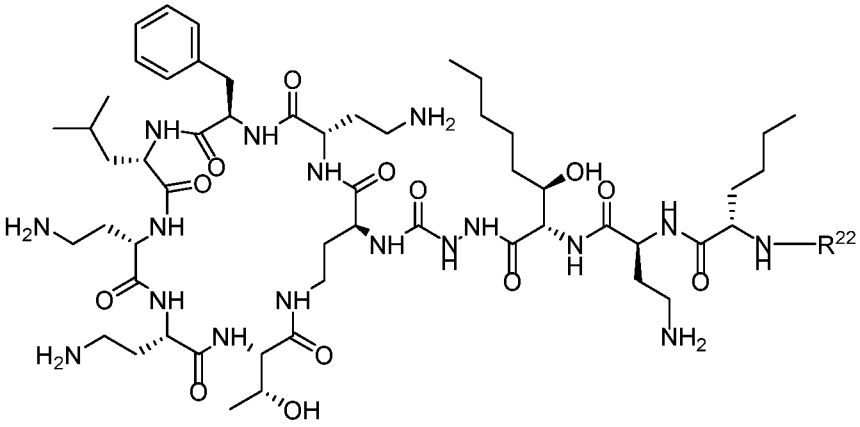
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(XXXV)



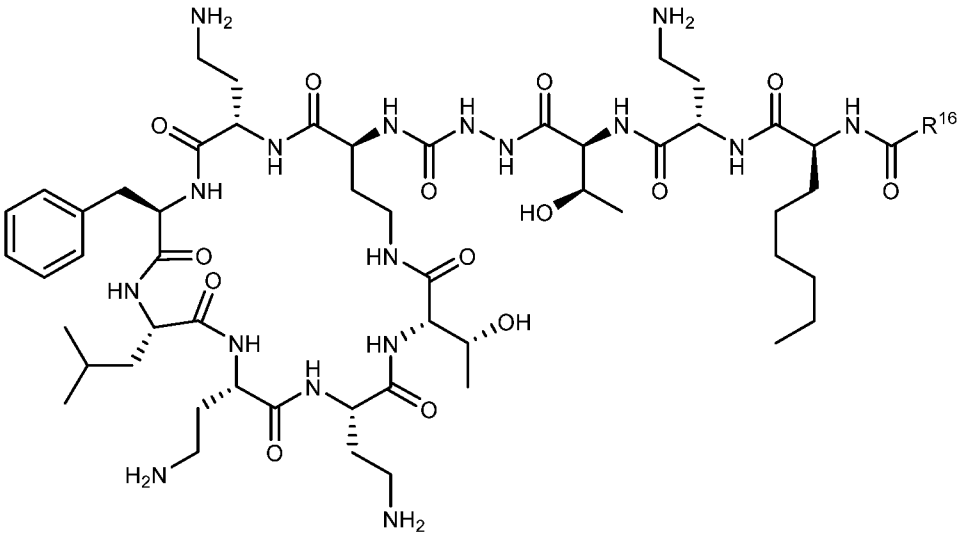
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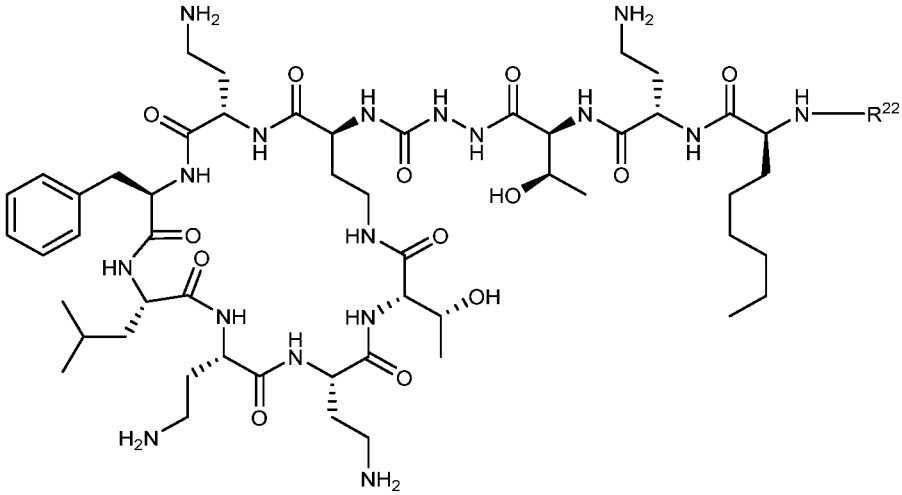
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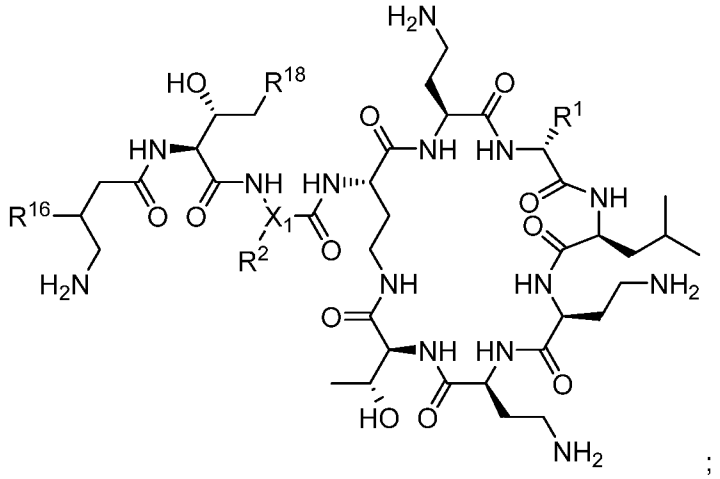
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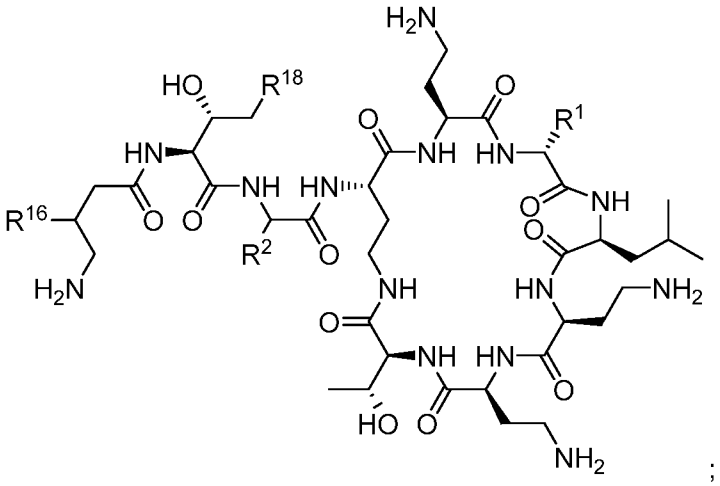
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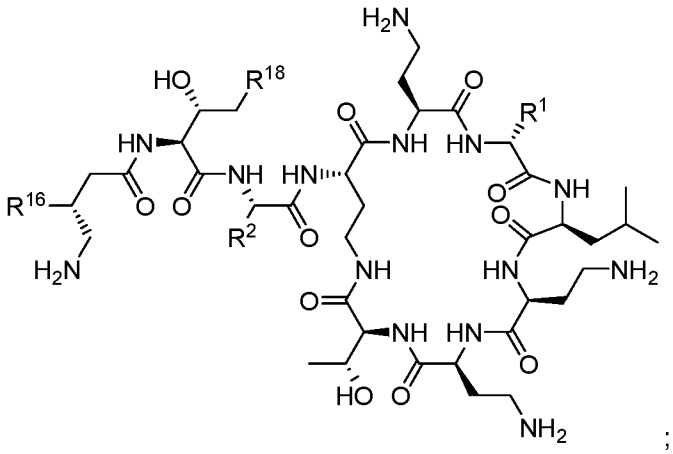
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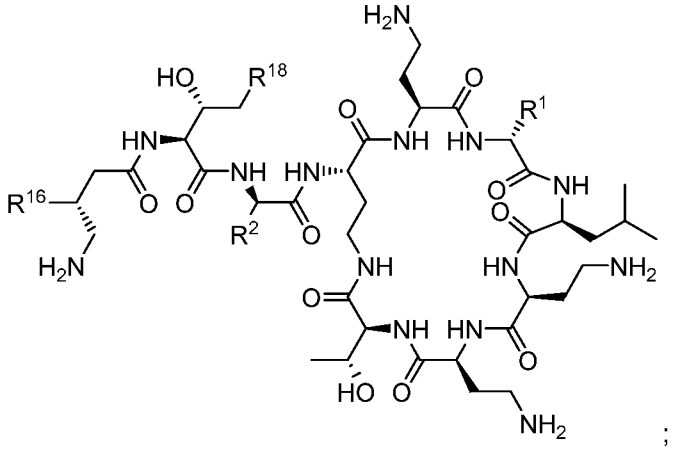
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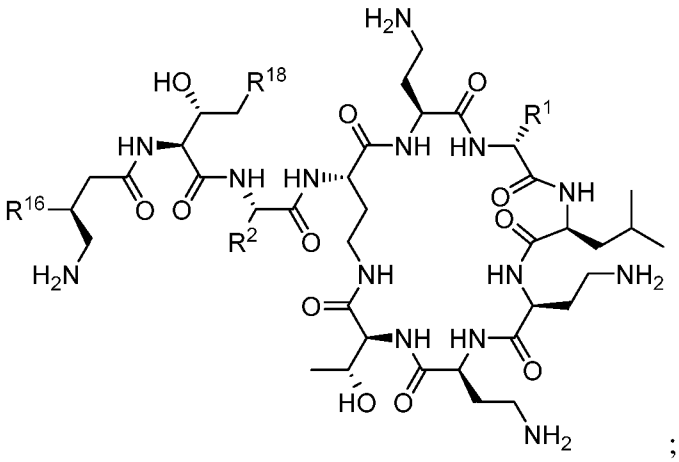
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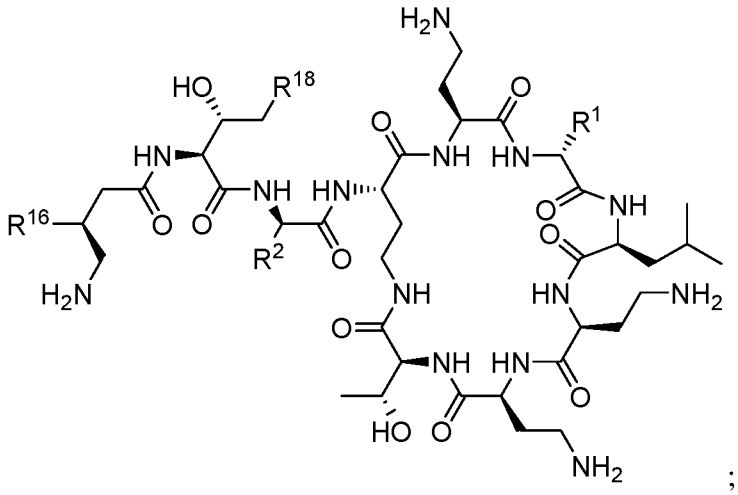
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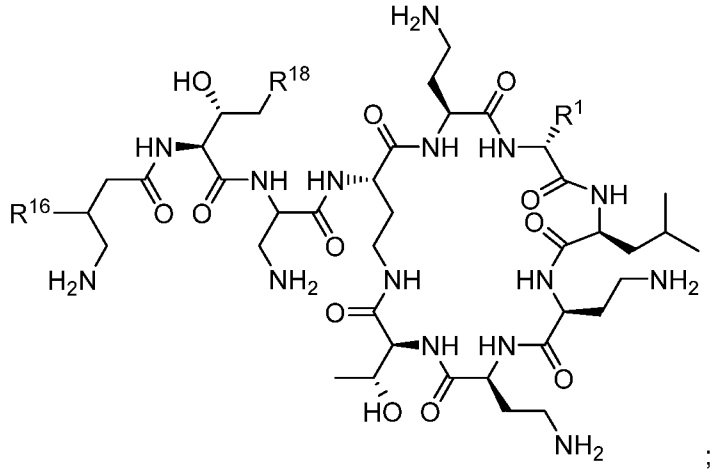
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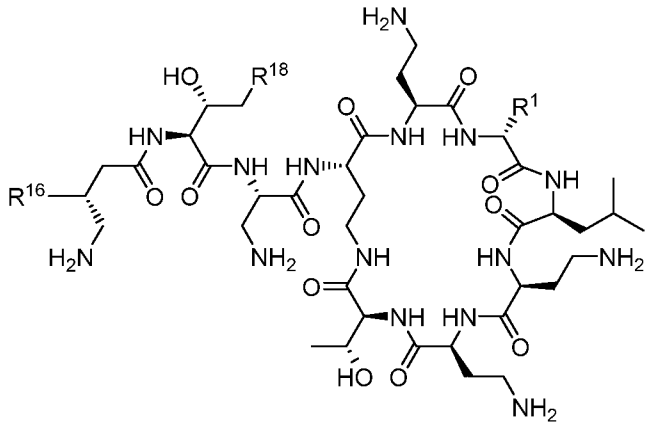
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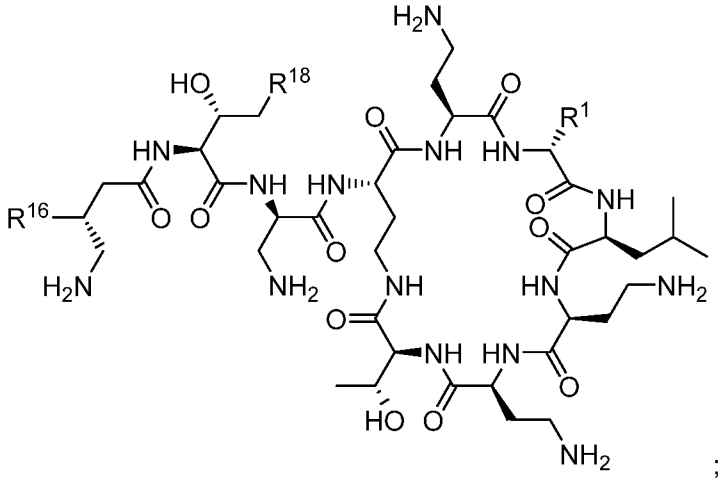
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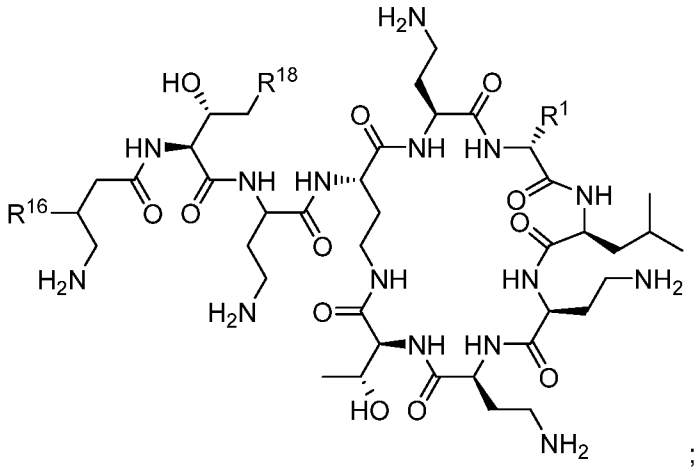
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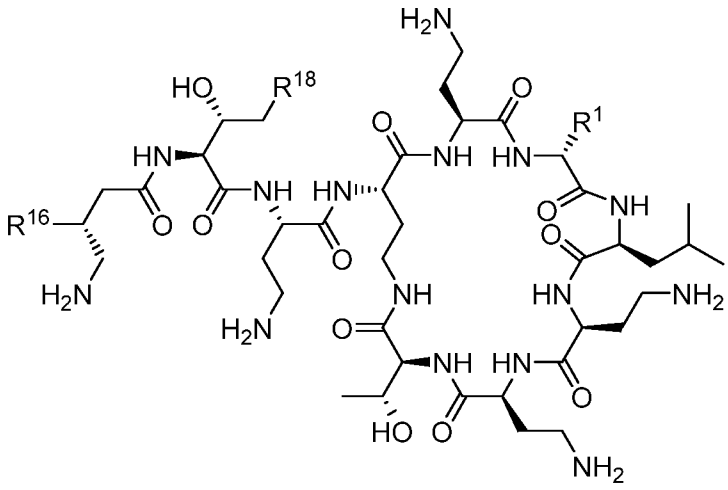
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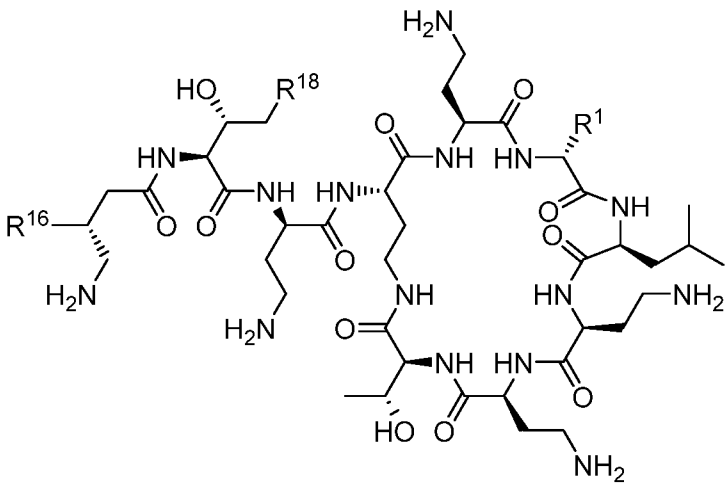
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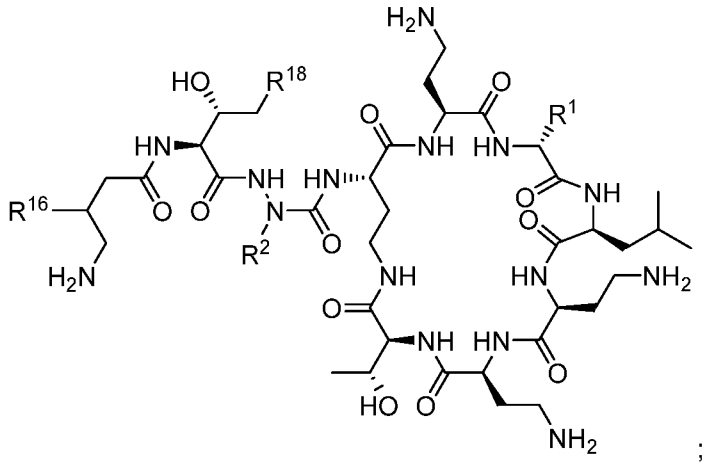
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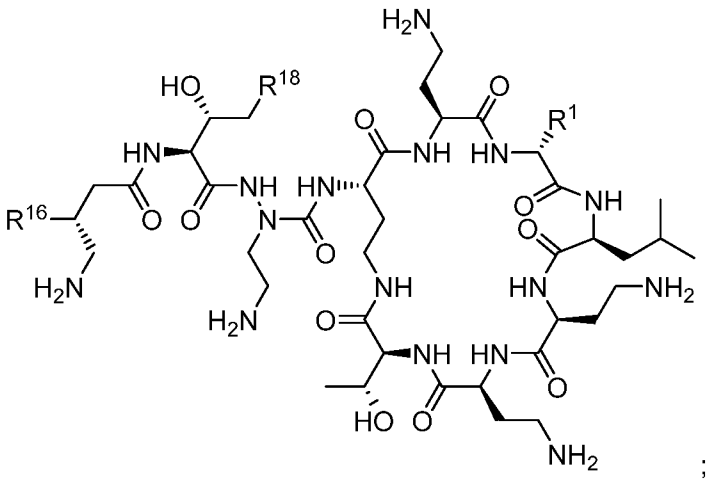
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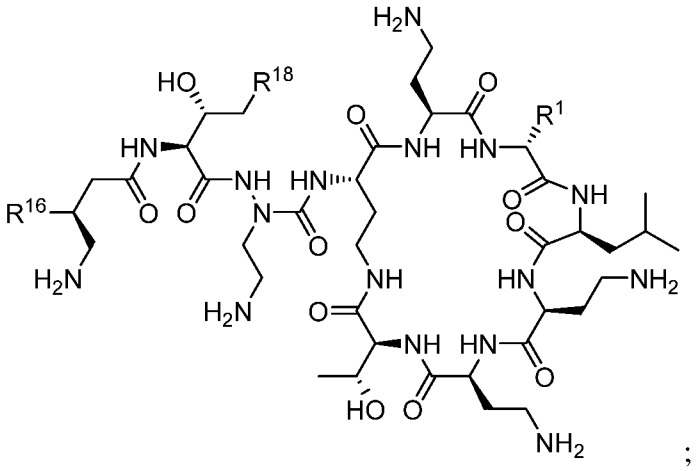
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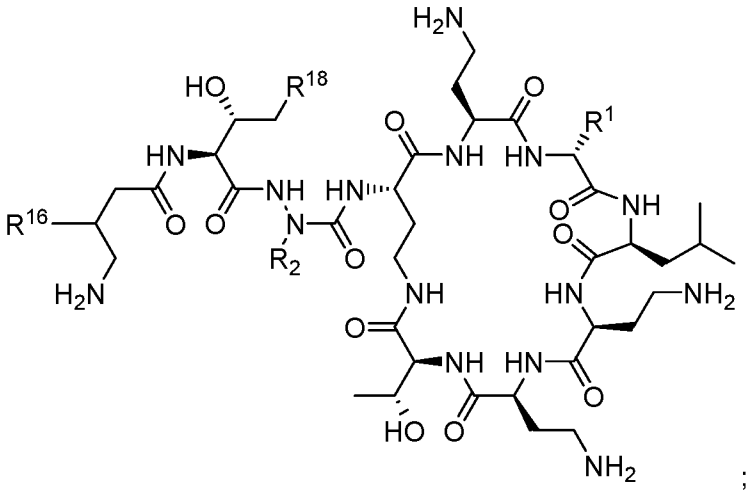
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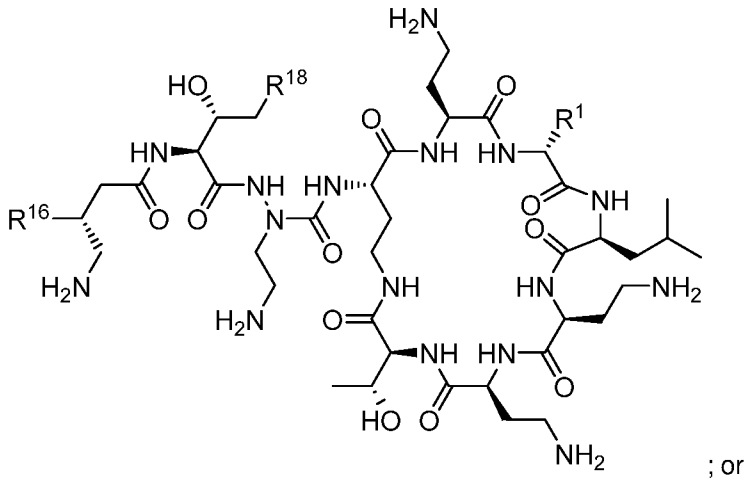
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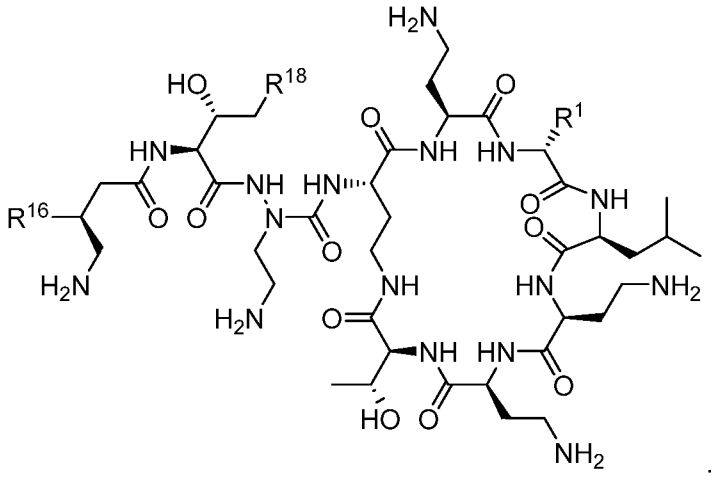
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(XXXXI)



; or

(XXXXI-1)



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(XXXXI-2)

In some embodiments, when a is 1, e.g., in the compound of any one of formulas (I)-(XXXXI), (i) each of R^2, R^3, and R^4 is, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted

heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (ii) R^2, R^3, and X^1 together form a ring (e.g., an optionally substituted 3-8 or 5-8 membered ring) comprising optionally substituted cycloalkyl, optionally substituted heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, and R^4 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (iii) R^3, R^4, N^1, and X^1 together form a ring (e.g., an optionally substituted 5-8 membered ring) comprising optionally substituted heterocycloalkyl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, or optionally substituted heteroaryl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, and R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl.

In some embodiments, when b is 1, e.g., in the compound of any one of formulas (I)-(XXXXI), (i) each of R^5, R^6, and R^7 is, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (ii) R^5, R^6, and X^2 together form a ring (e.g., an optionally substituted 3-8 or 5-8 membered ring) comprising optionally substituted cycloalkyl, optionally substituted heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, and R^7 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (iii) R^6, R^7, N^2, and X^2 together form a ring (e.g., an optionally substituted 5-8 membered ring) comprising optionally substituted heterocycloalkyl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, or optionally substituted heteroaryl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, and R^5 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally

substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl.

In some embodiments, when c is 1, e.g., in the compound of any one of formulas (I)-(XXXXI), (i) each of R^8, R^9, and R^{10} is, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (ii) R^8, R^9, and X^3 together form a ring (e.g., an optionally substituted 3-8 or 5-8 membered ring) comprising optionally substituted cycloalkyl, optionally substituted heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, and R^{10} is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (iii) R^9, R^{10}, N^3, and X^3 together form a ring (e.g., an optionally substituted 5-8 membered ring) comprising optionally substituted heterocycloalkyl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, or optionally substituted heteroaryl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, and R^8 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl.

In some embodiments, when d is 1, e.g., in the compound of any one of formulas (I)-(XXXXI), (i) each of R^{19}, R^{20}, and R^{21} is, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (ii) R^{19}, R^{20}, and X^4 together form a ring (e.g., an optionally substituted 3-8 or 5-8 membered ring) comprising optionally substituted cycloalkyl, optionally substituted heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, and R^{10} is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene,

optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl; or (iii) R^{19}, R^{20}, N^5, and X^4 together form a ring (e.g., an optionally substituted 5-8 membered ring) comprising optionally substituted heterocycloalkyl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, or optionally substituted heteroaryl comprising an N heteroatom and additional 0-2 heteroatoms independently selected from N, O, and S, and R^8 is a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted alkamino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenylene, optionally substituted cycloalkynylene, optionally substituted aryl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkenylene, optionally substituted heterocycloalkynylene, optionally substituted heteroaryl, optionally substituted alkaryl, or optionally substituted heteroalkaryl.

In some embodiments, the peptide include alkyl or alkamino substitution of the nitrogen atom of a backbone amide (e.g., alkyl or alkamino substitution of the linking nitrogen, N^4). Alkyl or alkamino substitution (e.g., C1-C3 alkyl or C2-C3 alkamino substitution) may increase stability (e.g., proteolytic stability) and/or activity of the compound (e.g., relative to the same compound where N^4 is H). In some embodiments, alkyl or alkamino substitution of the nitrogen atom of a backbone amide increases stability (e.g., proteolytic stability) of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound where N^4 is H). In some embodiments, alkyl or alkamino substitution of the nitrogen atom of a backbone amide increases activity (e.g., as measured by a reduction in minimum inhibitory concentration) of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound where N^4 is H). In some embodiments, alkyl or alkamino substitution of the nitrogen atom of a backbone amide decreases the minimum inhibitory concentration of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound where N^4 is H).

In some embodiments, the peptide includes an aza bond in place of a backbone amide bond (e.g., at least one of X^1, X^2, X^3, X'^1, X'^2, and X'^3 of, for example in anyone of formulas (I)-(XXXXI), is a nitrogen atom). The replacement of a backbone amide bond with an aza bond may increase stability (e.g., proteolytic stability) and/or activity of the compound (e.g., relative to the same compound having a standard amide bond in the peptide). In some embodiments, replacement of a backbone amide bond with an aza bond increases stability (e.g., proteolytic stability) of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound having a standard amide bond in the peptide). In some embodiments, replacement of a backbone amide bond with an aza bond increases activity (e.g., as measured by a reduction in minimum inhibitory concentration) of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound having a standard amide bond in the peptide). In some embodiments, replacement of a backbone amide bond with an aza bond decreases the minimum inhibitory concentration of the compound by 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%,

90%, 100%, 150%, 200%, 300%, 400%, 500% or 1000% or more (e.g., relative to the same compound having a standard amide bond in the peptide).

Convalent conjugation

Covalent conjugation of two or more components in a compound may be accomplished using well-known organic chemical synthesis techniques and methods. Complementary functional groups on two components may react with each other to form a covalent bond. Examples of complementary reactive functional groups include, but are not limited to, e.g., maleimide and cysteine, amine and activated carboxylic acid, thiol and maleimide, activated sulfonic acid and amine, isocyanate and amine, azide and alkyne, and alkene and tetrazine.

Other examples of functional groups capable of reacting with amino groups include, e.g., alkylating and acylating agents. Representative alkylating agents include: (i) an α-haloacetyl group, e.g., XCH_2CO- (where X=Br, Cl, or I); (ii) a N-maleimide group, which may react with amino groups either through a Michael type reaction or through acylation by addition to the ring carbonyl group; (iii) an aryl halide, e.g., a nitrohaloaromatic group; (iv) an alkyl halide; (v) an aldehyde or ketone capable of Schiff's base formation with amino groups; (vi) an epoxide, e.g., an epichlorohydrin and a bisoxirane, which may react with amino, sulfhydryl, or phenolic hydroxyl groups; (vii) a chlorine-containing of s-triazine, which is reactive towards nucleophiles such as amino, sufhydryl, and hydroxyl groups; (viii) an aziridine, which is reactive towards nucleophiles such as amino groups by ring opening; (ix) a squaric acid diethyl ester; and (x) an α-haloalkyl ether.

Examples of amino-reactive acylating groups include, e.g., (i) an isocyanate and an isothiocyanate; (ii) a sulfonyl chloride; (iii) an acid halide; (iv) an active ester, e.g., a nitrophenylester or N-hydroxysuccinimidyl ester; (v) an acid anhydride, e.g., a mixed, symmetrical, or N-carboxyanhydride; (vi) an acylazide; and (vii) an imidoester. Aldehydes and ketones may be reacted with amines to form Schiff's bases, which may be stabilized through reductive amination.

It will be appreciated that certain functional groups may be converted to other functional groups prior to reaction, for example, to confer additional reactivity or selectivity. Examples of methods useful for this purpose include conversion of amines to carboxyls using reagents such as dicarboxylic anhydrides; conversion of amines to thiols using reagents such as N-acetylhomocysteine thiolactone, S-acetylmercaptosuccinic anhydride, 2-iminothiolane, or thiol-containing succinimidyl derivatives; conversion of thiols to carboxyls using reagents such as α -haloacetates; conversion of thiols to amines using reagents such as ethylenimine or 2-bromoethylamine; conversion of carboxyls to amines using reagents such as carbodiimides followed by diamines; and conversion of alcohols to thiols using reagents such as tosyl chloride followed by transesterification with thioacetate and hydrolysis to the thiol with sodium acetate.

III. Antibacterial Agents

In some embodiments, one or more antibacterial agents may be administered in combination (e.g., administered substantially simultaneously (e.g., in the same pharmaceutical composition or in

separate pharmaceutical compositions) or administered separately at different times) with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1).

Antibacterial agents may be grouped into several classes, e.g., quinolones, carbapenems, macrolides, DHFR inhibitors, aminoglycosides, ansamycins (e.g., geldanamycin, herimycin, and rifaximin), carbacephem (e.g., loracarbef), cephalosporins (e.g., cefadroxil, cefaolin, cefalotin, cefalothin, cephalexin, e.g., cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, and ceftobiprole), glycopeptides (e.g., teicoplanin, vancomycin, telavancin, dalbavancin, and oritavancin), lincosamides (e.g., clindamycin and lincomycin), lipopeptides (e.g., daptomycin), monobactams (e.g., aztreonam), nitrofurans (e.g., furazolidone and nitrofurantoin), oxazolidinones, pleuromutilins, penicillins , sulfonamides, and tetracyclines (e.g., eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, and tetracycline). Quinolones include, but are not limited to, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, and temafloxacin. Carbapenems include, but are not limited to, ertapenem, doripenem, imipenem/cilastatin, and meropenem. Macrolides include, but are not limited to, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, and spiramycin. In some embodiments, a macrolide is solithromycin. DHFR inhibitors include, but are not limited to, diaminoquinazoline, diaminopyrroloquinazoline, diaminopyrimidine, diaminopteridine, and diaminotriazines. Aminoglycosides include, but are not limited to, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, and spectinomycin. Oxazolidinones include, but are not limited to, linezolid, tedizolid, posizolid, radezolid, and furazolidone. Pleuromutilins include, but are not limited to, retapamulin, valnemulin, tiamulin, azamulin, and lefamulin. Penicillins include, but are not limited to, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, penicillin G, temocillin, and ticarcillin. Sulfonamides include, but are not limited to, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (Co-trimoxazole) (TMP-SMX), and sulfonamidochrysoidine.

In some embodiments, the antibacterial agent used in combination with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is selected from the group consisting of linezolid, tedizolid, posizolid, radezolid, retapamulin, valnemulin, tiamulin, azamulin, lefamulin, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin,

penicillin g, penicillin v, piperacillin, penicillin g, temocillin, ticarcillin, amoxicillin clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (tmp-smx), sulfonamidochrysoidine, eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone, capreomycin, cycloserine, ethambutol(bs), ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole, and trimethoprim, prodrugs thereof, and pharmaceutically acceptable salts thereof.

In some embodiments, the antibacterial agent used in combination with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is tedizolid, azithromycin, meropenem, amikacin, levofloxacin, rifampicin, linezolid, erythromycin, or solithromycin. In some embodiments, the antibacterial agent used in combination with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is tedizolid, azithromycin, meropenem, amikacin, or levofloxacin. In some embodiments, the antibacterial agent used in combination with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is tiamulin. In some embodiments, the antibacterial agent used in combination with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is solithromycin.

IV. Methods

Methods described herein include, e.g., methods of protecting against or treating a bacterial infection (e.g., a Gram-negative bacterial infection) in a subject and methods of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria (e.g., Gram-negative bacteria). A method of treating a bacterial infection (e.g., a Gram-negative bacterial infection) in a subject includes administering to the subject a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or a pharmaceutical composition thereof. In some embodiments, the bacterial infection is caused by Gram-negative bacteria. In some embodiments, the bacterial infection is caused by a resistant strain of bacteria. In some embodiments, the resistant strain of bacteria is a resistant strain of *E. coli*. A method of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria (e.g., Gram-negative bacteria) includes contacting the bacteria (e.g., Gram-negative bacteria) or a site susceptible to bacterial growth (e.g., Gram-negative bacterial growth) with a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or a pharmaceutical composition thereof. In some embodiments, the bacterial infection is caused by Gram-negative bacteria. In some embodiments, the bacterial infection is caused by a resistant strain of bacteria. In some embodiments, the resistant strain of bacteria is a resistant strain of *E. coli*. In some embodiments, a compound used in any methods described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or

a compound of Table 1) may bind to LPS in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization to other antibiotics.

Moreover, methods described herein also include methods of protecting against or treating sepsis in a subject by administering to the subject a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). In some embodiments, the method further includes administering to the subject an antibacterial agent. Methods described herein also include methods of preventing lipopolysaccharides (LPS) in Gram-negative bacteria (e.g., a resistant strain of Gram-negative bacteria or a resistant strain of *E. coli* (e.g., *E. coli* BAA-2469)) from activating a immune system in a subject by administering to the subject a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). In some embodiments of the method, the method prevents LPS from activating a macrophage. In some embodiments, the method further includes administering to the subject an antibacterial agent. In some embodiments, a compound used in any methods described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) may bind to LPS in the cell membrane of Gram-negative bacteria to disrupt and permeabilize the cell membrane, leading to cell death and/or sensitization to other antibiotics.

In some embodiments, the methods described herein may further include administering to the subject an antibacterial agent in addition to a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1). Methods described herein also include methods of protecting against or treating a bacterial infection in a subject by administering to said subject (1) a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and (2) an antibacterial agent. Methods described herein also include methods of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria, by contacting the bacteria or a site susceptible to bacterial growth with (1) a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and (2) an antibacterial agent.

In some embodiments, the compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) is administered first, followed by administering of the antibacterial agent alone. In some embodiments, the antibacterial agent is administered first, followed by administering of the compound described herein alone. In some embodiments, the compound described herein and the antibacterial agent are administered substantially simultaneously (e.g., in the same pharmaceutical composition or in separate pharmaceutical compositions). In some embodiments, the compound described herein or the antibacterial agent is administered first, followed by administering of the compound described herein and the antibacterial agent substantially simultaneously (e.g., in the same pharmaceutical composition or in separate pharmaceutical compositions). In some embodiments, the compound described herein and the antibacterial agent are administered first substantially simultaneously (e.g., in the same pharmaceutical composition or in separate pharmaceutical compositions), followed by administering of the compound described herein or the antibacterial agent alone. In some embodiments, when a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and an antibacterial agent are administered together (e.g., substantially simultaneously in the same or separate pharmaceutical compositions, or separately in the same treatment regimen), the MIC of

each of the compound and the antibacterial agent may be lower than the MIC of each of the compound and the antibacterial agent when each is used alone in a treatment regimen.

V. Pharmaceutical Compositions and Preparations

A compound described herein may be formulated in a pharmaceutical composition for use in the methods described herein. In some embodiments, a compound described herein may be formulated in a pharmaceutical composition alone. In some embodiments, a compound described herein may be formulated in combination with an antibacterial agent in a pharmaceutical composition. In some embodiments, the pharmaceutical composition includes a compound described herein (e.g., a compound described by any one of formulas (I)-(XXXXI) or a compound of Table 1) and pharmaceutically acceptable carriers and excipients.

Acceptable carriers and excipients in the pharmaceutical compositions are nontoxic to recipients at the dosages and concentrations employed. Acceptable carriers and excipients may include buffers such as phosphate, citrate, HEPES, and TAE, antioxidants such as ascorbic acid and methionine, preservatives such as hexamethonium chloride, octadecyldimethylbenzyl ammonium chloride, resorcinol, and benzalkonium chloride, proteins such as human serum albumin, gelatin, dextran, and immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidone, amino acid residues such as glycine, glutamine, histidine, and lysine, and carbohydrates such as glucose, mannose, sucrose, and sorbitol.

Examples of other excipients include, but are not limited to, antiadherents, binders, coatings, compression aids, disintegrants, dyes, emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, sorbents, suspensing or dispersing agents, or sweeteners. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

The compounds herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds herein be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

Representative acid addition salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include, but are not limited to, sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

Depending on the route of administration and the dosage, a compound herein or a pharmaceutical composition thereof used in the methods described herein will be formulated into suitable pharmaceutical compositions to permit facile delivery. A compound (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or a pharmaceutical composition thereof may be formulated to be administered intramuscularly, intravenously (e.g., as a sterile solution and in a solvent system suitable for intravenous use), intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally (e.g., a tablet, capsule, caplet, gelcap, or syrup), topically (e.g., as a cream, gel, lotion, or ointment), locally, by inhalation, by injection, or by infusion (e.g., continuous infusion, localized perfusion bathing target cells directly, catheter, lavage, in cremes, or lipid compositions). Depending on the route of administration, a compound herein or a pharmaceutical composition thereof may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, preparations suitable for iontophoretic delivery, or aerosols. The compositions may be formulated according to conventional pharmaceutical practice.

A compound described herein may be formulated in a variety of ways that are known in the art. For use as treatment of human and animal subjects, a compound described herein can be formulated as pharmaceutical or veterinary compositions. Depending on the subject (e.g., a human) to be treated, the mode of administration, and the type of treatment desired, e.g., prophylaxis or therapy, a compound described herein is formulated in ways consonant with these parameters. A summary of such techniques is found in Remington: The Science and Practice of Pharmacy, 22nd Edition, Lippincott Williams & Wilkins (2012); and Encyclopedia of Pharmaceutical Technology, 4th Edition, J. Swarbrick and J. C. Boylan, Marcel Dekker, New York (2013), each of which is incorporated herein by reference.

Formulations may be prepared in a manner suitable for systemic administration or topical or local administration. Systemic formulations include those designed for injection (e.g., intramuscular, intravenous or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral

administration. The formulation will generally include a diluent as well as, in some cases, adjuvants, buffers, and preservatives. The compounds can be administered also in liposomal compositions or as microemulsions. Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds herein. Suitable forms include syrups, capsules, and tablets, as is understood in the art.

The pharmaceutical compositions can be administered parenterally in the form of an injectable formulation. Pharmaceutical compositions for injection can be formulated using a sterile solution or any pharmaceutically acceptable liquid as a vehicle. Formulations may be prepared as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Pharmaceutically acceptable vehicles include, but are not limited to, sterile water, physiological saline, and cell culture media (e.g., Dulbecco's Modified Eagle Medium (DMEM), α-Modified Eagles Medium (α-MEM), F-12 medium). Such injectable compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, such as sodium acetate and sorbitan monolaurate. Formulation methods are known in the art, see e.g., Pharmaceutical Preformulation and Formulation, 2nd Edition, M. Gibson, Taylor & Francis Group, CRC Press (2009).

The pharmaceutical compositions can be prepared in the form of an oral formulation. Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Other pharmaceutically acceptable excipients for oral formulations include, but are not limited to, colorants, flavoring agents, plasticizers, humectants, and buffering agents. Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets

may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Dissolution or diffusion controlled release of a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or a pharmaceutical composition thereof can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of the compound, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon. The pharmaceutical composition may be formed in a unit dose form as needed. The amount of active component, e.g., a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1), included in the pharmaceutical compositions are such that a suitable dose within the designated range is provided (e.g., a dose within the range of 0.01-100 mg/kg of body weight).

VI. Routes of Administration and Dosages

In any of the methods described herein, compounds herein may be administered by any appropriate route for treating or protecting against a bacterial infection (e.g., a Gram-negative bacterial infection), or for preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria (e.g., Gram-negative bacteria). Compounds described herein may be administered to humans, domestic pets, livestock, or other animals with a pharmaceutically acceptable diluent, carrier, or excipient. In some embodiments, administering comprises administration of any of the compounds described herein (e.g., compounds of any one of formulas (I)-(XXXXI) or a compound of Table 1) or compositions intramuscularly, intravenously (e.g., as a sterile solution and in a solvent system suitable for intravenous use), intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally (e.g., a tablet, capsule, caplet, gelcap, or syrup), topically (e.g., as a cream, gel, lotion, or ointment), locally, by inhalation, by injection, or by infusion (e.g., continuous infusion, localized perfusion bathing target cells directly, catheter, lavage, in cremes, or lipid compositions). In some embodiments, if an antibacterial agent is also administered in addition to a compound described herein, the antibacterial agent or a pharmaceutical composition thereof may also be administered in any of the routes of administration described herein.

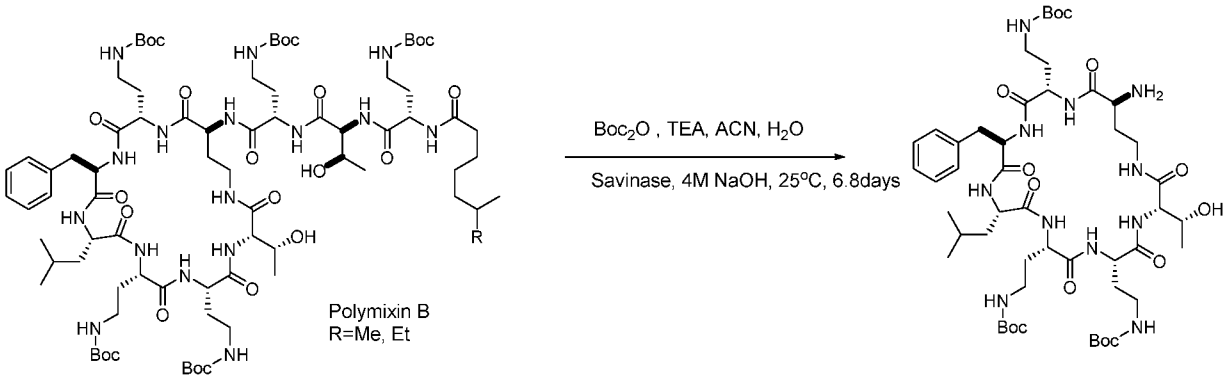
The dosage of a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or pharmaceutical compositions thereof depends on factors including the route of administration, the disease to be treated (e.g., the extent and/or condition of the bacterial

infection), and physical characteristics, e.g., age, weight, general health, of the subject. Typically, the amount of the compound or the pharmaceutical composition thereof contained within a single dose may be an amount that effectively prevents, delays, or treats the bacterial infection without inducing significant toxicity. A pharmaceutical composition may include a dosage of a compound described herein ranging from 0.01 to 500 mg/kg (e.g., 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg/kg) and, in a more specific embodiment, about 0.1 to about 30 mg/kg and, in a more specific embodiment, about 1 to about 30 mg/kg. In some embodiments, when a compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) and an antibacterial agent are administered together (e.g., substantially simultaneously in the same or separate pharmaceutical compositions, or separately in the same treatment regimen), the dosage needed of the compound described herein may be lower than the dosage needed of the compound if the compound was used alone in a treatment regimen.

A compound described herein (e.g., a compound of any one of formulas (I)-(XXXXI) or a compound of Table 1) or a pharmaceutical composition thereof may be administered to a subject in need thereof, for example, one or more times (e.g., 1-10 times or more; 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times) daily, weekly, monthly, biannually, annually, or as medically necessary. Dosages may be provided in either a single or multiple dosage regimens. The timing between administrations may decrease as the medical condition improves or increase as the health of the patient declines. The dosage and frequency of administration may be adapted by the physician in accordance with conventional factors such as the extent of the infection and different parameters of the subject.

EXAMPLES

Example 1 – Synthesis of Intermediate 1 (Int-1): Degradation of polymyxin B to tri-Boc polymyxin B cycloheptapeptide

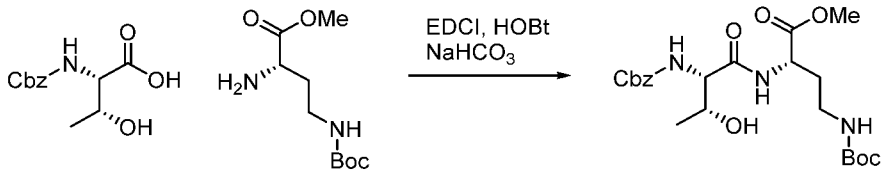


Polymyxin B (100 g, 72.2 mmol) was dissolved in acetonitrile (1000 mL) and water (500 mL) and stirred at room temperature for 10 mins. TEA (58.5 g, 8.0 eq) was added and the mixture stirred for a further 10 mins. Boc_2O (94.6 g, 6.0 eq) was subsequently added in one portion and the mixture stirred for 6 hrs at 20 °C. Savinase® (300 mL) was then added. The pH of the resulting mixture was adjusted to 9.0 with aq 4M sodium hydroxide solution (10 mL) and the reaction mixture stirred at 25°C. Additional Savinase® (100 mL) was added after 17 hrs, and another quantity of Savinase® (100 mL x2) was added after 26 hrs. After an overall reaction time of 80 hrs, the mixture was diluted with ethyl acetate (2000 mL). After separation of the layers, the organic phase was washed with 0.1 M NaOH solution (1000 mL x2,

10V x2), then water (1000 mL, 10V). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent evaporated at reduced pressure. The residue was purified by silica gel chromatography eluting with 80% (EtOAc : MeOH : $H_2O{\cdot}NH_3$ = 40:10:1) in ethyl acetate to give the title compound (49.8 g, 65.0%). LCMS: m/z $(M + H)^+$ calcd for $C_{50}H_{83}N_{11}O_{14}$:1061.61; found:1062.5

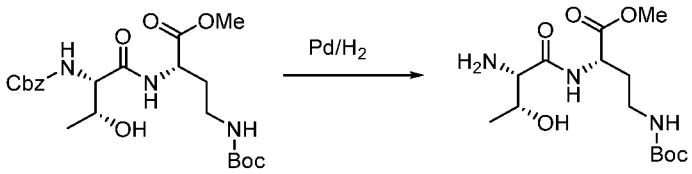
Example 2 – Synthesis of Int-2 (Tripeptide (Dab-Thr-Dab))

Step a.



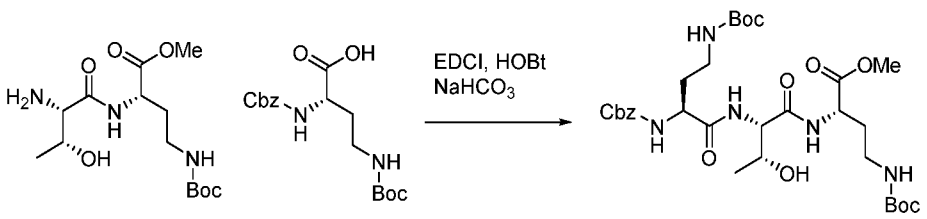
NH_2-Dab(Boc)-OMe (HCl salt) (5.000 g, 1eq.), Z-NH-Thr-OH (5.049 g, 1.05eq.), EDCI (5.350 g, 1.5eq.), HOBt (3.733 g, 1.5eq.) and $NaHCO_3$ (3.095 g, 2eq.) were weighed into a 100- mL round bottom flask. 24 mL of DCM/DMF (4:1) was added into the flask. The mixture was stirred at room temperature for less than 3 hrs. (TLC or LC/MS monitoring). After completion, EtOAc (200 mL) was added to dilute the reaction mixture and washed with 1N aq. HCl, saturated $NaHCO_3$ and brine. Dried with Na_2SO_4 and condensed. The residue was purified with normal phase silica (2~7% MeOH/DCM) to give 8.24 g pure desired product (>95%).

Step b.



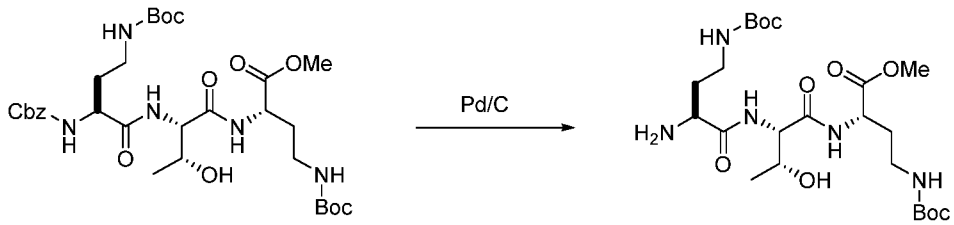
Starting material (SM) (8.24 g) was dissolved in 100 mL of MeOH/EtOAc. And 5%Pd/C (3.75 g, 0.1eq.) was added. Under H_2 balloon, the reaction mixture was stirred for 2h. Checked LC/MS. Celite filtration and MeOH wash. Dried to give 5.87 g of free amine (>99%). The material was used in the next step without purification.

Step c.



NH_2-Thr-Dab(Boc)-OMe (1.46 g, 1eq.), Z-NH-Dab(Boc)-OH(DCHA salt) (2.463, 1.05eq.), EDCI (1.260 g, 1.5eq.), HOBt (0.888 g, 1.5eq.) and $NaHCO_3$ (0.738, 2 eq.) were weighed into a 100- mL round bottom flask. 20 mL of DCM/DMF (4:1) was added into the flask. The mixture was stirred at room temperature for less than 3 hrs with TLC or LC/MS monitoring. After the completion, EtOAc (100 mL) was added to dilute the reaction mixture and washed with 1N aq. HCl, saturated NaHCO3 and brine. Dried with Na2SO4 and condensed. The residue was purified with normal phase silica (2~7% MeOH/DCM) to give 2.78 g pure desired product (>95% isolated yield). (The reaction was repeated at 4.4 g scale and gave the similar result.)

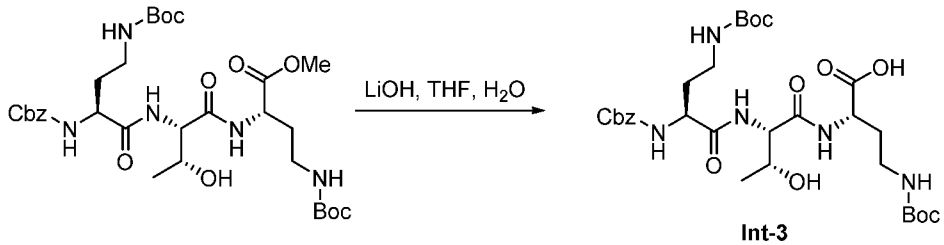
Step d.



Int-2

A solution of the Cbz-tripeptide (1.55 g, 2.32 mmol) in methanol (10 mL) was charged with 5% Pd/C (0.300 g) and flushed with hydrogen from a balloon. After stirring overnight under hydrogen atmosphere, LCMS showed complete conversion. Pd/C was removed by filtration through Celite. The filtrate was concentrated and used in the next Step without further purification.

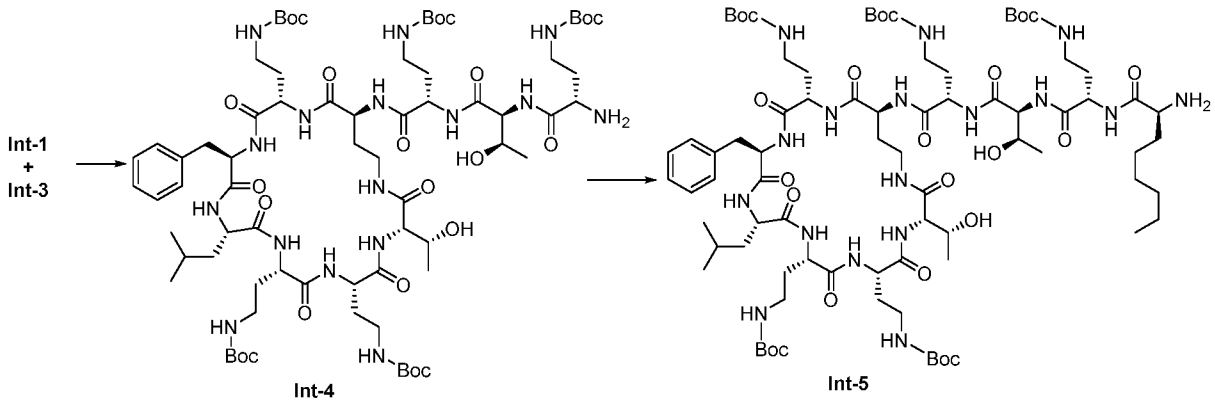
Example 3 – Synthesis of Int-3 (Tripeptide acid)



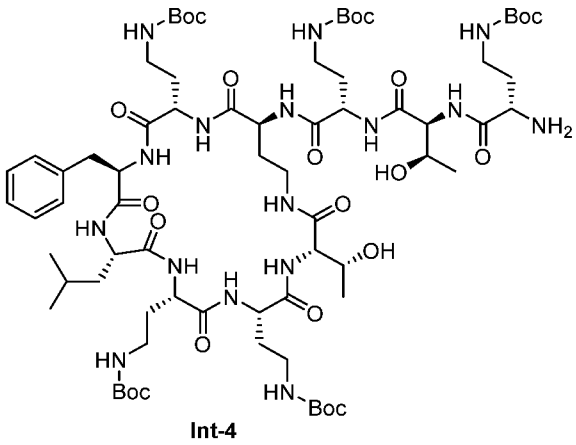
Int-3

A solution of the Cbz-tripeptide-OMe (7.85 g, 11.76 mmol, described in step c of Int-2 synthesis), dissolved in THF (30 mL), and water (30 mL), was treated with powdered LiOH (0.338 g, 14.1 mmol) and stirred at room temperature. After 15 minutes LCMS showed consumption of starting material. The reaction was made slightly acidic by adding concentrated HCl (aq), then extracted into ethyl acetate, dried over sodium sulfate, concentrated, and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using no modifier. Yield 7.2 g, 94%. Ion(s) found by LCMS: (M+H)+ = 654.2.

Example 4 – Synthesis of Int-5

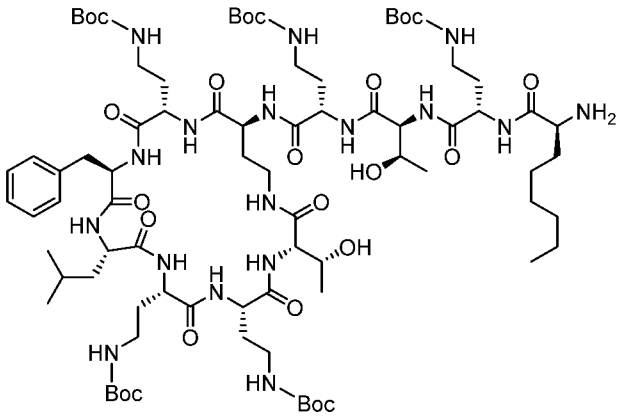


Step a. Synthesis of penta Boc polymyxin B decapeptide (Int-4)



Tri-Boc polymyxin B heptapeptide (0.464 g, 0.437 mmol, Int-1), and tripeptide acid (0.316 g, 0.398 mmol, Int-3), were dissolved in DMF (1 mL), DIEA (0.229 mL, 1.31 mmol), then treated with HATU (0.166 g, 0.437 mmol). After stirring for 30 min LCMS showed complete conversion. The crude Cbz-product was diluted with methanol (4 mL), and charged with 5%Pd/C (0.250 g) and placed under a hydrogen atmosphere. After 2 hr the mixture was filtered through Celite, concentrated, and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 10% to 100% methanol and water, using no modifier. Yield of Int-4 was 0.640 g, 94% (two steps). Ion(s) found by LCMS: [(M-1Boc)/2]+H+ = 1054.6, [(M-2Boc)/2]+H+ = 1004.6.

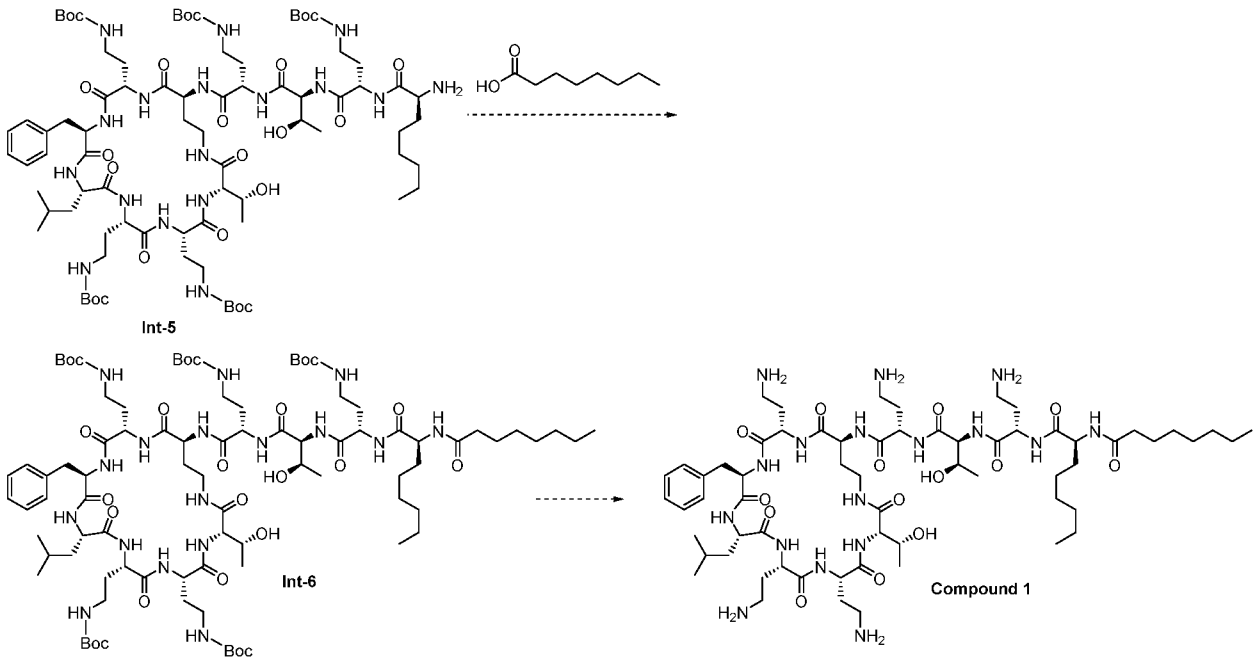
Step b. Synthesis of aminooctanoyl penta Boc polymyxin B decapeptide (Int-5)



Int-5

A solution of Int-4 (3.00 g, 1.918 mmol), Cbz-aminooctanoic acid (0.591 g, 2.01 mmol), and DIEA (1.05 mL, 6.04 mmol), in DMF (10 mL), was treated with a solution of HATU (0.766 g, 2.01 mmol) dissolved in DMF (3 mL), dropwise over 60 minutes. After 2h, LCMS showed complete consumption of starting material. The crude mixture was treated with 5% Pd/C (1.7 g), vacuum flushed with hydrogen, and stirred under a hydrogen atmosphere for 2hr or until complete by LCMS. The crude reaction was filtered through Celite, concentrated, and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 20% to 100% methanol and water, using no modifier. Yield of Int-5 was 2.59 g, 79% (two steps). Ion(s) found by LCMS: [M/2]+H+ = 853.4.

Example 5 – Synthesis of Compound 1

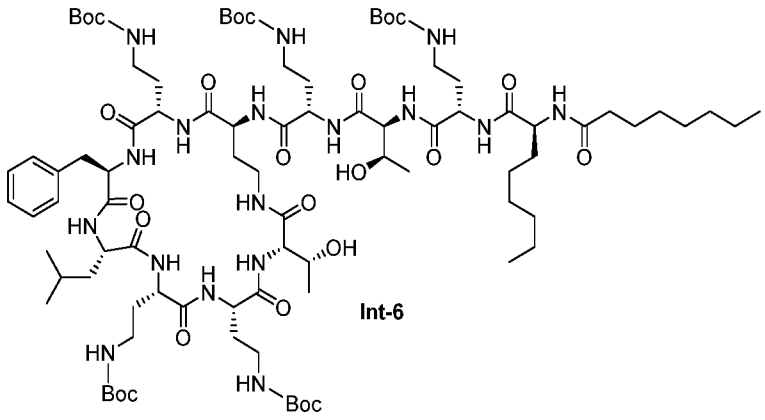


Int-5

Int-6

Compound 1

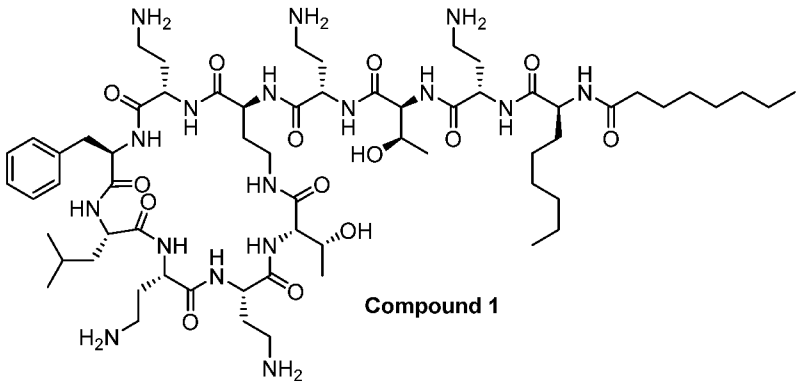
Step a. Synthesis of Int-6



Int-6

A solution of Int-5, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

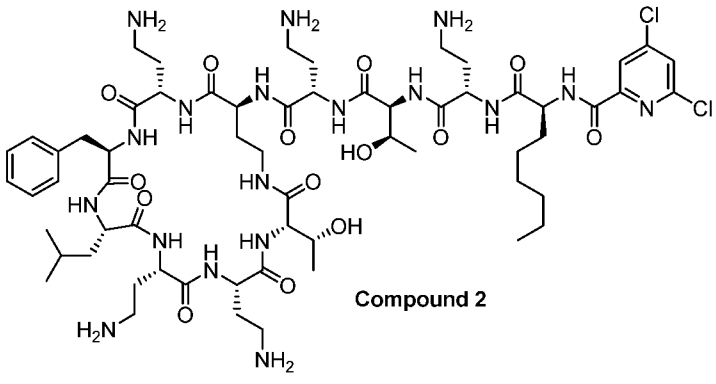
Step b. Synthesis of Compound 1



Compound 1

A solution of Int-6 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

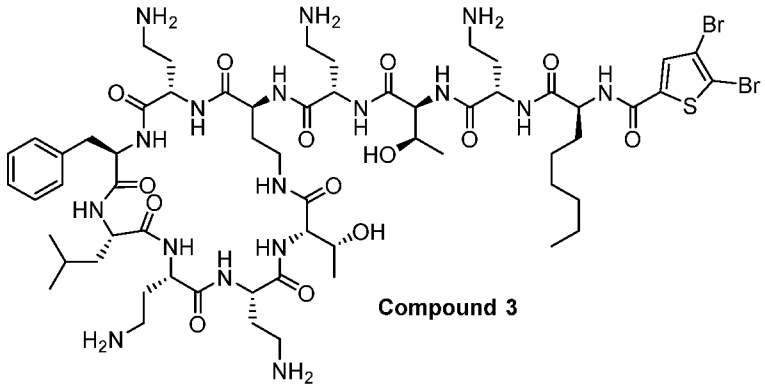
Example 6 – Synthesis of Compound 2



Compound 2

The title compound is prepared from Int-5 and 4,6-dichloropicolinic acid using the procedure described in Example 5.

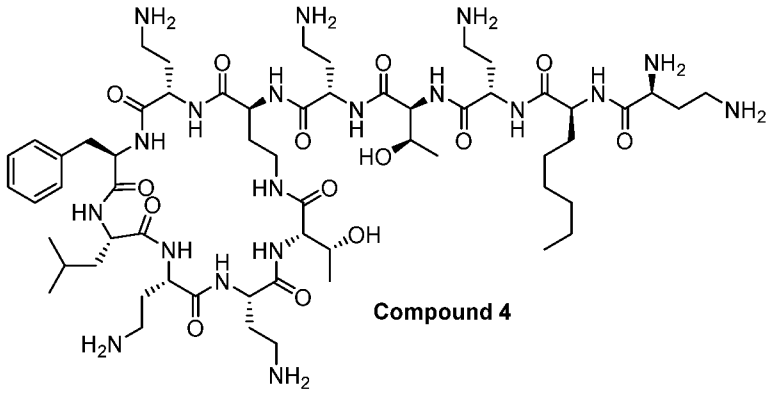
Example 7 – Synthesis of Compound 3



Compound 3

The title compound is prepared from Int-5 and 4,5-dibromo-2-thiophenecarboxylic acid using the procedure described in Example 5.

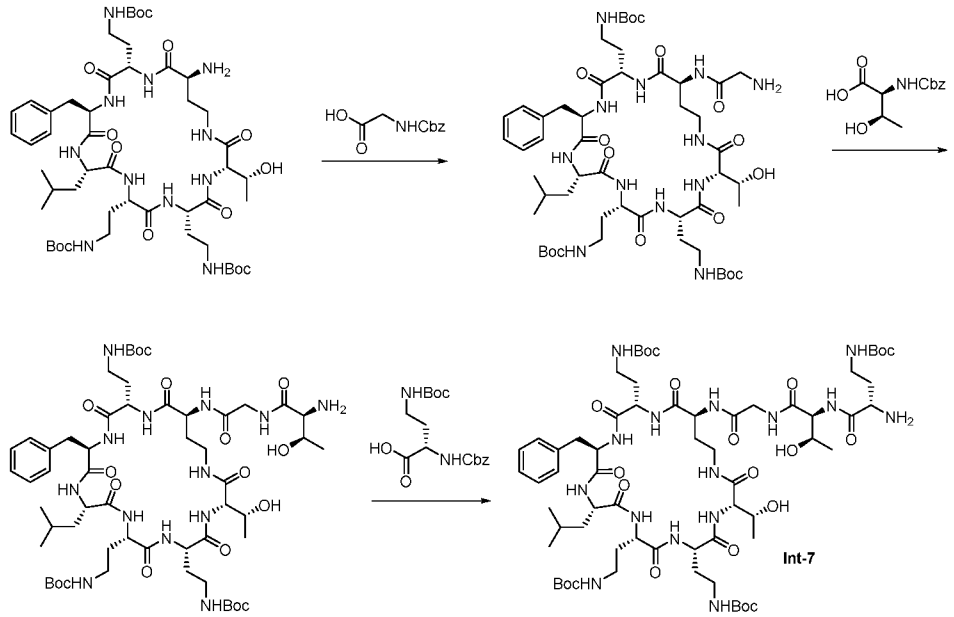
Example 8 – Synthesis of Compound 4



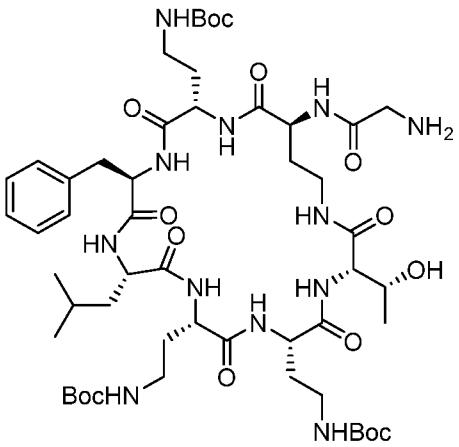
Compound 4

The title compound is prepared from Int-5 and (*S*)-2,5-Bis((*tert*-butoxycarbonyl)amino)pentanoic acid using the procedure described in Example 5.

Example 9 – Synthesis of Int-7

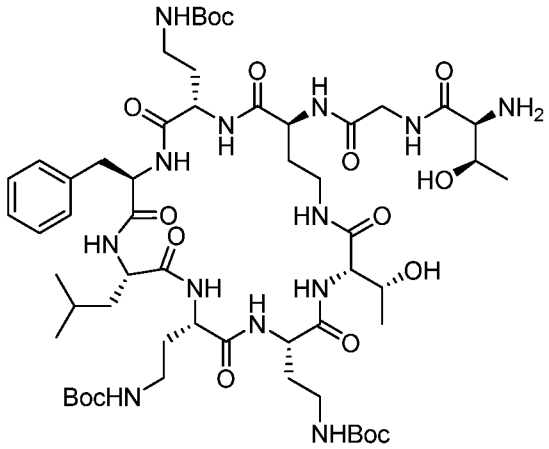


Step a. Synthesis of Int-1-Gly Conjugate



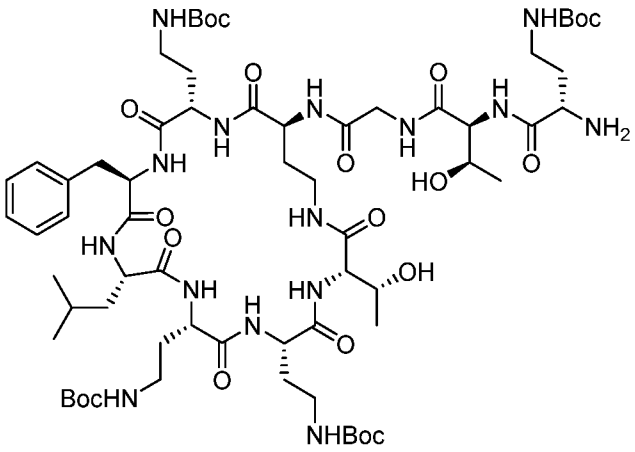
To a mixture of Int-1 (4.24 g, 4 mmol) and Z-Gly-OH (1 g, 4.8 mmol) in anhydrous DMF (8 mL) was added HATU (1.87 g, 4.9 mmol) in portions over 20 minutes, followed by DIPEA (936 mg, 7.2 mmol). After the reaction mixture was stirred for 15 minutes, it was poured into water (100 mL). The white solid product was collected by filtration and washed with water. The material was re-dissolved in MeOH (50 mL) and treated with Pd/C (1 g). The mixture was stirred under hydrogen overnight. Pd/C was then filtered off, and the filtrate was concentrated and purified through RPLC (150 g, 15 to 75 % MeOH and water). Yield 4.02 g, 89.8 %. Ion found by LCMS: $[(M - Boc + 2H)/2]^+$ = 510.4, $[(M - 3Boc + 2H)/2]^+$ = 410.2

Step b.



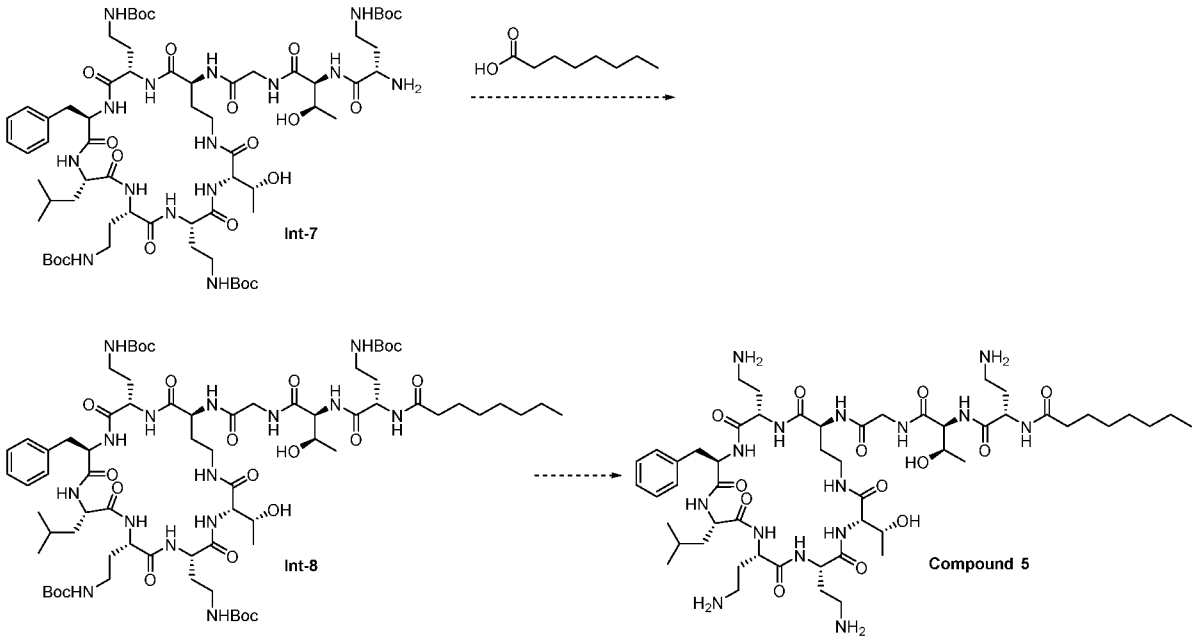
To a mixture of the step a product (4.02 g, 3.592 mmol) and Z-Thr-OH (980.3 mg, 3.87 mmol) in anhydrous DMF (5 mL) was added HATU (1.47 g, 3.87 mmol) in portions over 10 minutes, followed by DIPEA (755 mg, 5.8 mmol). After the addition, the reaction was stirred for 20 minutes and then poured into water (100 mL). The white solid product was collected by filtration and washed with water. The material was re-dissolved in MeOH (50 mL) and added with Pd/C (1 g). The mixture was stirred under hydrogen overnight. Pd/C was then filtered, and the filtrate was concentrated and purified through RPLC (150 g, 15 to 80 % MeOH and water). Yield 3.68 g, 83.9 %. Ions found by LCMS: $[(M - 2Boc + 2H)/2]^+$ = 511.

Step c.

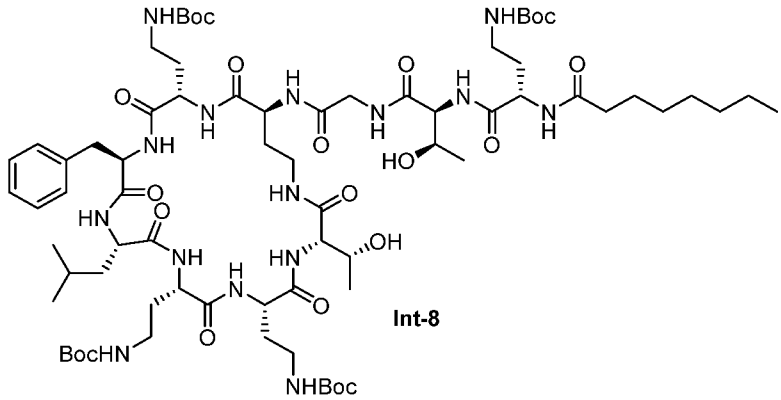


A mixture of the step b product (1.2 g, 0.984 mmol) and Z-Dab(Boc)-OH.DCHA (605 mg, 1.13 mmol) was dissolved in anhydrous NMP (3 mL). It was added with HATU (430 mg, 1.13 mmol) in portions over 5 minutes, followed by DIPEA (150 mg, 1.13 mmol). The reaction was stirred for 30 minutes and then directly purified through RPLC (100 g, 40 to 100 % MeOH and water). The collected fractions were concentrated by rotary evaporation to a white solid (Ion found by LCMS: $[M - 2Boc + 2H)/2]^+$ = 678). The material was re-dissolved in MeOH (30 mL) and treated with Pd/C. The mixture was stirred under hydrogen overnight. Pd/C was filtered, and the filtrate was concentrated by rotary evaporation and further dried under high vacuum. Yield 1.07 g, 76.6%. Ion found by LCMS: $[(M - 2Boc + 2H)/2]^+$ = 611.

Example 10 – Synthesis of Compound 5

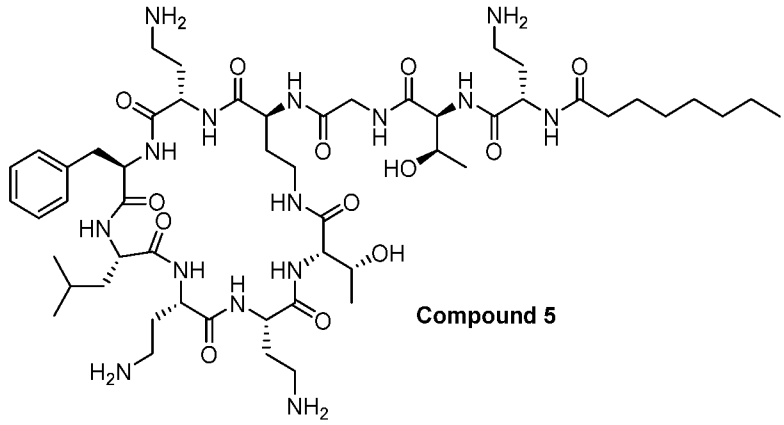


Step a. Synthesis of Int-8



A solution of Int-7, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

Step b. Synthesis of Compound 5

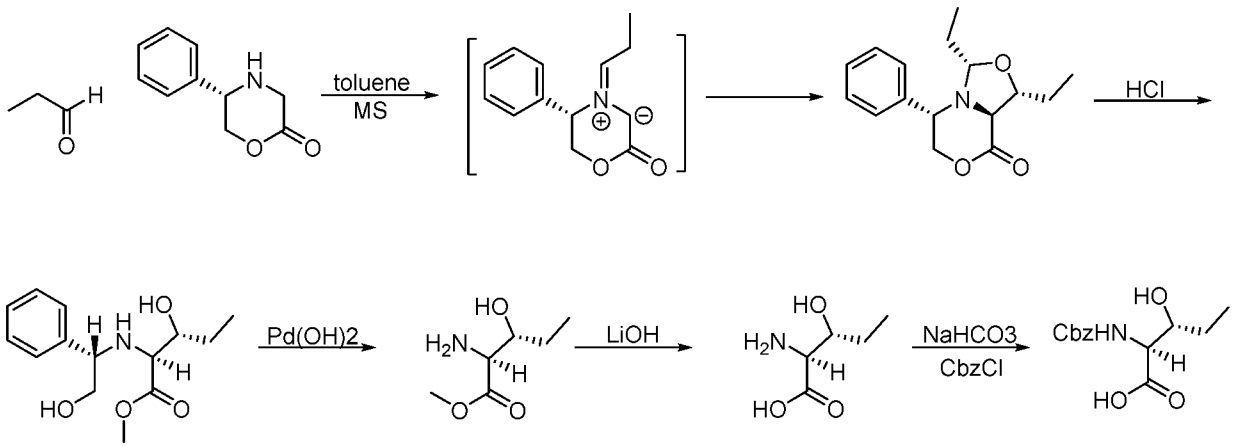


Compound 5

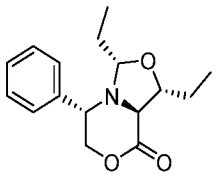
A solution of Int-8 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

Example 11 – Synthesis of Extended Threonines

The general method for the preparation of the extended threonines is described in Aiker et al., *Tetrahedron* 54 6089-6098 (1998).

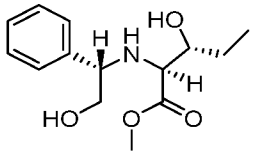


Step a.



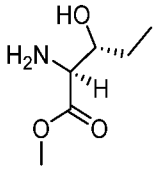
Propionaldehyde (7.4 g, 127 mmol, 3 eq.) was added to a solution of the 5-phenyl-morpholin-2-one (7.5 g, 42 mmol, 1 eq.) in 100 mL toluene along with 15 grams of activated 4Å sieves and a condenser. The reaction mixture was heated to reflux for 24 hours under nitrogen. The reaction was filtered and concentrated to give the crude product as an oil, which was used in the next step without any purification. Ion(s) found by LCMS: $(M+H)^+ = 276.2$.

Step b.



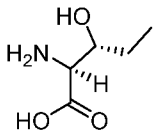
To the crude material from step a in methanol (50 mL) was added 2 M HCl (10 mL). The reaction mixture was heated to reflux under nitrogen until LCMS indicated the absence of starting material and the presence of a new compound (1-2h). The solvent was removed *in vacuo* to yield a yellow oil, which was then purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 10% to 100% acetonitrile and water, using 0.1% TFA as the modifier. Yield of the product as yellow oil: 5.6 g, 42% yield in two steps. Ion(s) found by LCMS: (M+H)+ = 267.2.

Step c.



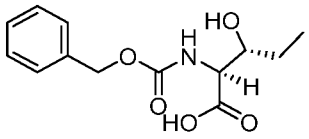
The compound from step b (1.3 g, 5 mmol) was dissolved into 30 mL methanol, Pearlman's catalyst (1.3 g) and ammonium formate (3.1 g, 10 eq.) were added to the reaction vessel and the solution degassed and heated to reflux for 4 hours. The solution was cooled and filtered to remove the catalyst. Solvent was removed *in vacuo* and the crude mixture was purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 10% to 100% acetonitrile and water, using 0.1% TFA as the modifier. Yield of product as yellow oil as TFA salt, 1.30 g, 100% yield. Ion(s) found by LCMS: $(M+H)^+$ = 147.1.

Step d.



Lithium hydroxide (120 mg, 5 mmol) in 2 mL water was added into a solution of the amino acid ester from the previous step (0.3 g, 2 mmol) in 2 mL water, 2 mL methanol and 2 mL THF. The reaction was monitored by LCMS. After completion, the solution was treated with Amberlite® IRN-77, ion exchange resin to adjust to pH 1, then filtered, concentrated, and used in next step without further purification.

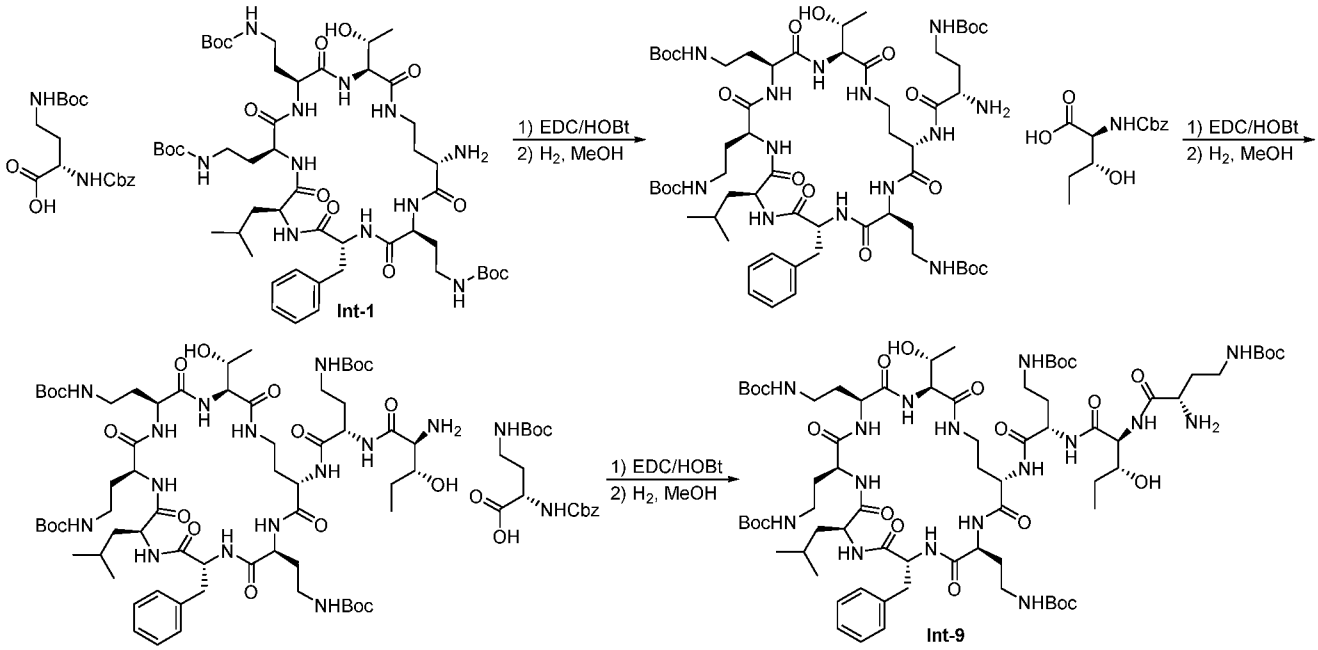
Step e.



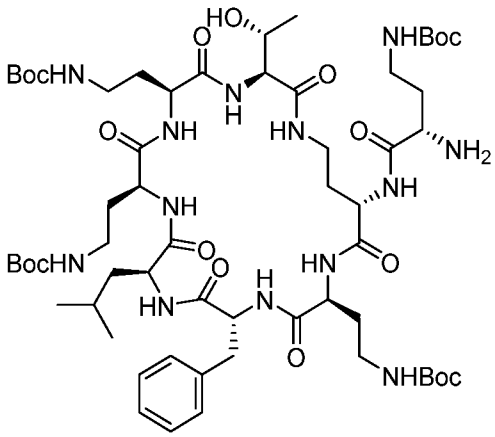
The amino acid from the previous step (0.3 g, 2 mmol) was dissolved in 5 mL methanol and 5 mL Sat. NaHCO3 solution, followed added CbzCl (510 mg, 3 mmol, 1.5 eq.), the solution was stirred for 1hour then neutralized by 1N HCl. The solution was extracted with ethyl acetate and dried over Na_2SO_4. The solution was concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 10% to 100% acetonitrile and water, using 0.1% TFA as the modifier. Yield of the product as a yellow oil, 450 mg, 92% yield. Ion(s) found by LCMS: (M+H)+ = 268.1.

Example 12 – Synthesis of Int-9

General method for the preparation of a decapeptide containing an extended L-threonine

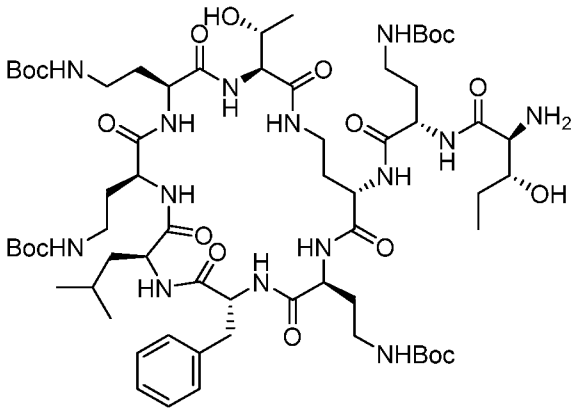


Step a.



To a solution of Int-1 (2.1 g, 2 mmol, Example 1) and (2S)-2-{[(benzyloxy) carbonyl]-amino}-4-[(tert-butoxycarbonyl)amino]butanoic acid (740 mg, 2 mmol) in DMF (30 mL) was added EDC (0.6 g, 3 mmol), HOBT (0.45 g, 3 mmol), and DIEA (0.7 mL, 5 mmol) at room temperature. The solution was stirred overnight. The resulting solution was concentrated and re-dissolved into 5 mL methanol, then added drop-wise to 200 mL vigorously stirred water, this heterogeneous solution was stirred for 1 hour, then filtered with Buchner funnel with Filter paper. The collected crude product was re-dissolved into 20 mL methanol, then 1 g of 5% Pd/C was added to the above solution, and the mixture was stirred at room temperature under a hydrogen atmosphere overnight. Palladium was removed by filtration after the reaction was complete as determined by LCMS. The filtrate was concentrated and used next step without further purification. Ion(s) found by LCMS: [M/2]+H+= 631.9, [M/3]+H+ = 421.6.

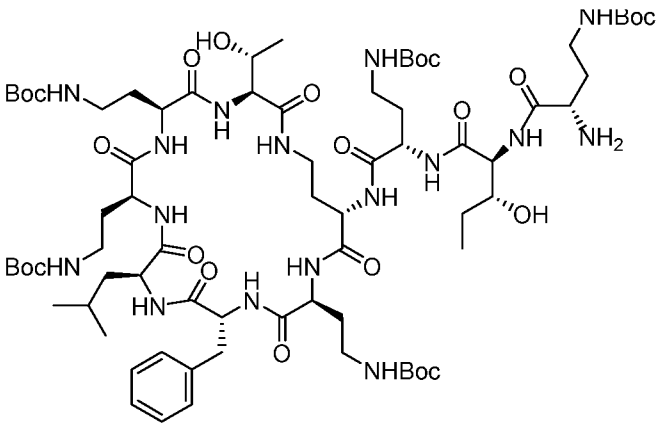
Step b.



To a solution of product from the previous step and (3R)-N-[(benzyloxy)carbonyl]-3-hydroxy-L-norvaline (540 mg, 2 mmol) in DMF (20 mL) was added EDC (0.6 g, 3 mmol), HOBT (0.45 g, 3 mmol), DIEA (0.56 mL, 4 mmol) at room temperature. The solution was stirred overnight. The resulting solution was concentrated and re-dissolved into 5 mL methanol and added dropwise into 100 mL vigorously stirred water, this heterogeneous solution was stirred for 1 hour, then filtered with Buchner funnel with filter paper. The collected crude product was re-dissolved in 20 mL methanol, then treated with 1 g of 5% Pd/C. The mixture was stirred at room temperature under a hydrogen atmosphere overnight. The

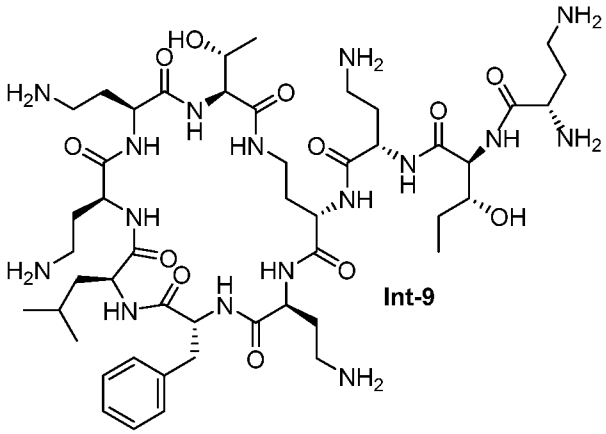
palladium charcoal was removed by filtration. The filtrate was concentrated and used next step without further purification. Ion(s) found by LCMS: [M/2]+H+= 689.4, [M/3]+H+ = 459.9.

Step c.



To a solution of PMB nonapeptide-NH2 from the previous step g and (2S)-2-{[(benzyloxy) carbonyl]-amino}-4-[(tert-butoxycarbonyl)amino]butanoic acid (720 mg, 2 mmol) in DMF (20 mL) was added EDC (0.6 g, 3 mmol), HOBT (0.45 g, 3 mmol), DIEA (0.56 mL, 4 mmol) at room temperature. The solution was stirred overnight. The resulting solution was concentrated and re-dissolved into 5 mL methanol, then added drop-wise into 100 mL vigorously stirred water. This heterogeneous solution was stirred for 1hour, then filtered with Buchner funnel with filter paper. The collected crude product was dissolved in 20 mL methanol, then treated with1 g of 5% Pd/C. The mixture was stirred at room temperature under a hydrogen atmosphere overnight. The palladium charcoal was removed by filtration. The filtrate was concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 10% to 100% acetonitrile and water, using 0.1% TFA as the modifier. Yield of product as a TFA salt: 2.3 g, 73% yield. Ion(s) found by LCMS: [M/2]+H+= 789.5, [M/3]+H+ = 526,7, [M/4]+H+ = 395.3.

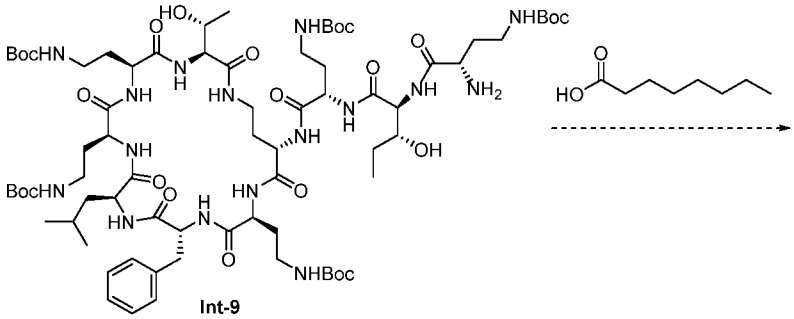
Step d.

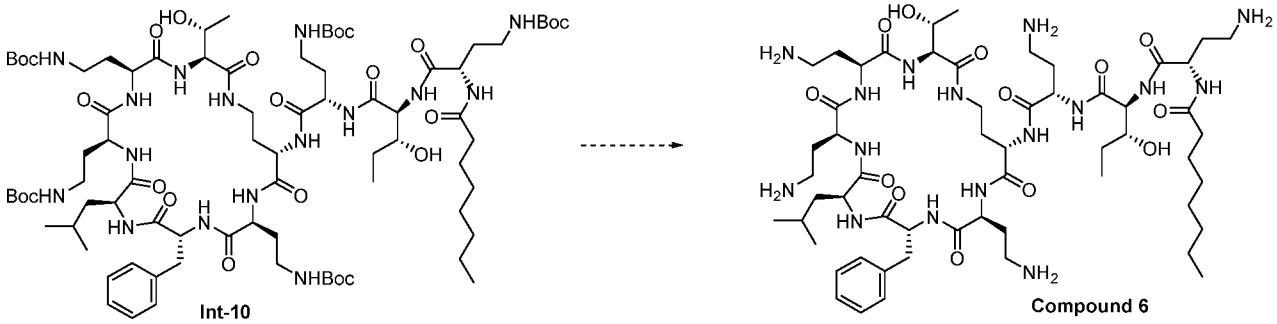


Int-9

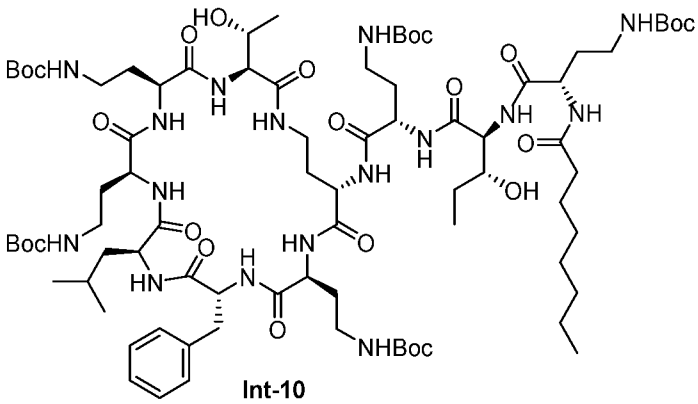
The product from step c is treated with TFA at room temperature. After complete conversion, the TFA is removed and the crude product is purified by RPLC.

Example 13 – Synthesis of Compound 6



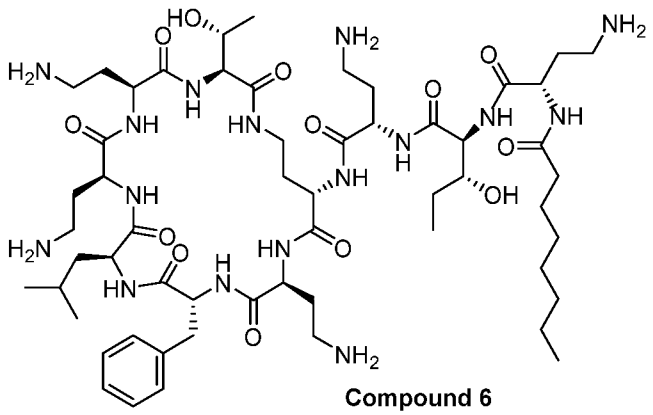


Step a. Synthesis of Int-10



A solution of Int-7, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

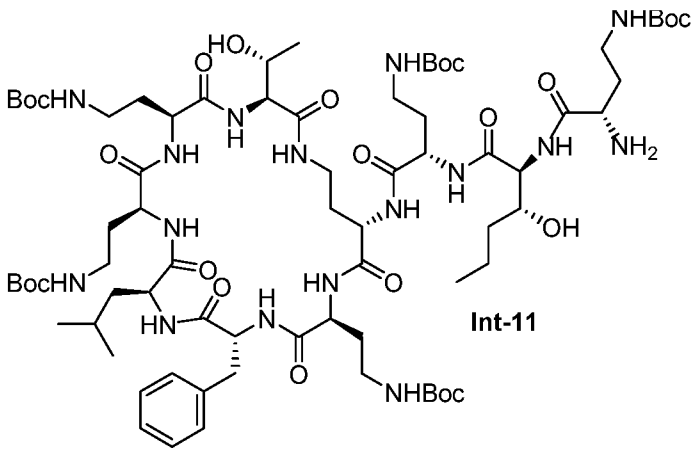
Step b. Synthesis of Compound 6



Compound 6

A solution of Int-8 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

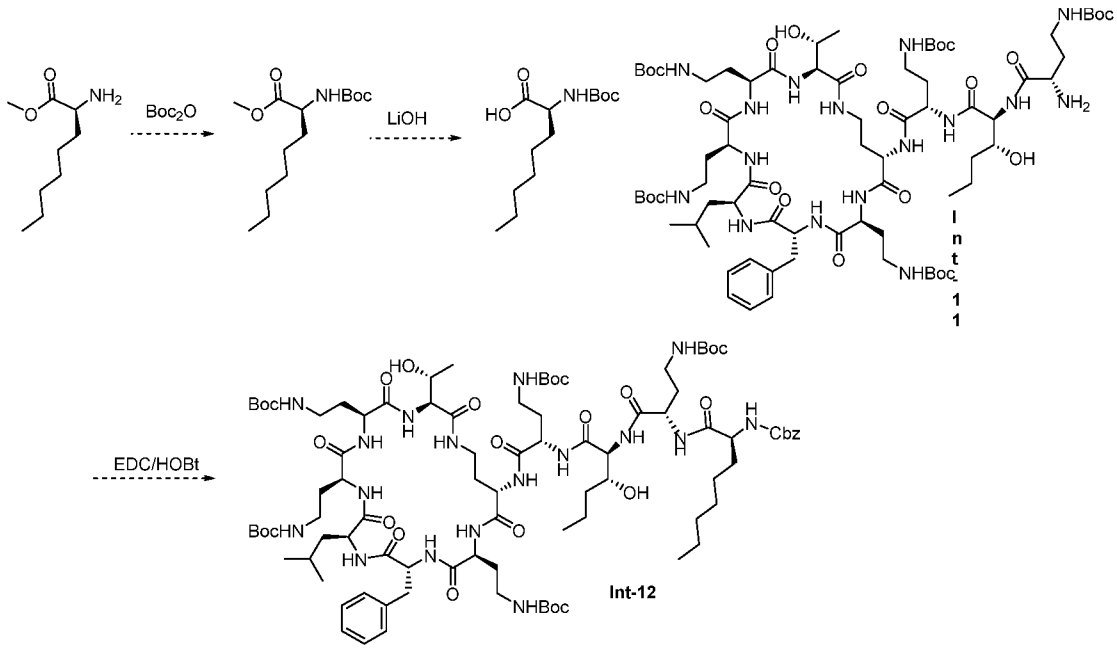
Example 14 – Synthesis of Int-11



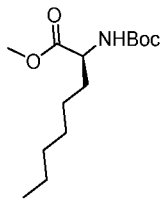
Int-11

The title compound is prepared analogously to Example 11 and Example 12, where propionaldehyde is substituted with butyraldehyde in step a of Example 11.

Example 15 – Synthesis of Int-12

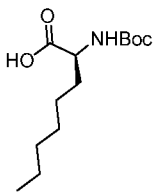


Step a.



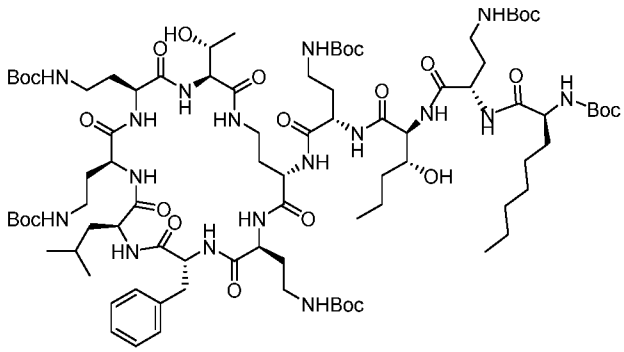
To a solution methyl L-norleucinate in DCM, TEA is added. The Boc_2O is added in one portion and the mixture is stirred until complete conversion. The reaction is concentrated and purified.

Step b.



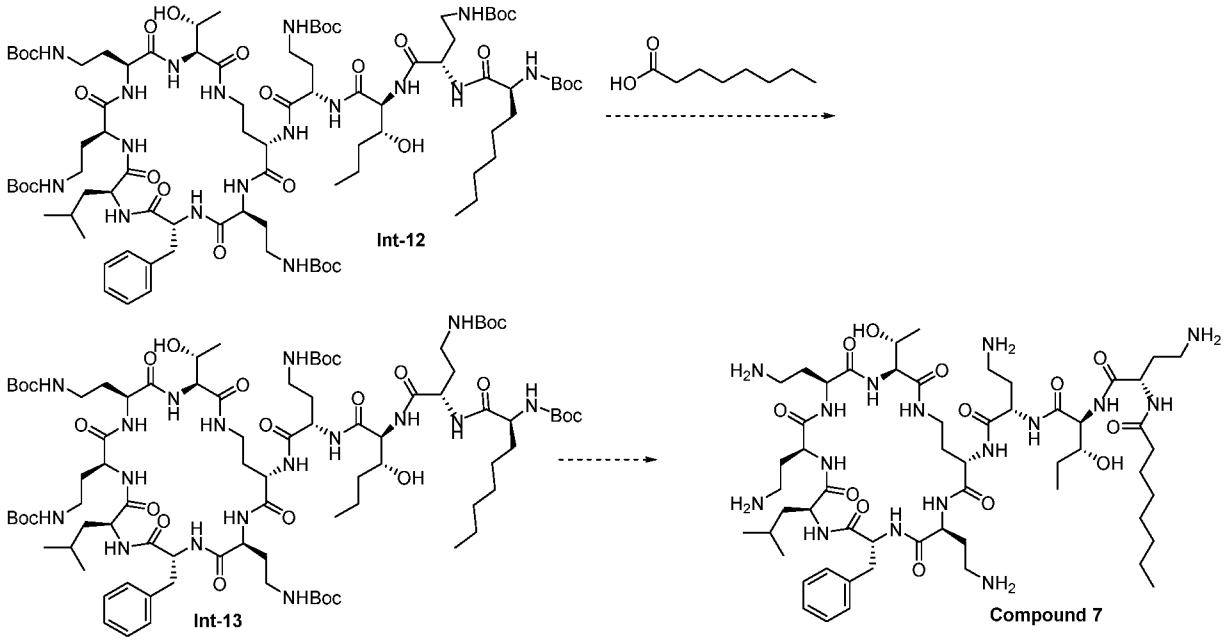
Lithium hydroxide in water is added into a solution of the amino acid ester from the previous step in methanol and THF. The reaction is monitored by LCMS. After completion, the solution is adjusted to pH 1 with Amberlite® IRN-77, and the resulting solution is filtered and concentrated.

Step c.

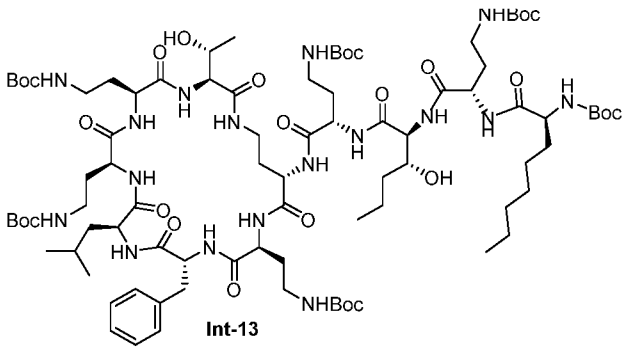


To the compound from step d and penta-Boc-polymyxin B decapeptide in DMF (5 mL) is added EDC, HOBT, and DIEA at room temperature. The solution is stirred overnight. The resulting solution is concentrated and re-dissolved into methanol. The resulting solution is added dropwise into vigorously stirred water. This heterogeneous solution is stirred for 1 hour, and then filtered with Buchner funnel with Filter paper. The crude product can be used in the next step without purification.

Example 16 – Synthesis of Compound 7



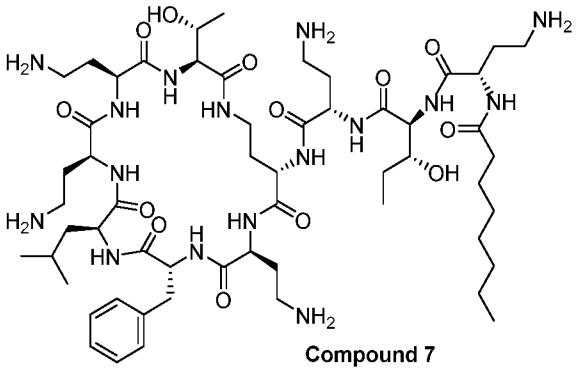
Step a.



Int-13

A solution of Int-12, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

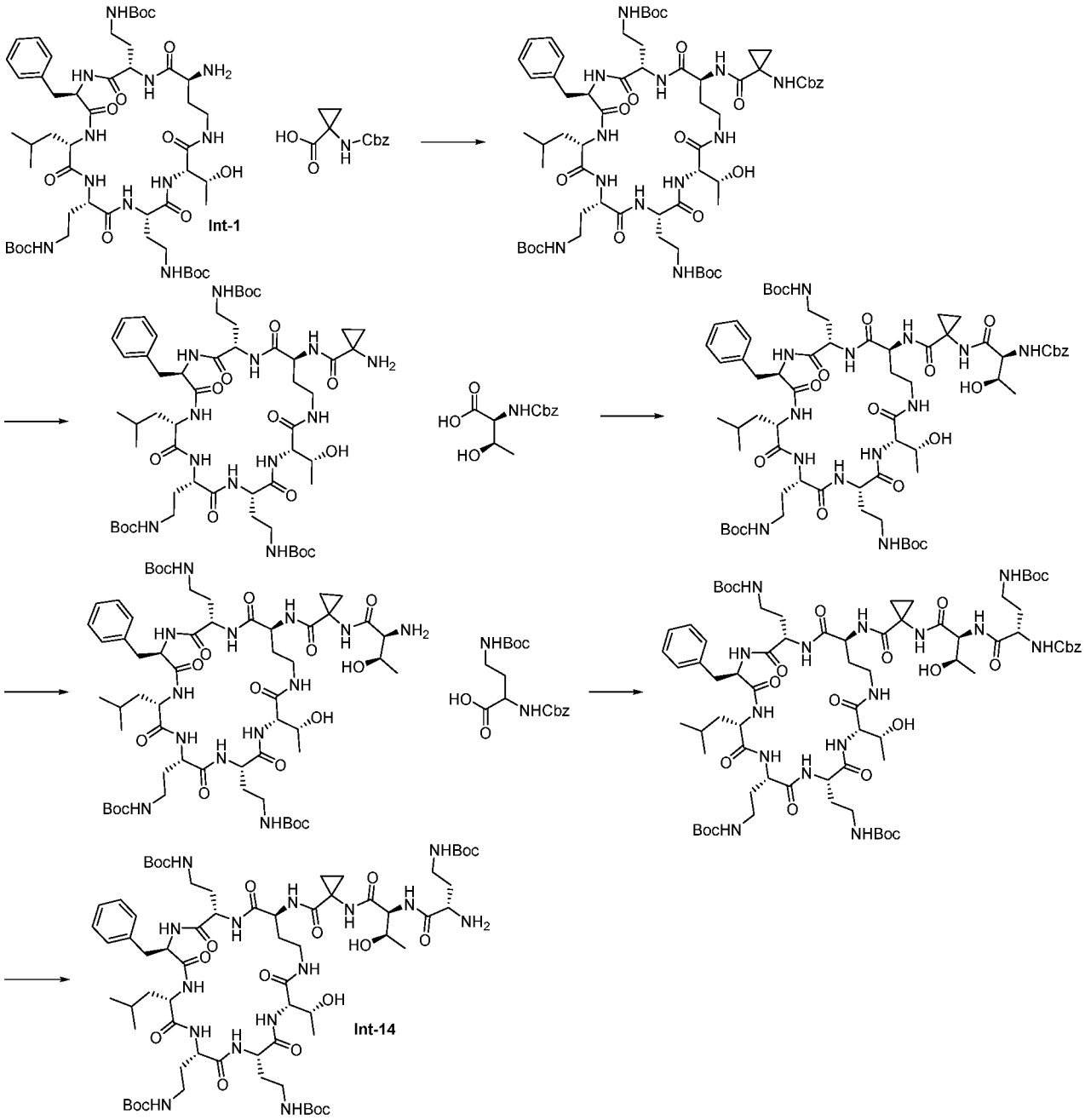
Step b. Synthesis of Compound 7



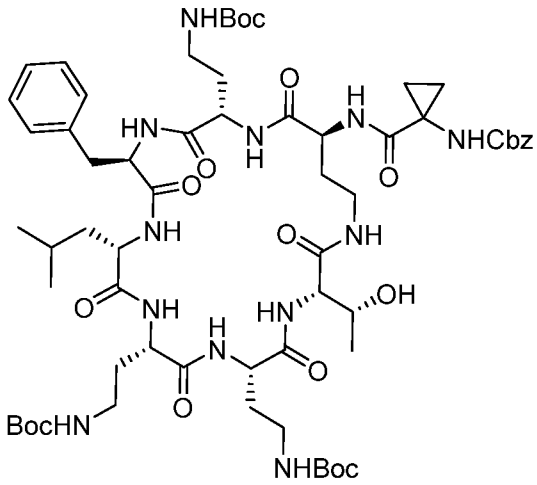
Compound 7

A solution of Int-13 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

Example 17 – Synthesis of Int-14

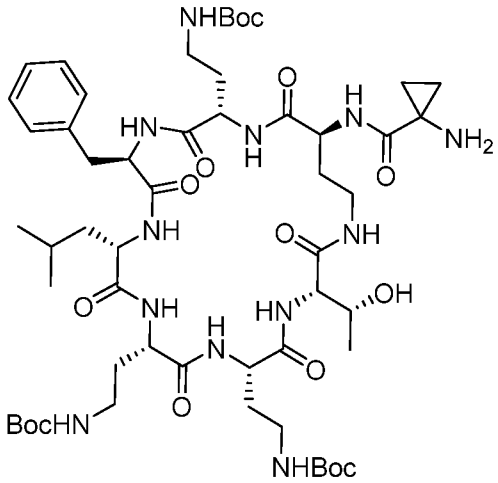


Step a.



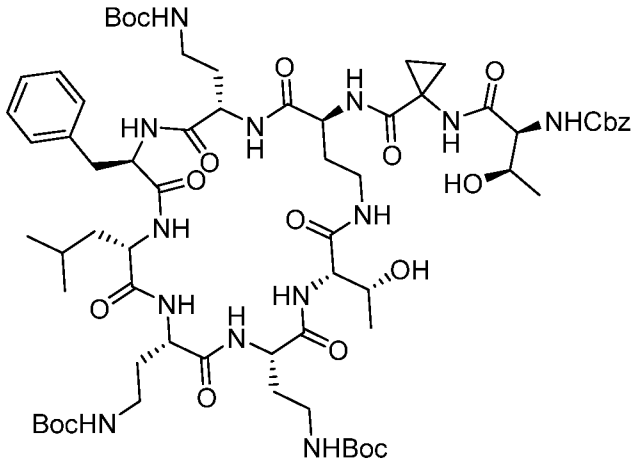
A flask was charged with tri-Boc-PMBH-(NH_2) (2.00 g, 1.883 mmol, Example 1, Int-1), 1-Cbz-aminocyclopropane carboxylic acid (0.542 g, 2.259 mmol) and DIEA (0.98 mL, 5.65 mmol) in DMF (19 mL). To this solution was added a solution of HATU (0.877 g, 2.259 mmol) in DMF (3.5 mL) via a syringe pump at rate of 2.5 mL/hr. The reaction was stirred overnight at ambient temperature. The reaction mixture concentrated to half of its volume using the rotary evaporator then purified by RPLC using an Isco CombiFlash eluting with 5% to 25% to 90% methanol and water, using 0.1% TFA as modifier. Yield 2.159 g, 90%. Ion(s) found by LCMS [(M-2Boc+2H)/2]+ = 540.5.

Step b.



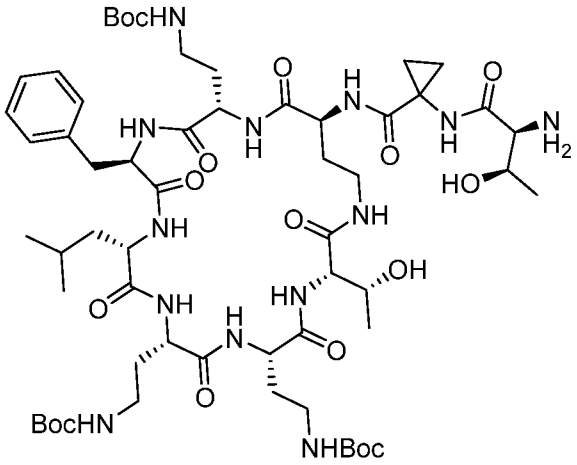
A solution of the product from the previous step (2.08 g, 1.62 mmol) in methanol (15 mL) was charged with Pd/SiO_2 (0.405 g, 0.081 mmol) and hydrogen gas balloon. The reaction mixture was stirred at ambient temperature overnight. It was filtered through a pad of Celite® and washed with methanol, then concentrated to the title compound as white solid. Yield 1.94 g, 104%. Ion(s) was found by LCMS: : [(M-2Boc+2H)/2]+ = 473.4, [(M-3Boc+2H)/2]+ = 423.3

Step c.



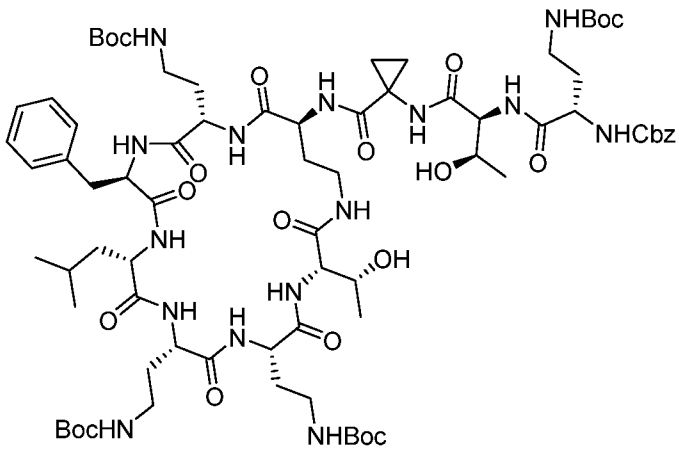
A flask was charged with product from the previous step (0.979 g, 0.855 mmol), N-Cbz-L-threonine (0.227 g, 0.898 mmol), HOAt (0.175 g, 1.282 mmol) and EDC (0.246 g, 1.28 mmol) in DMF (2.6 mL) then stirred for 10 minutes following by addition of DIEA (0.45 mL, 2.56 mmol). The reaction mixture was stirred at ambient temperature overnight. It was purified by RPLC using an Isco CombiFlash eluting with 5% to 25% then 100% acetonitrile and water, using 0.1%TFA as modifier. Yield 0.84 g, 71%. Ion(s) found by LCMS: [(M-2Boc+2H)/2]+ = 590.8

Step d.



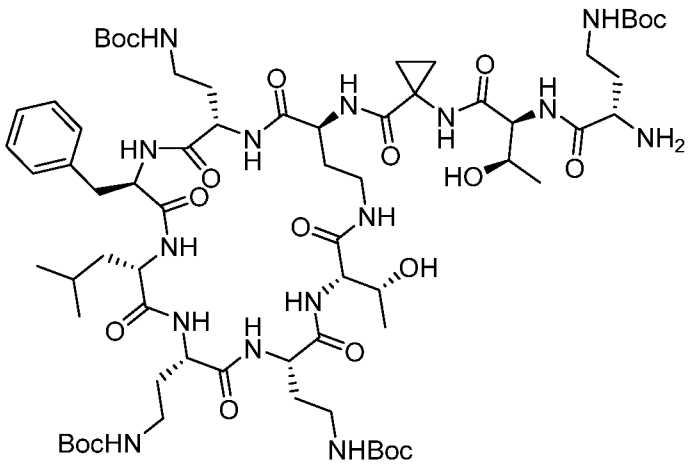
The title compound was prepared from the product of the previous step using the procedure described in Step b of this example. Yield 0.725 g, 96%. Ion(s) found by LCMS: [M-2Boc+2H)/2]+ = 523.6

Step e.



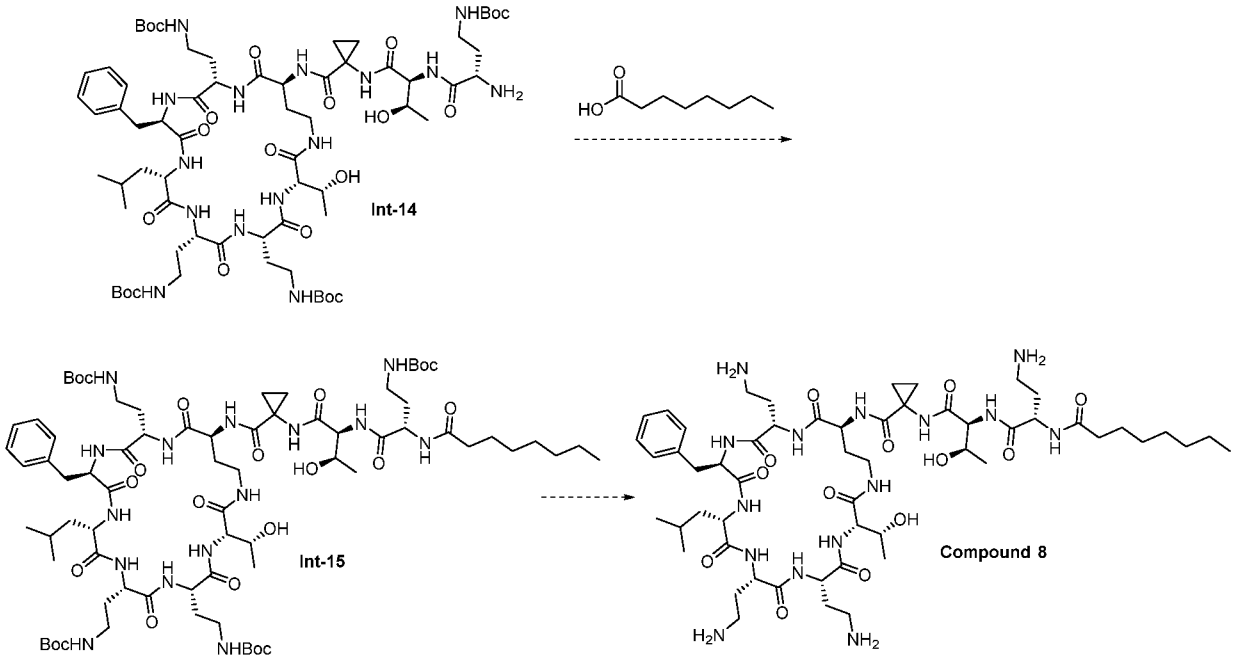
The title compound was prepared from the product of the previous (0.725 g, 0.581 mmol) and Z-dab(□Boc)-OH DCHA salt (0.341 g, 0.639 mmol) as described in procedure from step c. Yield 0.626 g, 68%. Ion(s) found by LCMS: [(M-2Boc+2H)/2]+ = 690.4

Step f.

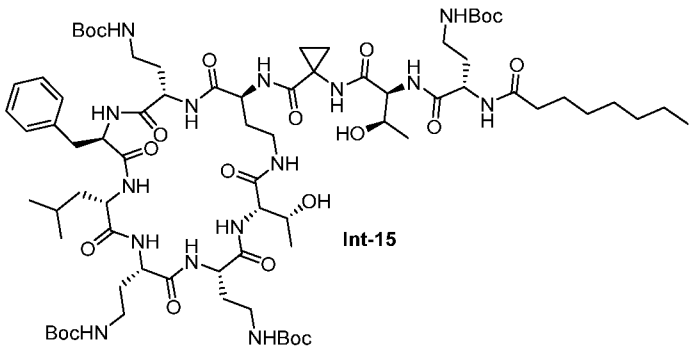


The title compound was prepared from the product of the previous step (0.626 g, 0.396 mmol) and Pd/SiO_2 (0.099 g, 0.02 mmol) as described in Step b of this example. Yield 0.575 g. 100%. Ion(s) found by LCMS: (M+Na)+ = 646.0.

Example 18 – Synthesis of Compound 8

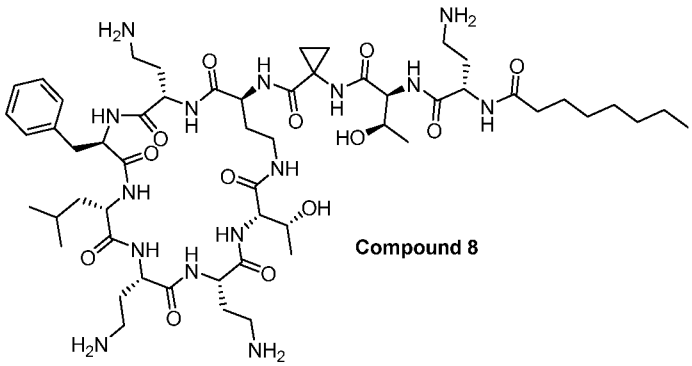


Step a.



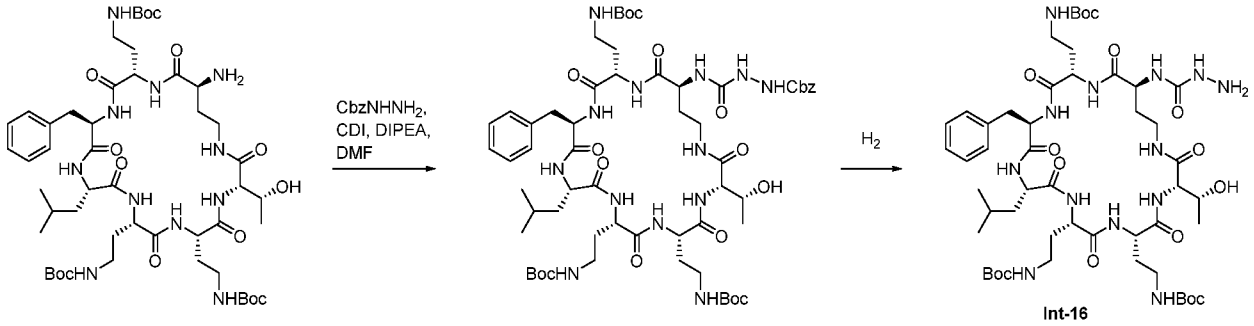
A solution of Int-14, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

Step b. Synthesis of Compound 8

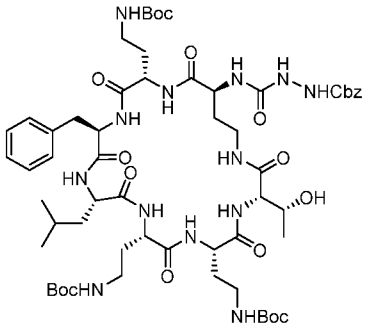


A solution of Int-15 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

Example 19 – Synthesis of Int-16

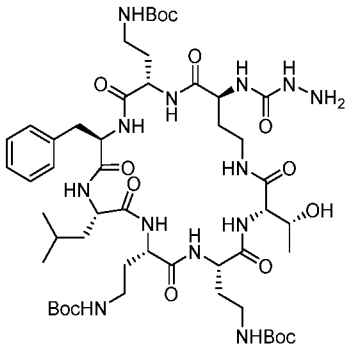


Step a.



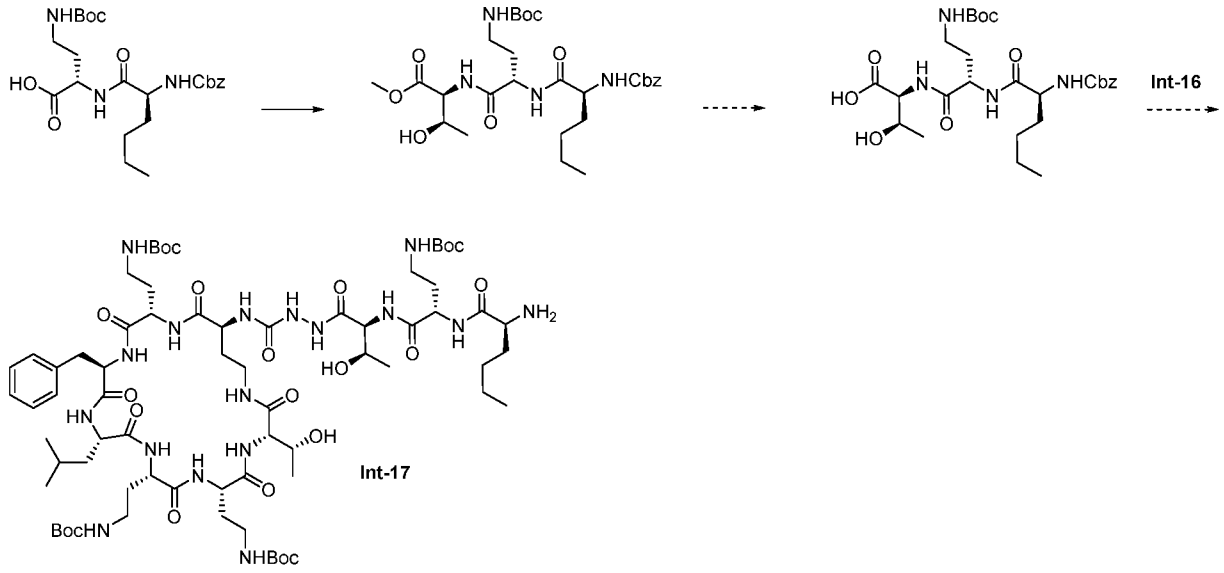
A solution of 1,1'-carbonyldiimidazole (972.6 mg, 6 mmol) in anhydrous DMF (6 ml) was cooled in an ice-water bath and treated with benzyl carbazate (1.097 g, 6.6 mmol). After stirring to dissolve all the solids, the resulting mixture was treated with DIPEA (390 mg, 3 mmol). The ice-water bath was removed, and the reaction mixture was stirred for 1 hour. PMBH (2.126 g, 2 mmol, Int-1) was slowly added, and the reaction was continued overnight. The reaction mixture was then precipitated into water (100 ml) containing 4N HCl in dioxane (6 ml). The precipitated product was collected by vacuum filtration and washed with water. It was then re-dissolved in MeOH and concentrated to a white solid. The material was dissolved in DMF (2 ml) and purified by RPLC (150 g, 65 to 80 % MeOH and water, using 0.1 % TFA as modifier). Yield 1.32 g, 52.6 %. Ions found by LCMS: $[(M - 2Boc + 2H)/2]^+$ = 527.8, $[(M - 2Boc - tBu + 2H)/2]^+$ = 499.8, $[(M - 3Boc + 2H)/2]^+$ = 477.8.

Step b.

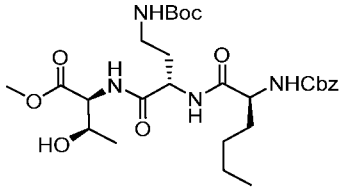


Acetyl chloride (108.9 mg, 1.39 mmol) was added drop-wise in MeOH/water (30 ml/1 ml). The solution was added to the step a product (1.16 g, 0.925 mmol). The reaction atmosphere was flushed with nitrogen, then Pd/C (dry basis, 270 mg) was added and the resulting mixture was stirred under hydrogen for 2 hours. Pd/C was filtered, and the filtrate was concentrated by rotary evaporation and purified by RPLC (150g, 30 to 65 % acetonitrile and water). Yield 1.02 g, 98.4 %. Ions found by LCMS: $[(M - 2Boc + 2H)/2]^+$ = 460.8, $[(M - 2Boc - tBu + 2H)/2]^+$ = 432.6, $[(M - 3Boc + 2H)/2]^+$ = 410.8.

Example 20 – Synthesis of Int-17

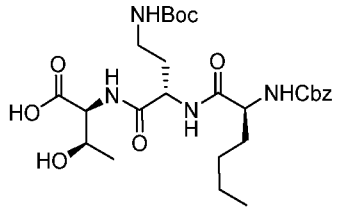


Step a.



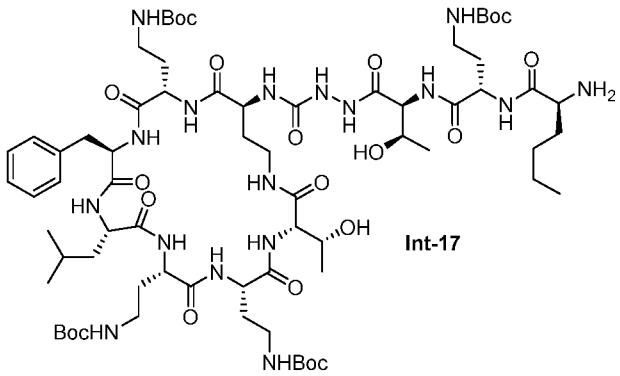
To a solution of a mixture of Z-Nleu-Dab-OH (371 mg, 0.792 mmol) and L-threonine methyl ester HCl (169.6 mg, 1 mmol) in anhydrous DMF (2 ml) was added HATU (304 mg, 0.8 mmol). After stirring to dissolve HATU, the reaction mixture was treated with DIPEA (390 mg, 3 mmol) and stirred for 30 more minutes. It was then directly purified by RPLC (100 g column, 20 to 75 % acetonitrile and water, using 0.1 % TFA as modifier). Yield 451 mg, 98.1 %. Ions found by LCMS: $[M + H]^+$ = 581.2, $[M - Boc + H]^+$ = 481.2.

Step b.



The step a product is dissolved in MeOH and cooled in ice-water bath and treated with a solution of LiOH monohydrate in water in portions over 30 minutes. After stirring for 1 hour, the reaction mixture is acidified with 4N HCl solution and purified by RPLC (5 to 70 % acetonitrile and water).

Step c.

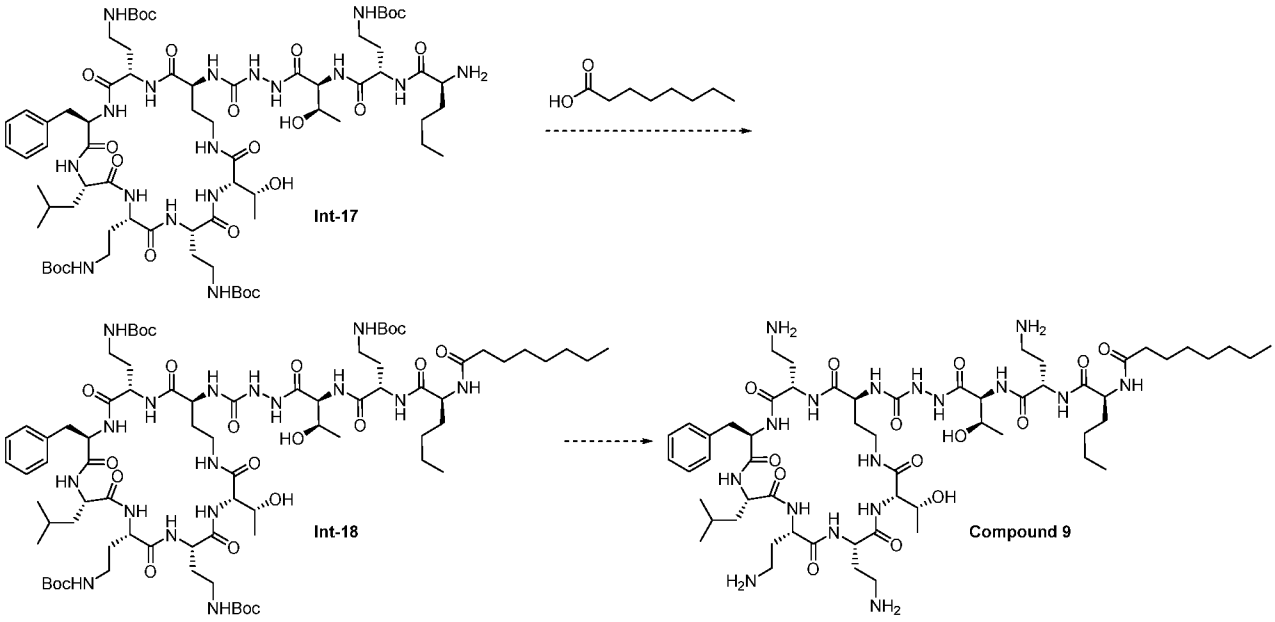


Int-17

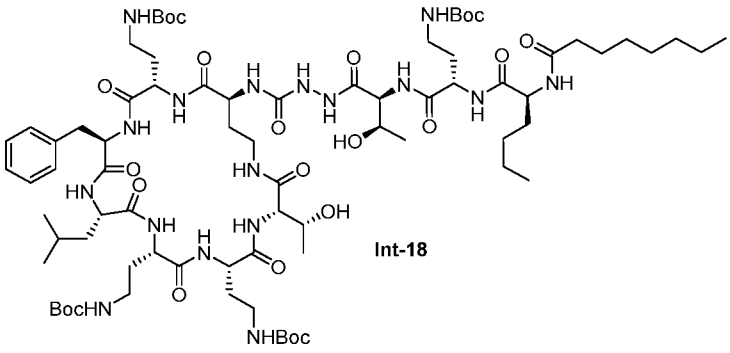
A mixture of Int-16 and the product form the previous step is dissolved in anhydrous DMF and DIPEA. After stirring for 10 minutes, the reaction mixture is treated with PMBH-AzaGly-NH2 and continued stirring for 1 hour. It is then directly purified by RPLC (30 to 90 % MeOH and water, using 0.1 % TFA as modifier).

The Cbz-intermediate is dissolved in MeOH and stirred with 5% Pd/C under hydrogen atmosphere. After complete conversion, the reaction mixture is filtered through celite, concentrated, and purified.

Example 21 – Synthesis of Compound 9

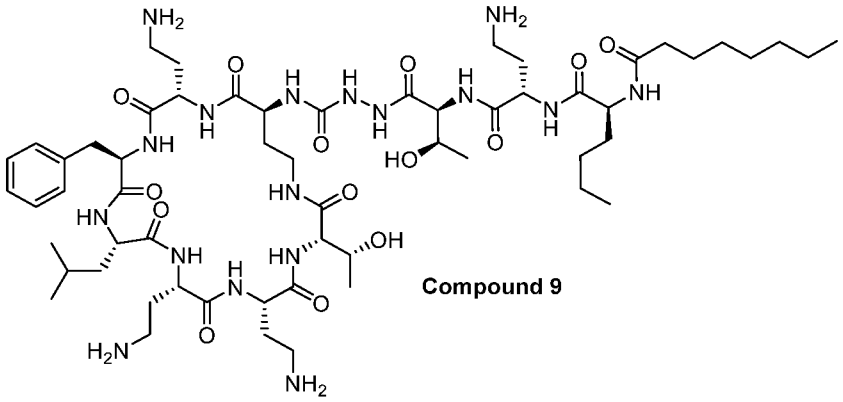


Step a.



A solution of Int-17, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

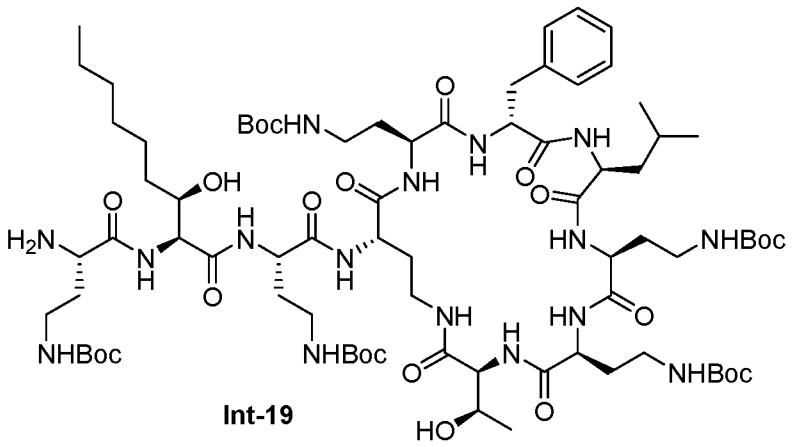
Step b. Synthesis of Compound 9



Compound 9

A solution of Int-18 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

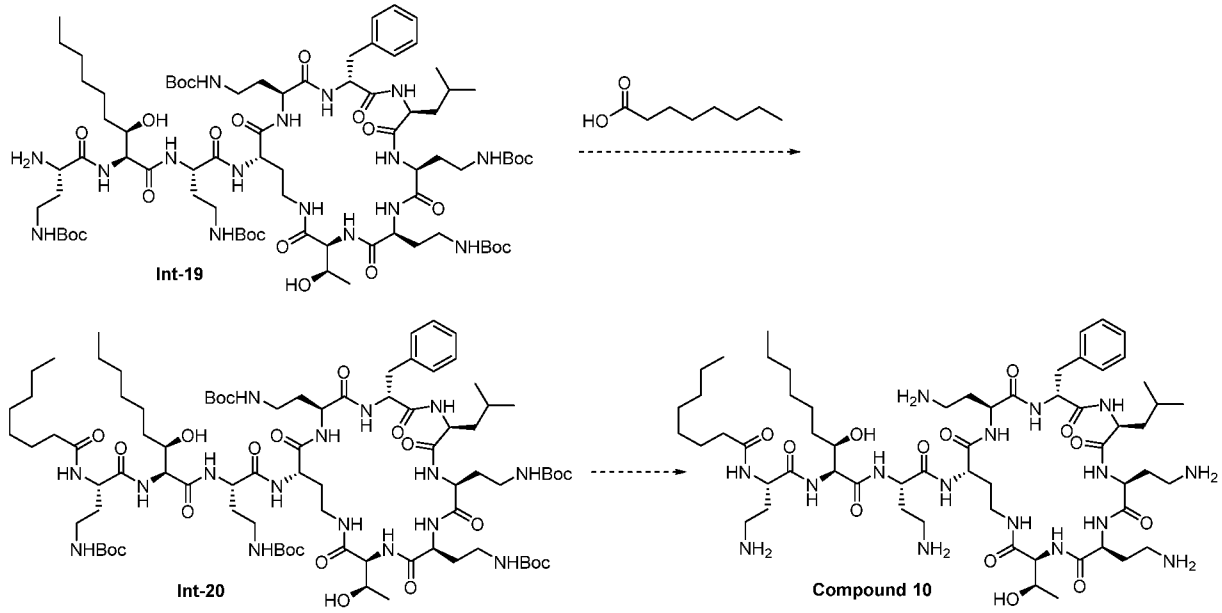
Example 22 – Synthesis of Int-19



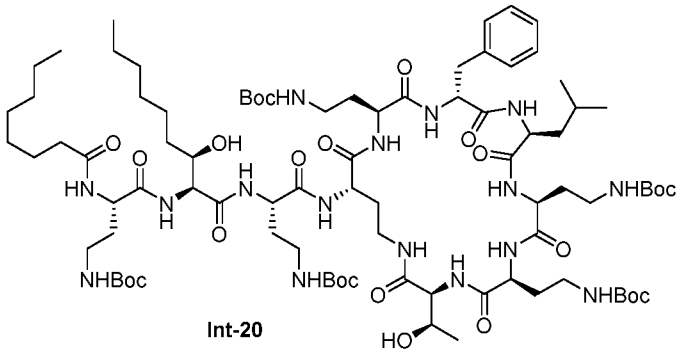
Int-19

The title compound is prepared analogously to Example 11 and Example 12, where propionaldehyde is substituted with heptanal in step a of Example 11.

Example 23 – Synthesis of Compound 10

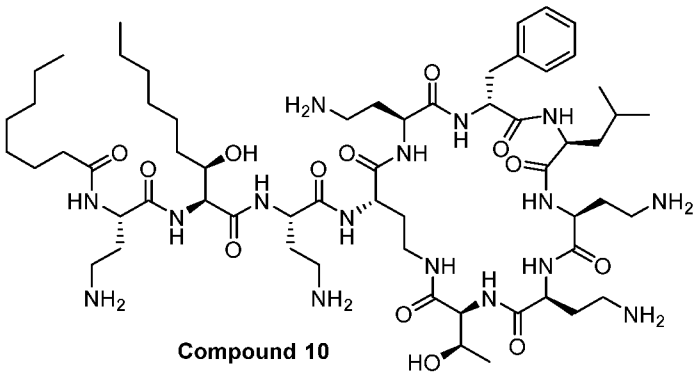


Step a.



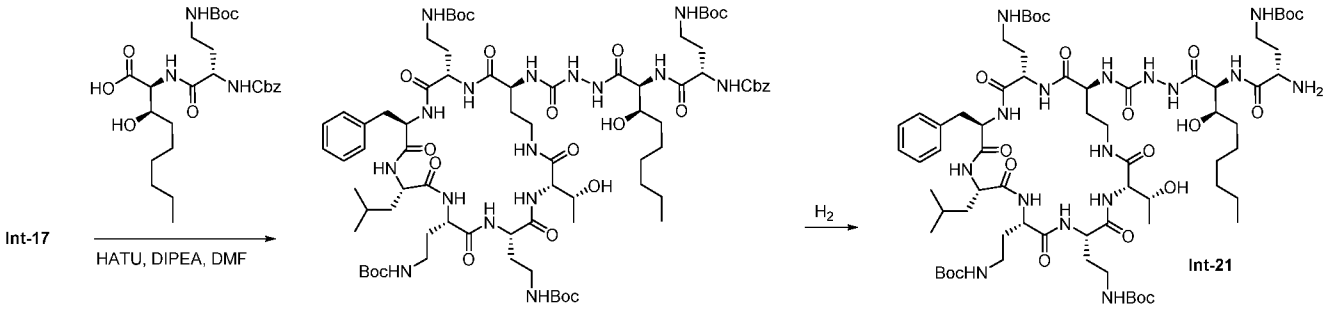
A solution of Int-19, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

Step b. Synthesis of Compound 10

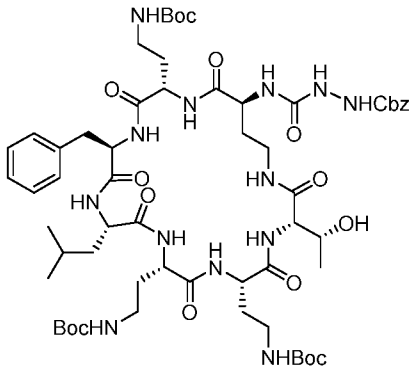


A solution of Int-20 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

Example 24 – Synthesis of Int-21

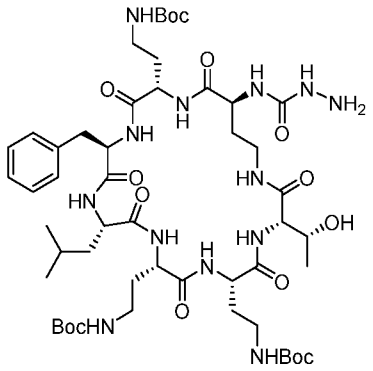


Step a.



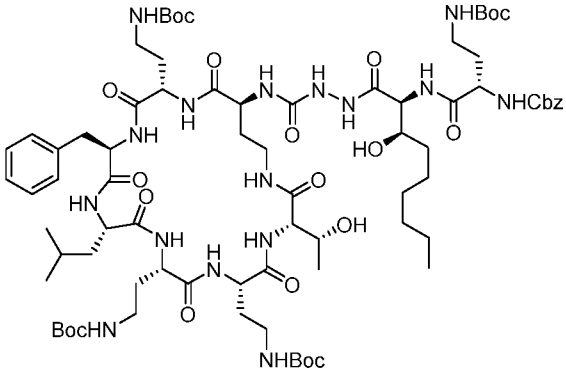
A solution of 1,1'-carbonyldiimidazole (972.6 mg, 6 mmol) in anhydrous DMF (6 ml) was cooled in an ice-water bath and treated with benzyl carbazate (1.097 g, 6.6 mmol). After stirring to dissolve all the solids, the resulting mixture was treated with DIPEA (390 mg, 3 mmol). The ice-water bath was removed, and the reaction mixture was stirred for 1 hour. PMBH (2.126 g, 2 mmol, described in Example 1) was slowly added, and the reaction was continued overnight. The reaction mixture was then precipitated into water (100 ml) containing 4N HCl in dioxane (6 ml). The precipitated product was collected by vacuum filtration and washed with water. It was then re-dissolved in MeOH and concentrated to a white solid. The material was dissolved in DMF (2 ml) and purified by RPLC (150 g, 65 to 80 % MeOH and water, using 0.1 % TFA as modifier). Yield 1.32 g, 52.6 %. Ions found by LCMS: $[(M - 2Boc + 2H)/2]^+$ = 527.8, $[(M - 2Boc - tBu + 2H)/2]^+$ = 499.8, $[(M - 3Boc + 2H)/2]^+$ = 477.8.

Step b.



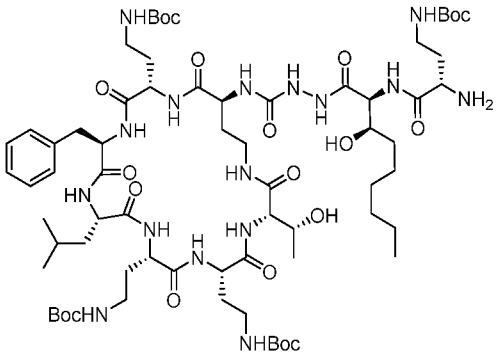
Acetyl chloride (108.9 mg, 1.39 mmol) was added drop-wise in MeOH/water (30 ml/1 ml). The solution was added to the step a product (1.16 g, 0.925 mmol). The reaction atmosphere was flushed with nitrogen, then Pd/C (dry basis, 270 mg) was added and the resulting mixture was stirred under hydrogen for 2 hours. Pd/C was filtered, and the filtrate was concentrated by rotary evaporation and purified by RPLC (150g, 30 to 65 % acetonitrile and water). Yield 1.02 g, 98.4 %. Ions found by LCMS: $[(M - 2Boc + 2H)/2]^+ = 460.8$, $[(M - 2Boc - tBu + 2H)/2]^+ = 432.6$, $[(M - 3Boc + 2H)/2]^+ = 410.8$.

Step c.



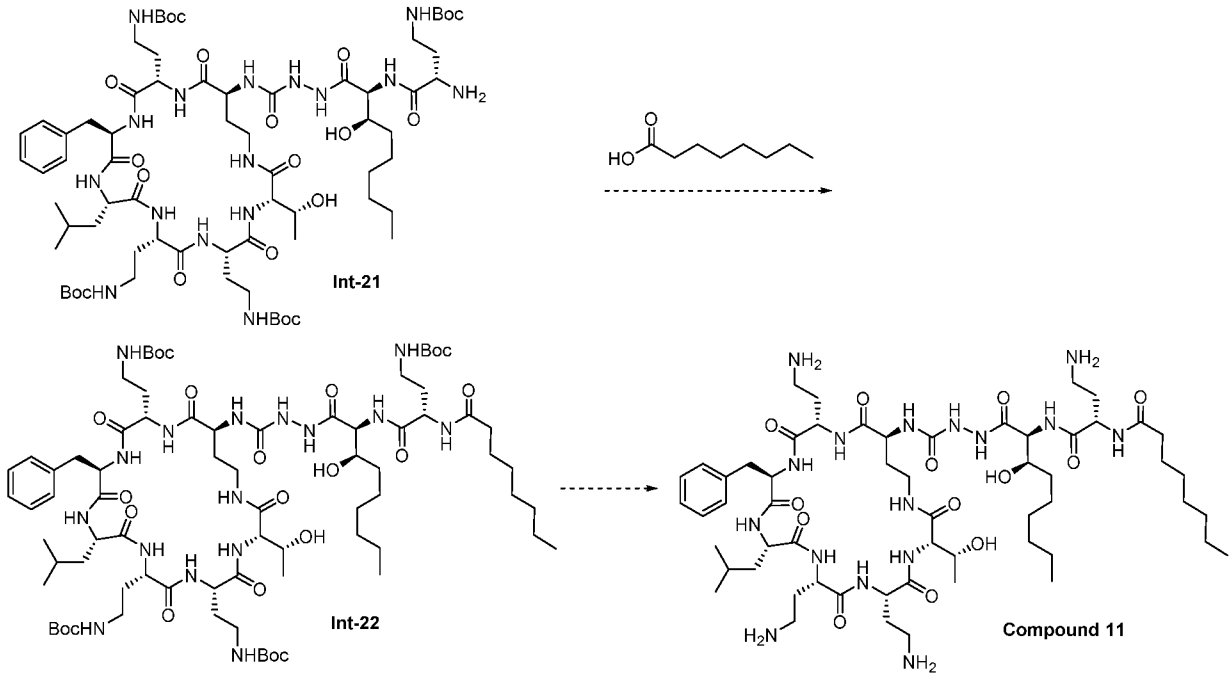
To a solution of a mixture of extended threonine-Dab-Z (366.5 mg, 0.7 mmol) and HATU (266.1 mg, 0.7 mmol) in DMF (1 ml) was added DIPEA (150 mg, 1.15 mmol). After stirred for 10 minutes, the reaction mixture was added with the step b product (560.2 mg, 0.5 mmol) and continued stirring at room temperature for 30 minutes. It was then purified by RPLC (100 g, 50 to 90 % MeOH and water). Yield 559.6 mg, 73.4 %. Ion found by LCMS: $[(M - 2Boc + 2H)/2]^+ = 713.5$.

Step d.

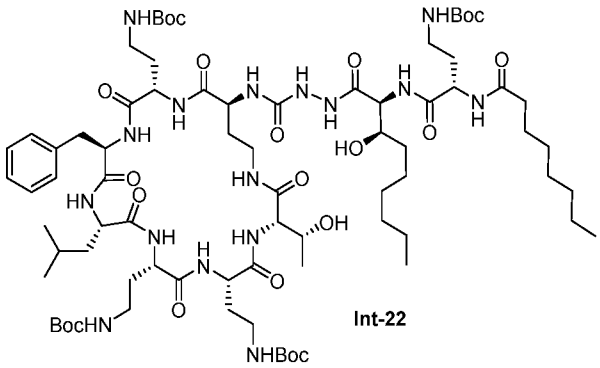


A 50 ml reaction flask was filled with nitrogen and charged with the step c product (250 mg, 0.154 mmol) and MeOH (20 ml). Pd/C (dry basis, 100 mg) was then added, and the resulting mixture was stirred under hydrogen for 4 hours. Pd/C was filtered, and the filtrate was concentrated by rotary evaporation and purified by RPLC (100 g, 40 to 85 % MeOH and water). Yield 125.2 mg, 54.5 %. Ion found by LCMS: $[(M - Boc + 2H)/2]^+ = 696.3$, $[(M - 3Boc + 2H)/2]^+ = 596.3$.

Example 25 – Synthesis of Compound 11



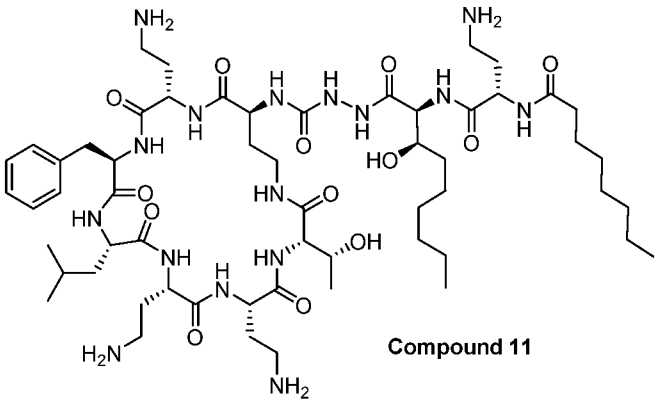
Step a.



Int-22

A solution of Int-21, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

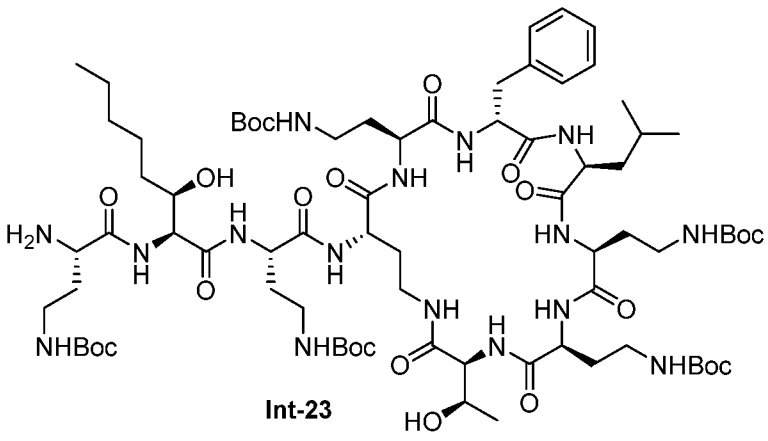
Step b. Synthesis of Compound 11



Compound 11

A solution of Int-22 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

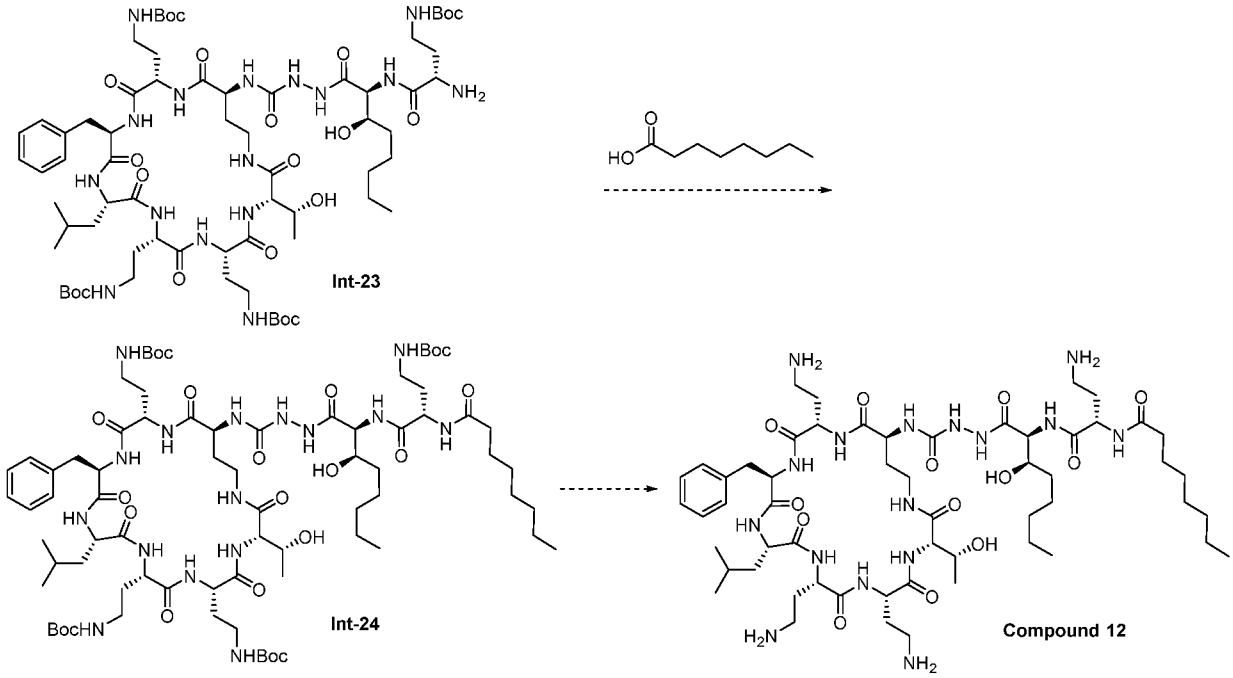
Example 26 – Synthesis of Int-23



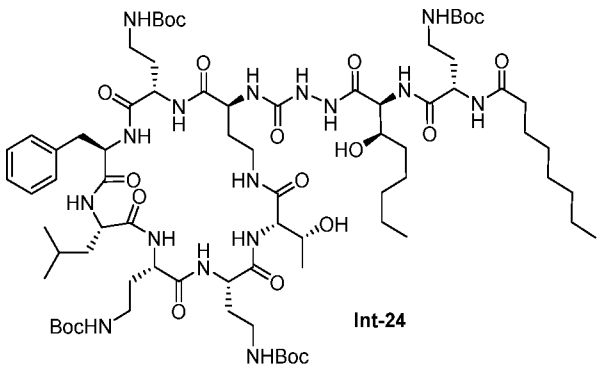
Int-23

The title compound is prepared analogously to Example 11 and Example 12, where propionaldehyde is substituted with hexanal in step a of Example 11.

Example 27 – Synthesis of Compound 12

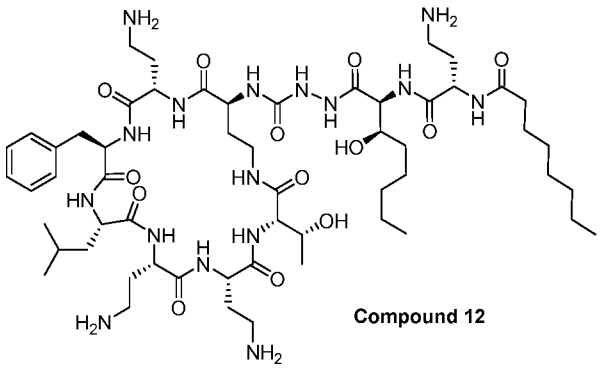


Step a.



A solution of Int-23, octanoic acid, and DIEA in DMF is treated with HATU dissolved in DMF over 60 minutes. After complete conversion, the reaction is concentrated and purified by HPLC or RPLC.

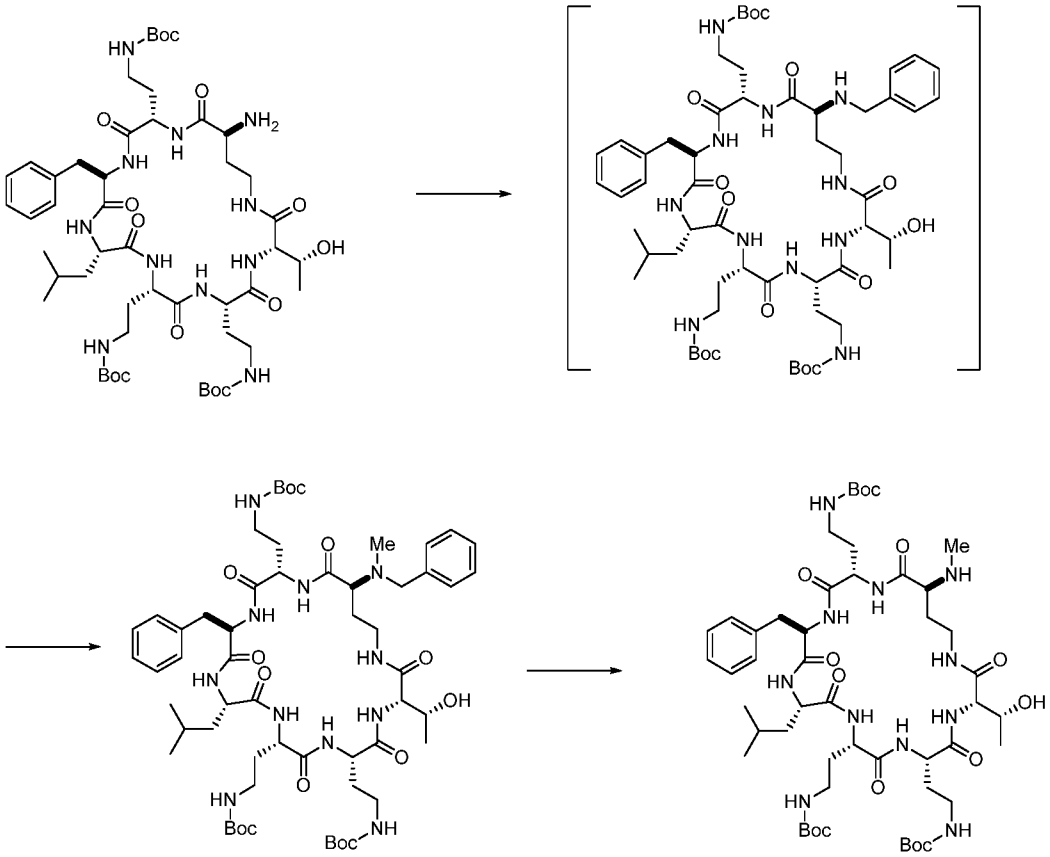
Step b. Synthesis of Compound 12



Compound 12

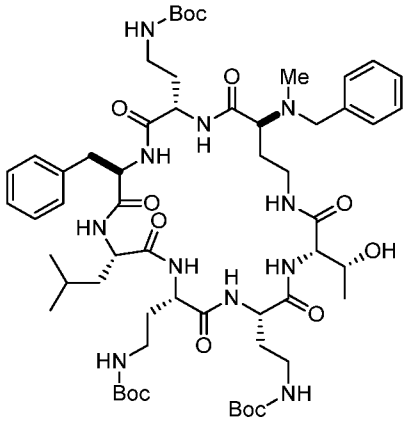
A solution of Int-24 dissolved in DCM is treated with TFA while stirring for 5 minutes at room temperature. The resulting solution is concentrated and purified by RPLC using an Isco CombiFlash liquid chromatograph eluted with 5% to 100% methanol and water, using TFA (0.1%) as the modifier.

Example 28 – Synthesis of N-Methyl-PMB-heptapeptide intermediate (Int-25)



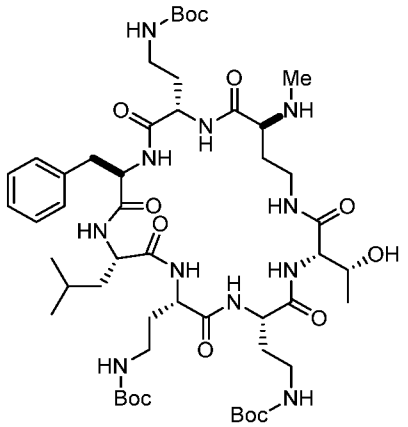
Int-25

Step a.



Dissolve PMBH (10g, 9.42 mmol, Int-1) in methanol (100 mL), add a few drops of glacial acetic acid (to pH~5-6), then add benzaldehyde (1.2 g, 11.3 mmol) and let stir for 15 minutes. Cool to 0*C, ice/water bath and add half (1.5 eq, 921 mg, 14.66 mmol) of sodium cyanoborohydride in 3 portions over 10 minutes. Remove ice bath and let stir ~12 hours (overnight). Check by LC/MS to insure complete conversion to the mono benzylated PMBH intermediate. Cool to 0 °C and add formaldehyde (7 eq, 5 mL, 67.7 mmol) followed by the additon of sodium cyanoborohydride (1 eq, 606 mg, 9.64 mmol) in 3 portions over 10 minutes, let stir at 0*C for 20 minutes and remove ice bath. Let reaction stir for 2 hours then add additional 3 eq of formaldehyde (2.1 mL, 29.0 mmol) and sodium cyanoborohydride (320 mg, 5.1 mmol) stir for 6 more hours. Dilute with saturated sodium bicarb (pH~8) and remove approx half the methanol by rotovap. Dilute with ethyl acetate and saturated sodium bicarb and extract into ethyl acetate (3x). Dry the combined organic extracts over sodium sulfate, filter and concentrate. Purify by normal phase silica gel chromatography (0-5% methanol in dcm containing 1% triethylamine, 35 minute gradient). The product elutes at ~3.3% methanol. 8.2 grams (74%) of the product was isolated as a white solid.LC/MS [M-Boc+2H+] = 533.8

Step b.



Int-25

8.2 gram of the N-methyl, benzyl PMBH(trisBoc) intermediate was dissolved in 100 mL of methanol in a 250 round bottom flask. 20% $Pd(OH)_2$ (2g) was added followed by a few drops of glacial acetic acid (to pH~6). The flask was evacuated and flushed with hydrogen gas (3x) and then the mixture was stirred under 1 atm of hydrogen gas for 12 hours. The reaction was monitored by LC/MS and HPLC to insure complete removal of the benzyl group. Upon completion the mixture was filtered through celite and the pH was adjusted to ~7 with a few drops of triethylamine. The solvent was removed by rotovap and the residue was purified by normal phase silica gel chromatography (0-7% methanol in dcm containing 1% triethylamine, 35 minute gradient). The product elutes at ~4.2% methanol. 6.65 grams (87%) of the product was isolated as a white solid.LC/MS [M-Boc+2H+] = 488.8.

Example 29 – Minimum Inhibitory Concentration (MIC) assays

MIC assays were performed according to CLSI broth microdilution guidelines (M07-A9, M100-S23) with the exception of using a 100 µL assay volume and preparing stock compounds at 25X final concentration. Briefly, stock solutions of all antibacterial agents were prepared fresh in appropriate solvents (i.e. PBS, pH 7.4, DMSO, DI, etc.). Stock concentrations for compounds were made at 25X the highest final assay concentration. All were serially diluted 2-fold, 8 or 12 times in a 96-well PCR plate (VWR cat. no. 83007-374). Bacterial cell suspensions generated from Mueller-Hinton agar (MHA) plate cultures were prepared in 0.85% saline and adjusted to ~0.1 OD_{600} nm. Next, cell suspensions were diluted 1:200 in cation adjusted Mueller-Hinton broth media (CA-MHB) to a concentration of ~5 x 10^5 CFU (colony-forming units)/mL. 96 µL of each cell suspension in CA-MHB were added to test wells in a 96-well assay plate (Costar cat. no. 3370). A Rainin model 20 µL Liquidator 96 was used to dispense 4 µL of each 25X stock compound into the plate containing 96 µL of each strain in CA-MHB. Compounds were tested against a 14-strain panel comprised of *E. coli* (Ec), *A. baumannii* (Ab), *P. aeruginosa* (Pa), and *K. pneumoniae* (Kp) that were obtained from ATCC (Ec 25922, Ec 2469, Ab 19606, Pa 27853, Pa PAO1, Kp 43816, Kp 10031), Centers for Disease Control and Prevention (Ec AR0349), BEI Resources (Ab AB5075), Micromyx LLC (Ab 8990, Kp 6951), and Belgian Coordinated Collections of Microorganisms (Pa LES431) or generated in-house (Ec 25922 64X-1). Four of the strains were colistin-resistant examples (COL^R) including: Ec 64X-1 (spontaneous mutant possessing a mutation in *pmrB* (A159V) that was selected by plating on MHA containing colistin at 64-fold the MIC concentration), Ec AR0349 (clinical isolate possessing the mobile *mcr-1* colistin resistance gene), Ab 8990 (a clinical isolate possessing unknown colistin resistance mechanisms) and Kp 6951 (clinical isolate possessing a mutation in *phoQ* (T244N)). *E. coli* strain ATCC 25922 and *P. aeruginosa* strain LES431 were run in the presence and absence of 50% heat-inactivated fetal bovine serum (FBS; Sigma, cat. no. F4135-100mL). Plates were mixed by shaking then incubated at 35°C overnight (16-20 h). MIC values were read visually at 100% growth inhibition (Table 4).

Table 4.

		MIC (μg/ml)																
Media	Compound	Ec 25922	Ec 25922 + FBS	EC 25922 64X-1 (COL^R)	Ec AR0349 (*mcr-1*, COL^R)	Ec 2469	Ab 19606 ($COLhet^R$)	Ab AB5075	Ab AB58705 (COL^R) lpxD, mut. (no LPS)	Ab 8990 (COL^R)	Pa 27853	Pa PAO1	Pa LES431	Pa LES431 +FBS	Kp 10031	Kp 43816	Kp 6951 (COL^R)	Sa RN4220
CA-MHB	6	0.5	≤0.06	ND	ND	0.25	1	1	ND	ND	1	1	ND	ND	0.5	0.5	ND	128
CA-MHB	10	2	0.5	4	2	2	4	2	ND	4	2	2	2	ND	2	2	16	8
CA-MHB	13	0.5	≤0.06	4	1	0.25	1	1	ND	16	1	2	0.5	ND	1	0.5	>32	64
CA-MHB	14	0.5	0.5	ND	ND	0.25	4	1	ND	ND	1	0.5	ND	ND	0.5	0.25	ND	>128
CA-MHB	15	32	0.25	ND	ND	0.5	1	1	ND	ND	1	1	ND	ND	0.25	0.5	ND	>128
CA-MHB	16	1	2	ND	ND	1	1	1	ND	ND	1	1	ND	ND	1	1	ND	64
CA-MHB	17	1	0.25	ND	ND	1	1	1	ND	ND	1	1	ND	ND	1	1	ND	32
CA-MHB	18	0.25	0.25	ND	ND	0.25	2	0.5	ND	ND	1	0.5	ND	ND	0.5	0.125	ND	>128
CA-MHB	19	1	0.25	ND	ND	1	2	1	ND	ND	1	1	ND	ND	2	1	ND	64
CA-MHB	20	0.25	0.125	ND	ND	0.5	1	0.5	ND	ND	1	1	ND	ND	0.5	0.25	ND	>128
CA-MHB	21	1	0.5	ND	ND	0.5	32	4	ND	ND	1	2	ND	ND	1	0.5	ND	>128
CA-MHB	22	1	0.5	ND	ND	2	1	2	ND	ND	2	2	ND	ND	2	2	ND	16
CA-MHB	23	2	1	ND	ND	2	1	2	ND	ND	2	2	ND	ND	2	2	ND	4
CA-MHB	24	2	1	ND	ND	2	2	2	ND	ND	2	2	ND	ND	2	2	ND	4
CA-MHB	25	0.5	0.125	16	2	1	2	1	ND	16	1	2	1	ND	1	1	>128	64
CA-MHB	26	0.25	≤0.06	8	1	0.5	0.5	0.25	ND	64	1	1	0.5	ND	1	0.5	>128	>128
CA-MHB	27	0.5	0.125	32	4	0.5	1	0.5	ND	64	1	1	0.5	ND	0.5	0.5	>128	>128
CA-MHB	28	2	1	64	2	2	32	8	ND	32	2	4	1	ND	4	4	>128	16
CA-MHB	29	2	0.5	8	2	2	2	2	ND	4	2	2	2	ND	2	2	64	8
CA-MHB	30	0.5	0.125	32	2	0.5	1	0.5	ND	>128	0.5	0.5	0.5	1	0.5	0.5	>128	>128
CA-MHB	31	1	0.5	8	2	1	1	1	ND	32	1	1	0.5	1	1	2	128	64
CA-MHB	32	0.5	0.25	ND	ND	0.5	1	0.5	ND	ND	1	1	ND	ND	0.5	0.5	ND	>128
CA-MHB	33	1	0.25	ND	ND	1	2	1	ND	ND	1	1	ND	ND	1	1	ND	32

CA-MHB	34	1	0.25	8	2	1	2	1	ND	16	1	2	≤0.25	ND	1	1	>32	64
CA-MHB	35	2	1	ND	ND	1	8	2	ND	ND	1	0.5	ND	ND	0.5	0.5	ND	>128
CA-MHB	36	1	0.25	ND	ND	1	1	1	ND	ND	1	1	ND	ND	2	1	ND	32
CA-MHB	37	1	0.5	8	2	1	1	1	ND	32	1	2	1	ND	2	2	64	64
CA-MHB	38	0.5	0.25	ND	ND	1	1	0.5	ND	ND	1	1	ND	ND	1	0.5	ND	>128
CA-MHB	39	4	1	8	4	2	2	4	ND	4	2	2	2	ND	4	4	32	4
CA-MHB	40	2	2	128	16	2	64	16	ND	>128	8	64	4	8	2	1	>128	>128
CA-MHB	41	0.5	0.125	ND	ND	0.5	1	0.5	ND	ND	1	2	ND	ND	1	0.5	ND	128
CA-MHB	42	0.5	0.5	64	16	0.5	1	0.5	64	>128	1	1	0.5	4	0.5	0.5	>128	>128
CA-MHB	43	2	0.5	ND	ND	2	2	2	ND	ND	2	4	ND	ND	2	2	ND	16
CA-MHB	44	0.5	0.125	16	4	0.25	0.5	0.25	ND	>128	1	1	0.5	ND	0.5	0.5	>128	>128
CA-MHB	45	0.25	0.125	32	4	0.25	1	0.5	ND	>128	1	1	0.5	ND	0.5	0.25	>128	>128
CA-MHB	46	1	0.25	64	8	0.5	1	0.5	ND	>128	1	2	0.5	ND	0.5	0.5	>128	>128
CA-MHB	47	0.5	0.125	8	2	0.5	0.5	1	ND	128	2	2	0.5	ND	1	1	32	>128
CA-MHB	48	0.5	0.125	16	4	0.5	1	0.5	ND	>128	1	2	0.5	ND	0.5	0.5	128	>128
CA-MHB	49	1	0.25	32	4	1	1	1	ND	>128	1	2	1	ND	1	1	128	>128
CA-MHB	50	1	0.5	32	4	1	1	1	ND	128	2	4	1	ND	2	1	>128	>128
CA-MHB	51	1	0.5	ND	ND	2	8	2	ND	ND	2	4	ND	ND	1	1	ND	128
CA-MHB	52	ND	ND	ND	ND	1	ND	2	ND	ND	ND	1	ND	ND	ND	ND	ND	ND
CA-MHB	53	ND	ND	ND	ND	0.5	ND	1	ND	ND	ND	0.5	ND	ND	0.5	ND	ND	ND
CA-MHB	54	0.5	0.125	ND	ND	0.5	1	0.25	ND	ND	1	1	ND	ND	1	0.25	ND	64
CA-MHB	55	0.25	≤0.06	8	2	0.25	0.5	0.25	ND	64	0.5	1	0.25	ND	0.5	0.25	>128	>128
CA-MHB	56	2	1	>128	128	1	8	4	>128	>128	8	8	4	32	1	1	>128	>128

Abbreviations: Ec – *Escherichia coli*, Ab – *Acinetobacter baumannii*, Pa – *Pseudomonas aeruginosa*, Kp – *Klebsiella pneumoniae*, COL^R – colistin-resistant, COL het^R – colistin-heteroresistant, FBS – fetal bovine serum (50%, heat-inactivated), ND – not determined, CA-MHB – cation adjusted Mueller-Hinton broth RPMI B - RPMI 1640 (+) L-glutamine, (+) sodium bicarbonate, pH 7.4, containing 5% LB

Example 30 – Efficacy of Compound 42 against *P. aeruginosa* UNT033-1 in a neutropenic mouse pneumonia model.

The efficacy of Compound 42 and different dosing schedules was assessed in a *Pseudomonas* pneumonia model (Fig. 1). All test articles were administered IP, either bid or tid starting 2 hours after bacterial challenge. Anesthetized mice were infected with *P. aeruginosa* intranasally (approx. 6.65 log CFU) and lungs harvested after 24 hours for enumeration. Total study dose of compounds in mgs is indicated on the x-axis of Fig. 1. The minimum activity to achieve bactericidal activity is highlighted by a dashed line. The comparator (colistin) is denoted using a hatched bar on the graph. In this study, Compound 42 dosed at 20 mg/kg (mpk) either bid or tid was significantly more active than colistin (P=0.015 & 0.0012 respectively). Importantly, these concentrations resulted in a greater than 1-log CFU reduction relative to the challenge inoculum and therefore reached bactericidality.

Example 31 – Protective effect of compounds of the invention against endotoxemia

Septic shock, resulting in systemic organ failure, is an important component of many bacterial infections. In infections caused by Gm-negative pathogens, or in some mixed infections, LPS (aka endotoxin) is the dominant mediator of this process which results from hyper-stimulation of the immune system.

Sensitized mouse model of endotoxemia.

Female immune competent C57BL/6 mice (Jackson Laboratories) between 8 and 10 weeks old are used as model of endotoxemia. After acclimation for 7 days mice are challenged IP with 18 ng of purified LPS (*Escherichia coli* 0111:B4; Sigma #L4130) in PBS mixed with 20 mg of D-galactosamine hydrochloride (Fisher #50-492-412) in a volume of 0.4 ml. Previously this dose was shown to result in 100% mortality of challenged mice within 5 days. The murine LD_{100} of this model is approximately equal to that of humans due to sensitization by D-galactosamine. Study mice are housed and cared for following standard IACUC approved protocols, and clearly moribund mice are humanely euthanized and scored as a death.

Efficacy of compounds of the invention in endotoxemia.

C57BL/6 mice are challenged with a lethal dose of LPS as described above. One hour prior to LPS challenge control groups of animals receive vehicle (PBS), or colistin at 10, 0.3, 0.1, or 0.03 mg/kg by IV injection. Compounds are also administered IV at T-1 hour (10, 0.3, 0.1, or 0.03 mg/kg).

Example 32 – Measurement of binding of compounds to LPS using the Limulus Amebocyte Lysate (LAL) assay

The LAL assay (Charles River) was used to determine the binding affinity of test articles to LPS. A decrease in absorbance by test articles demonstrates neutralization of LPS and correlates with binding of test articles to LPS.

For the assay, 25 µL purified LPS from *E. coli* O111:B4 (Sigma) at doses ranging from 1 – 10,000 ng/mL were incubated with 25 µL of test article at concentrations ranging from 0.25 – 10 µM. After 5 min incubation at 37°C, 50 µL of LAL reagent, which reacts with lipid A portion from LPS, was added to corresponding wells. After 15 min, absorbance at 405 nm is read on EnSpire plate reader (Perkin Elmer). The % LPS neutralization is calculated relative to a PBS control (background) and LPS control at each concentration (positive control).

LPS neutralization = (1- (absorbance test article – PBS with LAL reagent) / (absorbance no test article – PBS with LAL reagent)) x 100.

To obtain a single value of LPS neutralization for each test article, the area under the curve (AUC) for dose-response of test articles from 0.25 – 10 µm for each LPS concentration was calculated using Prism 7 software. The % LPS neutralization is the sum of the AUCs for each LPS concentration determined relative to the maximal AUC achievable x 100.

Results

Compounds bind to purified LPS from *E. coli* O111:B4 in dose-dependent manner and were tested at concentrations ranging between 0.25 – 10 µM and against a concentration range of LPS spanning 1 – 10,000 ng/mL (Table 5).

Table 5. LPS neutralization of compounds against LPS from *E. coli* O111:B4

Test article	% LPS neutralization
Colistin	9.7
PMB	18.8
PMBN	2.9
Compound 31	38.8

Example 33 – Measuring LPS neutralization using the HEK-Blue hTLR4 reporter cell line

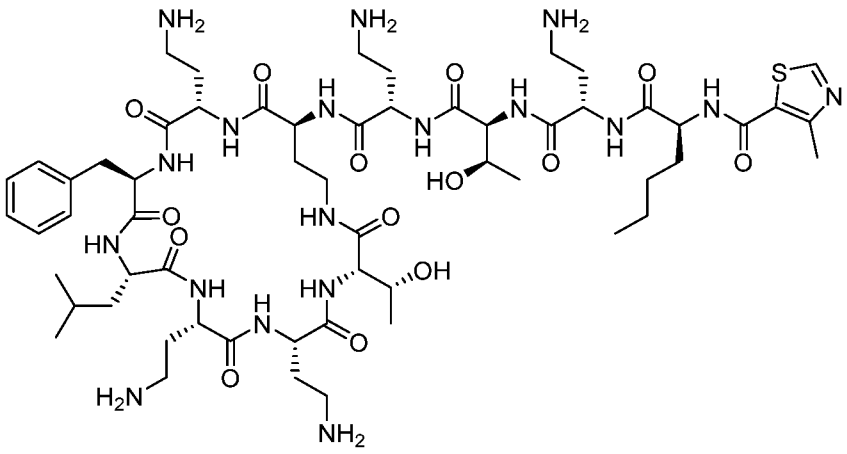
This method measurs the ability of compounds to neutralize lipopolysaccharide (LPS) and prevent the downstream activation of NF-κB-signaling mediated by LPS using the HEK-Blue hTLR4 reporter cell line (Fisher Scientific). HEK-Blue hTLR4 cells are cultured to 50-80% confluency in T150 cm^2 flasks according to the manufacturer's method, then gently rinsed with 20 ml 1X PBS pH 7.4. After aspirating the rinse, 10 ml 1X PBS is added and incubated for 1-2 min at 37°C, 5% CO_2. Cells are released from the flask by tapping the flask or by using a cell lifter. A single cell suspension is obtained by pipetting up and down, then 10 µl of cell suspension added to 80 µl of 1X PBS and 10 µl of trypan blue (0.4% stock solution) for hemocytometer enumeration. The cell concentration is adjusted to 140,000

cells/ml in HEK-Blue Detection medium (Fisher Scientific). 20 µl of test compound at the desired concentration is added to a flat-bottom tissue culture treated 96-well plate (Corning). 20 µl LPS stock (1 mg/ml) is added in a dose-response at the desired concentration to corresponding wells. 180 µl of HEK-Blue hTLR4 cells (~25,000 cells/well) is added to corresponding wells, and the plate is incubated at 37°C, 5% CO_2 for 6-16 h. The absorbance at 650 nm is measured using a Perkin-Elmer Enspire Multimode plate reader. Percent LPS inactivation (1-[absorbance test article with LPS / absorbance no test article with LPS] × 100%) is plotted versus concentration using GraphPad Prism software (version 7.0d, GraphPad Software, Inc.). The area under the curve (AUC) is used to rank-order compounds by LPS neutralizing activity.

Example 34 – LPS Neutralization Activity of Compounds in Human Blood

The ability of compounds to sequester LPS and inhibit immune cell activation in human blood measured to rank order LPS-binding affinities. Hirudin anti-coagulated human blood (complement active) is diluted 1:2 in in RPMI with L-glutamine and phenol red (Life Technologies) and 160 µl is added to wells of a non-binding 96-well plate (Corning 3641). 10 µl of 20X compound is diluted in RPMI (2.5– 0.0006 µM final concentration) and is added to wells, followed by 10 µl of 20X LPS from *E. coli* O111:B4 (Sigma; 100 or 1,000 ng/ml final concentration), and 20 µl RPMI for a final blood concentration of 40%. The plate is incubated under static conditions at 37°C for 4 h, centrifuged at 500 x *g* for 5 min at room temperature, and 60 µl plasma is carefully aspirated and transferred to a non-binding plate for overnight storage at -80°C. The following day, the concentration of TNF-α in plasma samples diluted 1:10 is determined using the human TNF-α ELISA kit, as per the manufacturer's instructions (BioLegend). The percent inhibition of TNF-α release, relative to the blood + LPS positive control (100% TNF-α release), is calculated and plotted for each compound concentration tested. The area under the curve (AUC) is calculated using GraphPad Prism software (version 7.0d, GraphPad Software, Inc.) and used to rank-order compounds by LPS neutralizing activity. LPS stimulation of whole blood is known to trigger the release of pro-inflammatory cytokine TNF-α (PMID: 26993088). Therefore, high levels of TNF-α inhibition, resulting in high AUCs, are indicative of compounds with good LPS neutralizing activity in human blood.

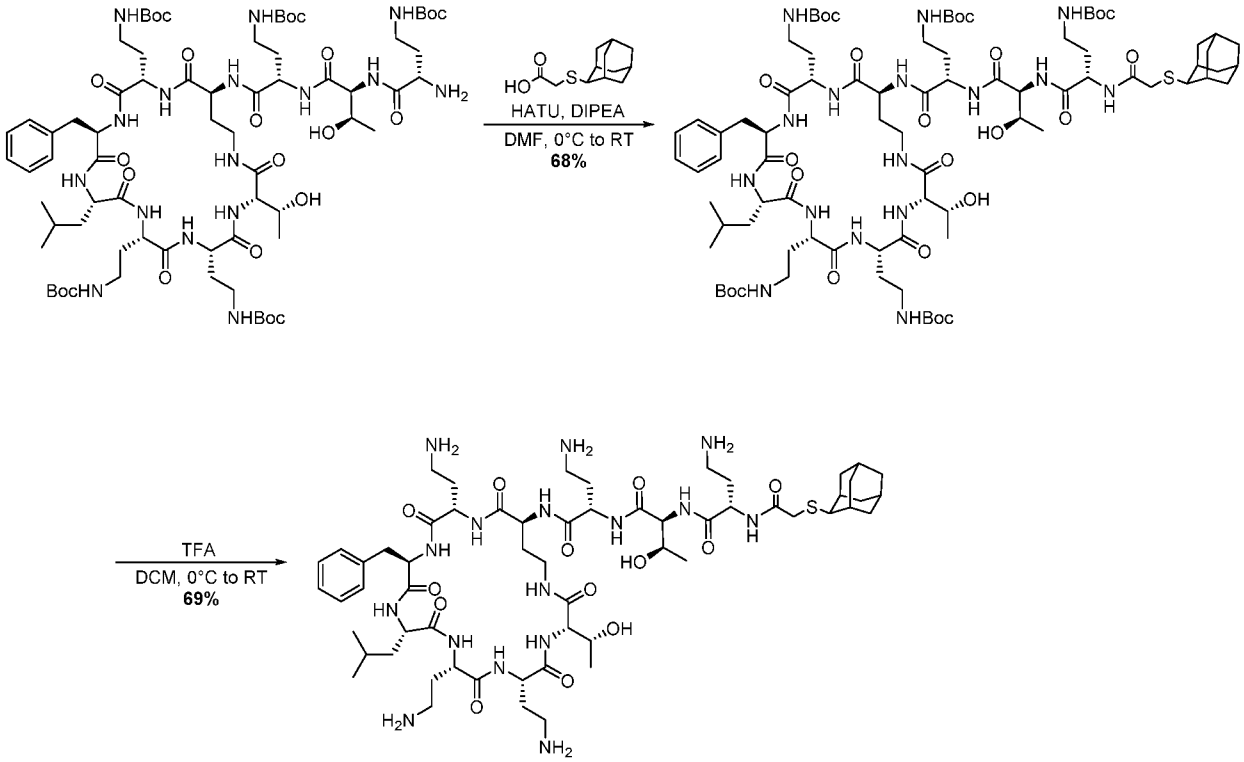
Example 35 – Synthesis of Compound 42



Compound 42

The title compound is prepared from Int-5 derived from L-aminohexanoic acid, and where 4,6-dichloropicolinic acid was replaced with 4-methyl-1,3-thiazole-5-carboxylic acid, using the procedure described in Example 5.

Example 36 – Synthesis of Compound 54



Compound 54

Step a.

Prepared from Int-4 (150 mg, 0.0959 mmol), and (1-adamantylthio)-acetic acid (21 mg, 0.0959 mmol), by HATU coupling. Ion(s) found by LCMS: [(M - 3Boc + 3H)/3]+ = 736.5.

Step b.

Deprotected with TFA in a manner similar to that of Compound 1. Yield 0.077 g (penta-TFA salt). 69%. Ion(s) found by LCMS: [(M + 2H)/2]+ = 636.4, [(M + 3H)/3]+ = 424.5.

Example 37. Thigh infection model with a colistin resistant isolate of *E. coli*.

In vivo efficacy of test articles were determined in a thigh model of infection against an MCR-1 producing *E. coli* strain (AR-0349) obtained from the Center for Disease Control and Prevention. In addition to being resistant to colistin, it is also resistant to most β-lactam antibiotics except carbapenems. It is also resistant to ciprofloxacin, gentamicin and trimethoprim/sulfamethoxazole but is susceptible to tigecycline and amikacin.

Groups of 5 female specific-pathogen-free ICR (CD-1) mice weighing 22 g were used for these studies. Animals were immunosuppressed by two intraperitoneal injections of cyclophosphamide, the first at 150 mg/kg 4 days before infection (day -4) and the second at 100 mg/kg 1 day before infection (day -1). On day 0, animals were inoculated intramuscularly (0.1 ml/thigh) into the right thigh with 0.5-1 x 10^5 CFU/mouse of *E. coli* AR0349. The test article was administered IP, 2 and 8 hours after challenge. At 26 hours following inoculation, animals were humanely euthanized with CO_2 asphyxiation and the infected thigh was harvested from the animal. The removed muscle was homogenized in 5 ml of PBS, pH 7.4, with a polytron homogenizer. Homogenates, 0.1 mL, were used for serial 10-fold dilutions and plated onto nutrient agar medium for colony count (CFU/g) determination. The activity of Compound 55 is shown in the graph of Fig. 3 and detailed in Table 6, below.

Table 6. Activity of Compound 55 relative to colistin in a thigh model.

Test article	Dose (mg/kg), bid, starting @ T+1 hr.	Route	CFU/g @ 26 hrs.	SEM
Initial counts	—	—	**5.45**	0.04
Vehicle only	—	IP	**8.92**	0.12
Colistin	10	IP	**6.44**	0.49
Colistin	10	SC	**5.94**	0.45
Compound 55	10	IP	**5.02**	0.43

Example 38 – Activity of compounds in a mouse model of septicemia

The activity of test articles was evaluated *in vivo* using an established mouse septicemia model. In this model, immune competent CD-1 mice (Charles River Labs; females, 20g; specific-pathogen-free) were challenged intraperitoneally (0.2 mL volume) with approximately $1x10^7$ CFU of *E. coli* 25922 grown in LB media. Prior to challenge, bacteria were diluted (1:1) in fresh LB + PBS with 5% gastric hog mucin to locally inhibit macrophages. Compounds were re-suspended in sterile PBS and injected IP one hour after bacterial challenge. Survival of animals was determined over 72 hours. Test articles were screened at 0.3 mg/kg in this model.

Table 7. Activity of Compounds 42, 54, and 55 in a mouse model of septicemia.

Test article	MIC (µg/ml)		% Survival
	E. coli ATCC 25922		0.3 mg/kg (IP, QD)
	No Serum	Serum	
Vehicle (PBS)	n/a	n/a	0
Colistin	0.5	0.25	100
Compound 42	0.25	<0.06	100
Compound 54	1	0.5	100
Compound 55	0.25	<0.06	100

Example 39 – Activity of compounds in a *Pseudomonas* lung model in neutropenic mice

Methods. The testing strain, *P. aeruginosa* LES 431 (BCCM/LMG 27624), was obtained from a frozen working stock and thawed at room temperature. A 0.2 ml aliquot was inoculated into 20 ml TSB and incubated at 35-37 °C with shaking (250 rpm) for 6 hr. One ml of the 6 hr culture was used to seed 99 ml TSB and incubated at 35-37 °C with shaking at 250 rpm for 16 hr. Cells in 20 ml culture were pelleted by centrifugation (3300 × g) for 15 minutes, then resuspended in 10 ml cold PBS (>1 × 10^9 CFU/mL, OD620 1.1-1.4). The culture was diluted in PBS to obtain the target inoculum of 5.0 x 10^7 CFU/ml. Groups of 8 female ICR mice weighing 22 g were used. Animals were immunosuppressed by two intraperitoneal (IP) injections of cyclophosphamide, the first one at 150 mg/kg 4 days before infection (day -4) and the second one at 100 mg/kg 1 day before infection (day -1). On day 0, animals were anesthetized with etomidate-lipuro emulsion (20 mg /10 mL; 20 mg/kg dose, IV) and then inoculated intranasally (IN) with *P. aeruginosa* LES 431 suspension, 0.02 mL/mouse. The target inoculation density was 1.0 × 10^6 CFU/mouse and the actual count was 1.41 × 10^6 CFU/mouse.

Table 8. Activity of compounds relative to colistin in a *Pseudomonas* lung study.

Test article	Dose (mg/kg), bid, starting @ T+1 hr.	Route	CFU/g @ 26 hrs.	SEM
Initial counts	—	—	**5.45**	0.04

Vehicle only	——	IP	**8.92**	0.12
Colistin	10	IP	**6.44**	0.49
Colistin	10	SC	**5.94**	0.45
Compound 42	10	IP	**2.99**	0.2
Compound 42	20	IP	**<2.0**	0.25
Compound 55	10	IP	**6.63**	0.32
Compound 55	20	IP	**4.26**	0.45

Example 40 – Rat model of nephrotoxicity

Preliminary kidney safety was determined for compounds by measuring Kidney Injury Marker 1 (KIM-1) in urine over time as an indicator of kidney damage in a rat nephrotoxicity study (25 mg/kg, bid, subcutaneous (SC)).

Rats were administered a total of 50 mg/kg/day SC of colistin or Compound 42. Urine was collected pre-dose and post-dose every 12 hours until 36 hours. The levels of KIM-1 protein in the urine at each interval was measured using a commercially available Rat KIM-1 ELISA kit (GenWay®) and is shown in Fig. 2. Compound 42 showed approximately a 30% reduction in KIM-1 signal compared to colistin.

Example 41 – Lung burden in *P. aeruginosa* pneumonia model in neutropenic mice

Lung burdens (CFU/g lung tissue) were determined in an MDR *P. aeruginosa* pneumonia model using neutropenic mice (10 – 20 mg/kg bid, IP at T+1 hour). Mice were dosed on Day -4 and -1 at 150 and 100 mg/kg of cyclophosphamide respectively. Compounds 42, 54, and 55 administered IP at a total dose of 20 or 40 mg/kg. After 24 hours, Compound 42 showed potent activity and was bacteriacidal at both doses, which was markedly superior to colistin, as shown in Fig. 4. Compounds 54 and 55 were also efficacious in this model of disease.

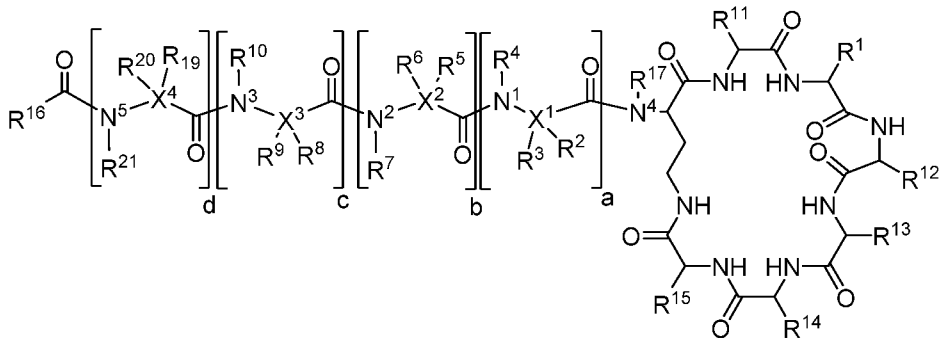
Other Embodiments

While the disclosure has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the disclosure following, in general, the principles of the disclosure and including such departures from the present disclosure come within known or customary practice within the art to which the disclosure pertains and may be applied to the essential features hereinbefore set forth.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

CLAIMS

1. A compound described by formula (I):



(I)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H;

R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H;

R^{15} is a lipophilic moiety or a polar moiety;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

each of a, b, c, and d is, independently, 0 or 1;

each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom,

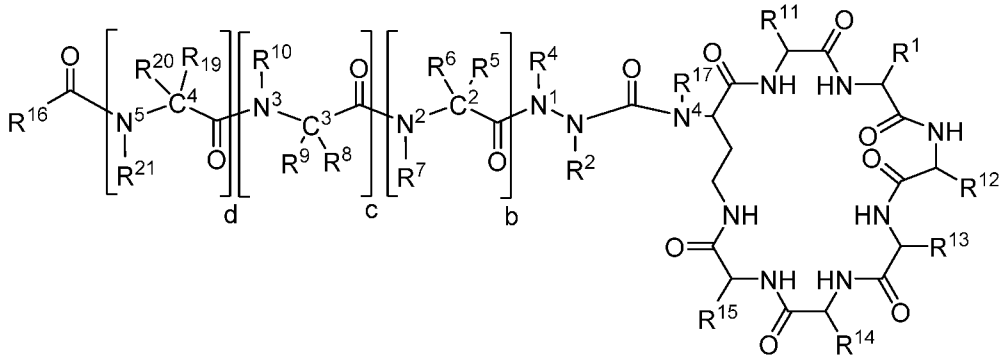
wherein at least one of X^1, X^2, X^3, and X^4 is a nitrogen atom,

wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; (vii) R^{19}, R^{20}, and X^4; or (viii) R^{19}, R^{20}, N^5, and X^4.

3. The compound of claim 1, wherein the compound is described by formula (I-1):



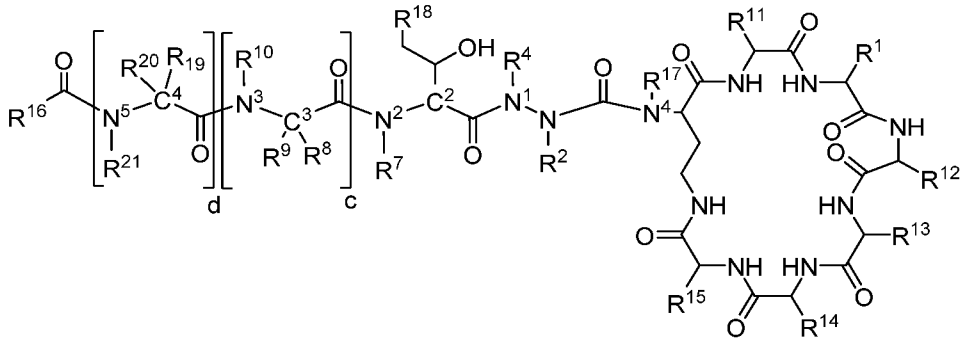
(I-1)

wherein each of b, c, and d is, independently, 0 or 1;

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^5, R^6, and C^2; (ii) R^6, R^7, N^2, and C^2; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

5. The compound of claim 3, wherein the compound is described by formula (I-2):



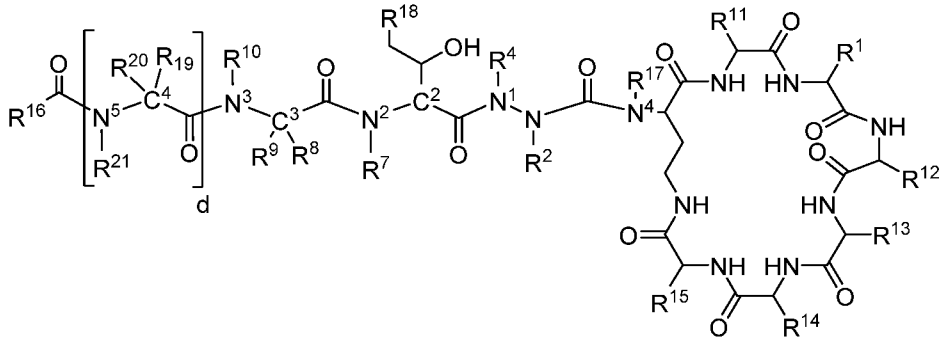
(I-2)

wherein each of c and d is, independently, 0 or 1;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein the compound is described by formula (I-3):



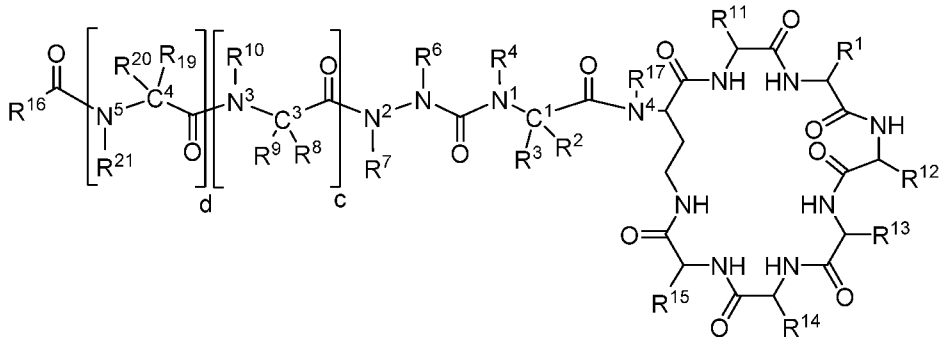
(I-3)

wherein d is 0 or 1,

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 5 or 6, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^8, R^9, and C^3; (ii) R^9, R^{10}, N^3, and C^3; (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4.

8. The compound of claim 1, wherein the compound is described by formula (I-4):

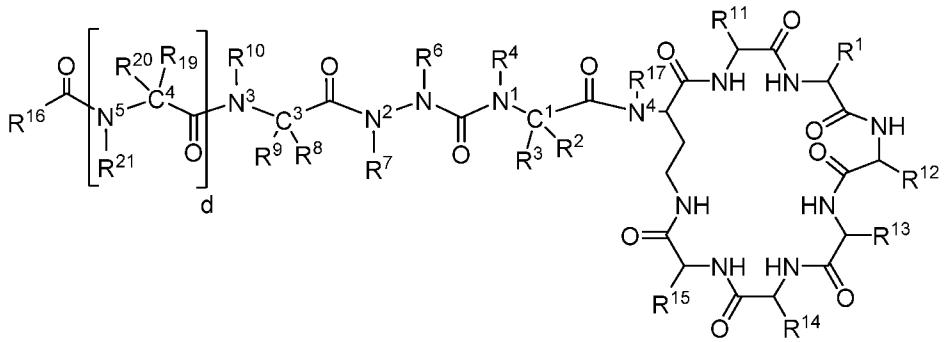


(I-4)

wherein each of c and d is, independently, 0 or 1;

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein the compound is described by formula (I-5):



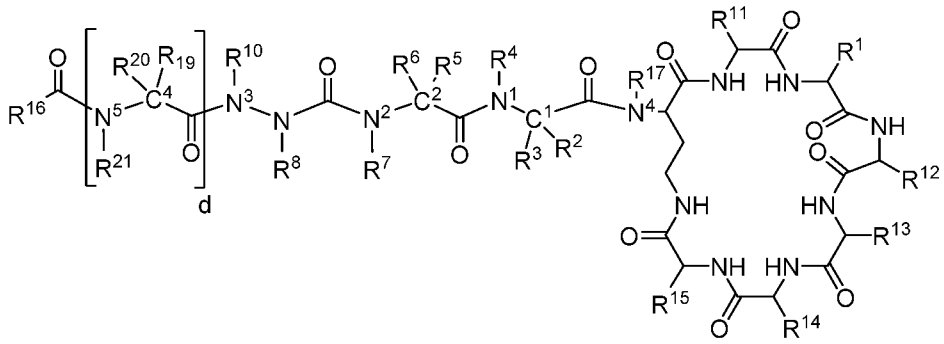
(I-5)

wherein d is 0 or 1,

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 8 or 9, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

11. The compound of claim 1, wherein the compound is described by formula (I-6):



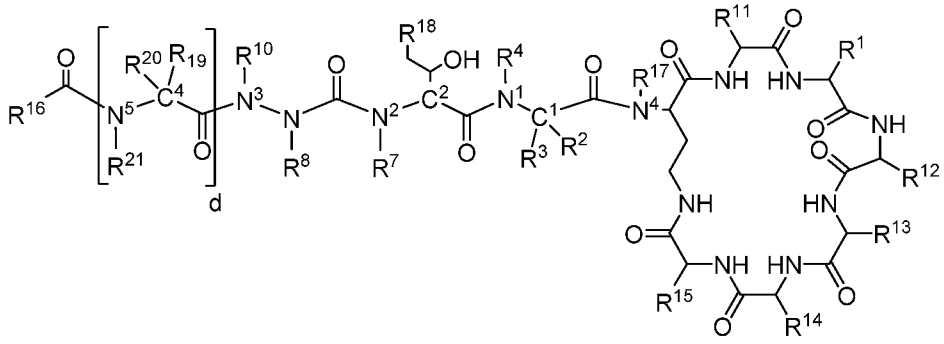
(I-6)

wherein d is 0 or 1,

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; or (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

13. The compound of claim 11, wherein the compound is described by formula (I-7):



(I-7)

wherein d is 0 or 1; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

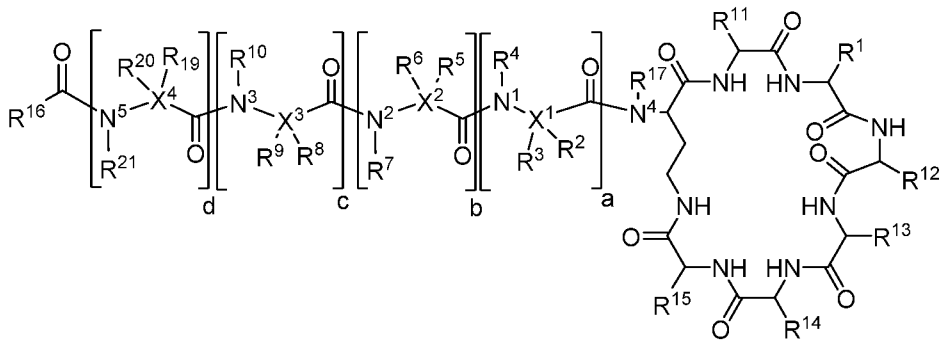
14. The compound of claim 13, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; or (iii) R^{19}, R^{20}, and C^4; or (iv) R^{19}, R^{20}, N^5, and C^4.

15. The compound of any one of claims 1-14, wherein R^{17} is H.

16. The compound of any one of claims 1-14, wherein R^{17} is methyl.

17. The compounds of any one of claims 1-16, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

18. A compound described by formula (II):



(II)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H;

R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H;

R^{15} is a lipophilic moiety or a polar moiety;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

each of a, b, c, and d is, independently, 0 or 1;

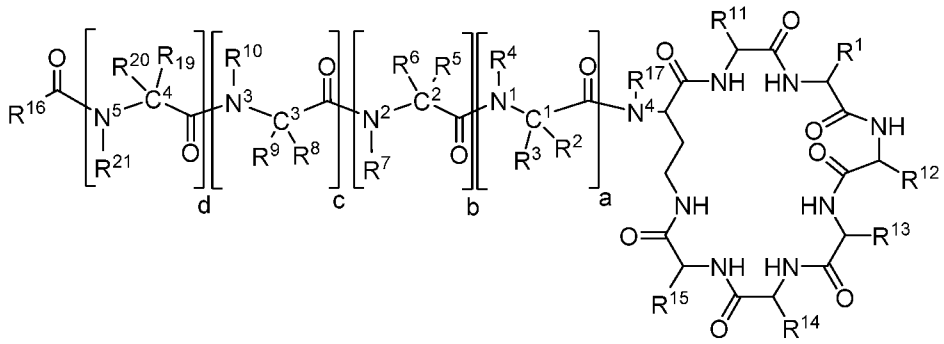
each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom,

wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent;

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 18, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

20. The compound of claim 18, wherein the compound is described by formula (II-1):



(II-1)

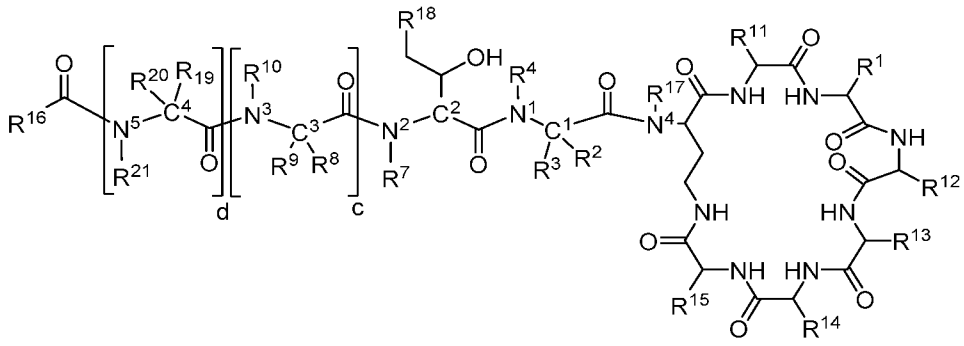
wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and

each of a, b, c, and d is 0 or 1;

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

22. The compound of claim 20, wherein the compound is described by formula (II-2):



(II-2)

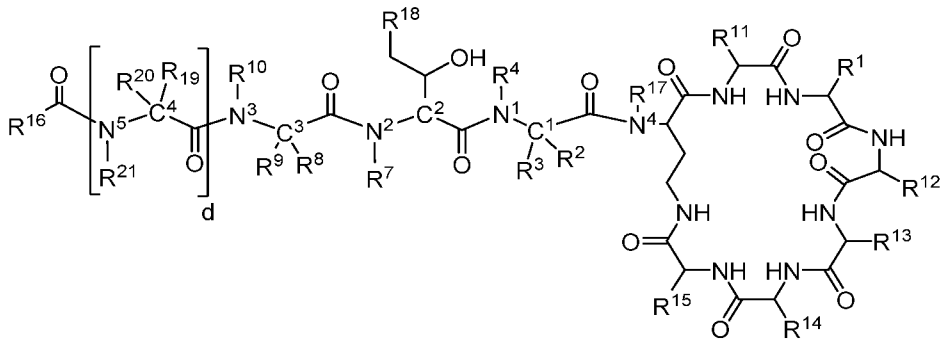
wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is C1-C3 alkyl or C2-C3 alkamino; and

each of c and d is, independently, 0 or 1,

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22, wherein the compound is described by formula (II-3):



(II-3)

wherein R^{17} is C1-C3 alkyl or C2-C3 alkamino; and

d is 0 or 1,

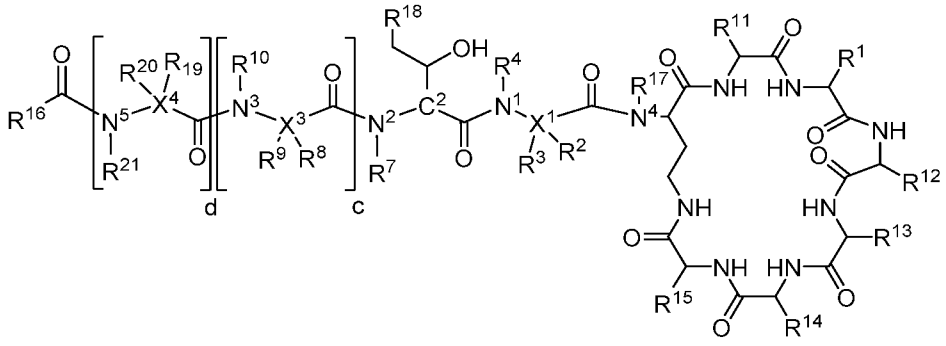
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 22 or 23, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

25. The compound of any one of claims 18-24, wherein R^{17} is methyl.

26. The compounds of any one of claims 18-25, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

27. A compound described by formula (III):



(III)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H;

R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H;

R^{15} is a lipophilic moiety or a polar moiety;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

each of a, b, c, and d is, independently, 0 or 1;

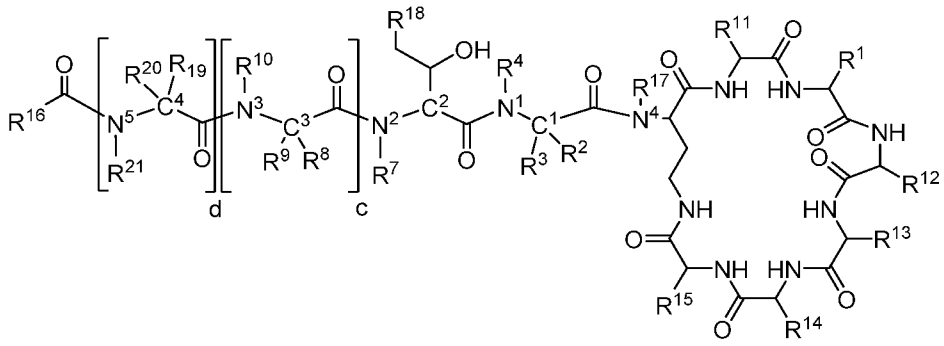
each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom,

wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent;

or a pharmaceutically acceptable salt thereof.

28. The compound of claim 27, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^8, R^9, and X^3; (iv) R^9, R^{10}, N^3, and X^3; (v) R^{19}, R^{20}, and X^4; or (vi) R^{19}, R^{20}, N^5, and X^4.

29. The compound of claim 27, wherein the compound is described by formula (III-1):



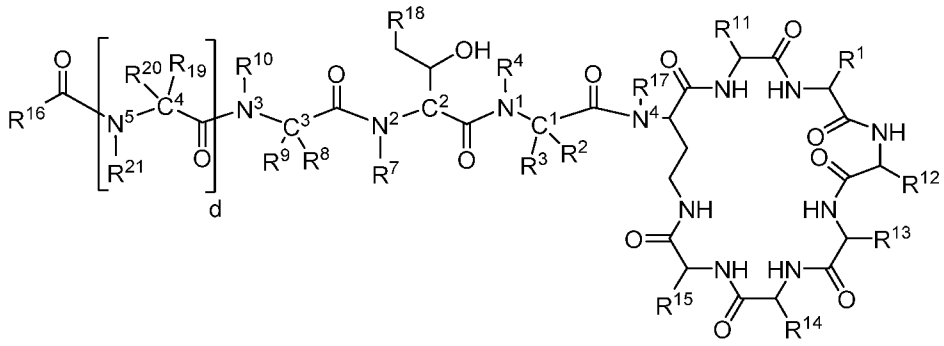
(III-1)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

each of c and d is, independently, 0 or 1;

or a pharmaceutically acceptable salt thereof.

30. The compound of claim 29, wherein the compound is described by formula (III-2):



(III-2)

wherein R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

d is 0 or 1;

or a pharmaceutically acceptable salt thereof.

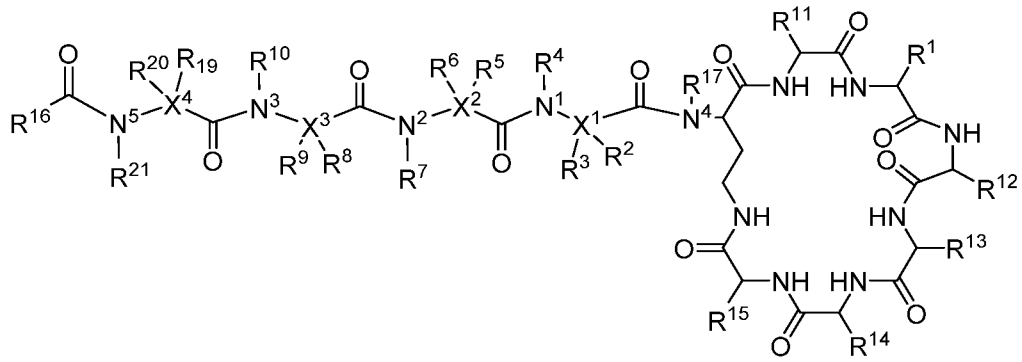
31. The compound of claim 29 or 30, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; (v) R^{19}, R^{20}, and C^4; or (vi) R^{19}, R^{20}, N^5, and C^4.

32. The compound of any one of claims 27-31, wherein R^{17} is H.

33. The compound of any one of claims 27-31, wherein R^{17} is methyl.

34. The compounds of any one of claims 27-33, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

35. A compound described by formula (IV):



(IV)

wherein R^1 and R^{12} are each, independently, a lipophilic moiety, a polar moiety, or H;

R^{11}, R^{13}, and R^{14} are each, independently, optionally substituted C1-C5 alkamino, a polar moiety, a positively charged moiety, or H;

R^{15} is a lipophilic moiety or a polar moiety;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{19}, R^{20}, and R^{21} are each, independently, a lipophilic moiety, a positively charged moiety, a polar moiety, H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl,

optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; or two R groups on the same or adjacent atoms join to form an optionally substituted 3-8 membered ring;

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

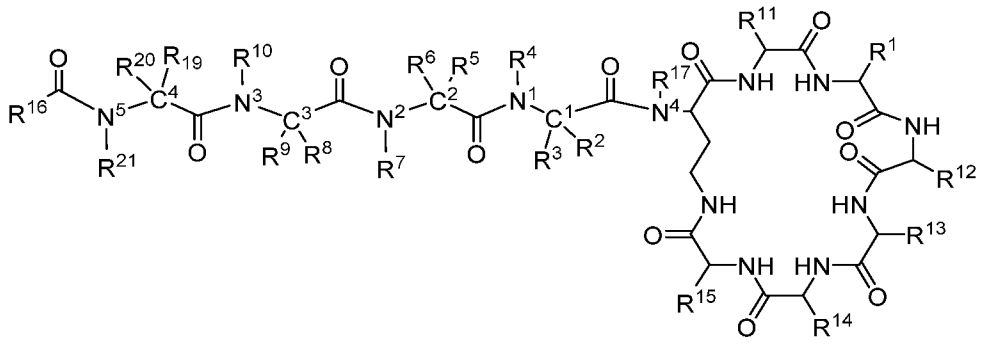
each of X^1, X^2, X^3, and X^4 is, independently, a carbon atom or a nitrogen atom,

wherein if X^1 is a nitrogen atom then R^3 is absent, if X^2 is a nitrogen atom then R^5 is absent, if X^3 is a nitrogen atom then R^9 is absent, and if X^4 is a nitrogen atom the R^{19} is absent;

or a pharmaceutically acceptable salt thereof.

36. The compound of claim 35, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and X^1; (ii) R^3, R^4, N^1, and X^1; (iii) R^5, R^6, and X^2; (iv) R^6, R^7, N^2, and X^2; (v) R^8, R^9, and X^3; (vi) R^9, R^{10}, N^3, and X^3; or (iii) R^{19}, R^{20}, and X^4; or (iv) R^{19}, R^{20}, N^5, and X^4.

37. The compound of claim 35, wherein the compound is described by formula (IV-1):



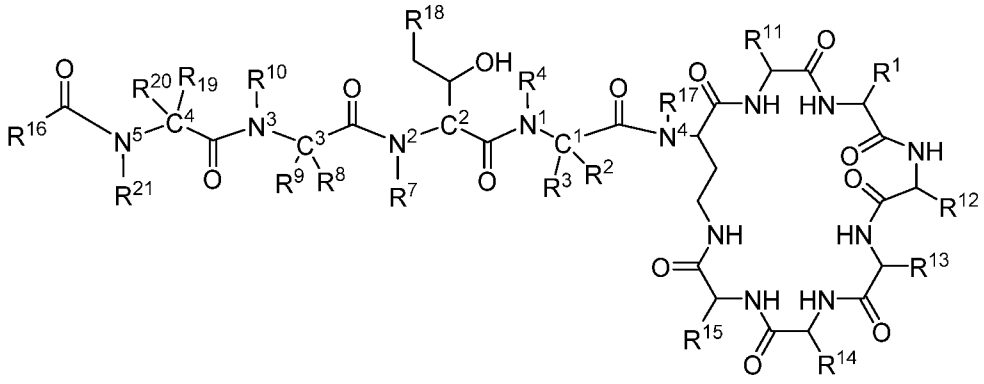
(IV-1)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

38. The compound of claim 37, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^3, R^4, N^1, and C^1; (iii) R^5, R^6, and C^2; (iv) R^6, R^7, N^2, and C^2; (v) R^8, R^9, and C^3; (vi) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

39. The compound of claim 37, wherein the compound is described by formula (IV-2):



(IV-2)

wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

40. The compound of claim 39, wherein the compound comprises at least one optionally substituted 3-8 membered ring formed by joining (i) R^2, R^3, and C^1; (ii) R^2, R^3, N^1, and C^1; (iii) R^8, R^9, and C^3; (iv) R^9, R^{10}, N^3, and C^3; or (vii) R^{19}, R^{20}, and C^4; or (viii) R^{19}, R^{20}, N^5, and C^4.

41. The compound of any one of claims 35-40, wherein R^{17} is H.

42. The compound of any one of claims 35-40, wherein R^{17} is methyl.

43. The compound of any one of claims 1-42, wherein

each of R^1 and R^{12} is a lipophilic moiety;

each of R^{11}, R^{13}, and R^{14} is, independently, optionally substituted C1-C5 alkamino, a polar moiety, or a positively charged moiety; and/or

R^{15} is a polar moiety.

44. The compound of any one of claims 1-43, wherein each of R^1 and R^{12} is a lipophilic moiety.

45. The compound of claim 44, wherein each lipophilic moiety is, independently, optionally substituted C1-C20 alkyl, optionally substituted C5-C15 aryl, optionally substituted C6-C35 alkaryl, or optionally C5-C10 substituted heteroaryl.

46. The compound of claim 44 or 45, wherein each lipophilic moiety is, independently, C1-C8 alkyl, methyl substituted C2-C4 alkyl, (C1-C10)alkylene(C6)aryl, phenyl substituted (C1-C10)alkylene(C6)aryl, or alkyl substituted C4-C9 heteroaryl.

47. The compound of any one of claims 44-46, wherein each lipophilic moiety is, independently, benzyl, isobutyl, sec-butyl, isopropyl, n-propyl, methyl, biphenylmethyl, n-octyl, or methyl substituted indolyl.

48. The compound of any one of claims 1-43, wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl.

49. The compound of any one of claims 1-47, wherein each of R^{11}, R^{13}, and R^{14} is independently optionally substituted C1-C5 alkamino.

50. The compound of claim 49, wherein each of R^{11}, R^{13}, and R^{14} is $CH_2CH_2NH_2$.

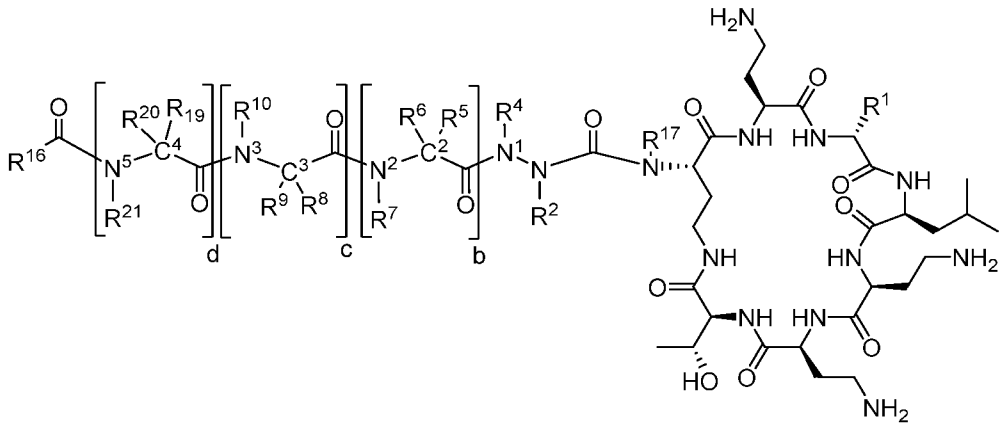
51. The compound of any one of claims 1-50, wherein R^{15} is a polar moiety.

52. The compound of claim 51, wherein each polar moiety comprises a hydroxyl group, a carboxylic acid group, an ester group, or an amide group.

53. The compound of claim 51 or 52, wherein each polar moiety is hydroxyl substituted C1-C4 alkyl.

54. The compound of any one of claims 51-53, wherein each polar moiety is $CHCH_3OH$.

55. The compound of claim 1, wherein the compound is described by formula (V):

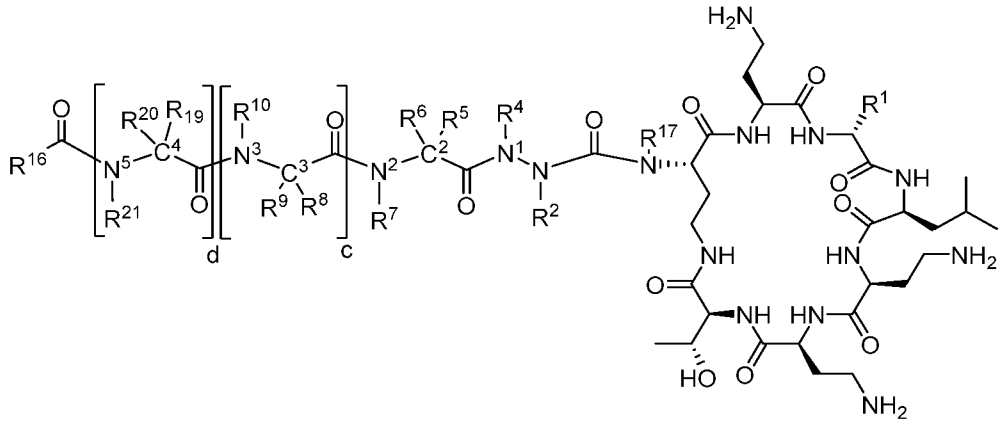


(V)

wherein R^1 is benzyl or $CH_2CH(CH_3)_2$,

or a pharmaceutically acceptable salt thereof.

56. The compound of claim 55, wherein the compound is described by formula (V-1):

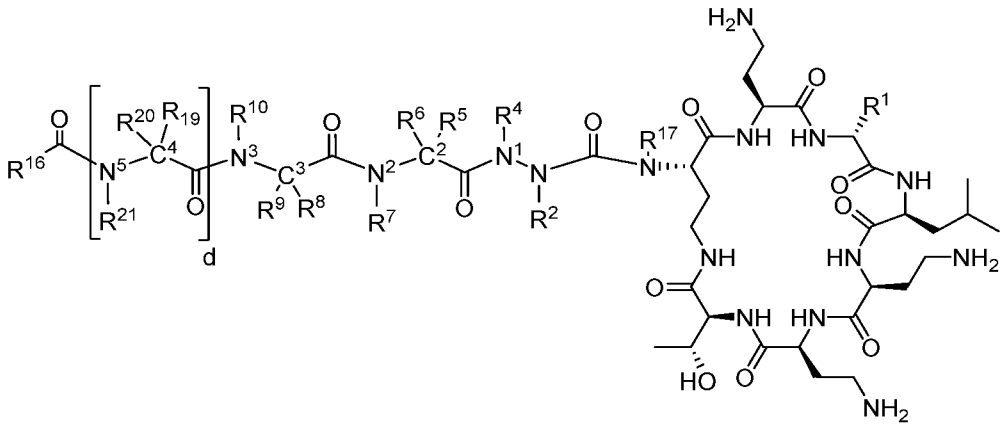


(V-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl,

or a pharmaceutically acceptable salt thereof.

57. The compound of claim 56, wherein the compound is described by formula (V-2):

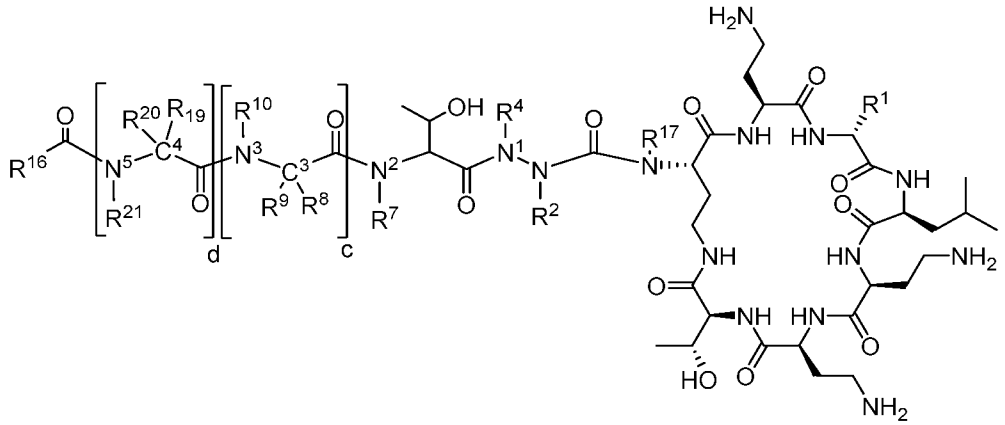


(V-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl,

or a pharmaceutically acceptable salt thereof.

58. The compound of claim 55, wherein the compound is described by formula (V-3):

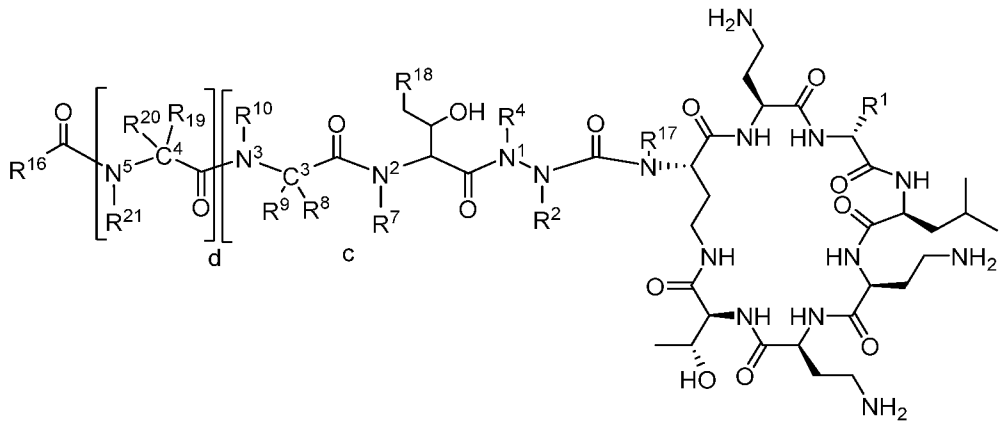


(V-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 55, wherein the compound is described by formula (V-4):



(V-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

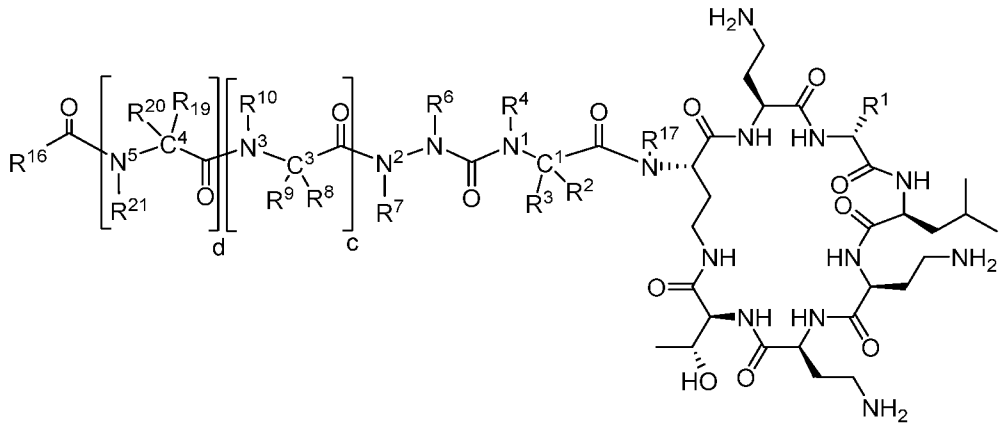
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

60. The compound of claim 59, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

61. The compound of any one of claims 55-60, wherein R^2 is H or C1-C8 alkyl.

62. The compound of claim 1, wherein the compound is described by formula (VI):

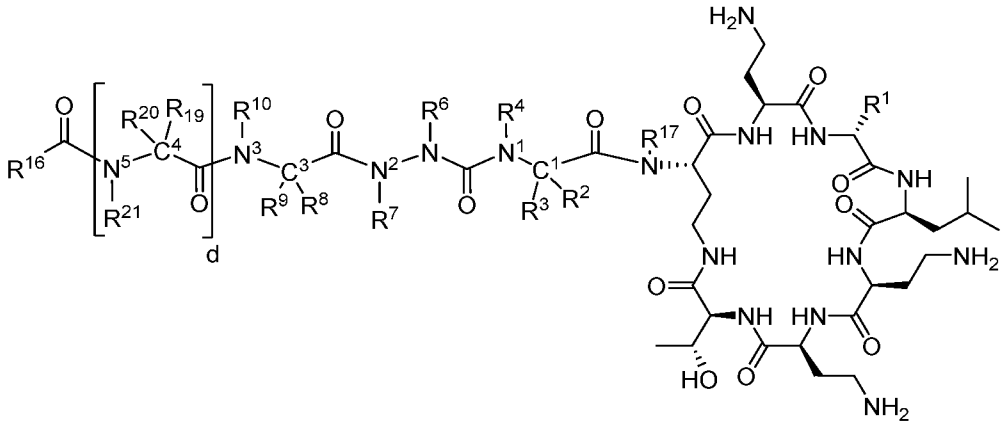


(VI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl,

or a pharmaceutically acceptable salt thereof.

63. The compound of claim 62, wherein the compound is described by formula (VI-1):



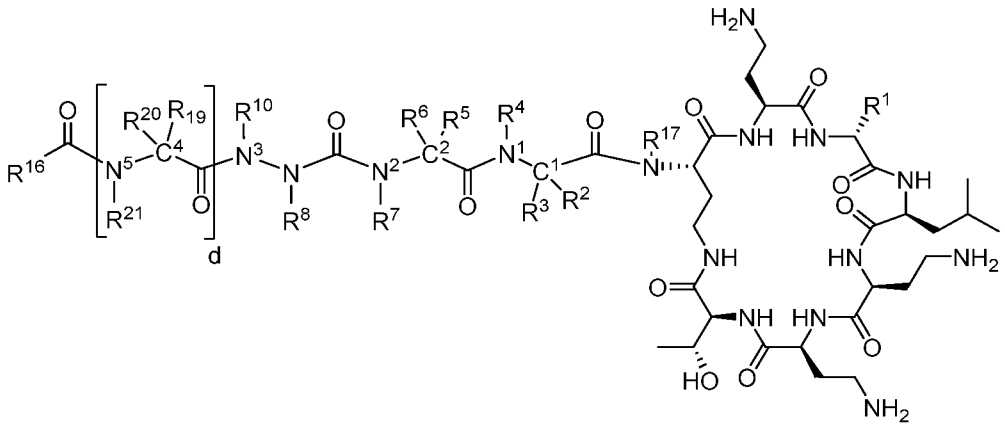
(VI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl,

or a pharmaceutically acceptable salt thereof.

64. The compound of claim 62 or 63, wherein R^6 is H or C1-C8 alkyl.

65. The compound of claim 1, wherein the compound is described by formula (VII):

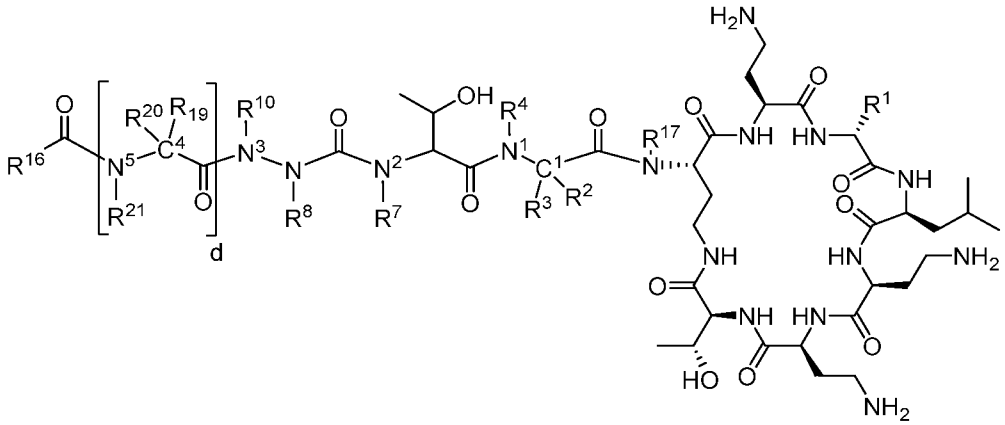


(VII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl,

or a pharmaceutically acceptable salt thereof.

66. The compound of claim 65, wherein the compound is described by formula (VII-1):

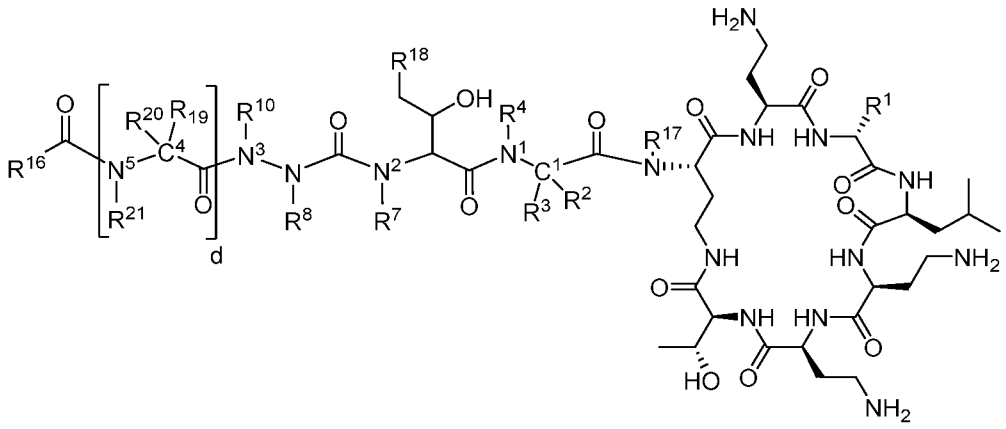


(VII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

67. The compound of claim 65, wherein the compound is described by formula (VII-2):



(VII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

68. The compound of claim 67, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

69. The compound of any one of claims 62-68, wherein R^8 is independently H or C1-C8 alkyl.

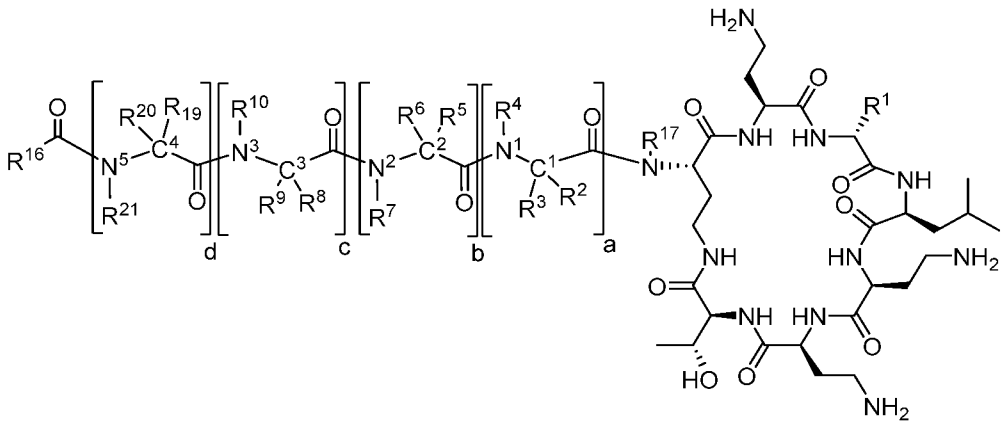
70. The compound of any one of claims 55-69, wherein R^{17} is H.

71. The compound of any one of claims 55-69, wherein R^{17} is methyl.

72. The compound of any one of claims 55-71, wherein R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$.

73. The compounds of any one of claims 55-71, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

74. The compound of claim 18, wherein the compound is described by formula (VIII):



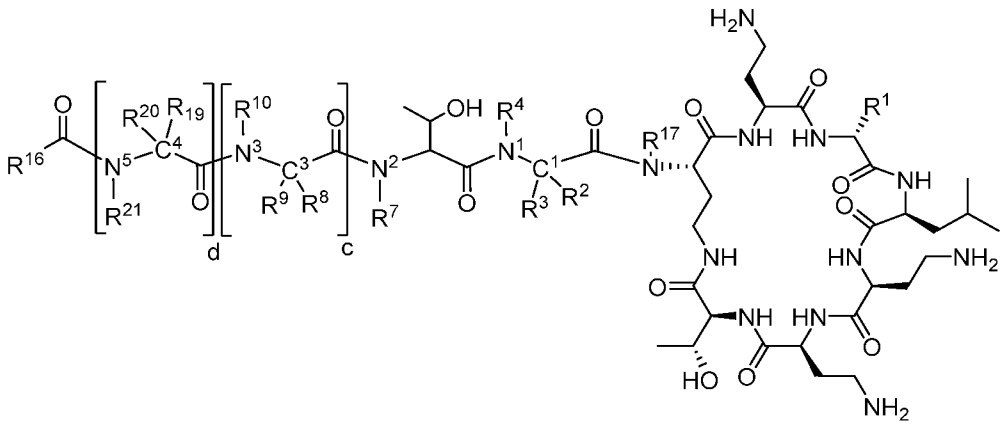
(VIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

75. The compound of claim 74, wherein the compound is described by formula (VIII-1):



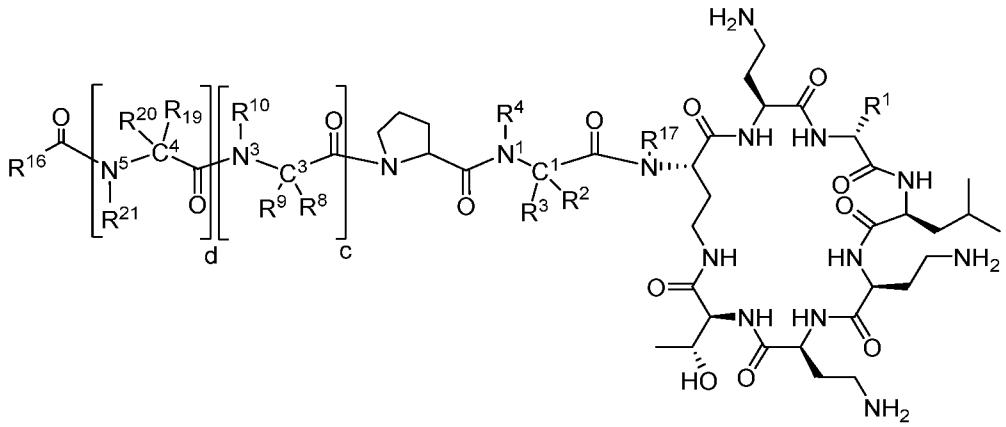
(VIII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

76. The compound of claim 74, wherein the compound is described by formula (VIII-2):



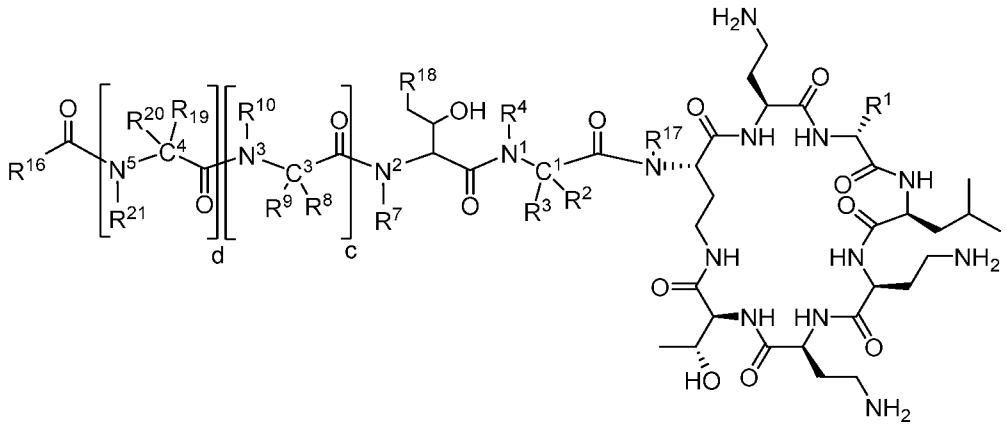
(VIII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

77. The compound of claim 74, wherein the compound is described by formula (VIII-3):



(VIII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{17} is C1-C3 alkyl or C2-C3 alkamino; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

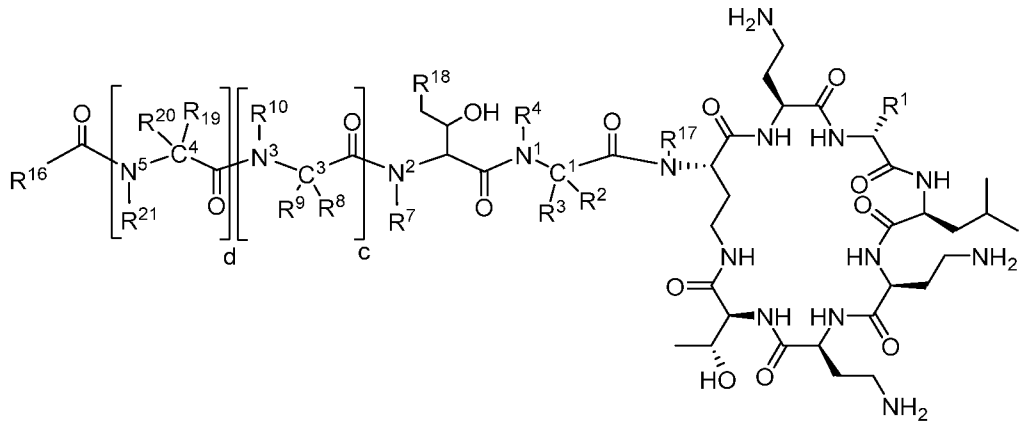
78. The compound of claim 77, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

79. The compound of any one of claims 71-78, wherein R^{17} is methyl.

80. The compound of any one of claims 74-79, wherein R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$.

81. The compounds of any one of claims 74-79, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

82. The compound of claim 27, wherein the compound is described by formula (IX):



(IX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

83. The compound of claim 82, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

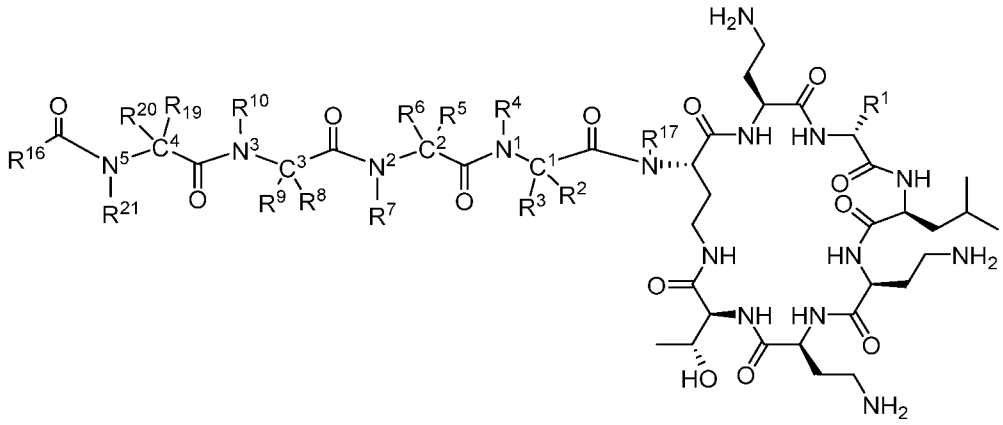
84. The compound of claim 82 or 83, wherein R^{17} is H.

85. The compound of claim 82 or 83, wherein R^{17} is methyl.

86. The compound of any one of claims 82-85, wherein R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$.

87. The compounds of any one of claims 82-85, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

88. The compound of claim 35, wherein the compound is described by formula (X):



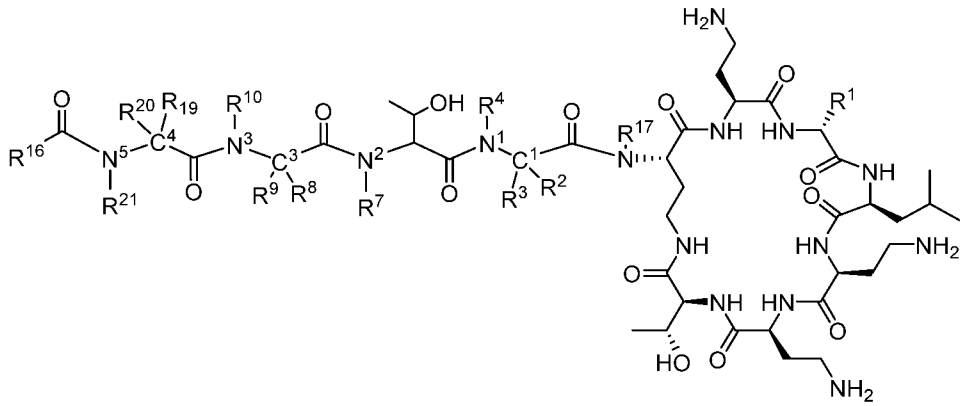
(X)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

89. The compound of claim 88, wherein the compound is described by formula (X-1):



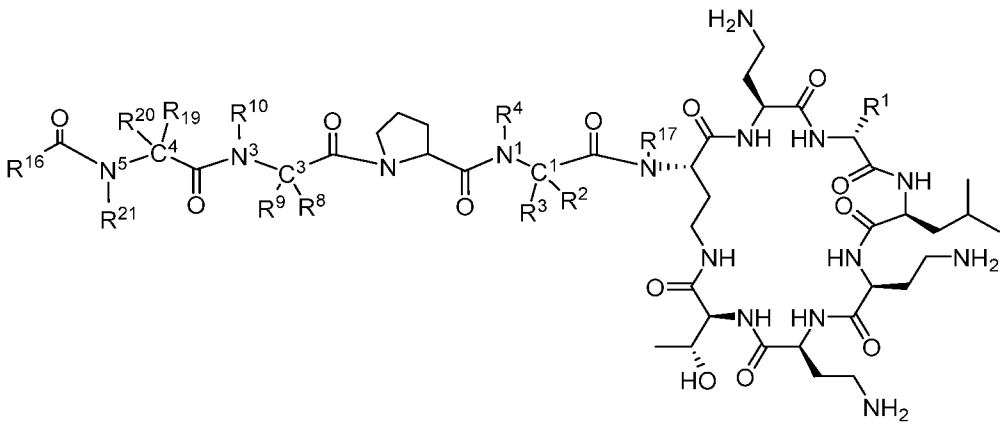
(X-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

90. The compound of claim 88, wherein the compound is described by formula (X-2):



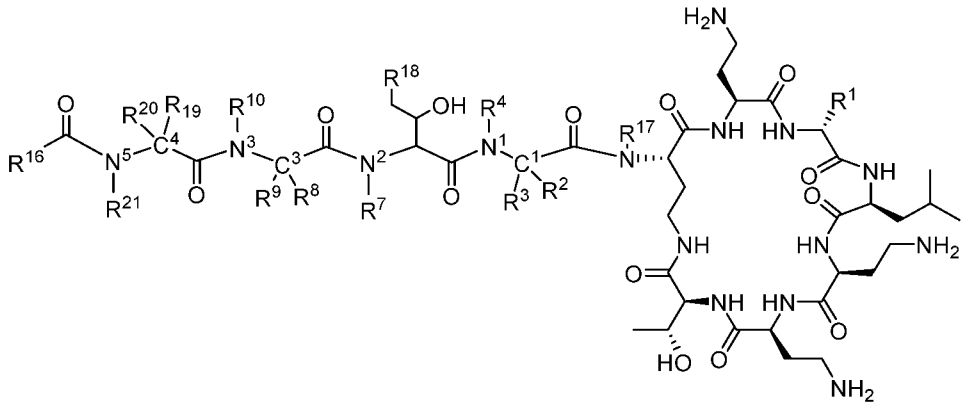
(X-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl, and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

91. The compound of claim 88, wherein the compound is described by formula (X-3):



(X-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

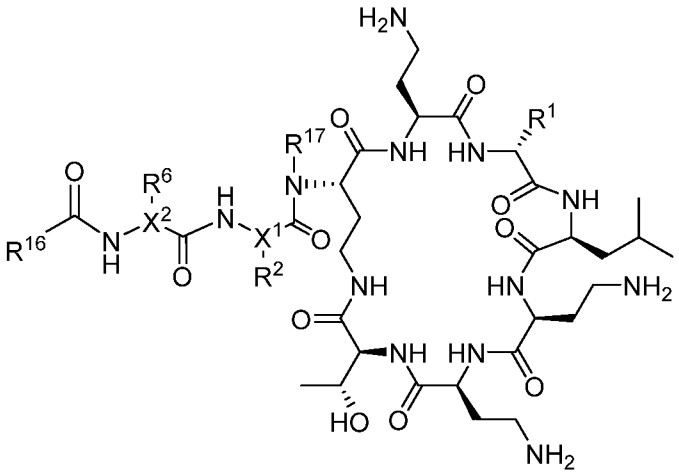
92. The compound of claim 91, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

93. The compound of any one of claims 88-92, wherein R^{17} is H.

94. The compound of any one of claims 88-92, wherein R^{17} is methyl.

95. The compound of any one of claims 88-94, wherein R^1 is optionally substituted benzyl, or $CH_2CH(CH_3)_2$.

96. The compound of claim 1, wherein the compound is described by formula (XI):



(XI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2 and R^6 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

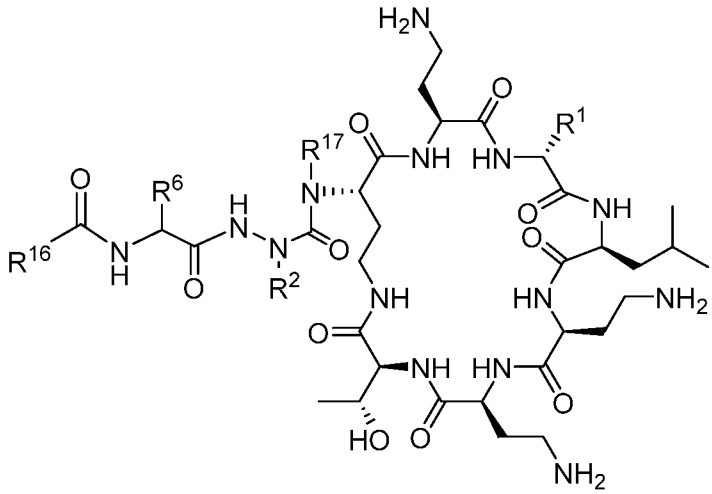
R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and

each of X^1 and X^2 is a carbon atom or a nitrogen atom,

wherein at least one of X^1 and X^2 is a nitrogen atom,

or a pharmaceutically acceptable salt thereof.

97. The compound of claim 96, wherein the compound is described by formula (XI-1):



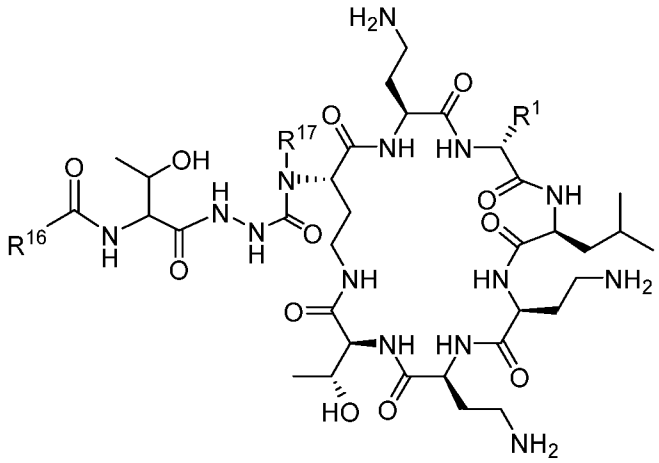
(XI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

98. The compound of claim 97, wherein the compound is described by formula (XI-2):

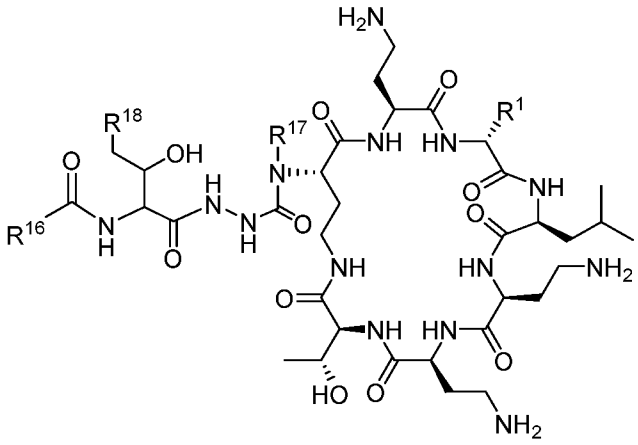


(XI-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

or a pharmaceutically acceptable salt thereof.

99. The compound of claim 97, wherein the compound is described by formula (XI-3):



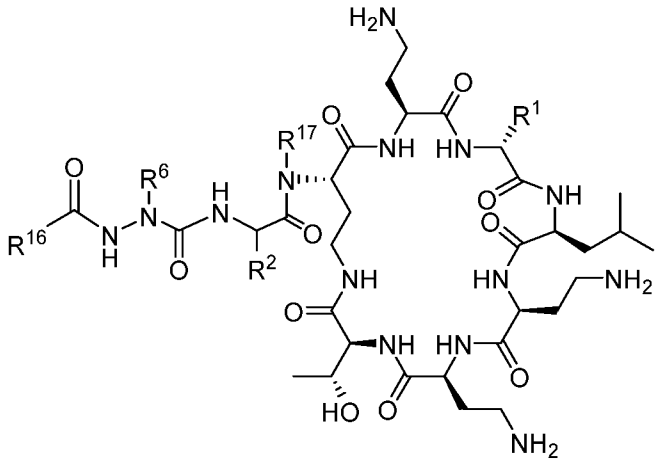
(XI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

100. The compound of claim 96, wherein the compound is described by formula (XI-4):



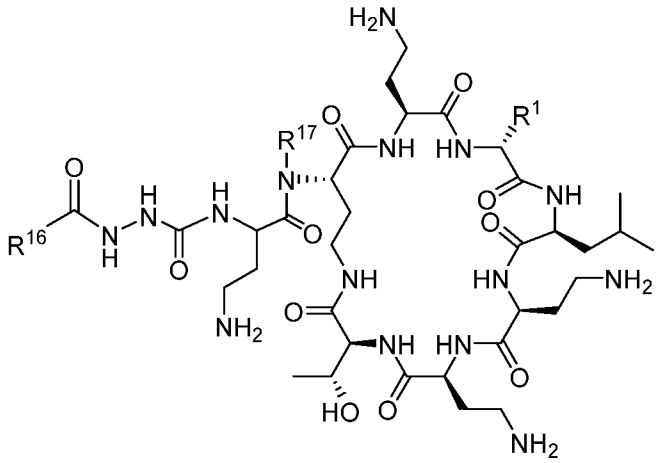
(XI-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

101. The compound of claim 100, wherein the compound is described by formula (XI-5):

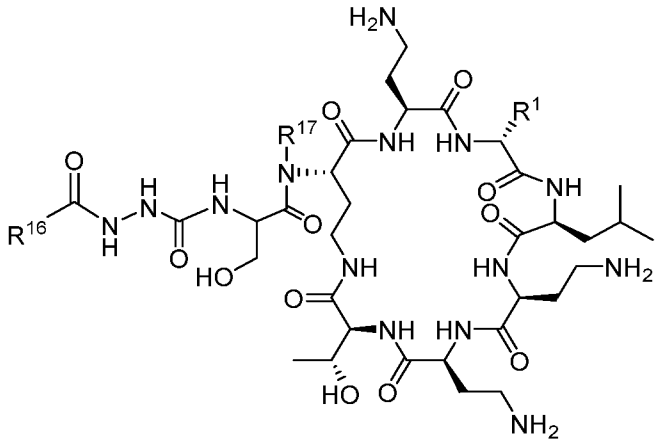


(XI-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

or a pharmaceutically acceptable salt thereof.

102. The compound of claim 100, wherein the compound is described by formula (XI-6):

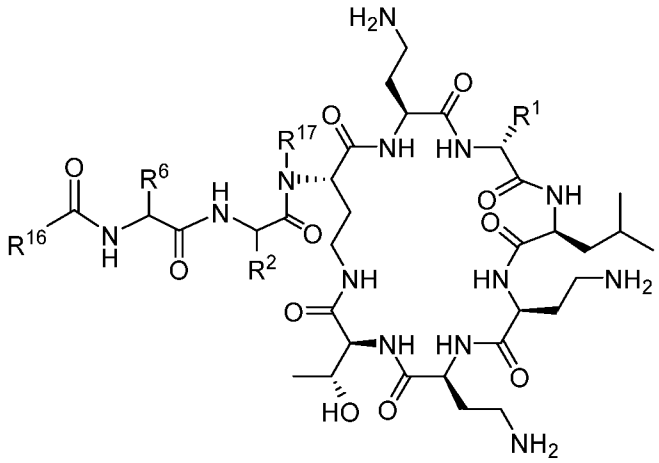


(XI-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

or a pharmaceutically acceptable salt thereof.

103. The compound of claim 18, wherein the compound is described by formula (XII):



(XII)

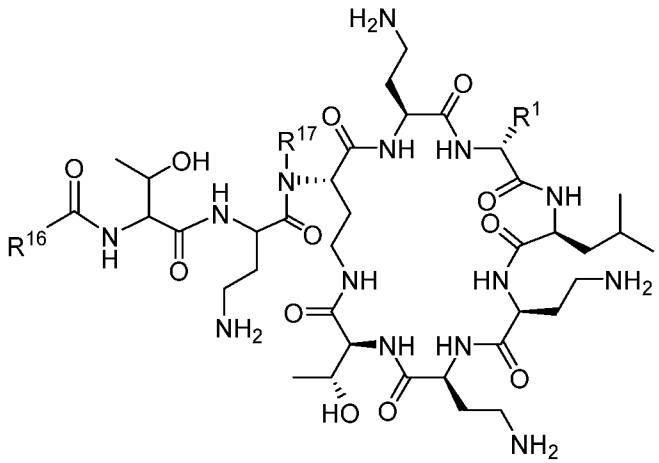
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2 and R^6 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

104. The compound of claim 103, wherein the compound is described by formula (XII-1):



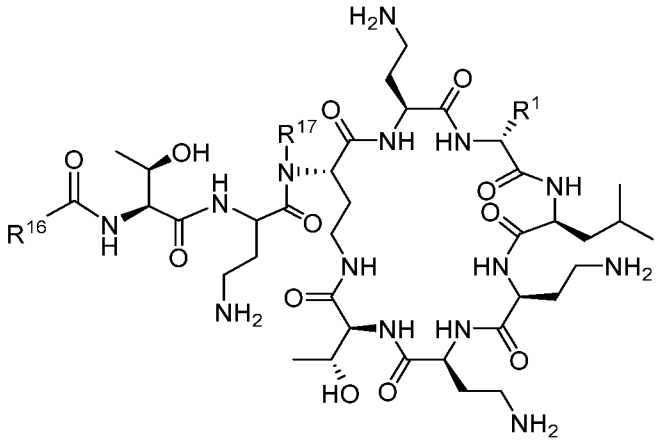
(XII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

105. The compound of claim 104, wherein the compound is described by formula (XII-2):



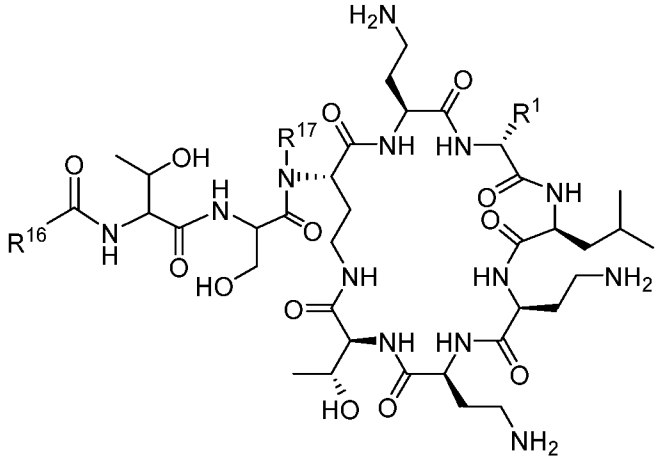
(XII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

106. The compound of claim 103, wherein the compound is described by formula (XII-3):



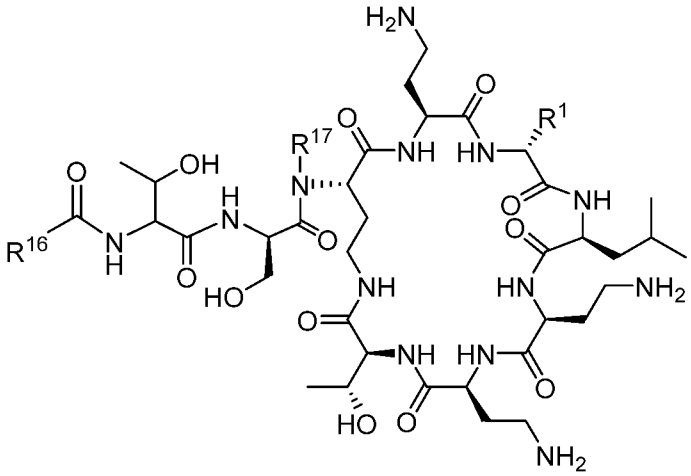
(XII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

107. The compound of claim 106, wherein the compound is described by formula (XII-4):



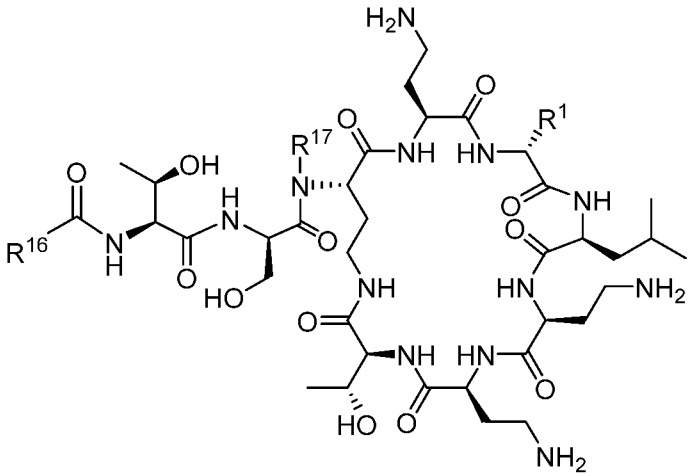
(XII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

108. The compound of claim 107, wherein the compound is described by formula (XII-5):



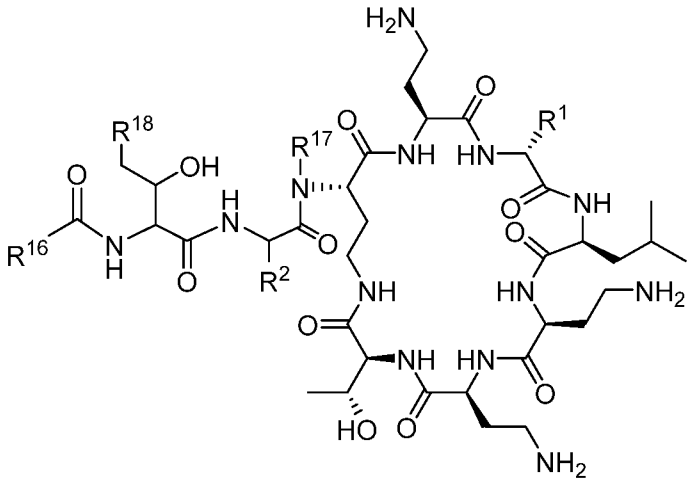
(XII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

109. The compound of claim 27, wherein the compound is described by formula (XIII):



(XIII)

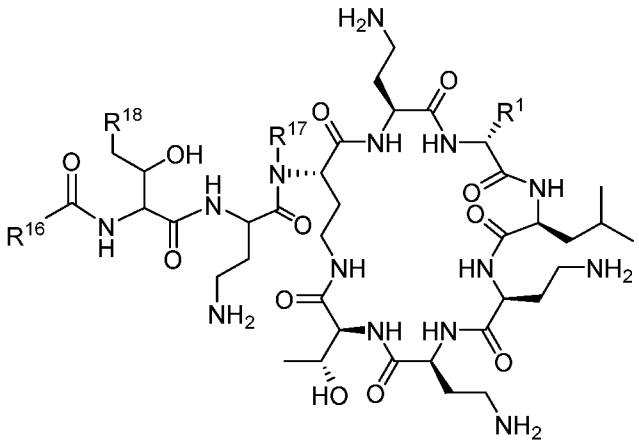
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^2 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

110. The compound of claim 109, wherein the compound is described by formula (XIII-1):



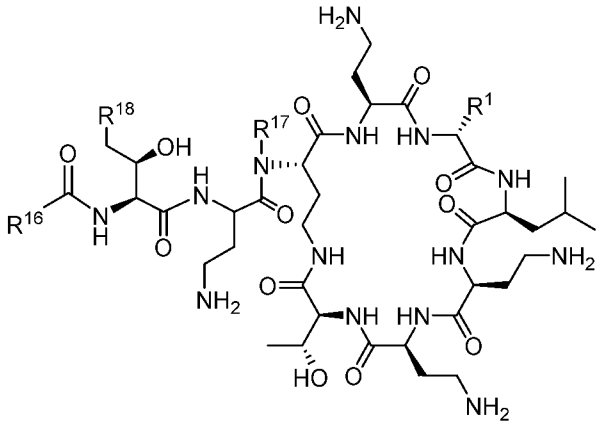
(XIII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

111. The compound of claim 110, wherein the compound is described by formula (XIII-2):



(XIII-2)

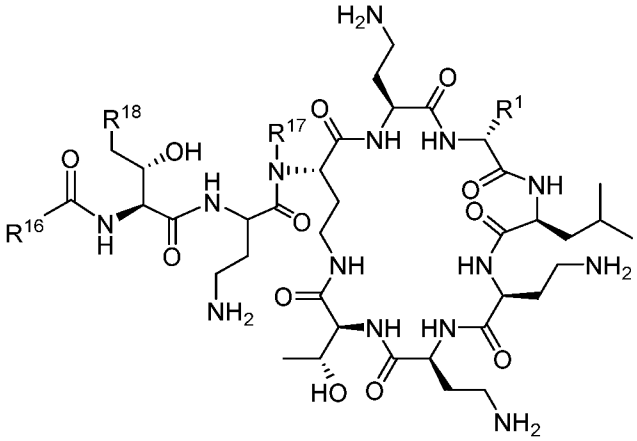
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

112. The compound of claim 110, wherein the compound is described by formula (XIII-3):



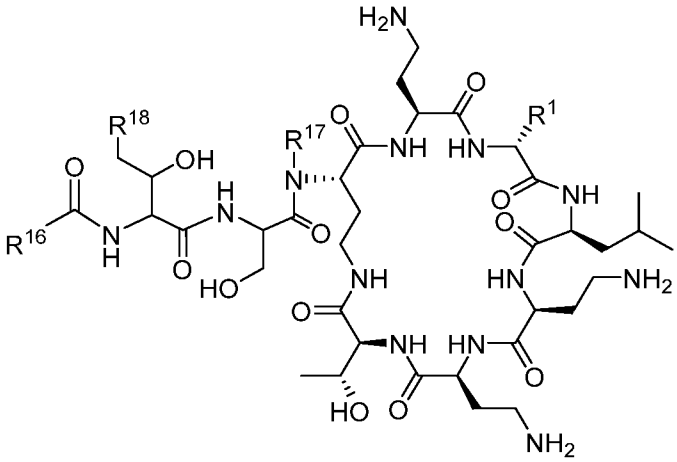
(XIII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

113. The compound of claim 109, wherein the compound is described by formula (XIII-4):



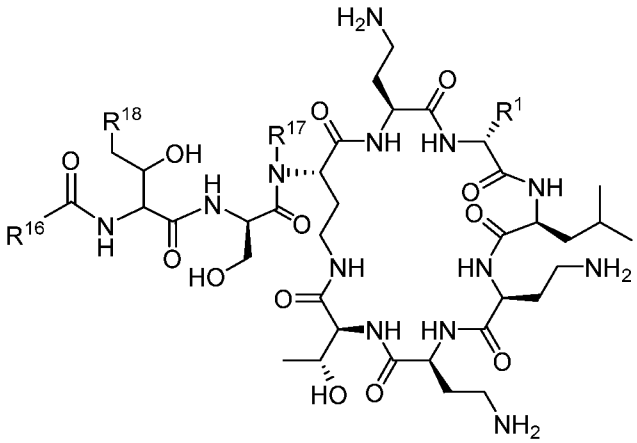
(XIII-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

114. The compound of claim 113, wherein the compound is described by formula (XIII-5):



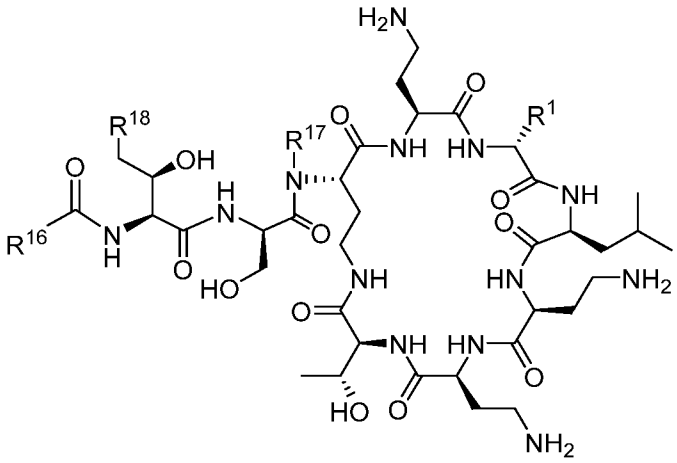
(XIII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

115. The compound of claim 114, wherein the compound is described by formula (XIII-6):



(XIII-6)

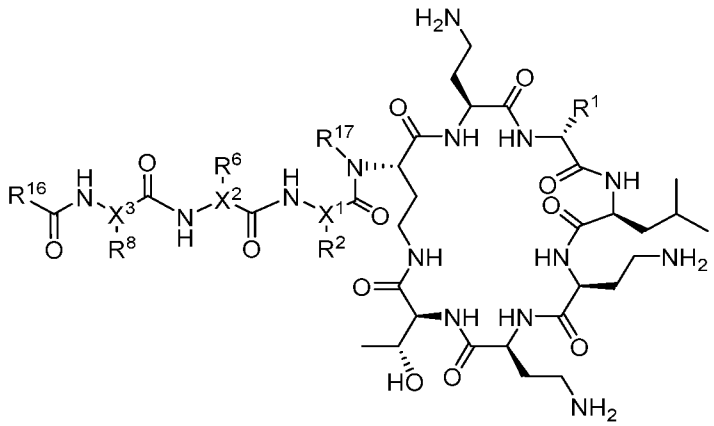
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

116. The compound of any one of claims 109-115, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

117. The compound of claim 1, wherein the compound is described by formula (XIV):



(XIV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

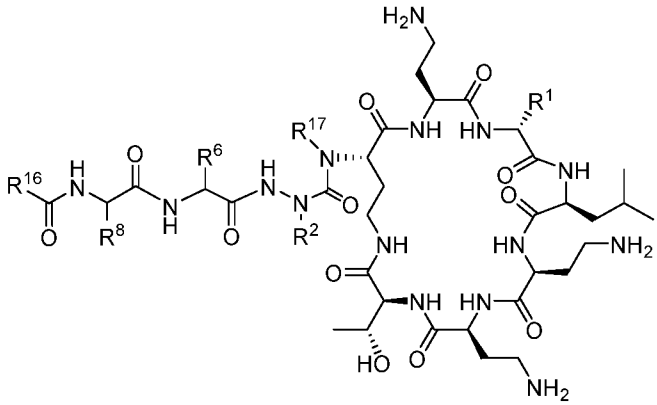
each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

each of X^1, X^2, and X^3 is, independently, a carbon atom or a nitrogen atom,

wherein at least one of X^1, X^2, and X^3 is a nitrogen atom,

or a pharmaceutically acceptable salt thereof.

118. The compound of claim 117, wherein the compound is described by formula (XIV-1):



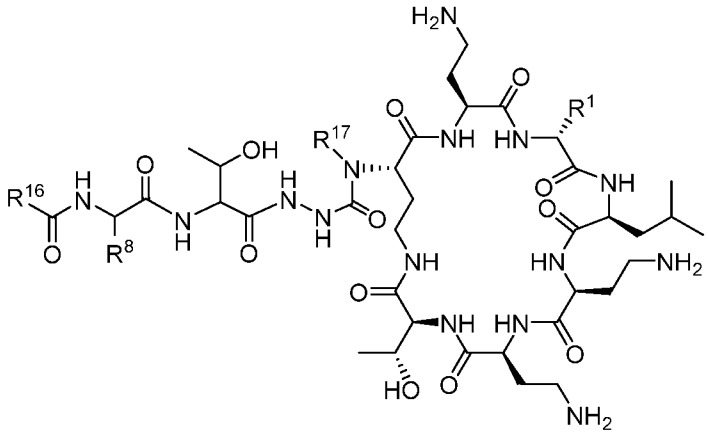
(XIV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

119. The compound of claim 118, wherein the compound is described by formula (XIV-2):



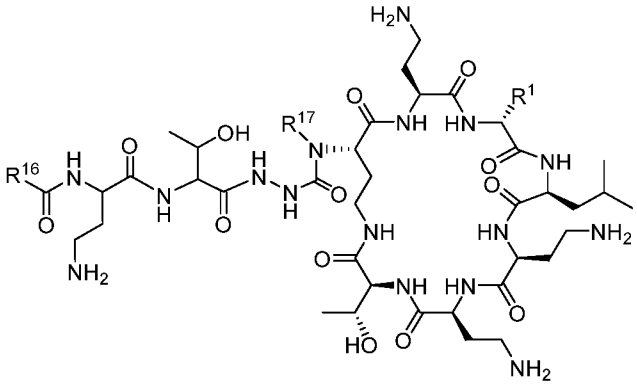
(XIV-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^8 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

120. The compound of claim 119, wherein the compound is described by formula (XIV-3):

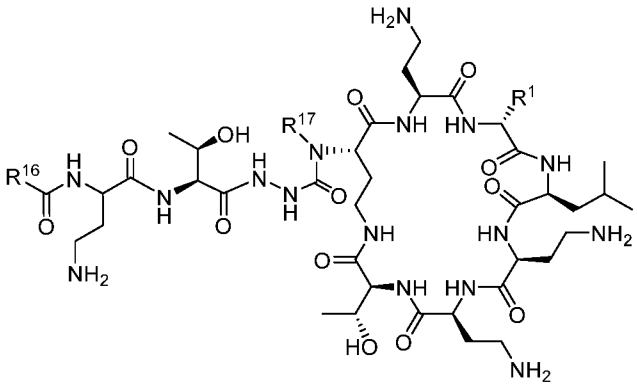


(XIV-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

121. The compound of claim 120, wherein the compound is described by formula (XIV-4):

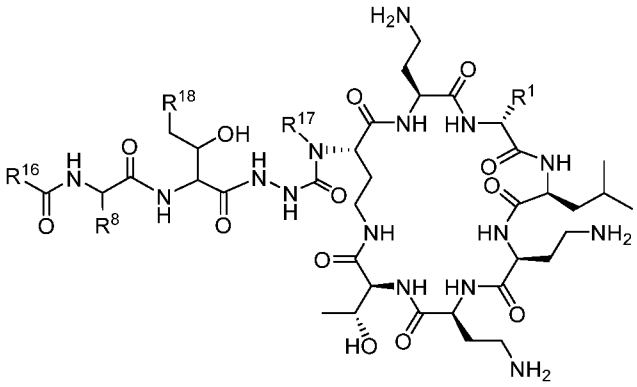


(XIV-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

122. The compound of claim 118, wherein the compound is described by formula (XIV-5):



(XIV-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

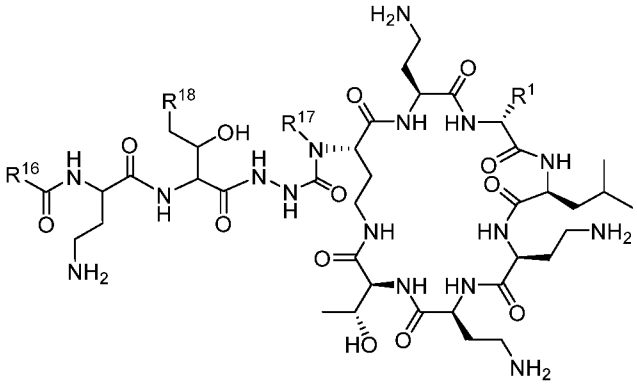
R^8 is H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

123. The compound of claim 122, wherein the compound is described by formula (XIV-6):



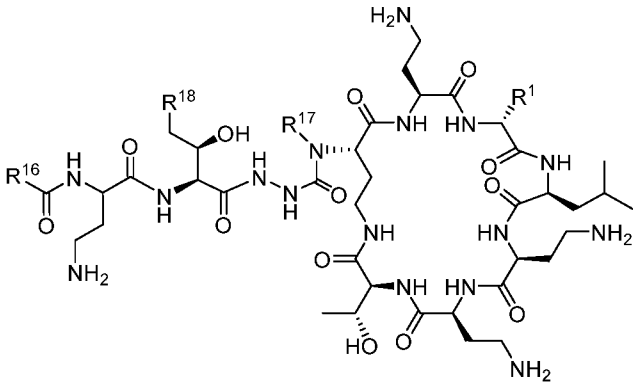
(XIV-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

124. The compound of claim 123, wherein the compound is described by formula (XIV-7):



(XIV-7)

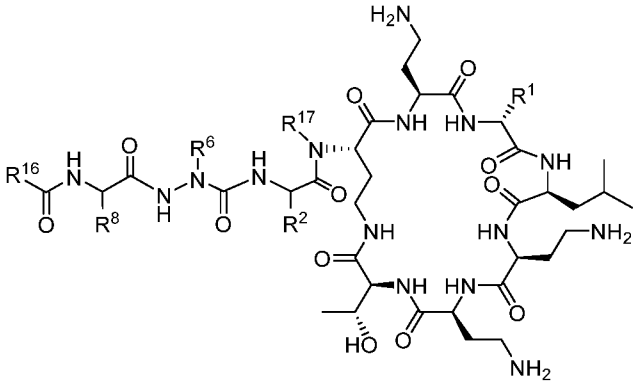
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

125. The compound of any one of claims 122-124, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

126. The compound of claim 117, wherein the compound is described by formula (XIV-8):



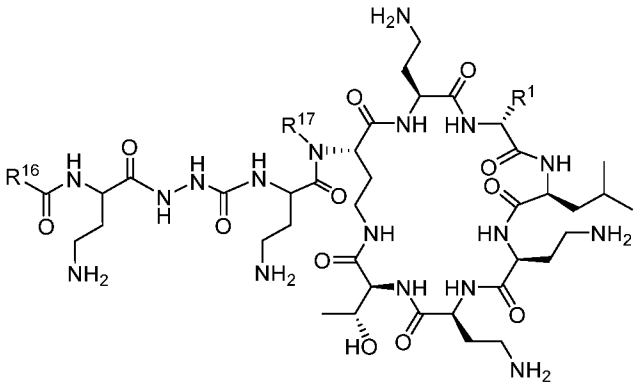
(XIV-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

127. The compound of claim 126, wherein the compound is described by formula (XIV-9):

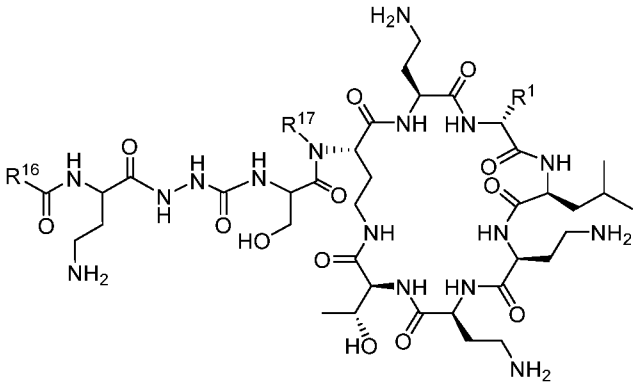


(XIV-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

128. The compound of claim 126, wherein the compound is described by formula (XIV-10):

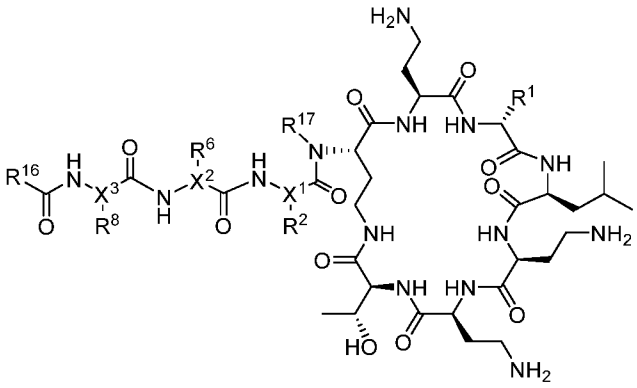


(XIV-10)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

129. The compound of claim 18, wherein the compound is described by formula (XV):



(XV)

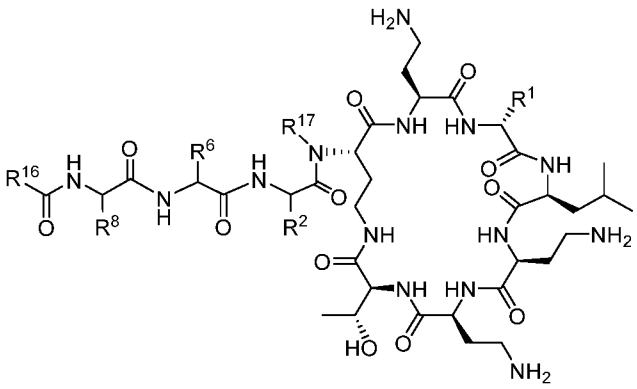
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

130. The compound of claim 129, wherein the compound is described by formula (XV-1):



(XV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

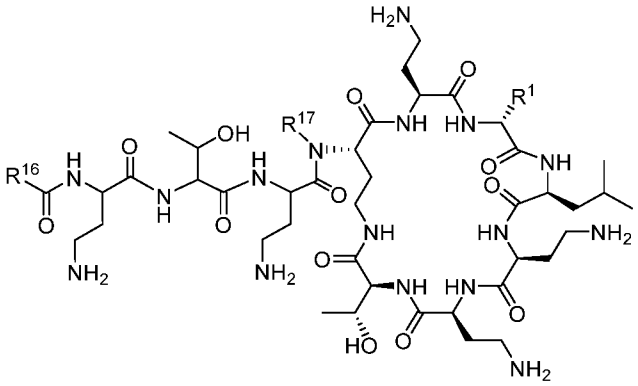
each of R^2, R^6, and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally

substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

131. The compound of claim 130, wherein the compound is described by formula (XV-2):



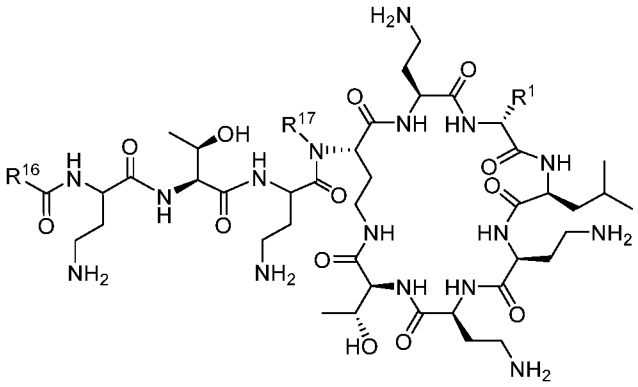
(XV-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

132. The compound of claim 131, wherein the compound is described by formula (XV-3):



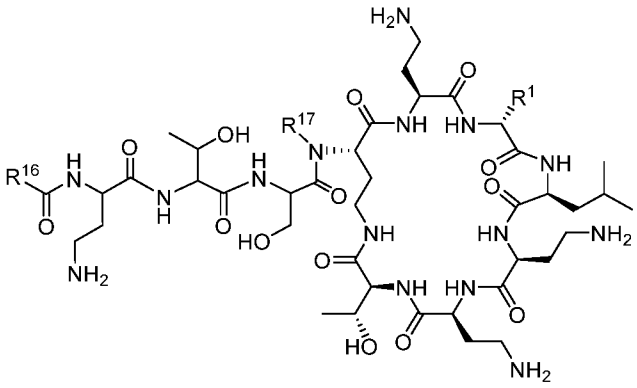
(XV-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

133. The compound of claim 130, wherein the compound is described by formula (XV-4):



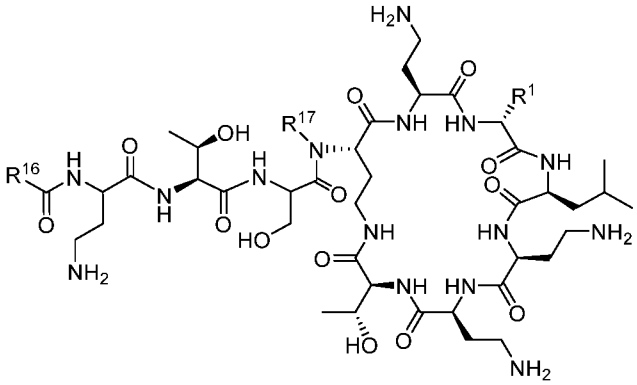
(XV-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

134. The compound of claim 131, wherein the compound is described by formula (XV-5):



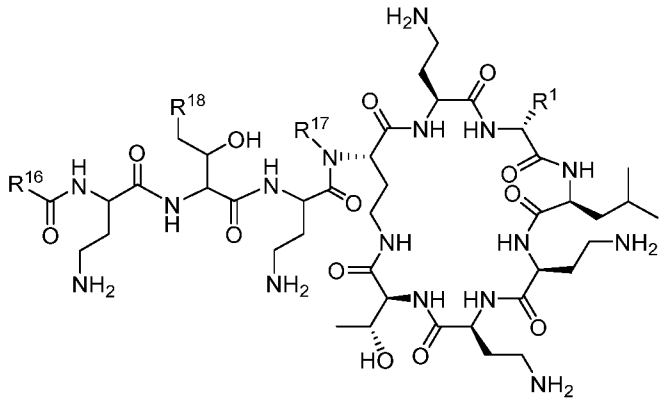
(XV-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

135. The compound of claim 130, wherein the compound is described by formula (XV-6):



(XV-6)

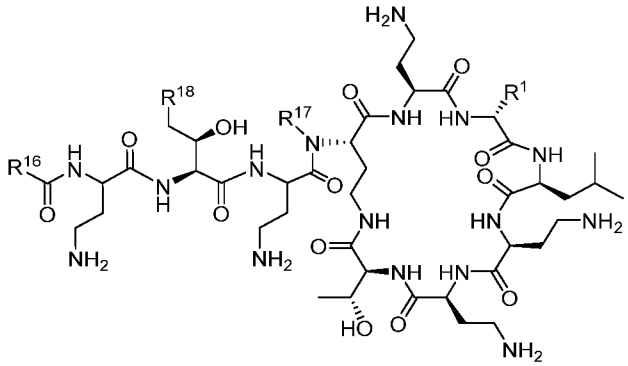
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

136. The compound of claim 135, wherein the compound is described by formula (XV-7):



(XV-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

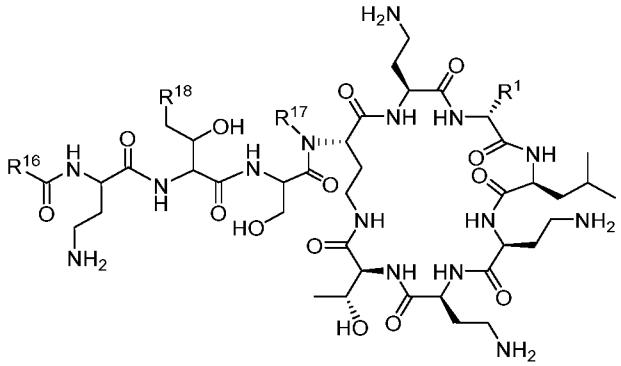
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

137. The compound of claim 130, wherein the compound is described by formula (XV-8):



(XV-8)

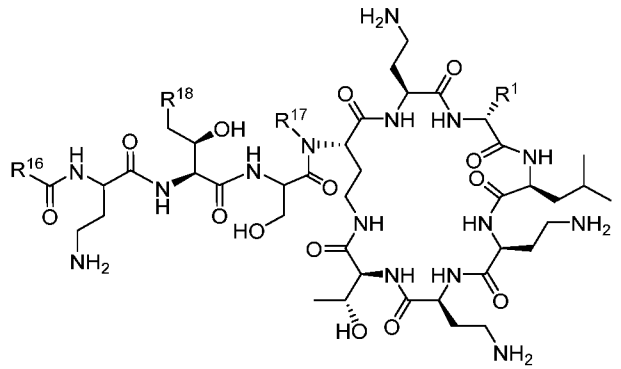
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

138. The compound of claim 137, wherein the compound is described by formula (XV-9):



(XV-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

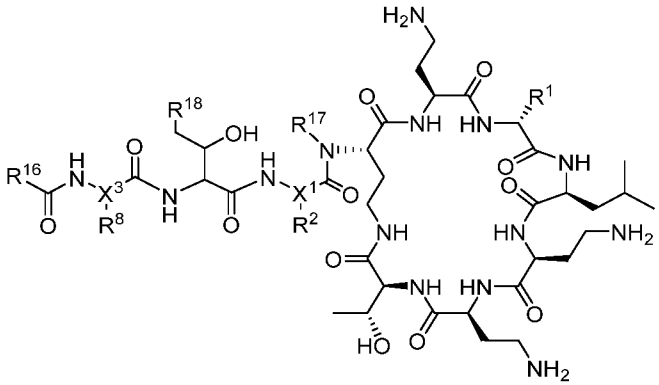
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof

139. The compound of any one of claims 135-138, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

140. The compound of claim 27, wherein the compound is described by formula (XVI):



(XVI)

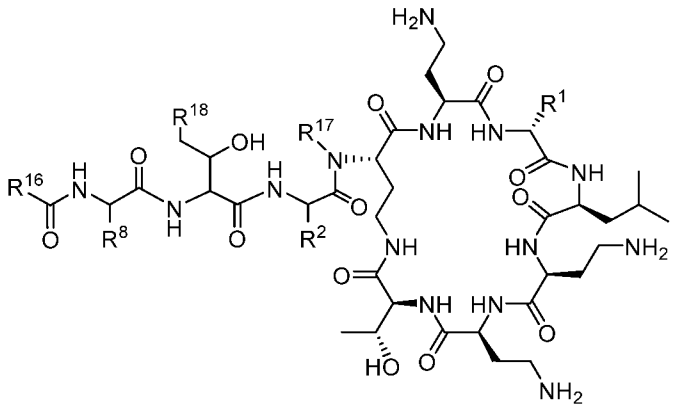
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2 and R^8 is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

141. The compound of claim 140, wherein the compound is described by formula (XVI-1):



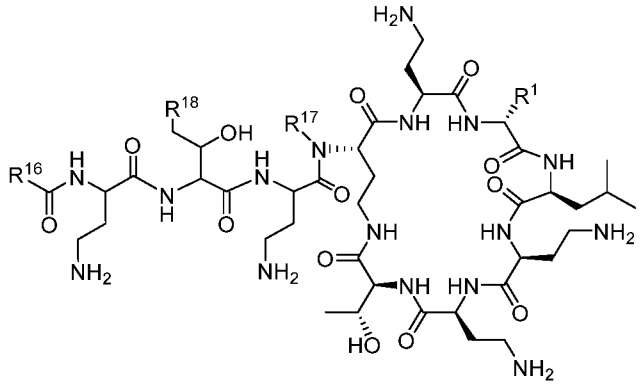
(XVI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

142. The compound of claim 140, wherein the compound is described by formula (XVI-2):



(XVI-2)

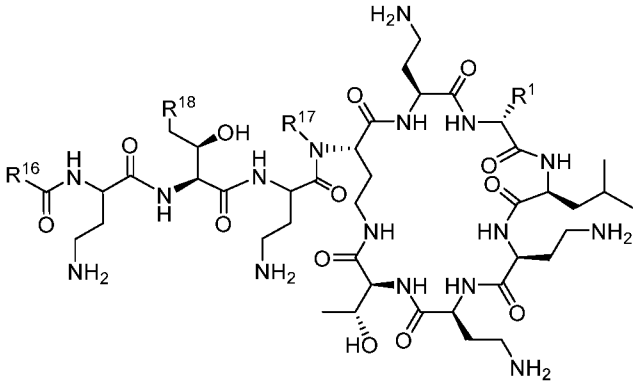
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20

heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

143. The compound of claim 142, wherein the compound is described by formula (XVI-3):



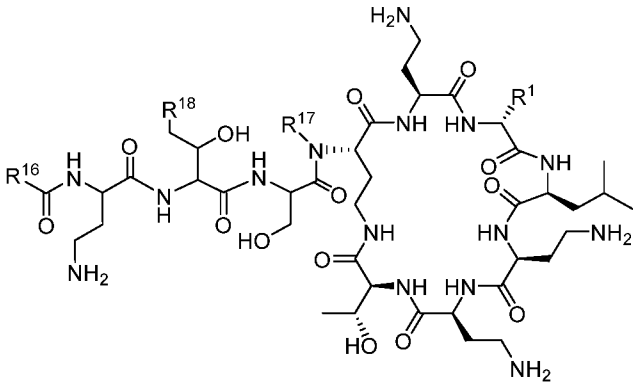
(XVI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

144. The compound of claim 140, wherein the compound is described by formula (XVI-4):



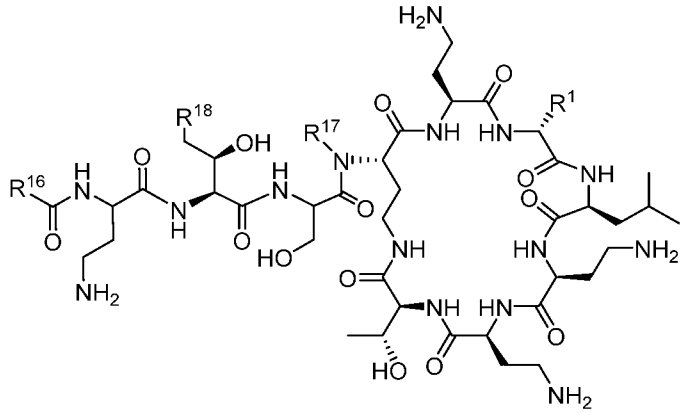
(XVI-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

145. The compound of claim 144, wherein the compound is described by formula (XVI-5):



(XVI-5)

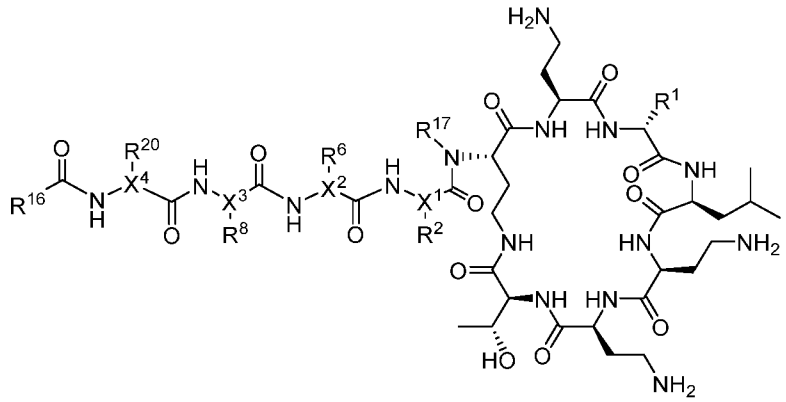
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof

146. The compound of any one of claims 140-145, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

147. The compound of claim 1, wherein the compound is described by formula (XVII):



(XVII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

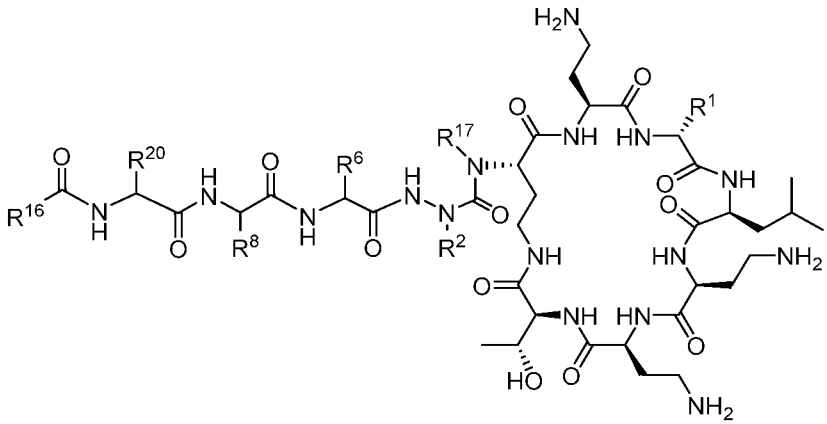
each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

each of X^1, X^2, and X^3 is, independently, a carbon atom or a nitrogen atom,

wherein at least one of X^1, X^2, and X^3 is a nitrogen atom,

or a pharmaceutically acceptable salt thereof.

148. The compound of claim 147, wherein the compound is described by formula (XVII-1):



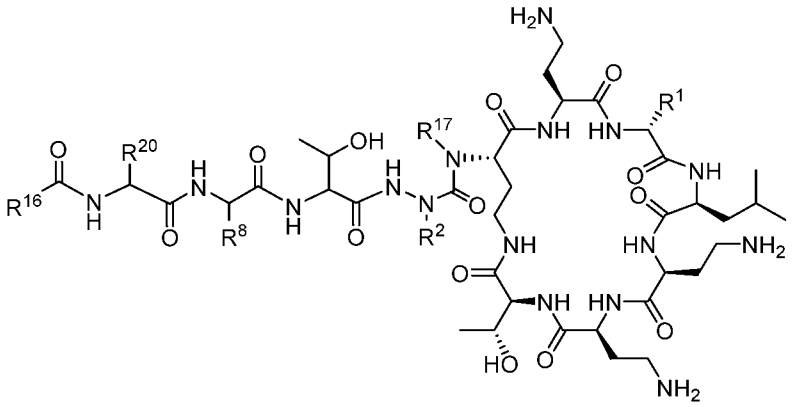
(XVII-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

149. The compound of claim 148, wherein the compound is described by formula (XVII-2):



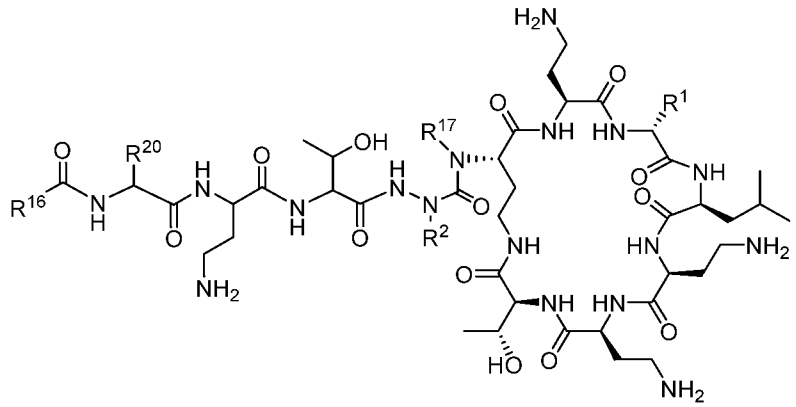
(XVII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

150. The compound of claim 149, wherein the compound is described by formula (XVII-3):



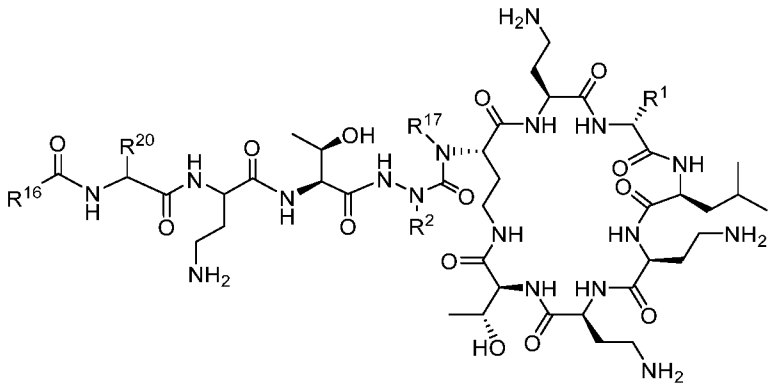
(XVII-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

151. The compound of claim 150, wherein the compound is described by formula (XVII-4):



(XVII-4)

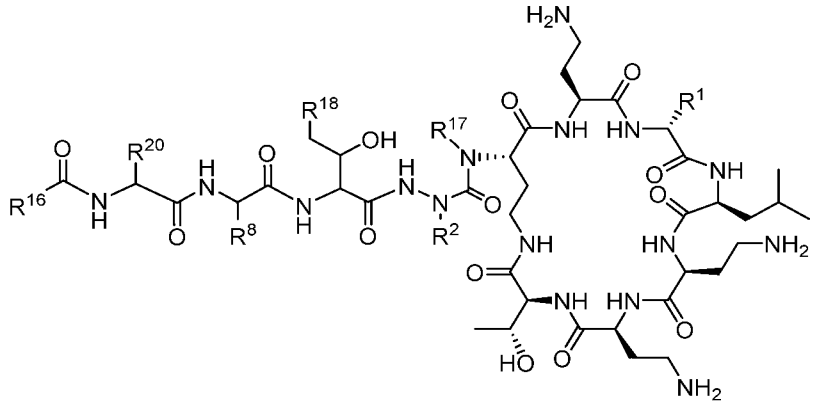
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-

C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

152. The compound of claim 148, wherein the compound is described by formula (XVII-5):



(XVII-5)

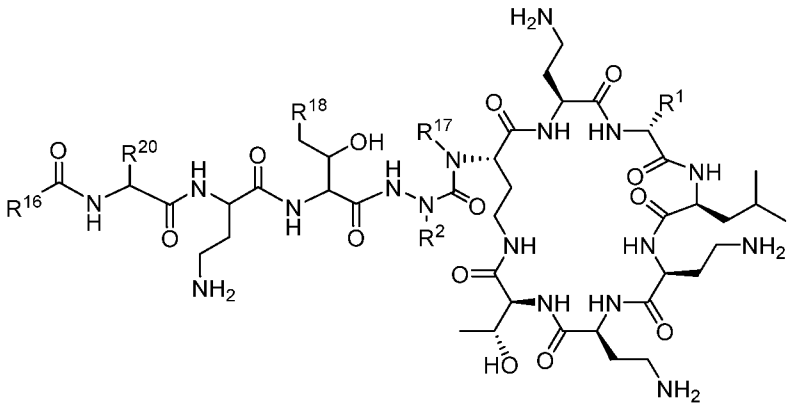
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

153. The compound of claim 152, wherein the compound is described by formula (XVII-6):



(XVII-6)

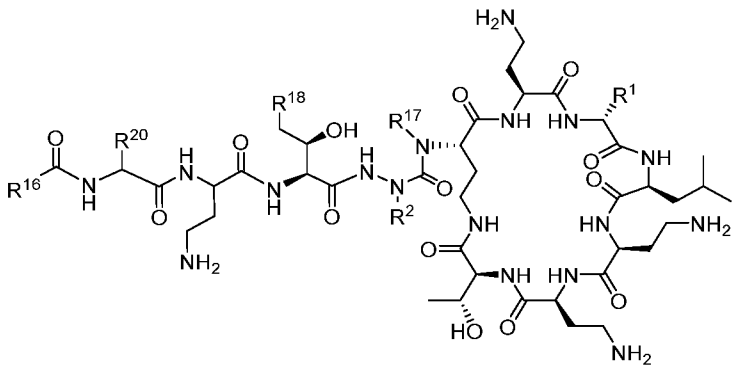
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a positively charged moiety, a lipophilic moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

154. The compound of claim 153, wherein the compound is described by formula (XVII-7):



(XVII-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

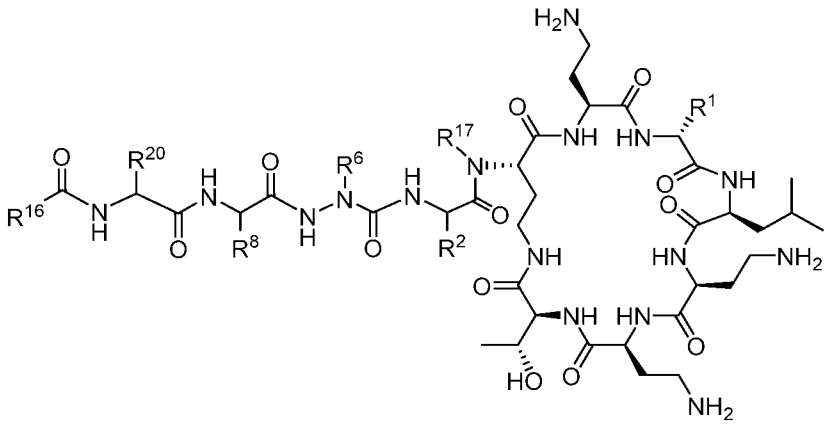
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

155. The compound of any one of claims 152-154, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

156. The compound of claim 147, wherein the compound is described by formula (XVII-8):



(XVII-8)

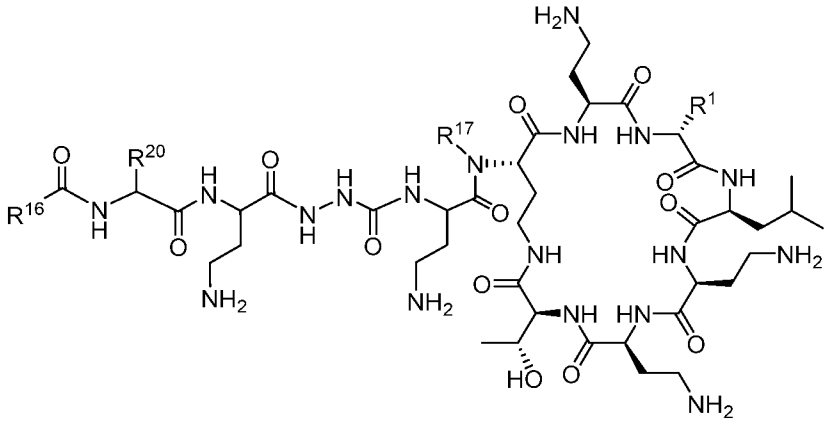
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally

substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

157. The compound of claim 156, wherein the compound is described by formula (XVII-9):



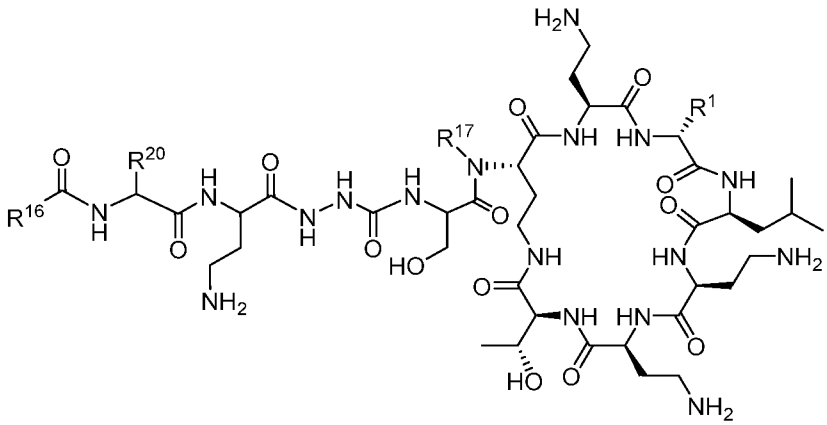
(XVII-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

158. The compound of claim 156, wherein the compound is described by formula (XVII-10):



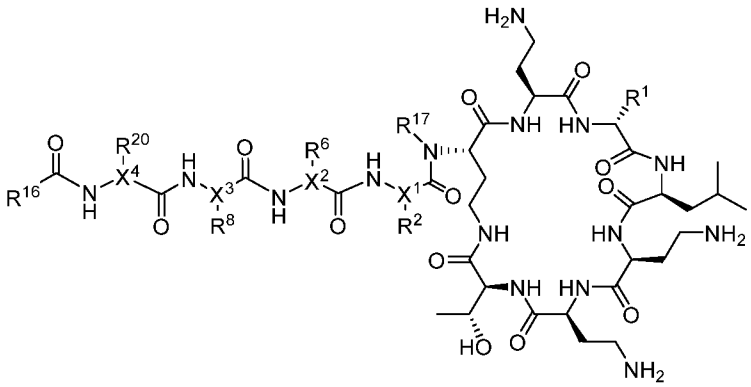
(XVII-10)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

159. The compound of claim 18, wherein the compound is described by formula (XVIII):



(XVIII)

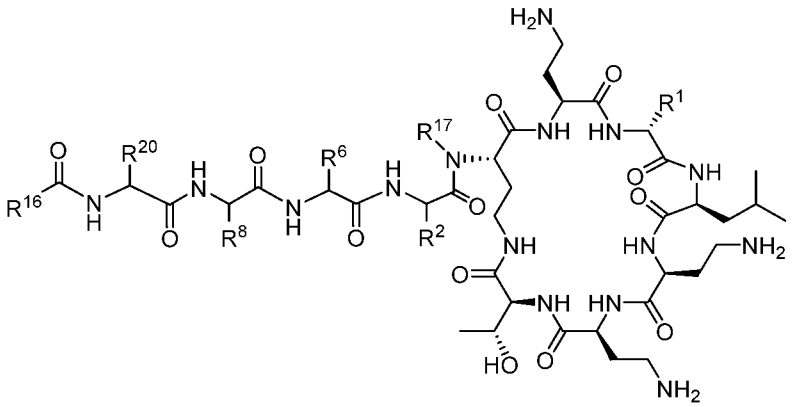
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^6, R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

160. The compound of claim 159, wherein the compound is described by formula (XVIII-1):



(XVIII-1)

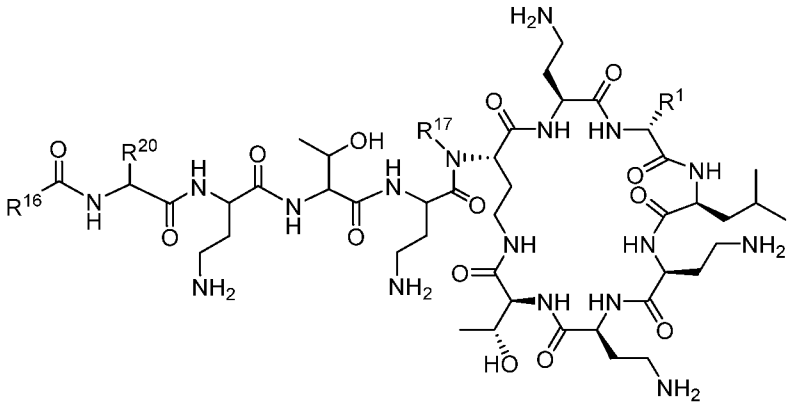
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

161. The compound of claim 160, wherein the compound is described by formula (XVIII-2):



(XVIII-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

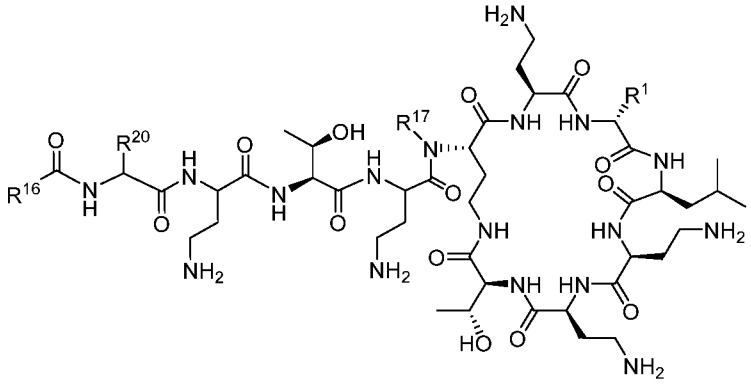
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally

substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

162. The compound of claim 161, wherein the compound is described by formula (XVIII-3):



(XVIII-3)

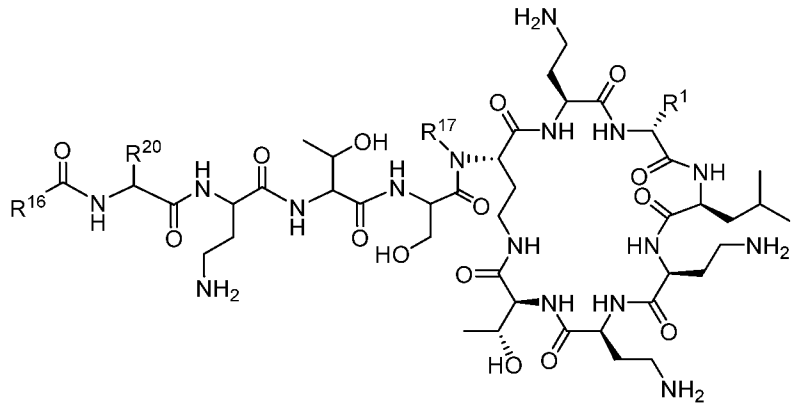
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

163. The compound of claim 160, wherein the compound is described by formula (XVIII-4):



(XVIII-4)

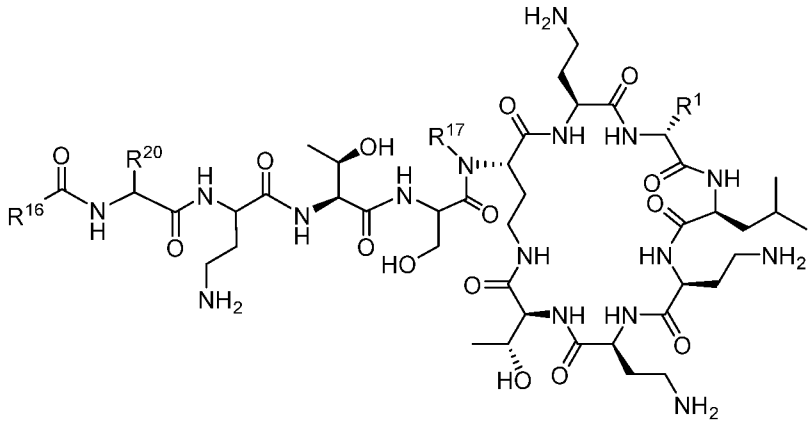
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

164. The compound of claim 161, wherein the compound is described by formula (XVIII-5):



(XVIII-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

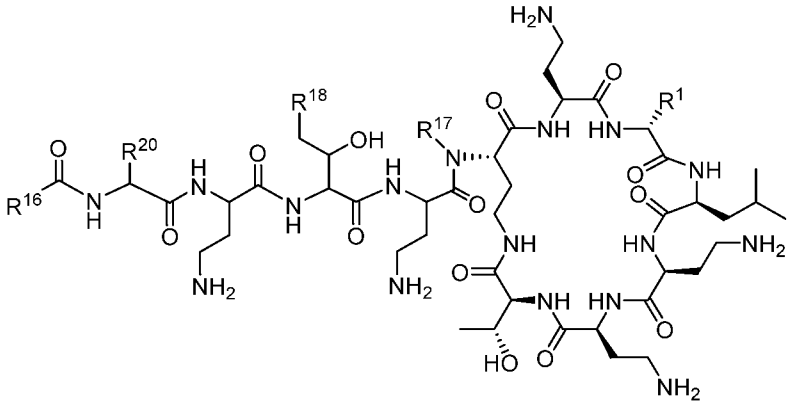
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally

substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

165. The compound of claim 160, wherein the compound is described by formula (XVIII-6):



(XVIII-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

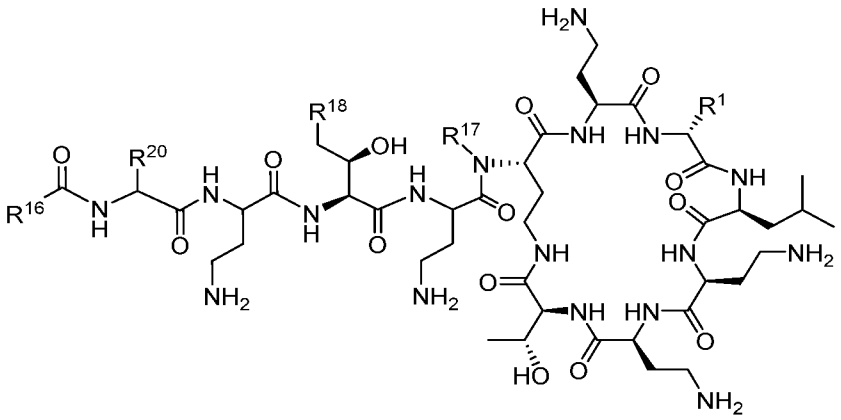
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

166. The compound of claim 165, wherein the compound is described by formula (XVIII-7):



(XVIII-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

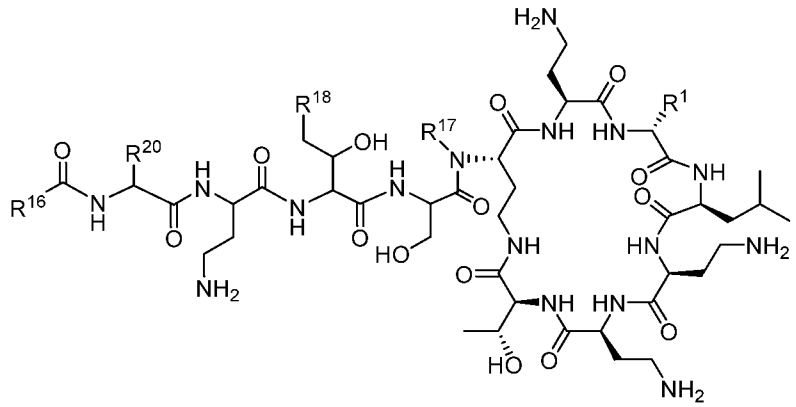
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

167. The compound of claim 160, wherein the compound is described by formula (XVIII-8):



(XVIII-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

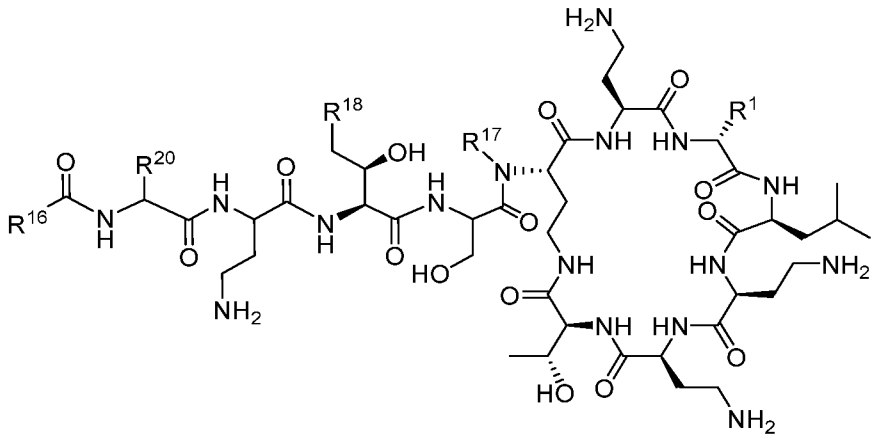
R^{20} is a lipophilic moiety, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof.

168. The compound of claim 167, wherein the compound is described by formula (XVIII-9):



(XVIII-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

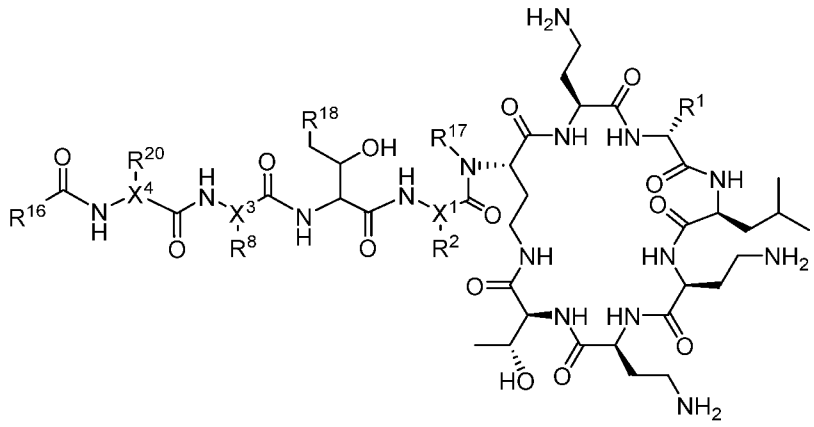
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino,

or a pharmaceutically acceptable salt thereof

169. The compound of any one of claims 165-168, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

170. The compound of claim 27, wherein the compound is described by formula (XIX):



(XIX)

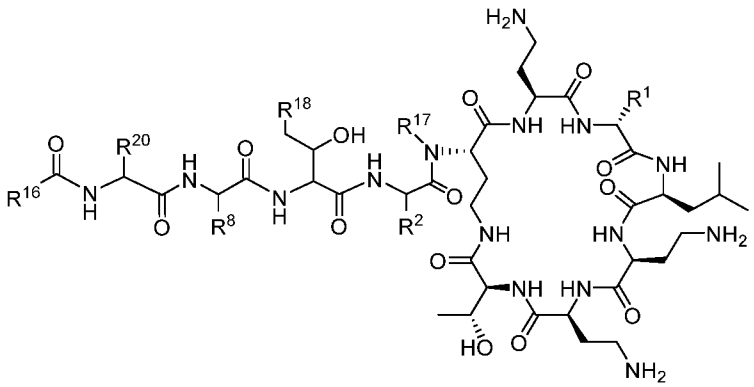
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^8, and R^{20} is, a lipophilic moiety, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

171. The compound of claim 170, wherein the compound is described by formula (XIX-1):



(XIX-1)

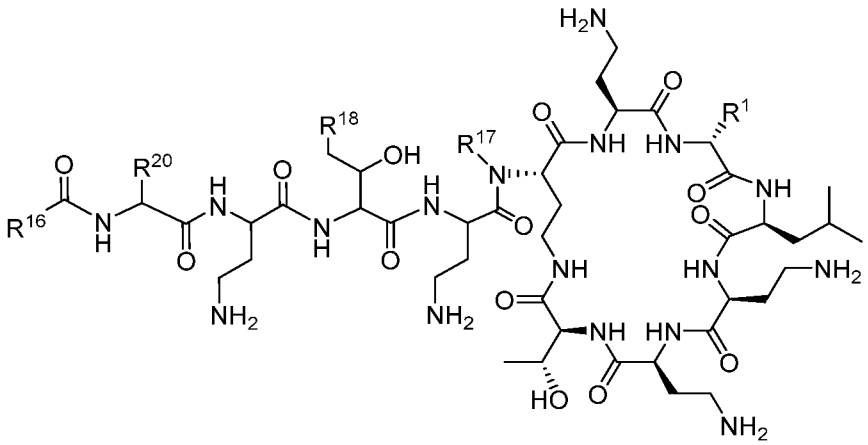
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^8, and R^{20} is, a lipophilic moiety, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

172. The compound of claim 170, wherein the compound is described by formula (XIX-2):



(XIX-2)

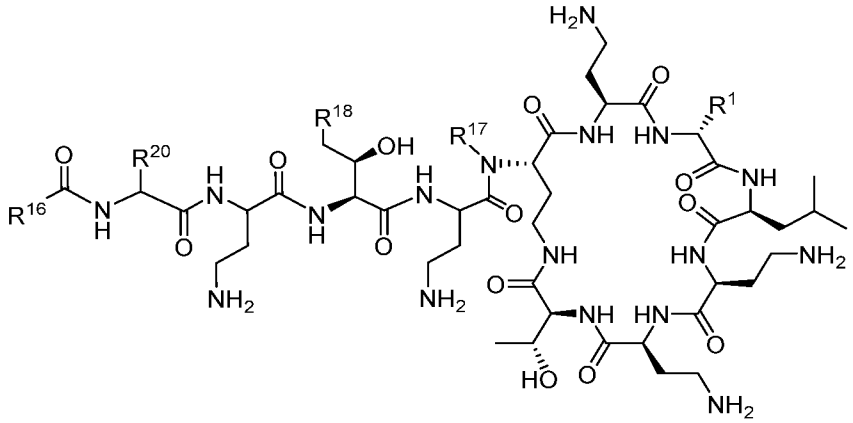
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is a lipophilic moiety, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

173. The compound of claim 172, wherein the compound is described by formula (XIX-3):



(XIX-3)

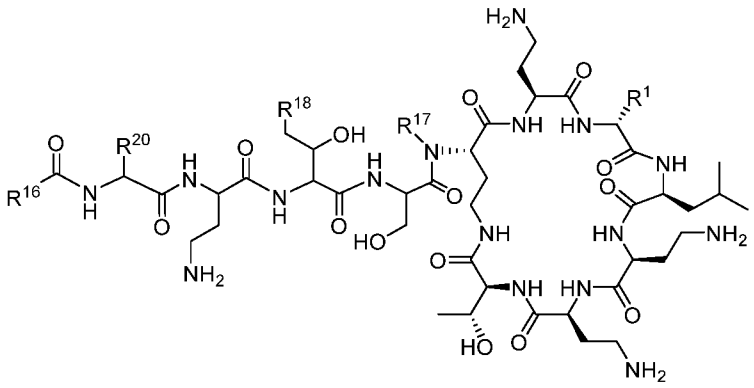
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is a lipophilic moiety, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

174. The compound of claim 170, wherein the compound is described by formula (XIX-4):



(XIX-4)

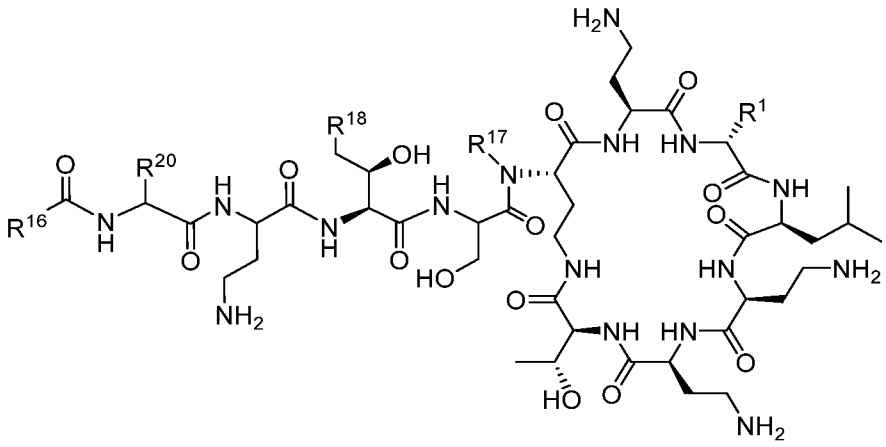
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is a lipophilic moiety, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof.

175. The compound of claim 174, wherein the compound is described by formula (XIX-5):



(XIX-5)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

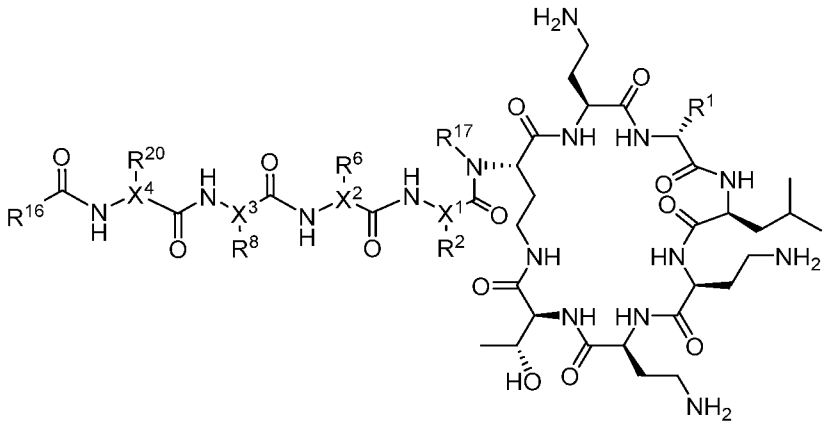
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

or a pharmaceutically acceptable salt thereof

176. The compound of any one of claims 170-175, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

177. The compound of claim 35, wherein the compound is described by formula (XX):



(XX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

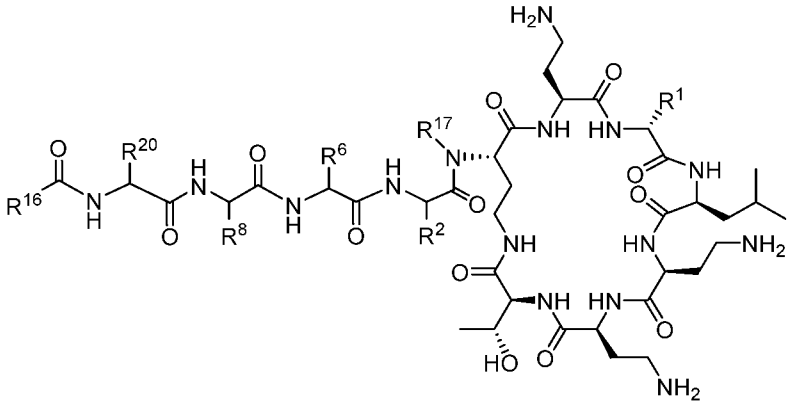
each of R^2, R^6, R^8 and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally

substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

178. The compound of claim 177, wherein the compound is described by formula (XX-1):



(XX-1)

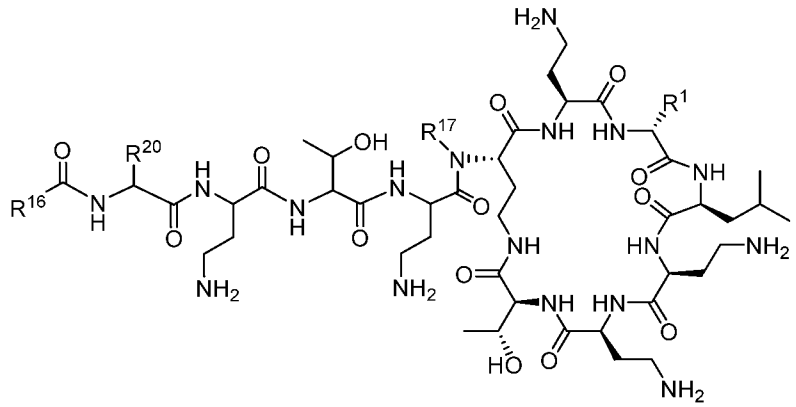
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

each of R^2, R^6, R^8, and R^{20} is, independently, a lipophilic moiety, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

179. The compound of claim 178, wherein the compound is described by formula (XX-2):



(XX-2)

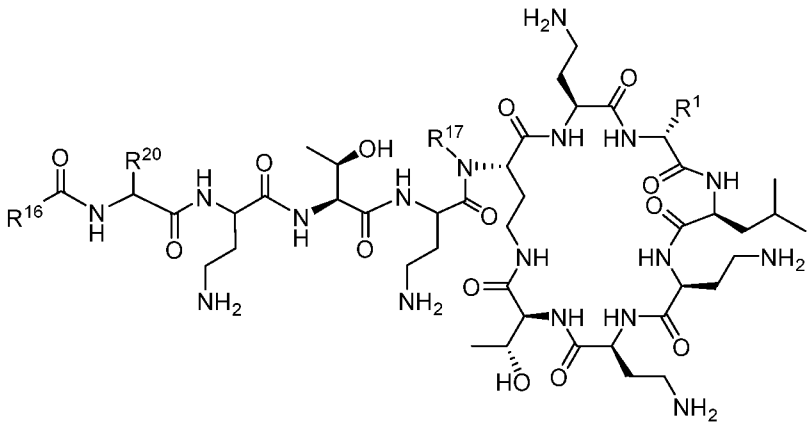
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

180. The compound of claim 179, wherein the compound is described by formula (XX-3):



(XX-3)

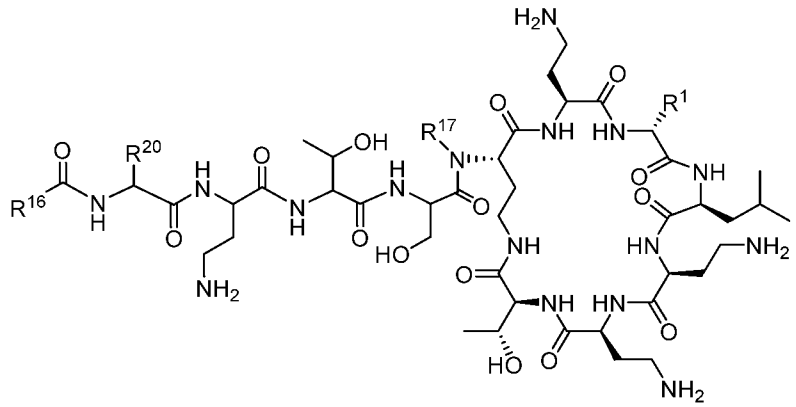
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

181. The compound of claim 178, wherein the compound is described by formula (XX-4):



(XX-4)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

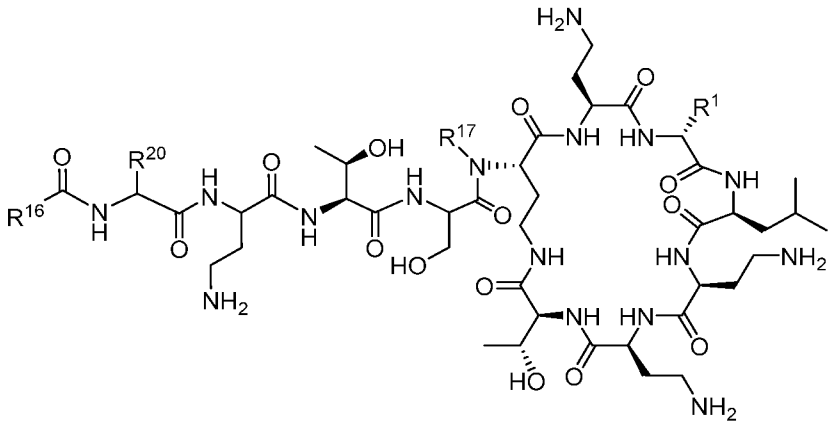
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-

C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

182. The compound of claim 179, wherein the compound is described by formula (XX-5):



(XX-5)

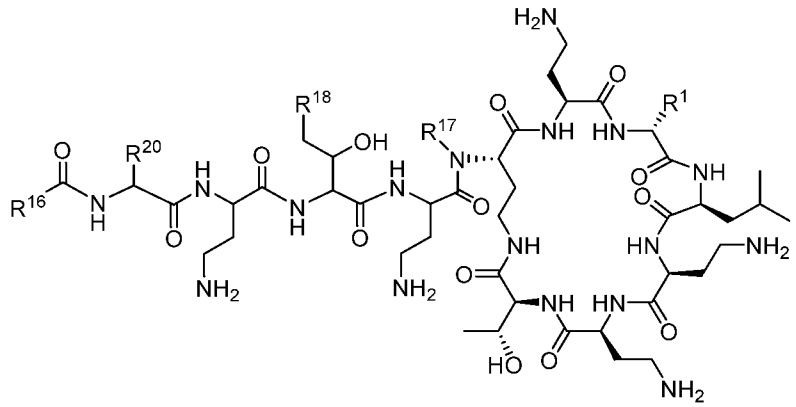
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl;

or a pharmaceutically acceptable salt thereof.

183. The compound of claim 178, wherein the compound is described by formula (XX-6):



(XX-6)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

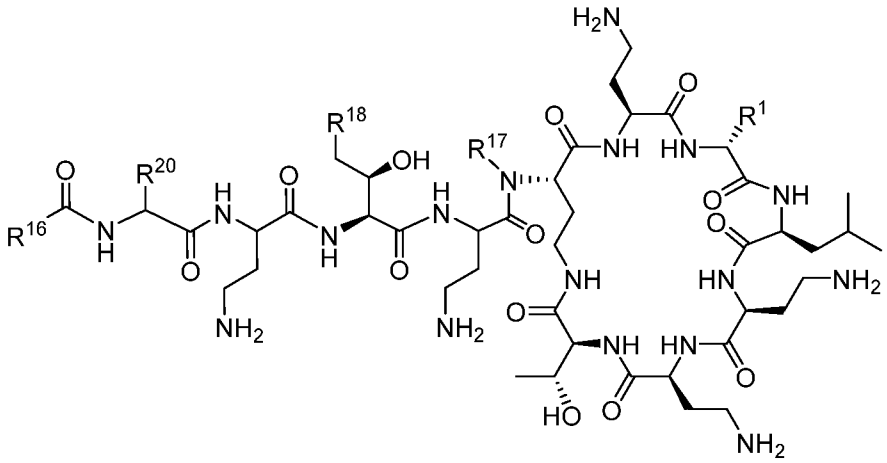
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

184. The compound of claim 183, wherein the compound is described by formula (XX-7):



(XX-7)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

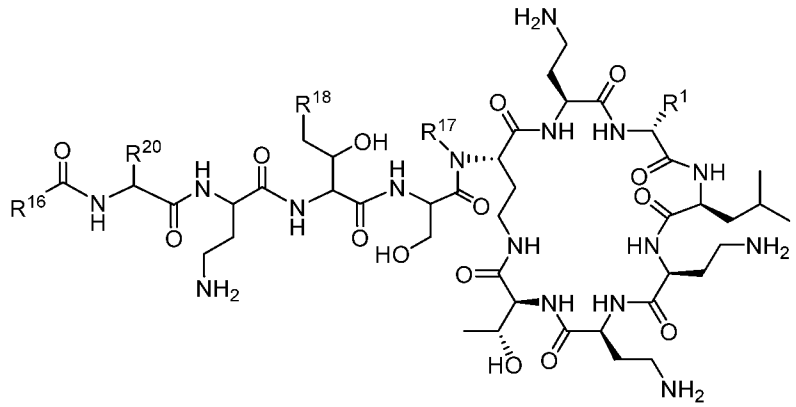
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

185. The compound of claim 178, wherein the compound is described by formula (XX-8):



(XX-8)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

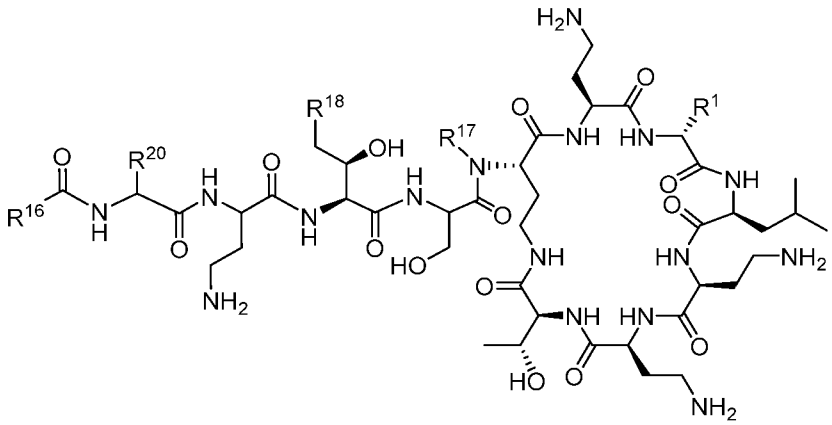
R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof.

186. The compound of claim 185, wherein the compound is described by formula (XX-9):



(XX-9)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^{20} is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

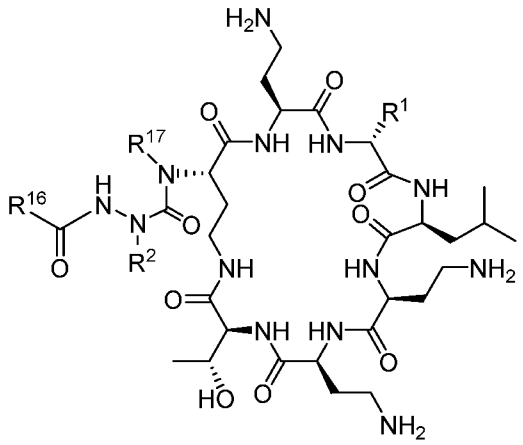
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl,

or a pharmaceutically acceptable salt thereof

187. The compound of any one of claims 183-186, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

188. The compound of claim 1, wherein the compound is described by formula (XXI):



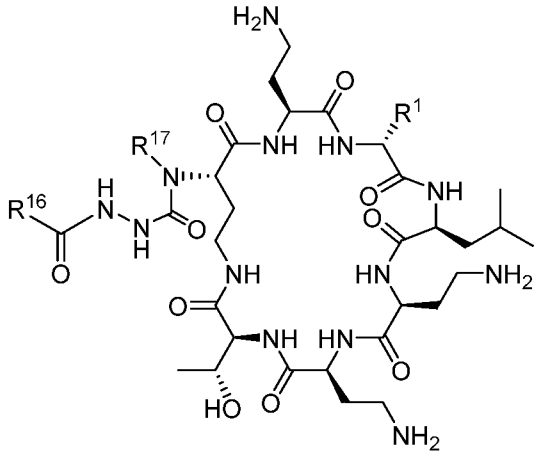
(XXI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^2 is a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

189. The compound of claim 188, wherein the compound is described by formula (XXI-1):

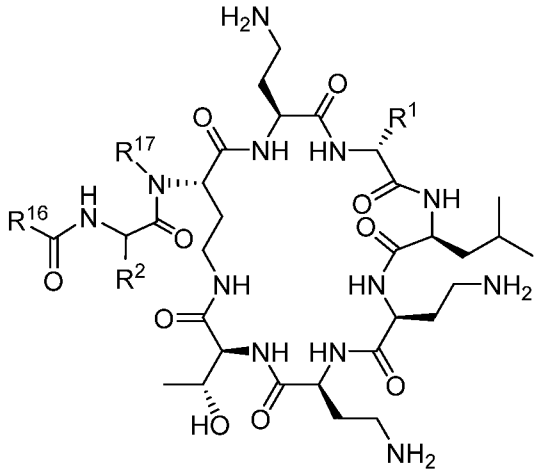


(XXI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

or a pharmaceutically acceptable salt thereof.

190. The compound of claim 18, wherein the compound is described by formula (XXII):



(XXII)

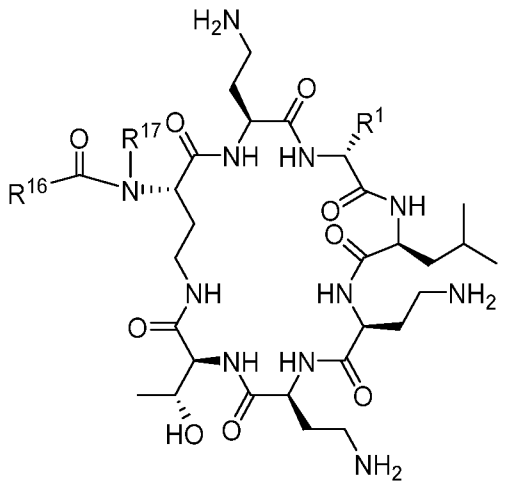
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^2 is a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

191. The compound of claim 18, wherein the compound is described by formula (XXIII):



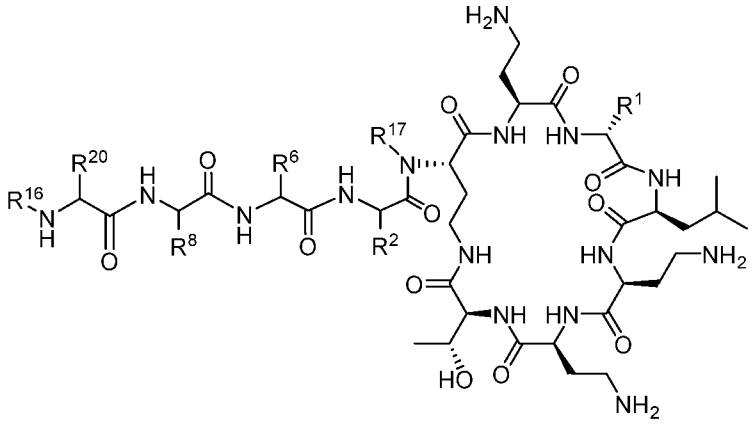
(XXIII)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{17} is C1-C3 alkyl or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

192. A compound described by formula (XXIV):



(XXIV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, and R^8, is, independently, H, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

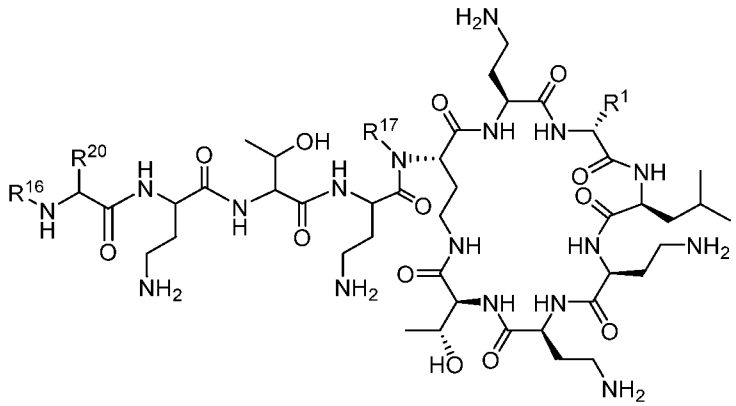
R^{20} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, optionally substituted C6-C35 heteroalkaryl, or absent; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

193. The compound of claim 192, wherein the compound is described by formula (XXIV-1):



(XXIV-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

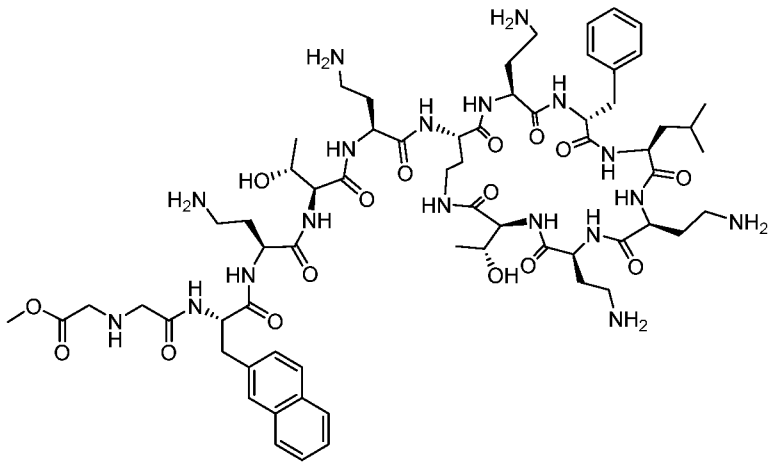
R^{20} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, optionally substituted C6-C35 heteroalkaryl, or absent;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

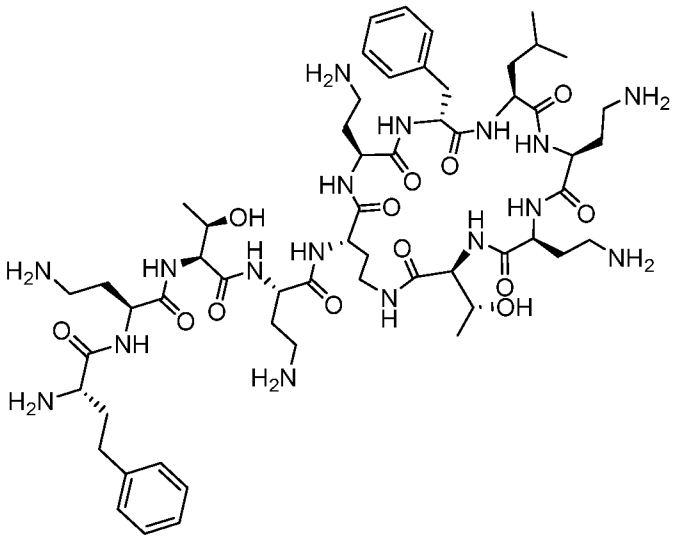
or a pharmaceutically acceptable salt thereof.

194. The compound of claim 193, wherein the compound is:



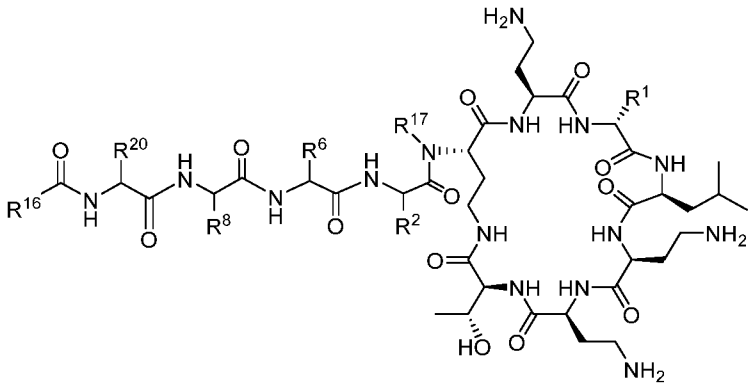
Compound 52.

195. The compound of claim 193, wherein the compound is:



Compound 53.

196. A compound described by formula (XXV):



(XXV)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

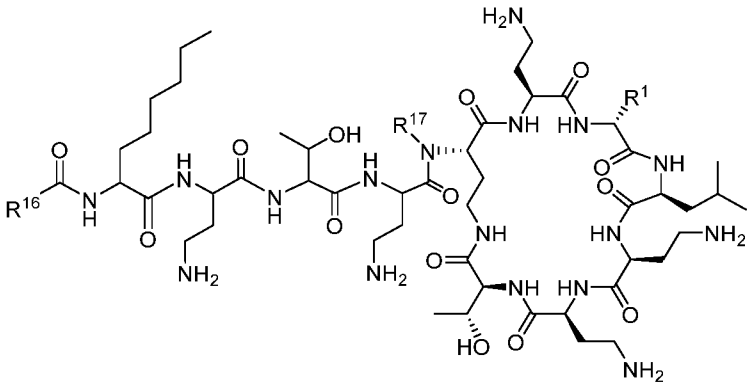
each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{16} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

197. The compound of claim 196, wherein the compound is described by formula (XXV-1):



(XXV-1)

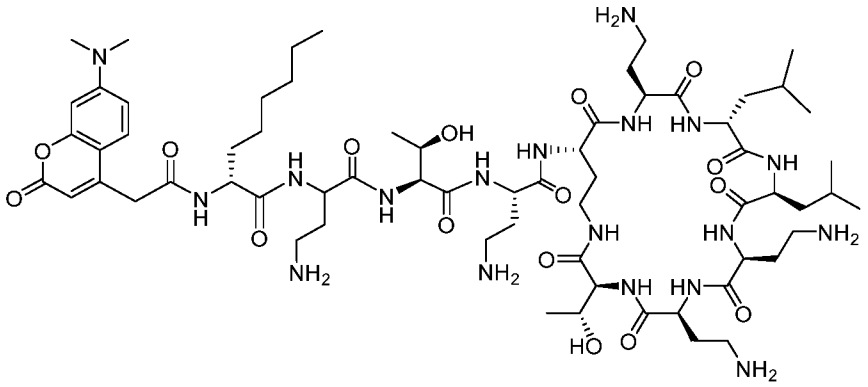
wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

R^{16} is optionally substituted C6-C35 alkaryl or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

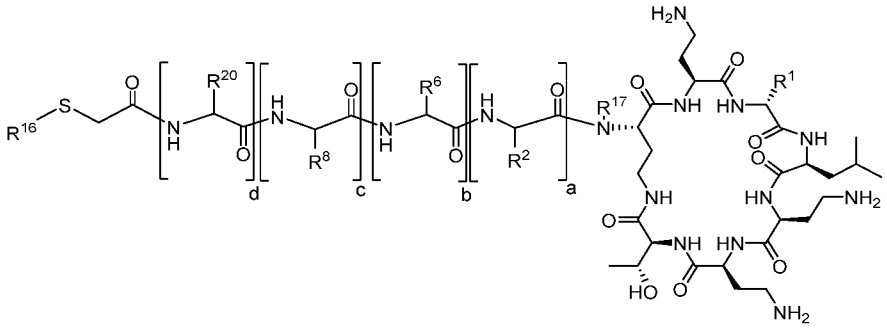
or a pharmaceutically acceptable salt thereof.

198. The compound of claim 197, wherein the compound is:



Compound 51.

199. A compound described by formula (XXVI):



(XXVI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

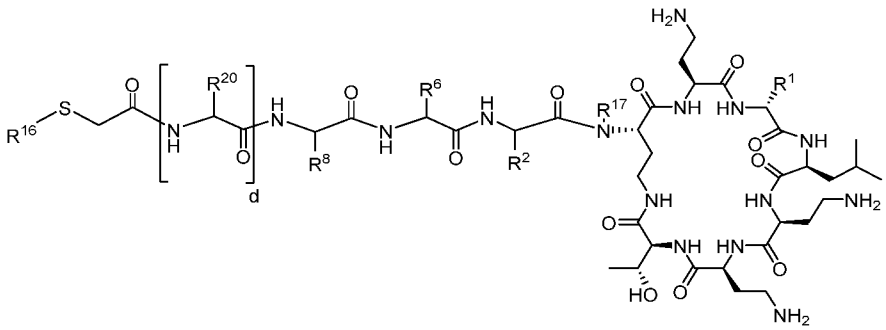
R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and

each of a, b, c, and d is, independently, 0 or 1,

or a pharmaceutically acceptable salt thereof.

200. The compound of claim 199, wherein the compound is described by formula (XXVI-1):



(XXVI-1)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

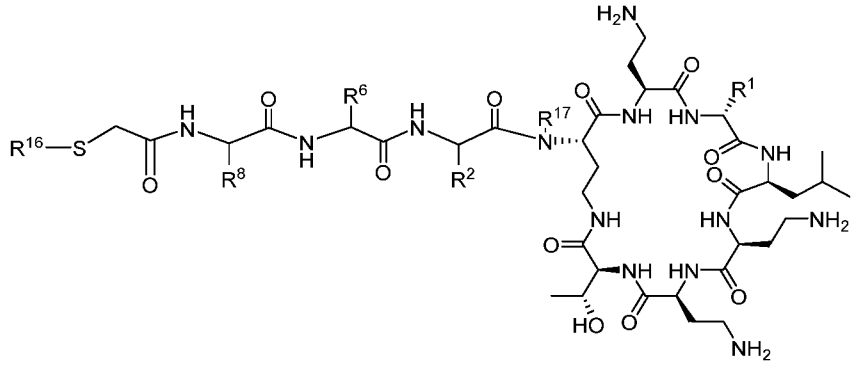
R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and

d is 0 or 1,

or a pharmaceutically acceptable salt thereof.

201. The compound of claim 200, wherein the compound is described by formula (XXVI-2):



(XXVI-2)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

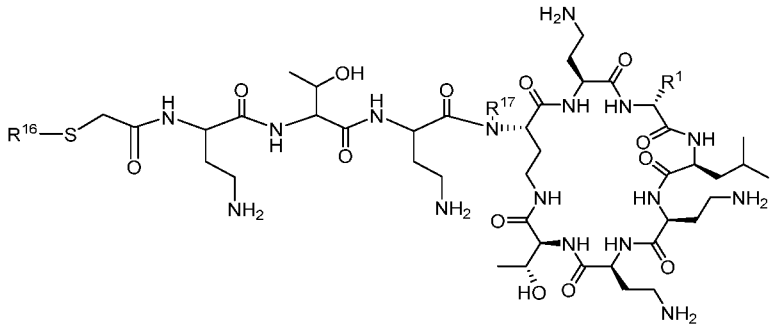
each of R^2, R^6, and R^8 is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

202. The compound of claim 201, wherein the compound is described by formula (XXVI-3):



(XXVI-3)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl; and

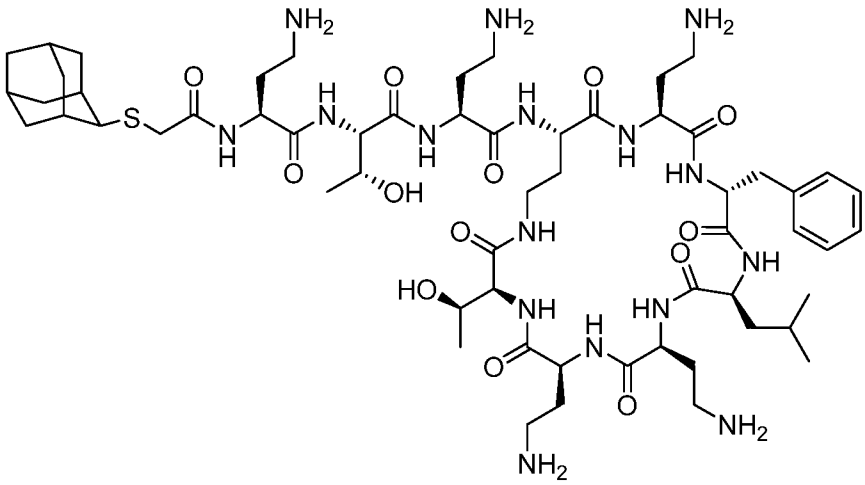
R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

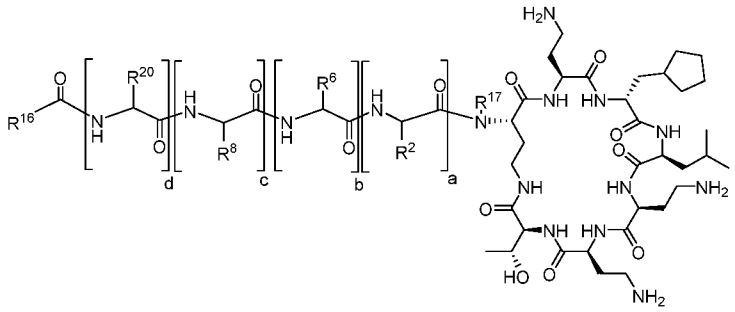
203. The compound of any one of claims 199-202, wherein R^{16} is adamantyl.

204. The compound of claim 202 or 203, wherein the compound is:



Compound 54.

205. A compound described by formula (XXVII):



(XXVII)

wherein each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

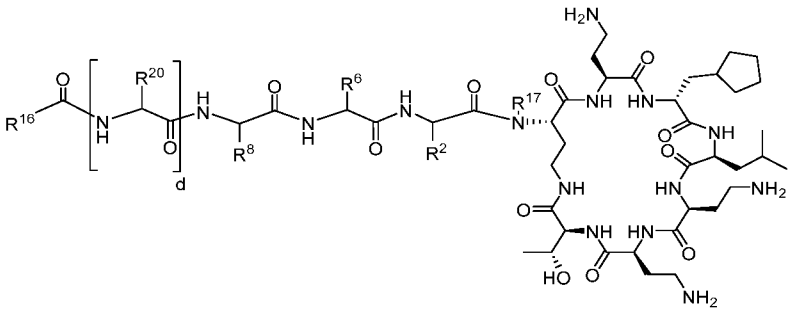
R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and

each of a, b, c, and d is, independently, 0 or 1,

or a pharmaceutically acceptable salt thereof.

206. The compound of claim 205, wherein the compound is described by formula (XXVII-1):



(XXVII-1)

wherein each of R^2, R^6, R^8, and R^{20} is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20

heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

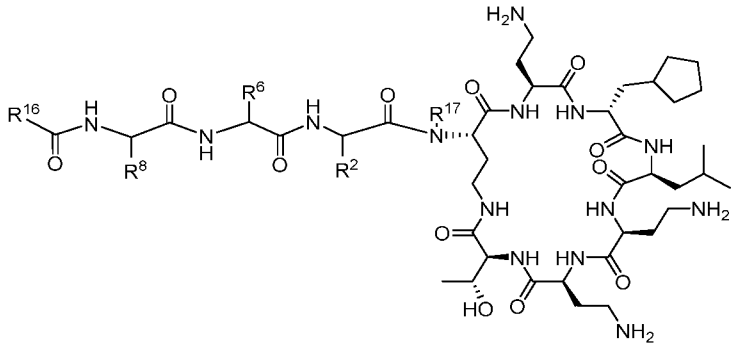
R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino; and

d is 0 or 1,

or a pharmaceutically acceptable salt thereof.

207. The compound of claim 206, wherein the compound is described by formula (XXVII-2):



(XXVII-2)

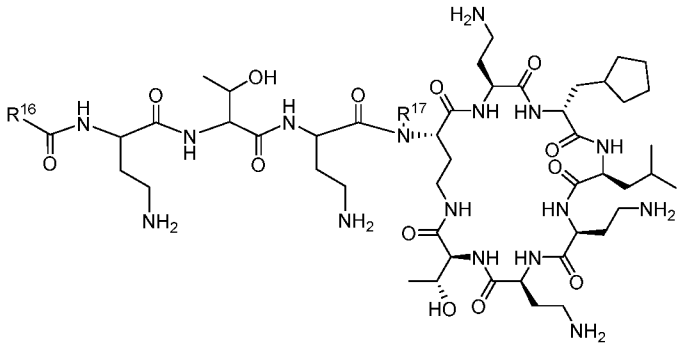
wherein each of R^2, R^6, and R^8 is, independently, H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

or a pharmaceutically acceptable salt thereof.

208. The compound of claim 207, wherein the compound is described by formula (XXVII-3):



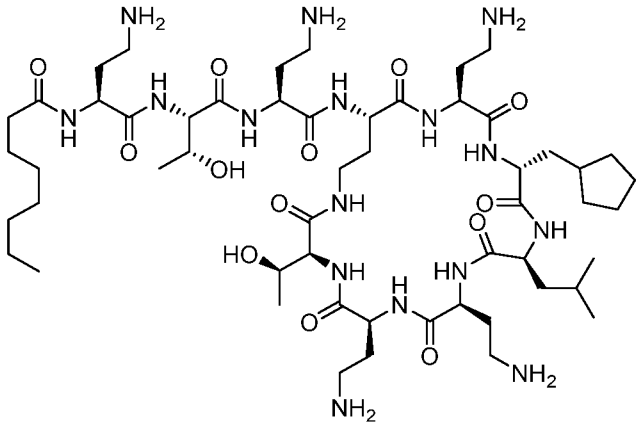
(XXVII-3)

wherein R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{17} is H, C1-C3 alkyl, or C2-C3 alkamino;

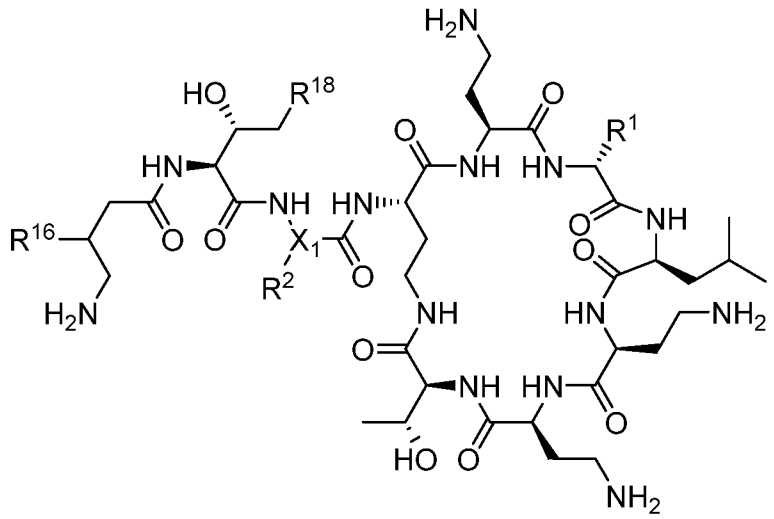
or a pharmaceutically acceptable salt thereof.

209. The compound of claim 208, wherein the compound is:



Compound 55.

210. A compound described by formula (XXXX):



(XXXX)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

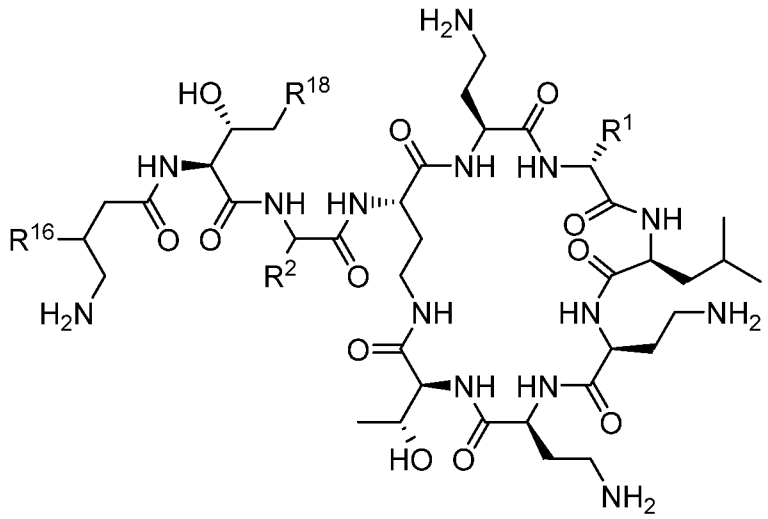
R^{18} is a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

X_1 is a carbon atom or a nitrogen atom,

or a pharmaceutically acceptable salt thereof.

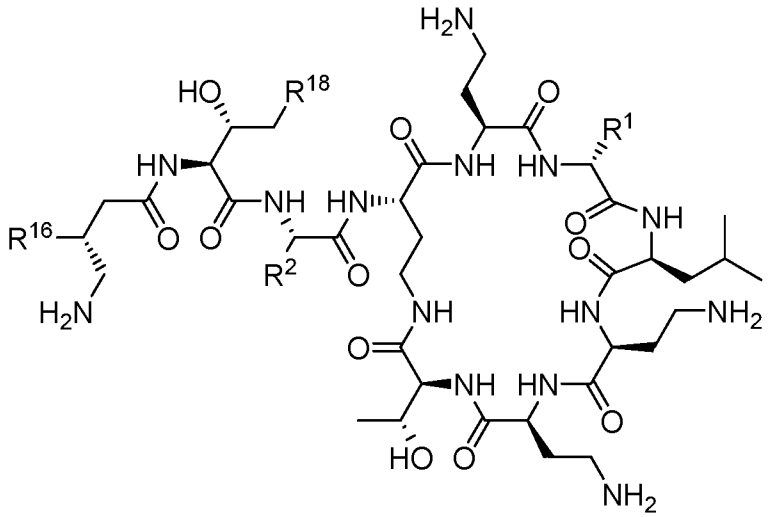
211. The compound of claim 210, wherein the compound is described by formula (XXXX-1):



(XXXX-1)

or a pharmaceutically acceptable salt thereof.

212. The compound of claim 211, wherein the compound is described by formula (XXXX-2):

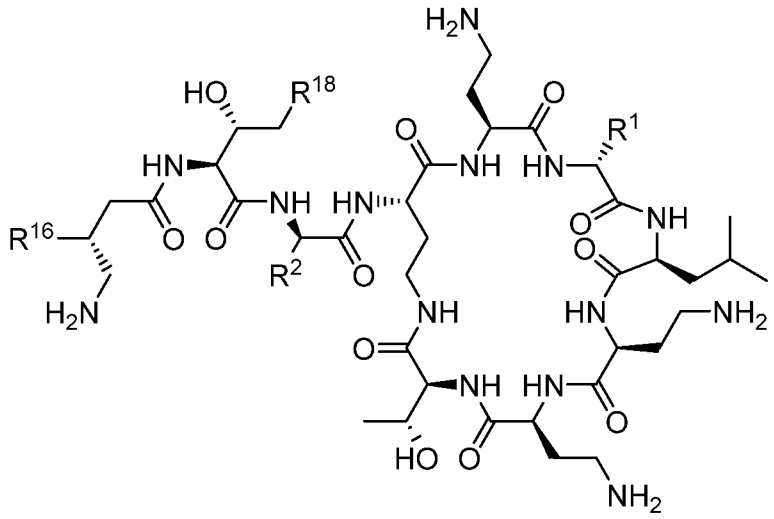


(XXXX-2)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

213. The compound of claim 211, wherein the compound is described by formula (XXXX-3):

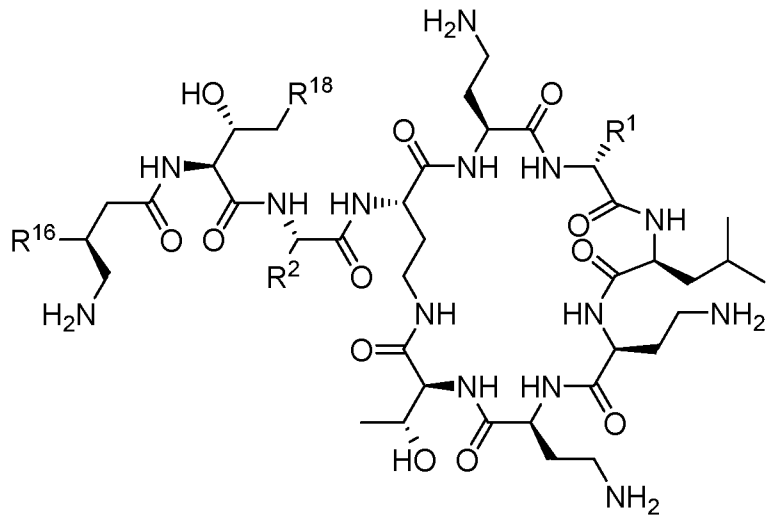


(XXXX-3)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

214. The compound of claim 211, wherein the compound is described by formula (XXXX-4):



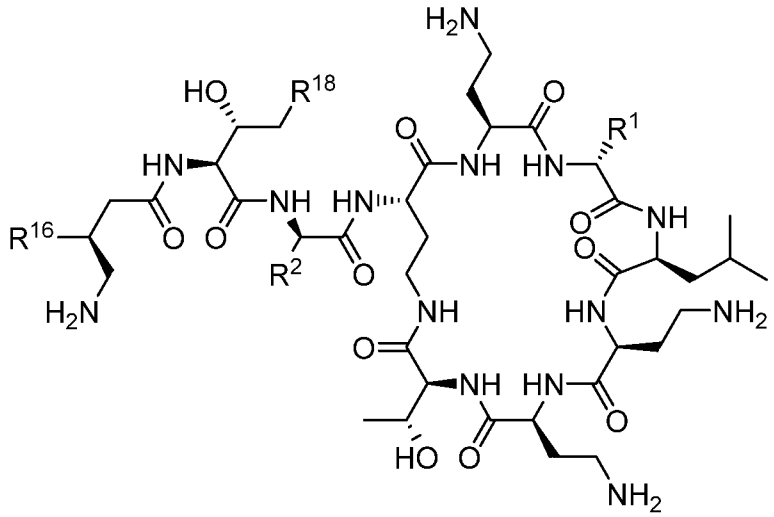
(XXXX-4)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally

substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

215. The compound of claim 211, wherein the compound is described by formula (XXXX-5):

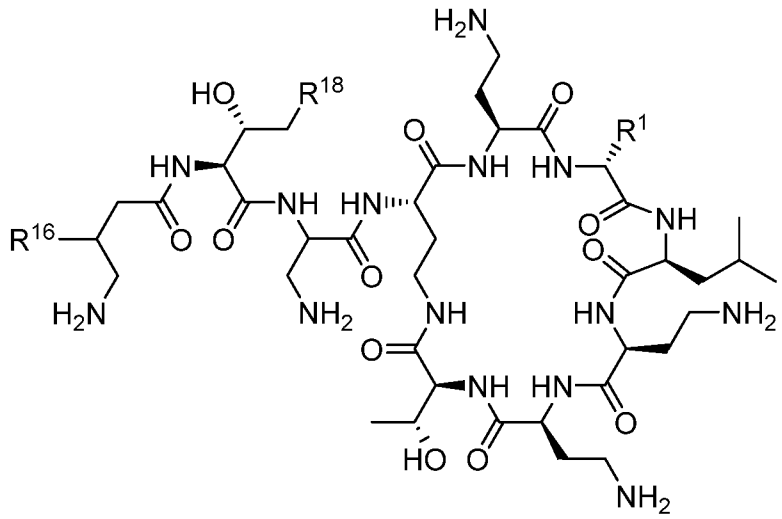


(XXXX-5)

wherein R^2 is a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

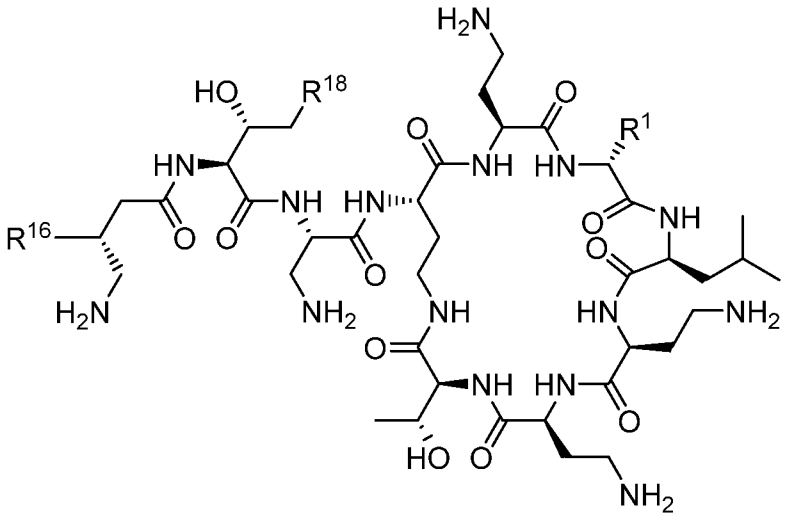
216. The compound of claim 211, wherein the compound is described by formula (XXXX-6):



(XXXX-6)

or a pharmaceutically acceptable salt thereof.

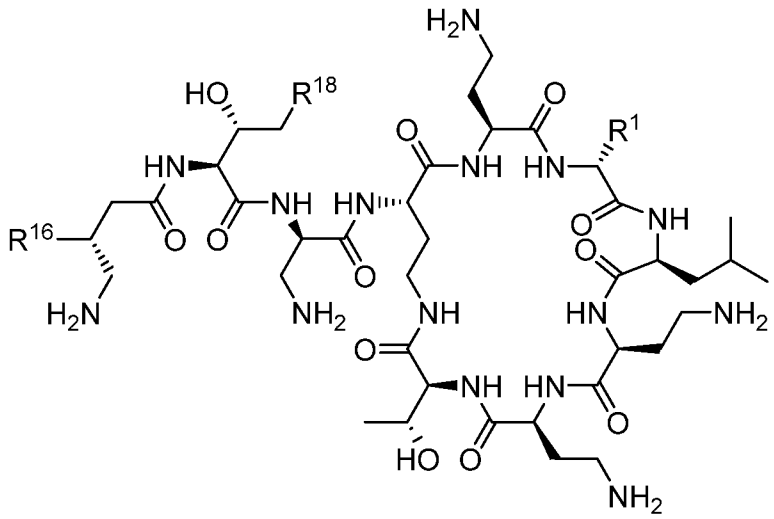
217. The compound of claim 216, wherein the compound is described by formula (XXXX-7):



(XXXX-7)

or a pharmaceutically acceptable salt thereof.

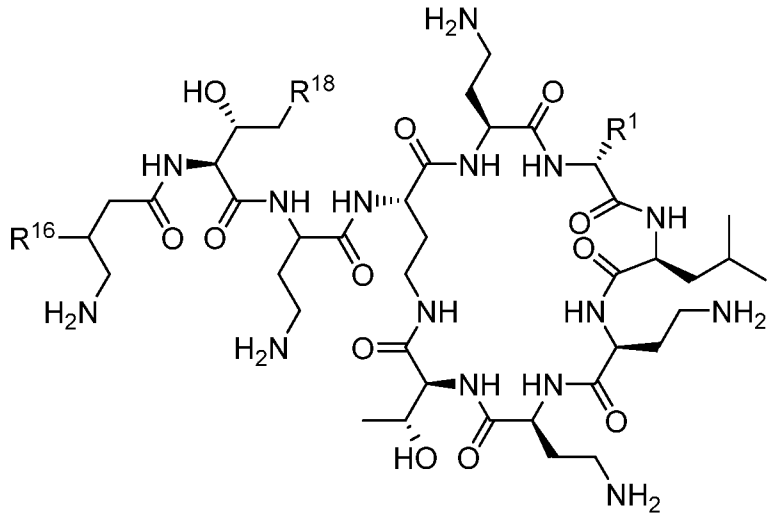
218. The compound of claim 216, wherein the compound is described by formula (XXXX-8):



(XXXX-8)

or a pharmaceutically acceptable salt thereof.

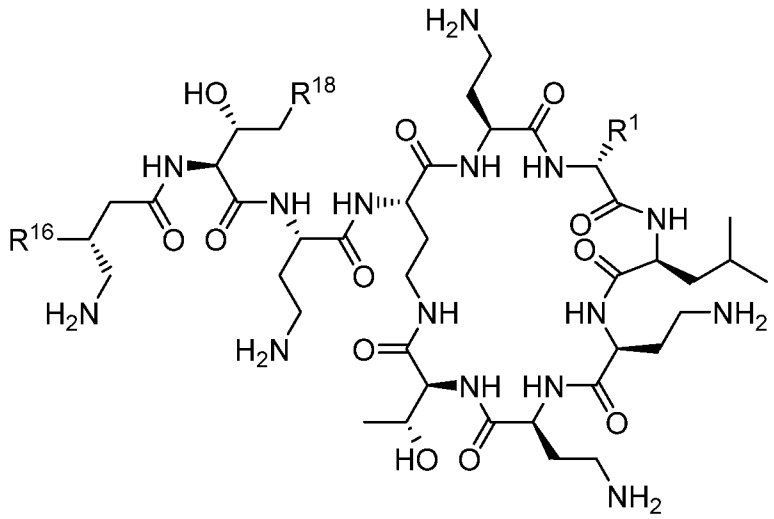
219. The compound of claim 211, wherein the compound is described by formula (XXXX-9):



(XXXX-9)

or a pharmaceutically acceptable salt thereof.

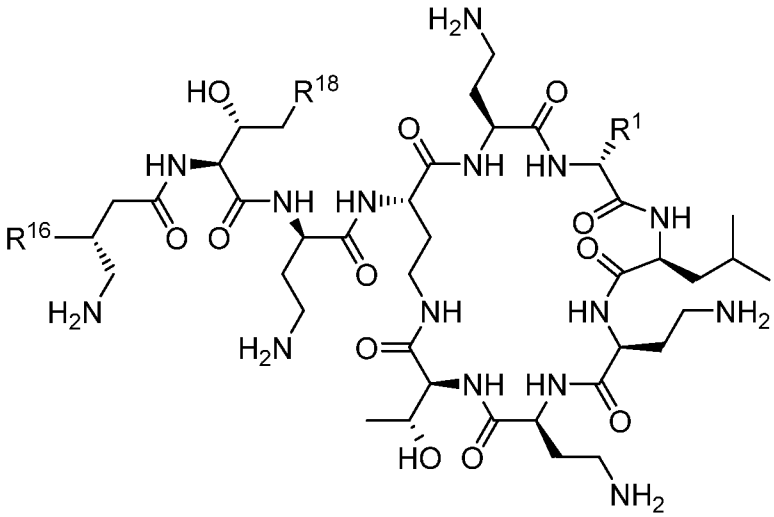
220. The compound of claim 219, wherein the compound is described by formula (XXXX-10):



(XXXX-10)

or a pharmaceutically acceptable salt thereof.

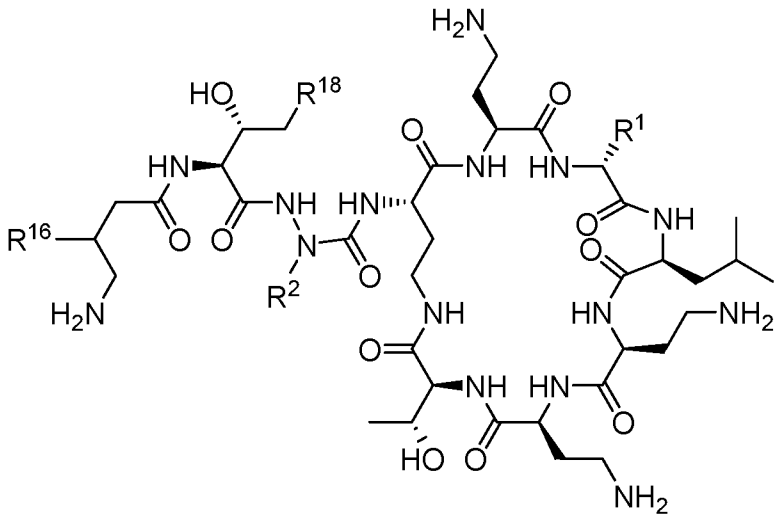
221. The compound of claim 219, wherein the compound is described by formula (XXXX-11):



(XXXX-11)

or a pharmaceutically acceptable salt thereof.

222. The compound of claim 210, wherein the compound is described by formula (XXXX-12):

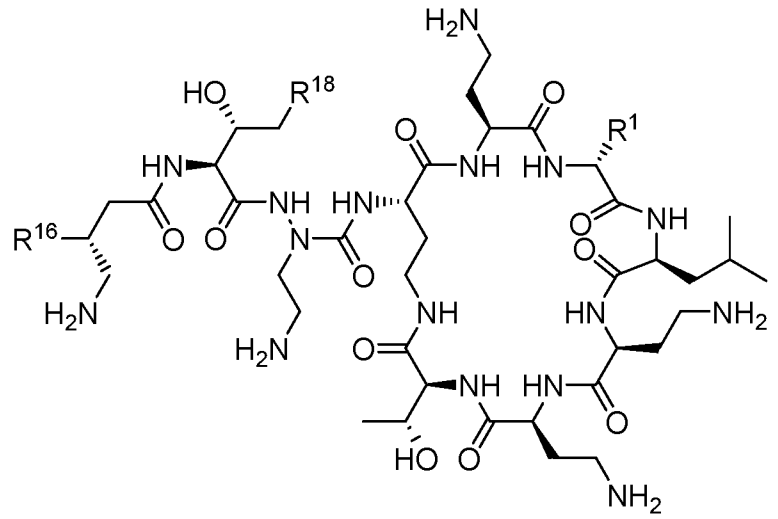


(XXXX-12)

wherein R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C2-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

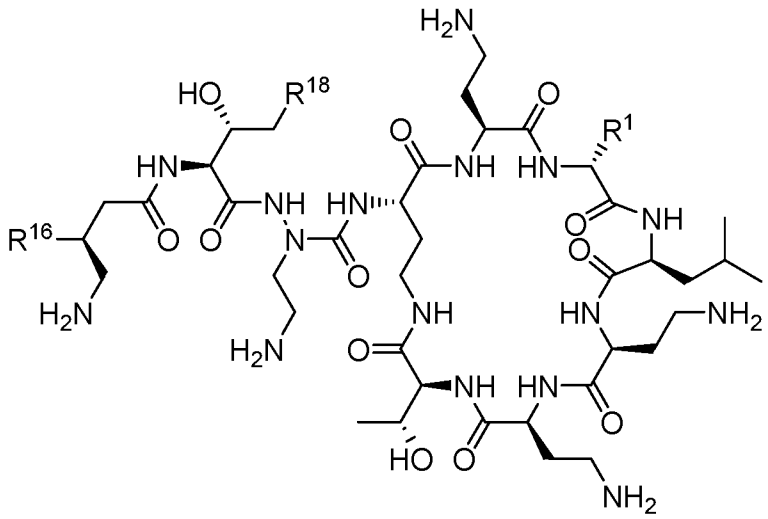
223. The compound of claim 222, wherein the compound is described by formula (XXXX-13):



(XXXX-13)

or a pharmaceutically acceptable salt thereof.

224. The compound of claim 222, wherein the compound is described by formula (XXXX-14):

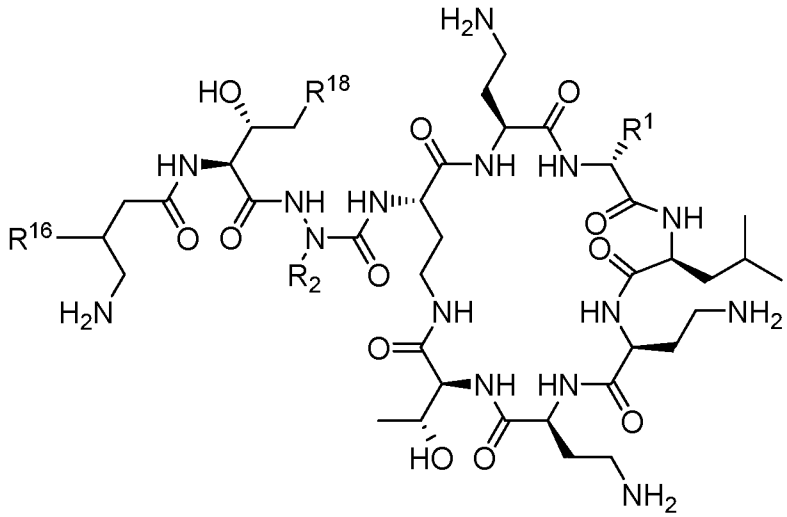


(XXXX-14)

or a pharmaceutically acceptable salt thereof.

225. The compound of any one of claims 210-224, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

226. A compound described by formula (XXXXI):



(XXXXI)

wherein R^1 is optionally substituted benzyl, $CH_2CH(CH_3)_2$, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, naphthylmethyl, optionally substituted thiophenylmethyl, or optionally substituted furanylmethyl;

R^2 is H, a lipophilic moiety, a positively charged moiety, a polar moiety, optionally substituted C2-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl,

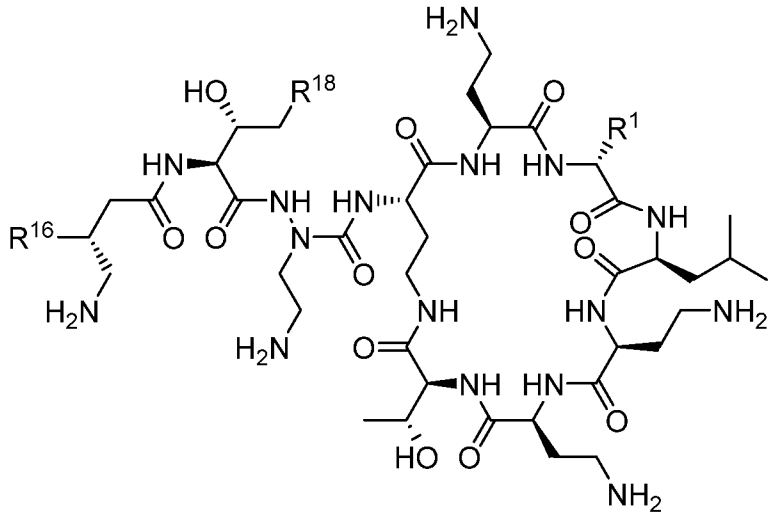
optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl;

R^{18} is H, a lipophilic moiety, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl; and

R^{16} is H, optionally substituted C1-C5 alkamino, optionally substituted C1-C20 alkyl, optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally substituted C5-C15 aryl, optionally substituted C1-C20 heteroalkyl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, optionally substituted C2-C15 heteroaryl, optionally substituted C6-C35 alkaryl, or optionally substituted C6-C35 heteroalkaryl,

or a pharmaceutically acceptable salt thereof.

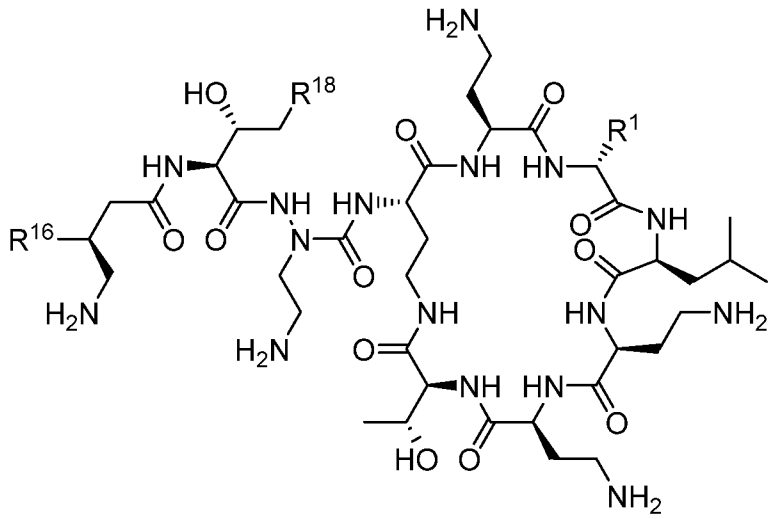
227. The compound of claim 226, wherein the compound is described by formula (XXXXI-1):



(XXXXI-1)

or a pharmaceutically acceptable salt thereof.

228. The compound of claim 226, wherein the compound is described by formula (XXXXI-2):



(XXXXI-2)

or a pharmaceutically acceptable salt thereof.

229. The compound of any one of claims 226-228, wherein R^{18} is is C1-C6 alkyl, benzyl, or phenethyl.

230. The compound of any one of claims 226-228, wherein R^{18} is H.

231. The compound of any one of claims 210-230, wherein R^{16} is 3-chlorophenyl, 4-chlorophenyl, benzyl, 3-methylphenyl, isobutyl, cyclohexyl, or phenyl.

232. The compound of claim 231, wherein R^{16} is 3-chlorophenyl.

233. The compound of any one of claims 96-232, wherein R^1 is benzyl or $CH_2CH(CH_3)_2$.

234. The compound of any one of claims 96-232, wherein R^2 is optionally substituted C1-C5 alkamino.

235. The compound of claim 233 or 234, wherein the optionally substituted C1-C5 alkamino is CH_2NH_2 or $CH_2CH_2NH_2$.

236. The compound of any one of claims 96-232, wherein R^2 is a polar moiety.

237. The compound of claim 236, wherein the polar moiety comprises a hydroxyl group, a carboxylic acid group, an ester group, or an amide group.

238. The compound of claim 236, wherein the polar moiety is hydroxyl substituted C1-C4 alkyl.

239. The compound of claim 238, wherein the polar moiety is $CHCH_3OH$ or CH_2OH.

240. The compound of any one of claims 96-232, wherein R^2 is H.

241. The compound of any one of claims 96-232, wherein R^6 is a polar moiety.

242. The compound of claim 241, wherein the polar moiety comprises a hydroxyl group, a carboxylic acid group, an ester group, or an amide group.

243. The compound of claim 241 or 242, wherein the polar moiety is hydroxyl substituted C1-C4 alkyl.

244. The compound of claim 243, wherein the polar moiety is $CHCH_3OH$ or CH_2OH.

245. The compound of any one of claims 96-232, wherein R^6 is H.

246. The compound of any one of claims 96-232, wherein R^8 is optionally substituted C1-C5 alkamino.

247. The compound of claim 246, wherein the optionally substituted C1-C5 alkamino is CH_2NH_2 or $CH_2CH_2NH_2$.

248. The compound of any one of claims 96-232, wherein R^8 is optionally substituted C5-C15 aryl.

249. The compound of claim 248, wherein the optionally substituted C5-C15 aryl is naphthyl.

250. The compound of any one of claims 96-232, wherein R^8 is H.

251. The compound of any one of claims 96-232, wherein R^{20} is optionally substituted C1-C20 alkyl or optionally substituted C6-C35 alkaryl.

252. The compound of claim 251, wherein the optionally substituted C1-C20 alkyl is $CH_2CH_2CH_2CH_3$ or $CH_2CH_2CH_2CH_2CH_2CH_3$.

253, The compound of claim 251, wherein the optionally substituted C6-C35 alkaryl is naphthylmethyl.

254. The compound of any one of claims 96-232, wherein R^{18} is C1-C6 alkyl, benzyl, or phenethyl.

255. The compound of any one of claims 96-232, wherein R^{17} is H.

256. The compound of any one of claims 96-232, wherein R^{17} is methyl.

257. The compound of any one of claims 96-232, wherein R^{16} is optionally substituted C3-C20 cycloalkyl, optionally substituted C4-C20 cycloalkenyl, optionally substituted C8-C20 cycloalkynyl, optionally

substituted C5-C15 aryl, optionally substituted C3-C20 heterocycloalkyl, optionally substituted C4-C20 heterocycloalkenyl, optionally substituted C8-C20 heterocycloalkynyl, or optionally substituted C2-C15 heteroaryl.

258. The compound of claim 257, wherein R^{16} is optionally substituted pyrrolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, thiphenyl, thiolanyl, furanyl, tetrahydrofuranyl, pyridinyl, piperidinyl, pyrimidinyl, pyrazinyl, azepinyl, 1,4-diazepinyl, 4F-pyranyl, tetrahydropyranyl, indolyl, quinolyl, isoquinolyl, chromanyl, purinyl, pteridinyl, triazolyl, benzotriazolyl.

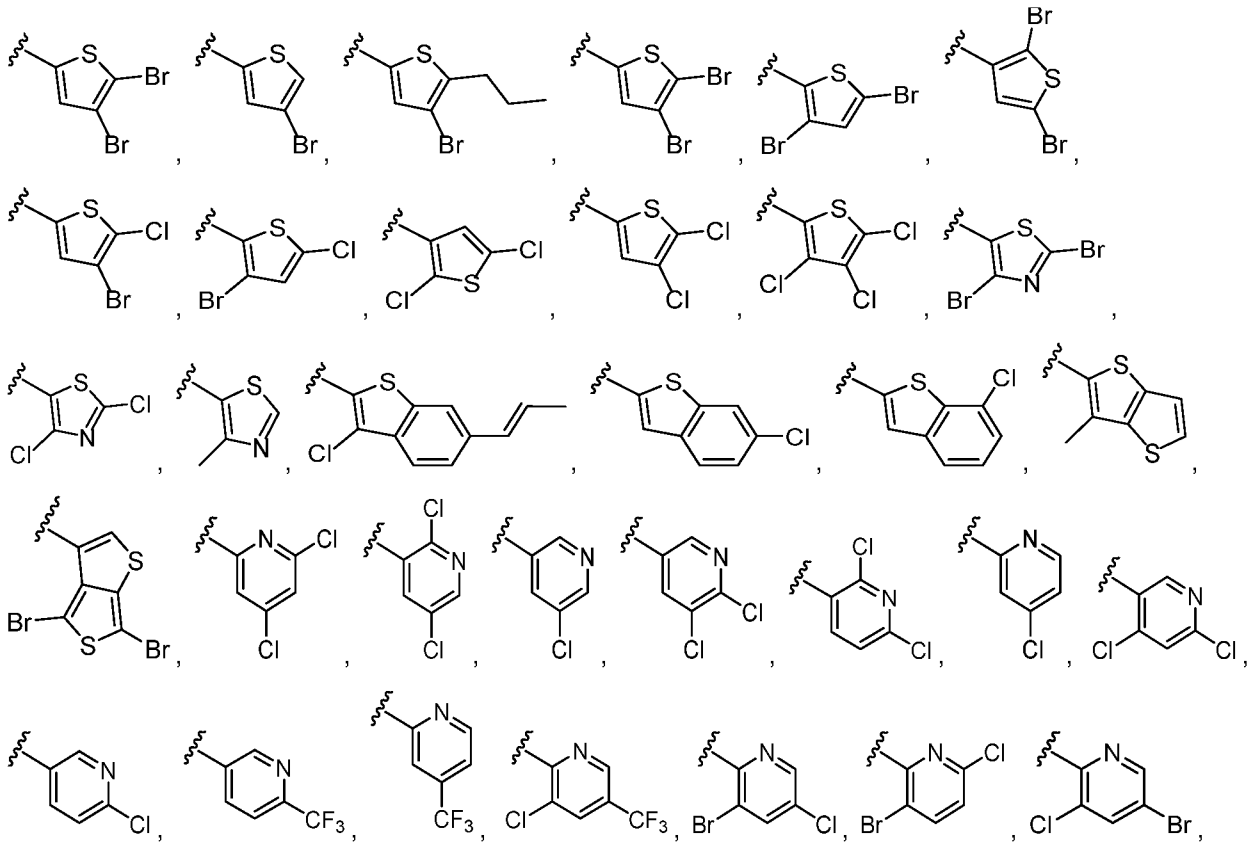
259. The compound of claim 257, wherein R^{16} is optionally substituted phenyl, naphthyl, or phenanthrene.

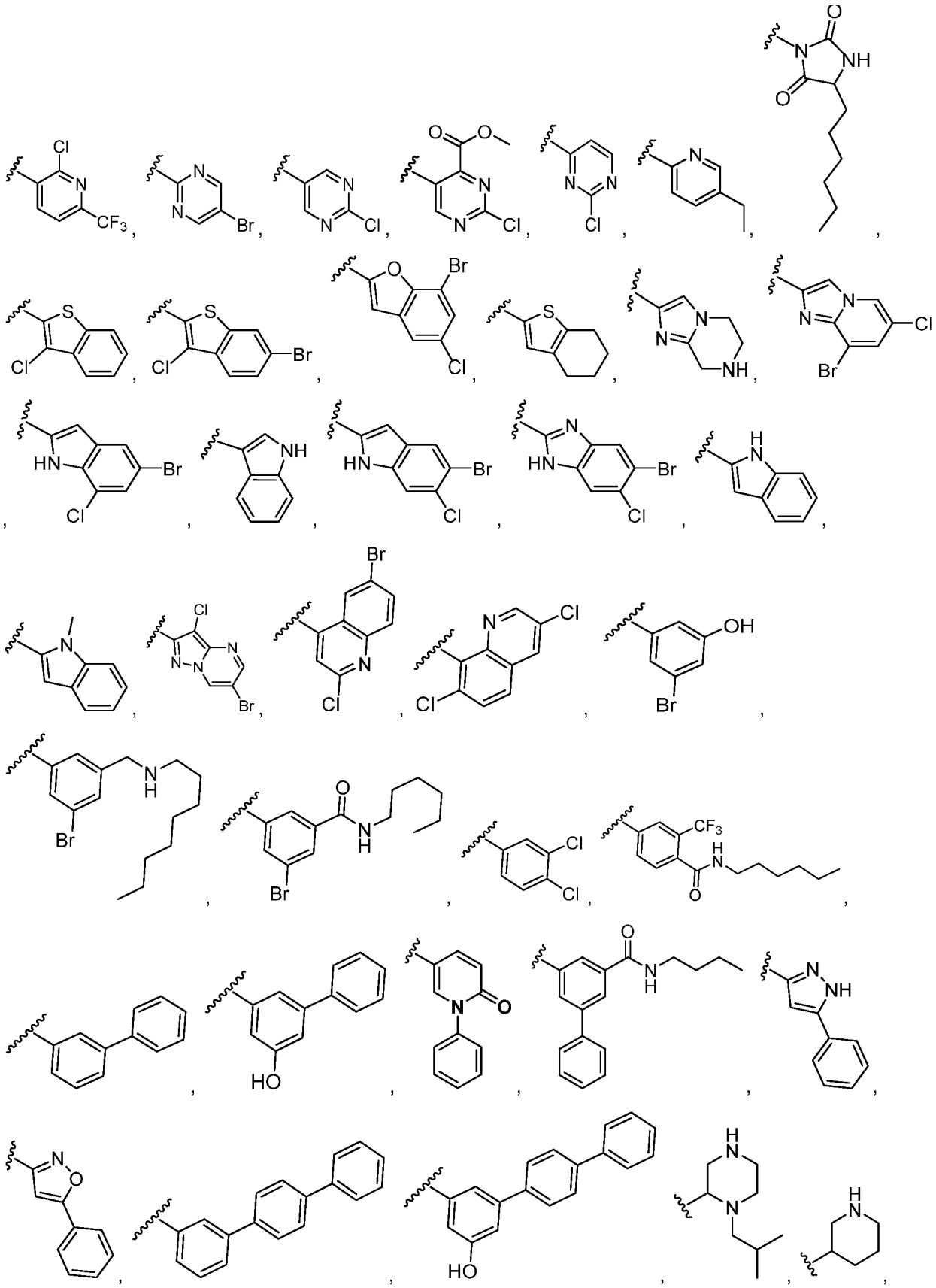
260. The compound of claim 257, wherein R^{16} is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, or cyclononyl.

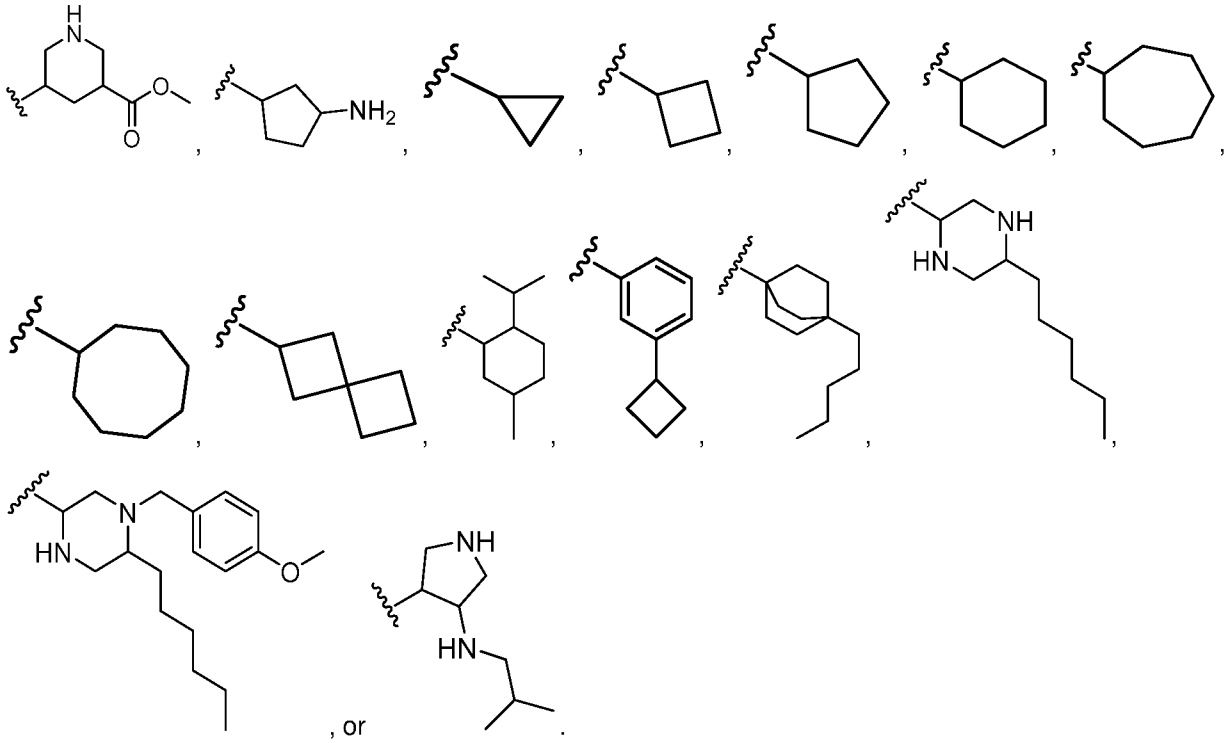
261. The compound of claim 257, wherein R^{16} is optionally substituted biphenyl or terphenyl.

262. The compound of any one of claims 96-232, wherein R^{16} is optionally substituted C1-C20 alkyl.

263. The compound of claim 96-232 wherein R^{16} is







264. A pharmaceutical composition comprising a compound of any of claims 1-263, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

265. The pharmaceutical composition of claim 264, further comprising an antibacterial agent.

266. The pharmaceutical composition of claim 265, wherein the antibacterial agent is selected from the group consisting of linezolid, tedizolid, posizolid, radezolid, retapamulin, valnemulin, tiamulin, azamulin, lefamulin, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin g, penicillin v, piperacillin, penicillin g, temocillin, ticarcillin, amoxicillin clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (tmp-smx), sulfonamidochrysoidine, eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone,

capreomycin, cycloserine, ethambutol(bs), ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole, and trimethoprim, prodrugs thereof, and pharmaceutically acceptable salts thereof.

267. The pharmaceutical composition of claim 266, wherein a prodrug of tedizolid is tedizolid phosphate.

268. The pharmaceutical composition of claim 266, wherein the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, levofloxacin, rifampicin, linezolid, erythromycin, or solithromycin.

269. The pharmaceutical composition of claim 268, wherein the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, or levofloxacin.

270. A method of protecting against or treating a bacterial infection in a subject, said method comprising administering to said subject a compound of any one of claims 1-263.

271. The method of claim 270, further comprising administering to the subject an antibacterial agent.

272. A method of protecting against or treating a bacterial infection in a subject, said method comprising administering to said subject (1) a compound of any one of claims 1-263 and (2) an antibacterial agent.

273. A method of inducing immune cell activation of the immune response in a subject having a bacterial infection, said method comprising administering to said subject a compound of any one of claims 1-263.

274. The method of claim 273, further comprising administering to the subject an antibacterial agent.

275. A method of inducing immune cell activation of the immune response in a subject having a bacterial infection, said method comprising administering to said subject (1) a compound of any one of claims 1-263 and (2) an antibacterial agent.

276. The method of claim 271 or 272, wherein the compound and the antibacterial agent are administered substantially simultaneously.

277. The method of claim 271 or 272, wherein the compound and the antibacterial agent are administered separately.

278. The method of claim 277, wherein the compound is administered first, followed by administering of the antibacterial agent alone.

279. The method of claim 277, wherein the antibacterial agent is administered first, followed by administering of the compound alone.

280. The method of claim 271 or 272, wherein the compound and the antibacterial agent are administered substantially simultaneously, followed by administering of the compound or the antibacterial agent alone.

281. The method of claim 271 or 272, wherein the compound or the antibacterial agent is administered first, followed by administering of the compound and the antibacterial agent substantially simultaneously.

282. The method of any one of claims 271-281, wherein administering the compound and the antibacterial agent together lowers the MIC of each of the compound and the antibacterial agent relative to the MIC of each of the compound and the antibacterial agent when each is used alone.

283. The method of any one of claims 270-282, wherein the compound and/or the antibacterial agent is administered intramuscularly, intravenously, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctival, intravesicularlly, mucosally, intrapericardially, intraumbilically, intraocularally, orally, locally, by inhalation, by injection, or by infusion.

284. A method of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria, comprising contacting the bacteria or a site susceptible to bacterial growth with a compound of any of claims 1-263.

285. The method of claim 284, further comprising contacting the bacteria or the site susceptible to bacterial growth with an antibacterial agent.

286. A method of preventing, stabilizing, or inhibiting the growth of bacteria, or killing bacteria, comprising contacting the bacteria or a site susceptible to bacterial growth with (1) a compound of any of claims 1-263 and (2) an antibacterial agent.

287. The method of any one of claims 270-286, wherein the antibacterial agent is selected from the group consisting of linezolid, tedizolid, posizolid, radezolid, retapamulin, valnemulin, tiamulin, azamulin, lefamulin, plazomicin, amikacin, gentamicin, gamithromycin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin,

daptomycin, solithromycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin g, penicillin v, piperacillin, penicillin g, temocillin, ticarcillin, amoxicillin clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole (tmp-smx), sulfonamidochrysoidine, eravacycline, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone, capreomycin, cycloserine, ethambutol(bs), ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole, and trimethoprim, prodrugs thereof, and pharmaceutically acceptable salts thereof.

288. The method of claim 287, wherein a prodrug of tedizolid is tedizolid phosphate.

289. The method of claim 287, wherein the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, levofloxacin, rifampicin, linezolid, erythromycin, or solithromycin.

290. The method of claim 289, wherein the antibacterial agent is tedizolid, azithromycin, meropenem, amikacin, or levofloxacin.

291. The method of any one of claims 270-290, wherein the bacterial infection is caused by Gram-negative bacteria.

292. The method of any one of claims 270-291, wherein the bacterial infection is caused by a resistant strain of bacteria.

293. The method of claim 292, wherein the resistant strain of bacteria possesses the *mcr-1* gene, the *mcr-2* gene, and/or a chromosomal mutation conferring polymyxin resistance.

294. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr-1* gene.

295. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr-2* gene.

296. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-3 gene.

297. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-4 gene.

298. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-5 gene.

299. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-6 gene.

300. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-7 gene.

301. The method of claim 293, wherein the resistant strain of bacteria possesses the *mcr*-8 gene.

302. The method of claim 293, wherein the resistant strain of bacteria possesses a chromosomal mutation conferring polymyxin resistance.

303. The method of any one of claims 270-302, wherein the resistant strain of bacteria is a resistant strain of *E. coli*.

304. A method of preventing lipopolysaccharides (LPS) in Gram-negative bacteria from activating an immune system in a subject, comprising administering to the subject a compound of any one of claims 1-263.

305. The method of claim 304, wherein the method prevents LPS from activating a macrophage.

306. The method of claim 304 or 305, wherein the method prevents LPS-induced nitric oxide production from a macrophage.

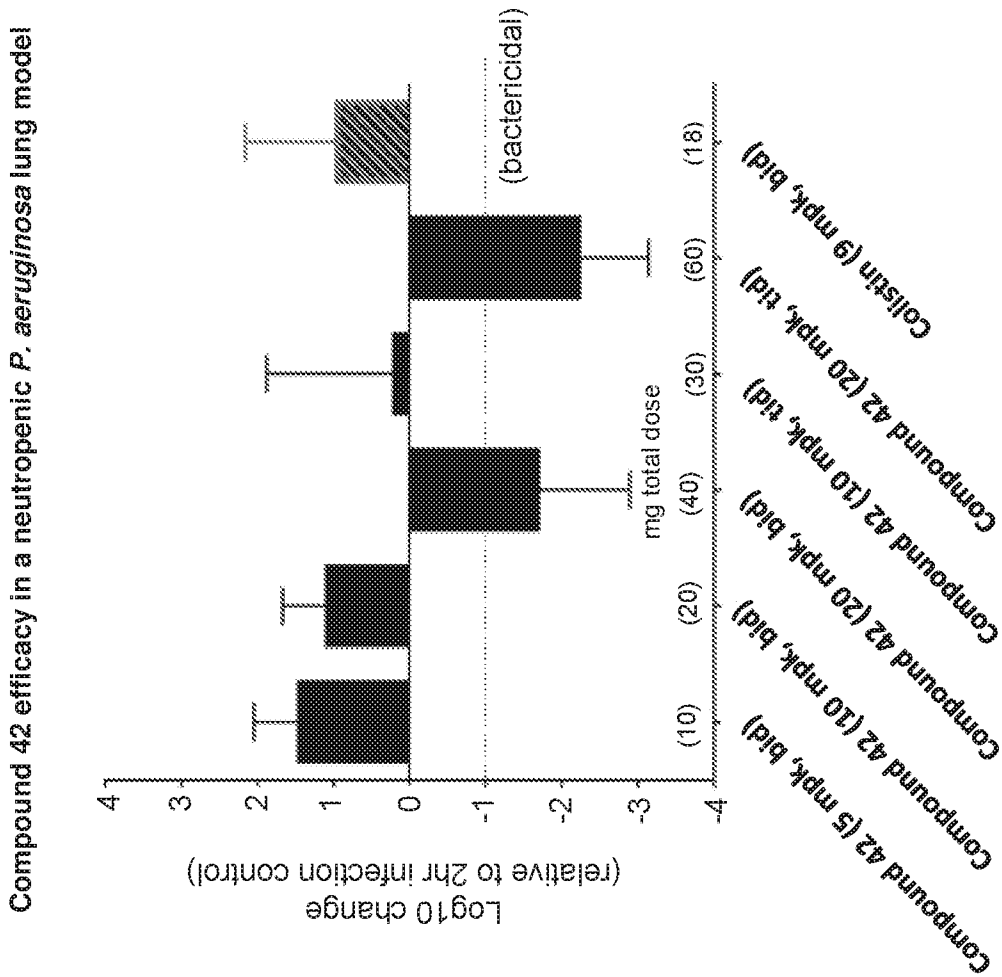

Compound 42 efficacy in a neutropenic *P. aeruginosa* lung model
Log10 change
(relative to 2hr infection control)
4
3
2
1
0
-1
-2
-3
-4
(bactericidal)
mg total dose
(10)
(20)
(40)
(30)
(60)
(18)
Compound 42 (5 mpk, bid)
Compound 42 (10 mpk, bid)
Compound 42 (20 mpk, bid)
Compound 42 (10 mpk, tid)
Compound 42 (20 mpk, tid)
Colistin (9 mpk, bid)

FIG. 1

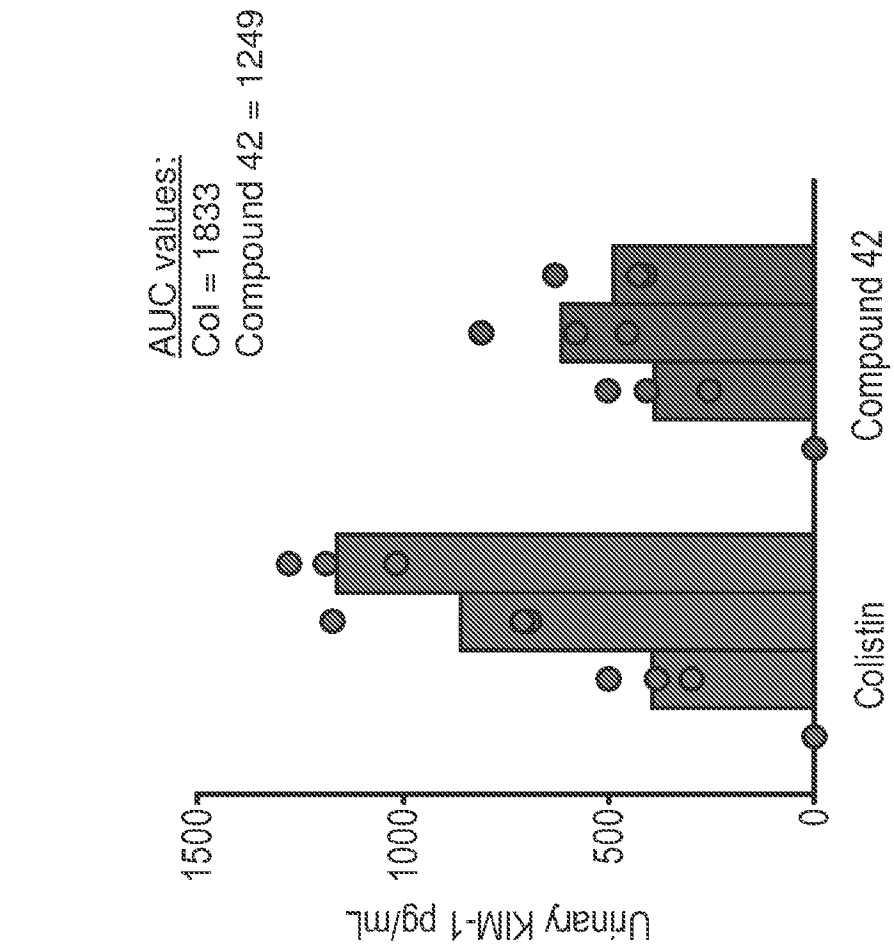

AUC values:
Col = 1833
Compound 42 = 1249
Urinary KIM-1 pg/mL
1500
1000
500
0
Colistin
Compound 42

FIG. 2

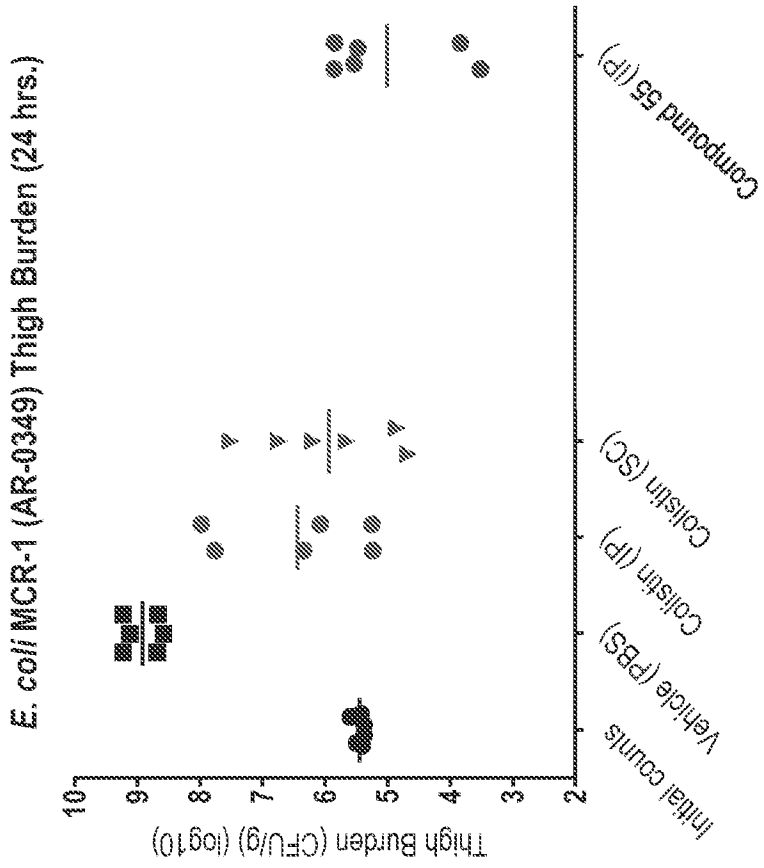

E. coli MCR-1 (AR-0349) Thigh Burden (24 hrs.)
Thigh Burden (CFU/g) (log10)
10
9
8
7
6
5
4
3
2
Initial counts
Vehicle (PBS)
Colistin (IP)
Colistin (SC)
Compound 55 (IP)

FIG. 3

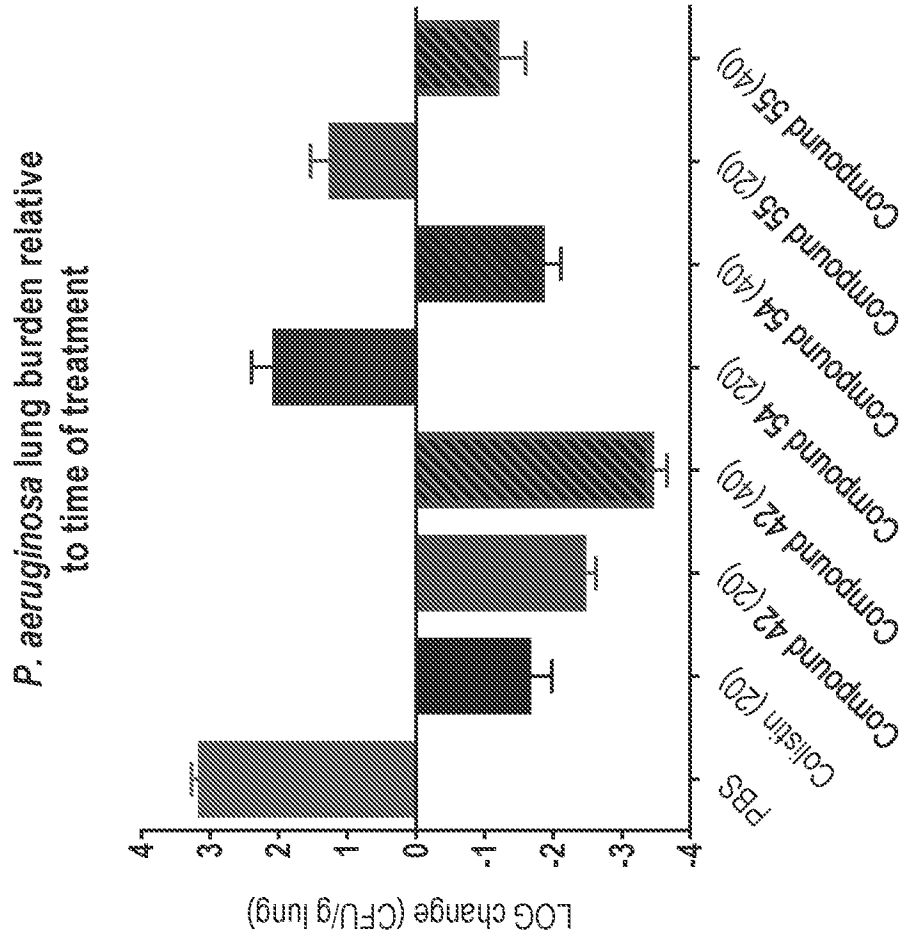

P. aeruginosa lung burden relative to time of treatment
LOG change (CFU/g lung)
4
3
2
1
0
-1
-2
-3
-4
PBS
Colistin (20)
Compound 42 (20)
Compound 42 (40)
Compound 54 (20)
Compound 54 (40)
Compound 55 (20)
Compound 55 (40)

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/041433

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15-17, 25, 26, 32-34, 43-54, 69-73, 79-81, 86, 87, 95, 204, 231-306
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/041433

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/04; A61K 38/12; C07K 7/62 (2019.01)
CPC - A61K 38/04; A61K 38/12; C07K 7/62 (2019.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/9; 514/21.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/006063 A1 (CIDARA THERAPEUTICS INC) 04 January 2018 (04.01.2018) entire document	1
A	WO 2017/189866 A1 (SPERO OPCO) 02 November 2017 (02.11.2017) entire document	1
A	US 2008/0287345 A1 (VAARA et al) 20 November 2008 (20.11.2008) entire document	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2019	15 NOV 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/041433

Continued from Box No. III Observations where unity of invention is lacking

Claim 1 has been analyzed subject to the restriction that the claim reads on a compound described by formula (I): wherein R1 and R12 are each, independently, a lipophilic moiety, wherein the lipophilic moiety is unsubstituted C1 alkyl; R11, R13, and R14 are each, independently, unsubstituted C1 alkamino; R15 is a lipophilic moiety, wherein the lipophilic moiety is unsubstituted C1 alkyl; R2, R3, R4, R5, R6, R7, R8, R9, R10, R19, R20, and R21 are each, independently, absent; R16 is H; R17 is H; each of a, b, c, and d is, independently 0; each of X1, X2, X3, and X4 is independently absent; or a pharmaceutically acceptable salt thereof.

Claims 15-17, 25, 26, 32-34, 43-54, 69-73, 79-81, 86, 87, 95, 204, 231-306 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-14, 18-24, 27-31, 35-42, 55-68, 74-78, 82-85, 88-94, 96-203, and 205-230 are drawn to compounds described by formula (I), (II), (III), (IV), (XXIV), (XXV), (XXVI), (XXVII), (XXXX) and (XXXXI), or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted based on the proviso wherein at least one of X1, X2 , X3, and X4 is a nitrogen atom, wherein if X1 is a nitrogen atom then R3 is absent, if X2 is a nitrogen atom then R5 is absent, if X3 is a nitrogen atom then R9 is absent, and if X4 is a nitrogen atom the R19 is absent; and is restricted to a compound described by formula (I): wherein R1 and R12 are each, independently, a lipophilic moiety, wherein the lipophilic moiety is unsubstituted C1 alkyl; R11, R13, and R14 are each, independently, unsubstituted C1 alkamino; R15 is a lipophilic moiety, wherein the lipophilic moiety is unsubstituted C1 alkyl; R2, R3, R4, R5, R6, R7, R8, R9, R10, R19, R20, and R21 are each, independently, absent; R16 is H; R17 is H; each of a, b, c, and d is, independently 0; each of X1, X2, X3, and X4 is independently absent; or a pharmaceutically acceptable salt thereof; and compounds described by formula (II), (III), (IV), (XXIV), (XXV), (XXVI), (XXVII), (XXXX) and (XXXXI) thereof, or a pharmaceutically acceptable salt thereof. It is believed that claim 1 reads on this first named invention and thus will be searched without fee to the extent that it reads on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound described by formula (I): wherein R1 and R12 are each, independently, a lipophilic moiety, wherein the lipophilic moiety is unsubstituted benzyl; R11, R13, and R14 are each, independently, unsubstituted C1 alkamino; R15 is a lipophilic moiety, wherein the lipophilic moiety is unsubstituted C1 alkyl; R2, R3, R4, R5, R6, R7, R8, R9, R10, R19, R20, and R21 are each, independently, absent; R16 is H; R17 is H; each of a, b, c, and d is, independently 0; each of X1, X2, X3, and X4 is independently absent; or a pharmaceutically acceptable salt thereof; and compounds described by formula (II), (III), (IV), (XXIV), (XXV), (XXVI), (XXVII), (XXXX) and (XXXXI), or a pharmaceutically acceptable salt thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, X1, X2, X3, X4, a, b, c, d, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound described by formula (I) or a pharmaceutically acceptable salt thereof; and subspecies of formula (I) as described by formula (II), (III), (IV), (XXIV), (XXV), (XXVI), (XXVII), (XXXX) and (XXXXI), or a pharmaceutically acceptable salt thereof; these shared technical features do not represent a contribution over the prior art as disclosed by WO 2018/006063 A1 to Cidara Therapeutics, Inc.

WO 2018/006063 A1 to Cidara Therapeutics, Inc. teaches a compound described by formula (I) wherein R1 and R12 are each, independently a lipophilic moiety; R11, R13, and R14 are each, independently, unsubstituted C2 alkamino; R15 is a polar moiety; R2, R3, R4, R5, R6, R7, R8, R9, R10, R19, R20, and R21 are each, independently, absent; R16 is substituted C1 alkyl; R17 is H; each of a, b, c, and d is, independently 0 (Pg. 114, Table 1A, Polymyxin B1, see shown structure).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.